Driving Sustainable Innovation in Peptide API Manufacturing

GREEN, LEAN & CLEAN:

25 years of green peptide chemistry at Aspen API

November 2025

Introduction

The global pharmaceutical industry is undergoing a profound transformation, driven by the rise of biologics, personalized medicine, and targeted therapies. Among these, peptide-based drugs have emerged as a powerful class of therapeutics, offering high specificity, low toxicity, and the ability to modulate complex biological pathways. Peptide-based therapies are increasingly recognized for their ability to offer targeted and often more tolerable treatment options compared to traditional small-molecule drugs. This surge in interest has led to an unprecedented expansion of the global peptide API (Active Pharmaceutical Ingredient) market, which is now poised to become one of the most dynamic segments in pharmaceutical manufacturing. Valued at approximately $9.2 billion in 2023, the peptide API market is projected to exceed $94 billion by 2034, reflecting a compound annual growth rate (CAGR) of over 22%. The expansion of the peptide API market is further fueled by the increasing prevalence of chronic diseases such as diabetes, obesity, and cardiovascular conditions.

However, this rapid growth also brings with it a host of challenges that manufacturers must address to meet the evolving demands of the industry, including scalability, cost-efficiency, quality control, and environmental impact. Aspen API addresses these challenges through its advanced manufacturing technologies. With over 60 years of experience in peptide manufacturing and a proven track record of uninterrupted supply, Aspen API combines in-depth expertise with strategic partnerships to deliver innovative, efficient, and sustainable solutions to the pharmaceutical industry. Its facilities are equipped to handle complex transformations, high-potency compounds, and stringent quality standards, making it a trusted partner for pharmaceutical companies worldwide. As a mid-size company, Aspen API guarantees full customer focus and offers a one-stop shop as CDMO and partner from lab to commercial production, covering analytical development, process development, and registration. Additionally, Aspen Pharmacare's global network offers comprehensive capabilities for the development and manufacturing of Finished Dosage Forms (FDF), ensuring seamless integration from API to final product.

GREEN CONTINUOUS LPPS

25 years of refinement

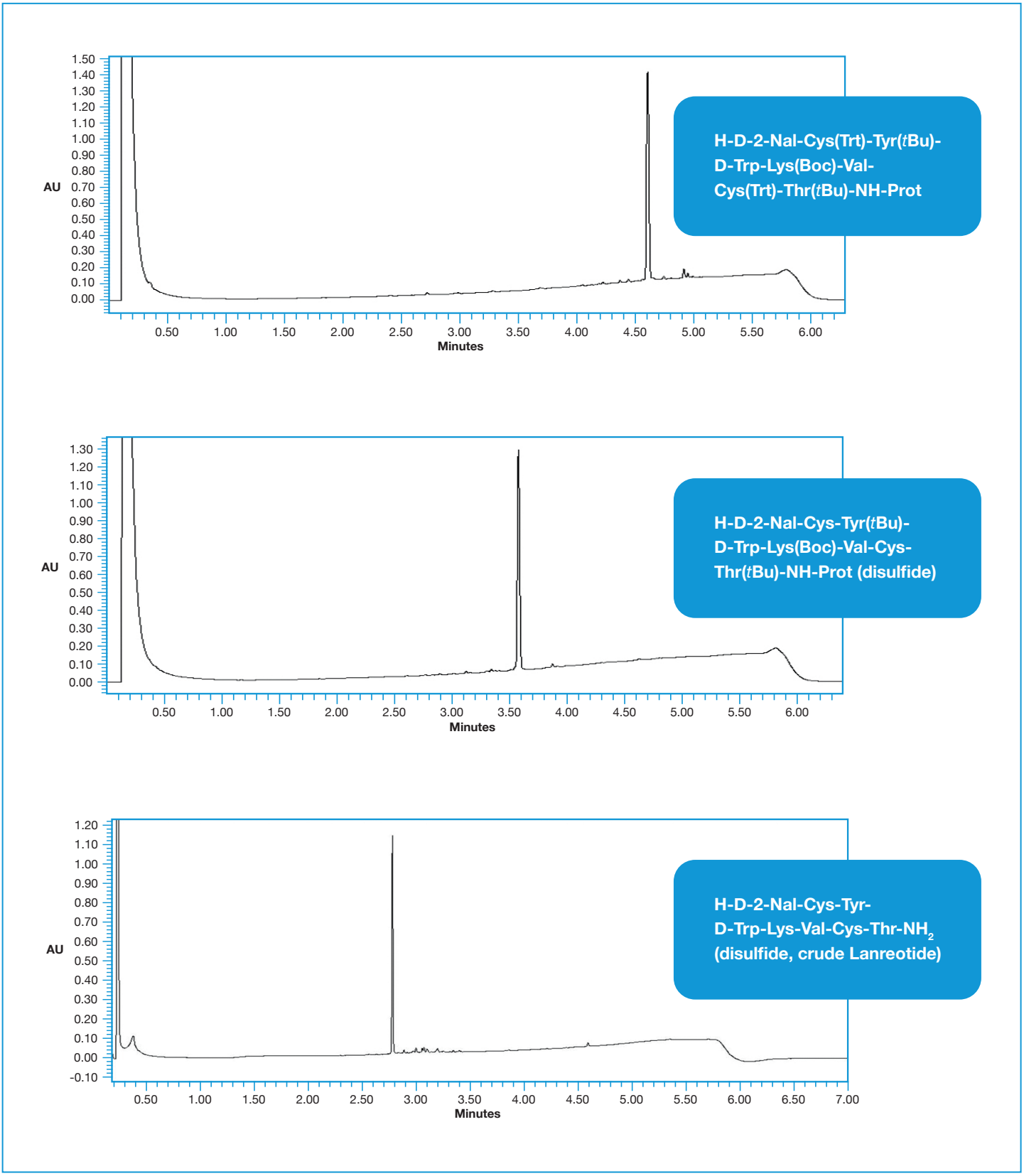
Twenty-five years ago, Aspen API's predecessor company Diosynth pioneered the Green Continuous Liquid-Phase Peptide Synthesis (GREEN CONTINUOUS LPPS) method, originally known as DioRaSSP - Diosynth Rapid Solution Synthesis of Peptides. This method combined the advantages of the homogeneous character of classical liquid-phase synthesis with the continuous character inherent to the solid-phase approach – "the best of both worlds". Aspen API has consistently applied and optimized this method for the commercial-scale manufacturing of peptide APIs, such as Leuprolide, since its inception. It offers numerous benefits, including standardized protocols, high robustness and quality control, improved scalability, reduced solvent usage, and generally enhanced sustainability. This innovative approach to peptide synthesis has positioned Aspen API as a leader in continuous solution-phase synthesis. While competitors are now introducing similar continuous methods in solution, Aspen API maintains a significant advantage with more than two decades of experience, during which the GREEN CONTINUOUS LPPS method has been continuously refined to deliver consistent quality and high efficiency, setting a benchmark for sustainable peptide manufacturing. The method enables efficient synthesis of peptides and peptide fragments with minimized environmental impact and optimized resource utilization.

In the GREEN CONTINUOUS LPPS method, the growing peptide is essentially anchored in a permanent organic phase, generally ethyl acetate, by means of its hydrophobic C-terminal and sidechain protecting groups. A synthesis according to the GREEN CONTINUOUS LPPS protocol is completely homogeneous and its intermediates are not isolated. Excess reagents and byproducts are intermittently removed by aqueous extractions. No organic waste streams are generated during the performance of the synthesis, thus resulting in a drastic reduction of organic waste streams with respect to classical SPPS protocols. Moreover, reprotoxic solvents *N,N*-dimethylformamide (DMF) and N-methylpyrrolidin-2-one (NMP) are substituted by one of the greenest solvents available, ethyl acetate.

One cycle of the GREEN CONTINUOUS LPPS protocol consists of a coupling step, quenching of residual activated carboxylic compound – resulting in the avoidance of insertion sequences - and deprotection of the N-terminal amino function with intermittent aqueous extractive work-up steps. The choice of the temporary amino protecting group offers flexibility in the GREEN CONTINUOUS LPPS protocol, including the Cbz (benzyloxycarbonyl), Fmoc (9-fluorenylmethyloxycarbonyl), and combined approaches, and can be tailored to the specific peptide sequence. On account of the homogeneous character, full quality control by *e.g.*, UHPLC in every step of the synthesis is guaranteed, whereas coupling reagents and amino acid derivatives may be applied in low molar excesses.

Aspen API has recently added Difelikefalin, Goserelin and Lanreotide to its generic development portfolio of peptides prepared according to GREEN CONTINUOUS LPPS. The high level of quality control is exemplified by the UHPLC chromatograms of Lanreotide intermediates as depicted in Fig. 1.

Figure 1: UHPLC chromatograms of Lanreotide intermediates according to GREEN CONTINUOUS LPPS (Prot = amide protecting group).



GREEN SPPS

Introducing new technology

In addition to GREEN CONTINUOUS LPPS, Aspen API has recently introduced its own Green Solid-Phase Peptide Synthesis (GREEN SPPS) method. This approach replaces reprotoxic solvents like DMF with greener alternatives such as ethyl acetate and DMSO. It also reduces the number of washing steps, lowers excesses of amino acid derivatives and reagents, and employs greener reagents. Peptide-specific optimizations minimize reaction times, resulting in a more sustainable and efficient synthesis process. These enhancements not only improve environmental sustainability but also contribute to leaner and more cost-effective manufacturing processes. GREEN SPPS once more underlines Aspen API's commitment to innovation and environmental stewardship.

GREEN, LEAN & CLEAN

Aspen API's dual green synthesis platforms - GREEN CONTINUOUS LPPS and GREEN SPPS -embody the principles of GREEN, LEAN & CLEAN manufacturing (Fig. 2). GREEN reflects the use of environmentally friendly solvents and reagents in optimized quantities, LEAN emphasizes process efficiency and resource optimization, and CLEAN ensures high purity and compliance with stringent quality standards. These platforms enable Aspen API to meet the growing demand for peptide APIs while maintaining a strong commitment to sustainability and operational excellence.

Figure 2: Aspen API's dual green synthesis platforms for peptides: GREEN CONTINUOUS LPPS and GREEN SPPS.

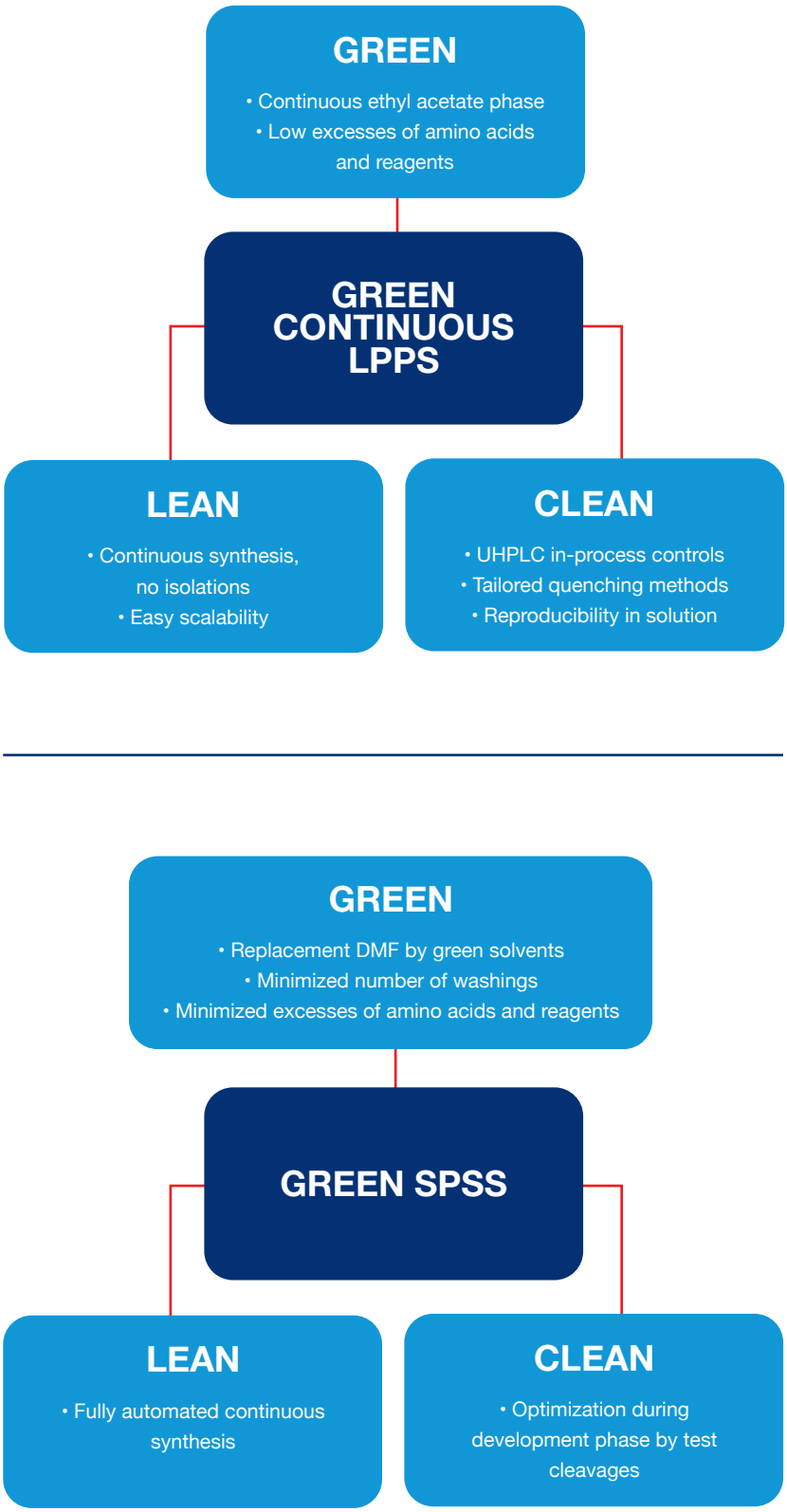


Table 1 compares the Process Mass Intensity (PMI) of GREEN CONTINUOUS LPPS and GREEN SPPS methods with classical SPPS for the synthesis of an exemplary decapeptide fragment, further demonstrating the advantages of Aspen API's dual green synthesis platforms in terms of solvent usage, reagent efficiency, and waste reduction.

Table 1: Comparison of Aspen API's GREEN CONTINUOUS LPPS and GREEN SPPS methods with classical SPPS in terms of sustainability impact.

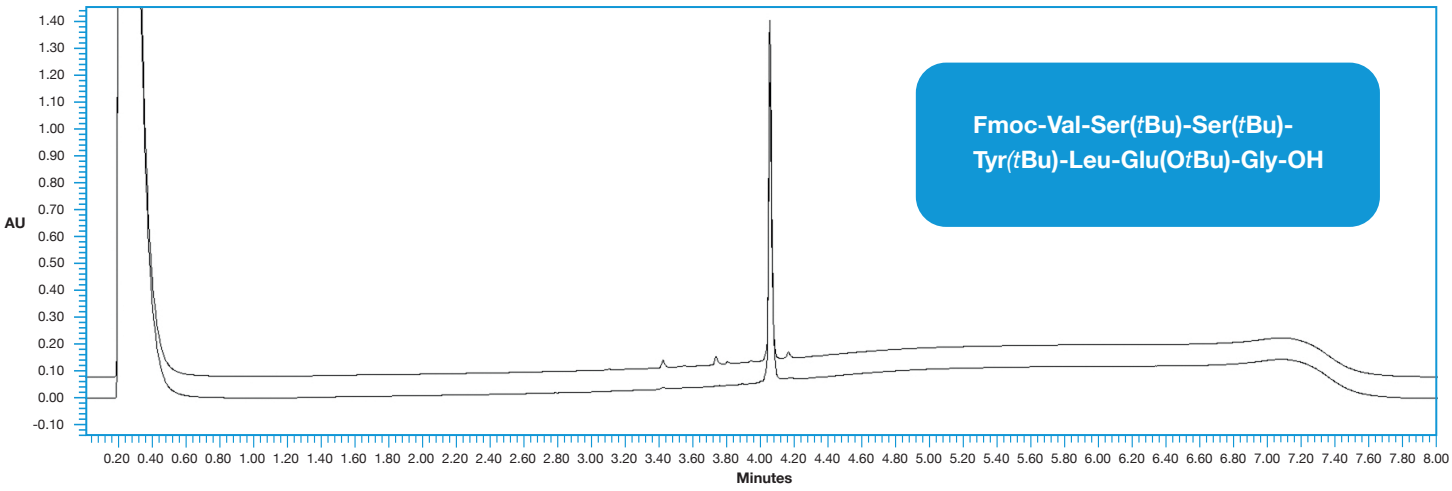
Synthesis method	PMI (kg/kg)	PMI reduction	Typical solvents
Classical SPPS	1561	Ref.	DMF, isopropanol
GREEN SPPS	648	58%	Ethyl acetate, DMSO
GREEN CONTINUOUS LPPS	186	88%	Ethyl acetate, water

Application of Aspen API's dual green synthesis platforms in the manufacturing of long peptides

Aspen API's leadership in peptide manufacturing is not only rooted in its decades of experience, but also in its proactive approach to innovation and sustainability. As the global demand for peptide APIs continues to surge, driven by the success of GLP-1 receptor agonists and other peptide-based therapeutics, Aspen API remains at the forefront of this transformation. The rapidly increasing demand for longer peptides in the range of 30-40 amino acids presents significant challenges in terms of manufacturing efficiency and environmental sustainability. To address these complexities, the industry is shifting from classical SPPS protocols toward hybrid manufacturing strategies, in which shorter fragments of 10-20 amino acids, produced either in solution or on solid phase, are combined to yield the desired longer sequences. Aspen API's dual green synthesis platforms, GREEN CONTINUOUS LPPS and GREEN SPPS, are ideally suitable for the purpose of generating the (protected) fragments in a highly efficient and sustainable way.

To illustrate the effectiveness of Aspen API's green synthesis methods, consider the synthesis of Semaglutide (11-17) fragment for use in hybrid manufacturing strategies. In initial lab feasibility studies according to GREEN CONTINUOUS LPPS and GREEN SPPS, the protected fragment Fmoc-Val-Ser(*t*Bu)-Ser(*t*Bu)-Tyr(*t*Bu)-Leu-Glu(O*t*Bu)-Gly-OH was obtained in *unoptimized* yields of approx. 70% in both approaches. UHPLC chromatograms of the products from both syntheses (Fig. 3) show purities exceeding 97.5 a/a%, after correction for trace amounts of dibenzofulvene (from Fmoc cleavage) and minor impurities resulting from *t*Bu cleavage during the final mild acidolysis step (removing the temporary C-terminal protecting group) in the GREEN CONTINUOUS LPPS process. This example highlights the flexibility and capability of Aspen API's dual green synthesis platforms to deliver intermediates for complex peptide APIs with superior performance and sustainability.

Figure 3: UHPLC chromatograms of protected Semaglutide (11-17) fragment according to GREEN CONTINUOUS LPPS (upper plot) and GREEN SPPS (lower plot).



Conclusion

Strategic partnerships further enhance Aspen API's capabilities. By collaborating with academic institutions, technology providers, and pharmaceutical companies, Aspen API stays at the cutting edge of peptide science and manufacturing innovation. These partnerships facilitate knowledge exchange, accelerate process development, and support the commercialization of novel peptide therapeutics.

As a mid-size company, Aspen API offers a unique value proposition: personalized focus and agile responsiveness. Clients benefit from direct access to technical experts, customized solutions, and transparent communication throughout the project lifecycle. Aspen API's integrated service model - from laboratory development to commercial production - ensures seamless execution and timely delivery of high-quality peptide APIs.

In conclusion, Aspen API stands as a leader in peptide API manufacturing, distinguished by its commitment to sustainability, efficiency, and quality. Through its pioneering GREEN CONTINUOUS LPPS and GREEN SPPS methods, Aspen API delivers GREEN, LEAN & CLEAN solutions that address the challenges of modern peptide production. With a proven track record, robust infrastructure, and customer-centric approach, Aspen API is well-positioned to support the pharmaceutical industry's evolving needs and drive the future of peptide therapeutics.

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