



Solving Solubility Challenges with Nanomilling

Overcoming bioavailability challenges and scaling a commercially viable formulation of Iterion's new cancer treatment

Lubrizol Life Science Health (LLS Health) combines its nanomilling expertise and GMP manufacturing capabilities to maximize bioavailability, improve patient experience, and take poorly soluble compounds into clinical and commercial production.

Iterion Therapeutics is a clinical stage biotechnology company based in Houston, Texas. Since it began operations in 2014, it has been dedicated to developing novel cancer therapeutics for a broad range of cancers that are difficult to treat through conventional drug therapies.

The company's lead product, a nuclear β -catenin inhibitor, Tegavivint, is currently the subject of a Phase 2a clinical trial in desmoid tumors. Tegavivint is unique among nuclear β -catenin inhibitors in that it binds to TBL1 (Transducin Beta-like Protein One), a novel downstream target in the Wnt-signaling pathways that binds β -catenin. Through binding TBL1, Tegavivint can potentially arrest tumor development.

Rahul Aras, Ph.D., CEO of Iterion, explained: "Nuclear β -catenin drives oncogenic gene expression. Inhibition can potentially disrupt cancer cell generation and proliferation, impeding tumor growth. Historically, Wnt-inhibitors have posed toxicity issues, as they affect

other Wnt/ β catenin functions in the cell membrane, disrupting normal healthy cell processes.

"Tegavivint enables silencing of Wnt-pathway gene expression without affecting necessary Wnt/ β catenin functions in the cell membrane. This means Tegavivint effectively disrupts oncogenic gene expression without the toxicity issues common to other drugs in this pathway."

However, developing Tegavivint posed challenges for Iterion. The drug substance has very poor solubility in water, which contributes to low bioavailability and reduces its therapeutic effect. As a semi-virtual company with 10 employees, Iterion needed a partner who could not only solve their bioavailability challenges, but also develop a scalable formulation with a viable manufacturing strategy. To address these challenges, Iterion turned to the team at Lubrizol Life Science Health's CDMO Division.

The challenge: low solubility

Poor water solubility and bioavailability are common challenges in oncology drugs due to the complex nature of the drug substances. Failure to address this issue reduces clinical efficacy of otherwise promising drugs and has negative consequences for the patient experience.

To address the problem, Iterion approached several contract development and manufacturing organizations (CDMO) for a solution. However, none of these partners could find an approach that could increase bioavailability and meet clinical goals, while offering a clear path to commercialization.

Iterion approached LLS Health to explore the potential of nanomilling the active pharmaceutical ingredient (API) to solve the problem. LLS Health is an expert in developing nanosuspension formulations capable of overcoming aqueous solubility issues and has the process development and scale-up infrastructure required to support Iterion's project.



If the bioavailability issue wasn't addressed when developing Tegavivint, we wouldn't have a drug today. It's unlikely we would have achieved exposure levels in patients necessary to see a therapeutic effect.

Developing a clinically viable formulation was absolutely necessary for us to advance the drug into human studies.

- Dr. Rahul Aras, CEO



The solution: nanomilling

LLS Health's team of experts began working on the issue, employing nanomilling to improve the solubility of Tegavivint and develop a formulation that could be scaled up for clinical and commercial supply.

Nanomilling is a solubility enhancement technique that has been used in marketed drug products for over twenty years. The basic principle behind nanomilling is increasing the surface area-to-volume ratio of an API by reducing the particle size below 1000 nm, typically in the 100s of nm range. This conversion of drug particles

into nanocrystals allows for greater interaction with water, which increases dissolution rate. In general terms, smaller particles dissolve more quickly.

Nanomilled versions of poorly soluble APIs such as Tegavivint often have improved bioavailability and avoid the use of potentially toxic excipients, such as Cremophor, to achieve the effect. With proper stabilizer selection, a nanosuspension can be formulated into a liquid injectable or lyophilized for reconstitution/incorporation into another dosage form.

Results in a tight timeframe

Iterion had a very short timeframe in which to prepare Tegavivint for clinical trial. To meet Iterion's needs, the LLS Health team began by utilizing a small-scale roller milling process to generate prototypes. LLS Health performed a feasibility screening to measure the particle size distribution and stability of various formulations, with the goal of identifying a lead candidate to optimize and scale.

Gowri Sukumar, Senior Director of CMC and Regulatory Affairs, noted: "LLS Health collaborated closely with the Iterion team to quickly and effectively mitigate unforeseen development issues, and to generate Good Laboratory Practice material for toxicity studies to progress Tegavivint into clinical trials on schedule."

The original product that LLS Health and Iterion developed was clinically viable but lacked the long-term storage stability for commercialization. LLS Health supported Iterion to optimize the formulation, providing input on incorporating lyophilization to stabilize the formulation and improve shelf life.

LLS Health offered great insight on optimizing the lyophilization process, by making better sense of the data from in-depth investigation into all the possible polymorphs for this API that was being generated by Iterion to keep the project on track. - **Gowri Sukumar, Senior Director of CMC and Regulatory Affairs**

Overcoming obstacles

As a small business, Iterion benefited from LLS Health's larger presence and footprint to overcome unforeseen challenges to keep its project on track.

When the COVID-19 pandemic disrupted the supply of container closure systems, for example, the LLS Health team worked with Iterion to find alternative packaging configurations that met Iterion's requirements. This minimized delays and ensured Iterion could move forward with their clinical trials.

Dr. Aras remarked: "The highlight for us is, without a doubt, the integrated nature of LLS Health's support. The company not only helped us develop a formulation for clinical trial, but it was also there to help us optimize the formulation process and find creative ways to refine our product.

"Even when there were challenges, LLS Health's Quality Team was quick to provide support to ensure clinical trials were not disrupted or delayed. When necessary, the team went above and beyond to arrange additional testing and work around scheduling challenges to make sure our project did not face delays."



A valued partner

Following this extensive development work, LLS Health is now working with Iterion to scale up the nanomilling process using high-energy media milling equipment.

Iterion is immensely satisfied with the support from LLS Health. For the Iterion team, LLS Health is more than just a development and scale-up partner, it is also a potential partner for long-term production.

“I have lots of experience working with CDMOs, and LLS Health stands out because they’ve truly presented themselves as a partner,” concludes **Dr. Aras, CEO of Iterion Therapeutics**.

“The Tegavivint project has not been a linear process, so there have been several times where LLS Health has worked hand-in-hand with us to overcome challenges. The relationship has not just been ‘you tell us what to do and we’ll do it.’”

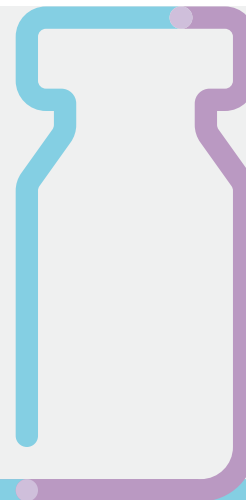


LLS Health has brought a **problem-solving mindset to our partnership, listening to our concerns and making the effort to meet our needs with care and attention. We look forward to working together more in the future.**

- Dr. Aras, CEO



To find out more about how LLS Health can take your next project into clinical or commercial manufacturing, [contact us today.](#)



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