As peptide-based therapies are increasingly becoming viable drug discovery and development targets, the industry is paying more attention to the quality concerns that underlie peptide-manufacturing processes. Peptide manufacturing can be tedious and time-consuming given the complexity of the product and the lengthy, intricate synthesis process. Regulatory compliance, quality control and quality assurance efforts are critical for the successful development and manufacture of peptides as active pharmaceutical ingredients (APIs). As a key element in the peptide production process, quality should be built into every step and thought of as a process parameter, not a process outcome; this is necessary to ensure the purity of the final product and effectively satisfy regulatory oversight.

**ELEMENTS OF QUALITY**

Achieving product quality and purity requires a meticulous quality-centric approach from discovery to final release of the product. While the notion of quality encompasses all activities designed to ensure the adequacy of manufactured products, protocols for the pharmaceutical industry are usually divided into two separate functions: quality assurance (QA), which oversees the entire manufacturing process and is responsible for the final release and disposition of the product; and quality control (QC), which is responsible for analytical testing and characterisation of raw materials and finished products. Essentially, QC monitors the endpoints of a production run – what comes in and what goes out. QA, by contrast, is responsible for quality throughout the entire manufacturing process.

The analytical chemists who are responsible for QC also ensure that analytical methods are developed and subsequently validated; their assessment of the structural integrity and purity of a peptide is critical during the development stages of a product. Without rigorous analytical characterisation and evaluation of potential impurities at the start of each manufacturing project, problems may be overlooked – only to resurface at a later point in the process, often as product recalls and sometimes with devastating consequences for patient health and safety.

**THE SUM OF ITS PARTS**

A quality system in a pharmaceutical manufacturing environment comprises several components including, but not always limited to, facilities and equipment, laboratory controls, materials, packaging and...
labelling. These components should be designed to incorporate redundancies and fail-safes, as the failure of one component can mean failure of the entire operation.

The facility and equipment component is a critical part of overall quality management, requiring consistent monitoring, maintenance and validation, and possibly a need for calibration. Regular evaluations of the humidity, ventilation and air-control (HVAC) system, compressed gases and water systems are key. These facility- and equipment-specific considerations should be addressed during facility design and then continually improved upon as needs evolve. For example, a quality standard operating procedure (SOP) should mandate regular cleaning and maintenance procedures and, to prevent contamination, it should call for regular testing and monitoring of the controlled environment. Lighting, flooring, potable water and sanitary facilities, as well as sanitisation and pest control, are also important considerations.

It is required that equipment and facility assets – such as pharmaceutical-grade water and emergency power supply systems – be validated prior to use (installation qualification, operational qualification and performance qualification). Clean room and all other controlled areas also need to be qualified prior to use.

**REGULATORY COMPLIANCE**

A focus on quality must have regulatory compliance as its ultimate goal. Adherence to current good manufacturing practices (cGMPs) and a robust documentation programme can ensure reproducible, verifiable quality procedures that stand up to regulatory scrutiny as well as guarantee a high-purity final product.

The US FDA mandates cGMPs as obligatory prerequisites to establishing a robust and reproducible manufacturing process. Apart from general guidelines – including the Code of Federal Regulations (CFR) and ICH (Q7A) Good Manufacturing Practice Guide for API – there is only one guideline specifically dedicated to peptides: the ‘Guidance for Industry for the Submission of Chemistry, Manufacturing, and Controls Information for Synthetic Peptide Substances,’ issued in 1994. The guideline stipulates that lot-release specifications (a set of tests and acceptance criteria that must be met before product is released) must be sufficient to ensure the identity, purity, strength and/or potency of the peptide, and demonstrate lot-to-lot consistency.
Specifically, documentation demonstrates compliance not only with cGMPs but also with 21 CFR 211, Part 211.42 – Design and Construction Features, which stipulates that any “building or buildings used in the manufacture, processing, packing, or holding of a drug product shall be of suitable size, construction and location to facilitate cleaning, maintenance and proper operations”. Companies must also prove compliance with CFR 211, Part 211.63 – Equipment Design, Size and Location, which indicates that equipment used in the “manufacture, processing, packing or holding of a drug product shall be of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance”.

An important step in the documentation process is the focus on accurate labelling and label accountability. This is where a lack of strict controls can spell disaster, as issues with mislabelling can often lead to recalls.

PROJECT ENGINEERING & PROCESS FLOW

Depending on a customer’s needs for a specific peptide manufacturing project, a peptide manufacturer will develop the basis for a manufacturing project design scheme. From there, a conscientious manufacturer will help define parameters for the engineering function, including operational and compliance requirements. Along with providing guided tours of the facilities, engineering the project will also involve assisting clients with preparing regulatory documents, including chemistry, manufacturing and controls (CMCs) and drug master files (DMFs) – at the same time discussing any discrepancies, product testing and technical support. This dialogue needs to be ongoing, starting at the beginning of the project before the initial design, and continuing until after release of the product.

With an approved production batch record, the process begins with qualification of the raw materials and equipment used in the process. The manufacturer must make sure that the in-process testing and verification of critical steps are documented within the production batch records.

A SYSTEMS APPROACH TO QUALITY

Consideration of these elements in a holistic fashion is critical for implementing a sound quality system. Indeed, the key word for any effective approach to quality outcomes is ‘system’. Given that every component of a peptide manufacturing process contributes to the quality of the final product, without a comprehensive systems approach to the entire process even a minor mis-step could compromise final outcomes. An approach that takes into account every miniscule aspect of the manufacturing operation – from documentation to capital equipment – is the surest way to guarantee the final quality of a peptide product.

References


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Peptide-based therapies

Peptides, the most basic of building blocks in physiology, continue to grow in prominence among pharmaceutical manufacturers. With their inherent abilities to block and/or enhance signal transfers in the human body, peptides – when harassed as active pharmaceutical ingredients – can treat a host of metabolic diseases, cardiovascular and heart conditions, and neurodegenerative disorders.

Peptide-based drug targets are being identified at an increasingly rapid pace, both in terms of recently introduced therapies and products in the development pipeline. A recent report by market and technology research firm Frost & Sullivan indicated that more than 40 approved peptide-based drugs are in use today, and approximately 400 are being developed to treat allergies, cancer and Alzheimer’s, Huntington’s and Parkinson’s disease.

Peptide-based therapies tap into the direct hard wiring of human physiology, yielding substantial and far-reaching benefits for drug treatments and therapies. Moreover, developments in peptide manufacturing and implementation have made these amino acid compounds more accessible to the market in terms of cost, flexibility and effectiveness.

Compared with small-molecule drugs, peptides offer lower toxicity, show higher specificity, and demonstrate fewer toxicology issues – and in some cases are leading to the development of new pharmaceutical compounds. For example, two biotechnology firms are currently working with American Peptide Company to develop peptide-based therapies for cardiovascular ailments, and specifically heart failure – a condition affecting 5.3 million Americans. One is a novel chimerical natriuretic peptide in clinical development for an initial indication of acute decompensated heart failure (ADHF). The other is a thrombin peptide that, in preclinical studies, has been shown to minimise cardiovascular tissue damage by initiating a series of anti-apoptotic events.

These examples are just two of the many life science projects currently underway for the development of peptide-based therapies. The manufacture of peptides can, however, be a complex process and requires the careful consideration of manufacturing and process variables.