CMC Process development and risk management in peptide manufacturing

Developing peptide and oligonucleotide active pharmaceutical ingredients (APIs) demands a precise balance of efficiency and attention to compliance. To meet the growing demand for APIs for both clinical and commercial purposes, Bachem has established a comprehensive Chemistry, Manufacturing, and Controls (CMC) development framework. This approach is tailored to each product, ensuring flexibility while maintaining rigorous quality standards. It involves a thorough analysis of process-related risks and ensures full alignment with both clinical timelines and regulatory guidelines.

This overview shares valuable insights into optimising CMC development, characterisation, and risk management — essential to delivering high-quality materials that meet the most stringent clinical and regulatory requirements.

Establishing process understanding

In the initial phase of process development (PD Part 1), historical and experimental data are gathered to define the normal operating ranges and proven acceptable ranges for each process parameter. This data forms the foundation for understanding how the process behaves and where risks might arise. Critical quality attributes (CQAs) and critical process parameters (CPPs) are identified and discussed with customers and related in-process controls (IPCs) are defined and incorporated in the control strategy of the molecule.

Planning for PD part 2

Following an initial risk assessment, attention turns to the second phase of development (PD Part 2). This phase addresses unresolved issues, such as tracking specific impurities or refining process controls. The result is a more detailed and targeted development plan aimed at ensuring the robustness of the process for future manufacturing.

Failure modes and effects analysis (FMEA): Example and application

The risk analysis is performed with the FMEA, which is based on the manufacturing protocol. In this rigorous, line-by-line approach, the risk of every step of the process is defined. For example, during the production of a peptide, a single “line” from the manufacturing protocol focuses on the coupling time of amino acid number seven in cycle eight of SPPS. Through experimental data analysis, normal operating ranges and proven acceptable ranges were determined. The analysis also considered edge cases where coupling extended to longer times.

A coupling time that is too short may result in incomplete coupling, potentially leading to impurity formation — an important concern since purity is a critical quality attribute. Severity, occurrence, and detection scores (on a 1–5 scale) are assigned. For example, a high severity score of 5 reflects the potential patient risk, while an occurrence score of 2 and a detection score of 4 yield a Risk Priority Number (RPN) of 40. Based on this RPN, the risk falls within a zone which indicates that no immediate mitigation is necessary.

Mitigation and reassessment

When higher risks are identified, additional measures are recommended or required before process validation. These may include deeper process development, enhancing impurity detection with additional IPCs, or performing fate and purge studies to demonstrate that impurities are eliminated during downstream processing.

After implementing corrective measures, a second FMEA is conducted to verify risk mitigation effectiveness. If risks are adequately controlled, the process is considered robust enough to move forward.

Finalising for production

Once the process is finalised, a final Master Batch Production Record (MBPR) is compiled. This document is essential for the production of material to be used in clinical Phase III studies or pre-PPQ (Pre-Process Performance Qualification)

batch. At this stage, the final specifications must be defined, and all release methods must be validated.

Process Performance Qualification (PPQ)

Process Performance Qualification (PPQ), also known as process validation, begins with the drafting of detailed validation protocols. These protocols describe how the product will be manufactured and define success criteria. Three consecutive full-scale batches are produced under these protocols. If all batches meet defined criteria , a validation report is prepared to support regulatory approval by demonstrating process consistency and reliability.

Analytical and IPC development

In parallel with process development, analytical methods are developed, refined and qualified. These include tests for purity, peptide content, water content, counter-ion analysis, and microbiological testing. These methods are validated prior to PPQ. IPCs are also developed as part of the control strategy, ensuring in-process quality of intermediates during manufacturing.

Stability and regulatory documentation

Comprehensive stability studies are conducted at multiple levels to support clinical trials and market approval. Additionally, regulatory documentation is prepared for all clinical phases. This includes support for investigational new drug (IND) applications and ultimately, the preparation of a regulatory dossier for market authorization.

Case study: Tailored CMC approaches

Two peptide projects from the same midsize biotech company illustrate how Bachem adapts its CMC strategy to each product.

- **Project 1**: A glucagon analog with a robust and high-purity process early in development.

As a lot of experience with similar molecules was available, only minimal early-stage development was needed, reducing financial risk for the customer. The FMEA was performed later and confirmed the process was well under control. Only minor adjustments were necessary before PPQ. The final regulatory submission was accepted without additional requests for the API production.

- **Project 2**: A more complex GLP hybrid molecule with a fatty acid modification.

Here, development began earlier due to anticipated solubility issues. The FMEA was conducted after supply for clinical Phase II, allowing ample time to define IPCs and complete development before Phase III supply and PPQ. This forward-planning created a highly developed process that made the product attractive for licensing and investment.

Smart risk management in a growing peptide market

The peptide market is rapidly expanding, with over 120 approved products and more than 350 in clinical development. Bachem supplies over 40% of these approved peptides and supports many under development. Its well-defined but flexible CMC framework ensures that each customer's project is managed according to its unique needs.

The FMEA-based approach plays a central role in risk management, and all CMC-related functions receive comprehensive training to apply it consistently. Each development program is tailored, considering the product's complexity, stage of development, and commercial goals. This ensures efficient resource allocation, reduced financial risk, and a clear path to regulatory approval.

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