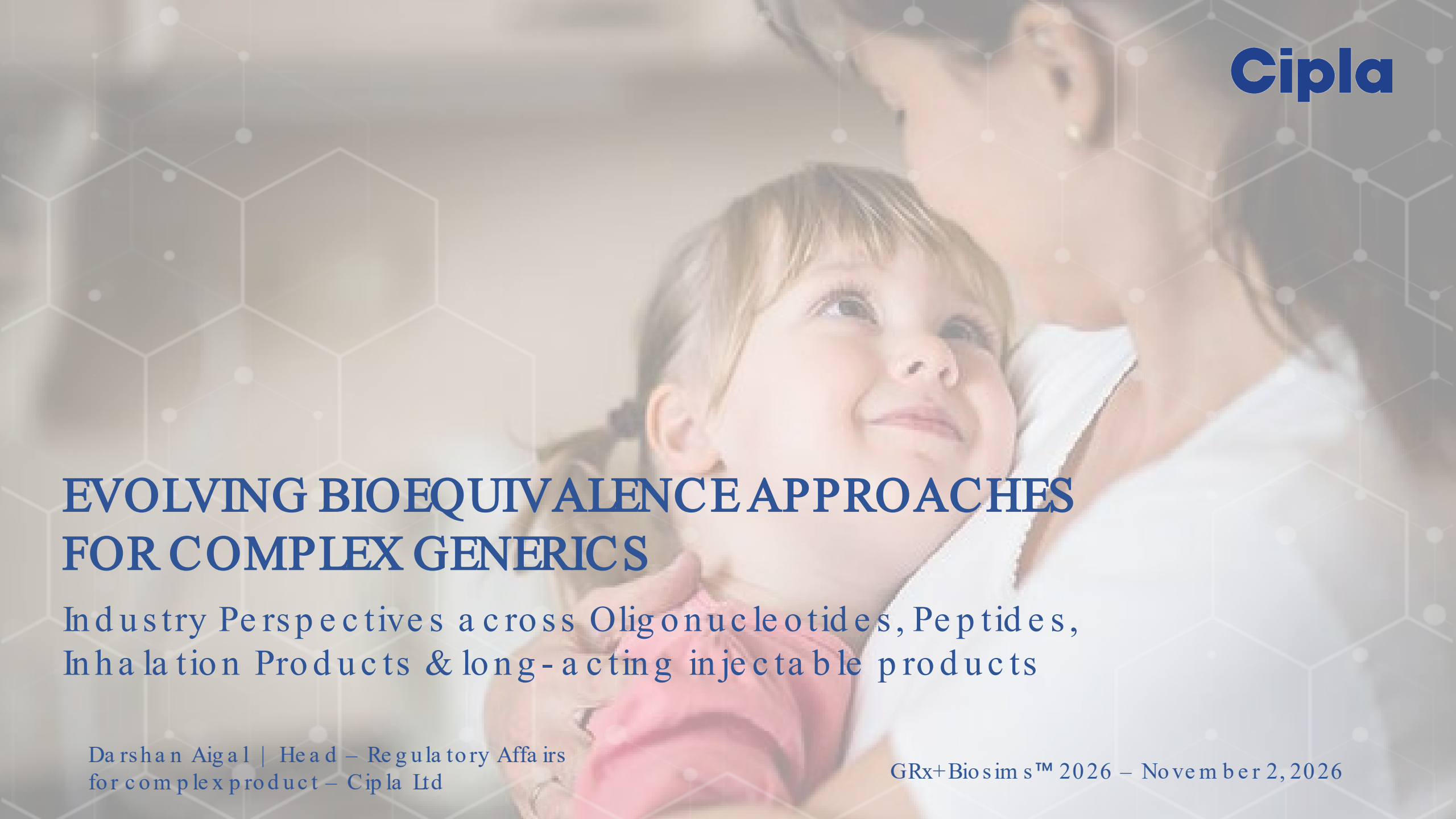


# EVOLVING BIOEQUIVALENCE APPROACHES FOR COMPLEX GENERICS

## Industry Perspectives across Oligonucleotides, Peptides, Inhalation Products & long-acting injectable products

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# PRESENTATION ROADMAP

From evolving peptides regulation to mechanistic bioequivalence pathways for inhalation and long-acting injectable products

01

**Oligonucleotides: Sameness & Impurity Framework**
Request a clear, predictable stereochemical sameness & impurity qualification framework.

02

**Peptides: July 2026 PSG Reset**
Recombinant-process controls, risk-based impurity qualification and clarity on when HOS or bioactivity testing may be waived.

03

**Inhalation Products: Mechanistic BE Pathways**
In vitro-led alternatives, batch expectations and science-based flexibility for efficient development.

04

**Long-Acting Injectables: Proportional-Strength Pathway**
Extend the fully in vitro BE approach through cross-strength bridging, lifecycle flexibility and practical QC methods.

# OLIGONUCLEOTIDE SAMENESS: MOVING FROM ANALYTICAL TOOLS TO CLEAR ACCEPTANCE CRITERIA

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**24** FDA-approved oligonucleotides

**16** Public FDA oligonucleotide PSGs

**PSG pathway:** Demonstrate active-ingredient sameness through sequence, structure, diastereomer profile and physicochemical comparison.

## FDA EXPECTATION: DIASTEREOMER CONTROL

| | | |
|---|---|---|
| 1 | **Control the process** | Identify factors affecting Rp/Sp outcomes. |
| 2 | **Establish a baseline** | Measure Rp/Sp ratios at PS linkages, where feasible. |
| 3 | **Compare Test vs RLD** | Assess overall diastereomeric composition. |
| 4 | **Demonstrate discrimination** | Use controls with deliberate stereochemical changes. |
| 5 | **Profile unresolved species** | Apply complementary high-resolution methods. |

## INDUSTRY REQUEST TO FDA

We sincerely request the Agency to consider providing clarity on diastereomer composition acceptable ranges and statistical rules,.

| | |
|---|---|
| **RLD-anchored range** | We request FDA to clarify acceptable variability across ≥3 RLD lots and the criteria for defining the range |
| **Statistical method** | We request FDA to clarify the recommended statistical method and approach for demonstrating comparability |
| **Invitro Functional assay** | We request FDA to clarify when a validated invitro functional assay can support stereochemical differences that are not functionally meaningful |

Reference: Development and manufacture of oligonucleotides - Scientific guideline | European Medicines Agency (EMA)
Reference: Product-Specific Guidances for Generic Drug Development | FDA

# OLIGONUCLEOTIDE IMPURITIES: MOVE FROM "CONTACT FDA" TO A PREDICTABLE FRAMEWORK

EMA provides numerical identification and qualification thresholds; FDA PSGs remain product-specific and direct applicants to engage the Agency.

## EMA — CLEAR BASELINE

**REPORT** from method LOQ

**IDENTIFY** ≥ 1.0%

**QUALIFY** > 1.5%

### Risk-based qualification

- **Class I:** terminal truncations / major metabolites
- **Class II:** natural nucleic-acid structural elements
- **Class III:** internal n−1/ n+1 sequence variants
- **Class IV:** non-natural structural elements

## FDA — CURRENT POSITION

**PSGs emphasize:**

- impurity-profile comparability for multiple test and RLD batches
- Assessment of immunogenicity and inflammation risk

At a pre-development meeting, industry requests FDA to provide clear reporting, identification, and qualification thresholds.

## INDUSTRY REQUESTS FDA TO:

1. **Thresholds**

   Request FDA to provide a clear framework for reporting, identification, and qualification of oligonucleotide-related impurities

2. **Impurity classification**

   Given the complexity and presence of unresolved impurity groups ,request to give impurity classification framework

3. **impurity qualification requirements**

   Request guidance on impurity grouping, nonclinical toxicity requirements, and impurity-spiked toxicology study design

**Predictability without lowering the safety standard**

Reference: Development and manufacture of oligonucleotides - Scientific guideline | European Medicines Agency (EMA)
Reference: Product-Specific Guidances for Generic Drug Development | FDA

# PEPTIDES: JULY 2026 PSGS RESET THE DEVELOPMENT PARADIGM

## 1| Recombinant peptides and impurity-control framework

**PSGs PUBLISHED FOR 17 PEPTIDES**

| TOPIC | JULY 2026 REVISED PSG – FDA WORDING | INDUSTRY REQUESTS FDA TO PROVIDE CLARITY |
|---|---|---|
| **Recombinant peptides: route, HCP/residual DNA & nonclinical evidence** | Demonstrate that HCP and residual DNA are well controlled using process controls and targeted comparative analytical studies. Nonclinical methods may support the expected clinical effect and safety profile. | We request FDA to clarify acceptable control for HCP/residual DNA levels, assay expectations (sensitivity), and when in-vivo toxicity studies are required. |
| **Total impurity burden** | Total active-ingredient-related impurities, including new impurities, should not exceed the RLD amount. Impurities above 0.1% are summed. | We request FDA to clarify an acceptable minimum total-impurity limit for highly purified RLDs (<1% total impurities). |
| **Higher-order structure (HOS)** | Higher-order structure, including secondary/tertiary structure and aggregates, where applicable. | We request FDA to clarify the minimum HOS characterization required, to demonstrate existence of HOS.. |
| **Biological activity** | Biological and functional assays are not always needed. Omission may be justified when the peptide lacks functional secondary or higher-order structure. | Request to clarify when activity is governed by covalent structure and no functional HOS exists; can FDA confirm that comparative bioassays may be omitted? |

Reference: FDA Publishes Revised Draft Product-Specific Guidances for Certain Generic Peptide Products | FDA

# INDUSTRY REQUEST: FLEXIBILITY FOR ACCELERATE DEVELOPMENT

Respectfully request FDA to consider, without reducing evidentiary rigor

01

LUNG | DPI / MDI

### rAPSD: route-specific application

Request FDA to consider waiving rAPSD for MDIs when comparability is demonstrated through MDI-specific tests.

02

ALL ROUTES

### Input-lot flexibility

Request FDA to allow ≥2 lots each of API, critical excipients, and applicable device/components across three test batches.

03

NASAL | NASAL SPRAY

### In-vitro test rationalization in line with MDI

Request FDA to reassess the added value of spray pattern and plume geometry for the nasal route when other in-vitro tests establish comparability.

04

LUNG | DPI / MDI

### Impurity expectations

Request FDA to clarify application of the 1998/2018 MDI–DPI CMC guidances, including the legacy 0.1% unspecified-impurity limit.

05

LUNG | DPI / MDI

### PK strength waiver

Request FDA to waive the middle-strength PK study for proportional products supported by highest- and lowest-strength data.

06

ALL ROUTES

### Charcoal PK flexibility

Request FDA to allow product-specific omission of a separate charcoal study when early PK or pAUC evidence provides adequate justification.

07

MDI

### Green propellant

Request FDA guidance on an in-vitro and PK-based pathway for non-Q1/Q2 green-propellant MDIs when pharmaceutical performance and regional/systemic exposure are comparable.

# LONG- ACTING INJECTABLES: EXTEND THE IN VITRO PATHWAY ACROSS PROPORTIONAL STRENGTHS

LAI extended-release suspension | FDA new draft PSG

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## FDA PSG: FULLY IN VITRO BE OPTION

**01** **Particle size distribution**

3 test + 3 RS batches 10 datasets each should be provided for D50 and SPAN; PBE analysis. 1representative strength,

**02** **Comparative IVRT**

3 test + 3 RS batches
≥12 units/batch; complete ER profile
1representative strength,

**03** **Supportive characterization**

Polymorph, morphology, appearance, pH, osmolality, specific gravity and viscosity

Q1/Q2 same • PSG permits testing any one strength

## INDUSTRY REQUESTS FDA: BRACKETING + PRACTICAL QC

1X | 2X | 3X | 4X | 6X

Essentially one formulation platform presented in different fill volumes

| | |
|---|---|
| 1. CROSS-STRENGTH RS FLEXIBILITY | Request to Allow ≥3 RS batches across proportional strengths when individual-strength lots are unavilable. |
| 2. LIFECYCLE FLEXIBILITY | Request risk-based lifecycle approach allowing a representative strength to support post-approval changes across proportional strengths,. |
| 3. QC METHOD FLEXIBILITY | Request to allow a validated accelerated dissolution method for routine release and stability testing when demonstrated to be discriminatory and linked to the extended-duration IVRT. |
| 4. CHARACTERIZATION STRENGTH CLARITY | Request to clarify in the PSG that comparative characterization studies can also be conducted using one representative strength,. |

**INDUSTRY POSITION | Preserve mechanistic assurance while avoiding repetitive strength-by-strength testing and impractical multi-day QC testing.**

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Thank You