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Accelerating Phase III Peptide API Manufacturing Through DOE-Driven Process Optimization

Case Study

Key outcomes

A tailored Design of Experiments (DOE) approach expediated reaction optimisation and process development

Corrosive materials handled appropriately and utilised on large scale (up to 100 kg)

Significant reduction of processing costs for the customer through judicious reagent selection

Close collaboration between process engineers and scientists ensured the stringent PSD and bulk density requirements for the final formulation were met

About the client

The client was a US-based biopharmaceutical company that focuses on the discovery, development, and commercialization of life-changing treatments for patients in key therapeutic areas such as neuroscience, immunology, and oncology. The collaboration began when the client was entering Phase III clinical trials, where scale-up was necessary and cGMP batches a stringent requirement.

Client objectives

The client tasked Neuland Laboratories with supply of an API from a key starting material (KSM), with on-site preparation of the KSM by Neuland scientists as another stipulation. There were four primary project objectives:

Preparation of the KSM in quantities suitable for large-scale API generation

Upscaling the optimised process for API production under cGMP conditions for Phase III trials

Controlling the levels of impurities to remain within ICH guidelines

Developing a robust process that furnished the final API in consistent yields

Key challenges: Corrosive materials, toxicity, costs and yield

The manufacturing process for the API included one stage for preparation of the KSM followed by a further five manufacturing stages, including peptide couplings, salt formations and purification, Figure 1. The original process generated several impurities, including some introduced during preparation of the KSM. In addition, several stages used corrosive or highly toxic reagents, or generated significant exotherms. Finally, two stages required use of costly peptide-coupling agents, significantly raising the overall cost of the manufacturing process.

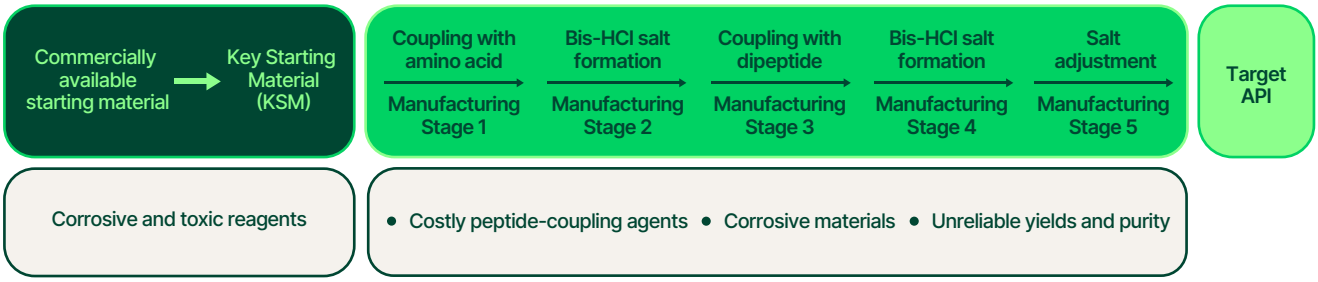


Figure 1: Schematic outlining the process for preparation of the API

Neuland's approach: Using appropriate methodologies to drive efficiencies

The Neuland team broke the manufacturing process down into smaller tasks that included optimisation of reaction conditions, identification of key impurities and investigation into how they were formed, as well as opportunities for reducing costs.

DOE in process design and optimisation

In Manufacturing Stages 1, 2 and 4, a Design of Experiments (DOE) approach was undertaken to expediate the optimisation process. Traditionally, optimisation of reaction conditions focusses on modifying one variable at a time – a process that is both labour- and time-intensive. DOE uses statistical methods to reduce the number of reactions necessary for optimisation, testing multiple variables in tandem that lead to material cost-savings, time-savings in experimental setup and analysis, thorough understanding of variable effects, and a systematic approach to optimizing multiple responses. In this project, full factorial, fractional factorial, response surface and Taguchi design were all performed using Minitab software. The experimental conditions derived successfully led to the manufacturing stage being completed more quickly, with higher yields and purity overall.

Identification of impurities at all stages

1. During KSM preparation:

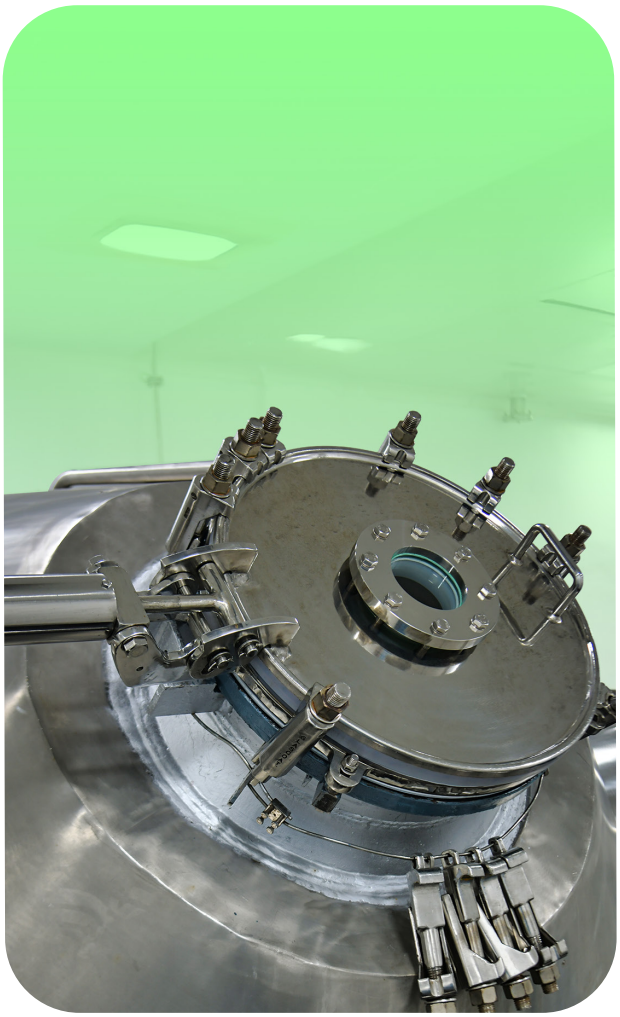
   During synthesis of the KSM using a previously disclosed method, formation of an unknown impurity was observed, which negatively impacted upon the later manufacturing stages. The Neuland team isolated and characterised this impurity, then developed and improved the process such that its formation was eliminated.

2. During API manufacture:

   Manufacturing Stages 2 and 4 both involved bis-HCl salt formation, and it was noted that over the course of the reaction, the original solvent, acetonitrile, formed the highly toxic by-product acetamide. In addition, the concentration of HCl in acetonitrile provided by a third-party supplier was found to be variable, leading to inconsistencies between batches that affected both product purity and yield. To address both these issues, a solvent switch was undertaken and HCl introduced directly to the reactor as a gas. This modified procedure prevented the formation of the carcinogenic impurity and ensured reproducible concentrations of HCl in the reaction mixture.

Alternative reagents can provide cost savings

Preparation of the requisite dipeptide for Manufacturing Stage 3 was undertaken in-house, allowing the Neuland team to control all purification processes and therefore limit impurity formation. Through this work, it was quickly realised that the cost of this reagent preparation and that of Manufacturing Stage 1 could be significantly reduced by substitution of the expensive coupling reagent HATU, used in the original procedure, with HBTU, a related but significantly cheaper reagent. This optimised process delivered this stage with improved yield and purity.



Outcomes: Consistent yields, improved purity and cost savings, alongside safe and efficient use of corrosive materials on large scale

The considered implementation of a DOE approach ensured that optimisation of manufacturing steps was quick and efficient, leading to time- and cost-savings. Where corrosive or toxic reagents were a necessity and could not be removed from a process, their use was subject to stringent controls, both in terms of safety and environmental aspects:

Large-scale usage of bromine and acetic acid (both toxic and corrosive chemicals) to effect bromination of a p-anisidine derivative during preparation of the KSM was safely achieved on scales of up to 50 kg in a 3 kL reactor and included scrubbing of corrosive effluent gases

HCl salt formation was successful on up to 100 kg scale, with strict safety controls implemented

Exothermic reactions were closely controlled to avoid thermal run-away and ensure high levels of safety during manufacture

Cost-savings, while still maintaining efficiency for the client, are front-and-centre for Neuland. In this case, peptide couplings were undertaken on scales of up to 50 kg and proceeded smoothly, providing high-purity material in excellent yield at lower overall cost through use of cheaper coupling agents.

Engaging with the Neuland team ensured that the client achieved their primary objectives of KSM and subsequent API production with consistent yields and purity. Scale-up and processing was under cGMP conditions that were compliant with ICH guidelines, and the Neuland team undertook thorough analytical method development and validation. During each manufacturing step, the level of any impurity was consistently controlled to below 1.5% and the particle size distribution (PSD) of D90 was 58 – 181 µm, meeting the client's PSD requirement. The final API was produced under cGMP conditions in 85.8% yield with purity of over 99.9%.

Conclusion: Collaboration between Neuland teams leads to success

The Neuland team successfully prepared the API required for Phase III clinical trials for the client on large scale, while stringently controlling all safety aspects. The use of DOE techniques was implemented, facilitating rapid reaction optimisation and implementation in the process plant. The physicochemical properties of the final API were optimised, with particle size distribution (PSD) and bulk density requirements for the final product formulation met. To achieve this, successful collaboration between the chemical engineers and scientists within the process engineering facility was necessary, leading to implementation of particle-size reduction technologies and state-of-the-art drying techniques.

About Neuland

Neuland is a global CDMO that delivers success for biotechnology and pharmaceutical clients that are seeking complex APIs at all phases of the product life cycle. We have extensive experience at overcoming the complex synthetic challenges faced when advancing drugs to market, having completed more than 150 NCE projects for custom APIs and developed more than 300 API processes. We've been in business for more than 40 years, with 500+ clients in more than 80 countries and boast an impeccable record of quality standards.

References

B. J. Wall, M. T. Koeritz, L. M. Stanley and B. Van Veller, A Practical Start-Up Guide for Synthetic Chemists to Implement Design of Experiments (DoE), ACS Catal., 2025, 15, 11, 8885. https://doi.org/10.1021/acscatal.5c01626

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