DRIVING CONTINUOUS IMPROVEMENT: EUROAPI OPTIMIZES PHASE 3 PROCESS FOR SMALL MOLECULE PROJECT

The R&D Small Molecules Team in FKT has successfully developed an efficient process to support a Phase 3 CDMO project with a small-sized company. The initial technical package included four steps and produced the API with a 52% overall yield and a PMI (Process Mass Intensity) of 159.
The top three issues identified during the development study were:

1. **High COGs**: The cost of goods attained using the customer process was unacceptably high. A contributing factor was the use of a homogeneous precious metal catalyst (not recycled) in one of the steps.

2. **Excessive Dilution**: One of the steps was extremely diluted (50 V volumetric bottleneck), partly due to the exothermic nature of the reaction.

3. **Crust Formation**: A solid crust formed on the reactor walls during one step, requiring full cleaning between batches and causing significant downtime. The reaction had to be quenched with water, but the reactor also needed to be dry for the next run—adding further delays. Additionally, the thick suspension couldn't be transferred for quenching, forcing all steps to occur in the same vessel. This created a major bottleneck, making process improvement essential for efficiency and scalability.

Our process development group addressed each of these issues, guided by the principle that good process development is inherently green.

From the start, we aimed to steer the process toward a "single solvent" approach, prioritizing green solvents and considering the availability of solvents on site for logistical reasons. We worked closely with the process engineering team and the production plants to find the best manufacturing solutions. At EUROAPI, R&D scientists stay actively involved from the initial quotation through to final validation—ensuring continuity, accountability, and deep commitment to project success.

Strong Process Improvement Background EUROAPI Track Record

Example: CDMO project (2023)

Process optimization and implementation supporting Phase III development

- Optimized synthetic route with same RSMs
- Catalyst change + process optimization = cost savings >50%
- Process intensification (PMI): 2-fold improvement

	Initial Process	Optimized Process
Overall Yield:	52%	72%
Process Steps:	4	3
Purified/isolated intermediates:	3	2
Crystallizations:	3	2
Solvents:	9	5
Transition metal catalysis:	Homogeneous (not recycled)	Heterogeneous (recycled)
PMI:	159	76

Solutions Implemented:

1. Catalyst Optimization:
Early in the project, a literature review identified heterogeneous precious metal catalysts as a cost-effective and recyclable option. We engaged multiple suppliers, conducted screening, and selected a suitable catalyst successfully used in both technical and registration batches. The switch altered the elemental impurity profile, which was effectively managed through enhanced purification. This change delivered a cost reduction of over 30%.

2. Dilution Issue:
This challenge was addressed through a combination of strategic equipment selection and process optimization. Given the corrosive and exothermic nature of the reaction, a Hastelloy reactor was selected for its superior corrosion resistance. On the process side, controlled dosing of oxidants was implemented to prevent accumulation and mitigate the risk of rapid heat release, ensuring safer and more consistent reaction conditions.

3. Crust Formation and Quenching:
The issue was resolved through equipment and process adjustments. Crust formation and poor stirring in acetone were mitigated by increasing temperature, improving solubility and mixing. Vigorous stirring dislodged existing crust, while gradual water addition enabled controlled crystallization. Further temperature adjustments resulted in additional yield optimization. Final cleanup involved water removal via spray balls, acetone rinsing, and drying through vacuum/nitrogen cycles.

Project Timeline:

March 2023:
Project start

October 2023:
Optimized frozen process delivered

November 2023
January 2024:
Technical campaign with 100-150 kg batch size, 2 m^3 scale. Scale-up factor – 1000.

August 2024
February 2025:
Registration campaign with 100-150 kg batch size, 2 m^3 scale

All customer expectations regarding the project timeline were met. **The Right First Time (RFT)** score was 100%, with all batches released within the specifications.

The optimized frozen process was successfully delivered through strong cross-functional collaboration. While the core development was led by an organic chemist and two technicians, the project was supported by a wider team including scale-up engineers, solid-state experts, plant assistants, and industrialization specialists. This collective effort led to a significant improvement in process performance, with the overall yield increasing to **72%** and the PMI reduced to **76**. The success of the project reflects the dedication and coordination of all contributors.

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