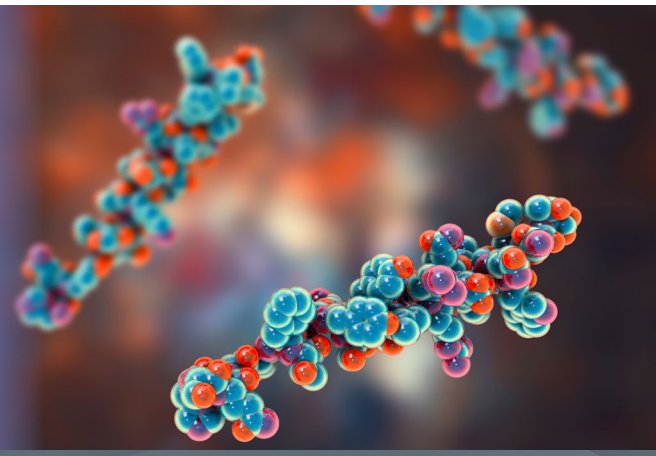
# Peptide Drugs: Clinical and Bioanalytical Drug Development



Peptide therapeutics are characterized by target selectivity, good efficacy and a favorable safety profile compared to small molecule drugs. In general, therapeutic peptides are composed of 40 or fewer amino acid and < 50 kDa, which distinguishes them from protein drugs.

Peptides usually have short half-lives and are rapidly eliminated by proteolytic cleavage processes. However, chemical or (albumin)-linker modifications or the use of modified amino acids during manufacturing can extend the half-life of peptide drugs from hours to days or even weeks and make oral administration more feasible. Extended half-lives allow a reduced dosing frequency, which can help limit the number of adverse effects and promote better drug adherence.

## Peptide Therapies and Administration Routes:

Peptide drugs can be administered via several routes. There are certain considerations and preferences that may drive the route of administration.

**Subcutaneous Injection:**

- Most common route for peptide drugs
- Administration procedures can be device-specific, requiring clinical staff and participant training
- Must evaluate for potential injection site reactions

**Oral:**

- Non-invasive route
- Gaining appeal as peptide stabilization technologies are overcoming gastric pH and enzymatic degradation challenges

**Inhalation & Intranasal:**

- Routes of interest for targeting peptides towards the lungs and brain, respectively

## Celerion Differentiators:

**Experience:**

- Conducted 45 peptide studies in the past decade
- Experience with multiple routes of administration for peptides (e.g. oral, inhalation and subcutaneous)

**Expertise:**

- Senior scientific team including Principal Investigators (PIs) and Protocol Writers with extensive peptide drug experience
- Peptide drug experience spans several therapeutic areas including metabolic disease, hormonal disorders, bone disease, and neurology (e.g. GLP-1 analogs and teriparatide)

**Efficiencies:**

- Vast database of healthy volunteers including drug naïve subjects
- Full bioanalytical capabilities to support protein & peptide drug development

## Recommended Clinical Pharmacology Studies for Peptide Drug Development:

Healthy volunteers (HV) studies can expedite peptide drug development. Particularly, clinical pharmacology studies in HV provide robust pharmacokinetic (PK) data compared to patient trials. Here is a list of recommended clinical pharmacology studies for peptide drug development, including when HV can be considered.

| Study Type | Recommendation | Study Population |
|---|---|---|
| Single Ascending Dose (SAD) | Required | HV often feasible |
| Multiple Ascending Dose (MAD) | Usually required | Potentially in HV (depending on drug characteristics) |
| Bioavailability/Bioequivalence (BA/BE) | In case of formulation change | HV often feasible |
| Drug-Drug Interaction (DDI) | If peptide modulates CYP enzyme or transporter activity; or in case of potential PD interaction | Potentially in HV (depending on drug characteristics) |
| Renal Impairment (RI) | Recommended | RI patients & HV control group |
| Hepatic Impairment (HI) | Recommended | HI patients & HV control group |
| Immunogenicity | Recommended | HV often feasible |
| Thorough QT (TQT) | If peptide modulates cardiac ion channels | HV often feasible |

**CYP**, cytochrome P450 enzyme; **PD**, pharmacodynamic

## Native vs. Exogenous Peptides:

- For peptide drugs that are recombinant homologues of endogenous peptides, PK concentrations need to be corrected for baseline levels of the endogenous peptide.
- If peptide drugs are not fully homologous mimetics of endogenous peptides, the endogenous peptide may still be able to interfere with the bioanalytical assay.
- Unless the bioanalytical assessment differentiates the peptide drug from the native peptide, pretreatment with antibodies against the human peptide may be required.

## Bioanalytical Capabilities & Platforms:

| State-of-the Art Platforms for Peptide Analysis | Cutting-Edge Cell Profiling and Functional Assays | Automated Approaches Support High Throughput Analysis |
|---|---|---|
| ✓ AlphaLISA<br>✓ ELISA<br>✓ Gyrolab®<br>✓ LC-MS/MS<br>✓ MSD<br>✓ SIMOA | ✓ Cell Signaling<br>✓ ELISpot<br>✓ Flow Cytometry<br>✓ Intracellular Markers<br>✓ Oxidative Stress Analysis<br>✓ Reporter Gene Assays | ✓ High and ultra-sensitive assays<br>✓ Large dynamic range<br>✓ Low matrix interference |

**ELISA**, enzyme-linked immunosorbent assay; **LC-MS/MS**, liquid chromatography with tandem mass spectrometry; **MSD**, meso scale discovery; **SIMOA**, single molecule array

## RESOURCES:

Key Clinical Pharmacology Studies to Support Biologic Drug Regulatory Submission

Bioanalysis of Peptide Drugs

Clinical Pharmacological Considerations for Peptide Drug Development Video

Perpetrator or Victim: Evaluating Therapeutic Proteins in Drug-Drug Interaction Studies