GRACE

Enhance Peptide Innovation With A High-Quality Supply Of Building Blocks

By Brian Graves, Global Business Manager, Grace Fine Chemical Manufacturing Services

The global peptide drug market continues to surge thanks to the unique offerings of these innovative therapeutics, including high selectivity and high specificity. Peptide therapeutics are composed of amino acid chains that can be designed to target specific indications, including metabolic diseases, neurological disorders, and cancer.[1] Amid this growing boon of therapeutic advances, the peptide market is forecasted to exceed $101.7 billion by 2033.[2]

Most recently, the key contributors to this growth are semaglutide and tirzepatide, glucagon-like peptide-1 (GLP-1) receptor agonists that have been FDA approved for the treatment of type 2 diabetes and obesity.[3] Both semaglutide and tirzepatide are administered via once-a-week injections, which can be costly for patients and challenging for drug sponsors working to guarantee market supply. As demand for these drugs has rapidly accelerated, some sponsors have been working to develop more accessible and affordable solutions for patients, including oral dosage formulations or peptides that are designed to require less frequent dosing.

One emerging option for adapting peptide compounds to increase their potency and elongate their half-lives is the usage of non-canonical amino acids (ncAAs), small peptides, and specialized peptide building blocks to engineer peptide therapeutics with differentiating functionality. If you are considering leveraging ncAAs or other complex peptide building blocks in the manufacture of your therapeutic, it is critical to develop a manufacturing plan and establish partnerships early to avoid potential delays or pitfalls as a program advances through development toward commercialization.

The Benefits Of Unique Peptide Building Blocks

There are 20 canonical amino acids found in the human body.[4] Natural peptides are made up of chains of amino acids joined by amide bonds that can be easily hydrolyzed or destroyed by enzymes in vivo.[5] As a result, peptides composed strictly of canonical amino acids can have short half-lives and fast elimination in vivo, and peptide therapeutics composed solely of these amino acids may require high-frequency, expensive dosing regimens with formulations that necessitate injectable drug delivery.

To expand the possibilities of peptide therapeutics, many drug sponsors use ncAAs to engineer unique properties by introducing novel chemical functionalities not found in naturally occurring amino acids. ncAAs and other unique peptide building blocks offer novel properties that can potentially increase the half-life of peptide drugs, enhance their potency, and improve oral consumption. Novel peptides like cyclic or stapled peptides can be used to help the structure better access binding sites on the cells, allowing the therapeutic to increase uptake within the body. If a therapeutic is adapted to demonstrate an increased half-life in the body, dosing regimens could be modified or reduced, creating more affordable and accessible options for patients.

With the possibilities presented by novel peptide building blocks, many drug sponsors are seeking approaches that allow for therapeutic optimization to improve the patient experience and the efficacy of their drugs. However, for drug sponsors exploring this route, the novelty of these building blocks is important to consider.

The Manufacturing Challenges Of Unique Peptide Building Blocks

Due to the novelty of ncAAs and other building blocks, there are inherent challenges to manufacturing these materials. In many cases, they may require a longer synthesis path, resulting in a longer development cycle that sponsors will need to consider when planning manufacturing timelines. Additionally, some suppliers of more traditional peptide building blocks may not be adept at or capable of producing ncAAs or other novel peptides at large scales.

ncAAs and novel peptide building blocks may also fall under different regulatory classifications than more traditional functionalized amino acid derivatives. For instance, these building blocks may be considered GMP intermediates that would need to be manufactured under GMP conditions, which may exclude some non-GMP manufacturers from consideration. Additionally, depending on which country's regulatory requirements must be met, compliance expectations for such materials could differ widely.

Beyond considering development timelines and regulatory compliance, the manufacturing processes for ncAAs and unique peptide building blocks require a level of expertise that may not be easily found among suppliers across the industry. If your team is hoping to leverage unique peptide building blocks, it is vital to identify a capable partner with experience developing and producing advanced amino acid and peptide derivatives at the scale and level of compliance that will be required for your peptide program. Conducting due diligence to procure a building block supplier that is skilled in novel amino acid chemistry will help ensure a steady supply of raw materials at the intended scale.

How To Identify A Reliable Amino Acid Supplier

As you search for a reliable supplier, prioritize the key attributes detailed above to help navigate any manufacturing obstacles that could arise. First and foremost, identify a partner with robust expertise and experience in chemical development; this is vital to ensure that they will produce your target compound with high quality while controlling impurities. A knowledgeable partner will have ample insight into what manufacturing approaches work well and which tried and true problem-solving techniques to turn to; this will help them efficiently troubleshoot any issues that might arise. Beyond that, confirm a partner can provide your materials at the necessary scale to accommodate clinical and/or commercial manufacture.

To assess a partner's regulatory knowledge and experience, ask how they have maintained compliance with global health authority regulations in the past and whether they have in-house regulatory experts to guide this process. Consider which technologies they have available to determine if their analytical toolkit will accommodate your molecule. Peptide building blocks generally contain at least one chiral center as well as a variety of substance-related impurities. A partner will need to have experience conducting chiral and chemical separations via liquid chromatography-mass spectrometry (LCMS) and nuclear magnetic resonance (NMR) spectroscopy to ensure proper characterization of the target compound and all necessary in-process controls. Often, these compounds may have different crystal polymorphs, which require solid state analytical capabilities such as X-ray powder diffraction (XRPD).

A partner should demonstrate robust experience identifying the impurities within a compound as well as the ability to minimize, control, and/or purge them.

Beyond assessing their technological offerings, there are a number of ways to vet prospective partners, including:

- **Schedule a visit to their facilities** to meet the teams you would collaborate with in person. This will help you determine whether this supplier is a reliable fit for the scope of your program.
- **Ask suppliers for references from their previous clients.** Touching base with sponsors they have worked with in the past will help you determine if this team is well-equipped to take on the challenges and specifics of your program.
- **Assess their process and analytical development experience.** A partner with ample previous experience will have the skills necessary to identify potential problems early in the process that can be avoided prior to scale-up. This will save significant time and money throughout development.

Though no two development timelines will be identical, if you are hoping to leverage ncAAs or other unique building blocks, find a partner as early in your process as possible to secure a timely, consistent delivery of supply down the road.

The Long And Short Of It

Unique peptide building blocks can yield a variety of benefits for your therapeutic, including extended half-life, increased potency, and improved patient experience. When leveraging these materials, it is crucial to come up with a robust manufacturing plan early to ensure a continuous supply of high-quality materials. A vital component of this plan is identifying an experienced chemical material manufacturer that will produce the necessary unique building blocks with quality, efficiency, and compliance in mind.

References

1. *Yahoo! Peptide therapeutics market surges towards USD 101.7 billion by 2033 | analyzing growth in therapeutic innovations and disease management. Yahoo! Finance. https://finance.yahoo.com/news/peptide-therapeutics-market-surges-towards-095600592.html*
2. *Peptide therapeutics market. Market.us. (2024, January 31). https://market.us/report/peptide-therapeutics-market/*
3. *Farzam K, Patel P. Tirzepatide. [Updated 2024 Feb 20]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK585056/*
4. *Lopez MJ, Mohiuddin SS. Biochemistry, Essential Amino Acids. [Updated 2024 Apr 30]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK557845/*
5. *Wang, L., Wang, N., Zhang, W. et al. Therapeutic peptides: current applications and future directions. Sig Transduct Target Ther 7, 48 (2022). https://doi.org/10.1038/s41392-022-00904-4*

About the Author

Brian Graves is a Global Business Manager for Grace's Fine Chemical Manufacturing Services (FCMS) business. He has 30 years of experience in the pharmaceutical and chemical industries, more than a decade of which has been focused on the development and production of amino acid derivatives. A graduate of Augustana College in Rock Island, IL, with degrees in chemistry and physics, Brian's past experiences include Aldrich Chemical Company, Cedarburg Pharmaceuticals, Synthetech, Genentech and Jubilant HollisterStier.

About Grace Fine Chemical Manufacturing Services

Grace's Fine Chemicals Manufacturing Services (FCMS) is a leading North American CDMO and a full-service provider of fine chemicals to the world's leading companies across the pharmaceutical, agrochemical, and specialty materials markets. Grace FCMS helps global customers complete successful projects through a powerful combination of proven chemistry expertise, game-changing process development, high-quality custom manufacturing and exceptional service. Our strategically located facilities in South Haven, MI, and Tyrone, PA, enable us to be a fully integrated domestic partner for the development and manufacture of regulatory starting materials (RSMs), intermediates, and custom active pharmaceutical ingredients (APIs). From innovative R&D to commercial-scale production, we deliver the knowledge, experience, resources and service needed to move products to market faster and accelerate business. For more information, visit **grace.com/finechemicals**

GRACE