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By Kishore Hotha, Ph.D., Dr. Hotha's Life Sciences LLC

The field of therapeutic development is undergoing rapid transformation, with oligonucleotides and peptides leading the way as promising solutions for addressing a wide array of diseases. However, these advanced molecules present unique complexities that require innovative problem-solving. Developing a practical chemistry, manufacturing, and controls (CMC) strategy for such therapies demands a shift in approach — focusing on precision, driving innovation, and fostering strong collaborations. Mastery of critical quality attributes (CQAs) and strategic partnerships with CDMOs are reshaping CMC methodologies, enabling these sophisticated therapies to become practical, reliable, and impactful solutions.

Why Quality Attributes Are The Heart Of The Matter

Quality isn't just important — it's the foundation of therapeutic success for oligonucleotides and peptides. These molecules rely on their precise structure and purity to work effectively, making **CQAs** indispensable in ensuring safety and efficacy.1 CQAs define the physical, chemical, and biological properties that must be carefully monitored and maintained throughout development and manufacturing. Identifying and addressing these attributes early for oligonucleotides and peptides is critical for minimizing risks and achieving consistent quality.2

Oligonucleotides, often described as tiny strands of genetic instructions, require exceptional sequence accuracy and stability. Even the slightest error in sequence can lead to off-target effects or reduced efficacy. Modifications like phosphorothioate backbones or methylated bases improve stability but complicate impurity profiles, necessitating precise tracking through tools like high-performance liquid chromatography (HPLC) and mass spectrometry (MS). Impurities, such as truncated sequences or chemical anomalies, must be carefully monitored as they can accumulate during production and compromise product integrity. Stability testing is equally important, as oligonucleotides are prone to degradation, which could undermine therapeutic effectiveness. Defining CQAs for these molecules early in development ensures that critical parameters like sequence fidelity, impurity levels, and structural integrity are prioritized and maintained.

Peptides, conversely, are intricate molecules composed of amino acids that require precise sequencing, folding, and modifications to perform effectively. Deviations in their sequence or structural conformation can lead to inactive or harmful products. Proper folding is especially critical, as incorrect structures render peptides ineffective or cause immune reactions. Post-translational modifications (PTMs), such as glycosylation or phosphorylation, further add complexity; these modifications enhance stability and functionality but must be applied accurately to avoid compromising therapeutic efficacy. Aggregation is another significant risk for peptides, as it can reduce effectiveness and increase the likelihood of adverse immune responses.3 Analytical techniques like dynamic light scattering (DLS) and circular dichroism are essential for monitoring aggregation and structural integrity.

Establishing CQAs isn't just about ensuring product quality; it's the backbone of effective collaboration with CDMOs. CQAs provide a shared framework for quality goals, ensuring alignment between developers and manufacturing partners. They enable proactive risk management by identifying potential issues, such as impurity risks or aggregation before they impact production. By allowing CQAs to be in development and production, manufacturers can mitigate risks, maintain consistency, and confidently deliver groundbreaking therapies. From ensuring sequence fidelity in oligonucleotides to preventing aggregation in peptides, CQAs ensure these complex therapies reach their full potential.

Challenges To Overcome In Manufacturing

Solid-phase synthesis — one of the most common oligonucleotide methods — becomes increasingly susceptible to inconsistencies as production scales. Slight variations in reaction conditions or reagent quality can lead to sequence fidelity or structural integrity errors, compromising the final product's therapeutic effectiveness. Peptide manufacturing poses similar challenges, especially with the precise application of post-translational modifications (PTMs). PTMs, such as glycosylation or phosphorylation, must be uniformly applied across the batch. Even a minor error in modification rates can result in defective or inactive products, leading to costly batch failures and delays in development timelines.

Compounding these challenges is the heightened need for advanced purification methods. Larger-scale production often introduces insignificant impurities at more minor scales, requiring processes like ion exchange chromatography or high-resolution HPLC to maintain therapeutic-grade purity. Scaling up can amplify defects without rigorous quality controls at every step, turning minor inconsistencies into significant risks.

Early CDMO Engagement: Setting The Stage For Success

Engaging a CDMO early in the development cycle is critical for navigating the complexities of oligonucleotides and peptides. Take the example of a biotech company developing an oligonucleotide-based therapeutic: early collaboration with their CDMO enabled them to address sequence degradation issues by optimizing synthesis conditions. For peptides, aligning on aggregation risks during folding ensured the development of a robust formulation from the outset.

Proactive alignment on CQAs transforms early challenges into opportunities for streamlined development and accelerated timelines.

Co-Developing Tailored Analytical Methods: Bridging Science And Scale

Identifying draft specification controls and custom analytical methods is vital for monitoring the unique properties of these complex molecules. Consider a CDMO partnership from my real experience where LC-MS techniques were refined to verify oligonucleotide sequences with higher sensitivity during scale-up. For peptides, the collaboration led to the integration of high-resolution HPLC for purity analysis, ensuring batch consistency during late-stage development. These tailored solutions ensure scalability without compromising precision.

Collaborative method development ensures analytical strategies evolve seamlessly from the lab bench to large-scale production.

Scaling Up Without Sacri cing Quality: Lessons From The Trenches

Scaling production for oligonucleotides and peptides presents unique challenges. For instance, one manufacturer that I worked with faced issues with truncated sequences during oligonucleotide synthesis. Early process adjustments by their CDMO minimized these impurities, ensuring therapeutic-grade quality. Similarly, during peptide scale-up, a CDMO implemented a continuous chromatography process to achieve uniformity across batches while maintaining cost efficiency.

Scaling up is more than increasing production — it’s about consistently delivering quality, even under the pressures of scale.

Phase-Speci c Validation: Tailoring Strategies For Success

Validation evolves with the molecule’s life cycle. A practical example involves a biotech startup focusing on oligonucleotide therapeutics: their early-phase validation prioritized impurity profiling and endotoxin control to meet initial safety requirements. By late-stage development, their focus shifted to stability studies and long-term storage conditions, ensuring readiness for regulatory submission. This phase-specific approach saved time and resources while meeting compliance requirements.

Validation strategies that grow with your molecule maximize efficiency and readiness for every regulatory milestone.

Real-Time Monitoring: Practical Tools For Continuous Improvement

Real-time monitoring tools transform process control into a proactive strategy. For example, during one project, online UV detection during oligonucleotide synthesis provided immediate feedback on incomplete coupling reactions, allowing timely adjustments to maintain sequence fidelity. Dynamic light scattering (DLS) was employed for peptides to track aggregation in real time, significantly reducing batch failures during pilot manufacturing.

Real-time monitoring ensures every process adjustment is data-driven, reducing risk and enhancing product reliability.

Aligning Regulatory Strategies: A Case Of Seamless Submission

Collaborating on regulatory strategies simplifies submission processes and mitigates risks. For example, one pharmaceutical company developing a peptide therapeutic worked closely with their CDMO to document impurity profiles and establish stability protocols early in the process. As a result, their regulatory filing encountered minimal questions, cutting approval timelines significantly.3

A well-executed regulatory strategy ensures your molecule moves smoothly through the complex pathways of global compliance.

Building A Future-Proof CMC Strategy With CDMOs: Turning Complexity Into Clarity

A future-proof CMC strategy for oligonucleotides and peptides requires proactive collaboration with CDMOs anchored by well-defined CQAs. Early engagement fosters alignment on molecular complexities and goals, while phase-appropriate analytical methods and scalable processes ensure consistency and efficiency.

Validation and monitoring strategies must evolve to meet regulatory expectations while maintaining product integrity. Leveraging CDMO expertise in scalability and regulatory alignment ensures readiness for commercialization. Integrating these principles creates a resilient, efficient pathway that accelerates innovation and positions your therapeutic for long-term success.

Collaboration and forward-thinking strategies are the cornerstones of delivering transformative therapies to patients worldwide.

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