

Scalable manufacturing for high-volume siRNA programmes remains underdeveloped

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The global contract development and manufacturing organisation (CDMO) industry has evolved from a cost-reduction outsourcing play into a critical strategic capability for the pharmaceutical and biotechnology industry, where North America holds the major share. In particular, the nucleic acid therapeutics CDMO segment is experiencing significant growth, driven by the increasing demand for personalised medicines. This aspect was well highlighted during TIDES USA 2026, held in Boston from 11th to 14th May, a premier forum for accelerating oligonucleotide, peptide, mRNA, genome editing and delivery innovations. BioSpectrum took this opportunity to interact with a key player in this sector, Hongene Biotech, a vertically integrated nucleic acid CDMO. David Butler, Chief Technology Officer, Hongene Biotech, US spoke about the company's new growth plans, and the current challenges facing the global CDMO sector.



What were the key takeaways for Hongene after attending TIDES USA 2026?

TIDES USA 2026 reinforced several themes that will define the next phase of nucleic acid therapeutics. The manufacturing conversation has shifted from whether enzymatic and ligation-based approaches can meet cGMP standards to how they are scaled and assessed by regulators. Delivery beyond the liver was also a strong theme, with presentations on targeted lipid nanoparticles (LNPs) and receptor-mediated CNS delivery using antibody-oligonucleotide conjugates. Genome editing sessions showed how RNA therapeutic programmes are becoming more complex, and increasing pressure on CDMOs to expand their capabilities. For Hongene, the conference reinforced our strategic direction: scalable ligation-based manufacturing, integrated end-to-end services and broad raw material capabilities.

Hongene has been described as a one-stop CDMO for nucleic acid therapeutics. What does end-to-end vertical integration actually mean in practice, and why does it matter for drug developers?

It means Hongene controls the entire value chain, from nucleosides and other building blocks through to cGMP drug substance and drug product, including LNP formulation and aseptic fill-finish. For drug developers, this translates into two practical benefits. First, it reduces vendor handoffs, avoiding the coordination burden of managing multiple timelines, quality

systems and technical interfaces. Second, it gives Hongene direct visibility across the full process, enabling faster troubleshooting and more transparent programme management. When a programme encounters a challenge, we can identify root causes and act quickly without waiting on multiple third parties.

The company has recently announced the first GMP manufacture of small interfering or siRNA using chemoenzymatic ligation to support a clinical-stage programme. What does that milestone mean for the field?

It demonstrates that chemoenzymatic ligation is no longer experimental, it is now a cGMP-ready manufacturing approach capable of supporting clinical-stage development. For drug developers evaluating next-generation siRNA programmes, it signals that a scalable alternative to solid-phase oligonucleotide synthesis (SPOS) now exists. For the broader field, it is a meaningful step toward solving the volume challenge that cardiometabolic targets such as APOC3, PCSK9, AGT and LPA will create. In our opinion, ligation-based manufacturing is the most credible path to meeting these demands and bringing these important medicines to patients.

SPOS has served the industry well for short, chemically modified oligonucleotides, but its limitations become apparent at scale and for longer molecules. Commercial SPOS platforms remain constrained to low-kg or limited multi-kg batch scales, forcing manufacturers to run multiple campaigns to support large-volume programmes. For longer molecules like single guide RNA (sgRNA), sequential coupling chemistry causes compounding and accumulation of impurities that are difficult to remove during purification.

Hongene addresses these issues through chemoenzymatic ligation, whereby full-length oligonucleotides are assembled from shorter SPOS-derived fragments using enzymatic ligation. The reaction runs in scalable reactors, and its selectivity reduces carry-through of fragment-related impurities into the final product, resulting in higher purity, better batch consistency and a more viable path to the multi-ton volumes that cardiometabolic siRNA programmes will eventually require.

RNA interference (RNAi)-based medicines targeting cardiometabolic diseases could eventually require multi-ton annual API supply. Is the industry actually ready for that volume?

Not yet. Some near-term approvals are for defined patient populations that conventional manufacturing can support. The harder scenario emerges when broader indications are approved with tens of millions of eligible patients. At those volumes, conventional SPOS becomes increasingly difficult to justify from a cost, capacity and sustainability perspective. Chemoenzymatic ligation addresses this by enabling solution-phase enzymatic assembly of fragments in scalable reactors. Hongene's crude-to-purified, or C-to-P, workflow processes unpurified SPOS fragments using ultrafiltration/diafiltration (UF/DF), eliminating intermediate chromatography before final siRNA purification. We are also developing a crude-to-crude, or C-to-C, workflow intended to entirely eliminate chromatography requirements for high-volume manufacturing.

Could you please elaborate the company's plans for 2026?

2026 is a year of focused execution across three areas. First, we are scaling our chemoenzymatic ligation platform, building on our 2025 milestone of manufacturing cGMP-grade siRNA for a clinical-stage programme. Second, we are investing in capacity, including our Hungary facility scheduled to open in 2028, which will strengthen supply continuity for European partners. Third, we are deepening our mRNA capabilities, particularly around HiXCap cap analog technology, LNP formulation and fill-finish. Across these priorities, our goal is to give customers an integrated, dependable path from critical raw materials through clinical and commercial drug supply.

Looking ahead to the next three to five years, where do you see the most significant unmet needs in nucleic acid manufacturing, and how is Hongene positioning to address them?

Three areas stand out. First, scalable manufacturing for high-volume siRNA programmes remains underdeveloped. Supplying cardiometabolic programmes at commercial scale will require significant investment in both technology and capacity, and Hongene is actively building both.

Second, delivery of RNA medicines outside the liver remains one of the field's largest unresolved challenges, and the modalities advancing into that space, including antibody-oligonucleotide conjugates (AOCs), multivalent oligonucleotide architectures and targeted LNPs, demand more sophisticated manufacturing capabilities than conventional CDMOs currently offer. Hongene is actively building its capabilities to support these programmes as they advance toward and through the clinic.

Third, complex mRNA therapeutics benefit from genuinely integrated end-to-end manufacturing solutions, spanning raw materials, plasmid, guide RNA synthesis, mRNA production, formulation and fill-finish, yet few CDMOs can deliver that within a single, integrated manufacturing partnership. Hongene's vertical integration positions us to close that gap.

What are the major challenges and opportunities facing the global CDMO sector?

The central challenge is matching capability to a rapidly diversifying pipeline. RNA therapeutics, cell and gene therapies, and AOCs each require specialised infrastructure, technical expertise and regulatory experience. General-purpose CDMOs may find it increasingly difficult to compete without the depth needed to support complex modalities. At the same time, supply chain scrutiny and policy pressures are reshaping where investment flows and which partners, developers trust. The opportunity lies in those same pressures: developers are consolidating around fewer, more capable partners and placing greater value on reliability, vertical integration and regulatory track record. For specialist CDMOs with proven infrastructure, the environment is favourable.

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