

Making peptides: enabling a medical revolution

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Headlines

Opportunities

- Peptide-based drugs like semaglutide and tirzepatide have seen rapid uptake, becoming top-selling global medicines and demonstrating the commercial viability of this class of molecules.
- Peptide-based medicines offer advantages such as higher selectivity, improved efficacy, and reduced toxicity compared to small-molecule therapeutics.
- Manufacturing is an essential step in the journey from drug discovery to patient, but peptide manufacturing technologies remain challenging as peptides occupy a unique space between small-molecule therapeutics and biopharmaceuticals.
- With the right investment in advanced manufacturing research, data infrastructure, and regulatory alignment, the UK can become a global hub for the sustainable production of next-generation peptide and hybrid therapeutics, reaping economic and health benefits.

Issues

- Peptide drugs are difficult and costly to manufacture due to complex synthesis and purification processes, resulting in a high environmental footprint and low scalability.
- There is insufficient understanding of and predictive capability for key peptide properties (e.g. solubility, gelation, crystallisation), which slows down process development and innovation.
- SMEs and CDMOs play a critical role in bringing manufacturing innovation to commercialisation but face limited access to capital, infrastructure, and regulatory engagement.
- Divergent global regulatory classifications and requirements for peptides increase costs, delay market access, and hinder adoption of advanced manufacturing technologies.

Solutions

- Establish a National Centre for Emerging Medicines Manufacturing (NCEMM), a central hub to integrate scientific discovery, engineering innovation, and scale-up, supporting end-to-end development of complex medicines like peptides.
- Stimulate research on platform technologies that can benefit the whole sector: understanding and prediction of peptide properties, innovation in synthesis and separation technologies, and implementation of process systems engineering, digitalisation and AI approaches.
- Launch a Peptide Genome Initiative (PGI) to support a coordinated effort to generate and share large-scale peptide structure–property data, enabling predictive modelling and reducing reliance on trial-and-error experimentation during process and product development.
- Support PharmaTech SMEs and Innovation Clusters by providing targeted funding, shared facilities, and regulatory engagement opportunities to help SMEs develop and scale disruptive manufacturing technologies.
- Pursue international regulatory harmonisation by working through MHRA and global bodies to align peptide classification and approval pathways, and promote recognition of digital and continuous manufacturing approaches.

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Objectives of the briefing paper

Imperial, UCL, and Queen Mary University London host experts in pharmaceutical manufacturing technologies, systems engineering, mathematical modelling, and data science. Through collaborations such as PharmaSEL, an EPSRC-Eli Lilly and Company Prosperity Partnership, they advance the state-of-the-art in pharmaceutical manufacturing, addressing challenges around efficiency and effectiveness, reliability of supply and sustainability.¹

In this paper, we focus on the challenges and opportunities in peptide manufacturing. Peptides are short chains of amino acids (AA), where we define “short” to mean up to 50 AAs. The first peptide medicine, insulin, was first given to a diabetes patient in 1922. Insulin now improves the health of millions of patients, with a market size of \$28 billion in 2023, projected to reach \$42 billion by 2033.² This has been made possible through technological innovation: what started as a complex manufacturing process, based on the extraction of insulin from animals, has evolved into a large-scale, highly reliable biosynthetic process that delivers a consistent supply. Despite this early success, insulin remained the only commonly prescribed peptide medicine for nearly a century. However, in recent years, peptides have emerged as a transformative class of medicines. Between 2004 and 2023, over 60 new peptide medicines were approved, with the rate of approvals nearly doubling over this period. More than 170 peptide drugs are currently in clinical trials.^{3,4} In parallel, pharmaceutical companies are rapidly expanding their pipelines of peptide-based medicines. We can expect an associated growth in the number and volume of peptide medicines on the market. Some of the peptide medicines approved in the last 8 years have been adopted at breathtaking speed: Novo Nordisk’s ‘semaglutide’ and Eli Lilly and Company’s ‘tirzepatide’, both belonging to the rapidly growing class of GLP-1 analogues and distributed as anti-diabetic medicines under the names Ozempic and Mounjaro, respectively, joined the list of top 10 drugs by retail sales in 2024.⁵ They have also had a transformational impact as weight-loss treatments under the names Wegovy and Zepbound, respectively, (17th and 36th by sales in 2024) and are also currently being pursued for alternative indications. For example, in December 2024, the US Food and Drug Administration approved Zepbound for the treatment of obstructive sleep apnea.⁶⁻⁸

Peptide molecules are significantly larger than most common therapeutic agents. This complexity presents major manufacturing challenges but also offers opportunities to establish a thriving deep tech ecosystem, especially by leveraging the UK’s existing Life Sciences industry and building on the recently released UK government Life Sciences Sector Plan.⁹ In this briefing paper, we explore these issues in more depth, concentrating on the implications for process development. Process development involves designing a manufacturing process to meet the demand for a medicine throughout clinical trials and in subsequent drug commercialisation, while maintaining regulatory compliance (Box 1). Here, we also include drug formulation, i.e., the development of the specific form in which the medicine is delivered to patients (e.g., tablet, injection). We approach this by:

- introducing the key elements of peptide manufacturing, and the role played by process development in the journey from discovery in the laboratory to patients;
- identifying the main challenges in peptide manufacturing and how these differ from more traditional types of medicines;
- highlighting the platform technologies and systems engineering approaches needed to overcome these challenges;
- examining the mechanisms to support the emergence of a world-leading peptide manufacturing industry in the UK.

Box 1 – What should process development achieve?

Process development is a collaborative and iterative activity through which a manufacturing process and a product emerge. It requires expertise from a range of disciplines, including, but not limited to, organic chemistry, physical chemistry, chemical engineering, product formulation, and mathematical modelling. The design of the process can evolve with time, as experience is gained and production quantities increase.

Successful process development should meet the following criteria:

- **Quick journey from lab to patient:** Process development should not delay clinical trials nor commercialisation. The manufacturing process should be rapidly scalable to meet the potentially growing demand for therapeutic agents.
- **Safe and effective product:** The final product should consistently meet safety and quality standards, meeting all physicochemical specifications and with any impurities remaining within accepted limits. The product should remain effective throughout its shelf-life. These are critical requirements for patient safety.
- **Reliable supply:** Patients should be able to access the medicine they require, whether starting a new treatment course (sufficient supply) or continuing an existing course (uninterrupted supply).
- **Cost effectiveness:** For new medicines, costs are driven by the vast investments required for molecule discovery and to run large-scale clinical trials. For generics, process costs become a more important component and should be minimised.
- **Environmental sustainability:** Peptide manufacturing often uses large amounts of materials. The process mass intensity (PMI), which quantifies the mass of material used to make 1 kilogram of medicine, is much higher for peptides and other emerging medicines such as oligonucleotides, relative to other therapeutics. There is substantial potential for reduction.
- **Easy adherence to treatment:** Whenever possible, the medicine should be formulated in a way that encourages patients to follow their treatment plans. Oral dose formulations (tablet, capsule) are generally preferred.

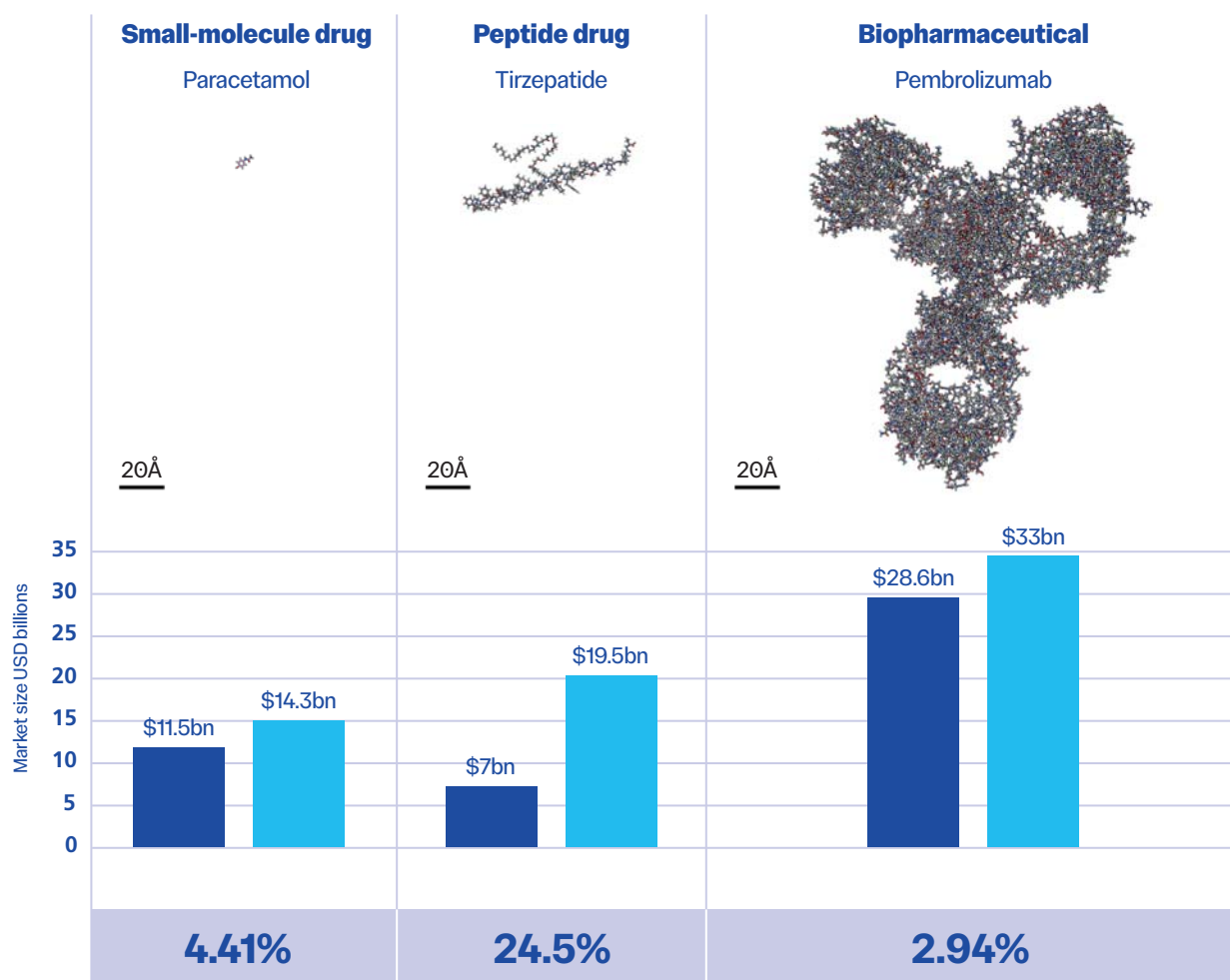
Section 1

Peptides: game-changing medicines but manufacturing hurdles stand in the road to delivery

Understanding peptides and their therapeutic potential

Peptides are relatively short chains of amino acids (AAs), typically comprising between 2 and 50 AAs. While proteins are made of many more amino acids, peptides are smaller and easier for the body to absorb. They occur naturally in many foods, such as eggs and milk, and play diverse and vital roles in the body, acting as messengers, hormones and regulators of functions like cell signalling, immune response, and muscle growth.

Peptide medicines have great therapeutic potential across a wide range of health challenges, including cardiovascular disease, urology, chronic pain, oncology, metabolic disorders, respiratory conditions, and antimicrobial resistance. Notable examples include insulin; enfuvirtide, a peptide used in HIV-1 combination therapy; ziconotide, a neurotoxic peptide approved for severe chronic pain, and teduglutide, a recombinant GLP-2 analogue used to treat short bowel syndrome.



Compound Annual Growth Rate CAGR 2025-2030

Figure 1: Comparison of the molecular structure and evolution of market size for a small-molecule drug, paracetamol, a painkiller and fever reducer; one peptide drug, tirzepatide, an anti-diabetic medicine; and pembrolizumab, a biopharmaceutical (monoclonal antibody), used to treat various types of cancer.¹⁰⁻¹²

'Molecular structures generated using 3D Software Chimera'

Based on their size, peptides are positioned at the interface between small-molecule therapeutics, such as paracetamol or aspirin, which are manufactured using synthetic chemistry, and biopharmaceuticals, which are manufactured using living cells. In medicine, peptides are typically categorised as biopharmaceuticals, alongside protein therapeutics, due to their size, composition, distribution, and administration routes. Although small molecules have long dominated the global drug market, benefiting from advantages such as cost-effectiveness, oral administration, and a comparative ease of synthesis, peptide-based therapeutics offer distinct advantages over small-molecule drugs, including higher selectivity, specificity of action, improved efficacy, lower toxicity and faster absorption into the bloodstream.⁴ However, the predominant administration method for peptide drugs is injection, as their oral bioavailability is limited due to degradation in the gastrointestinal (GI) tract and low intestinal permeability. Considerable efforts have been made to develop oral peptide drugs, which are generally preferred by patients and more affordable than injectable options, but this remains a challenge.

Peptide medicines are more complex to produce than small-molecule drugs due to their larger size. Small-molecule drugs (Figure 1) have a molecular weight of typically less than 500 Dalton, and always less than 1000 Dalton, and their manufacturing route typically includes a sequence of a few chemical reactions. Peptides have a complex structure, and their molecular weights are in the range of 1,000 Dalton to 50,000 Dalton (Figure 1), requiring more advanced manufacturing methods.

Methods of peptide manufacturing

The position of peptides between small-molecule drugs and biopharmaceuticals is also reflected in their manufacturing routes, where both biological and synthetic routes occur in the pharmaceutical industry.

The processes and timelines by which all medicines (including peptides) move from discovery in the lab to market approval and commercialisation involve several stages, including clinical trials and regulatory approval, and take several years to complete (Figure 2A). The manufacturing process can vary through these development phases: in phase 1 clinical trials, the quantities needed are relatively low, and they increase significantly in phases 2 and 3 (Figure 2B). This means manufacturing process scale up can take place in parallel with clinical development, with the exact manufacturing route and techniques evolving through clinical trials. The process design for phase 3 supply will often reflect that of commercial manufacturing, simplifying the regulatory approval process and associated data collection and documentation.

The first peptide to be manufactured on a commercial scale was insulin. Insulin manufacture previously relied on the extraction of insulin from pigs and cows, but the most recent production method is through recombinant biochemical techniques, where microbes are genetically modified to produce human insulin in fermentation processes, followed by downstream separation and purification. This innovative process has made human insulin available at scale, leading to a step change in the ability to treat diabetes. Nevertheless, recombinant biochemical techniques are not suitable to manufacture all peptides. Specifically, they are typically restricted to DNA-encoded (“natural”) amino acids, to the exclusion of D-amino acids, and to peptides that consist of a linear chain of AAs. Additional chemical modification is therefore required to incorporate non-natural amino acids or the side chains commonly found in therapeutic peptides. As an example, while the peptide backbone of semaglutide is manufactured using recombinant techniques, further chemical modification of the peptide is required to attach the complex side chain needed to achieve the desired therapeutic efficacy. Moreover, synthetic methods are needed for shorter peptides, which are more difficult to recover effectively from a cell-based bioprocess.

In this paper, we will thus focus on synthetic methods as alternatives to recombinant biochemical approaches. A peptide manufacturing process (Figure 2C) consists of two main stages: a primary manufacturing stage in which the peptide is produced and a secondary manufacturing stage in which it is formulated into the drug product (e.g., a liquid formulation) to be taken by patients. Primary manufacturing consists of one or more sequences of chemical synthesis and separation/purification steps. Chemical synthesis is an active area of research, with many new approaches emerging, but typical approaches include:

Solid-phase peptide synthesis (SPPS) is the most common peptide manufacturing process. Peptide chains are built while attached to a solid resin. This facilitates the addition of amino acids in sequence: the desired amino acid is added in large quantities to the reactor containing the resin, is allowed to react and excess amounts of amino acid are washed away with a solvent. This is repeated with different amino acids, until the peptide chain is complete and can be cleaved from the resin and purified. This process has been used to produce several commercial peptides, especially those of medium size (fewer than 30 AAs). For larger peptides, SPPS can suffer from poor purity and yield (Box 2). Leuprolide, an anti-cancer peptide, is an example of a peptide produced by SPPS.

Box 2 – Yield

The yield is the percentage of the main raw material (reactant) fed to the reactor that is converted to the desired product and recovered. There are many reasons why the yield is usually less than 100%. There are often side reactions taking place that consume some of the reactants or even some of the desired product. Furthermore, the desired product needs to be recovered from the reaction mixture, and this process usually leads to further losses.

Liquid-phase peptide synthesis (LPPS) utilises a soluble chemical, rather than a solid resin, to which the peptide is bound, with the process occurring fully in the solution phase. This can help to increase productivity and yield as amino acids can react with the growing peptide chain without having to diffuse through a solid resin first. This method is usually suitable for relatively small peptides (typically fewer than 10 AAs).

The **hybrid** approach aims to exploit the strengths of the SPPS and LPSS systems, whereby short peptide “fragments”, consisting of a few AAs, are produced via SPPS and then joined in the liquid phase via LPPS chemistry. There are trade-offs in terms of the number and size of fragments to be joined. Tirzepatide, a leading diabetes and weight-loss drug, is produced using a four-fragment method, with the four fragments being produced via SPPS and then coupled using LPPS.¹³ However, hybrid methods can suffer from high levels of waste.

The **membrane-enhanced peptide synthesis (MEPS)** processes can be used to grow the peptide from scratch, one AA at a time, or as a hybrid approach to join fragments produced using SPPS. It uses a membrane in combination with a liquid phase synthesis approach, whereby after each addition of an AA or fragment to the peptide, any unused reagents (AA or fragment) are removed using a dilution process before the next reagent in the sequence can be added. The membrane acts as a filter and prevents the growing peptide chain from being washed away with the unreacted reagent, reducing the amount of solvent required. An appropriate membrane should be used (AA-permeable or fragment-permeable).

The growing peptide chain, peptide fragments or complete chain often need to be separated from a mixture containing other compounds. Such **purification** steps (Figure 2C) are often carried out using high-performance liquid chromatography (HPLC), a process which requires large amounts of solvent but achieves high purity. Crystallisation, a highly effective method which is frequently used to isolate small-molecule drugs, can sometimes be used for peptide fragments, but the crystallisation of longer peptide chains is very challenging.

The purified peptide is finally sent to **secondary manufacturing** (Figure 2C) where it is further processed, for instance via freeze-drying, before being combined with excipients and other ingredients to create a formulated product that has the desired shelf-life and drug release profile.

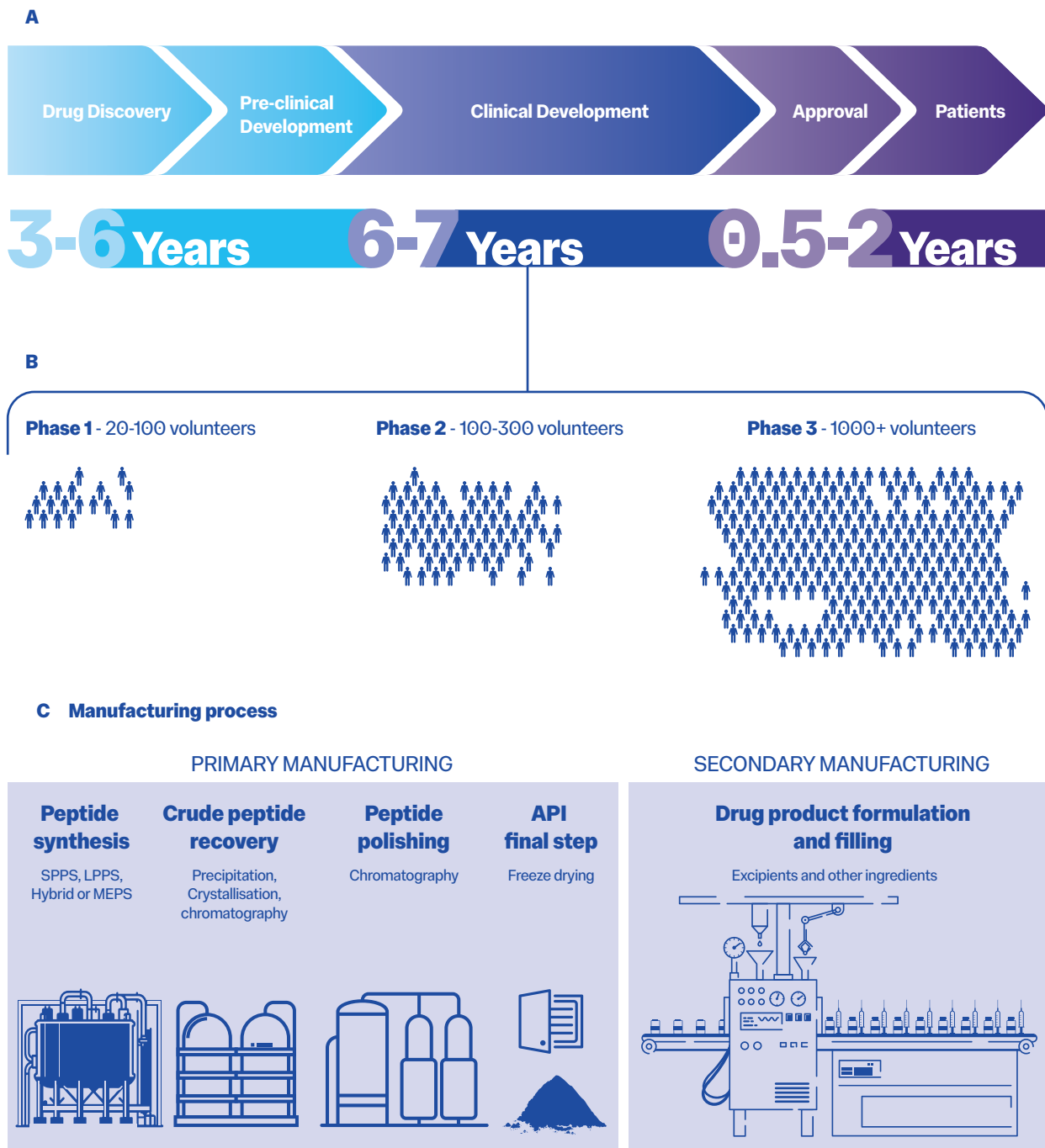


Figure 2: Timeline and stages for drug development and structure of the manufacturing process. A. Drug development is a lengthy and complex, multi-stage process that spans from initial discovery research to patient treatment. B. As the process advances, the quantities of medicine required increases, placing greater demand on manufacturing capabilities. C. Drug manufacturing process involves two main stages: primary manufacturing, which produces the Active Pharmaceutical Ingredient (API), and secondary manufacturing, which formulates the API into a final medicine product suitable for patient use.

Challenges in peptide manufacturing

Commercial peptide manufacturing presents a unique set of challenges, stemming from the complexity of synthesis and purification and from the scalability requirements needed to produce high-quality therapeutic peptides efficiently and consistently. Currently, peptide manufacture is associated with high manufacturing costs, low throughputs, and vast amounts of generated waste, which contribute unfavourably to economic, environmental, and supply chain factors. One of the main issues is the high process mass intensity (PMI), a measure of how much raw material is needed to produce a kilogram of medicine. For a peptide chain of only 13 AAs, the average PMI is 13,000 kilograms of raw material input per kilogram of product, compared to 200 kg/kg for small-molecule drugs and 8,300 kg/kg for much larger biopharmaceuticals).¹⁴ This is mostly due to the large volumes of solvent required for both chemical synthesis and purification steps, which also cannot be easily recycled.¹⁴ While recombinant synthesis can reduce the PMI to levels closer to that of biopharmaceuticals, current recombinant platforms are limited by the restrictions on amino acid selection mentioned earlier.

Peptide manufacture also demands specialised equipment, skilled personnel, and strict control on critical quality attributes such as purity and the presence of toxic impurities. These critical quality attributes are characteristics of the drug that have been agreed between manufacturer and the regulatory agency to ensure the drug is safe and effective for patients. Unlike small-molecule synthesis, which often relies on well-established, scalable chemical processes, peptide synthesis involves repetitive cycles of reactions, each requiring high precision to maintain product purity and yield. The equipment used, such as automated peptide synthesisers, High Performance Liquid Chromatography (HPLC) systems for purification, and freeze-dryers for solid isolation, must be optimised specifically for peptide handling. Furthermore, the process is highly sensitive to variations in reagent quality, moisture, temperature, and reaction times, demanding a level of operational expertise not always present in conventional pharmaceutical manufacturing environments.

Peptides also exhibit complex behaviours relative to simple solids or liquids. They frequently separate into two liquid phases and/or form gels, fibrils, and other aggregates during synthesis and purification steps. This is undesirable from a process perspective, as peptide gels are liable to cause clogging and fouling of reactors and piping, further hindering manufacturing. The need for specialised infrastructure and a deep understanding of these behaviours limits the number of facilities worldwide suitable for peptide production at commercial scale, contributing to current capacity constraints and supply bottlenecks.

Most peptide drugs are delivered by injection, which complicates manufacturing, particularly during formulation of the final drug product, and reduces patient adherence. The complex phase behaviour of peptides, notably fibrillation and emulsification, is also challenging from a formulation perspective, impairing stability.^{15,16} These stability issues may ultimately shorten the shelf-life of the final product, further complicating supply chain management, and/or they may reduce the drug's bioavailability and hence its efficacy. While alternative delivery routes (such as Novo Nordisk's Rybelsus® for the oral administration of semaglutide¹⁷) have seen some limited success,¹⁷ challenges with these novel delivery forms – most notably degradation of the peptide in the GI tract and difficulty in absorption across the gut wall – limit their applicability to peptides.

Supply chain issues are further complicated by the global nature of the demand for peptide-based therapeutics, while manufacturing is still concentrated in a limited number of facilities worldwide – a consequence of the complex process and high level of expertise required. This geographical bottleneck increases vulnerability to disruptions and puts additional pressure on existing production infrastructure. Additionally, peptide manufacturing companies are primarily focused on meeting demand for their products, with the optimisation of factors like PMI and solvent waste a secondary consideration. Installed capacity is now a limiting resource in the planning to launch new peptide pharmaceuticals, leading to significant new investments (Box 3). As a result, pharmaceutical companies will likely have to rely on contract development and manufacturing organisations (CDMOs) in lieu of in-house manufacturing capacity. Moreover, an increase in global demand could strain the availability and price of raw materials used in manufacture and formulation. Additionally, legislative changes to the formulated product (particularly regulatory restrictions on excipients, such as the European Medicines Agency's decision to restrict the use of titanium dioxide in food and medicines) may cause further supply chain instability.¹⁸

Box 3 - Challenges with GLP-1 analogues

The effects of peptide manufacturing challenges were well-exemplified during recent surges in demand for GLP-1 analogue therapeutics. Soon after their introduction in the market, there was a shortage of these anti-diabetic medicines which pushed producing companies to make extraordinary investments in their manufacturing networks. Novo Nordisk committed over US\$ 6 billion to expand facilities in Denmark and the U.S. to meet GLP-1 demand and Eli Lilly and Company is investing US\$ 9 billion in a new manufacturing site in Indiana, with a focus on Mounjaro® (tirzepatide).¹⁹ To address supply challenges associated with producing the final formulated product, Eli Lilly and Company began offering Zepbound® (tirzepatide) in single-dose vials alongside auto-injector pens in August 2024.²⁰ Unlike injector pens, which require a complex assembly process, vials are simpler and faster to produce. This shift allowed Eli Lilly and Company to better meet the increasing demand for the drug, while simultaneously cutting the cost to patients. This approach has since been extended to even higher doses of tirzepatide.²¹

Section 2:

Improving peptide manufacturing requires new platform technologies integrated within a systems engineering approach

While peptide manufacturing is challenging, the limited set of building blocks (AAs) from which peptide chains are constructed and the presence of a limited number of side chains in peptide molecules offer the opportunity to develop platform technologies for each step of the manufacturing process. Such platforms can exploit the similarities between peptides and can be complemented by systematic strategies to adapt a given platform from one peptide to another. If this adaptation step can be designed to be rapid and to require a minimum amount of material, e.g., via the use of small-scale high-throughput experimentation or computational tools, this could lead to a transformational acceleration of process development and could reduce the risks inherent in scale up. In addition, systems-based engineering approaches are required to ensure that the manufacturing processes developed meet all the requirements in Box 1, helping to achieve the desired critical quality attributes while reducing PMI. Here, we highlight some recent advances in the development of technologies that can help to address peptide manufacturing challenges.

Peptide Synthesis

As peptides enter mainstream use as pharmaceuticals, they present a rich range of opportunities for their accurate synthesis. Peptides are typically synthesised iteratively, monomer by monomer, requiring repeated purification after each addition.

This means that peptide synthesis requires processes combining reaction and separation. Solid Phase Peptide Synthesis (SPPS) is the dominant method for peptide production which is based on the Merrifield synthesis approach.²²

The reaction by-products generated at each step can be easily removed by washing through the solid support particles (resin), facilitating automation and simplifying purification. Moreover, attachment to the solid support prevents aggregation of the growing peptides. However, current SPPS methods present challenges in the large-scale synthesis required for the new wave peptide drugs. These include poor reagent diffusion within the solid support and inefficient mixing, which can lead to incomplete reactions. While these limitations can be mitigated by using excess reagents, such strategies are undesirable from both economic and environmental perspectives. As a result, there is growing interest in alternative methodologies that offer improved scalability while maintaining the advantages of SPPS. Recently, Orthogonal Peptides have pioneered a new SPPS method referred to as Merrifield 2.0, which allows easily the synthesis of new non-linear peptide structures, including cyclic peptides, which are superior for oral delivery.²³

Newer approaches include Liquid Phase Peptide Synthesis (LPPS), which is emerging as a promising alternative.²⁴ LPPS retains the key benefits of

solid-phase synthesis (automation and efficient removal of reagents and byproducts) while overcoming the handling limitations of SPPS. Selective separation of the growing peptide from unreacted reagents and byproducts is achieved by incorporating a support with distinct physicochemical properties (e.g., hydrophobicity or increased molecular size). Several LPPS strategies have been reported, often employing precipitation or extraction for purification.²⁵ However, these techniques introduce additional processing steps that can be challenging to automate and scale, especially since they depend on sequence-dependent solubility changes. An alternative approach is the use of specialised membranes to separate the growing peptide from reaction debris in the liquid phase.²⁶

In addition to the hybrid approaches previously mentioned,¹³ there is a growing body of research focused on environmentally sustainable synthesis, including the use of water or micelles, as well as using water-soluble protecting groups to reduce reliance on organic solvents. Additionally, new reaction strategies that can reduce the number of atoms used in each reaction are being investigated, potentially improving PMI by minimising the use of protecting groups (a set of atoms tacked onto a molecule to prevent undesired chemical reactions from taking place).

Peptide Purification

Despite the current limitations of conventional approaches, methods for peptide purification, primarily the vast volumes of solvents required, slow processing times and aggregate formation, reversed-phase and ion-exchange liquid chromatography remain the cornerstone of the peptide purification workflow.²⁷

These methods are essential for enabling the high purities required for the safe manufacture of peptide therapeutics, but simultaneously contribute to low manufacturing efficiency and high solvent waste.²⁸

As a general metric for peptide manufacture, 13,000 kg of waste is produced for each kg of a complex peptide manufactured.¹⁴ Up to 70% of this waste is directly due to the chromatographic purification process.¹⁴ Even with recent advances in multi-column chromatography, semi-continuous chromatography or continuous chromatography, this separation method remains a bottleneck. Although recent approaches have been shown to substantially decrease the waste levels by a factor of up to 4, whilst improving the process productivity,²³ there is nevertheless still a critical need to innovate peptide purification techniques both within and beyond chromatography.

The replacement of one or more chromatographic steps with alternative unit operations is an attractive option. Novel purification techniques such as the usage of magnetic nanoparticles, membrane filtration, liquid-liquid extraction, and precipitation, have all been investigated as alternative techniques to chromatography.^{27,28} A notable example is Amgen's etcalcetide, a peptide used for the treatment of chronic kidney disease. At manufacturing scale, a precipitation-based process has replaced chromatographic steps and freeze-drying cycles, resulting in order-of-magnitude improvements in throughput and reduced process complexity.²⁸

Crystallisation is another promising but under-utilised strategy with the potential to transform peptide purification. It offers several advantages, such as the combination of purification and solid form isolation into a single unit operation, reduced solvent consumption, higher throughputs, and improved product stability. The crystal form also provides a slower dissolution profile, which has the potential to improve drug formulation. However, the high flexibility of peptide molecules poses a challenge for crystallisation, limiting its broad applicability for peptide purification. To overcome flexibility challenges, "template-assisted" crystallisation techniques, already used in protein and monoclonal antibody workflows,^{29,30} are being explored for peptides. Early studies demonstrate their applicability to simple peptides and suggest that such methods may enable controlled and predictable crystallisation for more complex sequences.³¹⁻³³

Importantly, crystallisation can be applied to both full-length peptides and intermediate fragments. This highlights the need for a close, iterative integration between synthesis and purification, balancing synthetic accessibility with crystallisation potential. A 'back-and-forth' approach to optimise fragment length, sequence, and physicochemical properties will be required for successful implementation of crystallisation in a peptide manufacturing workflow.

Given the vast number of potential peptide fragments, experimental efforts alone are insufficient for efficient route selection. Here, digital design could play a key role in identifying the best production route, leveraging molecular and process modelling approaches to account for variability in both molecules and purification processes.

Ultimately, a hybrid, digitally informed strategy that combines chromatography with other sustainable purification technologies will be essential to meet the growing demand for high-quality peptide therapeutics at scale.

Peptide product stability

For peptide therapeutics to be viable, they must demonstrate both chemical and physical product stability. Peptide solution composition, time and temperature are the most critical factors impacting of physical stability of the formation. Unlike larger proteins that are stabilised by the 3-dimensional arrangements of AAs into specific structures (α helices and β sheets), peptides exhibit a significant degree of flexibility. This, combined with the hydrophobicity of some parts of the peptides, makes them more prone to aggregation in solution, requiring careful formulation design to control pH and other variables.

To establish the optimal solution conditions for formulating a peptide product, the use of high throughput screening methods is becoming increasingly important. Experimental techniques based on light scattering and fluorescence spectroscopy are especially noteworthy.

Peptide aggregation may result in loss of therapeutic potency or even toxicity. Aggregation typically manifests in four forms: oligomers, amyloid fibrils, micellular structures, and amorphous aggregates.

In addition to aggregation, proteolytic degradation in the stomach presents a major barrier to peptide stability, especially for oral delivery. The gastrointestinal environment contains a range of proteolytic enzymes (endopeptidases and exopeptidases) that break down peptides and facilitate the digestion and absorption of dietary proteins and amino acids. To counter this, several modification strategies are employed to stabilise the peptide while preserving pharmacological effect (Box 4).

Box 4 - Peptide modification against proteolytic degradation

The structure and primary sequence of the peptide can be modified to protect it from proteolytic degradation. These modifications include amino acid substitution, cyclisation and lipidation.

- Amino acid substitution is the simplest stabilising strategy and has the most flexibility. It entails substituting vulnerable AAs with more stable ones, such as proline, which can inhibit enzyme binding. Targeted substitutions at known cleavage sites can block the action of a particular enzyme through steric hinderance, minor conformational changes or charge alteration. Replacing L-amino acids with their D-counterpart increases rigidity and alters secondary structure, reducing the binding affinity of enzymes. However, excessive use of this technique can decrease peptide functionality or recognition at its target site.
- Cyclisation of the primary structure of the peptide also increases its proteolytic resistance through a reduction in both its conformational flexibility and its ability to bind to the active site of the enzyme. Backbone cyclisation of a linear peptide sequence has the additional benefit of removing the sites of the peptide that are susceptible to hydrolysis.
- Lipidation - the addition of long hydrophobic lipid groups to the peptide structure - has also been observed to increase peptide proteolytic resistance. It has been suggested that this occurs primarily on account of increased steric hinderance or the formation of complex conformations inhibiting enzyme access.

System-wide approaches

Innovation in each step of the manufacturing process is important, but manufacturing peptides at scale also requires careful design of the overall process via systems engineering. Traditional process design strategies used in chemical manufacturing entail multiple stages, starting with reaction route selection, screening of alternative process configurations, and the detailed design of the reaction and separation units including operational and control strategies. Digital technologies, which integrate knowledge- and data-driven mathematical modelling and systematic decision-making tools, and holistic systems engineering approaches, which integrate techno-economic objectives with environmental and social considerations, bring immense benefits, with a 10-fold return on investment expected from modelling efforts.³⁴ Transferring these systematic design strategies and computational methodologies to manufacturing of

peptides and biopharmaceuticals and adopting the digital system design blueprint shown in Figure 3 offers opportunities to enable rapid process scale up, minimise time-to-market, and reduce environmental impacts. However, the unique nature of peptide chemistry also presents distinct challenges.

Although a peptide's sequence is fixed to achieve the desired biological activity, reaction route selection in peptide synthesis retains considerable flexibility. Key decisions include choosing to use solid-phase or liquid-phase synthesis (or a hybrid of both), and whether to build the peptide one amino acid at a time (linear build) or by synthesising fragments and then coupling them (fragment build). Decision-making tools that leverage mathematical models can simulate different manufacturing options and guide early-stage decisions for how to partition a peptide's sequence into fragments in a hybrid process. The use of such tools can have a transformative impact on process performance (Box 5).

Box 5 - Systems Thinking in Peptide Manufacturing – Optimising the MEPS Approach

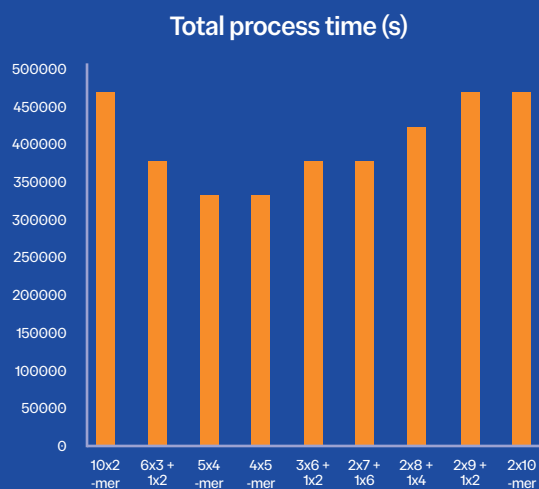
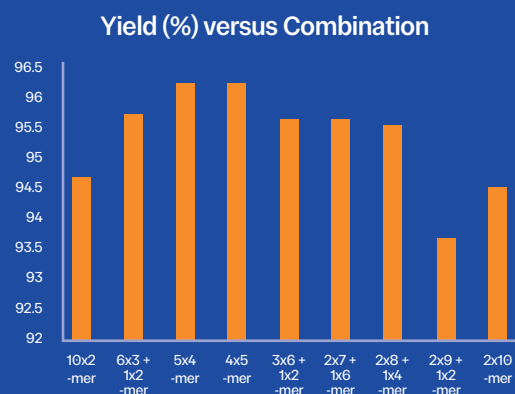
Traditional peptide manufacturing often relies on linear, stepwise solid-phase synthesis, which becomes increasingly inefficient for longer peptides due to cumulative yield losses and purification burdens. In contrast, MEPS integrates solution-phase synthesis with membrane-based purification, enabling continuous or semi-continuous processing.

Researchers at Imperial College London compared two synthesis strategies within the MEPS framework: conventional linear synthesis (adding amino acids one by one) and fragment-based synthesis (coupling pre-assembled peptide fragments, e.g., consisting of 5 AAs – a 5-mer). Using dynamic process modelling and global sensitivity analysis, they evaluated system performance across multiple configurations.³⁵

The findings reveal that, relative to linear synthesis, using fragment-based synthesis to make a 20 AA peptide can reduce total process time by up to 30% while maintaining or improving yield and purity – especially when paired with advanced membrane systems like cascades or double membranes.³⁶ This is due to fewer reaction steps and improved retention of larger fragments during purification. However, the study also highlights trade-offs: higher membrane rejection rates improve retention but significantly increase processing time for diafiltration, underscoring the need for balanced system design.

Crucially, this work demonstrates that optimising peptide synthesis cannot be achieved by focusing on individual steps in isolation. Instead, a holistic view – considering synthesis strategy, membrane configuration, and process dynamics – is essential.

Comparison of different combinations of fragment lengths.



Each of these labels represent a recipe for making the following 20 amino acid peptide, where each colour represents a different amino acid. For example, 4x5-mer indicates that the peptide is made by synthesising 4 fragments of 5 AAs each and then connecting them.



However, current models are not yet accurate enough to guide the design of complex peptides, particularly those prone to aggregation or side reactions. Addressing this gap requires new hybrid modelling approaches that combine experimental data with mechanistic knowledge, supported by optimal experiment design.³⁷ Optimal experimental campaigns, developed in concert with mathematical models, have been shown to reduce time and cost and improve the reliability of manufacturing decisions.

Moreover, the traditional trial-and-error approach to designing a typical peptide manufacturing process step by step can be replaced with process systems engineering methods frequently deployed to design large-scale chemical manufacturing processes. These methods offer opportunities for optimisation,³⁸ through streamlining the process and improving throughput, and support innovative strategies such as fragment-based synthesis and solvent recovery.³⁹ Systems approaches are also central to improving the sustainability of peptide manufacturing. Computer-aided methodologies that integrate molecular (e.g., solvent) and process-level decisions, alongside life-cycle analysis (LCA), offer a more holistic and effective path forward. This can lead to better designs than relying solely on standard green chemistry principles, as these approaches account for interactions between different elements of the overall production system. For instance, viewing water as the ultimate green solvent overlooks the substantial amount of water needed to dissolve complex molecules such as peptides as well as the high energetic cost of recovering and treating water contaminated with other solvents, byproducts, and unreacted reagents.⁴⁰ The integration of solvent choices across multiple processing steps has already been shown to lead to a reduction in solvent consumption in the context of small-molecule drug manufacturing.⁴¹ To realise these benefits, further efforts to integrate route selection and process development are needed, together with the development of libraries of predictive models of the relevant process units and of the properties of peptides.

Prediction of peptide properties

A deeper understanding of the physicochemical properties of peptides, such as solubility, crystallisability and crystal shape, octanol-water partition coefficient, and gelation (Box 6), is crucial for the development of manufacturing processes. Although peptides are made from a relatively small set of amino acids, the impact of the number and sequencing of these building blocks on the molecule's properties is not well understood. As a result, manufacturers rely on extensive and costly experimental campaigns to determine the properties of each new peptide that is to be manufactured and of all the intermediate compounds that arise during manufacturing. This empirical approach limits knowledge transfer and slows innovation.

Correlation-based methods can be very accurate, and fast to compute, but depend on access to experimental data. The ability to design manufacturing processes can be vastly enhanced by predictive methodologies that can estimate relevant properties when measured data are not available, be it because the peptide of interest has not been synthesised yet or because the measurement is especially hard to carry out. For example, solubility can be very low for many peptides, making data collection especially time-consuming and expensive in early-stage design.

Computational methods that can be applied reliably over wide ranges of conditions of pressure and temperature, including pH changes and different solvents, can support all aspects of process development. For example, quantum mechanical (QM) models that allow for the calculation of electronic structure of reactants and transition states are being used to identify reaction pathways at the (sub)atomic scale, and to calculate reaction rates for the synthesis of active ingredients or peptides at process scales.⁴² QM models are also being deployed within crystal structure prediction methods for organic molecules.⁴² Extending these methods to deal with more flexible molecules such as peptides could make it possible to identify the potential crystal structures of fragments and to help guide the search for crystalline intermediates.

Property prediction is also important in the purification and separation stages, where access to predictions of solubility in a range of solvents and of partition coefficients is critical. These properties can be computed from classical molecular models, such as Monte Carlo or molecular dynamics simulations, or equation of state models. Molecular-based equations of state, such as the statistical associating fluid theory (SAFT), offer fast and accurate predictions in comparison with experimental data, which makes them especially attractive in terms of incorporation in integrated process and product design platforms.^{43,44}

The manufacturing of solid-state formulations of peptides involves the combination of the peptide with excipients and other materials that improve flow or compression properties, for which stability must be also assessed. Among other factors, environmental moisture can greatly impact product stability. Here, calculations that aim to predict how much water is taken up by the system at any given temperature and relative humidity are often carried out using equation of state models, which deliver accurate predictions compared to measurements.⁴⁵

Box 6 - Peptide gelation

Peptides have a tendency to self-assemble into hydrogels, driven by a combination of weak forces, hydrogen bonding, hydrophobic interactions, electrostatics, and their macromolecular nature. The resulting hydrogels are typically dynamic, capable of self-healing and reassembling. The ability to form gels can be advantageous in designing effective peptide-based therapeutics but can be highly detrimental in manufacturing.

Peptide hydrogels are especially promising for drug delivery, as they can be injected or moulded and then reformed in situ, giving them great potential as drug-release systems. They are also of great interest as biomaterials since the structure of a peptide hydrogel closely mimics the natural environment of cells in the body. Peptide hydrogels are typically biocompatible and biodegradable, with tuneable mechanical stiffness and minimal immunogenicity. Gel formation can be triggered by changes in pH, temperature or enzymes, allowing precise control over the gel's properties. Ongoing research is being carried out to unravel the detailed molecular mechanisms of peptide gelation. A deeper understanding of how sequence and conditions control self-assembly will enable the rational design of peptide hydrogels with tailored properties.

However, gelation is a significant challenge in peptide manufacturing, as it can severely disrupt both processing and product quality. During synthesis or purification, peptides may self-assemble into semi-solid gels. This is particularly problematic for longer or aggregation-prone AA sequences. Gelation increases viscosity, impeding flow through pumps and tubing, and making mixing, filtration, and chromatography difficult or impossible. It can trap unreacted materials and solvents, reducing yield and complicating purification. These issues are often exacerbated during scale-up, where changes in mixing and heat transfer can trigger gelation that was not observed at lab scale. Furthermore, gels interfere with analytical techniques and may impede product development, particularly for injectable products where uniformity and viscosity are critical. Despite its impact, gelation remains poorly understood, with limited predictive tools available. Research into the mechanisms and triggers of gelation is essential to improve process robustness, reduce costs, and accelerate the development of novel peptide therapeutics.

Increasingly, researchers are turning to machine learning models as an additional tool to predict some properties directly from a knowledge of the AA sequence. One powerful approach is quantitative structure property relationship (QSPR) modelling. The transformative potential of machine learning in modelling complex molecules, particularly for proteins, was recognised by the 2024 Nobel Prize in Chemistry, which honoured advances in computational protein design, including the AlphaFold models.⁴⁶ Peptides are more complex than small-molecule therapeutics but smaller than proteins. Their properties depend on amino acid composition, sequence order, length, and conformational flexibility, which limits the effectiveness of traditional cheminformatics. Recent AI models, such as PeptideBERT, address these challenges using pretrained language models that capture long-range dependencies and functional sequence patterns, resulting in improved predictive performance.⁴⁷ Still, no single model captures all properties required for product and process development, prompting growing interest in hybrid strategies, such as the combination of sequence embeddings with 3D structural data from AlphaFold.⁴⁸

AI and automated platforms

Beyond prediction and design, AI also has the potential to transform peptide manufacturing, from process design to operations and supply chain management. However, the availability of high quality, relevant experimental data remains a critical limitation. This is where high throughput experimentation (HTE) comes in, playing a central role in enabling AI-driven peptide process development. Currently available platforms can support automated, parallelised, small-scale experimental campaigns that can generate the data needed to train and refine AI tools. By operating at a reduced scale, HTE has the potential to reduce material consumption and shorten some model and process development timelines. Though expensive, HTE platforms are already being used by the pharmaceutical industry. Their ability to conduct large, systematic studies efficiently makes them useful for bridging the gap between experimental data and model development. Integrating high throughput experimentation with AI and autonomous control is an important step for achieving truly digital and sustainable peptide manufacturing.

A key example is the automation of reaction design for amide bond formation, a central step in peptide synthesis. HTE platforms are being applied at the sub-microgram scale to investigate a myriad of reaction conditions, reagent combinations, and solvent effects across diverse peptide libraries. In ongoing studies, thousands of combinations are being systematically explored to map synthesis performance and generate high-quality data for developing ML-based reactivity

prediction models. These efforts accelerate synthesis optimisation and lay the foundation for closed-loop workflows.⁴⁹ As such systems begin to incorporate model-driven feedback, they signal a broader shift toward autonomous process development.

To fully unlock the potential of lab automation, the full sequence of execution-analysis-design-of-next-experiment should be carried out in a closed loop, relying on algorithms to analyse the results of one experiment and optimise the next one. Autonomous systems can explore complex design spaces, optimise conditions, and iterate over different conditions. An example of such an autonomous platform is the “Smart HPLC Robot”⁵⁰ developed at the Sargent Centre for Process Systems Engineering through the PharmaSEL Prosperity Partnership. This system enables the autonomous design of HPLC purification methods, identifying the conditions (e.g., flow rates, percentage of organic solvent, and column temperature) that lead to the best performance, e.g., minimum processing time.

Given a never-before-seen mixture that needs to be separated into individual components, the procedure begins by a calibration of pre-existing mechanistic (physics-based) models without manual input, followed by a virtual separation using a digital twin. This generates an improved model for the mixture of interest; the system then validates and refines this model experimentally. This refinement step may use AI to optimise isotherm models or apply AI driven algorithms when mechanistic models are insufficient, which is common for complex peptides. This hybrid approach is especially useful for scaling up production as it combines the flexibility of AI with the reliability of mechanistic models: data-driven models often do not transfer well across scales, whereas mechanistic components provide a reliable and generalisable foundation. Embedding them within autonomous platforms helps accelerate the transition from lab scale to full scale manufacturing.

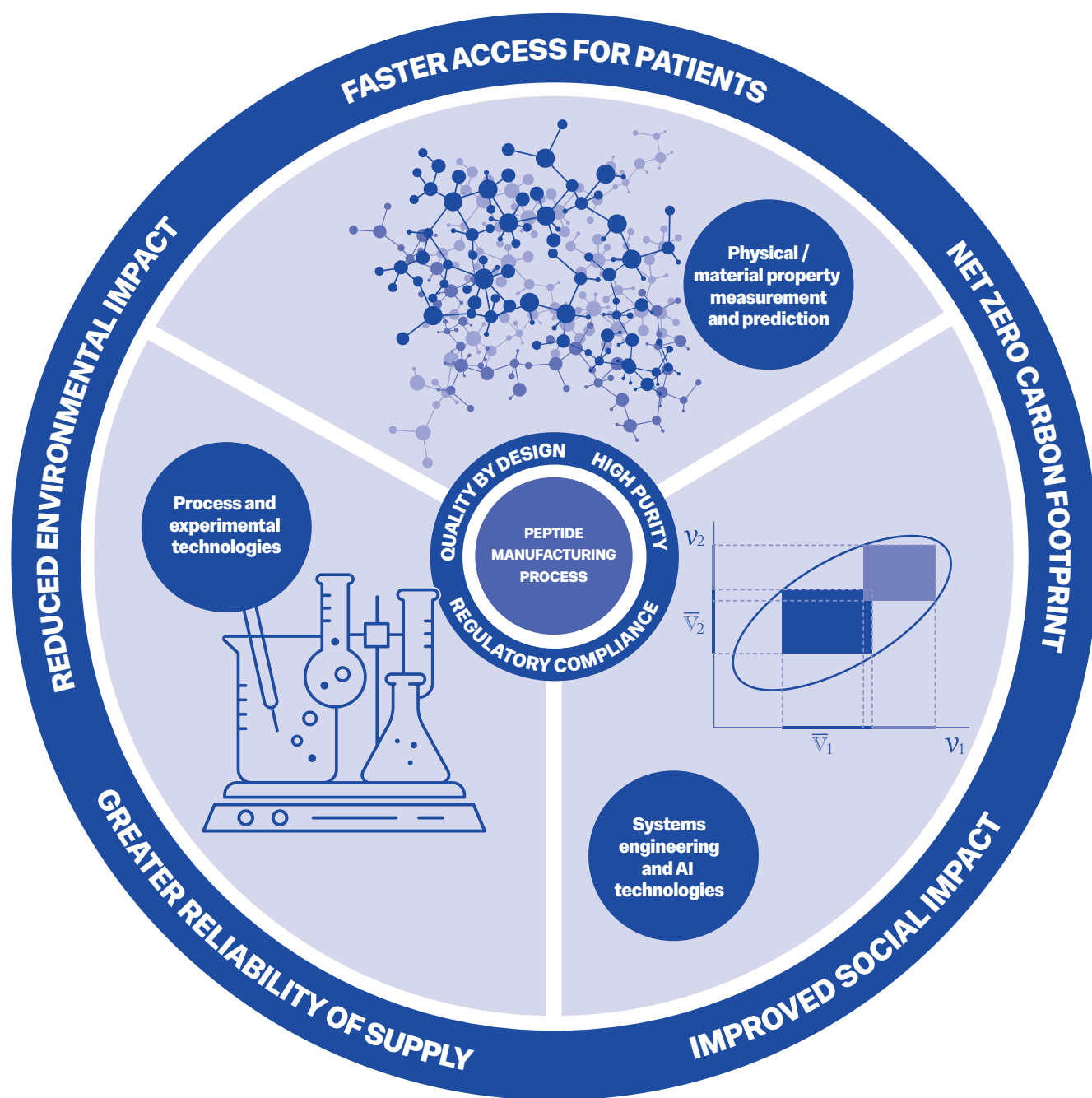


Figure 3: A holistic approach to manufacturing research and development. Key areas of manufacturing innovation that require a coordinated effort to support the UK Life Sciences sector in developing a world-leading peptide manufacturing capability, improving the health of the population and bringing economic benefits.

Section 3 :

Strategies to accelerate the peptide revolution

Enabling better peptide manufacturing

Lessons from Industry-Academia Collaboration: Insights from the PharmaSEL Prosperity Partnership

Effective collaboration between industry and academia is essential to advancing the UK's leadership in emerging medicines manufacturing. The PharmaSEL Prosperity Partnership offers valuable lessons on how such partnerships can be structured to deliver both scientific innovation and industrial impact.¹ For this collaboration to bloom and thrive, partners must recognise each other's own objectives and time horizons (academia seeks to make long-term contributions for a broad of community researchers and industry seeks to innovate to deliver on shorter-term business metrics). To be successful, a collaborative research programme should preferably define projects at the intersection of these objectives and timelines. Additional funding from non-profit sources (e.g., government) can greatly facilitate collaboration by supporting research that meets both parties' objectives but lies beyond the threshold of a standard business timelines.

One of the key takeaways of the PharmaSEL Partnership is the value of large, coordinated projects that maintain a sustained focus on bridging disciplinary divides and integrating different stages of the manufacturing process. These projects are most effective when they adopt a systems thinking approach and use common exemplars to align efforts across diverse teams. This fosters coherence and accelerates progress from fundamental research to practical application.

For industry to adopt innovations early, it is crucial that companies invest strategically in collaboration, allocating skilled personnel and resources to support testing, feedback, and onboarding. Two-way secondments – where academic researchers spend time in industry and vice versa – are critical to building mutual understanding and ensuring that research outputs are relevant and implementable.

A shared understanding of industry-relevant questions is also essential. In PharmaSEL, for example, the use of model-based design of experiments was not primarily about reducing the number of experiments, but about improving the reliability and informativeness of models.

This shift in focus emerged through close dialogue between academic and industrial partners, highlighting the importance of co-defining research goals.

Another important lesson is the need to balance different incentives. Academic researchers are often driven by the pursuit of fundamental understanding and the ability to publish, while industry partners may prioritise confidentiality and commercial outcomes. Successful collaborations recognise these differences and design research programmes that accommodate both. In PharmaSEL, access to peptide materials from a discontinued industrial project enabled researchers to develop and test new crystallisation protocols in a realistic yet publishable setting – demonstrating how model systems can bridge the gap between open science and industrial relevance.

These insights underscore the importance of long-term, well-resourced partnerships that are built on trust, shared goals, and mutual benefit. By embedding these principles into future initiatives, the UK can enhance the effectiveness of its innovation ecosystem and accelerate the translation of cutting-edge research into industrial capability.

A concerted effort on basic research on peptides and manufacturing technologies

To establish the UK as a global leader in peptide manufacturing, targeted investment in research is essential. Three major priority areas are proposed to guide funding and policy decisions that will strengthen the UK's innovation and manufacturing capabilities.

1. Understanding and Predicting Peptide Properties

The lack of fundamental understanding and data regarding peptide behaviour in complex environments is a major barrier to efficient development and manufacturing. Key properties include:

- solubility in mixed solvents and across pH ranges, to reduce the environmental impact of solvent use in manufacturing and to support the use of bioderived solvents.
- solid-state properties, whether for crystalline materials (structure, melting properties, crystallisation conditions) or amorphous dispersions (physical stability, peptide-polymer-solvent interactions), to control manufacturing and formulation.

- stability and shelf-life, which are essential for safe and cost-effective treatment.
- gelation, a frequent phenomenon in peptides that can affect synthesis and purification and is extremely poorly understood.

Research is required to develop mechanistic insights into how these properties relate to peptide structure (amino acid sequence, chain length, presence of side chains) and to the peptide environment. Such research should encompass a systematic experimental programme and a concerted effort on property prediction methods.

While predicting the properties of peptides is challenging, the fact that they are made from a limited set of building blocks presents the opportunity to launch an ambitious Peptide Genome Initiative (Box 7). The aim of such a programme would be to build a comprehensive dataset of peptide sequences and properties that will enable the development of models to predict manufacturability, solubility, and stability, reducing trial-and-error experimentation. This would be complementary to the Health Data Research Service (HDRS) proposed in the Life Sciences Sector Plan 2025, which is focused on health data rather than data relevant to manufacturing.

2. Innovation in Synthesis and Separation Technologies

To improve efficiency and sustainability, it is critical to recognise the unique space occupied by peptides, between small-molecule drugs and biopharmaceuticals, and to design peptide-specific synthesis and purification protocols. The UK has a track record of innovation in this area and can take the lead in developing next-generation peptide manufacturing technologies, including

- membrane-based liquid-phase peptide synthesis and advanced solid-phase synthesis techniques, with research into optimal build strategies.
- biocatalysis and enzymatic synthesis, offering greener, more selective alternatives for complex or cyclic peptides.
- improved separation technologies, including template-based approaches in crystallisation, smart method development for chromatography, as well as other novel technologies, to enhance purification and reduce environmental impact.

3. Process Systems Engineering, Digitalisation and AI

Advanced process systems engineering and digital tools, including modern machine learning, are essential components of a strategy to deliver rapid process development and to implement scalable, cost-effective

and sustainable manufacturing. The following areas are particularly important for peptides

- model-based design of experiments (MBDoe) and high-throughput reaction rate collection, integrated into process synthesis to optimise yield, purity, and sustainability.
- approaches to explore alternative synthetic routes and process design optimisation to improve robustness and scalability.
- Quality by Design (QbD), design space optimisation and whole process optimisation, ensuring regulatory compliance and consistent product quality while minimising cost.
- computer-aided solvent design, tailored for specific unit operations or plant-wide integration, to improve efficiency and reduce waste.
- advanced process analytics and soft sensing technologies, enabling high process reliability and product consistency

Box 7 - A peptide genome initiative: unlocking data driven therapeutics

There is significant future potential for the use of large-scale data-driven platforms in peptide manufacture and therapeutics. However, such platforms have focused primarily on proteins. The Protein Data Bank (PDB)⁵¹ – an international collaboration between the US, Europe, and Japan – provides a central open-source database of digitised three-dimensional structure for over 200,000 protein, peptide, RNA, DNA, and other biological macromolecules. The Protein Structure Initiative (PSI),⁵² funded by National Institute of General Medical Sciences (NIGMS) of the US to the tune of ~US\$ 764M (2000–2015) further supports the development of high-throughput structure determination. These protein-focused projects have enabled key breakthroughs such as AlphaFold.^{46,53}

Recent advances in automated peptide synthesis, combinatorial display libraries (e.g., phage, mRNA display), and AI-based bioinformatics have accelerated peptide discovery.⁵⁴ Machine-learning models are now increasingly used to predict some peptide properties (e.g. bioactivity, toxicity) directly from the peptide sequence allowing researchers to screen millions of candidate structures to pinpoint promising bioactive peptides, which are then synthesised and tested.

However, current peptide databases contain only a few thousand distinct well-characterised peptides, limiting the effectiveness of these tools. There is therefore an urgent need for a coordinated and intensive effort on a **Peptide Genome Initiative (PGI)** to generate large-scale peptide structure–property data. Inspired by the Human Genome Project (HGP) or PSI for proteins, PGI would systematically produce and catalogue peptides along with their structural descriptors, including sequences, predicted 3D conformations, physicochemical properties (solubility, stability, toxicity, etc.), and biological activity (binding to targets, antimicrobial or anticancer efficacy, etc.). The PGI would focus on large-scale collaborative peptide data generation, moving beyond isolated lab projects to a concerted, well-funded effort to put together an extensive dataset for peptide high-throughput activities. Uniquely, the PGI would also target peptide properties that are relevant to process and product development, such as solubility in organic solvents. This would involve four major pillars:

- data integration, aggregating and standardising existing peptide databases into a comprehensive resource;
- massive peptide libraries, using automated synthesis and display techniques to generate thousands of peptides at a time, simultaneously profiling the biological activities and physicochemical properties;
- multi-dimensional screening, assessing peptide sequences with respect to predefined physicochemical and bioactivity targets;
- open-data access, collected in a publicly accessible peptide knowledge-base.

Role of SMEs / support for SMEs and specialist providers

As with many areas of technology development, small and medium sized enterprises (SMEs) and specialist providers play a crucial and often underappreciated role in the development of peptide manufacturing technologies. The UK's life sciences sector is formed of around 977 companies, 800 of which are SMEs (80%) with 562 headquartered in the UK (60%). Of those, 105 are focused on manufacturing and 36 in biopharma and manufacturing.^{55,56}

Because peptide manufacture is complex, and solid phase synthesis at scale requires specialist equipment and skills, the peptide supply chain has evolved to comprise a range of Contract Development and Manufacturing Organisations (CDMOs) with specialist capabilities in manufacturing, analysis and regulation.⁵⁶ These CDMOs supply peptides to the large pharma companies who typically own the peptide assets, so that they can move the candidate peptide from the laboratory, through clinical trials to commercialisation.

Previous reports estimated the UK's CDMO market to be \$6.0 billion in 2023, with expected growth to \$7.1 billion by 2028.⁵⁶

A few Original Equipment Manufacturers (OEMs) sell the specialist synthesis and purification technology to the CDMOs. Because CDMO and OEM businesses are highly competitive, albeit with good margins, their scope for R&D based on profit from day-to-day operations is limited. Rather, the main share of the profits of a successful commercial drug go to the large pharmaceutical company that has made the largest investment in drug discovery. Large pharmaceutical companies tend to focus on drug assets rather than manufacturing innovation, and when they develop new technologies, they often retain the intellectual property (IP) for their own competitive advantage, limiting dissemination of innovations.

This creates a unique innovation space for SMEs with disruptive technologies, whose contributions can include creativity, agility, and bridge the gap between academic discovery and deployment at large-scale. We refer to these SMEs as **PharmaTech SMEs**, to differentiate them from **MedTech** and **BioTech** SMEs that are less focused on manufacturing. Because PharmaTech SMEs need to be innovative to attract investment, they often focus on a core innovation that challenges legacy methods such as traditional solid-phase peptide synthesis. Many peptide-focused SMEs originate as spinouts from academic institutions such as Exactmer Ltd, Origin Peptides Ltd, CatSci Ltd, Constructive Bio Ltd and most recently Orthogonal Peptides Ltd. This means they are in an excellent position to collaborate with university labs, and to develop and optimise new technology platforms to provide robustness, efficiency, and compliance with regulatory standards. They can work with CDMO and Pharma partners to translate innovative lab-scale processes into pilot or production-scale workflows. Moreover, by retaining intellectual property rights in the platform technology, they can enable dissemination across the industry to a wide range of drug assets, for the ultimate benefit of patients. As a part of this development, PharmaTech SMEs can produce early lab scale synthesis batches; demonstrate reproducibility, and establish manufacturing controls, critical steps in de-risking new technology before clinical trials and commercialisation.

To fully harness the potential of PharmaTech SMEs, targeted support is essential. This includes technical and business resources, access to capital for analytical and process equipment, and opportunities to engage with regulators, both through large pharma partners and directly by the SME. Policymakers and funders should also recognise that technology development may require repeated, iterative attempts at creating software or equipment to achieve the goals. Two of the actions in the Life Sciences Sector Plan are specifically targeted

at manufacturing innovation: Action 19, to deliver the £520 million Life Sciences Innovative Manufacturing Fund and Action 20, to continue to invest at scale in Life Sciences manufacturing. With a concerted effort, these actions could make a material difference to the UK's standing as a leader in the manufacturing of peptides and other emerging modalities accelerating innovation to the benefit of the UK's economy and the health of its population.

Regulatory implications

The pharmaceutical peptide manufacturing landscape is challenged by divergent regulatory requirements across regions, affecting expectations on scale up, control strategy, quality and compliance. Addressing varying requirements to enable global scale manufacturing of peptides can lead to higher overall costs to commercialise and potentially delayed patient access.

Classification of peptides by global regulatory frameworks (e.g., whether a chemical entity or a biologic) can include mode of manufacturing, chemical structure and length, and intended use, among other elements. Different designations across major markets such as US, EU, China and Japan can result in different expectations on quality, process portability, approval timelines, and patent exclusivity. For example, current regulations in the US favour a designation based on amino acid,⁵⁷⁻⁵⁹ while the UK's Medicines and Healthcare products Regulatory Agency (MHRA)⁶⁰, the European Medicines Agency (EMA)⁶¹ and Japan's Pharmaceuticals and Medical Devices Agency (PMDA)⁶² evaluate peptides based on their structure, origin (synthetic vs. recombinant), and intended use, which can lead to different classifications for the same molecule. China's National Medical Products Administration (NMPA)⁶³ is still evolving its regulatory framework for peptides. While it is moving towards stricter Good Manufacturing Practices (GMP) and clinical trial requirements, its classification system remains case-by-case and focuses on the method of synthesis and therapeutic application.

These differences in peptide designations and requirements can create a cascade of challenges:

- Duplicative regulatory submissions and non-transferable quality/Chemistry, Manufacturing and Controls (CMC) data across jurisdictions.
- Increased compliance resources and costs due to varying GMP standards and documentation requirements.
- Delays in global product launches, as companies must navigate multiple, often conflicting, regulatory pathways.
- Increased return on investments expectations for process changes that could enable advanced manufacturing.

Greater international alignment, potentially through ICH guidelines or bilateral agreements, would significantly streamline development and ensure consistent quality and safety standards worldwide. Ultimately, the harmonised recognition of advanced manufacturing approaches for peptides (e.g. hybrid synthesis, computer-based development, continuous manufacturing of complex APIs) could address these challenges robustly and agnostic to any regulatory framework. The utilisation of computer-based approaches could significantly lessen the development burden of the molecule to fulfil the strictest requirements.

Conclusions and policy recommendations

The UK government has stated its ambition to unlock the potential of the Life Sciences sector to drive economic growth and improve health.⁹ To achieve this goal, the recently published Life Sciences Sector Plan outlines a series of measures aimed at stimulating the discovery of new medicines and encouraging investment in manufacturing facilities. These initiatives are designed to enhance the speed and capacity for delivering commercial trials and research. These actions must be complemented by strategic investments in innovative manufacturing research to overcome the hurdles in the production of complex medicinal products.

This is especially critical for the manufacturing of emerging modalities, such as peptides, oligonucleotides, antibody-drug conjugates (ADCs) and peptide-drug conjugates (PDCs), for which the UK has the potential to become a global leader. These fast-growing modalities, which lie at the boundary between synthetic and biological therapeutics, are transforming the treatment landscape for a range of diseases, including diabetes, antimicrobial resistance, and cardiovascular disorders. However, their complex production processes require targeted investment and coordination across sectors to accelerate clinical trials, enable at-scale production, and overcome sustainability challenges.

To support this, we recommend a focused research effort on understanding and predicting peptides' properties, accompanied by a Peptide Genome Initiative (see Box 7), as well as the development of better synthesis and separation technologies. Such an initiative could build on the £600 million investment from the UK Government and the Wellcome Trust to establish the Health Data Research Service (HDRS), aimed at creating the world's most advanced health data platform. To maximise the potential of data for patients' benefit, other platforms such as 'Genomics England' or the 'UK Biobank' will also be expanding in the next few years. Extending these investments to manufacturing-relevant data would help to address the UK's commercialisation gap, where medicines are discovered but companies struggle to scale up production domestically. To further enable scale-up and commercialisation, we also propose investing in process systems engineering, digitalisation and AI innovation, building on the UK Government's AI action Plan and the 10 Year Health Plan, both of which highlight AI as the key to unlock new medicines.^{64,65}

In alignment with the Life Sector Plan's five interconnected action areas: access to finance, skills, manufacturing, net zero and high value partnerships; we propose the following interventions:

- higher investment to align basic manufacturing research and production at scale;
- international cooperation to achieve regulatory alignment;
- up-skilling through targeted training and education initiatives.

The Life Sciences R&D and manufacturing sector is one of the UK's leading industries. It employs around 300,000 people and contributes a gross value added of around £43 billion annually to the UK economy, of which £19.2 billion correspond to pharmaceutical development and manufacturing.^{56,66} To capitalise on these strengths, the UK should build on its world-class innovation and manufacturing capabilities to seize the opportunities offered by emerging classes of medicines such as peptides. This includes leveraging its advanced pharmaceutical manufacturing infrastructure and its strong academic research base in manufacturing. By aligning these assets with strategic investment, the UK can position itself as a key player in the global supply chain for peptide therapeutics while improving healthcare services and delivering benefits to patients.

- **Establishing a National Centre for Emerging Medicines Manufacturing (NCEMM).** A central recommendation is the creation of the NCEMM, which would integrate scientific discovery with engineering innovation and translation. The centre would support the full pipeline from basic research on platform technologies for manufacturing to commercial-scale production. It would serve as a hub for collaboration, bringing together academia, industry, and government to accelerate the development and scale-up of new modalities and to de-risk the adoption of new process technologies, from clinical trials to commercialisation. Such a centre would help drive health innovation and contribute to NHS Reform, ensuring safe, timely and cost-effective access to medicines and medical technologies for patients.

▪ **Partnering with industry to drive growth and innovation.**

Greater interaction between pharmaceutical companies, contract development and manufacturing organisations (CDMOs), manufacturing start-ups and SMEs, universities, regulators, and funders, including venture capitalists and UKRI, is essential. Facilitating these connections through innovation clusters, shared facilities, and public-private partnerships will foster a more agile and responsive ecosystem capable of rapidly translating manufacturing research into market-ready products. The creation of innovation clusters is a core objective of the UK's Industrial Strategy, aiming to concentrate efforts and develop dynamic ecosystems with great potential.⁹

▪ **Supporting NCEMM through coordinated R&D investment.**

The NCEMM's activities should be supported by a range of related R&D investments by UKRI and other parties in order to:

- i. obtain data on the behaviour of peptides and other emerging modalities within the process and product environments – the Peptide Genome Initiative;
- ii. increase our ability to exploit these data via AI and other digital modelling platforms;
- iii. support the invention and adoption of new technologies through fundamental research and translational projects.

A supportive policy framework is also critical. In addition to the targeted incentives for investment in manufacturing capacity afforded by the UK's Life Sciences Innovative Manufacturing Fund (LSIMF), the UK could provide transformative support to its PharmaTech and OEM companies by embedding them in the NIHR Innovation Catalyst and connecting its PharmaTech, MedTech and BioTech innovators.

▪ **Streamlining and aligning regulation.** The UK, through the MHRA, could assume global leadership by seeking streamlined regulatory pathways for emerging modalities through better alignment of the designation of these medicines across the world, contributing significantly to cutting red tape. Collaboration with the National Institute for Health and Care Excellence (NICE) would be key to facilitating market access for industry through common advice and parallel approval routes.⁹

The overarching aim should remain to prioritise regulatory reliance for medicines while shortening timelines to benefit patients.

▪ **Strengthening the skills and workforce development.**

The UK must strengthen its research and skills base to deliver a qualified and interdisciplinary workforce.^{9,67} This includes expanding training programmes for highly skilled graduates, particularly in areas such as advanced manufacturing, systems engineering, and digitalisation & AI. To achieve this, the UK government and higher education institutions (HEIs) should work with Life Sciences employers to identify sector needs and skills gaps. This would include updating existing training programmes and creating new sector-specific courses. Ensuring a steady pipeline of talent will be vital to sustaining innovation and maintaining competitiveness.

▪ **Net zero and sustainability.** Peptides and other emerging medicines, with their potential for exponential growth, pose specific sustainability challenges due to their much higher mass consumption than other medicines. Supporting innovative approaches to process development and sustainable process technologies is essential to ensure the alignment of the sector with the UK's net zero and sustainability goals.

By taking these coordinated steps, the UK can not only meet domestic healthcare needs but also become a global hub for the production of next-generation medicines – delivering economic growth, high-value jobs, and improved patient outcomes.

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Conflict of interest

Andrew Livingston is the co-founder and Chief Executive Officer of Exactmer Ltd. Daryl Williams is the interim Chief Executive Officer of Orthogonal Peptides Ltd.

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About the Sargent Centre for Process Systems Engineering

The Sargent Centre for Process Systems Engineering is a multi-institutional research centre of world-class departments at Imperial and University College London. It was inaugurated in 1989 by Professor Roger W.H. Sargent, the founding Director of the Centre to his retirement in 1992. Since then, the Sargent Centre has continued the legacy of Professor Sargent and remains a Centre of Excellence.

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