U.S. FOOD & DRUG ADMINISTRATION

Advancing Bioequivalence for Peptide, Inhalation, and Long-Acting Products

Recent PSG Updates and Opportunities for Improvement

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Outline

Peptide products	Recent PSG updates and opportunities for improvement
Inhalation products	BE approaches, common deficiencies and future directions for PSG improvement
Long-acting injectables (LAIs)	PSG overview, in vitro-only BE examples and research gaps to guide future PSG improvement

Peptide PSGs: Updates and Improvement

Recent draft PSG updates

Manufacturing origin

Recommendations for recombinant, synthetic, and semi-synthetic peptides

Impurity assessment

Revise reporting, identification, and qualification thresholds for peptide-related impurities

Structure and activity

Clarified that structure and activity testing to the peptide can be omitted with justification

Innate immune assessment

Clarified that in vitro tests are unnecessary when aggregation profiles are comparable and all process related impurities meet compendial standards

Opportunities for improvement

Clarify regulatory expectations for controlling process related impurities in recombinant process

Provide guidance on addressing impurities when they are outside of the thresholds

Clarify assay selection, validation and justification needed for supporting omission of testing

Clarify how to demonstrate aggregate comparability

2026 CRCG Workshop “Navigating the GLP-1 Generic Drug Pathway”: https://www.complexgenerics.org/education-training/navigating-the-glp-1-generic-drug-pathway/

Inhalation PSGs: Current BE Framework

Product-specific BE	Recommendations depend on the drug, formulation and delivery system: metered-dose inhalers (MDIs), dry powder inhalers (DPIs) and nebulized products.
Core evidence	Compare aerosol performance and systemic exposure. Product and device comparisons address delivery to the lung and use under labeled conditions.
Two BE approaches	Selected PSGs offer an alternative with expanded in vitro testing and PK studies, or an approach that includes comparative clinical endpoint or pharmacodynamic evidence.
Formulation and device	Eligibility depends on the selected option. Justify formulation differences and evaluate device attributes and user interface comparability.

Alternative approaches provide alternative studies to comparative clinical endpoint studies while retaining in vivo PK evidence.

Evidence in Alternative Inhalation BE Approaches

Aerosol performance	Single actuation content and aerodynamic particle size distribution (APSD). Apply PSG-specific flow rates, product lifestages and statistical comparisons.
Lung delivery	Realistic APSD uses mouth–throat models and representative inhalation profiles.
Drug dissolution	For relevant products, use a validated, reproducible dissolution method that discriminates meaningful formulation or manufacturing differences.
PK and modeling	PK studies with and without charcoal block, where specified, assess exposure with reduced GI contribution in the charcoal arm. Credible modeling can support interpretation. Alternative to charcoal block study (e.g., pAUC).

Common BE Deficiencies

- Inadequate documentations
  - Missing SOP/Protocol/CoA
  - Incomplete method development/ validation reports
  - Expired products without supporting stability data
  - Failed pivotal BE study reports
  - Raw data
- In vivo BE study
  - Subject exclusion without justification/supporting data
  - Protocol deviation
- In vitro BE study
  - Blinding/randomization
  - Actuation method and optimization of number of actuation
  - Outliers/Highly variable data
  - Repeat analysis
  - Analytical method
  - Mass balance

Future Efforts for Inhalation PSGs

Proposed priorities to improve scientific clarity and implementation

1 Strength Waivers	2 Study Relevance and Redundancy	3 Methods and Interpretation	4 Formulation and Global Alignment
Reduce testing across strengths when a scientific bridge supports BE.	Retain studies that resolve distinct uncertainties in product performance.	Improve predictability of method development and data assessment.	Clarify eligibility for alternative BE options and align approaches where appropriate.
Key considerations When can one strength or bracketing represent the product range? Which in vitro and PK studies can be waived? What evidence supports the bridge?	Key considerations When are both conventional and realistic APSD needed? What does morphology add to the evidence? Which tests can be removed without losing assurance?	Key considerations How should methods show sensitivity and discriminatory ability? How should mass balance, variability and repeat testing be handled? What examples would improve submissions?	Key considerations When is Q1/Q2 sameness important? What supports an alternative formulation? Which study designs and analyses can align with other agencies?

Reproduced from Dr. Bryan Newman's presentation in CRCG 2026 Workshop on Inhalation Products: https://www.complexgenerics.org/education-training/advancing-bioequivalence-frameworks-for-inhalation-drug-products-optimizing-in-vitro-in-vivo-and-in-silico-methods/

LAI Generics: Overview and PSG Progress

A broad formulation landscape with increasingly diverse BE approaches

Dosage forms	Drug suspensions, polymer microspheres, in situ forming implants/gels, solid implants and multivesicular liposomes.
BE approaches	BE studies with PK endpoint. Selected products offer in vitro-only BE. Others combine in vitro and PK studies. Modeling can provide complementary evidence.
Remaining gaps	Microspheres remain an opportunity for more efficient BE approaches.

The BE pathway follows the specific RLD, formulation and release mechanism.

Example Recommendations for In Vitro-Only BE

Selected suspension, in situ depot and solid implant PSGs

Drug suspension	Paliperidone palmitate: Q1/Q2, particle-size BE and discriminatory IVRT, supported by solid-state, morphology and suspension characterization.
In situ depot	Leuprolide acetate: Q1/Q2 and extracted-polymer characterization, complete drug-release comparison and supportive N-methyl-2-pyrrolidone (NMP)-release data.
Solid implant	Dexamethasone intravitreal implant: Q1/Q2, IVRT, extracted-polymer characterization and comparison of microstructure, mechanics and degradation.
Methods and integrated assessment	Provide complete method development and validation reports. Assess IVRT, polymer and physicochemical data together, interpreting differences across studies.

An integrated assessment links composition, characteristics, structure and release performance.

Research Gaps to Inform Future LAI PSGs

More specific methods and acceptance considerations with justified flexibility

Method development	Identify which test conditions best capture release mechanisms. Define how sample preparation and acceleration affect method relevance and reproducibility.
Discriminatory ability	Identify meaningful formulation and process variations for validation. Determine which methods detect changes that matter to in vivo performance.
Acceptance considerations	Clarify how to determine comparability. Provide more guidance on implementing holistic approach when analyzing in vitro BE and characterization studies.
Specificity and flexibility	Develop and recommend specific experimental conditions and/or parameters for method validation.

Research should support clearer recommendations and scientifically justified alternatives.

Summary

- Provide complete method development and validation information.
- Apply a holistic approach to interpret findings across studies.
- Clarify acceptance considerations, including variability and the relevance of observed differences.
- Address research gaps to support more specific recommendations on methods.
- Preserve flexibility for scientifically justified alternative approaches.

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Thank You

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