Industry in Focus

Pharma Manufacturing of the Future

Harnessing the Oligonucleotide Opportunity

pwc

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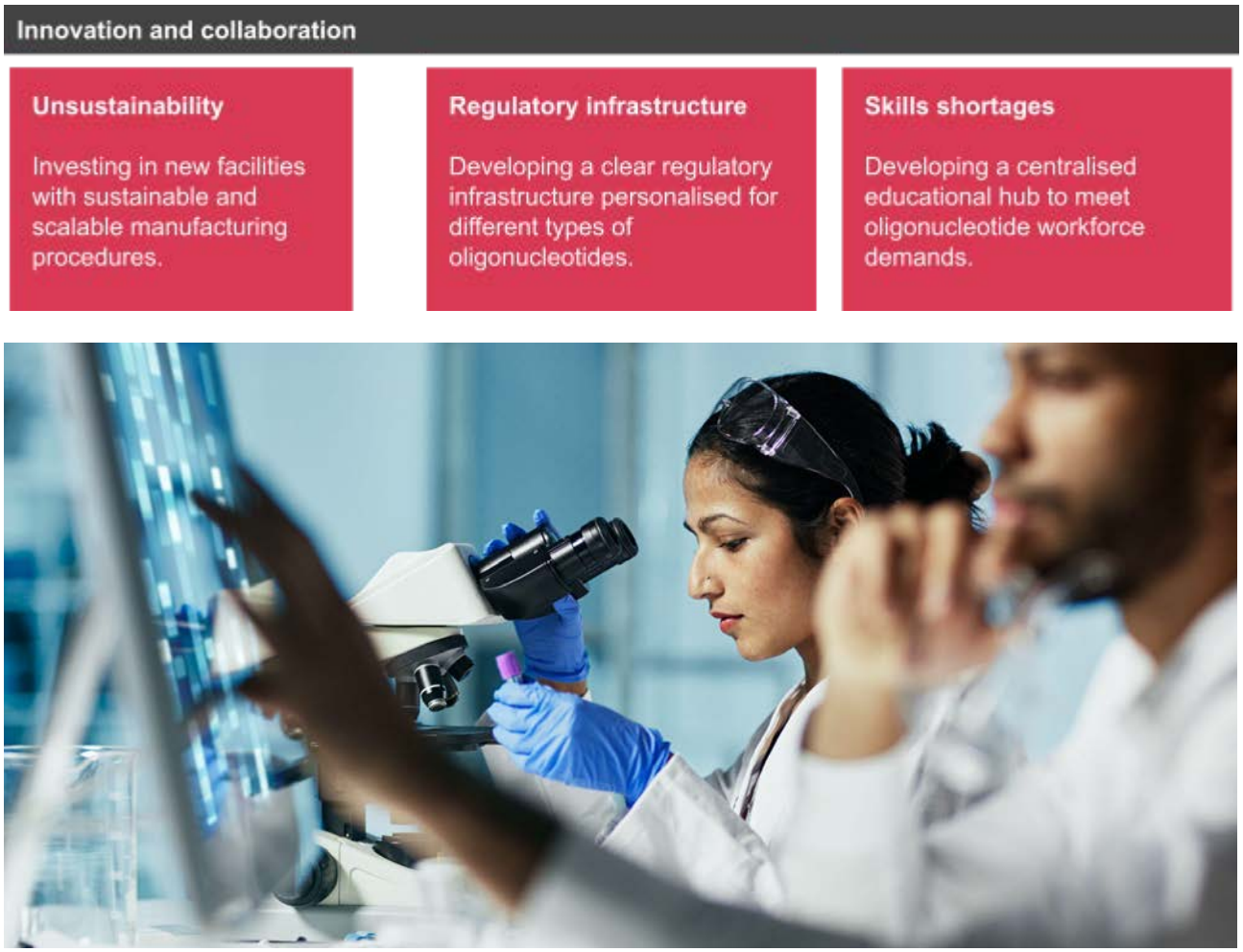
Executive summary

Oligonucleotide therapeutics have revolutionised the landscape of the pharmaceutical industry. They are a class of drugs composed of short strands of RNA or DNA that can be synthetically manipulated to alter the expression of a number of disease-causing proteins. Until recently, the majority of Food and Drug Administration (FDA) approved oligonucleotides on the market have been used for the treatment of rare diseases. However, the 2021 approval of inclisiran, used for the treatment of cardiovascular disease, has now highlighted their potential to treat a breadth of common clinical indications. Inclisiran demonstrates the opportunity oligonucleotides present, as a treatment modality for large patient populations targeting a breadth of common diseases, including cardiovascular disease, oncology, and metabolic disorders. It is important to acknowledge, however, that the current oligonucleotide supply chain is unsustainable and faces significant barriers to scaling up, highlighting a critical supply and demand gap which needs to be addressed.

This report aims to outline the importance of oligonucleotide therapeutics, their space in the UK market, key challenges facing the scaling of the supply chain, and suggests recommendations to address these challenges. Such an endeavour is important for keeping pace with the industry, and allowing oligonucleotides to meet the demand and have the impact they are capable of.

This report highlights three key areas as important considerations for change, and marks the importance of innovation and collaboration in making sustainable improvements to scale the oligonucleotide supply chain:

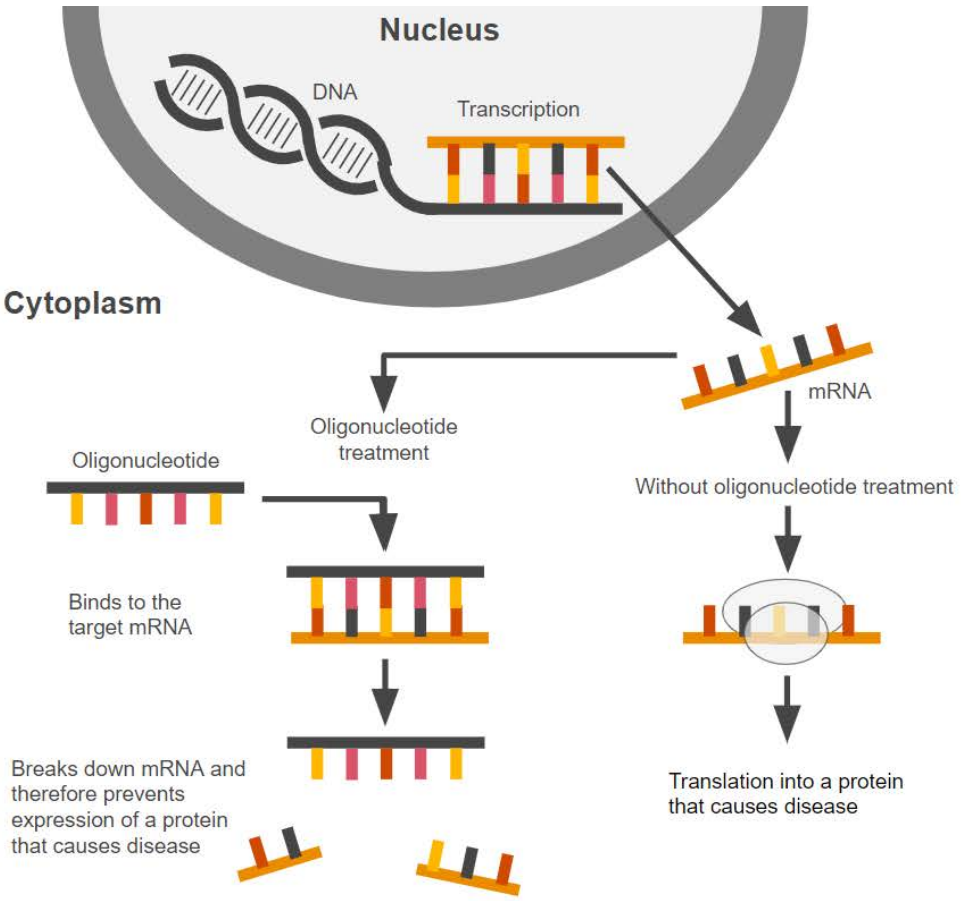


Introduction to oligonucleotides

It is estimated that 1.5% of the human genome encodes proteins, and remarkably, only 15% of these proteins have active binding sites that can be targeted using conventional therapeutics[1]. Due to this disparity, there are a breadth of diseases and disorders that are rendered 'untreatable' with inaccessible protein targets. The need to address this therapeutic gap has fostered a surge in interest surrounding oligonucleotides, a novel class of drugs that have revolutionised the landscape of the pharmaceutical industry. With the capability to target over 10,000 proteins within the human genome that were previously recognised as 'undruggable', with inaccessible protein targets, these small molecules represent a key cornerstone for the future of personalised medicine [2].

The term oligonucleotide derives from the Greek word 'oligoi', meaning small, and nucleotides, which are the building blocks of RNA and DNA. Lending truth to its name, oligonucleotides are short strands of synthetic DNA or RNA, typically 20-25 nucleotides in length. They can function using a variety of molecular mechanisms based on their structure and chemistry, whereby their mode of action classifies them as either: antisense oligonucleotides, RNA interference, or aptamers [3]. Antisense oligonucleotides are the most common type of oligonucleotide based therapy, and function via the mechanism in Figure 1. The unique sequences of nucleotides are complementary to target messenger RNA (mRNA) within a cell, that without intervention would encode a disease-causing protein. Once the oligonucleotide is inside a cell, it binds to the target mRNA and alters its gene expression, therefore preventing the expression of a protein product that causes disease.

Figure 1. The mechanism of action of antisense oligonucleotides

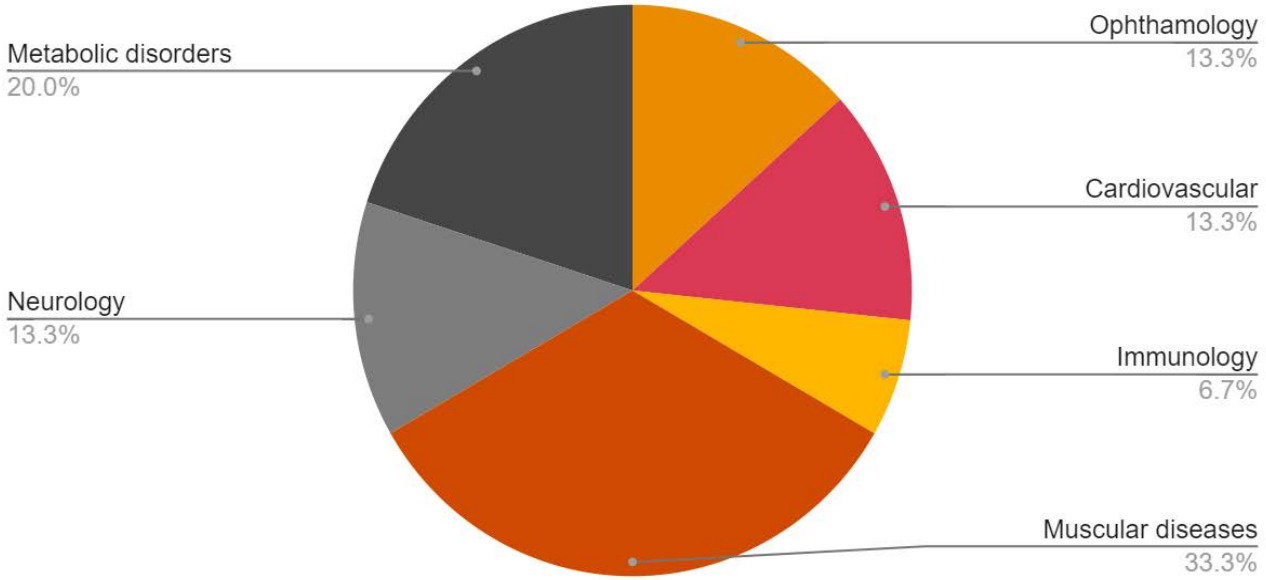


Growing oligonucleotide demand

Current FDA approved drugs target rare diseases

It is the adaptability of oligonucleotides that makes them such a key player in the future of precision and personalised medicine. Their ability to be designed and adapted to selectively target specific sequences of mRNA, mean that they can be personalised to treat a variety of rare diseases. Currently, there are 15 FDA approved oligonucleotide therapies on the market, used for the treatment of ultra-rare metabolic and degenerative diseases (Figure 2). These FDA approved drugs address significant unmet medical needs that justify high therapeutic value.

Figure 2. The therapeutic treatment areas of current FDA approved oligonucleotides. Based on global trial data.[4]

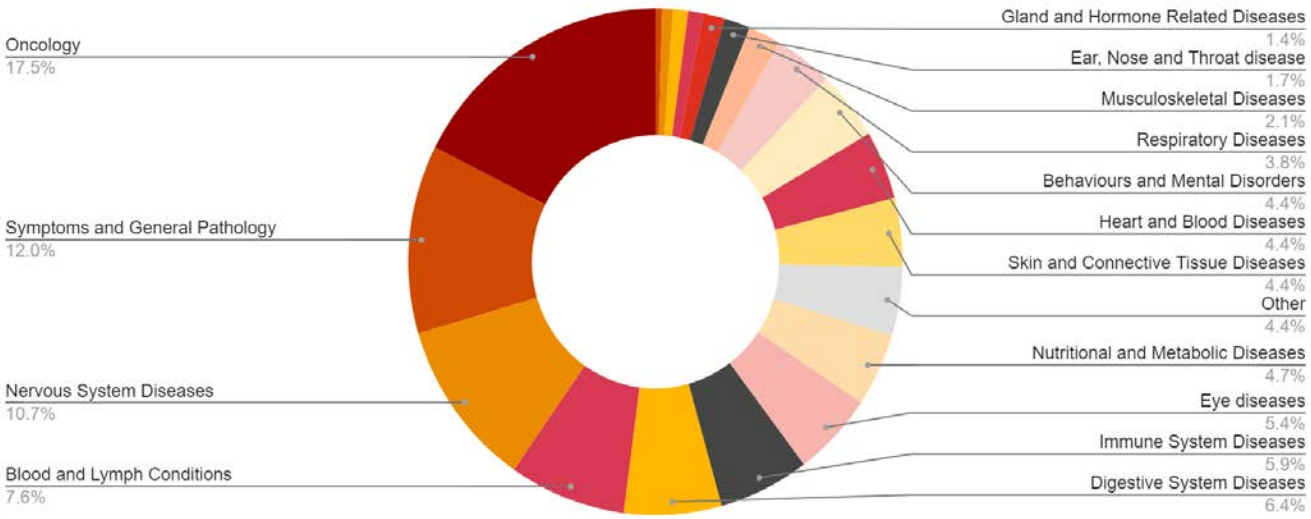


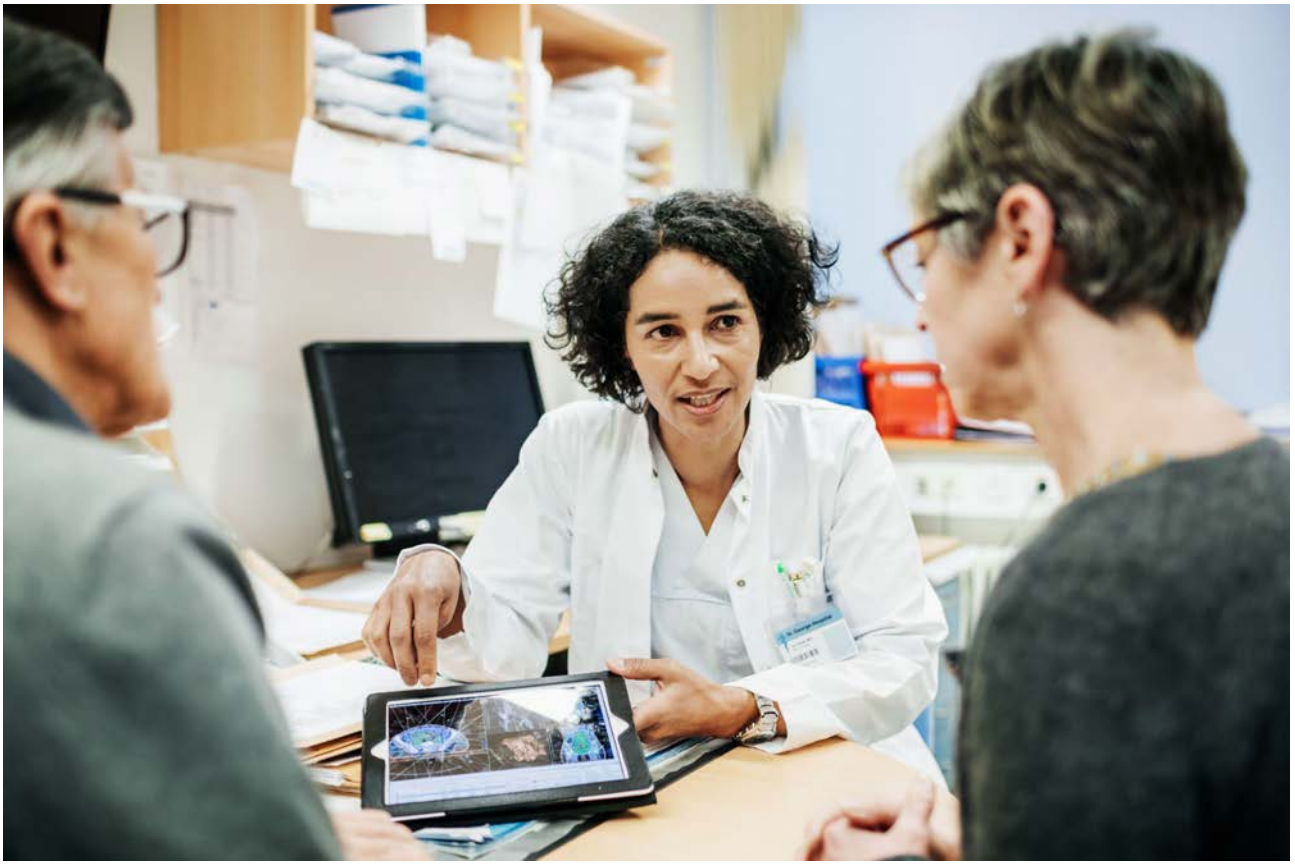
From rare to common diseases: Inclisiran is paving the way

Advancements in sequencing technologies have enabled a deeper understanding of the targets of oligonucleotides, and their applications. Initially targeting rare diseases, there are now a number of oligonucleotide therapeutics in clinical trials which will benefit large patient populations and common diseases, in particular in the treatment of cancers, metabolic disorders, and respiratory diseases (Figure 3). Marking this shift from rare to common diseases is the approval of inclisiran in 2021, an oligonucleotide used for the treatment of cardiovascular disease, the global leading cause of death [5]. This highlights the potential of oligonucleotides, and the significant impact they can have on public health and large patient populations.

It's important to acknowledge, however, that if oligonucleotides are to reach their full potential and be used for the treatment of common diseases, the manufacturing process must address significant technical obstacles. This report aims to highlight and address the challenges facing the scalability of the oligonucleotide supply chain, beginning with outlining their place in the global and UK market.

Figure 3. The therapeutic treatment areas of oligonucleotides in clinical development. Based on global trial data[4].





The oligonucleotide market

Global market: industry drivers, segmentation and growth forecasts

The COVID-19 pandemic shone a light on the potential of RNA-based therapeutics, and projected their potential onto the main stage. This exposure, coupled with increased investments, a rich pipeline of promising drug candidates in clinical trials and technological sequencing advancements, are key drivers for the industry. As such, the oligonucleotide synthesis, modification, and purification market is expected to register a **compound annual growth rate (CAGR) of 17.5% in the forecast period 2022-30, reaching $6.53 billion by 2030 [6].**

Geographically, the oligonucleotide market is segmented into North America, Europe, Asia Pacific, Latin America, the Middle East, and Africa. North America dominates the global market, with a revenue share of over 40%[7]. This is attributable to the presence of key market vendors such as Agilent Technologies, Thermo Fisher Scientific and Danaher providing tailored oligonucleotide products which drive the regional market[8]. Market growth is also mirrored within Europe, with a forecasted compound annual growth rate of 13.4% by 2027 [9]. New partnerships and acquisitions between pharmaceutical companies, and the availability of better healthcare infrastructures are key drivers of the European market.

It is important to consider that the current growth of the market is limited by concerns with the delivery of the drug to the disease target. This challenge highlights a key reason for the failure of many oligonucleotide therapeutics in clinical development. This said, promising new UK technologies, such as Touchlight's cell-free DNA vector synthesis, propose innovative solutions that may help overcome these challenges and foster global, and UK, market growth[10].

As of 2022, there are 15 oligonucleotide therapeutics on the market, approved for the treatment of rare diseases which have a prevalence making up 7.43% of the UK population[11-20]. In contrast, the diseases targeted by those in phase III of clinical development, have a prevalence of 68.27% of the UK population[21-46]. This highlights the impact oligonucleotides are set to have on the treatment of common diseases, and the anticipated demand increase that is also expected within the market.

‘Current FDA approved oligonucleotides treat diseases with a UK prevalence of 7%. However, drugs in phase III of clinical development target diseases which impact up to 68% of the UK population’

‘The global oligonucleotide market is expected to register a compound annual growth rate of 17.5% between 2022-30’

The oligonucleotide supply chain: key challenges and opportunities

Given the rapid growth the market is forecasted to witness in the coming years, it is a priority to meet scientific maturation by driving efficiency into the process of oligonucleotide discovery, development, and manufacturing. At present, the production of oligonucleotides is limited by unresolved challenges in the supply chain. The key barriers that face the scaling up of the supply chain are, a lack of certain regulatory infrastructure, a shortage of skill within the current workforce, and unsustainable manufacturing practices.

Lack of clear regulatory infrastructure

At present, there is a lack of clarity surrounding the regulatory infrastructure used for the development and manufacturing of oligonucleotides[47]. The FDA classifies oligonucleotides as small-molecule drugs, whereas the European Medicines Agency (EMA) classifies them as new chemical entities (NCEs) that do not occur naturally in biological systems[48]. Whilst oligonucleotides are not biologics, they do share attributes with new biological entities (NBE).

Falling in a regulatory grey area between biologics and new chemical entities presents a challenge towards outlining clear industry standards and manufacturing requirements. As such, a unique regulatory challenge is raised, which requires specific guidelines for oligonucleotides. Addressing this challenge will facilitate the development of an integrated control strategy to ensure consistent quality of synthetic oligonucleotide production, an important step for enabling large-scale oligonucleotide manufacturing in the UK. It is important to highlight that the UK is already making strides to address this challenge, with the Medicines and Healthcare products Regulatory Agency (MDRA) announcing a new point-of-care framework for innovative medicines manufacturing[49]. Establishing where oligonucleotide manufacturing is classified within this framework, and its impact, is an important next step, to limit uncertainty and outline clear industry standards.

Skill shortages

A further consideration is that current manufacturing procedures require an increase in skill and knowledge surrounding oligonucleotide development. This highlights a skills gap that has grown within the biopharmaceutical industry [50]. A full transformation of standard manufacturing processes from traditional chemical synthesis to the genetic manipulation of living organisms has brought new opportunities for using automation and technology. This presents a challenge from a skills perspective. A lack of skill within the current workforce exists particularly in engineering, data analytics, and process development[50]. An important step in plugging this gap is encouraging academic collaboration.

The industry is already taking strides to encourage collaboration, as demonstrated by PwC's partnership with the Medicines Manufacturing and Innovation Centre (MMIC), based in Glasgow[51]. Founded by GSK and AstraZeneca, it is a hub for collaboration, bringing together world-leading academic and innovative research between the founding partners, University of Strathclyde, UK Research and Innovation, Centre for Process Innovation, and the Scottish Enterprise. Concerted collaborative action is a key step for educating the future workforce and centralising academia.

Driving sustainability into the supply chain

Raw Materials

A notable challenge facing the supply chain, at present, is the requirement for high volumes of reactants and solvents needed for the synthesis of oligonucleotides, resulting in high costs and significant wastage. Additionally, the critical raw material 'acetonitrile' is facing a global supply challenge [52]. The significant waste burden and use of finite raw materials that oligonucleotide manufacturing relies on means that therapeutic advances will be stunted by their unsustainability.

It is estimated that there is 4,300kg of waste per kg of oligonucleotides developed, an order of magnitude larger than conventional small molecule drugs [53]. In the view of market growth and increased oligonucleotide reliance, it is a priority to implement innovative processes that reduce the volume of waste generated and invest in alternative, environmentally friendly, raw materials. Implementation will be more cost-effective, green, and will allow oligonucleotides to meet their growing demand and impact on disease burden.

A further issue facing sustainable oligonucleotide development is a lack of global manufacturing capability, which is creating a block in the accessibility of raw materials needed for clinical trials. At present, raw materials are being outsourced from Asia, Europe, and the US, and due to the requirement of small quantities for single-digit batches needed for clinical trials, priority is focused on commercial opportunities with bigger contracts. The UK therefore does not currently have the capacity to meet the demand needed for clinical development, and as such the source of materials for clinical development is currently at capacity, inflexible, and expensive.

Whilst this presents a significant barrier to both the clinical development and commercial manufacturing of oligonucleotides, it also presents a promising opportunity. If the UK can build facilities to support manufacturing capability, and invest in chemistry facilities to support innovation in the synthesis of oligonucleotides, it could serve as a powerful centralised hub for oligonucleotide development. A tipping point has been reached, and building an extension to increase UK manufacturing capabilities and limit supply chain restraints is an important step to keep pace with the industry.

Production process

Whilst the manufacturing of oligonucleotides is an extraordinary achievement, the process comes at an environmental cost. The chemical hazards, high levels of waste, and energy-intensive processes involved in production are unsustainable, and will only worsen as the production scales up [54]. As such, there is a critical unmet need to make sustainable changes to the manufacturing procedures currently in place. Whilst a careful assessment of the full sustainability impact of any improvements across the supply chain will be required before implementation, we have highlighted some potential sustainable changes that could be made. This will require innovation, whether adapting existing methods, or developing new technology altogether.

The manufacturing processes used for the production of oligonucleotides follow four key stages, (1) synthesis, (2) cleavage, (3) purification by chromatography, and (4) isolation by lyophilization (Figure 4).

Figure 4. The manufacturing workflow for oligonucleotides

Synthesis

Solid-phase oligonucleotide synthesis faces significant challenges when looking at the view of sustainable and scalable manufacturing[55]. The equipment used for solid-phase oligonucleotide synthesis is expensive, and the challenge of washing large beds of synthesis support is demanding and unsustainable. This highlights a serious gap that will open up between supply and demand, as the supply chain is scaled. Alternative liquid-phase synthesis could be an alternative solution, which reduces the wash volumes required and limits wastage.

Purification

A recent sustainability report indicated that the purification process is responsible for over 50% of the materials used in the production of oligonucleotides[54]. This highlights significant room for making sustainable change within the purification steps of development. As oligonucleotides are set to face higher volumes of production, a development in solvent recovery mechanisms could be both economically and environmentally beneficial. It is important to note though, that 50% of the waste volume generated is hazardous, and requires specialist discarding[54]. The potential, therefore, also lies within identifying alternative chromatography purification methods that have lower waste volumes, with aqueous and easily disposable waste products.

Isolation by lyophilization

Isolation by lyophilization is an extremely energy-intensive process, due to the requirement for refrigeration systems and vacuum pumps, which presents as a major bottleneck to oligonucleotide manufacturing[56]. One solution could include the implementation of alternative lyophilization methods that require less energy, such as spray drying[54]. One challenge that faces spray-drying is the comparatively low yields that are outputted. This said, as the losses in yield are a result of equipment hold-up, rather than batch size, they can be mitigated through using larger batch volumes. Given the high volumes of oligonucleotides that are projected to be demanded, spray-drying has been proposed as a plausible, lower-energy alternative to lyophilization, aiming to improve the sustainability of oligonucleotide manufacturing processes[54].

Addressing the challenges

Identifying the challenges that face oligonucleotide manufacturing is the first step towards implementing sustainable change, which is critical for scaling-up the supply chain and meeting demand. This report has highlighted key challenges facing the oligonucleotide supply chain, and recommends that addressing these obstacles will require a focus to be placed on:

- **Outlining a clear oligonucleotide definition and classification.**
- **Developing a clear and tailored regulatory framework for oligonucleotides.**
- **Recycling solvents used within the manufacturing process to limit waste and improve sustainability.**
- **Research into innovative, sustainable, and scalable manufacturing procedures.**
- **An investment in the development of manufacturing sites to increase UK capacity and limit restraints of global manufacturing capabilities.**
- **Industry collaboration to centralise education and bring together capabilities.**

The importance of innovation and collaboration

> Collaboration will aim to enhance the efficiency and yield of the manufacturing process and reduce the consumption of critical raw materials… which challenge the feasibility of large-scale manufacturing”

The challenges facing the oligonucleotide supply chain will require a clear focus on innovation and collaboration to navigate. To reach improved solutions, and meet the demand that faces oligonucleotide development, a concerted effort should be placed on achieving synergy between industry, academia, research, development and manufacturing organisations. This collaboration is fundamental for reaching innovative, sustainable, and efficient solutions to encourage engineering improvements that will allow the manufacturing of oligonucleotides to scale up sustainably.

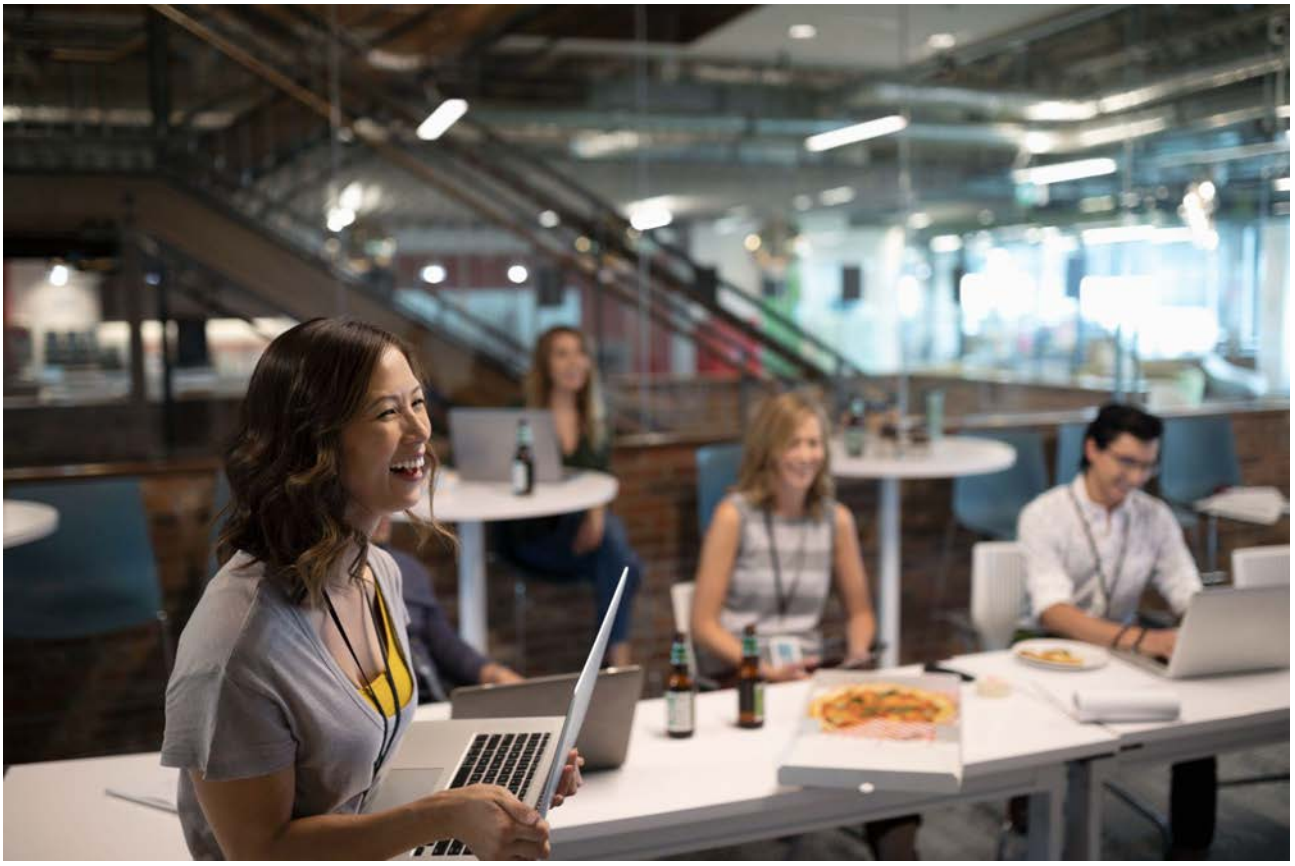
Such a collaborative and innovative approach is currently being addressed by the MMIC’s ‘Grand Challenge 3’ initiative, a partnership between pharmaceutical companies AstraZeneca, Novartis and Alynylam with Exactmer, and UK Research and Innovation. This project is part of a series of ‘Grand Challenges' that ‘aims to enhance the efficiency and yield of the manufacturing process and reduce the consumption of critical raw material (acetonitrile) of which global supply challenges the feasibility of large-scale manufacturing' [51]. PwC recognises the importance of this collaboration, and has joined the consortium to add value and facilitate the delivery of innovative medicines manufacturing solutions. It is the hope that through harnessing the combined expertise of the MMIC and its partners, multiple drugs will be identified and progressed which can be subsequently manufactured, at scale, in the UK.

Industry partnerships and the launch of Grand Challenge 3 demonstrates a step in the right direction – towards innovative, collaborative efforts which are critical for overcoming the obstacles facing the oligonucleotide supply chain. If the UK harnesses its combined expertise, it has the capability to cement itself as a global leader of innovative medicines manufacturing, serving as a core centre for supporting clinical development, centralising education, and developing innovative solutions to meet global health burdens.

The impact: concluding remarks

The oligonucleotide therapeutic market has gained significant momentum in recent years, attributed to advancements in technology and a growing understanding of their limitless applications. There is a rich pipeline of promising oligonucleotide drugs in clinical development, whose translation to the market is being challenged by unsustainable practices, and a lack of manufacturing capabilities.

The consistent challenges of scaling, regulating, and sustainably manufacturing oligonucleotides are detracting from their true capability to have an impact on clinical outcomes and human health. Mitigating these obstacles is a sizable task, but one which is critical for translating opportunity into impact. We suggest that the best place to start is with collaboration and innovation. The significant obstacles facing the current development of oligonucleotides require innovative solutions, for which the UK has novel technologies and resources to facilitate. Collaboration can allow technological, educational and research gaps to be bridged, bringing together existing capabilities to develop innovative solutions, efficiently and effectively. Once we encourage collaboration, innovation, and invest in new facilities, the UK could serve as a centralised educational, innovative, and strategic hub for the manufacturing and supply of oligonucleotides, better equipped to support its purpose – to have an impact on public health.



Talk to us if...

You want to drive sustainability in pharmaceutical manufacturing.

You want to implement technology to automate and optimise pharmaceutical manufacturing.

You want to address operational and delivery challenges facing pharmaceuticals manufacturing.

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