WILMINGTON PHARMATECH

CASE STUDY

From Low Purity to GMP Supply

Rescuing a Challenging Orphan Drug

Executive Summary

After multiple major development partners failed to scale its challenging compound to GMP standards, the client, a developer of an orphan drug for donor-heart preservation, turned to Wilmington PharmaTech to rescue its program.

By applying its disciplined, stepwise process-chemistry strategy that combines deep synthetic expertise, carefully targeted analytical testing, and close cross-functional alignment, Wilmington PharmaTech was able to rescue the candidate so that it could progress to the next development milestone on time, ensuring that it reliably met all quality expectations when scaled within GMP conditions. In downstream evaluation, the candidate went on to show excellent efficacy.

The Challenges

Even though the client, a developer of an innovative therapy for donor-heart preservation, had selected appropriate development partners based on their stated capabilities, it had been unable to advance its molecule into GMP production. The molecule, an orphan drug designed to protect donor hearts from ischemic injury during transplantation, faced a series of persistent manufacturing challenges, including:

- **Low product purity** caused by unreacted starting material and impurities such as difficult-to-remove positional isomers, or regioisomers
- **Poor conversion**, restricting overall yield and limiting scalability
- **Inadequate product quality control** with significant residual ethanol detected in samples
- **High levels of inorganic salt contamination**, including sodium chloride and sodium phosphate salts, resulting from reactions performed exclusively in aqueous media, of which both the client and previous vendors were unaware.

Despite engaging several large partners, none were able to resolve these issues, raising significant concerns about whether the compound was manufacturable at all.

The Wilmington PharmaTech Solution

Leaning on its seasoned team of medicinal chemistry experts and decades of specialized experience in solving the most complex synthetic challenges, Wilmington PharmaTech employed a disciplined, stepwise process-chemistry approach to overcome these barriers to the program's progression. To do so, the company leveraged its cross-functional team environment, which integrates process chemistry and analytical expertise, to advance and accelerate development and scale up to GMP production.

As a first step, the company began by reproducing the client's original procedure, introducing only minor yet strategically chosen adjustments to the workup. For example, one of the small adjustments involved the removal of an additional 40 volumes of water during workup. Once most of the inorganic salts were removed by evaporating the additional water, the unreacted cyclocreatine precipitated out at the same time. Previous vendors had been unable to remove this precursor at reaction completion, preventing them from achieving the required purity.

In parallel, Wilmington PharmaTech's analytical team developed a new HPLC method capable of identifying the regioisomer impurity. The client's existing method could not reliably detect this species, limiting their ability to control or track it. By establishing a more sensitive and selective analytical approach, Wilmington PharmaTech strengthened process understanding and enabled more effective purification strategies.

Even these initial refinements, both in process and analytics, increased product purity to approximately 90%, a level that previous vendors had been unable to achieve despite extensive attempts to repeat the same process.

Wilmington PharmaTech then employed systematic solvent screening to identify a mixed-solvent system of water and dimethyl sulfoxide (DMSO) that significantly improved reaction conversion, while preventing the product from decomposing back into the starting material. With this optimized system, a simple filtration after the reaction had been completed would consistently yield material at greater than 93% purity, a significant increase from the 69.9% that one of the previous vendors had achieved, already surpassing the client's expectations.

Further refinement of solvent ratios and slurry conditions reduced inorganic salt content from around 80% under the original process to approximately 7% under GMP production conditions.

Following its stepwise process chemistry program, Wilmington PharmaTech had improved the purity of the final product to routinely exceed 98%, significantly higher than the 93% purity requested by the client, and enabled the first successful GMP-grade manufacture of this compound, with 1.49 kg of product delivered from a 1.9 kg-scale run.

Wilmington PharmaTech also identified a previously unrecognized crystalline form in the GMP batch, an insight missed by all prior vendors, as well as the client, the discovery of which strengthened the client's IP position.

> "If WPT could not manufacture this product, no other company could."
>
> CLIENT SPOKESPERSON

Outcome for the Client

The compound was rescued, delivered on schedule, exceeded all quality expectations, and demonstrated excellent efficacy and stability during downstream evaluation. These results not only validated the robustness of the newly developed process but also provided the client with the confidence needed to advance its orphan drug into subsequent development stages. Additionally, the discovery of the crystalline structure strengthened the client's competitive IP advantage, and Wilmington PharmaTech's work directly contributed to the client's process chemistry patent.

Conclusion

The project underscored Wilmington PharmaTech's strength in turning high-risk development challenges into robust, scalable, GMP-ready processes. On the back of this success, the client has committed to a long-term strategic partnership with Wilmington PharmaTech.

To discuss your challenge with our experts, contact us at info@WilmingtonPharmaTech.com

93%
of inorganic salt content removed under GMP production conditions

98%
final product purity achieved, surpassing client requirement of 93% purity

1.49 kg
of product delivered from a 1.9 kg-scale run