# Quality Considerations for Peptide APIs

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**More than 50 years after the first peptide hormone (oxytocin) was synthesized,[1] there has been a considerable resurgence of interest in the use of peptides as active pharmaceutical ingredients (APIs). As a result, approximately 10 new peptide pharmaceuticals have been introduced during the last 5 years, compared with about 50 during the previous 50 years or so. While the number of approved peptides is relatively small (approximately 60), peptide drugs still represent a substantial market, with annual sales estimated to be in the range of USD 12 billion, and a growth rate in excess of 4% per year.[2] Not surprisingly, hundreds of peptides are now in various stages of clinical development.**

Peptides are, by nature, relatively complex molecules and their characterization can often be challenging. Unfortunately, they are specifically excluded from many guidance documents and, while general chemistry and manufacturing controls (CMC) requirements for peptides were published in 1994, this guidance was withdrawn in 2006. Even though a guidance document specific to peptides has reportedly been under consideration by FDA for some time, this has still not yet been published. Therefore, in the absence of such a document, sponsors of clinical studies with peptides usually set their own standards for characterization and quality assessment of peptide APIs, often with the assistance of the companies which manufacture the peptides.

Peptides for use in human clinical trials should, of course, be manufactured in strict compliance with **cGMPs**, as defined in *ICH Q7A Good Manufacturing Guidance for Active Pharmaceutical Ingredients*.[3] In addition, the drug substance should be characterized by a combination of different attributes and tests of the drug substance, including the following:

- Appearance
- Solubility
- Identity
  - Mass spectral analysis
  - Amino acid analysis
  - HPLC (comparison with Reference Standard)
- Purity/related substances
- Assay
  - Quantitative amino acid analysis
  - Nitrogen content
- Counterion content
- Water content
- Specific rotation
- Process residuals
  - Residual solvents
  - Trace counterions (e.g. trifluoroacetate, chloride, phosphate, etc.)
- Bioburden
- Endotoxins (LAL)

Additional testing, such as sequence analysis by MS/MS, chiral analysis and NMR analysis may also be performed on reference standard materials.

Of these tests, determination of purity and peptide-related substances is often the most critical and, unfortunately, there is a lack of clear guidance on the levels of organic related substances (i.e., peptide-related impurities) that are permitted in peptide APIs. Guidance for Industry ICH Q3A, Impurities in New Drug Substances, for example, specifies a reporting threshold of 0.05%, an identification threshold of 0.10% and a qualification threshold of 0.15% for drugs which are dosed a level of ≤2 grams per day. Unfortunately, peptides are excluded from the scope of the guidance, leading to a certain level of inconsistency in the demands imposed by regulatory agencies during the review of applications for peptides.

Recently, however, both the US FDA and EMEA have presented the following "unofficial" guidance for limits for related substances:

- **any peptide-related impurity above 0.2% but not more than 0.5% should be minimally identified and characterized;**
- **any peptide-related impurity above 0.5% should be fully identified and characterized; and**
- **any peptide-related impurity above 1.0% should be fully identified, characterized and qualified.**

It should be noted that these limits are, technically, only required at the time of registration. However, while they are considerably less challenging than those specified in ICH Q3A, they still require the development of an analytical method for purity determination which is both capable of resolving impurities and also capable of attaining a limit of quantitation which is below 0.2%. It is important that the investment in the development of such an analytical method (typically based on reverse-phase HPLC) should be made at an early stage of product development, in order to allow tracking of changes in the impurity profiles of the product as the manufacturing process is developed and optimized. This method development, which is often supported by LC-MS studies, is typically carried out using samples of the product which have been "stressed", for example by heating or subjecting to extremes of pH, since it is important to demonstrate that the method can separate degradation products, as well as impurities which are derived from the manufacturing process. Such development work will establish confidence in the suitability of the method to support the proposed clinical studies, and also that it is stability-indicating.

It is, of course, not a requirement for analytical methods to be fully validated at early stages of clinical development. However, the method development or "qualification" studies described above are extremely important, both from a regulatory perspective and also a "project risk" perspective. Sponsors of clinical studies should ensure that potential suppliers of the peptide API for their proposed studies meet the strictest of requirements, not only for their technical expertise and their compliance with GMPs, but also their ability to objectively develop and qualify discriminating methods for determination of peptide purity. As noted in a previous article on the subject,[4] the consequence of not doing this at an early stage of the project could be disastrous if a substantial and previously undetected impurity were to be discovered during late-stage clinical development.

**Clearly, therefore, price should not be the only criterion used in the selection of a supplier of a peptide API. At the end of the day, the cost of the peptide is "dwarfed" by the relatively enormous cost of conducting clinical trials. Therefore, the risk of using a supplier which does not have a reputation and track record for both delivering products of high quality and also providing technical and regulatory support for the project through all phases of clinical development and commercial launch, should be carefully evaluated.**

## References


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Dr. Michael Verlander is Executive Vice President and co-founder of PolyPeptide Laboratories, Inc., in Torrance, California, a position he has held since 1996. In this role, he has responsibility for the Quality and Regulatory Affairs functions in the company, and has guided the company through five successful Pre-Approval Inspections by FDA since the company's inception. PolyPeptide Laboratories, Inc. is a part of the PolyPeptide Laboratories Group, which is one of the leading contract manufacturers of peptides for use as Active Pharmaceutical Ingredients. Dr. Verlander has served as Director of Global Quality Assurance and Regulatory Affairs for the PolyPeptide Laboratories Group since 2003.

Prior to joining PolyPeptide Laboratories, Inc., Dr. Verlander was Vice President, Technical and Regulatory Affairs at Bachem California, Torrance, California (1986 - 1996); Director, Peptide Research and Peptide Production, Immunetech Pharmaceuticals, San Diego, California (1985 - 1986); and Research Director, BioResearch, Inc., San Diego, California (1978 - 1985).

Dr. Verlander was previously a member of the research faculty at the University of California, San Diego, Department of Chemistry (1972 - 1978). He completed his postdoctoral training at the Salk Institute for Biological Studies, La Jolla, California, after receiving his D.Phil. degree in Organic Chemistry from the University of Oxford in 1970. Dr. Verlander received his B.A. degree in Chemistry from the University of Oxford in 1967 and his M.A. degree in Organic Chemistry from the University of Oxford in 1968.

Dr. Verlander has authored more than 50 scientific papers and numerous patents on peptides and related topics.