Decoding Product-Specific Guidances (PSGs) for Complex Non-Oral Generics

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Learning Objectives

- Understand the scientific and regulatory logic underlying PSG development
- Systematically interpret PSG recommendations for complex non-oral products
- Be aware of responses to frequently asked questions on PSGs
- Translate PSGs into actionable generic development strategies

How is a PSG developed?

PSGs operationalize a science-based pathway from product complexity to BE strategy and product development

Three key questions

1. What makes the product complex?

2. What attributes control product performance?

3. What study type best evaluates the identified product attributes to establish BE?

Question 1: What Makes This Product Complex?

Identify the source of complexity:

- Complex Active Ingredient
  - Examples: iron-carbohydrate complexes, polymeric drug substances, oligonucleotides…
- Complex Formulations
  - Examples: suspensions, emulsions, nanoparticles, microspheres, liposomes…
- Complex Route of Delivery
  - Examples: ophthalmic, inhalation, topical, intrauterine…
- Complex Devices
  - Examples: autoinjector…

Question 2: What Attributes Control Clinical Performance?

Determine the critical quality attributes (CQAs) as they are proxies for product performance

Examples (not exhaustive CQAs per example):

Product Type	CQA	Clinical Link
Suspension	Particle size	Absorption
Liposome	Size/stability	Exposure
Inhalation	APSD	Deposition

Question 3: What Study Type Best Evaluates These Attributes?

PSGs translate CQAs into appropriate BE studies:

Possible study types:

- Conventional:
  - PK BE studies
  - Comparative Clinical endpoint BE studies
  - Pharmacodynamic studies
- Alternative:
  - ✓ In vitro BE studies
  - ✓ Comparative physicochemical characterization

➢Complex products often involve a 'totality-of-evidence' approach.

- ○Tier 1: Pivotal BE evidence (PK, clinical, validated in vitro BE)
- ○Tier 2: Supportive evidence (comparative characterization)
- ○Tier 3: Justification/bridging data

What a PSG can do for generic development?

PSGs can help industry align four decisions early:

Formulation / device sameness

Q1/Q2, no significant formulation differences, user interface analysis

Targeted in vitro characterization and performance tests

Examples: Particle size/size distribution, dissolution/in vitro drug release testing, in vitro permeation test, realistic aerodynamic particle size distribution

In vivo studies when recommended and selected

PK, PD, or comparative clinical endpoint studies remain product-specific and route-specific
Alternative study design, data analysis, study subjects

Role of in vitro studies and retention samples

In vitro BE study: yes, retention samples are needed.
In vitro comparative characterization studies: no, retention samples are not required.

Key messages:

- **PSGs define a *development blueprint*, not just study recommendations.**
- **Alternative approaches can be proposed, but the burden is on the applicant to justify them. Regulatory dialogue on gaps is highly encouraged.**

Common Misinterpretation of PSG Recommendations

➢ Misinterpretation:

- PSGs define requirements

➢Regulatory Perspective:

- PSGs provide recommendations based on current scientific understanding; alternative approaches or deviations may be acceptable with adequate justification

How to Read a PSG
Example 1: Complex Injectable

Purpose:

- ✓ Identify BE options and decision pathways
- ✓ Determine pivotal vs supportive studies
- ✓ Assess feasibility and development risk

Active Ingredient:	Buprenorphine
Dosage Form:	Solution, extended release
Route:	Subcutaneous
Strengths:	8 mg/0.16 mL (50 mg/mL), 16 mg/0.32 mL (50 mg/mL), 24 mg/0.48 mL (50 mg/mL), 32 mg/0.64 mL (50 mg/mL), 64 mg/0.18 mL (356 mg/mL), 96 mg/0.27 mL (356 mg/mL), 128 mg/0.36 mL (356 mg/mL)
Recommended Studies:	Two options: (1) two in vitro bioequivalence studies with supportive characterization studies, or (2) two in vivo bioequivalence studies with pharmacokinetic endpoints

- ➢ Overview of the product
- ➢ Summary of the recommended approaches
- ➢ When approaches are recommended as options, they are selective

How to Read a PSG
Example 1: Complex Injectable

In vitro BE option

I. Option 1: Two in vitro bioequivalence studies with supportive characterization studies

To be eligible for the bioequivalence studies recommended in this guidance, the test product[1] should be qualitatively (Q1)[2] and quantitatively (Q2)[3] the same as the reference listed drug (RLD).

[1] The manufacturing process for the exhibit batches should be reflective of the manufacturing process to be utilized for commercial batches.
[2] Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the RLD product.
[3] Q2 (Quantitative sameness) means that concentrations of the inactive ingredient(s) used in the test product are within ±5% of those used in the RLD product.

1. Type of study: Comparative in vitro drug release test (IVRT)
   Design: In vitro bioequivalence study on at least three batches of both test and RS products
   Strength: Any one of the strengths including 8 mg/0.16 mL, 16 mg/0.32 mL, 24 mg/0.48 mL, 32 mg/0.64 mL

2. Type of study: Comparative in vitro drug release test (IVRT)
   Design: In vitro bioequivalence study on at least three batches of both test and RS products
   Strength: Any one of the strengths including 64 mg/0.18 mL, 96 mg/0.27 mL, 128 mg/0.36 mL

   Additional comments: A properly developed and validated IVRT method that can detect potential formulation difference (e.g., phase structure variations resulting from differences in lipid ratios and lipid grades) and capture the complete release profile of buprenorphine should be provided. Equivalence in buprenorphine release should be established using a proper statistical method from test and RS products. One suggested approach is a model independent similarity (f2) factor. For more information on calculation of f2 factor, refer to the most recent version of the FDA guidance for industry on *Dissolution Testing of Immediate Release Solid Oral Dosage Forms*.[a]

- Eligibility for following the option
- Footnote indicating commercial scale is not recommended for batches for BE studies, but manufacturing process should be representative
- Type of study and design indicates the role of the study: in vitro BE study, which means this is a pivotal study and retention samples are needed

How to Read a PSG
Example 1: Complex Injectable

In vitro BE option

Supportive characterization studies:
Comparative physicochemical characterization of the weekly and monthly test products and the corresponding RS. The comparative studies should be performed on a minimum of three exhibit batches of the test product and three batches of the RS and should include:

a. Soybean phosphatidylcholine (as phosphatidylcholine) concentration and glycerol dioleate concentration
b. Specific gravity
c. Appearance
d. Viscosity
e. Water uptake kinetics in phosphate-buffer saline (PBS) (pH 7.4)[4]
f. Properties of liquid crystal depot fully hydrated in PBS, including appearance, phase structure[5], and rheological properties (complex viscosity and elastic modulus)
g. Time required to fully degrade liquid crystal depot in vitro

Additional comments:

- Liquid crystal depot can be formed in vitro by injection of the formulation into PBS.[6] The time required to reach full hydration can be informed by the water uptake kinetics study. For comparative characterization studies examining appearance, phase structure, and rheological properties, applicants should use fully hydrated depots to ensure assessment of the mature depot structure. However, for IVRT study, the applicants do not need to use fully hydrated depots since the depot will be exposed to a dissolution media during the test, which will naturally induce hydration as part of the release process.
- The degradation study may be combined with the IVRT or be conducted under a different experimental condition.

[4] Jenni Engstedt, René In 't Zandt, Justas Barauskas, Vitaly Kocherbitov. Swelling kinetics of mixtures of soybean phosphatidylcholine and glycerol dioleate. Colloids Surf B Biointerfaces. 2024 Jul:239:113955. doi: 10.1016/j.colsurfb.2024.113955.
[5] Fredrik Tiberg, Markus JohnssonMarija Jankunec, and Justas Barauskas, Phase Behavior, Functions, and Medical Applications of Soy Phosphatidylcholine and Diglyceride Lipid Compositions. Chem. Lett. 2012, 41, 10901092
[6] Jenni Engstedt, Martynas Talaikis, Justas Barauskas, Gediminas Niaura, Vitaly Kocherbitov. Hydration-induced lipid redistribution in swelling of controlled release liquid crystalline depots. Commun Chem. 2025 Oct 14;8(1):309. doi: 10.1038/s42004-025-01739-0.

- General expectations for comparative characterization studies:
  - ✓ Three lots of RS (if available) and T
  - ✓ No specific statistical requirements
  - ✓ Comparability established by comparing the range of the characterization data
  - ✓ Differences observed could require scientific discussion and justification
  - ✓ Data should be discussed based on mechanistic understanding of the overall product

- Relevant literatures are included as references. Methods may be used as starting points per applicants' discretion.

How to Read a PSG
Example 1: Complex Injectable

In vivo BE option

II. Option 2: Two in vivo bioequivalence studies with pharmacokinetic endpoints

1. Type of study: Bioequivalence study with pharmacokinetic endpoints
   Design: Single-dose, randomized, parallel, in vivo
   Strength: Any one of the weekly strengths including 8 mg/0.16 mL, 16 mg/0.32 mL, 24 mg/0.48 mL, 32 mg/0.64 mL
   Dose: 8 mg, 16 mg, 24 mg, or 32 mg
   Subjects: Males and non-pregnant, non-lactating females with moderate or severe opioid use disorder (OUD), 18 to 65 years old

Additional comments:

- Buprenorphine extended-release injection, for subcutaneous use is under a Risk Evaluation and Mitigation Strategy (REMS) program with Elements to Assure Safe Use (ETASU) to mitigate the risk of serious harm or death with intravenous self administration. All pertinent elements of the REMS must be incorporated into the protocol and informed consent in the bioequivalence study.
- The patients with moderate to severe OUD should currently being treated with a transmucosal buprenorphine-containing product. The applicant can employ a washout before the dose of buprenorphine extended-release injection, for subcutaneous use.
- During the washout period, subjects should be closely monitored by an experienced healthcare professional for signs and symptoms of opioid withdrawal. Nonopioid rescue medications to treat the signs and symptoms of withdrawal may be used as clinically appropriate.
- It is important that patients not use any other buprenorphine-containing product, either therapeutically or illicitly after administration of buprenorphine extended release injection, for subcutaneous use.

Analyte to measure: Buprenorphine in plasma

Bioequivalence based on (90% CI): Buprenorphine

The 90% confidence intervals of the following PK parameters should meet the acceptable limits of [80.00-125.00]: Log-transformed C_{max}, AUC_{0-t}, and $AUC_{day5-day7}$, where C_{max} is the maximum plasma concentration, AUC_{0-t} is the area under the curve from 0 to the last sampling time point, and $AUC_{day5-day7}$ is the area under the plasma concentration time curve from Day 5 to Day 7. Note that the last sampling time point 't' equals the dosing interval of the product used in the in vivo PK study. The applicant should submit time to maximum concentration (T_{max}) as supportive data.

- Strength: to provide clarity on the strength to be used for conducting the BE study taking formulation strategies into consideration
- Additional comments provide specific recommendations on clinical design to ensure safety of study subjects
- Specific PK metrics are recommended considering the characteristics of the PK profile of this product

How to Read a PSG
Example 2: Complex Drug Device Combination Product

Active Ingredient:	Glucagon
Dosage Form:	Solution
Routes:	Intravenous, subcutaneous
Strengths:	0.5 mg/0.1 mL, 1 mg/0.2 mL
Recommended Studies:	Comparative characterization studies to support active ingredient sameness and request for waiver of in vivo bioequivalence study requirements. For test and reference products with an auto-injector presentation, two in vitro bioequivalence studies on delivered volume and extended needle length; and supportive characterization studies on trigger force and ejection time

Recommendations to Support Active Ingredient Sameness and Impurity Assessment:

In addition to ensuring active ingredient sameness (i.e., same primary sequence and physicochemical properties) for the drug substance, it is recommended to conduct the following comparative analyses of the proposed generic glucagon and the designated reference standard (RS) on no less than three batches of the proposed drug product tested on or near release and at the end of the proposed shelf life and no less than three batches of the RS aged prior to expiry, after aging under conditions consistent with the label storage conditions:[1]

1. Secondary structure.
2. Oligomer/aggregation states: oligomer/aggregation propensity and the nature of the aggregates formed for the proposed product should be similar to that of the RS.

[1] Samples should be aged under conditions consistent with the worst-case label storage conditions.

- Product complexities:
  - ✓ Active ingredient sameness
  - ✓ Impurity assessment and potential immunogenicity risk
  - ✓ Complex device
  - ✓ For emergency use
- Recommendations on studies to support active ingredient sameness.
- Footnotes provide additional recommendations on sample preparations, literature references, regulations, and more.

How to Read a PSG
Example 2: Complex Drug Device Combination Product

3. Biological activities[2].
4. Active ingredient-related impurity profile comparison: new impurities found in the proposed generic drug product but not in the RS and impurities found at a significantly higher level in the proposed generic drug product than in the RS, should be identified and characterized. If upon Agency assessment, an impurity is identified that has the potential to increase the immunogenicity risk, further immunogenicity assessments or studies may be recommended.
5. Comparative study demonstrating comparable innate immune response risk of the test product and RS.[3]

Non-clinical methods can be used to demonstrate comparable safety and efficacy profiles between a proposed generic peptide (recombinant or synthetically produced) and the RS. Unlike synthetic peptides, recombinant peptides may also contain impurities, such as host cell proteins and residual DNA, from the host cell. Therefore, FDA recommends that applicants demonstrate and justify these host cell related impurities are well controlled if the proposed generic peptide product is manufactured using a recombinant process.[4]

[2] An applicant may provide justification for not characterizing biological activities as part of the comparative analyses if it can be demonstrated the formulated peptide active ingredient lacks functional secondary or higher order structure.

[3] Demonstrating comparable innate immune activities can be accomplished through analyzing aggregates and non-peptide process-related impurities, which may alter the product's immunogenicity profile. Differences found in comparability studies assessing aggregates should be mitigated using manufacturing strategies. Levels of non-peptide process-related impurities including particulate matter, microbial contaminants, residual organic solvents, elemental impurities and leachables, should meet compendial acceptance criteria and toxicological limits. If non-peptide process-related impurities meet these criteria and limits, and aggregation profiles are comparable to that of the RS, applicants should not conduct in vitro innate immune testing.

[4] For any inquiries regarding the use of non-clinical assays to assess risk in recombinant generic peptides, please submit pre-ANDA product development meeting requests. For additional information, refer to the most recent version of the guidance for industry on *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA*.

- Footnote 2 provides additional information on potential justification for not characterizing biological activities.
- Recommendations provide updated thinking on the original of peptide indicating recombinant peptides could be filed through the 505(j) pathway with appropriate strategies.
- Footnote 3 provides details on develop strategy for assessing risk of innate immunogenicity.

How to Read a PSG
Example 2: Complex Drug Device Combination Product

Two in vitro bioequivalence studies with supportive comparative studies on the test and reference auto-injectors containing glucagon:

FDA recommends that the following in vitro studies be conducted with the test and reference auto-injectors containing glucagon.

Two in vitro bioequivalence studies:

1. Type of study: Delivered volume
   Design: The delivered volume test should be performed to determine the volume of fluid ejected out of the device.
   Equivalence based on: Population bioequivalence (PBE) analysis of delivered volume.
   Please refer to the most recent version of the FDA product-specific guidance on *Budesonide Inhalation Suspension* (NDA 020929)[a] for additional information regarding PBE.

2. Type of study: Extended needle length
   Design: The extended needle length test should be performed to determine the needle length that extends out of the device after ejection of the volume of fluid.
   Equivalence based on: PBE analysis of extended needle length.

Supportive comparative characterization studies:

1. Type of study: Ejection time
   Design: The ejection time test should be performed to determine the time to eject the volume of fluid out of the device.

2. Type of study: Trigger force
   Design: The trigger force test should be performed to determine the force required to activate the device.

- In vitro bioequivalence studies on device performance are recommended as this is an emergency medicine.
- In vitro bioequivalence studies require retention samples
- In vitro comparative characterization studies do not require retention samples

How to Read a PSG
Example 2: Complex Drug Device Combination Product

Additional information:

Device:
The RLD has three different presentations: (1) an auto-injector, (2) a pre-filled syringe, or (3) a kit that consists of a vial of drug co-packaged with a syringe with staked needle. The auto-injector, pre-filled syringe, and co-packaged syringe with needle are the device constituent parts for these presentations respectively.

FDA recommends that prospective applicants examine the size and shape, the external critical design attributes, and the external operating principles of the RLD device when designing the test device including:

1. Auto-injector presentation:
   a. Single-dose, fixed-dose, auto-injector format capable of delivering the same dose as the RLD
   b. Medication viewing window
   c. Needle gauge and length
2. Pre-filled syringe presentation:
   a. Single-dose, fixed-dose, prefilled syringe format with staked needle
   b. Needle gauge and length
3. Kit:
   a. Syringe with staked needle
   b. Needle gauge and length

User interface assessment:
An abbreviated new drug application for this product should include complete comparative analyses so FDA can determine whether any differences in design for the user interface of the proposed generic product, as compared to the RLD, are acceptable and whether the product can be expected to have the same clinical effect and safety profile as the RLD when administered to patients under the conditions specified in the labeling. For additional information, refer to the most recent version of the FDA guidance for industry on *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*.[h]

- Device and User Interface Assessment session provides recommendations on evaluation of device from the user interface perspective.

- Information included are:
  - ✓ descriptions of the RLD presentation and its device constituent part(s)
  - ✓ recommendations for studies to examine and characterize design differences between the proposed generic and the RLD
  - ✓ guidance on conducting comparative analyses, with references to relevant FDA guidance

Frequently asked questions - formulation / reference / strategy

01	Can fewer than 3 RS lots be justified for in vitro BE or active ingredient sameness studies? Can an Authorized Generic be used as the reference product for BE studies?	In general, 3 lots of RS are recommended to properly and sufficiently capture potential lot to lot variability of the RLD/RS product. However, if due to availability issues, it may be acceptable to use less than three lots of the RLD/RS products provided that 1) sufficient justification/evidence is provided to support the claim; and 2) data on 3 batches of the test product should still be submitted. Note that when authorized generics are available, they can be used to fulfill the recommendation.
02	For ophthalmic solution products, is in vivo BE study warranted for non-Q1Q2 formulations?	Applicants are encouraged to discuss justification for not conducting in vivo BE study to support ANDA filing and approval.
03	For presentations that differ only by fill volume, can lots from different fill volumes be combined for in vitro BE studies?	When strengths only differ in fill volume, an applicant may use three lots of a single strength (either the recommended or an alternative strength), or a combination of lots from the different strengths. Given there is a chance that different strength of the RS may actually be filled from the same bulk batch, applicants should keep this potential in mind and try to make sure discrete lots for different strengths of the RLD/RS product.
04	What level of data is expected to justify an alternative BE approach in a pre-ANDA request or controlled correspondence?	The type of data to justify an alternative BE approach is product and approach specific. In general, applicants should provide in depth scientific discussion on the rationale for the proposed alternative approach and corresponding preliminary data. Simple citation of another PSG, even when the products are similar in terms of dosage form and/or route of administration, may not be sufficient.

Frequently asked questions - formulation / reference / strategy

05	For inhalation products, which is the correct T product to use for BE studies when there are multiple doses available in different packaging/dose number configurations?	To ensure device robustness across the maximum number of doses, the packaging configuration with the highest number of doses should be used for BE testing. Additional packaging configurations at lower doses may rely on (1) acceptable BE studies on the packaging configuration with the highest number of doses, (2), the same formulation composition across all configurations, and (3) same device components critical to product performance across all configurations.
06	Applicability of in vitro BE options for non-Q1/Q2 formulations?	It is possible for a non-Q1/Q2 formulations to utilize an in vitro BE approach provided sufficient justification is provided. Applicants are encouraged to submit a PDEV meeting request or a CC to discuss the eligibility of a non-Q1/Q2 formulation provided sufficient scientific justification and supportive information/data is included in the inquiry.
07	Is it acceptable to use different RS batches between in vitro and in vivo BE studies	Ideally, the same RLD/RS batch used in the in vivo study is also used for the in vitro BE studies. However, if that is not feasible, applicants should provide rationale/justification of why batches differ. The Agency will review the justification and may request additional bridging data if deemed necessary.
08	If a new RS has been designated, can the previous RS still be used in BE studies?	If product development was initiated and completed using a previously designated RS, it may be scientifically justifiable to use it to support an ANDA submission. It may be beneficial to justify the selection of the product used as the comparator product in the ANDA, to avoid IR issues during filing. You can also get confirmation through a CC.

Frequently asked questions - formulation / reference / strategy

09	How should population bioequivalence (PBE) analysis be applied to PSD sameness, including the need to assess different product life stages?	PSD analysis of particle size/size distribution of suspensions and globule size/size distribution of emulsions does not need to assess different product life stages. The reference of the PSG on *Budesonide Inhalation Suspension* (NDA 020929) only intends to provide guidance on computation of PBE analysis. A footnote indicates that testing samples at different life stages is NOT applicable in recent PSGs.
10	For pivotal in vitro BE IVRT, how should multiple-batch release profiles be compared when 3 batches are evaluated?	When three batches each of the RS and test products are used to conduct the IVRT for BE purposes, applicants may pool the data for f2 analysis or conduct individual f2 analysis.
11	For inhalation realistic APSD, how should mouth-throat (MT) model size and breathing profiles be selected?	Two MT models (e.g., small [S] and large [L]) and two representative breathing profiles (e.g., weak and strong) are recommended. Choices may be justified such that they are representative of the patient population of interest and consider the critical characteristics of the inhalation drug product.
12	For PK BE with a charcoal block (CBPK) what is the ideal study design, including inhalation/actuation for dosing, and the appropriate charcoal dose amount and timing for administration? Also, when is the use of a pAUC approach in a PK BE study in lieu of a CBPK study appropriate?	Applicants are encouraged to discuss study plans with the Agency through a CC or pre-ANDA product development meeting. pAUC may be used in lieu of a CBPK study when appropriately justified.

Frequently asked questions - formulation / reference / strategy

13	Geographic considerations for study population for in vivo studies: can the study population be entirely in India for comparative clinical endpoint (CCEP) BE study?	It is generally acceptable to conduct a CCEP BE study outside the US. Refer to the guidance for industry and FDA staff on *FDA Acceptance of Foreign Clinical Studies Not Conducted Under an IND: Frequently Asked Questions* (March 2012), available at https://www.fda.gov/media/83209/download, for general regulatory advice related to conduct of foreign clinical studies. The study should be conducted using products approved by the FDA, obtained from the U.S. market, and designated by the FDA as the reference standard (i.e., the reference listed drug (RLD) and/or reference standard (RS) product).
14	Can a PK BE study subjects or BE strength differ that those recommended in a PSG?	Applicants may propose a different population for conducting the PK study. A different strength from the one recommended in the PSG can be used in BE studies when the strengths only differ in fill volume. For a particular dose, a portion of a strength/fill volume can be used with evidence justifying the portion is representative of the strength.
15	For comparative active ingredient sameness characterization, do we need to isolate the active ingredient from the RLD first?	Not necessarily. It is applicants' decision based on the capability of the analytical method and sample requirements.
16	For naturally derived complex mixtures, can a different starting material be used (e.g., 1. Use of bioengineered molecules or Bovine heparin to replace porcine heparin; 2. Safflower oil to replace poppy seed oil)?	For generic versions of complex, naturally derived drugs, applicants may use a different starting material than the one used for the RLD. However, they must demonstrate that the resulting active ingredient is the 'same as' the RLD's, following all recommendations in relevant PSGs. The application must also contain a clear justification that this difference in starting material will not alter the safety and efficacy of the generic product.

Summary

1. **PSGs reflect a science-based decision framework**
   - Product complexity → performance drivers → BE strategy
   - Recommendations are tailored to product-specific risk and uncertainty
2. **Critical Quality Attributes (CQAs) are central**
   - CQAs serve as mechanistic links between formulation and clinical performance
   - BE approaches are selected based on the ability to adequately capture these attributes
3. **BE strategies rely on totality of evidence**
   - Combination of in vitro and/or in vivo and comparative characterization
   - Increasing emphasis on well-justified in vitro or other alternative (e.g., modeling) approaches for complex products
4. **PSGs provide a development blueprint—not a constraint**
   - Enable efficient study design and early risk identification
   - Alternative approaches are acceptable with robust scientific justification
5. **Early and proactive regulatory engagement is critical**
   - Pre-ANDA meetings and controlled correspondence are key tools
   - Success depends on aligning scientific rationale with regulatory expectations