Considerations on the Development and Manufacturing of Generic Peptides

The development of generic versions of peptides such as Semaglutide, the drug substance inside Novo Nordisk's blockbuster drugs like Ozempic®, Rybelsus® or Wegovy®, or Tirzepatide, the API in Eli Lilly's Mounjaro®, has emerged as a significant area of interest and opportunity. However, generic companies face critical decisions regarding the choice between recombinant and synthetic semaglutide. The path chosen can significantly impact regulatory approval, safety considerations, and market competitiveness.

The Importance of Generic Competition

GLP-1 agonist drugs were developed to treat Type II Diabetes but became blockbusters after getting approved or prescribed off-label for weight loss. An analysis of electronic health records shared with CNN by Epic Records estimates that around 1.7% of all Americans have been prescribed a semaglutide medication in 2023 alone, reflecting a nearly 40-times increase over the past 5 years. In a Fierce Pharma article published in September 2023, J.P. Morgan's market projection for GLP-1 drugs was of $71 billion by 2032, with Novo and Eli Lilly each accounting for 45% of its sales. Pfizer's CEO Albert Bourla, Ph.D., estimated that the market could reach $90 billion by 2031.

The demand for semaglutide is growing faster than Novo's efforts to build up capacity, creating shortages in the supply-chain and negatively impacting access to Type II Diabetes patients. As of May 2023, Ozempic® and Wegovy® are both listed on FDA's Drug Shortages list. To make it worse, FDA issued a form 483 after inspecting Novo's Clayton facility between July 6 and July 13, 2023, flagging manufacturing shortfalls at the Danish drugmaker's production plant in North Carolina, where Semaglutide API is manufactured for Rybelsus®. In December 2023, the European Medicines Agency issued an announcement on the shortage of Ozempic explaining that "*Increased demand for Ozempic coupled with capacity constraints at some of the manufacturing sites have led to shortages. Although the company is taking mitigating measures, the shortage is expected to worsen in December 2023 and continue throughout 2024. It is uncertain when supplies will be sufficient to fully meet current demand.*" In January 2024, in the UK, the NHS England and the Department for Health and Social Care issued a National Patient Safety Alert to address supply issues with GLP-1 RA medication, stating that "*The global shortage in supply is partly due to a surge in off-label prescriptions of the drug semaglutide being issued for weight loss, which is exceeding supply.*"

Seven out of 10 adults and three out of 10 children in the United States are overweight or obese, according to the Centers for Disease Control and Prevention. Total annual medical costs for obese adults are an average of $1,861 higher than medical costs for people with healthy weight. That amount increases to $3,097 for a severely obese adult. By 2035, half of the world's population – about four billion people – will meet the definitions of being overweight or obese, according to an estimate from the World Obesity Federation. While weight management and sustainable weight loss could drive significant health savings and improved health outcomes, quantifiable results will likely take time.

In the US, without insurance, the average monthly cost of a Mounjaro® (Tirzepatide) prescription to treat Type 2 diabetes is between $1,000 to $1,200. The cost for Rybelsus® oral tablet 3 mg is around $1,029 for a supply of 30 tablets, while a supply of 2 milliliters subcutaneous solution of Wegovy® is around $1,430 and of $1,029 per 1.5 milliliters of Ozempic®. About 60% of adults who are trying to lose weight, and 25% of those who aren't currently trying to lose weight, would be interested in trying a safe and effective weight-loss prescription drug. However, only 16% would be interested in the drug if it was not covered by insurance or available as an affordable generic.

The Good – The key Novo Nordisk patent covering the original recombinant Semaglutide expires in most countries in 2026, while Lilly's Tirzepatide key patent ensures protection from generics until May 2036, giving it another decade of protection. After 2026 the market opens up for generic semaglutide manufacturers to offer bioequivalent alternatives, offering cost savings, increased access to essential therapies, reducing shortages and reducing the risk of illegal and sub-standard/ fake drug sales.

The Bad – When a drug is in shortage, compounders may be able to prepare a compounded version of that drug if they meet certain requirements in the Federal Food, Drug, and Cosmetic (FD&C) Act. However, FDA has received reports that in some cases, compounders may be using salt forms of semaglutide, including semaglutide sodium and semaglutide acetate. The salt forms are different active ingredients than is used the approved drugs, which contain the base form of semaglutide. The agency is not aware of any basis for compounding using the salt forms that would meet the FD&C requirements for types of active ingredients that can be compounded.

The Ugly – When a high value drug is in shortage, criminals take advantage and start selling life-threatening counterfeit versions through the internet and other illegal distribution channels, sometimes even infiltrating the legitimate supply-chain. In December 2023, the USFDA found counterfeit Ozempic (semaglutide) injection 1 mg in the legitimate U.S. drug supply chain and has seized thousands of units of the product. The agency advised wholesalers, retail pharmacies, health care practitioners and patients to check the product they have received and not distribute, use, or sell products labeled with lot number NAR0074 and serial number 430834149057. (for more information visit https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-consumers-not-use-counterfeit-ozempic-semaglutide-found-us-drug-supply-chain).

The Hope – While ANDA full generic versions of the oral drug need to wait further for patent extension expiry dates, the availability of a generic drug substance has the potential to address shortages and immediately opens door to 505(b)2 super-generics, creating opportunities for generic innovation.

Understanding the Differences Between Recombinant and Synthetic Peptides

Glucagon-Like Peptide 1 (GLP-1) agonists, such as Semaglutide, Tirzepatide, Liraglutide or Exenatide, can help regulate blood sugar, slow digestion, and decrease appetite. They can be synthesized through recombinant DNA technology (recombinant peptides) or by solid-phase synthesis (synthetic peptides).

Solid-phase Peptide Synthesis (SPPS) is a widely used method for the chemical synthesis of peptides. In SPPS, the peptide chain is assembled step by step on a solid support matrix, typically a resin bead. The process begins with the attachment of the C-terminal amino acid to the resin, followed by sequential addition of protected amino acids. Each amino acid is activated with coupling reagents to facilitate its attachment to the growing peptide chain. After each coupling step, the unreacted amino groups are capped to prevent unwanted side reactions. Cleavage of the fully assembled peptide from the resin and removal of side-chain protecting groups yield the desired peptide product. Historically, dichloromethane (DCM) was used as a solvent for solid phase synthesis as the kinetics of amino acid activation and amine coupling were much more favorable. However, solubility concerns, particularly for Fmoc-protected amino acids limited the utility of the solvent. Nowadays, dimethylformamide (DMF), N,N-dimethylacetamide (DMA) and N-methylpyrolidone (NMP) are the three principal solvents for both microwave assisted and room temperature solid phase peptide synthesis.

Recombinant peptide synthesis involves the production of peptides through genetic engineering techniques, typically utilising host organisms such as bacteria, yeast, or mammalian cells. These organisms are cultivated in aqueous growth media containing nutrients, salts, and other essential components required for cell growth and protein expression. The recombinant peptides are produced intracellularly or secreted into the culture medium, where they can be harvested and purified through various downstream processes. Therefore, while organic solvents may be used in purification steps such as chromatography, their use in the actual manufacturing process is minimal compared to chemical peptide synthesis methods, making it much more sustainable. In the recombinant process, genes encoding the desired peptide sequence are inserted into the host organism's genome, leading to the production of recombinant proteins, which are then cleaved to yield the target peptide. Recombinant peptide synthesis offers several advantages, including precise control over peptide sequence, high purity, and scalability. Furthermore, this method allows for the incorporation of post-translational modifications and facilitates the production of peptides that may be challenging to synthesize using traditional chemical methods.

Regulatory Considerations

Regulatory agencies are issuing guidance on the development and manufacturing requirements for approval and market entry of generic peptides. Some generic companies may be enticed to expedite their development process by leveraging the USFDA's Guidance for Industry on "ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin." This guidance offers a waiver for clinical validation using the fully synthetic pathway.

However, it's essential to recognise the potential challenges associated with using the waiver when filling an ANDA with a significantly different fully synthetic peptide route. Those using the 'shortcut' may expect to receive a thick Complete Response Letter (CRL) requesting evidence that new specified peptide-related impurities, even if present in concentrations below 0.5% of the drug substance, do not compromise the safety or effectiveness compared to the recombinant peptide RLD. Such evidence typically requires extensive biological evaluations, as outlined in the "Sameness Evaluations in an ANDA – Active Ingredients" Draft Guidance for Industry.

The use of generic recombinant peptides offers a compelling alternative, reducing risk by mirroring the manufacturing approach used by innovators. By adopting the appropriate

recombinant process for their generic peptide, companies benefit from a demonstrated similar impurity profile, thus reducing the risk of immunogenic reactions stemming from newly specified peptide-related impurities.

Patient and Healthcare Providers Perspectives

Type II Diabetes patients and other patients in need of weight loss treatment look forward to the end of the drug shortage. However, both patients and healthcare providers may express concerns about switching between recombinant originator and fully synthetic generic products, particularly in chronic or life-threatening conditions where treatment consistency is paramount. Therefore, the availability of affordable generic recombinant peptides reduces questions about safety, efficacy, and therapeutic interchangeability. Like in any other drug in the market, robust pharmacovigilance and post-marketing surveillance mechanisms are essential to monitor and address any potential safety issues associated with generic substitutions.

Health Economics and Sustainability

The adoption of generic recombinant peptides has significant implications for health economics and affordability as well as for sustainability. Generic competition has the potential to reduce healthcare expenditures, particularly in disease areas with high treatment costs. However, the realisation of cost savings depends on factors such as market dynamics, pricing strategies, insurance plans and reimbursement policies, and patient access

pathways. Policymakers and healthcare stakeholders must strike a balance between promoting competition and ensuring economically sustainable access to essential therapies.

From an environmental sustainability perspective, a recombinant process offers significant environmental advantages over a fully synthetic process, often replacing tens of chemical reactions with huge volumes of organic solvents and toxic chemical reagents that end up as waste streams by a single step of aqueous media fermentation. As such, generic pharma companies with sustainability goals can only take the recombinant process pathway.

Conclusion

The development and approval of generic versions of peptides such as Semaglutide and Tirzepatide is a focus and evolving aspect of today's pharmaceutical industry. While generic competition holds promise in enhancing affordability, expanding patient access, and stimulating innovation, it also presents challenges related to regulatory requirements, market dynamics, patient safety, health economics and sustainability. A balanced approach that prioritises scientific rigour, regulatory oversight, patient-centricity, and healthcare sustainability is essential to realise the full potential of generic recombinant peptides while safeguarding public health and promoting therapeutic innovation. As the landscape continues to evolve, collaboration between stakeholders across the healthcare ecosystem will be critical in navigating the complexities and opportunities associated with generic peptides. Embracing the right strategic approaches to generic development will be paramount in driving success and facilitating access to affordable, high-quality and sustainable therapeutics for patients worldwide. Selecting regulatory savvy and cGMP inspected manufacturers to produce the API with the appropriate recombinant process is key to success.

Rafael Antunes

Rafael Antunes is the Vice President of Business Development of Aurisco Pharmaceutical in Europe. He has over 20 years of Pharma Industry Experience, working in International European and Chinese, Generic and CDMO companies. Broad experience in multiple roles in Process Chemistry R&D, Tech-Transfer, Scale-up, Pilot-Scale and Commercial cGMP Manufacturing, Procurement, Management, Product Development and Licensing and Business Development. Strong Scientific and Business Management backgrounds and relevant HSE, Quality and Regulatory experience. Has been a qualified cGMP and ISO14001 auditor and participated as industry representative in RX360 and EFCG (European Fine Chemicals Group – a pharma industry CDMO lobby group, member of the broader European Chemical Industry Council (CEFIC). It has represented the EFCG at USFDA GDUFA II implementation meetings and Regulatory Science meetings. Championed the adoption of Science Based targets (SBTi), Ecovadis Sustainability ranking and joined the Sustainable Procurement Pledge (SPP).