In Vitro Bioequivalence Approaches for Injectable Drug Substance Suspension Products: Medroxyprogesterone Acetate

SBIA 2023—Advancing Generic Drug Development: Translating Science to Approval

Day 1, Session 3: Noteworthy Guidances for Injectable Products

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Learning Objectives

- Understand the in vitro approach for demonstrating bioequivalence (BE) of injectable drug substance suspensions
- Examine noteworthy product-specific guidance (PSG) on medroxyprogesterone acetate
  - Common deficiencies observed for the in vitro BE studies
  - What should be submitted for the in vitro BE studies

Injectable drug substance suspensions

- Drug substance particles are the only insoluble component in the formulation (or reconstituted formulation)
- There are no insoluble excipients in the solution phase
- Drug release does not rely on release controlling excipients (e.g., poly(lactic-co-glycolic acid) copolymer)
- Dissolution rate is generally determined by particle size and solubility of the drug substance

$$\frac{dC}{dT} = \frac{D \cdot A}{h \cdot V}(C_s - C_i)$$

Demonstrating bioequivalence

- BE studies should be sensitive, accurate, and reproducible
- In vivo BE studies with pharmacokinetic (PK) endpoints have been commonly recommended by FDA in product-specific guidances (PSGs)[1] for systemically acting injectable suspensions
- FDA has also recommended in vitro BE studies for some injectable drug substance suspensions

1. https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm

How are in vitro BE approaches developed: a case study of the PSG on medroxyprogesterone acetate

PSG on medroxyprogesterone acetate

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

To qualify for the in vitro option for this drug product, all the following criteria should be met:

1. The test and reference listed drug (RLD) formulations are qualitatively (Q1)[1] and quantitatively (Q2)[2] the same.

2. Acceptable comparative physicochemical characterization of the test and the reference standard (RS) products. The comparative study should be performed on a minimum of three exhibit batches of the test product[3] and three batches of the RS product and should include:
   a. Polymorphic form of medroxyprogesterone acetate
   b. Crystalline shape and morphology of medroxyprogesterone acetate
   c. Appearance, pH, osmolality, specific gravity, sedimentation rate and volume, and viscosity over a range of shear rates

In vitro bioequivalence study 1:
Drug particle size and size distribution of medroxyprogesterone acetate

Additional comments: The particle size distribution should be compared using population bioequivalence (PBE) (95% upper confidence bound) based on D50 and SPAN [i.e. (D90-D10)/D50)]. The applicant should provide no fewer than ten data sets from three different batches of both the test and RS products for PBE analysis. Full profiles of the particle distribution should also be submitted for all samples tested. Refer to the most recent version of the FDA product-specific guidance on *Budesonide Inhalation Suspension*[a] for additional information regarding PBE.

In vitro bioequivalence study 2:
Comparative in vitro drug release of medroxyprogesterone acetate from the test and RS products.

II. Option 2: One in vivo bioequivalence study with pharmacokinetic endpoints

1. Type of study: In vivo bioequivalence study with pharmacokinetic endpoints
   Design: Single-dose, parallel, in vivo
   Strength: 150 mg/mL
   Subjects: Healthy non-pregnant females

The PSG recommends two options to demonstrate BE:

- Option 1: In vitro studies

  OR

- Option 2: In vivo BE study with pharmacokinetics (PK) endpoints

The in vitro option

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To be eligible for the in vitro option:

- Q1/Q2* to the reference listed drug **(RLD);**
  - Ensure identical formulation components
- Comparative physiochemical property to the reference standard **(RS)**
  - Q1Q2 sameness alone may not be sufficient to ensure comparable formulation characteristics as differences may arise from differences in manufacturing, processing, or excipient grade/source

* Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the RLD product. 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.

The in vitro option (Cont.)

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Drug particle size and size distribution of medroxyprogesterone acetate

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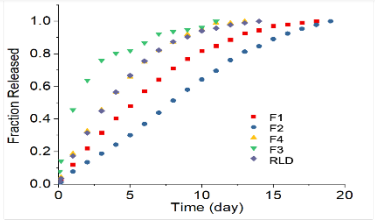
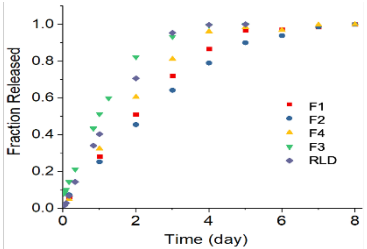
In vitro bioequivalence study 2:
Comparative in vitro drug release of medroxyprogesterone acetate from the test and RS products.

- GDUFA research to understand the relationship of product critical quality attributes to the in vivo performance using compositionally equivalent medroxyprogesterone acetate suspensions prepared with different particle size

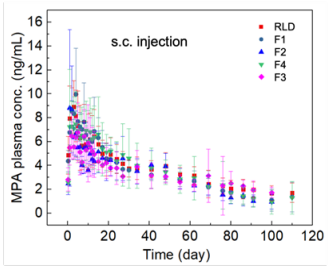
USP apparatus 2 with enhancer cells

USP apparatus 4 with semi solid adaptor





Formulation	Dv10	Dv50	Dv90	Span
F1	7.21±0.42	13.40±0.54	24.09±0.74	1.26±0.04
F2	8.73±0.31	21.73±0.28	41.08±0.53	1.49±0.04
F3	0.69±0.33	3.67±0.43	10.13±0.99	2.61±0.44
F4	7.00±0.13	13.03±0.23	23.44±0.37	1.26±0.01
RLD	10.37±0.99	18.23±1.36	30.61±1.78	1.11±0.05



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How to execute the in vitro option: common deficiencies

Information and data to be included

Data based on the RLD

- Q1Q2 sameness

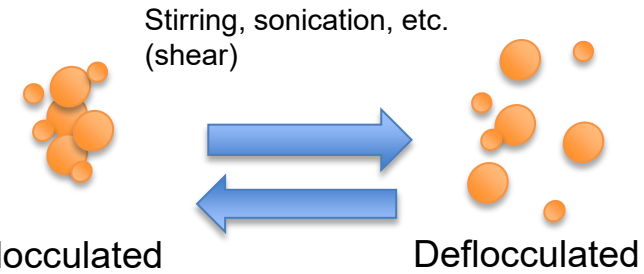
Data based on RS

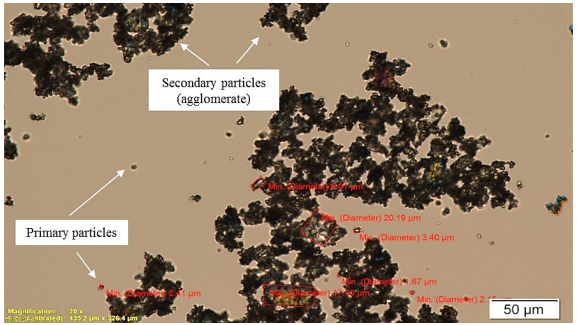
- Comparative physiochemical characterization
- Particle size and particle size distribution (PSD)
  - Method development and validation
  - Statistical analysis per PSG's recommendations
  - Justification when a different statistical method is used
- In vitro drug release study (IVRT)
  - Method development and validation
  - Statistical analysis for supporting similarity in release profiles

Common deficiencies in PSD study

No method development report/validation report

- Flocculated vs. deflocculated particles
  - Stabilizer and/or viscosity agents may be used to induce flocculation and prevent agglomeration/Ostwald ripening
  - Inter conversion between these two types of particles is reversible, and highly dependent on the shear conditions





Triamcinolone acetonide injectable suspension

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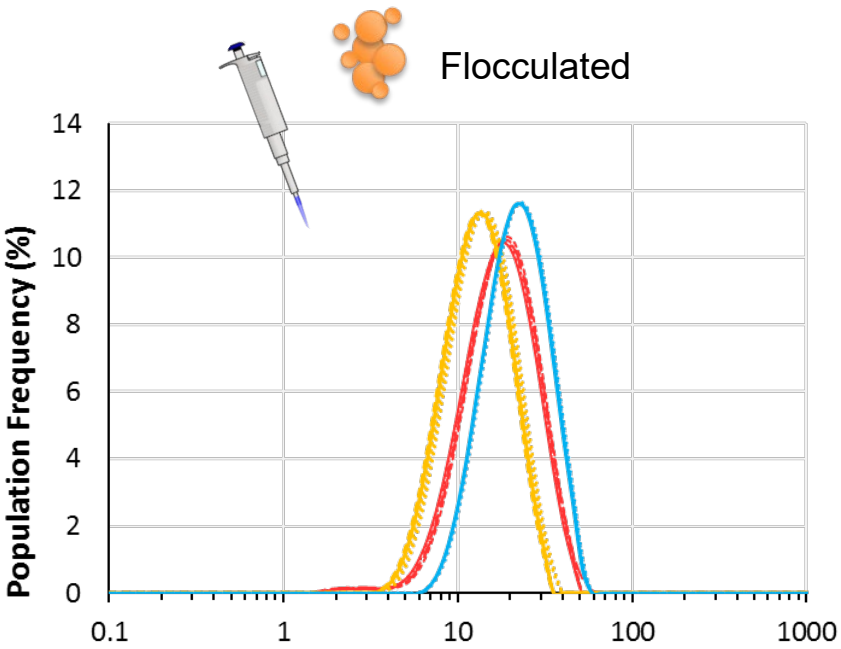
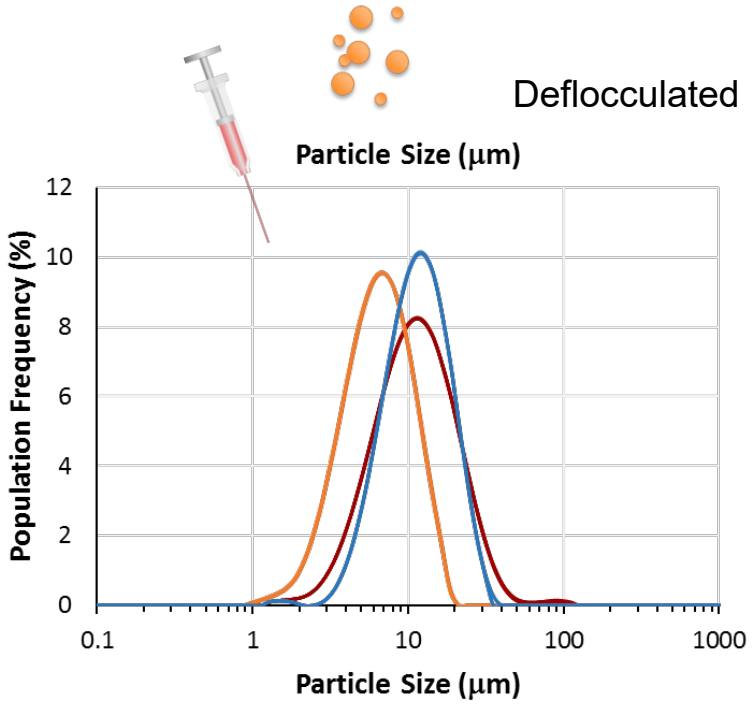
Common deficiencies in PSD study (cont.)

- Flocculation could introduce variations in particles size





William Smith et al. IJP, 604 (2021) 120767

Things to consider for PSD study

- Method development
  - How the PSD study sample analysis parameters have been chosen (e.g., dispersant, sample dilution range, stirring speed, etc.)
- Method validation
  - Precision and robustness
- Results
  - Full profiles of the PSD, particle size results (e.g., D_{50} and SPAN), and statistical analysis (e.g., population bioequivalence)

Common deficiencies for IVRT study

- Use the “FDA method” from the Dissolution Methods Database[2] without additional information and rationale to support the IVRT method is suitable for assessing the proposed generic product
- Lack of IVRT validation data and/or incomplete evidence to demonstrate discriminatory ability of the IVRT method toward critical quality attributes of the product (e.g., particle size)
- No statistical analysis of the release data

2 https://www.accessdata.fda.gov/scripts/cder/dissolution/

Things to consider for IVRT study

- Method development and validation:
  - How the experimental parameters are selected (e.g., media composition, media volume, stirring rate, etc.)
  - Discriminatory ability and reproducibility: formulations with intentional and meaningful variations are good testing samples to verify the method is “discriminatory” and “reproducible”
- Results:
  - Data presentation (e.g., cumulative % in vitro drug release profile)
  - Statistical analysis (e.g., model independent similarity ($f2$) factor)

Summary

- Injectable drug substance suspensions are formulated without release modifiers and the drug substance is the only insoluble component in the product
- An in vitro BE approach is based on the understanding of the critical quality attributes of the product that affect bioequivalence and relies on totality of evidence
- The PSD study and IVRT study should contain sufficient information regarding method development, method validation and study result

Challenge Question #1

Is this statement correct? The particle size distribution method should be validated with regard to precision and robustness

A. True

B. False

Challenge Question #2

Which of the following statements for the IVRT study in the PSG for injectable drug substance suspensions are true:

A. IVIVC is required to justify the used IVRT study

B. No method development and validation report need if the dissolution study information can be found in the FDA's Dissolution Methods database

C. The dissolution study information in the FDA's Dissolution Methods database serves as a starting point and ANDA applicants need to submit sufficient method development and validation reports.

D. The used IVRT method should be able to discriminate the critical quality attributes (e.g., particle size)

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Questions?

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