CASE STUDIES

Fast and Efficient: Significant Cost Reduction of a Starting Material

Background:

To address the high market cost and critical downstream impact of a key starting material, back integration was pursued to benefit the final API. Porton initiated lifecycle management for the project, with the Porton Slovenia and China teams collaborating to develop the process and manufacture the material in-house, thereby reducing costs. Porton's agile response and integrated project team facilitated swift troubleshooting and implementation, ensuring alignment with the client's timeline and performance targets. This responsiveness was crucial for maintaining project momentum and delivering a commercially viable solution within a compressed timeframe.

Highlights:

- 3 parallel chemical reactions, controlled crystallization process.
- Successful preparation, purification and characterization of all relevant impurities.
- High quality product.
- Successful development of relevant analytical methods.
- Successful cross-team and cross-site collaboration.

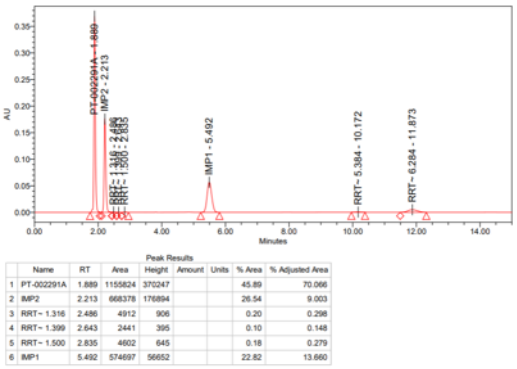
Achievements:

- 52 % Cost Reduction
- API Quality Product
- 78 % Greener Process

Efficient Process and Analytical Development

Leveraging experience in process and analytical method development PSI completed the route scouting, process optimization and scale-up (up to several L) of the process for the preparation of the target compound. Due to the complexity of the reaction (multiple impurities, Figure 1a.), careful control of process parameters (reaction time, temperature, equivalents, pH, etc.) was necessary to ensure a robust and reproducible reaction purity profile. After reaction completion, an efficient and robust crystallization process was crucial for obtaining the product in high purity (Figure 1b.).

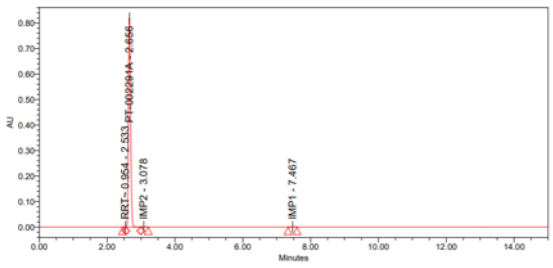
To develop a safe and commercially viable process that delivered significantly lower production costs compared to published methodologies, Porton employed a comprehensive, data-driven approach. This not only created substantial value for the client but also enhanced the overall competitiveness of the final API. A suite of advanced tools was leveraged throughout the development (Figure 2.). Mettler Toledo EasyViewer™ 400 enabled real-time monitoring of crystallization, Crystal16 was utilized to generate solubility curves in various solvent systems, which aided solvent selection and cooling strategies. Mettler Toledo Dynochem™ software supported robust process modelling, including filtration modelling and vapor–liquid equilibrium simulations, ensuring scalability and robustness. Additionally, the use of IC control facilitated precise management of stirring and thermal profiles, as well as calorimetric studies essential for safe scale-up. Together, these tools allowed for the rapid identification and optimization of a low-cost process with excellent reproducibility and safety. Porton Slovenia efficiently developed and refined the process, ensuring the project stayed on schedule and met key technical targets. The flexible and solution-oriented approach allowed for quick adjustments based on client feedback, supporting a smooth transition from lab to scale-up and delivering a reliable, cost-effective outcome.



Peak Results

	Name	RT	Area	Height	Amount	Units	% Area	% Adjusted Area
1	PT-002291A	1.889	1155824	370247			45.89	70.066
2	IMP2	2.213	668378	176894			26.54	9.003
3	RRT~ 1.316	2.486	4912	906			0.20	0.298
4	RRT~ 1.399	2.643	2441	395			0.10	0.148
5	RRT~ 1.500	2.835	4602	645			0.18	0.279
6	IMP1	5.492	574697	56652			22.82	13.660

1a

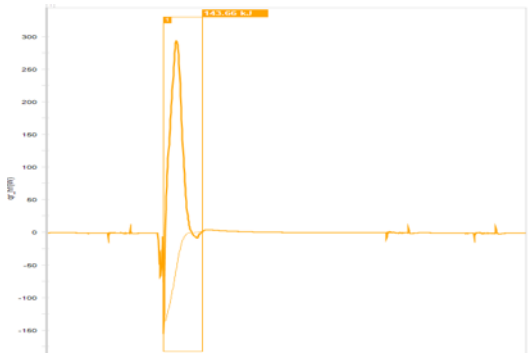


Peak Results

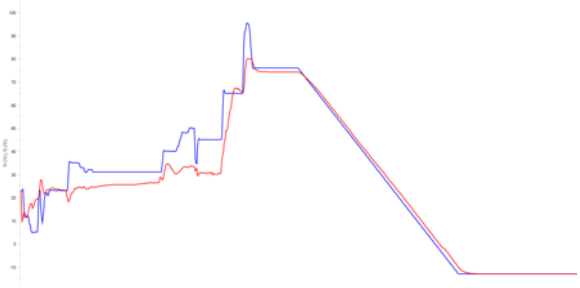
	Name	RT	Area	Height	EP Plate Count	EP s/n	Resolution	% Adjusted Area	Symmetry Factor
1	RRT~ 0.954	2.533	2304	739				0.064	
2	PT-002291A	2.656	3573097	819502	8.590658e+03			99.860	1.215065e+00
3	IMP2	3.078	6707	1221	8.602607e+03		3.417317e+00	0.042	
4	IMP1	7.467	3137	409	2.038724e+04		2.574128e+01	0.034	1.029215e+00

1b

Figure 1. Typical chromatogram of: a) the reaction mixture; b) the isolated product

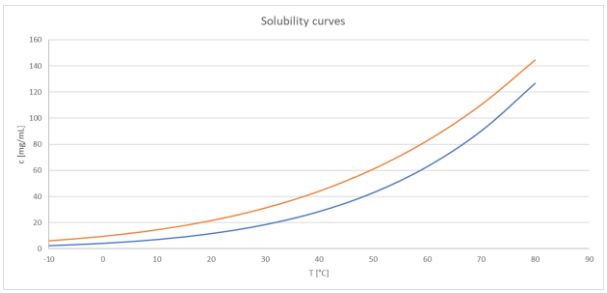


Calorimetry studies (IC control)

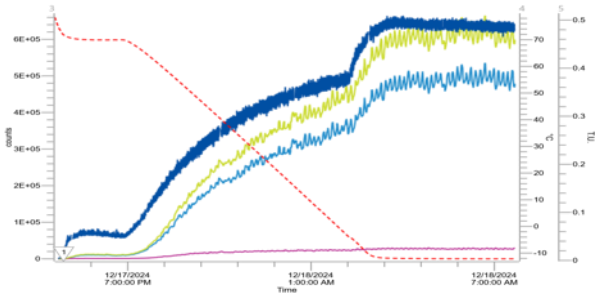


Control of heating/cooling (IC control)

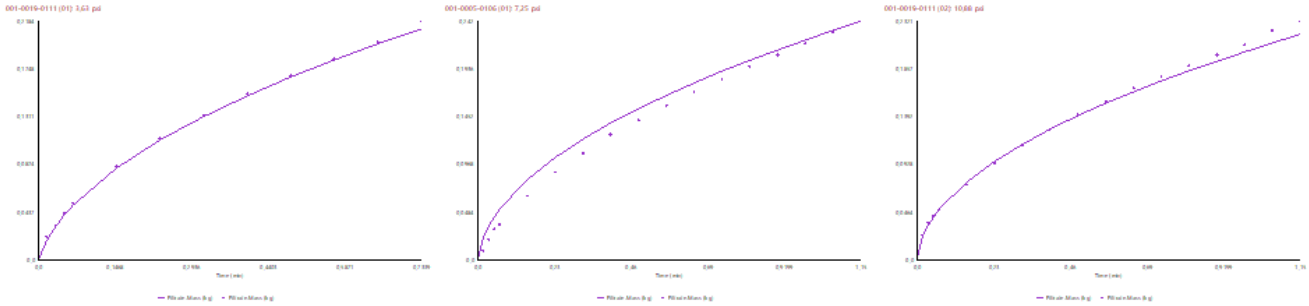
Figure 2. Overview of tools used for process development 1/2



Solubility curves (Crystal 16)



Crystallization monitoring (Mettler Toledo EasyViewer™ 400)



Filtration evaluation (Mettler Toledo Dynochem™)

Figure 3. Overview of tools used for process development 2/2

To support regulatory robustness and ensure consistent product quality, the development team at Porton Slovenia defined and implemented both a Proven Acceptable Range (PAR) and a Normal Operating Range (NOR) for key process parameters. The PAR refers to the experimentally validated range of conditions, such as temperature, pH, and reaction time, within which the process consistently delivers product meeting all predefined quality criteria. In contrast, the NOR represents a narrower, controlled subset of the PAR, selected for routine manufacturing to minimize variability and maintain process stability. By establishing these ranges through rigorous experimentation and risk assessment, and then aligning them with the process equipment capabilities at the Porton China site, the team ensured regulatory compliance under the Quality by Design (QbD) framework while enabling reliable scale-up to commercial production.

Analytical Strategy and Contributions

A comprehensive analytical strategy was established by integrating both customer-provided and PSI-developed methods to ensure complete characterization and quality assessment of the starting material, in-process control and final product.

The customer provided methods included:

- FTIR-ATR (Identification)
- Karl Fischer (KF) titration for water content
- Manual titration for assay

These methods served as the baseline for initial identification and quantification.

To enhance method robustness, sensitivity, and compliance with current regulatory expectations, PSI developed and pre-validated the following methods:

- GC-HS for volatile compound purity and assay determination
- Potentiometric titration as an improved alternative for assay determination
- KF titration for water content
- FTIR-ATR for material identification
- HPLC for both assay and purity determination
- LC-MS for structural elucidation and impurity profiling
- GC-HS for residual solvent determination

The PSI-developed methods offer improved specificity, automation and reproducibility, supporting a more robust control strategy. Together, the full set of methods enables comprehensive in-process control and release testing aligned with quality standards.

Successful Cross-team and Cross-site Collaboration

Porton successfully executed a cross-site and cross-team collaboration between its Slovenia and China facilities by integrating diverse expertise and maintaining clear, consistent communication channels. The Slovenian team led early-phase development, process optimization and initial scale-up (several L), while the China site focused on further scale-up and implementation for commercial manufacturing. Cross-functional teams, including process chemists, analysts, and engineers, collaborated closely, using aligned project management tools and shared data platforms to ensure continuity and transparency. This global, multidisciplinary effort enabled rapid decision-making, minimized development risk, and maintained high quality standards. The result was a robust, cost-effective process, showcasing Porton's strength in global coordination and technical execution.

Strategic Advantages of the PSI Developed Process

The developed process offers clear, quantifiable advantages over previously published methods. PSI delivered a process that is not only scalable and more cost-effective, but also faster and more sustainable.

Significantly shorter reaction time

Compared to literature methods that required extended reaction durations, ranging from 8 to 24 hours, the developed process achieves complete conversion in just 1.5 to 2 hours. This translates into increased throughput and improved manufacturing efficiency.

Greener and simpler solvent use

PSI's process utilizes ethanol as the solvent, which is easier to handle and distil than the water or THF used in other methods. Ethanol also supports a greener profile and reduces solvent recovery costs, contributing to 78 % improvement in process greenness as assessed by the iGAL 2.0 sustainability scorecard.

High purity directly from crystallization

Through the implementation of controlled crystallization strategies, the PSI team was able to produce crude material with >99.8 % purity, which would typically require multiple rework or carbon treatments in literature methods. This was achieved by optimizing parameters such as pH, temperature, water content and volume ratios.

Data-driven process design

A suite of advanced tools supported the development of a robust, scalable process: EasyViewer™ 400 for real-time crystallization monitoring, Crystal16 for solubility profiling and solvent system design, Dynochem™ for filtration modelling and vapor–liquid equilibrium (VLE) simulations, and IC Control for precise thermal and calorimetric profiling. These tools enabled the rapid establishment of a PAR and NOR for critical parameters, laying the foundation for a stable, validated process suitable for tech transfer and regulatory submission.

Substantial cost reduction

By eliminating unnecessary purification steps, optimizing raw material equivalents (e.g., 5 equivalents of a reagent vs. 10 in older methods), and improving yield and work-up efficiency, the final cost of the PSI-developed process came to just 27 % of the original market price, surpassing both initial and updated cost targets. Considering the updated market price, the PSI-developed process reached a 52 % reduction in cost.

Effective impurity management

Initial batches presented challenges with a residual reagent, which threatened downstream reactivity. PSI addressed this through pressure filtration to reduce deliquoring, and re-crystallization to purge up to 15 % w/w of the residual reagent. These improvements minimized downstream risks and simplified quality control.

Seamless cross-Site integration

Throughout the development lifecycle, PSI maintained real-time communication with Porton China, adjusting the process to align with commercial manufacturing equipment. Filtration models were scaled and simulated to match centrifuge parameters at the China site, ensuring a smooth transition from lab-scale to plant-scale production.

Key Contributors

The successful outcome of the project was made possible by a dedicated team of scientists, engineers, and project leaders who brought their expertise, agility, and collaborative spirit to every stage of development. The cross-functional coordination and commitment to excellence ensured delivery of a robust, optimized and regulatory compliant process.

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ARD Deputy Manager
Porton Pharma

Porton Slovenia (PSI)

Porton Slovenia (PSI) plays a vital role within the Porton group, focusing on process research and development for small molecule APIs. Strategically located near major European logistics hubs, the site offers state-of-the-art R&D and kilo lab facilities, including GMP and non-GMP capabilities. With a growing international team and advanced analytical and process labs, Porton Slovenia is well-equipped to support early- to late-phase development and scale-up activities, delivering high-quality, data-driven solutions to global pharmaceutical partners. Porton Slovenia also offers Quality by Design (QbD) capabilities, supporting efficient process understanding and risk management from early development through scale-up. With dedicated tools, experienced scientists and a structured QbD framework, the PSI R&D teams deliver robust experimental design, critical parameter assessment and data-driven process optimization tailored to each project's needs.

Porton Slovenia was tasked to develop an efficient, cost-effective process for the preparation of the target compound. The published processes were time and energy consuming and required further purification which resulted in a higher cost.