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Quality Control Status and Research Progress of Synthetic Peptide Pharmaceuticals

1.Research Background

Synthetic peptide medicines sit between small-molecule chemicals and biotech drugs, combining high purity & good stability of small-molecule drugs as well as high bioactivity and low toxic side effects of biologic products. The global peptide pharmaceutical market expands rapidly: global annual sales exceeded USD 50 billion in 2019, with over 170 peptide candidates under clinical trials and dozens of new agents approved by FDA annually from 2017 to 2022 including Semaglutide, Tirzepatide and Abaloparatide.

Nevertheless, peptide molecules feature structural heterogeneity caused by amino acid isomerization and side-chain modification; complicated chemical synthesis routes create diverse impurity profiles harder to identify than conventional small-molecule drugs. Current global regulatory guidance for synthetic peptide quality management is limited: FDA revoked its early peptide guidance in 2002, USP issued <1503> in 2021, EMA began drafting relevant guidelines in 2022, while NMPA

updated its technical guidance draft for synthetic peptides in late 2022. Fragmented regulatory standards bring prominent obstacles to uniform quality control of synthetic peptide drugs. Besides, inherent drawbacks including short in-vivo half-life and poor oral bioavailability once restricted clinical application, though novel modification and sustained-release technologies have partially solved these bottlenecks recently.

2.Research Significance

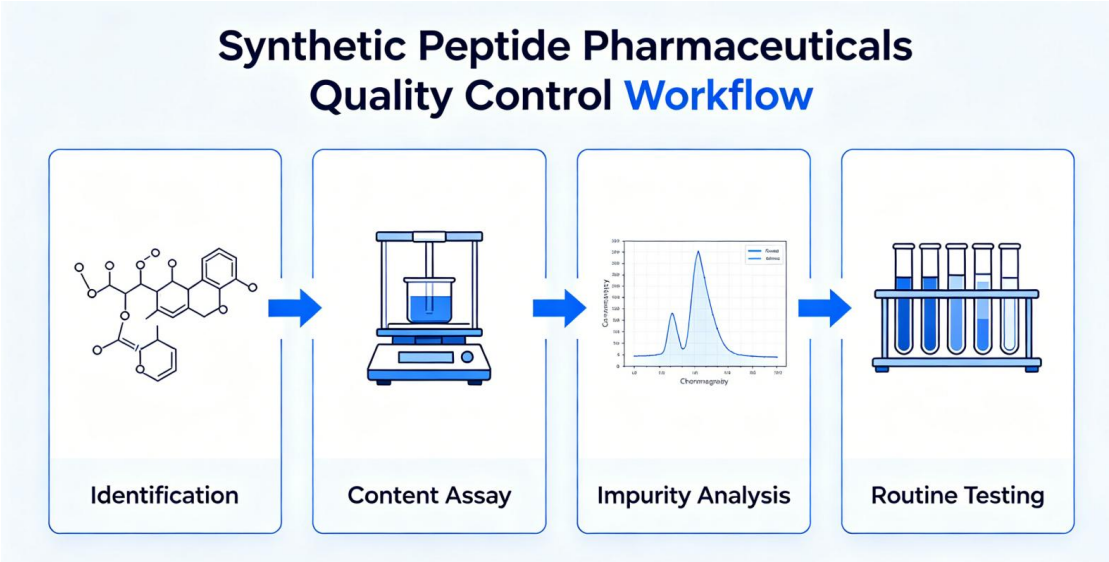
This summary sorts out mainstream global regulatory requirements and latest analytical technologies for synthetic peptide quality control. It helps pharmaceutical R&D and production teams systematically grasp standardized inspection specifications covering identification, content assay and impurity control. The summarized control strategies can guide domestic and overseas pharmaceutical enterprises to optimize synthetic processes, reduce miscellaneous impurities and accelerate the R&D and registration of innovative & generic peptide drugs. Meanwhile, it provides practical reference for regulators to refine targeted industrial standards and promotes standardized, high-quality development of the global synthetic peptide industry.

3.Research Content

- The research systematically sorts synthetic peptide quality control frameworks based on USP, EP, NMPA and ICH guiding principles, splitting core research into four core modules: identification testing,

active ingredient quantification, multi-category impurity analysis and auxiliary routine property inspection.

- Item of Identification: Summarize mainstream identification approaches across global pharmacopoeias, including RP-HPLC, mass spectrometry, amino acid analysis(AAA), NMR, UV/IR spectroscopy, peptide mapping and biological activity testing, and compare application frequency of each method in ChP, USP, EP and Indian Pharmacopoeia.



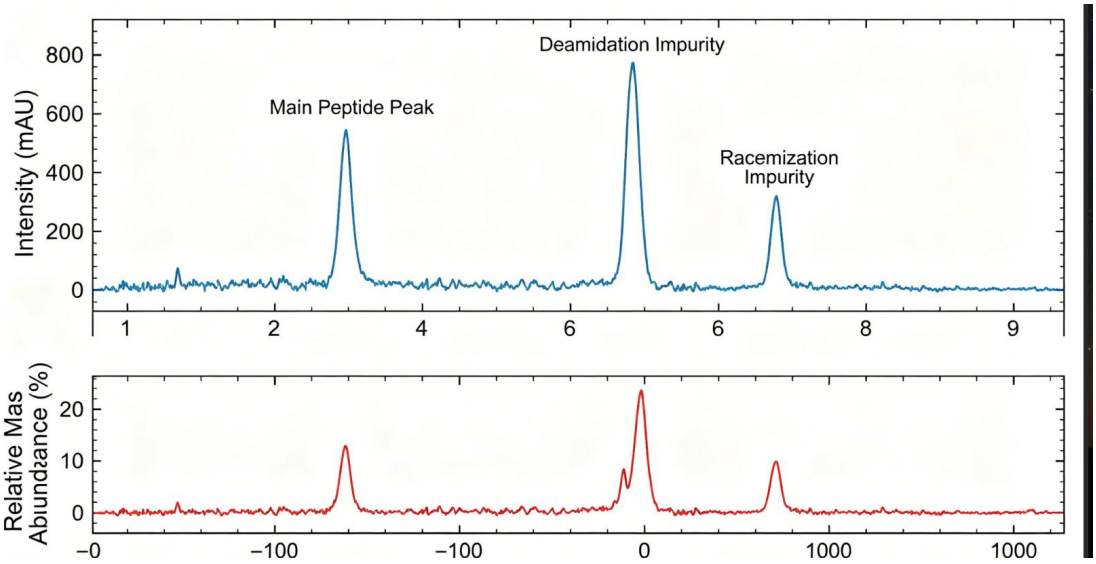
- Peptide Content Determination: Collect common quantitative techniques such as HPLC external standard method, QNMR, UV spectrophotometry, nitrogen quantification and mass balance calculation, and clarify applicable scenarios for each testing technology.
- Impurity Research: Classify impurities into peptide-related impurities and non-peptide impurities, elaborate impurity generation sources, specific subtypes and corresponding orthogonal detection methods;

organize impurity limit criteria from ICH, EP and Chinese draft guidance.

- Additional Quality Tests: Cover routine physicochemical indicator detection including isoelectric point, optical rotation, water content, counter-ion content, microbial limit and bacterial endotoxin test.

4.Research Results

- Identification: RP-HPLC is the preferred identification method worldwide; MS serves as critical supplementary identification in USP; amino acid composition analysis is gradually phased out yet still widely adopted by EP. For peptides with specific tertiary structures, cell-based bioassay is recommended as an orthogonal identification verification.
- Content Testing: RP-HPLC external standard is the dominant quantification method. QNMR and ultraviolet detection are efficient supplementary means; mass balance and elemental analysis are classic absolute quantification methods for raw material standard calibration without official reference standards.



- Impurity Control: Peptide-associated impurities mainly derive from amino acid deletion, substitution, racemization, deamidation and aggregation, requiring orthogonal chromatographic combinations including RP-HPLC, HILIC, SEC and ion-exchange HPLC coupled with high-resolution MS for full-spectrum detection. For non-peptide impurities such as residual solvent and elemental contaminants, GC and ICP-MS are standard detecting tools. In terms of impurity thresholds, EP and the latest NMPA draft set consistent limits: 0.1% reporting threshold, 0.5% identification threshold and 1.0% qualification threshold, stricter standards of ICH Q3A are not applicable to peptide products.
- Auxiliary Inspection: Capillary isoelectric focusing, Karl Fischer titration and ion chromatography are mature standard detection methods for isoelectric point, moisture and counter ion respectively.

5.Discussion

Along with rising complexity of newly-developed synthetic peptides (long-chain peptides, cyclic peptides and peptide-drug conjugates), existing analytical technologies face new challenges on full impurity characterization. Current inconsistent global regulatory guidelines restrict unified industrial quality benchmarks, calling for further detailed regulatory specifications focusing on impurity profiling and limit formulation.

In the future, combined multi-dimensional orthogonal analytical techniques and Quality by Design(QbD) philosophy will become mainstream directions for synthetic peptide quality control. Continuous progress in peptide cyclization, PEG modification and oral delivery technology will further expand clinical application scope of peptide medicines, while pushing iterative upgrading of corresponding quality control standards and analytical methodologies for the whole industry.