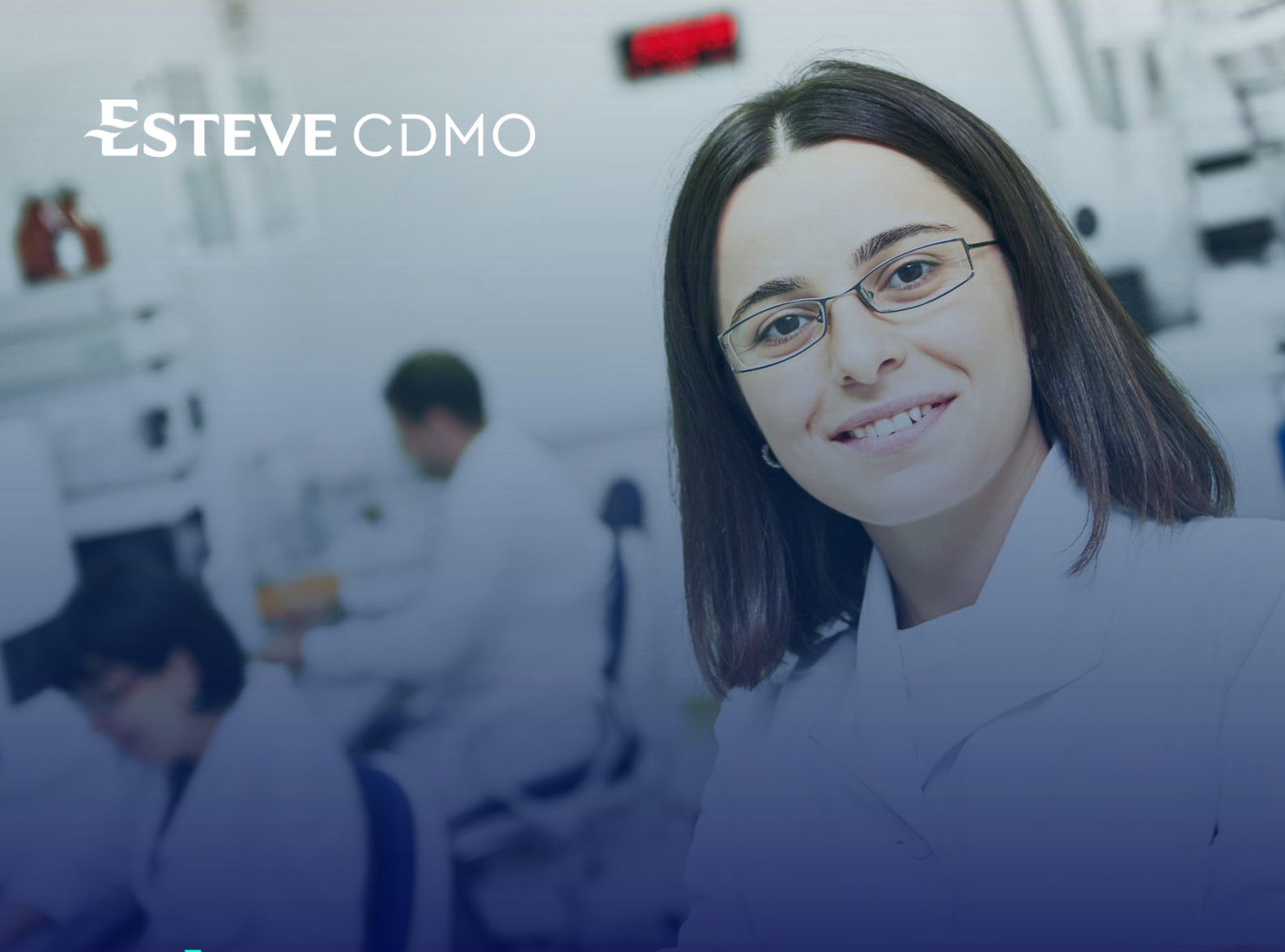
ESTEVE CDMO



Fixing the Unscalable

Rapid CGMP Transformation of an Active Pharmaceutical Ingredient

Case Study

ESTEVE CDMO

FIXING THE UNSCALABLE: RAPID CGMP TRANSFORMATION OF AN ACTIVE PHARMACEUTICAL INGREDIENT

Program Background

A U.S.-based biotechnology company developing a therapy for a neurodegenerative disorder transferred its API process to ESTEVE CDMO for CGMP manufacturing to support an Investigational New Drug / Investigational Medicinal Product Dossier (IND/IMPD) filing and Phase I clinical trials.

The project was initiated under a four-month deadline to deliver 8 kg of GMP Active Pharmaceutical Ingredient (API), with the route provided as "CGMP-ready." On technical intake, ESTEVE CDMO identified that the process was not fit for CGMP manufacture. Changes in the raw material synthesis had introduced new impurities, and the existing analytical package was insufficient for process control and release testing.

To safeguard the IND timeline, ESTEVE CDMO launched an accelerated process and analytical development program, delivering a scalable, inspection-ready process that supported predictable clinical supply.

ESTEVE CDMO specializes in refining processes that are not scalable or CGMP-compliant into reliable, robust manufacturing routes.

Challenges and Key Factors

The program presented three key challenges:

1. **Process robustness:** The transferred route generated impurities linked to Raw Starting Material (RSM) changes and lacked appropriate control points.
2. **Analytical readiness:** Existing methods were unsuitable for impurity tracking or release, requiring full redevelopment.
3. **Timeline pressure:** Delivery of CGMP material was required within four months of contract signature.

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Solution Overview and Execution

Unlike other CDMOs, **ESTEVE CDMO applies a risk-based approach involving rapid delayed-parallel processing.** This allows the team to correct route flaws, build analytical control strategies, and hit aggressive clinical timelines. **By developing the process and analytical methods simultaneously,** rather than in sequence**, ESTEVE CDMO can deliver high-purity CGMP API under compressed deadlines.**

Process Development

- Performed Process Safety assessment and modified one of the steps to avoid rapid heat generation
- Optimized the process to develop a scalable, phase appropriate process that was suitable for CGMP Manufacture
- Demonstrated the viability of the optimized route via a lab scale pilot batch

Analytical Development

- Developed and validated methods for testing of Potential Genotoxic Impurities (PGI's) and residual materials that were not part of the original scope of work
- Rebuilt and validated analytical methods for in-process control and API release.
- Established a phase-appropriate end-to-end control strategy

Execution

- Completed a 500 g demonstration batch and subsequent CGMP campaign, delivering 9.2kg API of very high purity — two weeks ahead of schedule.

Scale-Up to Phase II/III

- Following the IND batch success, ESTEVE CDMO was asked to scale the process to support Phase II/III clinical trials (50 kg target).

Key process refinements included

- Removal of intermediate isolation and optimization of Step 1 resulting in a more efficient process with a 30% yield improvement
- Elimination of a Class 2 solvent and control of residual levels of another to within ICH compliance.
- Integration of recrystallization and polish filtration to improve purity and appearance
- Validation of all analytical methods to support the updated process.

The second-generation process increased overall yield by 26% and significantly improved impurity control, appearance, and residual solvent levels. Two non-GMP engineering batches (~7 kg each) preceded the successful production of 60 kg CGMP API (20% over target quantity) within five months — one month ahead of the client's target completion schedule.

Summary

- ESTEVE CDMO partnered with a U.S. biotech developing a neurodegenerative therapy to develop an Active Pharmaceutical Ingredient process originally transferred as "CGMP-ready".
- The route, however, was found to have many flaws; it was not scalable, introduced new impurities to changes in RSM manufacture, and there were inadequate analytical controls.
- Under a four-month deadline, ESTEVE CDMO re-engineered the process, rebuilt the analytical package, and delivered 9.2 kg of high-purity CGMP API two weeks ahead of schedule.
- A second-generation process for Phase II/III removed a problematic transient intermediate isolation, eliminated Class 2 solvents, introduced a recrystallization/polish filtration and improved overall yield by 26%, enabling delivery of 60 kg one month ahead of schedule.

This case study highlights the importance of choosing a CDMO with the expertise and strategic capabilities to turn flawed processes into robust, scalable CGMP routes, delivering quality and speed under pressure.

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ESTEVE CDMO, *The Science of Collaboration*

ESTEVE CDMO is a global pure-play partner in small-molecule APIs and advanced pharmaceutical intermediates, collaborating closely with our customers to turn complex science into scalable solutions.

Powered by 1,500+ experts worldwide and recognized as the 2025 CDMO Leadership Award Global Champion in Small-Molecule API, we support programs from early development through large-scale commercial manufacturing.

Our end-to-end capabilities include process R&D, analytical and stability services, CMC, and commercial intermediates, with proven expertise in Spray Drying and HPAPI (up to OEB5) across six sites in the U.S., Spain, Mexico, and China.

THANK YOU

infoCDMO@esteve.com