

INNOVATION TRANSFORMING OLIGONUCLEOTIDE MANUFACTURING

One of Bachem's [mission](#) is to provide excellence to its customers and be a major player in their success. To achieve this, we are constantly advancing our technologies and manufacturing processes. Throughout the years, we have developed technical leadership, which positions Bachem as a leading contract development and manufacturing company (CDMO) for peptide and oligonucleotide manufacturing. Therefore, [innovation](#) is a cornerstone of Bachem's success. We work with passion and dedication to support our customers in achieving breakthrough medical advances that will significantly transform the life of patients. Bachem has successfully invested in a capacity expansion for large-scale production of [oligonucleotide](#) active pharmaceutical ingredients (APIs). In our manufacturing processes, we optimize all steps with innovative solutions in order to deliver the highest quality and operate as sustainably as possible. Thus, we have set up unique, innovative equipment that optimizes capacity, delivers high-quality products and increases sustainability, while maintaining process safety and efficiency for our large-scale oligo manufacturing.

This article will highlight our innovative equipment designed with unique features in the oligonucleotide industry. Large-scale manufacturing capacity is available, and we are working on multiple customer development programs. Thus, Bachem is ready to tackle your projects!

INCREASING CRUDE QUALITY: OUR TAILOR-MADE OLIGONUCLEOTIDE SYNTHESIZER

At Bachem, we strive to provide the highest quality oligonucleotide to customers. To this end, we have designed and customized a large-scale oligonucleotide synthesizer with innovations that improve and optimize the process of oligonucleotide synthesis. The synthesizer has been qualified for GMP batches from 0.2 mol to 2 mol scale.

One of the novel engineering solutions for our synthesizer is in-line mixing of dichloroacetic acid (DCA) and toluene. DCA-toluene solution is used as the first step for all coupling cycles of oligonucleotide synthesis, deprotecting the 5'-dimethoxytrityl (DMT) group and releasing the 5'-hydroxy group in order to perform the coupling reaction. However, on most synthesizers the percentage of DCA in toluene is fixed. With our new skid there is the possibility to change the ratio of DCA in toluene. Typical operating ranges are from 3% up to 10% or even higher. Changing the concentration of DCA can be beneficial, as repeatedly using too much DCA during the synthesis is risky. This can bring undesired side-reactions and eventually decrease API quality. We customized our synthesizer with in-line mixing of DCA to adjust to the needs of the deprotection solution throughout the synthesis. This innovation enables the right amount of DCA to be transferred and avoids side reactions, providing a higher crude API quality.

In addition to in-line mixing of DCA, we have introduced other customizations to further control and optimize oligonucleotide synthesis. A heat exchanger has been set up to ensure full temperature control to reach the optimum conditions for the deprotection and coupling steps. This temperature control will minimize side reactions and ultimately optimize the yield and quality of the crude oligonucleotide API. A third example for tailor-made innovative features of our synthesizer is dynamic axial columns (DAC) containing a piston that can move throughout each synthesis cycle of the process. The presence of an adaptable piston enables full control of the column's volume, avoiding any dead volume and optimizing the amount and flow of solvent needed for the synthesis. This new set-up will provide a more efficient and cost-effective process and ultimately result in a high-quality crude API.



BACHEM'S LARGE-SCALE OLIGONUCLEOTIDE SYNTHESIZER

OUR AUTOMATED C&D EQUIPMENT: STREAMLINING OUR LARGE-SCALE OLIGONUCLEOTIDE SYNTHESIS

After synthesis, an oligonucleotide has to be cleaved off from the solid support and to deprotect from the protecting groups. At Bachem, we equipped our oligonucleotide production line with a unique streamlined and automated large-scale C&D system. Our set-up brings significant benefits such as time optimization, cost-efficiency and lower solvent consumption during the C&D step.

Our large-scale 250 L pressure vessel automated C&D equipment uses a continuous two-step process. Once the synthesis is complete, the same column is moved and installed onto the C&D skid. The first step is to deprotect the cyanoethyl groups and then the cleavage of the oligonucleotide from its solid support. A solution of room temperature ammonia circulates through the column of a given volume. Then it goes to the 250 L collector vessel, with the released oligonucleotide. The collector vessel is made from a Hastelloy® material that provides strong resistance to highly corrosive solutions, such as fluoride-based reagents. The C&D system also includes a bunch of process control parameters such as temperature, UV, conductivity and volume. The second step is the deprotection of the protecting groups from the oligonucleotide. Once the ammonia solution has recirculated several times between the vessel and the column, all the oligonucleotide is cleaved from its support and eventually collected in the vessel. The vessel is then closed and heated under pressure with the ammonia solution with an automated temperature program, another unique feature of our C&D system. If other deprotection solutions are required for

the oligonucleotide, the C&D machine is equipped with a multi-port inlet. It enables delivery of the right reagents such as fluoride-based reagent for deprotection of silyl containing protection groups. After completing the C&D step, the oligonucleotide is free from the support and protecting groups. The crude API is now ready for the next step: ultrafiltration. Alternatively, it may go directly to the purification step if ultrafiltration is not required.

CONTINUOUS CHROMATOGRAPHY: PUSHING THE LIMITS OF OLIGONUCLEOTIDE PURIFICATION

At Bachem, we have set up the first continuous chromatography equipment for industrial scale. The innovative Multicolumn Countercurrent Solvent Gradient Purification (MCSGP) technology represents great progress in the downstream process for peptide and oligo manufacturing. For more information on continuous chromatography, watch our webinar!

Place youtube link here: <https://youtu.be/LrDEzMFgLK4>

WEBINAR ON CONTINUOUS CHROMATOGRAPHY

By enabling continuous recycling of side-cuts (mixed fractions of impurities and API), a typical decrease in solvent consumption of more than 30% can be seen compared to single-column batch purification. Therefore, MCSGP improves sustainability during the purification step. Furthermore, this unique technology leads to attractive economic benefits due to its automated system. In regular batch processes, achieving target purity often comes with a decrease in yield and productivity. MCSGP runs 24/7 providing high product yield without a negative impact on purity, and potential for additional savings in cycle time. Savings in cycle time can reach up to 70%, depending on the batch chromatography it is being compared with. This achievement reflects one of our most important commitments to our customers: safeguarding the environment.

We have introduced this technology for peptide APIs and subsequently demonstrated its large-scale feasibility for oligonucleotides. We are convinced that MCSGP technology will be cost-effective and substantially reduce waste.



BACHEM'S CONTINUOUS CHROMATOGRAPHY EQUIPMENT FOR API PURIFICATION

BACHEM KEEPS INNOVATING

At Bachem, we are driven by the desire to transform oligo manufacturing through innovation. For decades, we have shaped our technical leadership and implemented cutting-edge technologies to optimize our peptide manufacturing processes that benefit our customers. Our experience in peptides gives the expertise we need to develop innovative solutions for our oligonucleotide processes. Our unique custom-built synthesizer, C&D system and MCSGP equipment will bring significant advantages to our customers regarding quality, sustainability and cost-effectiveness for the production of their oligonucleotide APIs. We will continue to drive innovation and expand our capabilities to help transform lives of patients.

Get in touch with our expert team to get more insights!

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.