Development of Complex Generic Drugs in the United States

Markham C. Luke, MD, PhD

Director

Division of Therapeutic Equivalence 1

Office of Research and Standards| CDER | U.S. FDA

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What are Complex Generic Products?

- **Complex active ingredients**
  - Complex mixtures of APIs, polymeric compounds, peptides
- **Complex formulations**
  - Liposomes, suspensions, emulsions, gels
- **Complex routes of delivery**
  - Locally acting such as dermatological and inhalational drugs
- **Complex dosage forms**
  - Long acting injectables, implantable drugs
- **Complex drug-device combination products**
  - Transdermals, metered dose inhalers (MDIs)
- Other products where complexity or uncertainty concerning the approval pathway or other alternative approach would benefit from early scientific engagement

https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf

GDUFA Regulatory Science and PSGs

- GDUFA provides resources to allow FDA to perform and fund research to advance generic drug regulatory science and decision-making
  - Goal: Access to generics in all product categories
  - 90+ on-going projects
  - Recent focus on complex drug products
- Research provides new tools for FDA and industry to evaluate generic drug equivalence, to enable more efficient development of generic drugs and thus improve access
- Results from GDUFA research manifest in our product-specific guidances (PSGs) as recommendations for new alternative approaches to demonstrate bioequivalence

Generic Drug Science & Research Website:
https://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/genericdrugs/ucm567695.htm

PSGs for Complex Drug Products

- **There are currently over 2,000 published PSGs.**
- **These guidance documents have helped provide public access to current thinking on bioequivalence (BE) approaches for our regulated drugs.**
- **The PSGs helped industry in reducing the need for submitting controlled correspondence requests to FDA, allowing better utilization of FDA and industry generic drug development resources.**
- **In recent years, approximately 40% of published PSGs have been for complex products.**
  - BE for some complex products have historically utilized comparative clinical endpoint BE studies. PSGs would provide outlines of the recommended study protocols.
  - As science evolves, PSGs become the conduit for alternative approaches.
  - These approaches are outlined for new PSGs, and as revisions to currently published PSGs.

FDA's Complex Product Teams

- Who are the folks at FDA responsible for conducting complex drug research, communicating our findings, and translating science into regulatory policy in the form of FDA guidance documents?
- Dedicated Teams in the Office of Research and Standards, most working in the Division of Therapeutic Performance 1, who are well-versed in clinical pharmacology and chemistry.
  - Complex API Drugs (including Peptides)
  - Complex Inhaled and Nasal
  - Complex Topical and Transdermal
  - Complex Combination Drug-Devices
- Collaborators across OGD, CDER, and FDA – including our legal and regulatory staff, our statisticians, quality reviewers, biomedical engineers.

Examples of Complex PSGs and Value-Added

- PSGs are a “value-added proposition” – resources go into producing information that will:
  - Provide a new pathway to generic drug approval in addition to or instead of a previous one, or when none existed before
  - Provide clarity and transparency on possible approaches to demonstrate BE
  - Risk reduction
- Let’s briefly explore some of the individual therapeutic areas for complex drug products and some of the results of our efforts

Topical Complex Products

BE Recommendations for topical generic drugs used on the skin have evolved greatly in recent years

From: Comparative Clinical Endpoint BE studies

To: Q1 and Q2 sameness with “Q3” physico-chemical characterization (including in vitro release/permeation testing – IVRT/IVPT)

To: Greater flexibility - allowing for updated “sameness” criteria - topical dermatological products by regulation do not need to be Q1/Q2 identical - but having a formulation where any variation does not affect the bioavailability of the product at the site of action reduces the risk of “non-BE”. “Sameness” language has been updated in recent PSGs.

Inhalation Complex Products

- As evidenced in the PSGs that were published and guided recent inhalation product approvals:
  - Alternative approaches to use of a comparative clinical endpoint BE study have been recommended after careful evaluation by FDA.
  - FEV1 studies are cumbersome and may not always be sufficiently “sensitive” to detect product performance differences for BE determinations
  - Careful FDA guided GDUFA research demonstrated that certain excipient considerations for inhaled products were very important and these were incorporated in PSG recommendations

Nasal Complex Products

- Valuable studies were conducted or coordinated by FDA clinicians and scientists that resulted in alternative approaches for generic nasal suspension drugs
- These included much testing using specialized equipment, dynamic flow modeling, and comparisons of drug products.
- The results were published in peer-reviewed literature and are now included in PSGs
- Methods to evaluate nasal suspension drug products now include morphological particle analysis with Raman spectroscopy allowing for greater precision and accuracy when it comes to BE determinations

Complex API/Formulation Products

- Research resources were invested in understanding the role of polymers (such as PLGA) and liposomes in bioavailability and BE.
  - A good example of research outcomes leading to guidance for industry are liposomal products - based on FDA funded research, we revised certain PSGs to compare free versus encapsulated portions of a drug for BE.
- The clinical study portion of certain complex PSGs have been revised to allow for clinical studies to be more feasible, for example providing details on how to study in healthy volunteers instead of patients, thus reducing variability in an acceptable manner to establish BE.

Complex API/Formulation Products

- Peptides and oligonucleotides fall within the sphere of NDA drug products and are appropriate for generic drug development
- General guidance has been published on how FDA looks at peptide products with consideration for product sameness, including immunogenicity concerns
- Product specific guidances are being published for oligonucleotide products based on FDAs careful assessment of what is needed for bioequivalence

Complex Drug-Device Products

- Some drug products contain device components with specific design features that result user interface characteristics that may need to be considered in the context of bioequivalence
- FDA currently requests and conducts evaluation of these products in the following manner:
  - Identify any differences in design of the device constituent of the product
  - Are the differences minor or ”other than minor”?
  - If the difference is “other than minor” then consideration may be needed for comparative use studies or some other way of determining that the difference does not impact bioequivalence significantly
- We are currently providing consistent language in our PSGs to describe the device constituent(s) of the reference listed drug products

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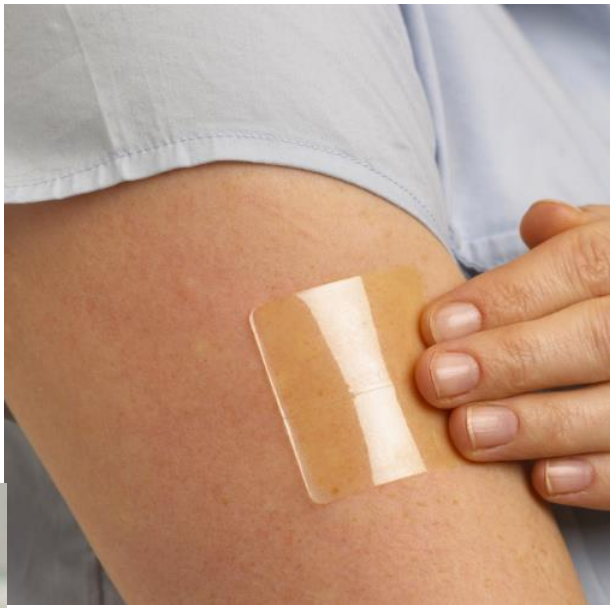

Example of PSG for an Inhaled Complex Product

Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Tiotropium Bromide

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient:	Tiotropium bromide
Dosage Form; Route:	Spray, metered; inhalation
Strengths:	EQ 0.0025 mg Base/inh EQ 0.00125 mg Base/inh
Recommended Studies:	In vitro and in vivo studies

FDA recommends the following in vitro and in vivo studies to establish bioequivalence (BE) of the test (T) and reference (R) inhalation sprays containing tiotropium bromide.

In Vitro BE Studies

FDA recommends that prospective applicants conduct the following in vitro studies for all strengths of the T and R products. For each strength, use at least three batches each of the T and R products, with no fewer than 10 units from each batch. FDA recommends that three primary stability batches be also used to demonstrate in vitro BE. The three batches of T product should be manufactured from, at minimum, three different batches of drug substance(s), excipient(s), and device components. The T product should consist of the final device constituent part and final drug constituent formulation intended to be marketed.

1. Type of study: Single actuation content (SAC)
   Design: The SAC test should be performed at the beginning (B), middle (M), and end (E) lifestages[1] of the product, using a flow rate of 28.3 L/min. U.S. Pharmacopoeia (USP) <601> Apparatus A or other appropriate apparatus may be used to determine the SAC using a validated assay. The number of actuations per determination should be one.

   Equivalence based on: Population bioequivalence (PBE) analysis of SAC. Refer to the product-specific guidance for *Budesonide Inhalation Suspension* for additional information regarding PBE analysis procedures.

[1] Based on the labeled number of actuations, the terms B lifestage, M lifestage, and E lifestage represent the first actuation(s) following the labeled number of priming actuations, the actuation(s) corresponding to 50 percent of the labeled number of actuations, and the actuation(s) corresponding to the labeled number of actuations, respectively.

Recommended Nov 2020

Types of Studies Needed

2. Type of study: Aerodynamic Particle Size Distribution (APSD)
Design: The APSD test should be performed at the B and E lifestages of the product using a flow rate of 28.3 L/min. The USP <601> Apparatus 1, Apparatus 6, or other appropriate method may be used to determine APSD using a validated assay. The APSD determination of each unit should be performed with a minimum number of actuations justified by the sensitivity of the validated assay. Water evaporation should be minimized by performing the APSD test under high humidity conditions (as close as possible to 100% relative humidity) or by cooling the cascade impactor (CI) to low temperatures (e.g., 5°C) or by any other suitable method.

Additional comments: Drug deposition on individual sites, including the mouthpiece adapter, the induction port, each stage of the CI, and the filter, is requested. Mass balance accountability should be reported based on the sum of all deposition sites. For electronic submission of the individual CI data for the T and R products, provide a table using the format in the Appendix, and send them as part of the abbreviated new drug application (ANDA) submission for BE evaluation.

Equivalence based on: PBE analysis of impactor-sized mass (ISM).[2] The CI profiles representing drug deposition on the individual stages of the CI along with the mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD) and fine particle mass (FPM) should be submitted as supportive evidence for equivalent APSD.

3. Type of study: Spray pattern
Design: The spray pattern test should be performed at the B lifestage of the product at two different distances from the nozzle. The selected distances should be at least 3 cm apart and based on the range of 3 to 7 cm from the R mouthpiece edge.[3] Impaction (thin-layer chromatography plate impaction), non-impaction (laser light sheet technology), or other suitable method may be used to determine the spray pattern.

Additional comments: The spray pattern test should be measured quantitatively in terms of ovality ratio and area within the parameter of the true shape (to include a high proportion, e.g., 95% of the total pattern) for the automated analysis or ovality ratio and D_{max} for the manual analysis. Ovality ratio is defined as the ratio of D_{max} to D_{min}. D_{max} and D_{min} are the longest and shortest diameters, respectively. The number of sprays per spray pattern would preferably be one.

Equivalence based on: At two selected distances, (i) qualitative comparison of spray shape, and (ii) PBE analysis of ovality ratio and area within the perimeter of the true shape or ovality ratio and D_{max}.

4. Type of study: Plume geometry
Design: The plume geometry test should be performed at the B lifestage of the product. The timed-sequence sound-triggered flash photography method, laser light sheet

[2] ISM is defined as a sum of the drug mass on all stages of the CI plus the terminal filter but excluding the top CI stage because of its lack of a specified upper cutoff size limit.
[3] The distance between the nozzle and point of spray pattern measurements should be the same for T and R.

PK Study Specifics, Including Analyte

Pharmacokinetic (PK) BE Study

FDA recommends that prospective applicants conduct the following PK BE study for all strengths of the T and R products.

8. Type of study: Fasting
   Design: Single-dose, two-way crossover
   Dose: Minimum number of inhalations that is sufficient to characterize a PK profile by using a sensitive analytical method
   Subjects: Adult males and non-pregnant females, general population

   Additional comments: (1) Subjects enrolled for in vivo studies should be trained in the use of the inhalation sprays in a standard fashion, prior to each treatment session, to assure a relatively consistent inspiratory flow rate and inspiratory duration. (2) A Bio-IND is required prior to conduct of the PK study if the dose exceeds the maximum labeled single dose.

   Analyte to measure: Tiotropium in plasma

   Equivalence based on: AUC and C_{max} for tiotropium. The 90% confidence intervals for the geometric mean T/R ratios of AUC and C_{max} should fall within the limits of 80.00 - 125.00%.

Additional Relevant Information (e.g. Device Constituent for Combination Product)

Additional information

Formulation:

FDA recommends that the T formulation be qualitatively (Q1)[5] and quantitatively (Q2)[6] the same as the R formulation.

Device:

[4] Velocity at the front edge of the aerosol cloud.
[5] Q1 (qualitative sameness) means that the test formulation uses the same inactive ingredient(s) as the reference formulation.
[6] Q2 (quantitative sameness) means that the concentrations of the inactive ingredient(s) used in the test formulation are within ±5% of those used in the reference formulation.

Prospective applicants should refer to FDA's guidance for industry *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA* (January 2017), which, when finalized, will provide the Agency's current thinking on the identification and assessment of any differences in the design of the user interface for a proposed generic drug-device combination product when compared to its RLD.

FDA recommends that prospective applicants consider the following characteristics of the R product when designing the T product:

- Active, metered, multi-dose device
- Size and shape of the R product
- Number of doses in the R product
- External operating principles and external critical design attributes of the R product
- Dose indicator/counter

Example of PSG for a Transdermal Patch Complex Product

Contains Nonbinding Recommendations

Draft Guidance on Scopolamine

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Active Ingredient: Scopolamine

Dosage Form; Route: Film, extended release; transdermal

Recommended Studies: Three studies

1. Type of study: Bioequivalence (BE) study with pharmacokinetic (PK) endpoints
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 1 mg/72 hr
   Subjects: Males and non-pregnant, non-lactating females, general population

   Additional comments:

   - In this document, this dosage form is referred to as a transdermal delivery system (TDS) and includes products that may be described elsewhere or known as *patches* or *extended release films*.
   - Unless otherwise justified, the scopolamine TDS should be applied to the same anatomical site on all subjects, as recommended for dosing in the approved labeling for the reference listed drug (RLD) product, and worn for 72 hours. Applicants should randomize subjects to receive either the test or RLD product in a given study period. When possible, the TDS administered in the second study period should be applied to the same anatomical site as in the first study period, but on the contralateral side of the body.
   - Contact of the TDS with the skin is essential for the in vivo performance of the TDS, and the PK may be altered when a TDS loses its adherence to the skin. Therefore, the adhesion of each TDS should be monitored and recorded throughout the PK study. The PK samples should be collected and analyzed from all subjects at all sampling times regardless of the adhesion scores of the TDS. Provisions should be included in the study protocol to ensure that deliberate actions with the intent to re-apply a detached area of the TDS, to apply pressure to the TDS, or to reinforce TDS adhesion with the skin (e.g., overlays) are avoided throughout the study.
   - The applicant should follow FDA's current thinking in the guidance "Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA" for the design and conduct of the PK BE study.

   Analytes to measure (in appropriate biological fluid): Scopolamine in plasma

   Bioequivalence based on (90% CI): Scopolamine

Recommended Aug 2009, Revised Dec 2009, Oct 2016, Oct 2018

Types of Studies Needed

2. Type of study: Adhesion study
Design: Single-dose, two-treatment, two period crossover in vivo
Strength: 1 mg/72 hr
Subjects: Males and non-pregnant, non-lactating females, general population

Additional comments:

- The applicant may elect to evaluate the PK BE (study 1) and the adhesion (study 2) in a single study with a combined purpose, or in independent studies. In either case, the studies should be adequately powered to evaluate the BE, and independently, the comparative assessment of adhesion.
- The applicant should follow FDA's current thinking in the guidance "Assessing Adhesion With Transdermal and Topical Delivery Systems for ANDAs" for the design and conduct of the independent adhesion study or the combined study to evaluate both PK BE and adhesion.

3. Type of study: Skin irritation and sensitization study
Design: Randomized, evaluator-blinded, within-subject repeat in vivo
Strength: Vehicle TDS and positive control (TDS containing active pharmaceutical ingredient should not be used in this study due to safety concerns)
Subjects: Males and non-pregnant, non-lactating females, general population

Additional Relevant Information (e.g., Safety information)

Additional comments relating to all studies:

In addition to the recommendations in the general guidances referenced above, and the product specific recommendations related to the individual studies, the following product specific recommendations should be considered.

- Exclusion Criteria (the applicant may add additional criteria):
  a. Subjects with a history of angle closure or open angle glaucoma
  b. Subjects with a history of pyloric obstruction or urinary bladder neck obstruction.
  c. Subjects with a history of seizures or psychosis
- The RLD product contains aluminum. Subjects should be advised to remove all TDS prior to magnetic resonance imaging or cardioversion to avoid skin burns.

[1] The optional vehicle TDS should contain all the inactive ingredients in the test product, and be identical to the test product in every manner except for the absence of the active ingredient.
[2] Safety concerns preclude the use of comparative studies with the test and RLD products, therefore, the test product can be evaluated by testing a vehicle TDS versus a positive control TDS that produces mild irritation (e.g., ≤ 0.1% sodium lauryl sulfate).
[3] An example of the optional negative control treatment is an occlusive cover or device with normal saline applied on a polyester pad under the cover or within the device chamber.

Example of an in vitro option for a complex product

Contains Nonbinding Recommendations

Draft Guidance on Silver Sulfadiazine

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Active Ingredient: Silver sulfadiazine

Dosage Form; Route: Cream; topical

Recommended studies: In vitro study

To qualify for the in vitro approach to demonstrate bioequivalence for silver sulfadiazine topical cream 1% the following criteria should be met:

A. The test and Reference Listed Drug (RLD) products should be pharmaceutically equivalent as defined in the Agency publication *Approved Drug Products with Therapeutic Equivalence Evaluations* (commonly known as the Orange Book) and should be qualitatively (Q1) and quantitatively (Q2) the same as defined in the Guidance for Industry *ANDA Submissions – Refuse-to-Receive Standards*.[1] To demonstrate acceptable Q1 and Q2 sameness of the test product with respect to the RLD product, the test product should contain the same inactive ingredients in the same quantitative composition (±5% of the RLD concentration of that inactive ingredient), and no concentration of any inactive ingredient should exceed the allowed limit listed in the inactive ingredient database for the applicable route of administration.

B. The test and RLD products should be physically and structurally similar based upon an acceptable comparative physicochemical characterization of a minimum of three lots of the test and three lots (as available) of the RLD product, including the following characterizations for each lot:

1. Assessment of appearance
2. Analysis of the silver sulfadiazine polymorphic form in the drug product
3. Analysis of globule and/or particle size distribution and crystal habit with representative microscopic images at multiple magnifications
4. Analysis of the rheological behavior, which may be characterized using a rheometer that is appropriate for monitoring the non-Newtonian flow behavior of semi-solid dosage forms. The following evaluations are recommended:

In Vitro Release Testing

4. **IVRT Method Development:** The results of relevant IVRT method development studies should be submitted for review, although such exploratory studies may not be performed using validated test method or sample analytical procedures, or within a quality management system that is compatible with applicable GLP principles:

   a. **Method Parameters:** Information should be provided to support the selection of the IVRT apparatus, product dose amount, sampling times, stirring/agitation rate, and other parameters of the test method.

   b. **Membrane:** Information on silver sulfadiazine membrane binding and chemical compatibility with relevant receptor solutions should be provided to support the inertness of the membrane selected, and information on the linearity and precision of the resulting silver sulfadiazine release rate in an IVRT should be provided to support the selection of a membrane for the test method.

   c. **Receptor Solution:** Information on the empirical solubility and stability of silver sulfadiazine in the receptor solution, as well as information on the linearity and precision of the resulting silver sulfadiazine release rate in an IVRT should be provided to support the selection of a receptor solution for the test method.

5. **IVRT Method Validation:** The apparatus, methodologies, and study conditions utilized in the IVRT pivotal study should be appropriately validated, qualified, verified, and/or justified. Detailed protocols and well-controlled study procedures are recommended to ensure the precise control of dosing, sampling, and other IVRT study variables or potential sources of experimental bias. The validation of the IVRT method should incorporate the following qualifications and controls, performed using validated sample analytical procedures, as applicable:

   a. **IVRT Apparatus Qualification:** Suitable apparatus for the IVRT method are described in USP General Chapter <1724>. These include different models of a vertical diffusion cell, an immersion cell, and a flow through cell used with USP Apparatus 4. The operating principles and specific test procedures differ among the various apparatus; relevant procedures for installation, operational and performance qualification available from the manufacturer may be utilized. The laboratory qualification of each diffusion cell should, at minimum, qualify the diffusional area of the orifice in which the membrane is mounted, the volume of the receptor solution compartment in each diffusion cell, the control of a 32°C ± 1°C temperature (at the membrane), and the control of the rate of stirring or agitation, as applicable.

   b. **IVRT Membrane Qualification:** Membrane inertness may be evaluated in relation to membrane binding of silver sulfadiazine in the receptor solution (at a concentration relevant to the average concentration of silver sulfadiazine in the receptor solution at the end of the test). Determinations may be based upon 3 replicate membrane

Conclusions and Key Points

- The U.S. Food and Drug Administration is tasked with approving generic drug products that are bioequivalent and pharmaceutically equivalent to their reference product precursors.
- Some of these drug products are ”complex” and have been defined as such.
- FDA works to encourage good generic drug development practices for complex drugs by publishing expectations in product specific guidances, conducting research to fill identified knowledge gaps.
- Prior to developing a complex generic drug for the United States it is important to read and understand the product specific guidance for that drug.