Public Comment: Peptide API Testing Standard

Docket	HHS-OASH-2026-0496, Enforcement Discretion Policy Regarding 503A Compounding Using Certain Peptide Bulk Drug Substances
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I am a PhD chemist with about 25 years in pharmaceutical quality and regulatory affairs, supplying bulk drug substances to 503A and 503B compounders. I support a quality based alternative to research use only peptides. These comments address the testing standard and supplier information requirements in Appendix B, which as drafted is ambiguous on several points.

I request that HHS clarify the following:

I. The acceptance thresholds intended for peptide related impurities, given that ICH Q3A excludes peptides.

II. Aggregates, higher order structure and biological activity are characterization tests, not lot release tests.

III. Conditional tests apply only when their condition is met, as in USP <1503>.

IV. The “intended dosage form” statement may be met by stating the routes the lot’s testing supports.

V. What evidence satisfies the Immunoassay row, and where each footnote 1 item beyond standard COA content is expected to reside.

I. Peptide related impurity limits and ICH Q3A

Appendix B sets the acceptance criteria for peptide related impurities (individual specified, any unspecified and total) as “Comply with ICH Q3A.” USP <1503>, which the same row cites, notes that ICH Q3A(R2) sets 0.10% for unspecified impurities at doses up to 2 g/day, but that “peptides are excluded from this guideline.” It also notes the higher identification threshold (0.5%) adopted by the European Pharmacopoeia, and adds that FDA “may consider the limits for unspecified impurities for new peptides on a case-by-case basis.” As drafted, suppliers, compounders and inspectors can apply different limits to the same chromatogram, and that difference decides whether a lot passes.

Request: state the reporting, identification and qualification thresholds intended for peptide related impurities in these six substances, or confirm that the ICH Q3A(R2) thresholds are to be applied to them as written.

II. Aggregates, higher order structure and biological activity: characterization, not lot release

Appendix B lists these three attributes “for complex peptides 8 amino acids or larger” and cites USP <1503>, but does not state whether they must be tested on every lot. Of the six Appendix A peptides, only BPC-157 (15 residues) and MOTS-c (16 residues) reach that threshold; the other four are 7 residues or fewer. USP <1503> answers the frequency question. Its Table 2 marks the tests “recommended… as part of the release”; higher order structures, bioidentity and optical rotation do not carry that mark. Bioidentity is described as “no longer a routine test for most peptides,” though it “may be required for large peptides or those with complex sequences,” and the chapter states that “for small molecules and many simple, small peptides, bioassay methods are not used for release once the more precise physicochemical methods are validated and justified.” It adds that for “more complex or long peptides, regulatory authorities may require that a bioassay remain as a release test.” Neither BPC-157 nor MOTS-c is large or conjugated, and neither contains a disulfide. Aggregates appear in <1503> as an impurity class (oligomers, measured by SEC and orthogonal techniques) to be characterized.

There is also a practical problem. Higher order structure is described in <1503> as an attribute “in aqueous solutions,” and aggregation depends on pH, ionic strength, buffer and concentration. The API supplier does not know the compounder’s formulation, so lot by lot results on the dry API say little about the compounded product.

Request: clarify that these three attributes may be established by characterization of at least three representative batches of the manufacturer’s process, consistent with the three batch approach USP <1503> recommends for stereoisomeric purity, repeated on significant change (site, synthetic route, purification or lyophilization process), and that the lot COA may reference the characterization report, which the supplier makes available to the compounder and to regulators on request.

III. Conditional tests should carry their conditions

Appendix B already conditions several rows: thiol groups (“Required only if Cysteine is present”), host cell related impurities (“for recombinant product”), the three attributes limited to complex peptides of 8 or more amino acids, and nitrosamines (“when applicable”). Two rows that USP <1503> conditions carry no condition in Appendix B:

Test	Condition in USP <1503>
Residual fluoride	Required if hydrofluoric acid is used, e.g. Boc chemistry
Elemental impurities	Required if metal catalysts are used; otherwise based on risk assessment

Most commercial peptide synthesis uses Fmoc chemistry without hydrofluoric acid.

Request: clarify that these tests apply when their stated condition is met, and that a documented justification in qualification documents satisfies the requirement otherwise.

IV. The "intended dosage form" statement

Footnote 1 to the testing table requires "a statement of purpose (i.e., intended dosage form, such as injectable, oral, etc.)." The Table 1 footnote adds that if the substance is intended for an alternative dosage form, tests specific to that form should be reported on the COA. A bulk supplier to 503A pharmacies cannot know at release whether a given lot will become an injection, a capsule, a troche or a nasal spray; that is decided by the prescriber and the compounder.

Request: clarify that the requirement is met by a statement of the dosage forms the lot's testing supports, for example "suitable for compounding subcutaneous, intramuscular, oral and topical dosage forms" for BPC-157, matching the routes in Appendix B, with injectable routes stated only for lots tested for bacterial endotoxins.

V. The Immunoassay row, and where footnote 1 information belongs

- **Immunoassay row:** It lists in vitro adaptive and innate immunogenicity assays, ELISA and surface plasmon resonance. The row cites FDA's guidance on Immunogenicity Assessment for Therapeutic Protein Products (August 2014), which centers on clinical risk mitigation, immunogenicity risk profiling, and patient factors rather than quality control release tests for synthetic peptide APIs. USP <1503> instead ties immunogenicity risk to the impurity profile and states that "more sensitive and specific LC-HRMS method is recommended for characterizing peptide-related impurities." **Request:** state what evidence an API supplier is expected to provide for this row, and confirm whether peptide related impurity characterization by LC-HRMS or other equivalent method satisfies it.
- **Footnote 1** lists 14 items of API and manufacturer information but does not say where they must appear. **Request:** clarify where each item in footnote 1 beyond ICH Q7 Section 11.4 COA content and the manufacturing site required on the COA by condition 4 is expected to reside: on the lot COA, in supplier qualification documentation provided to the compounder, or in records available on request. Static substance data (structure, sequence, formula, molecular weight) are already published in Appendix B. Because condition 5 requires compounders to report the manufacturer's facility identifier, I suggest the manufacturer FEI appear on the COA and the remaining items reside in qualification documentation.
- **Table 1 footnote 1** (injectable specific CQAs) is attached only to Solubility, while the same text in the main table is attached to Bioburden and Bacterial Endotoxins. **Request:** confirm the intended placement.

Closing

The policy's goal, moving patients from research use only material to characterized, CGMP sourced API, depends on a testing standard that suppliers, compounders and inspectors interpret the same way. The clarifications above do not ask for less assurance; they ask that each attribute be controlled where it is meaningful, by lot release or characterization, as USP <1503> already provides. Left ambiguous, the same requirement will be read differently by each supplier and each inspector, which serves neither quality nor patients. I would welcome the chance to discuss any of these points.

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