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Achieving Sustainable, Higher-Yield, Cost-Effective API Through Phase-Appropriate Scale Up and Optimization

Case Study

Key outcomes

Increased overall yield of the three-stage process by 80%

Reduced raw materials cost contribution by 50%

Delivered 500 grams of product two weeks ahead of schedule

Prepared process for the next stage of scale up

About the client

A European mid-sized biotech company involved in the research, development, and manufacture of biologics, small molecules, and over-the-counter drugs.

Client objectives

This biopharmaceutical company had a new chemical entity molecule in early-phase, preclinical trials as a non-steroidal anti-inflammatory drug (NSAID), and needed to scale their 5-gram medicinal chemistry process to a 500-gram, non-GMP process to produce material for preclinical studies. The company's goal was a safe, efficient, economical, and reproducible process to scale preclinical materials with the desired purity and quality. They brought this project to Neuland, which offers global CDMO services from early-stage drug development through commercial manufacturing of complex APIs.

Existing Process Challenges: Low yield, scale up issues

The NCE is an aryl sulfonamide derivative that is synthesized in a three-stage process. The client's 5-gram-scale process involved:

Synthesis of sulfonamide via condensation of aryl sulfonyl chloride and an aniline with DMF as a solvent

Sonogashira coupling reaction with a palladium (Pd) catalyst followed by purification using column chromatography

Hydrogenation of the alkyne to an alkane at high pressure using a Pd catalyst and dioxane as a solvent

With expertise in developing small molecules and peptides for clinical trials and beyond, and capacity to scale up through every stage of the product lifecycle, Neuland identified key challenges and risks in scaling the client's existing process to 500 grams. One significant challenge is that the solvents commonly used in medicinal chemistry are not always suitable for larger scales and GMP production, where environmental impact and process safety become even more critical. For instance, DMF, a Class 2 solvent, may contain residual dimethylamine, posing a risk of nitrosamine formation. Additionally, dioxane, another Class 2 solvent, can form peroxides, presenting an explosion risk in the third stage.

Another challenge was that the client's process yielded only moderate results across all three stages. This is particularly problematic because low yields often lead to increased costs, extended timelines, and inefficient resource utilization. Moreover, low yields can affect quality, as they may indicate unresolved underlying issues within the process.

Neuland's Phase-Appropriate Approach: Expertise to identify process improvements

Neuland's problem-solving approach to a new chemical process is to look for ways to improve yield, efficiency, safety, and quality. For this early-phase project, the team addressed the client's immediate objective of 500 grams of product for testing, while also facilitating future technology transfer to larger scales and future GMP production.

Neuland's scientific team used their expertise in process development to:

1. **Quickly identify modifications to the client's process to provide more reproducible, consistent quality at the 500-gram scale**
2. **Identify solutions that reduce costs and shorten timelines**
3. **Improve environmental impact and safety**
4. **Optimize the complex, three-stage process to improve yield and efficiency**

Stage 1

Sulfonamide synthesis

Neuland's scientists, who are experienced with sulfonamide synthesis, reduced the amount of a key starting material (KSM-I) from 2.0 eq. to 1.1 eq., resulting in a 45% savings in material consumption. This both reduced raw material cost and improved yield. Reducing the excess volume of reactants also lowered the risk of forming genotoxic impurities that could carry through to the end product. Neuland eliminated DMF in this stage to prevent the formation of nitrosamines from residual dimethylamine.

Stage 2

Coupling reaction and purification

Familiar with challenges posed by the palladium catalyst, the team reduced the Pd content and implemented an anti-solvent crystallization as an alternative isolation method, which improved the yield. The client's 5-gram process called for the coupling reaction to be followed by purification using column chromatography. Although column purification works at medicinal chemistry scales, Neuland's team knew it can be slow and inefficient at the larger scale sought by the client, as well as at commercial scale. The team suggested an anti-solvent crystallization as an alternative isolation method to speed up the process and bring in efficiency at a larger scale. The reduction in Pd content saved cost and lowered the risk of having too much residual Pd content in the end product.

Stage 3

Hydrogenation at high pressure using a Pd catalyst

The Class 2 dioxane solvent used in this stage of the client's process may form peroxides and thus presents an explosion risk. Neuland replaced dioxane with methanol, which is safer to handle in this process and mitigates any issues related to peroxide formation.

To improve the hydrogenation process, Neuland designed experiments to optimize the reaction conditions—including the reaction time, pressure, and Pd loading—to reduce impurity formation to 0.35% as well as improve yield and minimize cost. For commercial-scale materials, additional process optimization would be required to bring impurities to below 0.10-0.15%.

When a client is ready for commercial-scale materials, Neuland examines the impurity profile to learn where the impurities are developing and then designs an appropriate control strategy. An overall phase-appropriate approach, enabled by Neuland's expertise in all phases, saves cost and time while producing the required quality.

Outcomes: Significant yield and purity improvements, speed, and savings

Neuland's efforts improved overall yield by 80%, reduced impurities below 0.35%, and delivered 500 grams of material two weeks ahead of schedule, with cost savings. Yield improvements of 10-20% in each of the three stages increased total yield from approximately 34% in the client's process to more than 61% in the scaled up process. The higher yield allowed production of the required quantity in fewer batches, which saved multiple days. Impurities were reduced to levels acceptable for preclinical use, while the process was designed to identify and accommodate further impurities reductions necessary for commercial scale. In addition, the optimized process allowed Neuland to produce the required 500 grams of product two weeks faster than expected and to reduce the raw materials cost contribution by 50%. This cost reduction was the result of reduced material consumption, reduced catalyst, and improved yield.

Conclusion: Phase-appropriate approach delivers sustainable, cost-effective API yield improvement

With experience taking API manufacturing processes to commercial scale, Neuland identified the right scientific solution to save their client time and money as they prepared for preclinical trials with 500 grams of material. Neuland's scientists resolved issues in the client's 5-gram process that hindered scale up, optimizing the medicinal chemistry process to increase yield, reduce cost, enhance safety for operators, and reduce environmental impact. Importantly, Neuland's approach considered future clinical scale requirements, laying the foundation for successful tech transfer.

About Neuland

A global CDMO, Neuland delivers success for biotechnology and pharmaceutical clients seeking complex APIs at all phases of the product life cycle. Their strength lies in overcoming complex chemistry challenges to advance drugs to market, having completed more than 150 NCE projects for custom APIs and developed more than 300 API processes. In business more than 40 years, with 500+ clients in more than 80 countries, Neuland boasts an impeccable 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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