U.S. FOOD & DRUG ADMINISTRATION

Challenges in the Approval of Complex Otic & Ophthalmic Generic Products: Bioequivalence Perspectives

SBIA 2021: Advancing Generic Drug Development: Translating Science to Approval

Day 1, Session 3: (Complex Injectable, Ophthalmic and Otic Products Pt. 2)

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Learning Objectives

- Describe FDA's current thinking regarding in vitro bioequivalence (BE) determination for complex otic and ophthalmic drug products

- Discuss challenges with in vitro BE determination for complex otic and ophthalmic drug products

Complex Otic and Ophthalmic Dosage Forms

- Suspensions & emulsions:
  - Suspension: a dispersion of a solid material (the dispersed phase) in a liquid (the continuous phase)
  - Emulsion: liquid disperse system consisting of at least two immiscible liquids (or two liquids that are saturated with each other)
- Ointment & gels:
  - Ointment: semisolid dosage form consisting of solid or semisolid hydrocarbon base of melting or softening point close to human body temperature
  - Gel: semisolid dosage form with gel-forming polymers

Complex Otic and Ophthalmic Drug Products

Otic
Suspension

Ophthalmic
Suspension, Gel,
Emulsion,
Ointment, Gel
Forming Solution

Criteria to Qualify for the In Vitro Option for Otic/Ophthalmic Suspension/Gel Drug Products

- For most of these types of dosage forms, to qualify for the in vitro option under CFR 320.24(b)(6):
  - (1) Test and reference products are Q1(qualitatively) and Q2 (quantitatively) the same,
  - (2) The comparative physicochemical characterization of the test and reference products are acceptable, and
  - (3) The comparative in vitro drug release rates from the test and reference products are acceptable.

  If any of these three criteria are not met, a comparative clinical endpoint study is needed.
- Certain drug characteristics may impact recommendations for BE determination, e.g., microbial kill rate studies

Choi S. and Lionberger S.A., The AAPS Journal, Vol. 18, No. 4, July 2016

Formulation (Q1/Q2) Sameness

(1) All inactive ingredients are the same as those in the reference listed drug (RLD): Q1 the same

(2) The difference in the amount of inactive ingredients between test and RLD are not more than 5%: Q2 the same

A test product that does not meet the above criteria would not be considered Q1/Q2 the same as the RLD.

Compare Physicochemical Characteristics

- Number of batches- at least three batches each of test and RLD/Reference Standard (RS)
- Depending on the active pharmaceutical ingredients (APIs) and drug product, the following comparative studies may be recommended:
  - ✓ Polymorphic state/crystalline habit of insoluble APIs
  - ✓ Appearance, pH, specific gravity, osmolality, viscosity, surface tension, buffer capacity
  - ✓ Re-dispersibility of the final product
  - ✓ Soluble fraction of insoluble APIs in the final drug product
  - ✓ Unit dose content (per unit dose, for all APIs, a minimum of 10 units per batch, 3 batches each of T and R). The unit dose content should be compared using population BE (PBE)
  - ✓ Drug particle and particle size distribution (PSD, a minimum of 10 datasets per batch, 3 batches each of T and R), using PBE on D50 and SPAN (D90-D10)/D50 or polydispersity index

Compare the Test Product to the RLD/RS

- Comparative in vitro drug release from the test and RLD/RS, evaluating the effect of manufacturing differences
- Comparative in vitro microbial kill rates of the test and RLD/RS formulations, if contains antibiotic components

Case-1 Otic Suspension

- Comparative physicochemical characterization of the test and RLD/RS products
  - Pooled sampling strategy is not encouraged when single unit volume meets instrument requirement (e.g., osmolality and viscosity)
  - When pooled samples are used, provide justifications (e.g., volume requirement by instrument: PSD)
  - Method validation for all studies, e.g., precision, accuracy and robustness

Case-1 Otic Suspension

- Request in vitro drug release testing (IVRT) for insoluble APIs in suspension dosage forms
  - For BE demonstration, the IVRT method can be different from QC methods, e.g., different USP apparatus
  - Complete method development/optimization and validation reports, e.g., selection of medium and USP apparatus, volume for dissolution condition, flow-rate, sample stability, membrane selection and recovery, test product with different particle sizes for discriminating ability
  - At least 12 units one batch each of test and RLD/RS

Case-1 Otic Suspension

- Comparative microbial kill rate study for antibiotic containing drug product
  - Reference Draft PSG for Dexamethasone and Tobramycin Ophthalmic Suspension, e.g., organisms selection (USP <51> Antimicrobial Effectiveness Testing and "Indications" of the RLD labeling)
  - Method optimization/validation, e.g., dose selection (concentrations of drugs in media), antibiotic carryover, colony counts of organisms on survival media
  - Pivotal study, e.g., inappropriate dose, raw data of colony counts, statistical method

Inappropriate Dose Selection for Microbial Kill Rate Study

	Test		RLD/RS	
Time (mins)	Organisms (cfu/mL)	% Reduction	Organisms (cfu/mL)	% Reduction
0	4.5×10^5	-	5.3×10^5	-
5	<10	100%	<10	100%
15	<10	100%	<10	100%
30	<10	100%	<10	100%
60	<10	100%	<10	100%
120	<10	100%	<10	100%

Summary of Case-1 (Otic Suspension)

- Physicochemical characterization study
  - Pooling sample is not encouraged in general

- IVRT method optimization/validation
  - Apparatus selection
  - Medium selection
  - Discriminating ability

- Microbial kill rate study design
  - Dose selection
  - Statistical analysis method

Case-2 Ophthalmic Gel

Two options: in vitro or in vivo study

I. In vitro option:

i. Q1 and Q2 the same as the RLD

ii. Physicochemical characteristics (Q3): Comparative appearance, pH, specific gravity, and osmolality, Comparative drug particle size distribution

iii. Comparative IVRT

II. In vivo option: BE study with Pharmacokinetic (PK) endpoints

Case-2 Ophthalmic Gel

- **Comparative Drug Particle Size Distribution (PSD)**

  - Method development, e.g., sample preparation (range of dilution) and instrument parameter for PSD

  - Method validation, e.g., invalid validation samples, etc.

  - BE determination: PBE based on D50 and SPAN with a minimum of 10 units per batch from 3 different batches of each T and R

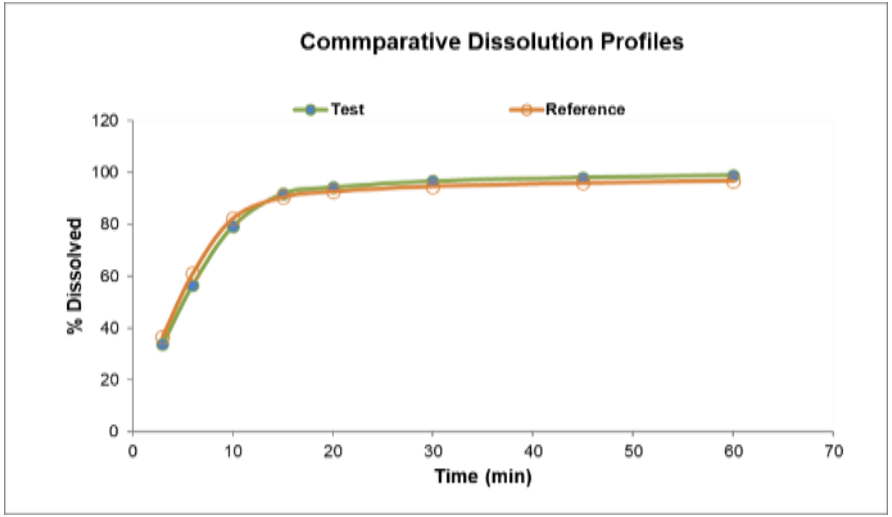
Case-2 Ophthalmic Gel

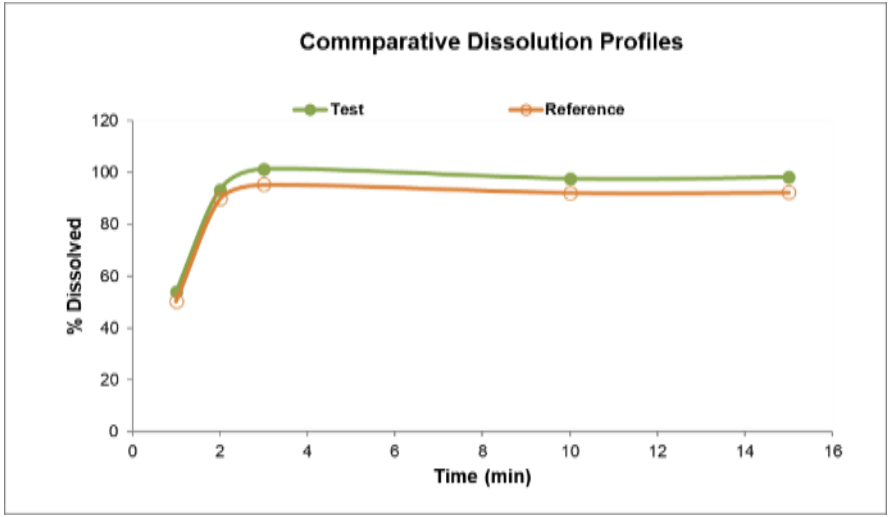
- **In Vitro Release Test (IVRT)**

  - Method development/optimization/validation, e.g., physiologically relevant medium, dissolution and analytical conditions, discriminating ability, etc.

  - Pivotal IVRT study, e.g., timepoints used for the f2 calculations, at least 12 units of one batch of freshly manufactured T and one batch of unexpired RLD, complete release profile (≥85% mean), etc.

Discriminating IVRT Method





Accepted for BE determination

Too rapid release, lack of discriminating ability

Summary of Case-2 (Ophthalmic Gel)

- PSD study
  - Sample dilution range
  - Using valid samples for method validation
  - Sufficient number of replicates for PBE analysis

- IVRT Study
  - Method discriminating ability
  - Complete release by the last sampling time point
  - Explain timepoint used for f2 calculations

Summary of The Two Cases

- Currently, for complex otic/ophthalmic suspensions/gels, the recommended in vitro option reflects FDA's current thinking for BE establishment
- Challenges:
  - PSD: method validation, sample preparation
  - IVRT: method discriminating ability, avoid very rapid release
  - Microbial kill rate study: dose selection, statistical method for BE determination

Challenge Question #1

Currently, the prerequisite for using in vitro options for BE demonstration is

A. The test formulation is exactly the same as the RLD

B. The test product does not contain an inactive ingredient that is not contained in the RLD

C. The test formulation is Q1 and Q2 the same as the RLD

Challenge Question #2

Currently, for particle size distribution study, the Agency recommends how many datasets each of the test and reference products for the PBE analysis:

A. A minimum of 10 datasets from each batch for 3 batches each of test and RLD/RS

B. A minimum of 5 datasets from each batch for 3 batches each of test and RLD/RS

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Questions?

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