

How the “tides” have turned in pharma manufacturing

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Two seasoned experts from CPI, Medicines Manufacturing Innovation Centre, detail how the “tides” have turned in pharma manufacturing

Oligonucleotides and peptides are two of the fastest-growing pharmaceutical drug modalities with the potential to revolutionise the treatment of many human diseases.

The incredible demand for new type II diabetes and obesity peptide therapies recently launched by Novo Nordisk (semaglutide) and Eli Lilly (tirzepatide) and the acceleration in approvals of oligonucleotide therapies make them a hot topic in the pharmaceutical world.

Whilst pharmacologically very different drug therapies, they are often grouped together (as Tides) due to the similarity in the approach to their manufacture.

Whilst the respective pharma manufacturing processes were discovered decades ago and have undergone extensive optimisation, they both suffer similar problems and pose similar challenges to manufacturers.

Manufacturing Tides:

Complex challenges Manufacturing Tides presents a few complex challenges. Not only is it very hard to reach a final product that meets the standards required to treat patients, but the way we currently manufacture them is quite unsustainable and creates incredible amounts of waste when producing the finished product.

With cycles of multiple chemical reactions required to produce the drugs, the process can involve over 100 chemical steps. Each chemical step requires the use of multiple reagents and, due to the support-filled column approach, the consumption of large volumes of solvent in column washes.

Whilst the chemistry has been highly optimised, due to the complexity and number of chemical steps involved, the product of the synthesis process is significantly below the purity required for a pharmaceutical for human use.

Consequently, Tides are subjected to chromatographic purification, which, because many of the impurities are closely related to the desired product and, therefore, difficult to separate during the chromatography, is challenging and results in poor recovery of the product.

Different pharmaceutical modalities sustainability

So, while the solid-phase pharma manufacturing approach can produce complex, high-quality oligonucleotides and peptides, relative to traditional 'small-molecule' pharmaceuticals, the products are very expensive and have a very poor sustainability.

The American Chemical Society (ACS) Green Chemistry Institute Pharmaceutical Roundtable (GCIPR) has used data collected from multiple pharmaceutical companies to assess the relative sustainability of different pharmaceutical modalities.

The assessment used the relatively crude, but useful measure of process mass intensity (PMI) to compare modalities. PMI estimates the number of kilogrammes of materials consumed to manufacture 1 kg of the product. The chart below shows the average PMI for traditional small-molecule pharmaceuticals (1), oligonucleotides (2) and peptides (3):

Not only is the sustainability profile of the pharma manufacturing process for oligonucleotide and peptide synthesis dramatically worse than traditional small molecules, but the scale of operation is also severely limited by the manufacturing technology.

Improving the pharma manufacturing process for life-altering therapies

Column-based processes rely on a uniform plug-flow of solutions passing through the column to produce consistent chemical reactions or efficient chromatographic separation. To avoid issues of non-uniform flow and column back-pressure, the size of the system is constrained, limiting Tides synthesis to 10-20kg per batch. This compares to small-molecule pharmaceutical synthesis, where batch sizes in the hundreds of kilos are common.

Whilst some approaches are commercially available that partially address some of these challenges, and some peptides (or fragments of) can be made using recombinant microbial methods, the challenge of improving the manufacturing process for these exciting and life-altering therapies to make them available to more patients and reduce their impact on the environment is very real.

Revolutionising Tides therapeutics manufacturing process

At CPI's Medicines Manufacturing Innovation Centre, the challenge of revolutionising the manufacturing process for Tides therapeutics is one of our key focus areas.

Utilising our 'Grand Challenge' model, we have brought together global pharmaceutical companies, academics and entrepreneurial innovators, supported by the UK Government, to develop paradigm-shifting technologies.

We are coordinating efforts to industrialise a liquid phase synthetic approach that would not only allow significant scaling of manufacture, but also more efficient consumption of organic solvent through the use of innovative membrane technology.

We are also exploring radically different methods to produce pure products by fully exploiting the potential of fragment assembly and different approaches to purification. More radical still, we are driving the development of enzymatic synthetic processes that

would completely eliminate organic solvents and significantly simplify the purification process.

Oligonucleotide and peptide manufacturing innovation

The recent creation of the Oligonucleotide Manufacturing Innovation Centre of Excellence, based in CPI's Medicines Manufacturing Innovation Centre, provides a vehicle to coordinate and deliver oligonucleotide and peptide manufacturing innovation, support therapies through clinical trials, and deliver skills development.

We believe that by developing and deploying a range of alternative pharma manufacturing approaches, the sustainability and cost of patient access to oligonucleotide and peptide therapies can be fundamentally changed.

Whilst there is an urgent need and many opportunities to improve the sustainability of oligonucleotide and peptide therapies, comparing the planetary burden of Tides with traditional small-molecule therapies is not as simple as comparing manufacturing. The dosing regimen of oligonucleotide and peptide therapies is significantly different from that of traditional pharmaceuticals.

Where traditional therapies often require medication to be taken multiple times daily, Tide therapies are commonly administered at a frequency of weeks, months, or even longer, and the dose of the active ingredient is often lower. Statins, the traditional small-molecule therapy for reducing LDL cholesterol, are taken daily.

Inclisiran, an oligonucleotide alternative

In contrast, inclisiran, an oligonucleotide alternative, is administered twice yearly. Despite the PMI of an average oligonucleotide being 23 times higher than that of an average small molecule, drug supply for a patient on statins may be less resource efficient than that for a patient on the oligonucleotide inclisiran. A similar picture is obtained if patients receiving traditional metformin therapy for Type II diabetes are compared with semaglutide peptide therapy.

Whilst these analyses are very generic, exclude the drug formulation process, and rely on average PMI data, they show that the comparison at the patient level between the traditional therapies and oligonucleotide or peptide therapies with resource-consuming manufacturing processes can be surprising.

The enormous potential of life-changing new therapies

Further, when opportunities to improve the sustainability profile of oligonucleotide and peptide therapies are delivered, the enormous potential of these life-changing new therapies can be realised while simultaneously reducing healthcare's environmental impact.

References

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CPI's Medicines Manufacturing Innovation Centre

CPI connects the dots within the innovation ecosystem to make great ideas and inventions a reality. We're a pioneering social enterprise that accelerates the development, scale-up and commercialisation of deep tech and sustainable manufacturing solutions.

