

FDA PEPTIDE PSG: INDUSTRY PERSPECTIVES ON RISK- BASED DEVELOPMENT AND AREAS REQUIRING CLARITY

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PRESENTATION OVERVIEW

FDA Peptide PSG: Industry Perspectives on Risk-Based Development and Areas Requiring Clarity

01 Shelf-life Comparability & Worst-Case Storage

02 Higher-Order Structure: "Where Applicable"

03 Biological Activity: "Where Appropriate"

04 Recombinant Peptides: Non-Clinical Risk Assessment

PEPTIDE PSG: A RISK- BASED PATH TO REVIEW - READY LIFECYCLE COMPARABILITY

1 FDA DRAFT PSG

Comparative analyses should include:

- ≥3 test batches at or near release
- ≥3 test batches at end of shelf life
- ≥3 RLD batches aged prior to expiry

All aged under conditions consistent with the worst-case label storage conditions.

Industry concern

Waiting for 18–24 month test-batch data may prevent first-cycle approval.

2 INDUSTRY- PROPOSED BRIDGING PATH

Maintain scientific rigor without delaying review

1 **During submission - Scale-up bridge**

Demonstrate sameness of 3 laboratory-scale batches versus 3 ANDA exhibit-scale batches using the same formulation, API and proposed commercial packaging.

2 **Mid-cycle – Shelf-life data**

Compare near-shelf-life laboratory batches (18/24 months), available aged exhibit-batch samples, and 3 RLD batches; submit the mature comparative data package in a mid-cycle DRL

Request to FDA

Please clarify whether FDA consider a pre-specified, risk-based bridging strategy for near-shelf-life data package?

3 CLARIFICATION REQUEST

Application of "worst-case label storage"?

Examples covered by one question

- Refrigerated vial: up to 12 months at 20–25 °C
- Multidose pen: 56-day in-use storage at 15–30 °C or refrigerated

Request to FDA

Please clarify can testing three batches under the worst-case labelled storage condition eliminate the need for additional data under each alternative storage or in-use condition?

HOS "WHERE APPLICABLE": INDUSTRY INTERPRETATION OF A TIERED EVIDENCE APPROACH

FDA PSG: "Higher order structure (e.g., secondary and tertiary structure, and aggregates), where applicable."

TIER 1

Assess Secondary & Higher-Order Structure

Test product and RLD, in the proposed formulation

- Far-UV CD: secondary-structure profile
- FTIR: orthogonal backbone confirmation
- SEC / aggregate assessment: monomer, oligomer and aggregate profile

Decision: Is the peptide predominantly unstructured in both Test and RLD?

NO / UNCLEAR

YES, justify omission of higher order structure study

TIER 2

Resolve residual uncertainty

Triggered only when Tier 1 is inconclusive or shows structure organization

- 1D NMR: chemical environment and conformational behavior
- 2D NMR (NOESY/ROESY): persistent spatial contacts
- Fluorescence / thermal studies:
- Aggerates study by orthogonal methods

INDUSTRY INTERPRETATION

If Tier 1 provides concordant evidence that Test and RLD are predominantly disordered, detailed Tier 2 HOS characterization should not be necessary.

Tier 2 should be risk-triggered

CLARITY REQUESTED FROM FDA

Please clarify whether FDA agree with the proposed tiered approach and clarify the circumstances under which additional HOS characterization would be warranted?

BIOLOGICAL ACTIVITY "WHERE APPROPRIATE": INDUSTRY CASE STUDY

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FDA PSG: Biological/functional assays are not always needed if the formulated peptide can be shown to lack functional secondary or higher-order structure.

PATH A | PRODUCT-SPECIFIC DATA

Analytical demonstration

Use orthogonal Test/RLD data to show absence of functional HOS:

- Far-UV CD
- FTIR
- Aggregation assessment
- NMR and orthogonal aggregate only if the initial evidence is inconclusive

Proposed outcome: comparative bioactivity testing not needed

PATH B | PUBLISHED EVIDENCE

Mechanism-based justification

Use published information to establish that biological function is driven by the primary sequence rather than a stable folded conformation.

Support with product-specific evidence confirming:
- Test and RLD have the same primary sequence
- Published evidence is relevant to the same molecule, mechanism and formulation context

FDA acceptance of literature as sufficient evidence requires clarification

INDUSTRY REQUEST & CLARIFICATION

Please clarify whether either pathway can justify that comparative biological activity testing is not needed?

RECOMBINANT PEPTIDES: PROPOSED RISK- BASED NON- CLINICAL APPROACH

Case study: resolving residual safety risk from host-cell and process-related impurities

FDA EXPECTATION — Use manufacturing/process controls and targeted comparative analytical studies to control recombinant-process impurities; discuss non-clinical assays through a pre-ANDA meeting.

RECOMBINANT- SPECIFIC RISK

Characterize and control

- Host cell proteins (HCP)
- Residual host-cell DNA
- Other process-related impurities
- Aggregates / higher-molecular-weight species

Proposed evidence

Validated process controls + targeted impurity testing + relevant compendial limits + toxicological risk assessment

INDUSTRY- PROPOSED DECISION PATH

Target studies to the identified residual risk

LOW RESIDUAL RISK — Analytical/process-control package sufficient → no additional non-clinical assay proposed

UNRESOLVED RISK — Request FDA to clarify on targeted non-clinical assay :

- Innate immune activation / cytokine-response assay for immunostimulatory impurity risk
- Cell-based functional assay where a biologically active impurity is plausible
- Targeted local-tolerance or repeat-dose study only if analytical/in vitro evidence cannot resolve the safety concern

INDUSTRY REQUEST & CLARIFICATION — Please clarify whether a risk-based approach can support no additional testing for low residual risk and targeted testing for unresolved risk?

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Thank You