

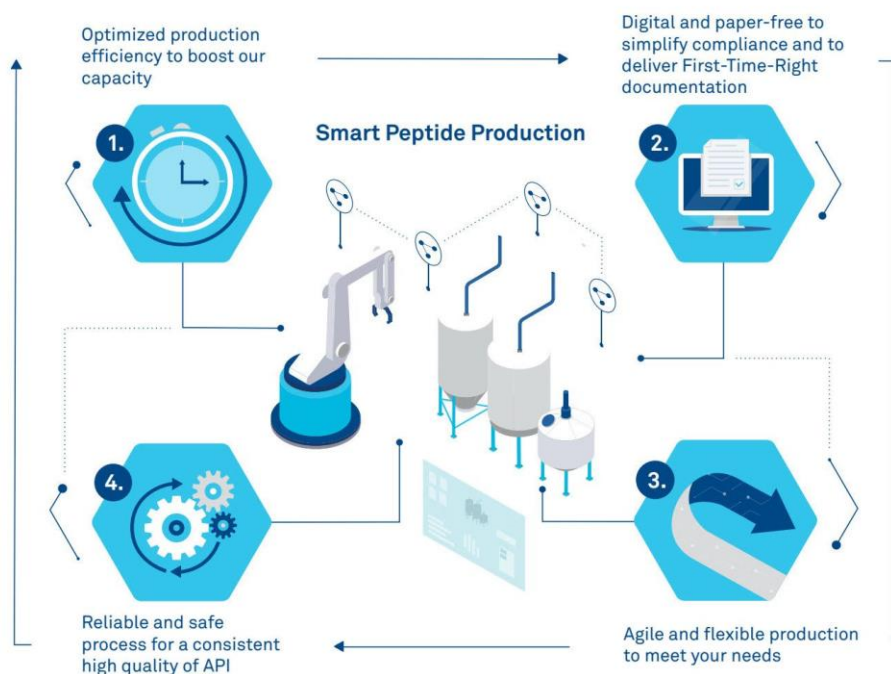
# Innovative Approaches for Large-scale Peptide Production

[Peptides](#) have the potential to expand the space of “druggable” targets. No wonder the number of them being under investigation in clinical trials or used as therapeutics is growing. This is accompanied by an increasing need to produce them efficiently and cost-effectively. However, large-scale manufacturing of these active pharmaceutical ingredients (APIs) involves many challenges from decreasing yields when synthesizing molecules with more building blocks to the enormous amounts of solvents needed for synthesis and purification. The only way to make the chemical production of these APIs more efficient and sustainable is to bring new solutions for all steps of the manufacturing processes. This can be achieved either through process optimizations or by using new innovative technologies.

There are a variety of ideas and solutions to tackle these challenges. We would like to share a few examples where we have first-hand experience:

## 1. Automation of SPPS

Implementation of a new level of automation and digitalization of solid-phase peptide synthesis (SPPS) to meet the predicted rise in demand for capacity and compliance.



## Benefits of SPPS Automation:

- Automation and digitalization are increasing our capacities with more flexible, reliable, and scalable manufacturing processes delivering consistently high-quality API.
- Thanks to our full automation of the SPPS process we can optimize equipment usage and reduce operating times.
- Full digitalization of the SPPS process allows for paperless documentation, improved first-timeright rates, data analytics and improved data safety and integrity.
- Our GMP documentation has been simplified and improved.

## 2. Molecular Hiving™ Technology

Produce shorter peptides without hazardous solvents, with more efficient scale-up and enhanced process controls using Molecular Hiving™ technology. Fewer washing and filtration steps are needed compared to classic peptide synthesis, resulting in a reduction of up to 60% in the use of organic solvents.

### Benefits of Molecular Hiving™:

- This is a CMR free process by which peptides can be synthesized without the use of DMF, NMP, or any other hazardous solvents and reagents.
- There is a significant reduction in solvent consumption compared to SPPS processes, and to traditional peptide synthesis in solution (LPPS).
- Compared to SPPS, fewer equivalents of Fmoc [amino acid derivatives](#) and coupling reagents are required.
- Direct in-process control is possible, e.g., by HPLC.

## 3. Chemo-enzymatic Peptide Synthesis (CEPS)

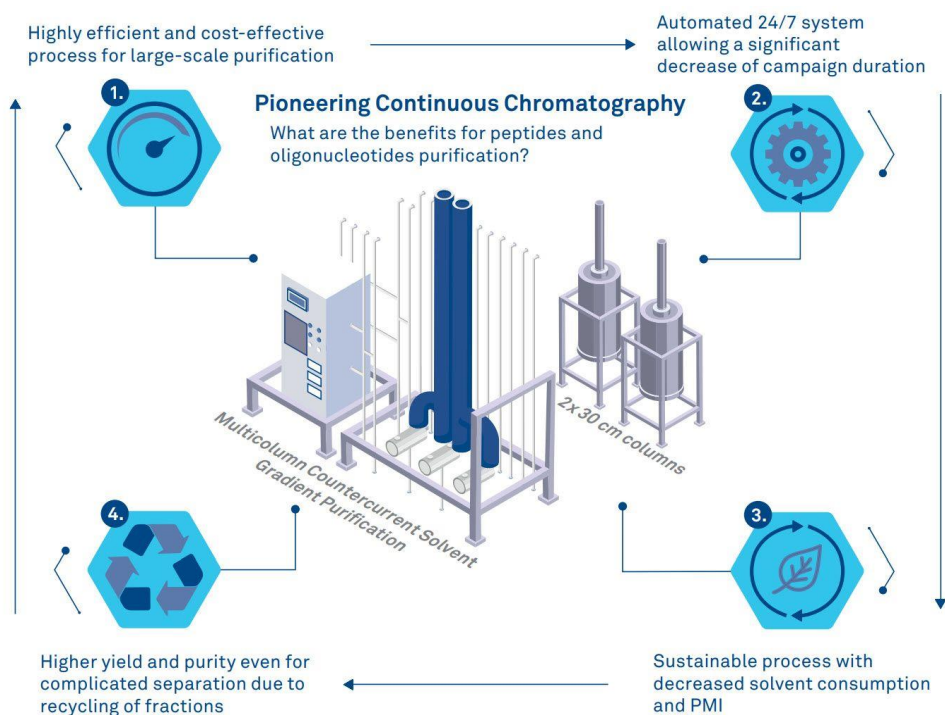
Using CEPS for the production of larger peptides with more than 40 amino acids or even the production of small proteins. Peptilgase enzymes offer a scalable alternative for large-scale manufacturing and enable a more economical manufacturing not only of large linear peptides but also of cyclic peptide drugs and (bio)conjugates. We are investigating this together with our partner EnzyTag.

Benefits of CEPS:

- CEPS enables the regio- and stereoselective synthesis of peptides that cannot be (efficiently) manufactured by stepwise SPPS.
- In combination with SPPS long peptides with more than 40 amino acids and cyclic peptides with more than twelve amino acids can be made in high purity.
- Protection of side-chain functionalities is not necessary, as side reactions and racemization are absent.

#### 4. Multi-column Countercurrent Solvent Gradient Purification (MCSGP)

Purification can be a bottleneck in the production of peptides and oligonucleotides because of the enormous amounts of solvents involved. We addressed this challenge with incorporation of MCSGP into the downstream process and set up the first continuous chromatography system for center cut purification of peptides and oligonucleotides at industrial scale. Compared to single-column batch purification, solvent consumption is typically decreased by over 30%, thus contributing to a higher level of sustainability. The process has a higher capacity and often reaches the target product purity often with a higher yield, typically 10% more.



Benefits of MCSGP:

- Increases the capacity, quality, and sustainability of the purification process.
- It is a scalable, highly efficient technology, that is particularly useful for large-scale production.
- Using an automated system, it can run 24/7, allowing a significant decrease in purification campaign cycle times.
- More sustainable purification is possible with MCSGP, as it reduces solvent consumption and process mass intensity.
- It deploys standard chromatographic conditions, and API quality is not adversely affected by changing from batch mode to continuous mode

The last three innovations (Molecular Hiving™, CEPS and MCSGP) mentioned are examples of our green chemistry success stories.

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### **About Bachem**

Bachem is a leading, innovation-driven company specializing in the development and manufacture of peptides and oligonucleotides.

With over 50 years of experience and expertise Bachem provides products for research, clinical development and commercial application to pharmaceutical and biotechnology companies worldwide and offers a comprehensive range of services.

Bachem operates internationally with headquarters in Switzerland and locations in Europe, the US and Asia. The company is listed on the SIX Swiss Exchange.