United Therapeutics
A PUBLIC BENEFIT CORPORATION

GREEN CHEMISTRY IN RARE DISEASE THERAPY: Patient-Centric and Environmentally Preferable

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Modern synthetic chemistry has delivered life-saving medicines – but it can also leave a legacy of waste, bioaccumulation, and toxicity.

Applying green chemistry principles is how we prevent hazards and waste at the source – by design.

Since our founding, United Therapeutics (**UT**) has held a clear conviction: improving human health shouldn't come at the planet's expense – and that responsible innovation is a competitive strength. In 2021, we strengthened that commitment by becoming a public benefit corporation (**PBC**)– requiring us to balance patients, people, planet, and shareholders in how we make decisions and deliver results.

"As a PBC, we are committed to creating a brighter future for patients while recognizing the deep connections between human health and environmental impact," said **Dr. Hitesh Batra**, VP of Chemical R&D and Production. "Applying green chemistry principles aligns with our purpose—and it is simply the right strategic choice for long-term impact."

*Hitesh Batra, left, speaking with colleague **Sri Harsha Tummala** in a UT R&D lab.*

> "The fields of chemistry and material science advanced beyond anyone's wildest dreams but came with a price – waste and hazardous materials that weren't foreseen or understood…. Now we recognize the power and potential of creative design, rather than believing the old myth of a trade-off between environment, health, and economics."
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> **Dr. Paul Anastas**
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> Interview with *Forbes Magazine*, 2012. Dr. Anastas is credited with establishing the field of green chemistry

In its phase 3 clinical study, ralinepag – an investigational, once-daily oral prostacyclin agonist for the rare, potentially fatal disease, pulmonary arterial hypertension (**PAH**) – showed durable efficacy in delaying disease progression. UT plans to submit a New Drug Application to the U.S. Food and Drug Administration during the second half of 2026, a key milestone as we advance toward potential commercialization.

As we prepare for commercial-scale manufacturing of ralinepag, our R&D team re-engineered the legacy synthetic route using green chemistry principles to simplify execution, improve throughput, and reduce risk at scale.

Patient safety is paramount: the redesigned process (patent application filed March 2025) delivers output equal in quality to the legacy route while preventing pollution at the source. It also reduces hazardous substances, increases batch output, lowers greenhouse gas (**GHG**) emissions, and reduces potential occupational health and safety risks for employees running the process – supporting safer operations and stronger manufacturing readiness.

PREVENTION IS KEY

The U.S. Environmental Protection Agency introduced the idea of green chemistry in response to the Pollution Prevention Act of 1990, which encouraged eliminating pollution through better design rather than treatment and disposal.[1]

In the 1990s, international collaboration accelerated growth in the field of green chemistry, leading to the publication of the12 Principles of Green Chemistry in 1998. These principles gave green chemistry a clear framework to guide research, design, and innovation.

Prevention – the first of the 12 Principles – played a central role in our team's redesign of the ralinepag manufacturing process.

Challenges with the original process: The legacy route ~~is~~ long, complex, and inefficient. It creates impurities that required added cleanup, reducing yield and increasing in-process testing. It also relies on harsh reagents and conditions – creating added risk for employees, especially at scale. Finally, redundant steps ~~add~~ time and complexity without improving quality, lengthening timelines and reducing usable product.

What changes with the new process: The redesigned route cuts unit operations from nine steps to six. A new starting material blocks impurity formation early, removing downstream cleanup steps, reducing waste, and avoiding many harsh chemicals – while preserving product quality.

Environmental and safety improvements: The new process **reduces chemical inputs by about 24%**, using far fewer hazardous and corrosive chemicals, replacing more toxic solvents with safer alternatives, and avoiding toxic byproducts. These changes improve worker safety and significantly reduce hazardous waste.

Efficiency and climate benefits: The streamlined process uses less material, produces on average **55% less waste**, and finishes more quickly. It produces more product per batch and requires fewer production days. Because fewer batches are needed, overall energy use is lower than the legacy process, leading to lower GHG emissions.

Cost and operational benefits: By cutting waste, labor for in-process testing and associated administrative oversight, energy use, and repeated steps, the new process is also less expensive. These savings free up resources that can be reinvested in research and development.

SMALL AND MEANINGFUL

The redesigned ralinepag process shows what deliberate, science-driven innovation can deliver in drug development: fewer hazardous inputs, fewer operations, less waste and energy use, and improved operator safety – without compromising quality. By rethinking the route end-to-end, the team designed out impurity pathways at their source while improving yield and shortening cycle time – improving reliability for patients and efficiency for the business.

For a rare disease therapy like ralinepag – where volumes may be modest but the impact on patients is profound – these improvements matter. Designing out hazards instead of managing them downstream strengthens product quality, reduces environmental burden, improves worker safety, and supports long-term scalability and reliable supply as demand grows.

United Therapeutics became a PBC in 2021 – the first publicly traded biopharmaceutical company to do so. Our **PBC purpose** has two parts: ***to create a brighter future for patients through the development of novel pharmaceutical therapies and technologies that expand the availability of transplantable organs.*** Our first purpose helps delay or avoid the need for transplant; our second helps ensure organs are available when patients need them – supporting long-term value creation. We align this purpose with three pillars – our patients, our people, and our planet.

[1] P.T. Anastas and Evan S. Beach. Green Chemistry Education: Changing the Course of Chemistry. 2009 ACS Symposium Series.