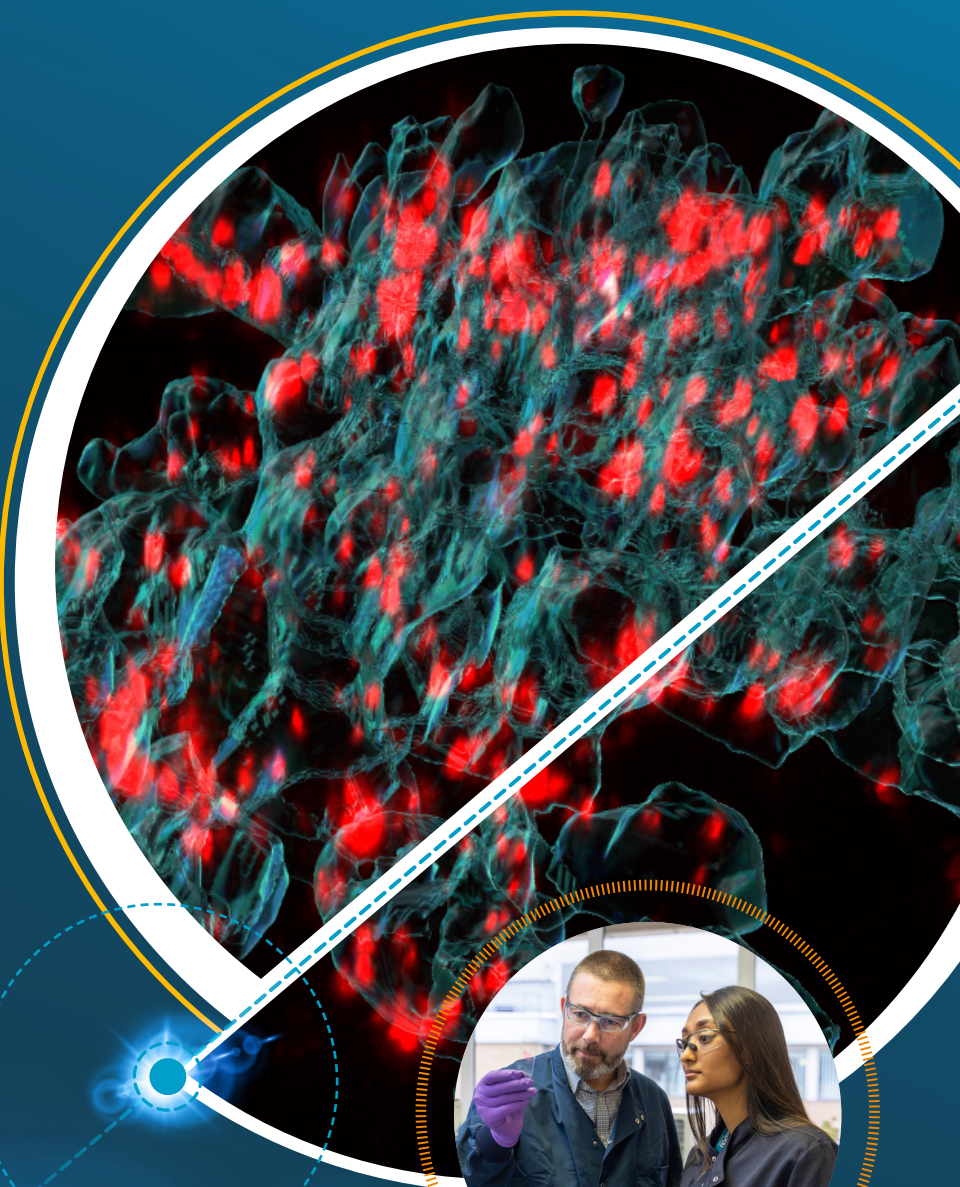


# Shaping the UK into an epicentre for complex medicines

Medicines Discovery Catapult and CPI



Reshaping  
Discovery  
Together

**CATAPULT**  
Medicines Discovery





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## 1 | About MDC and CPI

Medicines Discovery Catapult (MDC) is focused on reshaping the UK's medicines discovery industry.

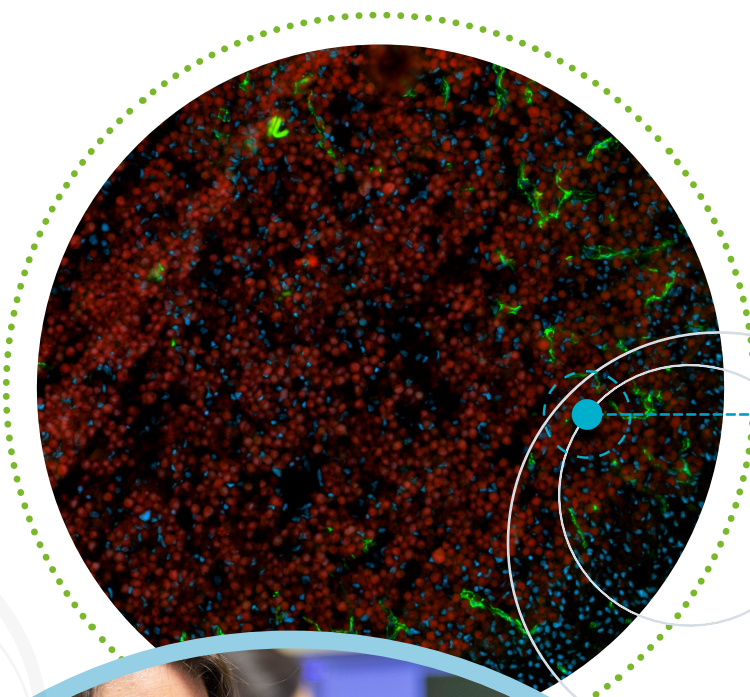
Part of a network of Catapults established by Innovate UK, MDC is an independent, not-for-profit organisation. MDC's not-for-profit status enables a risk-taking mindset that allows a focus on pioneering the next generation of medicines discovery approaches and technologies. We can take risks and pursue objectives that are understandably challenging for commercial, for-profit companies.

[md.catapult.org.uk](https://md.catapult.org.uk)

CPI is a leading independent deep-tech innovation centre and a founding member of UK's High Value Manufacturing Catapult.

CPI acts as a catalyst bringing together academia, businesses, government and investors to translate bright ideas and research into the marketplace, primarily focused on innovations in healthcare, sustainability and digital. CPI has world-class capabilities in medicines manufacturing innovation spanning multiple modalities, including small molecule pharmaceuticals, biological pharmaceuticals, nucleic acid therapeutics and microbiome therapeutics, and the development and scale-up of nanotherapeutic drug delivery systems. We work with our partners across diverse markets in the UK and around the world, driving their innovations forward and helping them to reduce the risk and cost associated with product development.

[uk-cpi.com](https://uk-cpi.com)





## 2 | Foreword

A new wave of medicines has emerged in recent years, to supplement the established small and large molecule platforms. These include modified RNA, antisense and siRNA oligonucleotides, antibody–drug conjugates and nanomedicines.

In 2019–2020, the FDA approved 5 antibody–drug conjugates and 4 RNA therapeutics. Lipid nanoparticles as carriers of next-generation vaccines also came to global prominence in 2021 as the platform for both the Pfizer-BioNTech and the Moderna COVID-19 vaccine. These rapidly emerging therapeutic classes offer the potential to address targets and disease indications that have to date been intractable to drug discovery, and to open up a new field of industrial ‘complex medicines’ discovery, development and manufacture.

While there is a large market opportunity in this sector, new capabilities are required to develop complex medicines, including technical and commercial expertise, access to equipment and infrastructure, drug discovery expertise, manufacturing and scale-up expertise, drug delivery know-how, regulatory and commercialisation support and both public and private translational funding.

MDC and CPI have engaged stakeholders across the UK, through surveys and interviews, to develop an understanding of the complex medicines landscape, the challenges encountered by those working in this area, and to develop clear recommendations to support the sector for national growth and impact in this space. The definition of complex medicines is deliberately inclusive of a variety of advanced drug chemistries and therapeutic targeting vehicles, across complex active pharmaceutical ingredients, complex formulations and complex delivery routes.

In 2020, CPI led the Lipid Nanoparticle (LNP) Taskforce, on behalf of the UK Vaccines Taskforce. This group identified the current UK landscape of product and process development expertise to enable the development, manufacture and supply of lipid nanoparticle-based products for vaccines and therapeutics. It provided a view on how accessible this capability is in the UK and the key gaps that exist. This working group was also asked by the Medicines Manufacturing Industry Partnership to review a broader set of nanotherapeutic delivery technologies, or complex formulations, for intracellular drug delivery, in response to its technology and innovation road mapping. Nanodelivery systems demonstrate the potential to deliver the next generation of nucleic acid therapies and vaccines, and other emerging modalities such as CRISPR therapies. Some key themes that emerged during the work of the LNP Taskforce are also captured in this report.

The insights given by these innovators inform the nation on the support needed to build on the considerable UK promise to deliver an exciting, productive future in complex medicines.



Professor Peter Simpson  
Chief Scientific Officer  
**Medicines Discovery Catapult**



Dr Caroline Kelly  
Head of Technology Strategy, Formulation  
**CPI**



### 3 | Executive summary

Complex medicines will become as important as traditional small molecule drugs in the coming years, with market values of hundreds of billions of pounds. Pharmaceutical and biotech companies working in complex medicines in the UK include those specialising in antibody–drug conjugates, firms developing oligonucleotide therapeutics, entities focusing on proprietary delivery technologies for a range of cargoes, vaccine developers, and others.

The State of the Discovery Nation (2021) gathered opinions from 21 UK-based organisations working in complex medicines – over 30% of the existing community. As a follow-up to the questionnaire, interviews were run with eight of the respondents, enabling them to provide more detailed information against the themes in the survey. Nine organisations, and six academics, from across the innovation ecosystem also inputted into the work of the Lipid Nanoparticle (LNP) Taskforce to provide a clear understanding of the capability needs and gaps in the UK for the development and manufacture of complex medicines where a delivery vehicle, such as an LNP, is required.

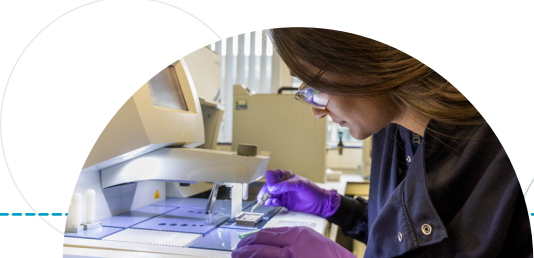
More than three-quarters of respondents believed having nationally available resources to coordinate complex medicines development would help to progress therapeutics for unmet medical needs. Over two-thirds wanted more government investment in complex medicines. Training programmes to upskill the next generation would also be greatly valued by many start-ups.

Understanding the regulatory process was a major barrier for most companies (only 19% had no issues at all with the regulatory hurdles). There was a widespread request for a form of ‘road map’, comprising both guidance and practical support to take early preclinical research technologies through regulatory approval and into the clinic. Among the main issues in this area was a lack of precedent for complex medicines regulatory submissions and little community understanding of what would be important to regulators – in particular, the generation of non-clinical data to demonstrate *in vivo* efficacy, safety and toxicology.

Over 50% of participants cited the most pressing technical challenge as gaining access to imaging facilities for preclinical investigations using cell models or *in vivo* – to allow the study of how therapeutics are distributed in the body and access target cells and tissues. This was followed closely by challenges in developing new bioanalytical methods and validation assays.







Another key theme for the small and medium-sized enterprises (SMEs) was collaboration. Just over two-thirds of respondents wanted support for collaborative partnerships and access to various forms of technical expertise. The need for partnerships appeared to focus on developing the science and technology rather than strategic financial concerns. Perhaps unsurprisingly, grants and investment were the hardest resources for these companies to secure. Expertise and tissue samples were also difficult to access for many SMEs, as they are across all sub-sectors of medicines discovery.

LNPs are currently the most clinically advanced nanotherapeutic delivery system for complex medicines but may not be the optimal choice of delivery vehicle for all drug substances. With these systems, factors such as long-term storage and cold-chain requirements are not yet well-defined and understood. The LNP Taskforce interviews and questionnaires identified that this could be addressed through a deeper understanding of how product composition affects physicochemical properties, intracellular delivery and biological performance.

Manufacturing process development support and the accessibility of good manufacturing practice (GMP) facilities to provide supplies for early-stage clinical trials were also identified by the LNP Taskforce as critical gaps in the UK for SMEs developing complex medicines.

## Recommendations

The following recommendations would provide crucial support to this promising field of complex medicines discovery, development and manufacture in the UK.

- **Establish a network of support, expertise and infrastructure** with the Catapult Network as a hub that gives a single entry point for companies requiring all the elements of support, from preclinical assessment through to process development and scale-up, and GMP manufacture for clinical trials supply.
- **Develop a road map** to help complex medicines to move from the lab to the clinic, including guidance on the regulatory journey and access to expertise and education on drug development and regulatory affairs.
- **Develop training programmes** to increase the skilled workforce in complex medicines – this is a key opportunity to develop a skills, training and knowledge exchange programme that will inspire, engage and train the future complex medicines workforce.
- **Create a networking and learning portal** to match individuals, companies and research organisations to partners for work placements, secondments and individual knowledge exchange, and to run workshops and events.
- **Target the sector with investment** to support UK start-ups in generating the required package of data to give investor confidence.

SMEs in the complex medicines sector need access to opportunities and partnerships to take part in this exciting new chapter in UK medicines discovery and development. This report offers some insights into the ways the industry can become better integrated for the success of UK innovators, in a market worth hundreds of billions.





## 4 | The UK landscape for complex medicines

From increasing the bioavailability and therapeutic index of existing agents, to targeting new types of drugs to untapped molecular targets, the field of complex medicines holds much promise.

Recent success in FDA approvals of antibody–drug conjugates (ADCs), RNA therapeutics and coronavirus vaccines has shown that the field of complex medicines is already having global impact. In the case of COVID-19, the availability of mRNA vaccines has transformed the present outlook for the world – as a direct result of lipid nanoparticle (LNP) technology. Complex medicines offer huge market potential, and the UK is poised to take further advantage of an array of opportunities in this sector.

### Global market value

Changes in the global market for medicines create opportunities for innovators who can rapidly develop and exploit new therapeutics. Small molecules and therapeutic antibodies have dominated the market in the last decade, but drug pipeline trends and investments are showing how complex medicines are becoming a third wave of therapeutics:

- The nanomedicine market is expected to reach a value of £267 billion by 2025 (with a compound annual growth rate, CAGR, of 17.1%).<sup>1</sup> The development of these new drugs and therapies is driven by the need for fewer side-effects and more cost-effective treatments, particularly for cancer.
- The market for ADCs was valued at £1 billion in 2016 and is predicted to reach a value of more than £7 billion by 2025 (25.9% CAGR).<sup>2</sup> A rise in the demand for cost-effective cancer treatment is expected to drive this market.
- The oligonucleotide drug market size is expected to reach £6 billion by 2027 (16.7% CAGR),<sup>3</sup> but the recent success of mRNA coronavirus vaccines is likely to drive more rapid growth in this area.
- Complex medicines contribute to the market for precision medicines, which is forecast to have a value of £91 billion in 2025 (with a CAGR of 12.9% against 2017).<sup>4</sup>

### Complex medicines companies in the UK

A mapping of the UK landscape identified 67 companies that met the definition of complex medicines (see page 7). As well as being characterised as complex medicines companies, they can be sub-categorised as:

- Companies specialising in ADCs
- Companies specialising in oligonucleotide therapeutics or RNA-based vaccines
- Pharmaceutical and biotech companies that have complex medicines as a subset of their therapeutic portfolios
- Companies focusing on a proprietary delivery technology platform (complex formulation or complex delivery route)
- Other companies, such as contract research organisations (CROs) and contract development and manufacturing organisations (CDMOs) supporting the sector

Each of these categories reflects a unique set of strengths and technical challenges that accompany each class of complex medicine and their targeted therapeutic areas. ADCs have been focused almost exclusively on oncology, for example, while antisense oligonucleotide drugs are particularly well suited to the treatment of genetic disorders, for example those whose pathology is driven by an aberrant or misfolded protein. While this research explored some of the modality-specific challenges companies had, it also sought to identify the common barriers faced by companies across the complex medicines field.

1. 'Nanomedicine market size, growth, global industry report, 2018-2025', Grand View Research, April 2017 (viewed on 15 March 2021)  
2. Nanomedicine market size, growth, global industry report, 2018-2025  
3. 'Global oligonucleotides market research report 2020', 360 Research Reports, January 2020 (viewed on 15 March 2021)  
4. 'Precision Medicine Market Overview', Market Research Future, August 2019 (viewed on 15 March 2021)

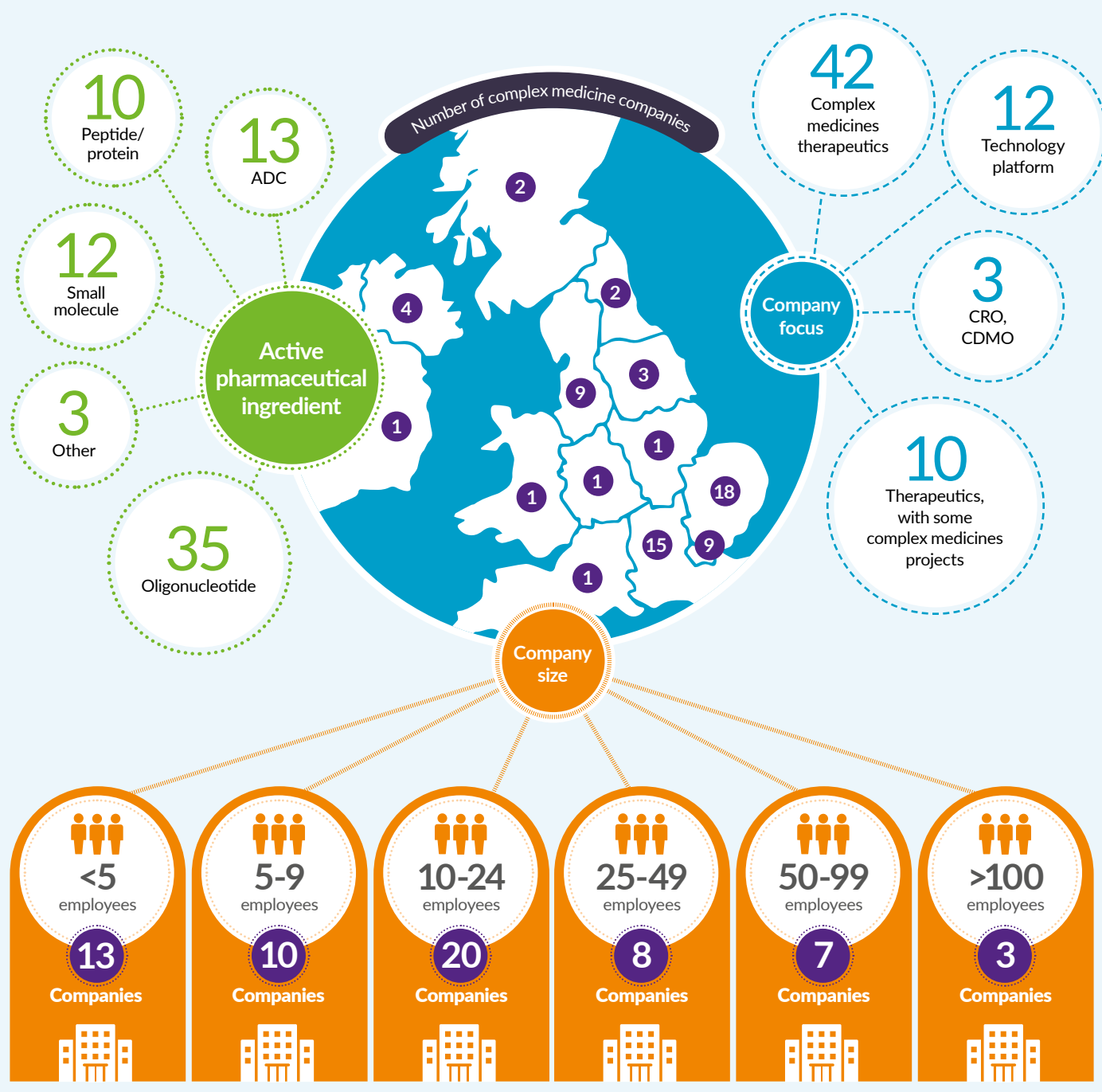




**Figure 1.**  
**A mapping of complex medicines companies in the UK**

The mapping shows that 42 of the 67 companies are exclusively focused on the development of complex medicine therapeutics, with a further 10 companies running a complex medicine project as part of a wider portfolio. 12 companies are currently focused on the development and exploitation of their technology platform, rather than a therapeutic, and three companies are complex medicine specialists in the CRO/CDMO sector.

Delivery technology is at the core of this sector, with 27 of the 67 companies focused on the development and exploitation of a novel delivery system. In terms of the complex medicine API, 35 companies are focused on oligonucleotides (delivery and therapeutics), 13 companies are focused on ADCs (or variants thereof), 12 are focused on small molecules and 10 on peptides/protein delivery.





## 5 | Case study: The investment opportunity in complex medicines – a venture capitalist's view

Exposure to cutting-edge innovation is key for ensuring a good return for any investor portfolio, but for specialist funds in the life sciences, it is essential – and it can be fund-defining. The emergence of complex medicines as a new frontier has become, if not the sole focus, at least the cornerstone of many funds.

The reasons for this are simple. Complex medicines offer not only an ability to address many of the efficacy and safety limitations of more traditional approaches (like small molecules and antibodies) but have the potential to unlock previously inaccessible intracellular targets. Success here opens the potential for a step change in outcomes for patients. Given the competition for truly differentiated products among pharma, this optimises an investor's chance of securing highly lucrative upfront licensing fees, if not full mergers and acquisitions for early clinical candidates. The recent acquisition of Pandion Therapeutics by MSD, for example, exemplifies such demand.

While exploring new modalities continues to be a high-risk endeavour, the clinical success of the first-generation 'adjacent' complex medicines (bispecific antibodies and antibody–drug conjugates) continues to drive a flock of investors to this field – not least because it has shown that many of the safety risks are manageable, in turn de-risking the investments.

This industry continues to innovate at speed, with the explosion of second- and now third-generation complex medicines, and an expansive list that runs from T-cell receptor immunotherapies, chimeric antigen receptor T-cell therapies and next-generation gene therapies, to novel delivery systems using exosomes and nano-syringes.

As with all new technologies, challenges remain – in this case with assay development due to the absence of tools, manufacturing and complex supply and distribution models. An ever-nimble industry of contract organisations also continues to upskill, however, ensuring that the established outsourcing model on which big pharma relies can continue to supply the needs of complex medicines. From an investor's perspective, this field provides an avenue for even generalist investors to also capitalise on cutting-edge science.

The complex medicines train is just leaving the station, so the journey is far from over – but the savviest investors will have secured the first-class tickets.

**Dr Claire Brown**  
Interim Chief Investment Officer  
Oxford Science Innovation





## 6 | Research findings: opportunities and challenges for complex medicines

To hear the views of UK companies involved in complex medicines, the MDC-led State of the Discovery Nation survey was open online from the end of November 2020 to the first week of January 2021. Twenty-one companies working in complex medicines, a sample size of over 30%, provided responses. As a follow-up to the questionnaire, remote interviews were conducted with eight of the respondents, enabling them to provide more detailed information against the themes in the survey.

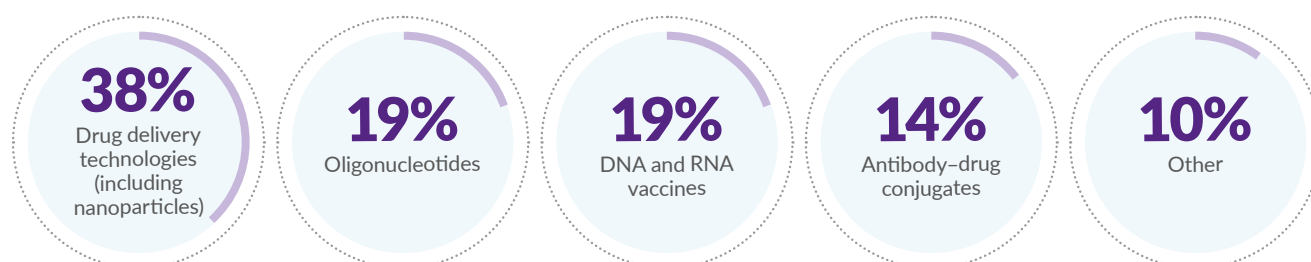
Nine companies (five of which responded to the MDC-led research survey), along with six academics active in complex medicines, also contributed to the findings of this report through their involvement in the LNP Taskforce.

Figure 2 summarises the modalities and therapeutic areas of interest for the companies surveyed. The greatest proportion (38%) were working on drug delivery technologies, including nanoparticles, and oncology was the dominant therapeutic area, cited by 62%.

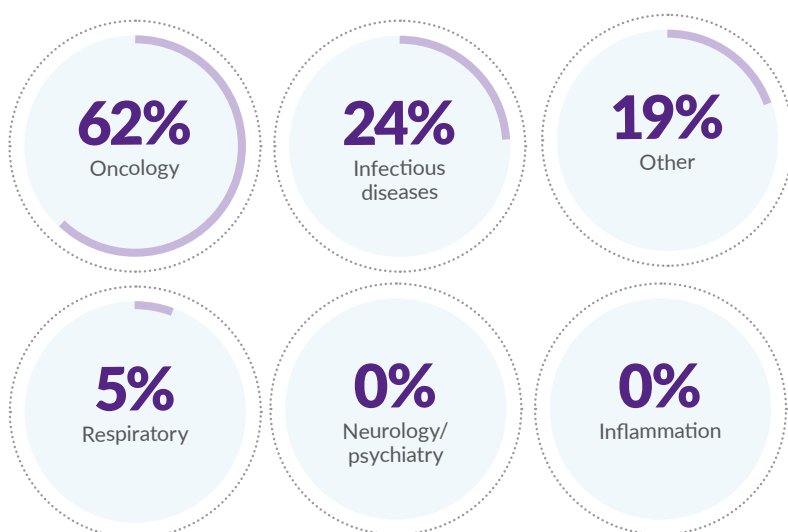
**Figure 2.**

### Areas of focus for surveyed complex medicines companies

What typical class of molecule/delivery are you working on?



### Therapeutic area



Notes: N = 21. For both questions, respondents could select more than one answer



## 7 | Access to technical expertise, facilities and samples

Technical hurdles to the development of complex medicines often originate from the fact that these are cutting-edge therapeutic approaches.

Therefore, emerging companies may not know, what is available in the UK – and traditional consultants and CROs may not yet be sufficiently experienced to provide a full range of services.

Many start-ups in the complex medicines sub-sector are embedded within universities. This can help with access to advanced analytical technologies, but there remain common stumbling blocks, including access to industry-class safety, efficacy and toxicology studies. There is often a need for experienced, complex technical and analytical skills, the precise nature of which may not always be possible to anticipate.

The SMEs taking part in this research said they needed access to a best-practice road map for the development of these assets. This would provide tick boxes to help to identify the assays and

expertise that would be needed at each step of developing a typical complex medicine. Regardless of a company's specific technology, the road map's broad structure could give valuable guidance, but would be linked specifically with the regulatory issues covered later in this report.

### Key survey findings

Figure 3 summarises some of the pressing technical challenges faced by UK companies in the complex medicines field. The most common problem identified in the survey was gaining access to imaging facilities for preclinical investigations using cell models or animals. This was followed closely by challenges developing new bioanalytical methods and validation assays.

### The voice of the sector

The nanoscale at which these scientists are working makes measurements complex – and demands frontier technology and technical experts. "Access to that sort of high-end technology at the nano level," said one participant, "is what we need as a company, and I suspect there are lots of other companies in the same boat." Another explained: "Potentially delivering a few tens of molecules or maybe a couple of hundred molecules to a cell – that's not always the easiest thing in the world to measure."

A crucial technical requirement for companies working at this level is imaging, which was the most frequently cited issue in the online survey (Figure 3). "At the nano level," said one interviewee, "being able to take a cell and visualise where your different components end up in the cell is actually quite difficult." This need to show that a new technology is on target, confirmed another, is key: "I think that imaging to see whether this stuff is going in the right places becomes increasingly important."

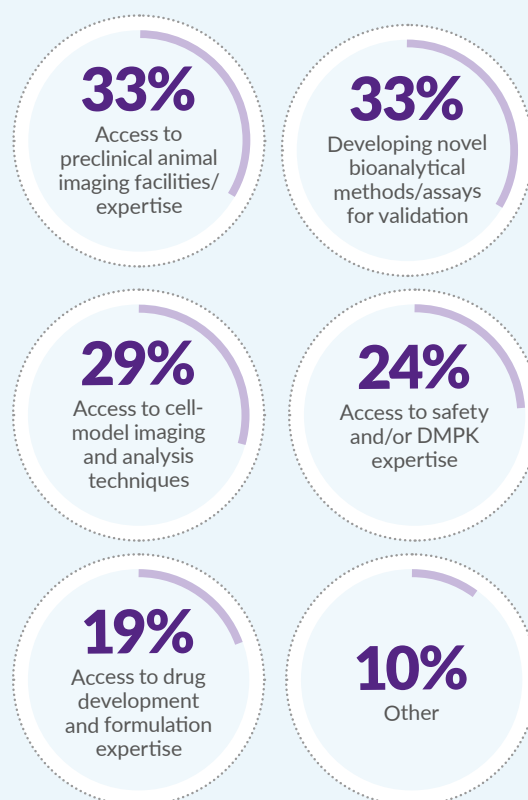
One participant described their experience with sharing expertise and said relationships needed to be facilitated if start-ups were to gain access to expertise:

*"Industry samples, industry expertise are not available unless you have established a relationship with somebody. Having worked in this industry for 30-odd years, I wasn't that open to sharing in those days either. That's where people like you [MDC] are really critical in that, because your technology is ahead of what others have available, and if that can come out to the small companies, that's where progress will happen quickly."*

Figure 3.

### Technical challenges faced by complex medicines companies

What is the most pressing technical challenge or barrier to developing your complex drug/technology?



Notes: DMPK – drug metabolism and pharmacokinetics; N = 21 (respondents could select more than one answer)



## 8 | Case study: pHion Therapeutics

pHion Therapeutics is a vaccine development company spun out of the technology developed by Professor Helen McCarthy from the School of Pharmacy at Queen's University Belfast in 2017. pHion's technology, when combined with mRNA, generates a potent therapeutic immune response, without provoking an innate immune response.

It also stabilises mRNA, enabling storage at room temperature. pHion is currently developing its lead vaccine, working with MDC to achieve the goal of getting it to the clinic, while in tandem planning the scaling up of the product with CPI. The company says that having access to MDC's team of industry experts has helped with accelerating its preclinical programme and has introduced pHion to the wider life sciences ecosystem at Alderley Park; while CPI's manufacturing and technology translation know-how has ensured a seamless move to the next stage of clinical development.

*"For early-stage SMEs in this space, I thoroughly recommend engaging with MDC and CPI, who collectively have the end-to-end knowledge in complex medicines, can support your in-house team and provide access to key equipment that start-ups may not have"*

**Professor Helen McCarthy**  
Chief Executive Officer  
pHion Therapeutics





## 9 | Collaborative networks

According to one participant, more opportunities to collaborate with early-stage technologies could have wide-ranging and long-term benefits.

The ideal shape of collaborative partnerships was elaborated by the research participants, who valued personal connections and shared scientific goals over other strategic concerns. Connections with experts they would otherwise be unaware of, access to pharma partners, connections with regulators, and links to universities – including to train the next generation of chemists and biologists in complex medicines – are all features of the collaboration desired.

The solution coming through from many of the responses was a network or a one-stop shop of experts – the “*concept of a network works just perfectly for us*”, was one of the comments.

A network drives collaboration and the inclusion of multiple expert points of view, and produces a clear road map to help companies to progress from the lab to the clinic. It would be

key to encouraging university spin-outs, de-risking innovation and providing advice and reassurance about regulation, funding and resources.

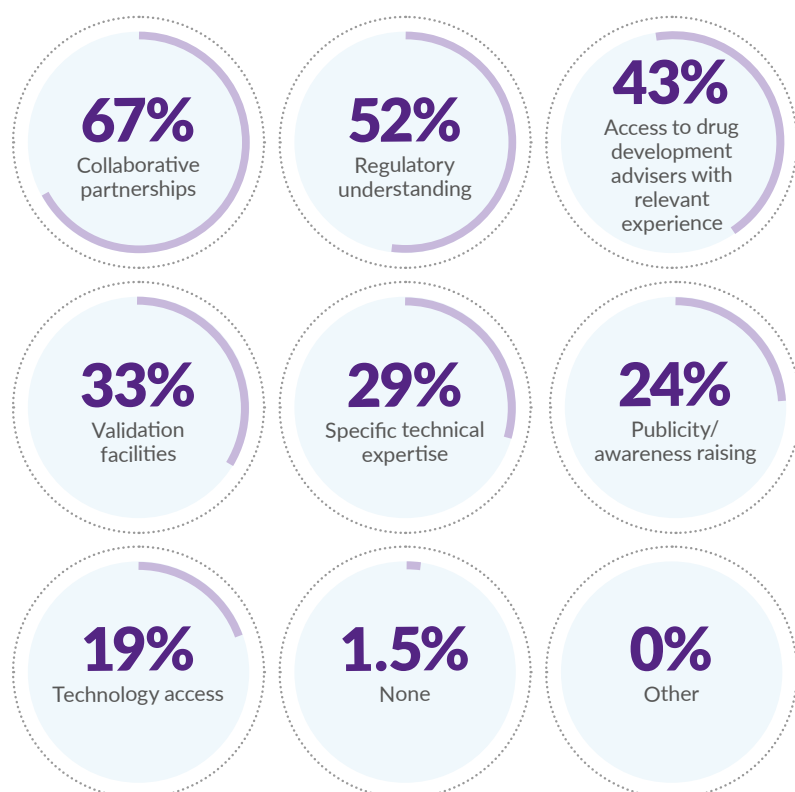
Patients are also key partners, of course, and there is room for deeper engagement in, for example, the field of oligonucleotide medicines that align well with rare diseases and their advocates.

### Key survey findings

The survey findings confirmed collaborative partnerships as the top response regarding the support needed to develop complex medicines. Figure 4 shows that partnerships were desired by 67% of respondents and that access to expertise was a key theme overall. On patient engagement, over three-quarters of the organisations had not yet engaged with patients, but half planned to do so at a later stage (Figure 5).

**Figure 4. The support most desired by complex medicines companies**

What further support would you most benefit from to ensure the complex medicine is developed?



Notes: N = 21 (respondents could select more than one answer)





## Insights from interviews

Collaboration for these companies is not so much of a commercial question as a technical one. The money may be less important than the technical progress:

*"We're keen that these partnerships aren't just a way for the company to generate a bit of cash. The partnerships have to tell us something about what the system is capable of, or where it might be useful."*

For many of the teams working on complex medicines, partnering was the way to take technologies forward, often to gain validation to move to the next stage. Data would be key to establishing collaborations, added one interviewee:

*"The more data we have to show activity in these vaccine fields and oncology fields, the greater the chance will be of getting these collaborations together."*

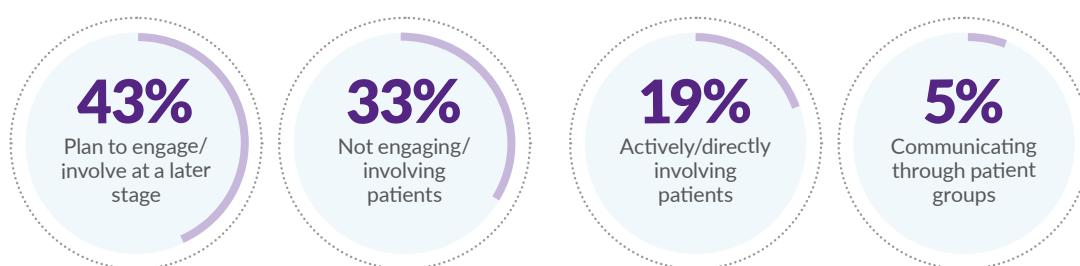
Finally, the scientific focus and less commercial approach desired by complex medicines companies rely on good relationships.

*"I would say the best partner for successful spin-out is a partner you get on with, understands the science and wants to deliver with you," said one interviewee, "rather than somebody who's just going to take your molecule, do a bit of investigation, and you not be involved."*

Figure 5.

### Patient engagement

How have you engaged with your target patient population to identify clinical need and patient impact?



Notes: N = 21

### Potential collaborators

There are many good potential partners active in the field of complex medicines that could form a network of collaborators, including:

- MDC (for the assessment of where a complex medicine localises, to assess intracellular delivery and for the analysis of therapeutic versus toxicological biological effects)
- CPI, a member of the High Value Manufacturing Catapult (process development, process and product characterisation, scale-up, and manufacturing and formulation for therapies and vaccines based on small molecules, biologicals, nucleic acids and nanomedicines)
- A range of expert CROs and CDMOs
- The University of Strathclyde (defining novel LNP compositions at a small scale to address nucleic acid-based drug delivery challenges)
- The Cell and Gene Therapy Catapult (supports the translation of early-stage research into commercially viable and investable therapies), including the new Cell and Gene Therapy Manufacturing Innovation Centre, which will also support vaccine manufacture
- Imperial College London (developing mRNA/self-amplifying RNA – saRNA – platforms, with a recent focus on saRNA as a COVID-19 vaccine candidate)
- The University of Liverpool (physical and chemical characterisation alongside biological compatibility and pharmacokinetics)
- The Nucleic Acid Therapy Accelerator, a research initiative funded by the Medical Research Council (specialist oligonucleotide synthesis and analytical capabilities)
- The Vaccines Manufacturing Innovation Centre (innovative vaccine manufacturing processes and manufacturing at a variety of scales)



## 10 | Access to support in formulation, process development, scale-up and manufacturing of nanotherapeutic delivery systems

Many of the drug substances used in complex medicines require more complex formulation, such as encapsulation of the active payload into drug delivery vehicles (liposomes, LNPs, etc.) to overcome key challenges relating to the successful delivery to sites of biological activity, and to ensure stability and compatibility with biological systems, the immune system in particular. Examples of this class of complex medicines include several of the leading nucleic acid vaccines against COVID-19, such as those from Pfizer/BioNTech and Moderna where mRNA is encapsulated in an LNP.

There are, however, technical, logistical and commercial challenges to the development, commercialisation and deployment of these types of complex medicine. These create barriers to entry and investment for companies developing such products. Despite a strong UK research base in certain areas, there are clear gaps to address to enable translation from bench concepts to preclinical testing and regulatory approvals. The manufacturing technology, characterisation capability and supply chain are also immature for these emerging technologies. As a result, there is a very limited industrial footprint for LNPs and other delivery platforms in the UK.

The LNP Taskforce engaged in this research identified key areas for assistance in the development and manufacture of these complex medicines. The industry needs access to support in developing compositional understanding; for example, in the case of LNPs, how the choice of lipid can ensure optimal physicochemical, biological and toxicological performance and potentially reduce or even remove

the need for cold-chain storage. Integrated capabilities are also needed for physicochemical and biological characterisation to develop predictive, clinically relevant testing for development. The rapid development of robust manufacturing processes and supply chains is needed to ensure the security of supply at large scale via efficient technology transfer to good manufacturing practice (GMP) facilities to support manufacture for clinical trials and commercial supply. GMP facilities with the appropriate skills, expertise and equipment for some complex medicines, including nanotherapeutic delivery systems, are currently a gap in the UK ecosystem.

Many of these capabilities are found in pockets of expertise within the UK, but there is no single point of access to a breadth of integrated expertise and infrastructure to support the development of these types of vaccines and therapeutics.





## 11 | Regulatory assistance

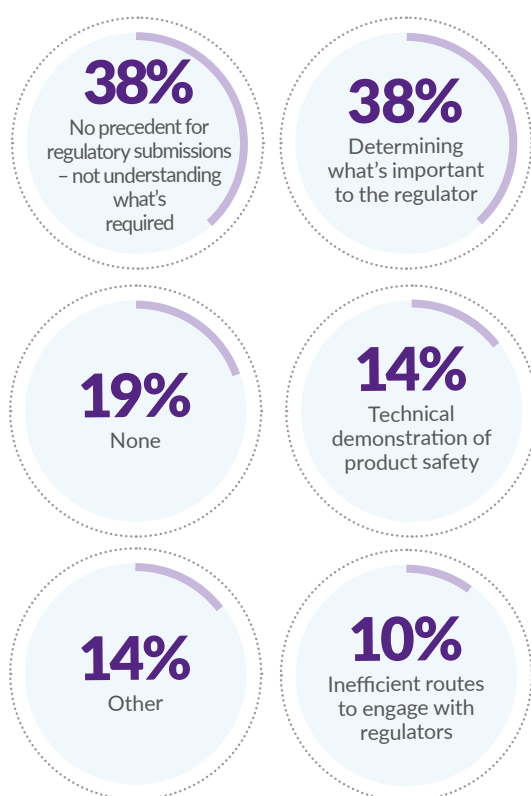
After research and development partnerships, the support most wanted by complex medicines companies was “regulatory understanding” (52%; see Figure 4). Scientists aiming to translate their technologies into therapeutics have not typically been exposed to the process of drug development, when compared with the knowledge held by big pharma, CROs and CDMOs.

The difficulty of identifying the regulatory pathway for complex medicines is deepened because these technologies can straddle different regulatory areas. The regulatory process for complex medicines could be improved through dialogue among experts, companies and regulators. There was much positivity in the interviews about the support that is already given by regulators (which the UK regulator itself champions – see ‘Partnership with the medicines regulator’), but also a desire nonetheless for more guidance and for a road map that helps to progress a product to the clinic.

### Key survey findings

Almost three-quarters of respondents had a lack of understanding of what regulators require or need to be assured of in the development of complex medicines (Figure 6).

**Figure 6.**  
**Regulatory hurdles faced by complex medicines companies**  
What regulatory hurdles have you faced, if any?



Notes: N = 21 (respondents could select more than one answer)

### Partnership with the medicines regulator

*“The MHRA recognises the regulatory challenges of bringing healthcare innovation, including complex medicines, to patients in the UK.*

*“Our new innovative licensing and access pathway (ILAP) has been designed to reduce the time to market for innovative medicines, and addresses the key issues outlined in this report. The ILAP combines the MHRA’s globally recognised strengths of independence and high standards of quality, safety and efficacy with improved efficiency and flexibility, readying the MHRA for a new era in medicines approvals in the UK. Central to realising this ambition is how the ILAP provides a single integrated platform for sustained collaborative working between the MHRA and partners (the National Institute for Health and Care Excellence and the Scottish Medicines Consortium), and the medicine developer.*

*“The MHRA Innovation Office is open to ideas for innovative medicines, medical devices and manufacturing processes. We provide free and confidential expert regulatory information, advice and guidance to organisations of all backgrounds, including academia and SMEs.”*

### Dr Siu Ping Lam

Director of licensing at the Medicines and Healthcare products Regulatory Agency (MHRA)

### Insights from interviews

One interviewee indicated that trying to persuade regulators was the next hurdle after persuading investors. *“Funding is always going to be competitive, as it should be – you want to fund the best science for the most important diseases,”* they said. *“But once you get past that hurdle, it’s the help with changing and pivoting towards how you get a complex medicine approved by the regulator that I think is the most challenging.”*

Many interviewees used the term road map. One said: *“I just think there is an assumption that every spin-out, SME or whatever knows the road map to get to the clinic, and they don’t.”*

Conflicting information from regulatory consultants may also complicate things when nanotechnologies straddle different regulatory areas. One interviewee said: *“We have nano-silica: do we need to do toxicology on that particle on its own or do you do toxicology when it has got its payload on board? If you ask that to three different consultants in the area, you’ll frankly get three different answers.”*

One company mentioned the MHRA’s ILAP (see ‘Partnership with the medicines regulator’) and its benefits: *“There is a need to redefine the classification of therapeutics as the current 20th century definition is not a fit for complex medicines. We welcome the new initiative from the MHRA, the innovative licensing and access pathway programme, as it supports companies developing medicines for conditions with unmet clinical need. This promotes innovation in the area of precision and complex medicine as certainty is given to the sponsor if specific, agreed targets are met. This efficient, certainty led process permits better planning and financing for sponsors to facilitate therapies for unmet clinical needs to market.”*



## 12 | Case study: N4 Pharma

N4 Pharma is a speciality pharmaceutical company developing a patented silica nanoparticle (Nuvec), which is designed to bind oligonucleotides and deliver the payload into the cell where expression/translation occurs. At present this technology is being developed to deliver DNA and mRNA vaccines after parenteral administration.

N4 Pharma is a virtual organisation with no laboratory facilities of its own, and therefore uses a number of CROs to conduct manufacturing development, and *in vitro* and *in vivo* experiments.

Working with MDC and CPI over the past year has allowed N4 Pharma access to technology that has provided an understanding, at the cellular level, of the mechanism of action of Nuvec, which has been instrumental in progressing its development.

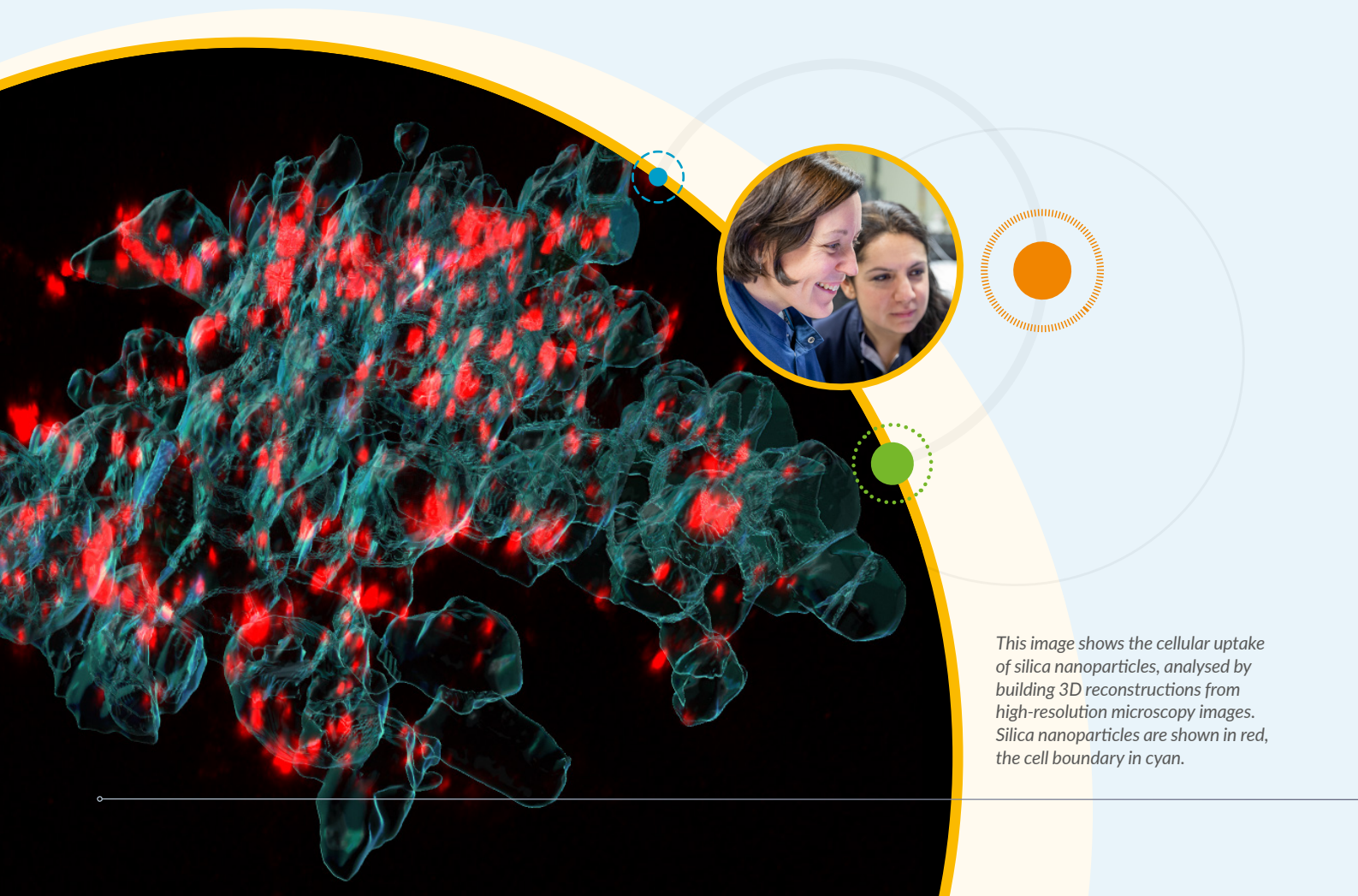
Importantly, as well as providing access to high-end technology, working with MDC has also provided expertise and intellectual input. It has also enabled access to a wider network of companies providing specialist services.

As an example, studies conducted by MDC using Nuvec particles labelled with a fluorescent dye have shown that the particle enters the cell by a known endocytotic pathway and releases the payload plasmid, resulting in effective transfection. Using this labelled particle, it has been possible to estimate the number of particles that enter the cell. This is an important statistic, which will also allow an estimate of the number of plasmids required to effect transfection.

Using this technology, it has also been possible to estimate the depth of penetration of the nanoparticle within the cell, providing a fuller understanding of the mechanism of action of Nuvec.

**Dr David Templeton**

Technical Director  
N4 Pharma



*This image shows the cellular uptake of silica nanoparticles, analysed by building 3D reconstructions from high-resolution microscopy images. Silica nanoparticles are shown in red, the cell boundary in cyan.*



## 13 | Access to funding

This research has identified gaps in awareness about access to investment funding and government grants.

The typically young companies are not seasoned fundraisers, and there is an opportunity to support them in seeking finance. The opportunity to fund the promise of the complex medicines sector could therefore be realised by supporting people in candidate companies to access existing resources, combined with translational funding targeted to the field.

### Key survey findings

The respondents to the survey found investment and grant funding the hardest resource to secure (over half cited this as the most difficult; Figure 7). Most respondents wanted further government support through access to resources to help them to develop complex medicines – 81% and 67% asked, respectively, for more coordination and investment.

### Insights from interviews

While financial resources are the obvious concern for companies trying to develop complex medicines, the follow-up interviews offered detail on the findings that 19% of respondents found human tissue samples hard to secure (Figure 7). One of the entrepreneurs interviewed is a surgeon and was able to ask for human tissue, ethically, in the course of their clinical work. But while the need for access was commonplace, visibility, access routes and administrative hurdles remained unsurmountable for many.

*“Availability of tissue in rare disease is always going to be challenging,”* summed up one participant.

Returning to the question of fundraising, one participant said their engagement with MDC helped them to show investors that they were working with experts:

*“The biggest challenge we’ve faced is with investors...and we’ve kind of got round it by integrating with yourselves [MDC] – showing that we work with experts that can help us. That makes a big difference. And, also, just being honest with them, saying, ‘we are entirely flexible’ – and, to be honest, the best investors have responded well.”*

One participant said investor presentations were similar, in the challenges they presented, to academic fellowship applications, and a network could help with guidance on these.

*“They need to be pristine,”* they said of investor presentations. *“This is a high-level, business discussion. Therefore, it’s not to be undertaken lightly. These need to be turned into a standard that you would expect for a sort of senior fellowship. I think sometimes you don’t get great guidance on that from universities and that was a journey for us, but I think that’s very important for investment.”*

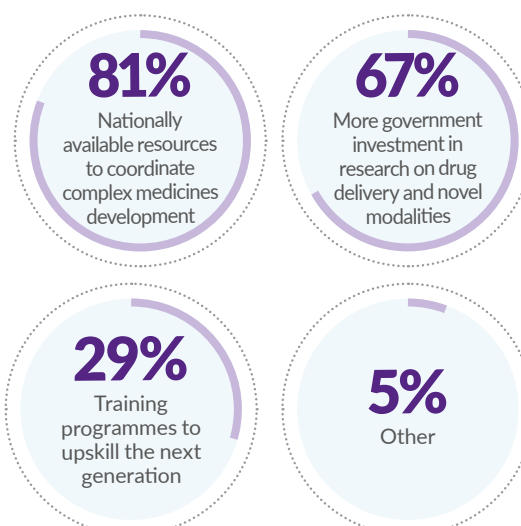
Figure 7.

### Resource difficulties faced by complex medicines companies

Which of the following resources are hard to secure?



What could be done to progress complex medicines for unmet diseases?



Notes: N = 21 (respondents could select more than one answer)



## 14 | COVID-19

### The effect of the COVID-19 pandemic on the complex medicines sector has been mixed.

Some companies have found themselves pivotal to the COVID-19 response. While these opportunities have arisen, there has also been significant disruption for many in the sub-sector.

The pandemic has showcased the value of complex medicines, in particular in the importance of LNPs as a delivery technology for mRNA vaccines. The race to find a vaccine against COVID-19 accelerated the development of LNP-based nucleic acid technology, but the pandemic has also demonstrated some fragility and technical challenges that need to be overcome. This research has found many international examples of SMEs applying their drug delivery platforms such as LNPs to coronavirus vaccines.

The companies responding to our research have been nimble in adapting to the pressing needs, and in redirecting their energies and resources to the pandemic. The speed at which the UK has approved the coronavirus vaccines demonstrates the potential for positive long-term change to the drug development journey.

MDC and CPI, along with others in the Catapult Network, have been at the forefront of the UK's response to COVID-19, creating national-scale diagnostic testing, national vaccine manufacture

readiness and laying down a foundation for how the UK can be better prepared for pandemics.

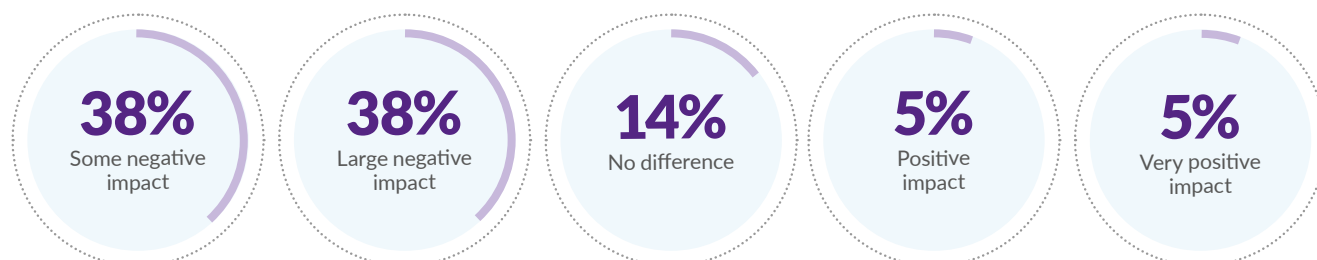
Through this work and listening to the R&D community, a great opportunity has been identified to address gaps in UK support for the next generation of nucleic acid-based vaccines and therapeutics. This can be achieved by connecting existing national capabilities and developing better compositional understanding, more robust testing and validation methods, and supporting process development and scale-up.

For companies developing vaccines and therapeutics, a single point of access could be provided by a future centre of excellence in the UK, potentially modelled on a distributed network. This would give essential support for technologies needing an advanced drug delivery system such as LNPs, helping therapeutic candidates to be accelerated towards clinical trials and manufacturing. Such a network centre could build on the existing innovation ecosystem and research and development infrastructure, led by the Catapult Network, to foster a world-class sector for the UK and for patients.

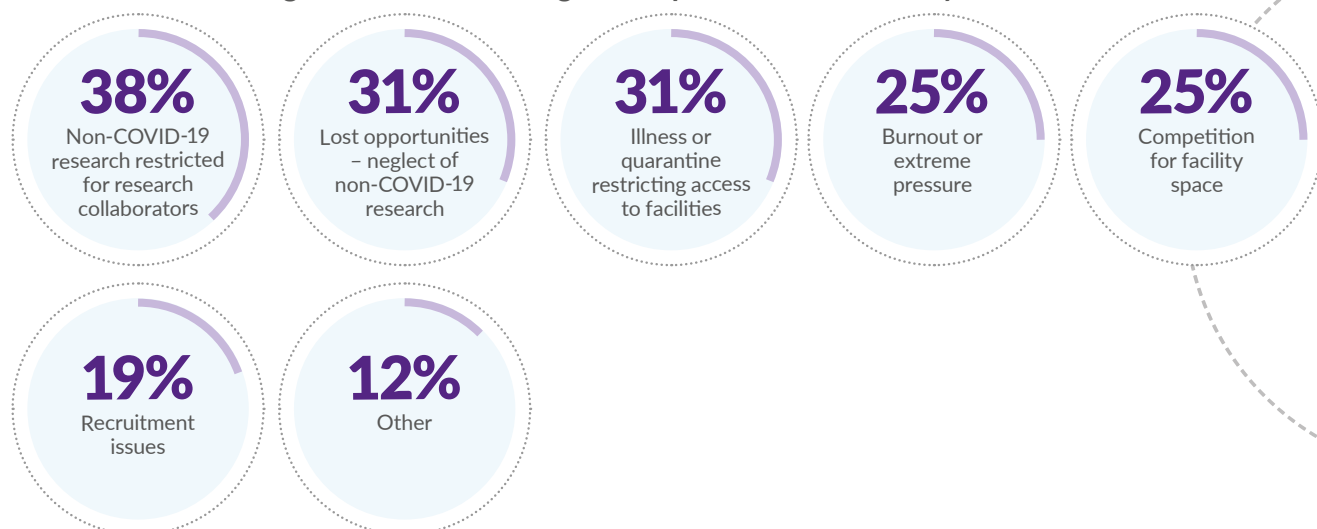
**Figure 8.**

#### Impact of COVID-19

To what extent has COVID-19 impeded progress, from your company's perspective?



Which of the following best describe the negative impact of COVID-19 on your business?



Notes: N = 21 (respondents could select more than one answer)



### Key survey findings

Despite the halo effect from the success of the coronavirus vaccines, 76% of the survey respondents had some form of negative impact from COVID-19 (Figure 8). The biggest impact was the restriction on research collaborators involved in non-COVID-19 research (cited by 38%). The more direct effects included not being able to access facilities because of illness, quarantine and the capacity limits on shared spaces.

### Insights from interviews

For some, COVID-19 has focused attention on key platform technologies. *"What we've actually done,"* one participant said, *"is really focused down into mRNA vaccinations because that's where we think we've got a real USP."* For others, the pandemic has delivered opportunities in both prevention and treatment:

*"We saw how we could use and apply our technology, not only for a therapeutic for COVID as an RNAi to the lungs, but also in a COVID vaccine. And then, obviously, the government supported us on this."*

Yet another SME is now considering its nanoparticle technology for use in an oral vaccine. *"The emergence of COVID meant that some of our work took a back seat whilst we diverted our attention to COVID-related activity. It's been a distraction and a disruption, I would say, but also an opportunity."* The participant explained that, for their interest in oral delivery, getting access to patient groups was crucial for a product driven partly by preference. *"Patient need, patient compliance, the ability for the patient to have a simple tablet rather than an injection. The COVID injection is trivial, certainly, but there will be people who will still not be comfortable; some people just don't like it. And also the cold-chain supply; if you can have a simple oral...all of those aspects."*







## 15 | Recommendations

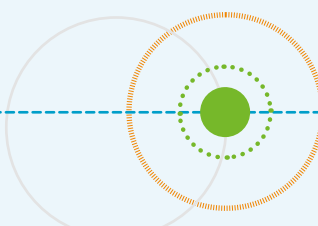
This research increases the national understanding of the needs of those working to develop complex medicines.

It highlights several themes, against which clear recommendations can be made. Action against each of the recommendations will provide essential support to this promising field of medicines discovery in the UK.

- **Establish a network of support, expertise and infrastructure** with the Catapult Network as a hub that gives a single entry point for companies requiring all the elements of support, from preclinical assessment through to process development and scale-up, and GMP manufacture for clinical trials supply
- **Develop a road map** to help complex medicines to move from the lab to the clinic, including guidance on the regulatory journey and access to expertise and education on drug development and regulatory affairs
- **Develop training programmes** to increase the skilled workforce in complex medicines – this is a key opportunity to develop a skills, training and knowledge exchange programme that will inspire, engage and train the future complex medicines workforce
- **Create a networking and learning portal** to match individuals, companies and research organisations to partners for work placements, secondments and individual knowledge exchange, and to run workshops and events
- **Target the sector with investment** to support UK start-ups in generating the required package of data to give investor confidence

Nurturing companies will help to deliver long-term growth opportunities and will position the UK as the leading destination for inward investment in this sector. There are levelling-up opportunities in giving support to the many SMEs in this sector that fall outside the known technology hubs yet need the same support and skills development.

MDC, CPI and the Catapult Network can augment the capabilities of large pharma with unique specialist expertise, giving SMEs in the complex medicines sub-sector the best opportunity to take part in an exciting new chapter in UK medicines discovery and development.





## 16 | Case study: Sixfold Bioscience

While the advent of small molecule and antibody drugs revolutionised the market for advanced therapy medicinal products (ATMPs), there remain many unmet clinical needs.

These otherwise undruggable targets can be modulated at a cellular level using RNA therapeutics, such as small interfering RNA (siRNA) and messenger RNA (mRNA). One of the biggest bottlenecks for RNA therapies, however, is the lack of an effective systemic delivery platform to precisely target them to diseased cells.

Sixfold Bioscience seeks to overcome this challenge by integrating the development of the delivery platform and the therapeutic. The modular design of its Mergo platform means Sixfold can rapidly engineer systems for RNA therapies with enhanced specificity and safety profiles – and the platform’s versatility offers huge commercial potential against a wide range of clinical indications. Sixfold is collaborating with MDC to strengthen its preclinical data through MDC’s state-of-the-art facilities and drug discovery expertise.

*“By reframing how we think about the RNA therapeutics development process, we have been able to build a technology that can be engineered to treat a wide variety of target indications”*

*“It’s great to see the clinical landscape of RNA therapeutics maturing, including its manufacturing and supply-chain capabilities, but if the RNA therapeutics industry is to realise its full potential, we need systems to target extra-hepatic indications. We are excited to be leading this effort”*

**Dr Anna Perdrix Rosell**

Managing Director and Co-Founder  
Sixfold Bioscience





## 17 | How MDC and CPI can help

MDC and CPI have world-leading, complementary capabilities to support companies along the complex drug development pathway, with an offering that can go further than simply meeting the in-house offering of large pharma.

Simplifying access to technologies, facilities, samples and expertise is at the heart of the Catapult Network's role – connecting innovators with others who can help, actively enabling more effective research and development, and providing access to in-depth technical expertise.

This is accessed through commercial or grant-funded collaborative research and development work; both Catapults have extensive skills in the development of compelling proposals, and managing consortia with the right partners.

MDC helps partners to characterise their novel technologies and therapeutics in biological systems. These assess biological penetration, efficacy and pathway impacts in cells, tissues and preclinical animal models. MDC's informatics skills and tools analyse and make sense of extensive internal and literature data. All these characterisation efforts improve the success of medicines in the clinic.

CPI owns and operates several national centres to support companies to develop commercially viable manufacturing processes for complex medicines:

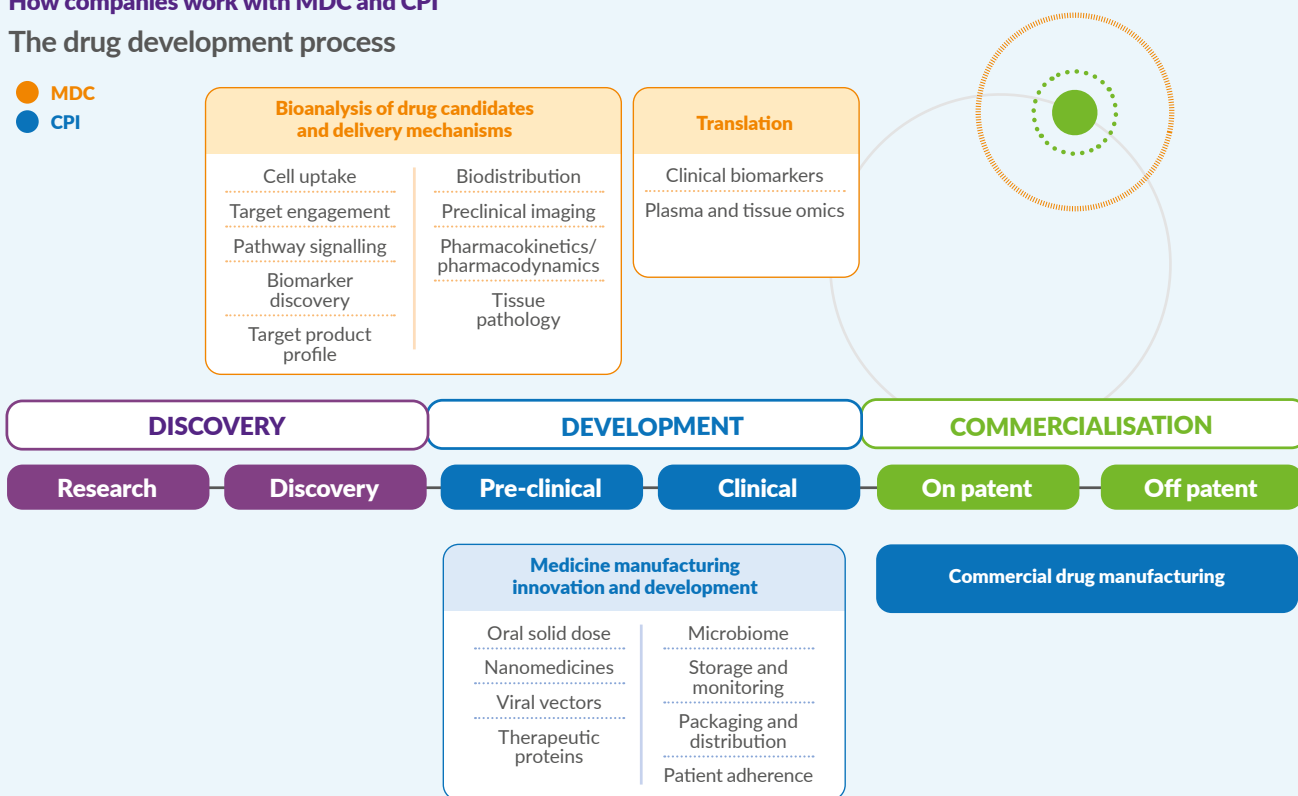
- The National Biologicals Manufacturing Centre supports the design, development, optimisation and demonstration of bespoke manufacturing processes for biologicals and mRNA-based products
- The National Formulation Centre supports the development of emerging nanotherapeutics, where an active payload, such as a nucleic acid, needs to be encapsulated in a delivery vehicle, such as a liposome, LNP or polymeric nanoparticle
- The Medicines Manufacturing Innovation Centre supports technology and innovation in pharmaceutical manufacturing, including technology translation and manufacture for small molecule and oligonucleotide drugs

**Figure 9.**

### How companies work with MDC and CPI

#### The drug development process

- MDC
- CPI





### Areas of technical expertise and capability within MDC include:

- An *in vivo* imaging facility equipped with positron emission tomography, computed tomography, high-frequency ultrasound, bioluminescence and near-infrared imaging. These platforms are applicable for longitudinal studies with multiple imaging endpoints to study the biodistribution, organ accumulation and efficacy of complex medicines
- Access to novel and bespoke radiochemistry to track drugs and their effects.
- High-resolution microscopy imaging suite, including multiphoton confocal microscope with live-cell imaging capability, super-resolution microscope, slide scanner and image analysis software. These platforms are used to assess the cellular uptake and subcellular trafficking of complex medicines.
- A bespoke suite of cellular assays for the tracking of complex medicines' biodistribution and *bioactivity*
- Multiplexed immunohistochemistry and immunofluorescence analysis of *ex vivo* tissues
- Label-free analysis of complex medicines' localisation and effects in tissues using mass spectrometry imaging
- Assessment of a wide range of pathway signals and molecular markers by transcriptomic analysis of cells and tissues, including spatial localisation

### Areas of technical expertise and capability within CPI include:

- Development, optimisation and scale-up processes for a wide range of biological products using microbial and mammalian expression systems
- Strain characterisation and cell banking
- *In vitro* synthesis, purification and formulation for the production of mRNA products (such as vaccines) and the cell-free expression of recombinant proteins, and reaction scale-up for clinical manufacture
- Novel manufacturing approaches for oligonucleotide drugs
- Downstream process purification development and optimisation, including high-throughput and small-scale screening and process development, scale-up and demonstration
- Analytical measurement and characterisation
- Formulation and stability optimisation
- Process development for the scale-up of nanoparticulate-based systems, including the choice of manufacturing process; development and scale-up of purification strategies; and formulation with cryoprotectants for successful lyophilisation via freeze drying
- Characterisation: a toolbox to assess key nanoparticle attributes
- Development, scale-up and optimisation of viral vector production to support product development and manufacturability

These sit alongside a broader range of capabilities to support formulation development and manufacture, including extensive automated experimentation; modelling, informatics and data science; and chemistry and process engineering expertise to develop robust and optimised processes viable at commercial scale





## 18 | Appendix

### Acknowledgements

MDC and CPI wish to thank the many UK company representatives who took part in the survey and follow-up interviews to provide the valuable insights summarised in this report. We would also like to thank the Medicines and Healthcare products Regulatory Agency for its input.

### Abbreviations

<b>ADC</b>	Antibody–drug conjugate	<b>ILAP</b>	Innovative licensing and access pathway
<b>API</b>	Active pharmaceutical ingredient	<b>LNP</b>	Lipid nanoparticle
<b>ATMP</b>	Advanced therapy medicinal product	<b>MDC</b>	Medicines Discovery Catapult
<b>CAGR</b>	Compound annual growth rate	<b>MHRA</b>	Medicines and Healthcare products Regulatory Agency
<b>CDMO</b>	Contract development and manufacturing organisation	<b>mRNA</b>	messenger RNA
<b>COVID-19</b>	Coronavirus disease 2019	<b>RNA</b>	Ribonucleic acid
<b>CPI</b>	Centre for Process Innovation	<b>RNAi</b>	RNA interference
<b>CRO</b>	Contract research organisation	<b>saRNA</b>	self-amplifying RNA
<b>CRISPR</b>	Clustered regularly interspaced short palindromic repeats	<b>siRNA</b>	small interfering RNA
<b>FDA</b>	Food and Drug Administration	<b>SMEs</b>	Small and medium-sized enterprises
<b>GalNAc</b>	N-acetylgalactosamine		
<b>GMP</b>	Good Manufacturing Practice		





## What are complex medicines?

The following is the definition of complex medicines adopted by this report.

A complex medicine is one that requires the application of novel technologies for the delivery and targeting of drugs, through the modification of an active pharmaceutical ingredient or formulation and/or through a novel route of delivery.

This report is written on the basis that complex medicines include, but are not limited to, any biological or non-biological drug that falls into one or more of the following three categories.<sup>5</sup>

### Complex active pharmaceutical ingredients (APIs)

Drug-dendrimer conjugates, glatiramoids, polymeric compounds, antibody-drug conjugates, oligonucleotide conjugates and N-acetylgalactosamine (GalNAc)-small interfering RNA (siRNA) conjugates.

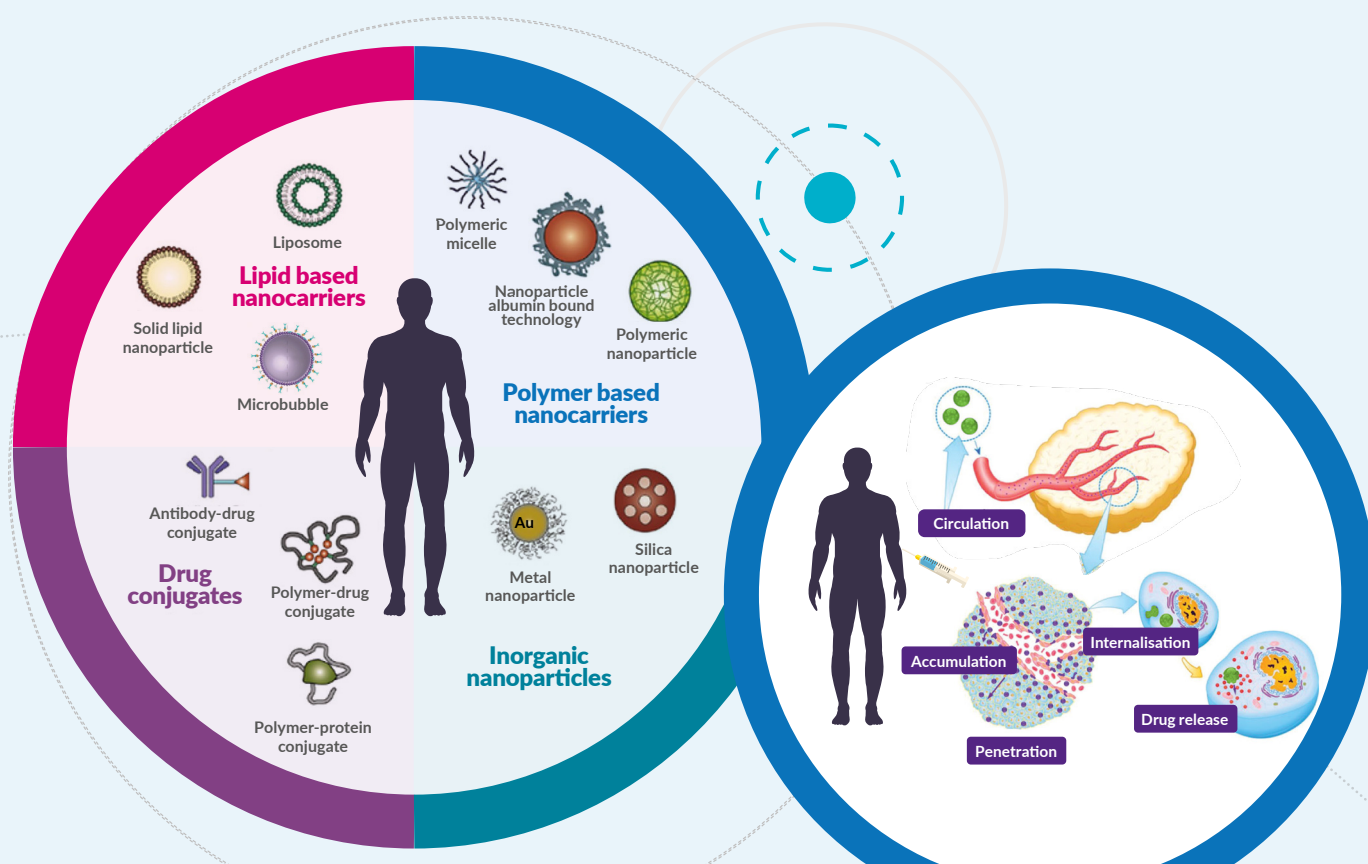
### Complex dosage forms/formulations

Nanomedicines such as liposomes, lipid nanoparticles, inorganic nanoparticles, polymeric nanoparticles, polymersomes, micelles, nanocrystals, colloids, microbubbles, other carriers (chitosan-based carriers, for example), albumin-bound agents, extracellular vesicles (exosomes, microvesicles) and extended-release injectables.

### Complex routes of delivery

Products with a non-systemic site of delivery, including intra-tumoural targeted therapies.

We believe that each of these categories needs further investment and support to drive innovation, to enable and grow a successful complex medicines sub-sector for the UK.



5. The following are in scope only when they need an innovative drug delivery system (not an exhaustive list): naked siRNA, antisense oligonucleotides, monoclonal antibodies/nanobodies, proteins/peptides, vaccines, drug-device combinations and advanced therapy medicinal products (including gene therapy medicines such as CRISPR-Cas9 gene editing, somatic-cell therapy medicines and tissue-engineered medicines, except those formulated in complex drug delivery systems).





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