Bioequivalence of Long Acting Injectable (LAI) Suspensions: Current Perspective and Future Directions

2020 CRS workshop

June 27, 2020

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Outline

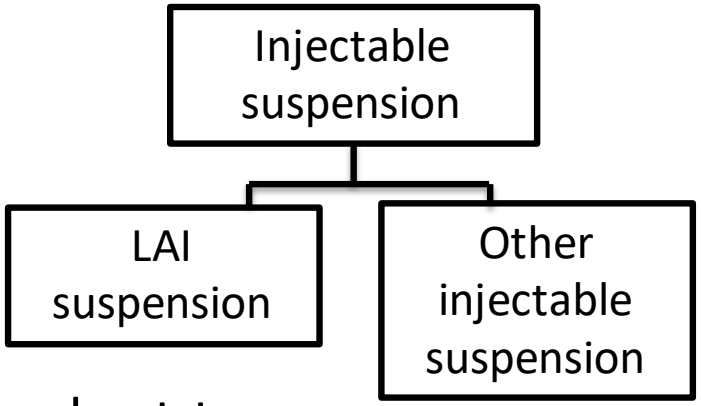
- Grouping of injectable suspension products into two broad classes based on indication(s) and dosing frequency: LAI suspension products and other injectable suspension products
- Approaches for demonstrating bioequivalence of injectable suspension products
- Challenges and future direction

Injectable suspension products

- Consists of nano- and/or micro-sized solid drug particles suspended in aqueous vehicle
- Route of administration: intramuscular, subcutaneous, intravitreal, intravenous, and other
- Supplied as powder for suspension, suspension in vial, or prefilled syringe
- Injectable suspensions generally offer various levels of sustained release, which is controlled by the water solubility of the drug substance and the particle size

Long acting injectable (LAI) suspension products

- Designed to achieve stable therapeutic drug exposure for prolonged period of time
- Dosing interval and frequency
  - Weeks to months *vs* daily
  - Multiple doses *vs* one-time dose
  - Long-term use for chronic therapies *vs* short-term use



- LAI suspension products are generally administrated via intramuscular or subcutaneous route

Examples of LAI suspension products

Drug	Dosing frequency	Indication(s)	Local or systemic delivery
Aripiprazole	4 weeks	Antipsychotic	Systemic
Aripiprazole Lauroxil*	4 weeks, 6 weeks	Antipsychotic	Systemic
Olanzapine Pamoate	2 weeks, 4 weeks	Antipsychotic	Systemic
Paliperidone Palmitate*	1 month or 3 months	Antipsychotic	Systemic
Medroxyprogesterone acetate*	Weekly or 12-14 weeks	Metastatic carcinoma or contraceptive	Systemic

* Drug substance of two or more injectable suspension products

Examples of other injectable suspension products

Drug	Dosing frequency	Indications	Local or systemic delivery
Azacitidine*	Daily	FAB myelodysplastic syndrome	Systemic
Triamcinolone acetonide*	Daily or not specified	Anti-inflammatory	Systemic or local
Dexamethasone	Single dose	Anti-inflammatory	Local
Dantrolene sodium	Single dose	Treatment or prevention of malignant hyperthermia	Systemic
Penicillin G Benzathine	Single dose or 1 to 4 weeks	Bacterial infections	Systemic

* Drug substance of two or more injectable suspension products

Demonstrating equivalence of injectable suspension product to RLD

- Regulatory requirements include, but not limited to:
  - Same active ingredient(s), strength, dosage form, and route of administration, condition of use, labeling
  - Qualitatively (Q1) and quantitatively (Q2) the same inactive ingredients as the reference listed drug[1]
  - Bioequivalence (BE)
    - In vivo BE studies
    - In vitro BE studies

1. Differences in preservative, buffer, or antioxidant are permissible, per 21 CFR 314.94(a)(9)

Generic injectable suspension landscape

	PSG available	Generic Available
LAI suspension	• Medroxyprogesterone acetate • Aripiprazole • Olanzapine pamoate • Paliperidone palmitate (1-month)	• Medroxyprogesterone acetate
Other injectable suspension	• Triamcinolone acetonide • Azacitidine • Dantrolene sodium	• Triamcinolone acetonide • Azacitidine

FDA's Product-Specific Guidances (PSGs) for Generic Drug Development available at https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm

In vivo BE approach

- There are three types of in vivo BE studies, all are done compared to the reference standard (RS) product:
  - Pharmacokinetic (PK), comparative clinical endpoint, or pharmacodynamic endpoint study
- Currently all the posted PSGs for LAI suspension products recommend using in vivo PK study to demonstrate BE
- Considerations for PK study:
  - Study design: single-dose vs. steady-state
  - Subjects: healthy subjects vs. patients

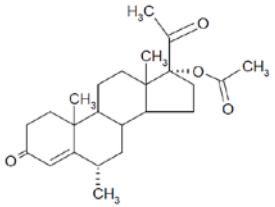
Product specific guidances for LAI suspension products

Drug	Study design	Subjects	PK metrices for Statistical analysis
Aripiprazole	In vivo, steady-state, crossover	Patients	AUC and Cmax
Olanzapine pamoate	In vivo, steady-state, parallel or crossover	Patients	AUC and Cmax
Paliperidone palmitate*	In vivo, steady-state, parallel or crossover	Patients	AUC and Cmax
Medroxyprogesterone acetate	In vivo, single-dose, parallel	Healthy subjects	AUC and Cmax

*1 month product

Example of in vivo BE study

Medroxyprogesterone acetate injectable suspension, 150 mg/mL



Medroxyprogesterone acetate

Single-dose PK study in healthy, nonpregnant subjects

- Indication: contraception, prevention of pregnancy.
- Dosing interval: 3 months
- Route: intramuscular injection

Draft Guidance on Medroxyprogesterone Acetate

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Active Ingredient: Medroxyprogesterone acetate

Dosage Form; Route: Suspension; intramuscular injection

Recommended Studies: One study

1. Type of study: Fasting
   Design: Single-dose, parallel, in vivo
   Strength: 150 mg/mL
   Subjects: Healthy nonpregnant females
   Additional Comments: Females should not be pregnant and if applicable, should practice abstention or contraception during the study.

   Both sites of injection (gluteal and deltoid) should be included in the study design. Subjects should be randomized into the following four (4) groups: Test treatment at gluteal site, Test treatment at deltoid site, Reference treatment at gluteal site, and Reference treatment at deltoid site. In addition, if more than one dosing date is planned, approximately equal number of subjects representing each of the 4 groups should be included in each of the dosing dates.

   Demonstration of BE at each of the injection sites is not recommended, only demonstration of BE between the test and reference formulations, with the effect of the two injection sites taken into account and analyzed; i.e., the factor, injection site, should be included in the statistical analysis model.

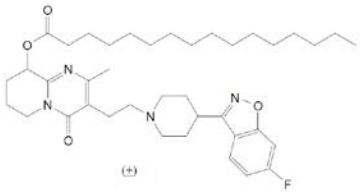
The formulation of test and reference products should be qualitatively (Q1) and quantitatively (Q2) same per CFR 21 314.94 (a)(9)(iii).

Analytes to measure: Medroxyprogesterone acetate in plasma

Bioequivalence based on (90% CI): Medroxyprogesterone acetate

Example of in vivo BE study (cont.)

Paliperidone palmitate extended release suspension injectable suspension



Paliperidone palmitate

- Indications: schizophrenia and schizoaffective disorder
- Dosing interval: 1 month
- Route: intramuscular

Draft Guidance on Paliperidone Palmitate

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Active Ingredient: Paliperidone palmitate

Dosage Form; Route: Extended Release Suspension; Intramuscular

Recommended Studies: One study

Steady state study

1. Type of study: Bioequivalence (BE) study with pharmacokinetic (PK) endpoints
Design: Parallel or crossover steady-state
Strength: ~~39 mg/0.25 mL, 78 mg/0.5 mL, 117 mg/0.75 mL, 156 mg/mL, 234 mg/1.5 mL~~
Subjects: Male and nonpregnant female patients with schizophrenia or schizoaffective disorder who are already receiving a stable regimen of paliperidone palmitate extended release suspension via the intramuscular route. Patients who are already receiving any dosage regimen of paliperidone palmitate injection every month would be eligible to participate in the study by continuing their established maintenance dose.
Additional comments: (1) FDA does not recommend that studies be conducted using healthy subjects or patients on a different antipsychotic treatment. (2) Both sites of injection (gluteal and deltoid) should be included in the study design for adequate site representation to support the results of the study. (3) More than three doses may be required to reach steady state. PK data should be submitted to demonstrate that steady state has been reached for each individual. (4) All strengths of the test product need to be from the same bulk in order for all strengths of the Test to be administered in the PK BE study.

Special considerations for patients

Need to demonstrate steady-state was achieved prior to PK sampling

In vitro BE approach

- An in vitro-only BE approach generally relies on totality of evidence
  - When a product is formulated Q1/Q2 same, there could be differences in the arrangement of matter within the dosage form, which may impact product performance
  - These differences in arrangement of matter arise from differences in manufacturing, processing, or excipient grade/source
  - These differences can be evaluated by comparative physicochemical tests
  - Sameness in physicochemical characteristics can demonstrate overall product sameness, and thus equivalence
- An in vitro-only BE approach has been recommended in the PSGs for the following injectable suspension products:
  - triamcinolone acetonide, azacitidine, and dantrolene sodium

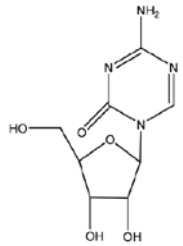
General physiochemical characteristics of injectable suspension

- Polymorphism, crystalline shape, and morphology
  - Crystalline form can affect solubility, dissolution, pharmacokinetics
- Particle size distribution (PSD)
  - The particle size distribution can affect the physical stability, dissolution behavior, and therapeutic efficacy of suspension products
- pH
  - Solubility can be pH-dependent
- Osmolality
- Viscosity
  - Related to injectability and sedimentation

Population bioequivalence statistical approach is recommended to establish equivalence of PSD (e.g., D50 and SPAN)

Example of in vitro BE approach

Azacitidine injection



Azacitidine

- Indication: FAB myelodysplastic syndrome
- Dosing interval: daily
- Route: subcutaneous injection (as suspension) or iv infusion (as solution)

Formulation considerations (i.e. Q1/Q2)

Recommended in vitro testing (viscosity, osmolality, pH, particle morphology, particle size distribution, in vitro drug release)

Draft Guidance on Azacitidine

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Active Ingredient: Azacitidine

Dosage Form; Route: Powder; IV (infusion), subcutaneous

Strength: 100 mg/vial

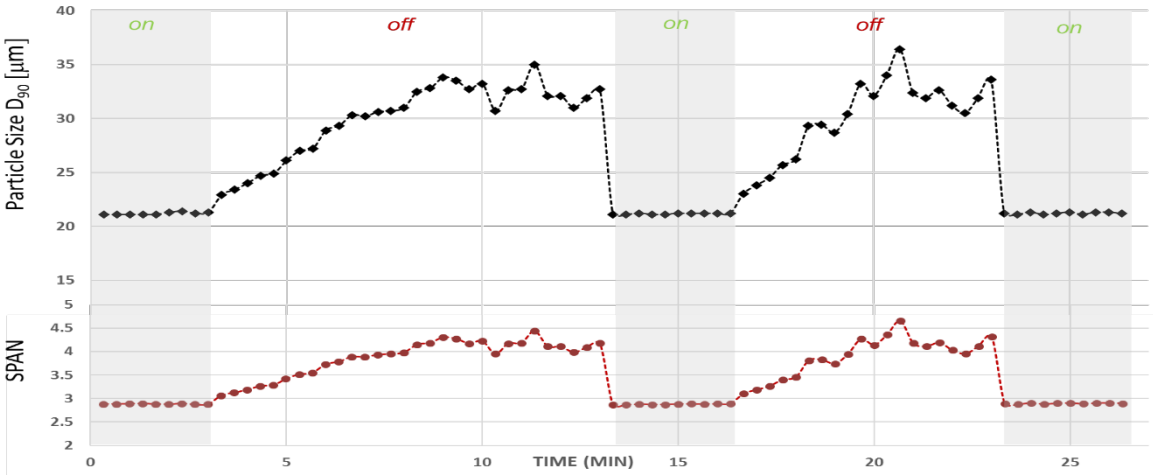
Additional Comments: The proposed drug product should be qualitatively (Q1)[1] and quantitatively (Q2)[2] the same as the Reference Listed Drug (RLD). Bioequivalence may be established based on comparative in vitro testing of three batches, if available, of both the test product and designated Reference Standard (RS) product.

The criteria of in vitro evidence that the test product, when reconstituted as a suspension for subcutaneous administration, demonstrates bioequivalence to the RLD product are:

1. **Physicochemical Characteristics**. Evidence that test and RS products have comparable physicochemical properties, such as viscosity, osmolality, and pH.
2. **Particle Morphology**. It is recommended that a suitable method for qualitative determination be used to allow observation of particles in the size range in which azacitidine particles are expected to fall. Representative micrographs should be submitted. These data are supportive, and formal statistical testing is not applicable.
3. **In Vitro Drug Release.** Acceptable comparative in vitro drug release of azacitidine from the test and RS formulations. It is recommended that the developed in vitro drug release method to support bioequivalence be based on USP Apparatus 4 (flow-through cell) and be appropriately designed to measure the rapid solubility of the product.
4. **Particle Size Distribution**. Particle size distribution should be compared using the population bioequivalence (PBE) statistical procedure (95% upper confidence bound) based on D_{50} and SPAN [i.e., $(D_{90}-D_{10})/D_{50}$]. Refer to the product-specific *Guidance on Budesonide* inhalation suspension for additional information regarding PBE.

Analytical considerations for particle size characterization of injectable suspensions

- Particle size determination of flocculated particles could be highly sensitive to the testing conditions (e.g., agitation and sonication)



Trend in D90 and SPAN upon the cycling of sonication. Dispersion of Triamcinolone acetonide injection sample stirred at constant 3000 rpm stir rate, sonication is applied continuously (shaded region) for 10 measurements

(Smith et al. 2020 CRS annual meeting poster)

Challenges of Developing Generic Injectable Suspensions

- Formulation sameness
  - Demonstrating Q1 and Q2 sameness is generally straightforward
  - 3 proposed formulations can be submitted for FDA assessment/comment [1]
- In vitro drug release testing
  - Balance between reasonable timeframe and discriminative ability
- Bioequivalence considerations
  - LAI suspensions
    - Long study duration
    - Potential high drop-out rate
    - Large number of subjects
    - Determination of steady state
  - "Other" injectable suspensions
    - Particle size determination and comparison

[1] *Controlled Correspondence Related to Generic Drug Development* Draft Guidance for Industry (Nov 2017)

The Million-Dollar Question

Whether an in vitro-only approach can be recommended for any long acting injectable suspension product?

Knowledge gap of LAI suspension products

The prolonged exposure and potential adverse side effects of most LAI suspension products typically present a higher risk compared to injectable suspension products for short-term use (e.g., Kenalog 40)

- What are critical quality attributes of LAI suspension products?
- How do physiochemical characteristics correlate with in vitro/in vivo drug release?
- How does in vitro drug release testing correlate with in vivo bioavailability?

Future direction

- Establishing in vitro-in vivo correlation (IVIVC) or in vitro-in vivo relationship (IVIVR) to support proposed in vitro BE approach
  - What are the best methods to measure in vitro properties
  - What are the appropriate statistical approaches for comparison
  - Understanding which product attributes affect PK profile to establish IVIVC or IVIVR
- Developing new modeling tools to support evaluation of alternate study designs

GDUFA research efforts

- Two Generic Drug User Fee Amendment (GDUFA) funded research projects have been awarded in this area
  - In vitro in vivo correlation of long-acting injectable suspensions to improve scientific approaches to evaluate generic drugs

    Awarded to University of Connecticut ((#HHSF223201710135C) FY2017
  - Development of model-informed bioequivalence evaluation strategies for long-acting injectable products

    Awarded to Uppsala University, Sweden (75F40119C10018) FY2019
- GDUFA-funded research publications and resources: https://www.fda.gov/drugs/generic-drugs/generic-drugs-research-publications-resources

Summary

- Based on therapeutic duration, dosing interval and indications, injectable suspension drugs may be categorized into two broad categories: LAI suspension products and other injectable suspension products.
- A BE approach must provide the most accurate, sensitive, and reproducible measure to ensure bioavailability and BE. An in vitro approach needs to establish that it meets this compared to an in vivo PK BE study.
- Knowledge gaps remain and research is needed to facilitate in vitro BE approaches for LAI suspension products.

Acknowledgements

Office of Generic Drugs

- Rob Lionberger
- Lei Zhang
- Markham Luke
- Darby Kozak
- Liang Zhao
- Yan Wang
- Mohammad Sabir Aqueel

Office of Pharmaceutical Quality

- Xiaoming Xu
- William Smith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