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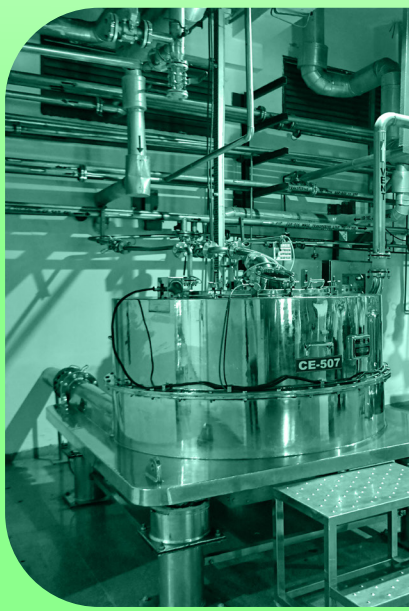
Scale-up of a malodorous, hygroscopic API intermediate using large-scale vacuum distillation: all in a day's work for Neuland Labs

Case Study





Key outcomes

Overall yield of API intermediate was significantly improved from 55% to 70%

Impurities were identified and removed, with analytical techniques validated to monitor their formation. Final API intermediate was produced with impurities controlled to below 0.1% satisfying ICH guidelines

Demonstrated expertise in handling malodourous and hygroscopic compounds at scale

Delivery of 50 kg of a hygroscopic thioether intermediate with ≥99.9% purity under cGMP conditions

About the client

Our client is a UK-based clinical development company that specializes in the development of sulforaphane-based compounds for treatment of oncology and behavioral brain disorders.

Client objectives

Our client required a CDMO partner to scale-up the synthesis of a key intermediate necessary for cGMP manufacture of the sulforaphane component present in the final API, as well as optimize yields and ensure high purity. In addition, all impurities were to be fully characterized and monitored such that they comprised less than 0.1% of the final API intermediate to meet ICH guidelines.

Key challenges: Stench and hygroscopicity

While the scale-up of compounds can be straightforward, in this case two substantial challenges needed to be overcome. Firstly, the stench associated with preparation and use of sulfur-based compounds and secondly, the target material was highly hygroscopic.

While odor can be successfully controlled through scrubbing of exhaust gases and ensuring thorough cleaning of equipment between batches, the inherent hygroscopicity of the final product is often more problematic. For example, hygroscopicity can cause instability of crystal forms, polymorphism and issues with particle size distribution (PSD). In addition, materials that are hygroscopic can retain residual solvents and contaminants causing challenges with achieving acceptable levels of purity. Finally, during processing, hygroscopic materials can suffer from clumping and therefore increase loss of material. This means that during synthesis and processing of hygroscopic compounds, close attention must be paid to both humidity levels and the accumulation of impurities.

Neuland's approach: Experience and expertise matters

When working with our client, Neuland scientists drew upon nearly 40 years of expertise in working with odorous and hygroscopic compounds as well as extensive experience in identification and characterization of impurities, underpinned by thorough assessment of how impurities arise in synthetic processes. This latter point is particularly important, as once it is understood how impurities form, steps can be taken to reduce or prevent impurities forming, as well as devise appropriate techniques for their removal.

In this sequence, one purification step was known to be especially problematic: distillation of the target intermediate. In the original procedure this step required extended heating, which caused significant decomposition and product degradation. The Neuland team therefore exploited fractional distillation at high vacuum (20–30 millitorr) for this step, enabling reduction of the temperature required to only 80 °C, rather than the 180 °C needed at ambient pressure.

In addition, the final material was hygroscopic by virtue of a primary amine present. However, the fact that it was purified by vacuum distillation provided the opportunity to ensure that moisture could be excluded, allowing full control of humidity once the product was returned to ambient pressure.

Outcomes: Excellent purity and yields, even at scale

Overall, the Neuland team optimized the manufacturing process and demonstrated that the API could be reliably produced at multi-kg scale under cGMP conditions, accessing the final, hygroscopic API intermediate with ≥99.9% purity, satisfying ICH guidelines. In particular:

- The overall yield was improved from 55% to 70% under a cGMP process
- Impurities were successfully controlled to <0.1%
- A total of 50 kg of the key thioether amine intermediate was produced
- Hygroscopicity was addressed through purification under distillation, then storage under dry argon and use of a dehumidifier

Conclusion: Vacuum distillation can reduce decomposition and aids storage of hygroscopic materials

Drawing upon their extensive experience, the team at Neuland Labs was able to work with, rather than against, the key material required. Understanding the root causes of impurities allowed adjustment of the synthetic approach to ensure that material was handled and purified appropriately to minimize by-products. Through a stepwise approach to scale-up and ensuring optimal handling of materials at each stage, yields of the key intermediate were significantly improved from 55% to 70%. The optimized cGMP process delivered 50 kg of the required intermediate with ≥99.9% purity. In addition, analytical techniques were developed and validated to ensure that all batches met ICH guidelines and fulfilled the client's brief. Finally, the highly hygroscopic nature of the final product meant that control of humidity during processing and close monitoring of solvent and impurities was necessary, a challenge that Neuland addressed successfully.

About Neuland

Neuland is a global CDMO that works closely with biotechnology and pharmaceutical clients to manufacture complex APIs and intermediates across all phases of the product life cycle. With expertise across a range of areas, they are well-placed to address the complex challenges that synthetic chemistry can present when advancing drugs to the market. Having completed more than 150 NCE projects for custom APIs and developed more than 300 API processes with 500+ clients in over 80 countries, Neuland has an excellent track-record of quality standards.

Make Neuland your strategic partner for improved process efficiency, quality, and ultimately, faster time-to-market for your drug product.

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