In Vivo Pharmacokinetic Bioequivalence Studies for Long-Acting Injectables (LAIs): Considerations and Challenges

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Outline

- Long-Acting Injectables (LAIs): An Introduction
- Bioequivalence (BE) study recommendations
- General considerations in the study design of in vivo pharmacokinetic (PK) studies
- Challenges in the conduct of in vivo BE PK studies
- Example deficiencies found in Abbreviated New Drug Applications (ANDAs)
- Key takeaways

Long-Acting Injectables (LAIs): An Introduction

- LAIs provide sustained and continuous release of drug substance over a period of days to months when administered via intramuscular, subcutaneous, epidural, and intra-articular routes.

- LAIs improve patient compliance and treatment adherence by reducing dosing frequency through maintenance of plasma drug concentrations over a longer time period than other dosage forms.

- Example therapeutic areas: antipsychotic, hormonal therapy, substance abuse disorders.

- For most LAIs, there is no generic approval to date.

LAIs: An Introduction - continued

- Regulatory consideration for ANDAs: Generally, a drug product intended for parenteral use must contain the same inactive ingredients and in the same concentration as the reference listed drug. However, differences in preservative, buffer, and antioxidant are allowed if appropriately justified by the applicant [per 21 CFR § 314.94].

- Formulation types: polymer-based (poly lactide-co-glycolide [PLGA] and non-PLGA), oil-based, drug crystal suspension

- Pharmacokinetics (PK): absorption rate slower than elimination rate ("flip-flop" PK); long apparent elimination half-life actually reflects the rate of absorption; long time to achieve steady-state

Bioequivalence (BE) Study Recommendations for LAIs

Depending on the specific LAI, one of the following approaches may be recommended to demonstrate BE between test and reference products:

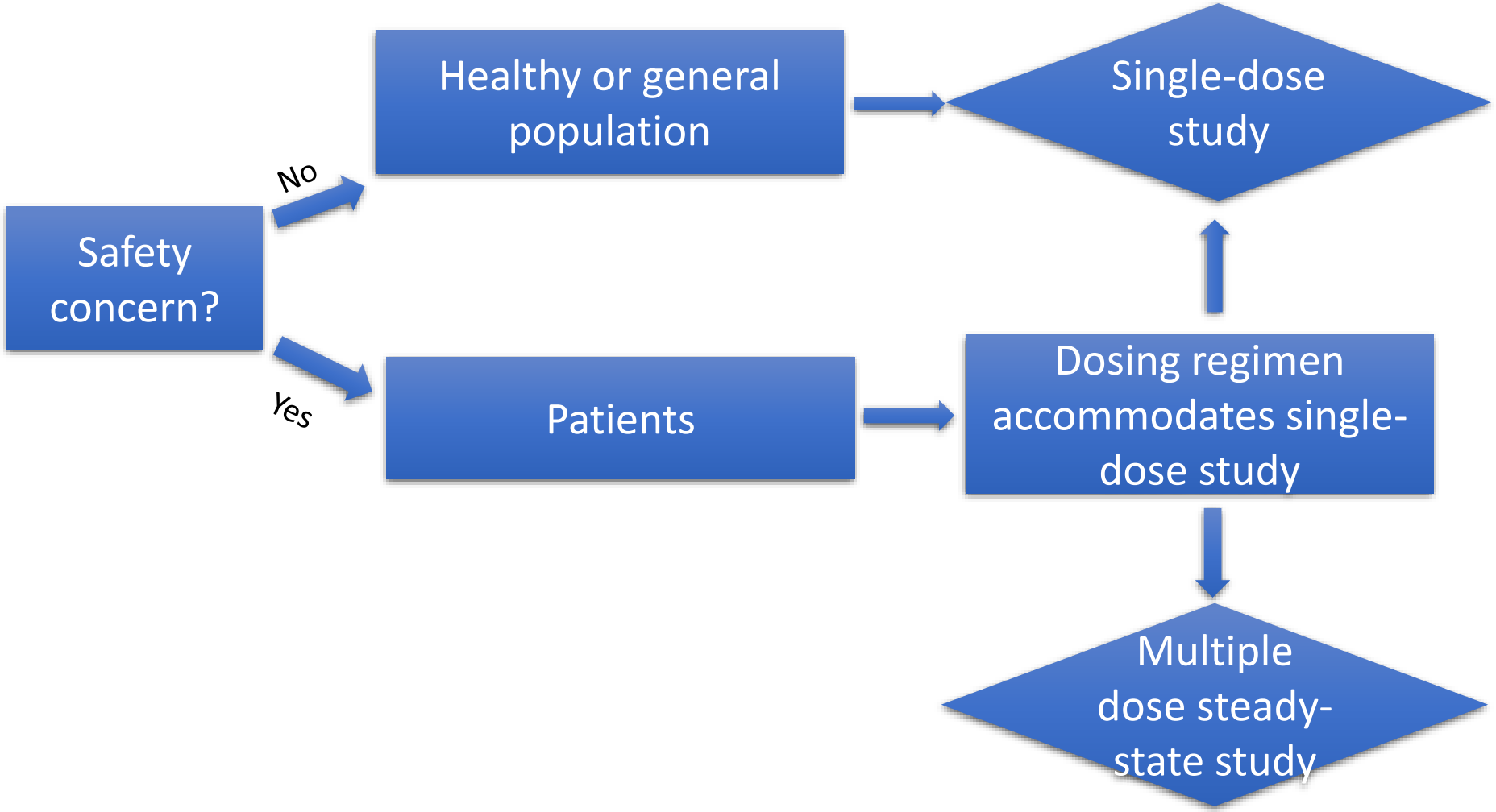
- In vivo BE study with PK endpoints
- In vitro studies in combination with an in vivo PK BE study: qualitative (Q1) and quantitative (Q2) sameness + comparative in vitro physicochemical characterization (Q3) + comparative in vitro drug release testing + in vivo PK BE study
- In vitro studies as an alternative to an in vivo BE study based on a totality of evidence approach for Q1/Q2 generic formulations: comparable Q3 characteristics + comparable in vitro drug release profile

BE Study Recommendations - Example Product-Specific Guidance (PSG) for LAIs

LAI drug product	BE recommendation in PSG
Medroxyprogesterone Acetate Injectable Suspension	In vivo single-dose parallel BE study with PK endpoints
Risperidone Injection	Q1/Q2 sameness, physicochemical characterization of PLGA, in vitro drug release testing, and in vivo crossover steady-state BE study with PK endpoints
Penicillin G Benzathine Injectable Suspension	Two options • In vitro option: Q1/Q2 sameness, physicochemical characterization, and in vitro drug release testing • In vivo option: single-dose parallel BE study with PK endpoints

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

General Considerations in the Study Design of In Vivo PK Studies for LAIs



General Considerations in the Study Design of In Vivo PK Studies for LAIs - continued

Crossover vs. parallel:

- Generally parallel design for single dose study to avoid washout concerns due to long half-life (e.g., Depo-Provera® [Medroxyprogesterone acetate] Injectable: approximately 50 days; Vivitrol® [naltrexone] ER Suspension: 5-10 days)
- Parallel or crossover design for steady state study

Strength to be studied:

- In general, the highest strength is recommended unless there is a safety concern
- Multiple strengths may be recommended in some cases
- For certain LAI products (e.g., Risperidone injection), any strength may be used

PK metrics:

- Single dose study: Cmax, AUCt, AUCinf, Tmax
- Multiple-dose study: Cmax, AUCtau, Tmax, Cmin, Fluctuation
- Partial AUC based on clinical relevance and formulation characteristics, e.g., Naltrexone ER Injectable Suspension: inclusion of AUC1-10 and AUC10-28 to account for the multi-phasic release profile and therapeutic threshold
- Cmax and AUCs are subject to 90% confidence interval

General Considerations in the Study Design of In Vivo PK Studies for LAIs - continued

Injection site:

- Based on reference listed drug (RLD) information (e.g., labeling), both gluteal and deltoid sites are included in the study design for adequate administration site representation for certain LAIs. However, typically demonstration of BE at each of the injection sites may not be necessary, e.g., Paliperidone Palmitate ER Injectable Suspension, Medroxyprogesterone Acetate Injectable Suspension.

Steady-state:

- Sufficient number of doses should be administered to achieve steady-state (e.g., antipsychotic injectables)

Challenges in the Conduct of In Vivo BE PK Studies for LAIs

- Recruiting difficulty
- Long study duration
- High dropout
- High variability for parallel study
- Variability being contributed from multiple factors (demographics, clinical center, injection site, etc.)
- Steady state determination
- Safety concerns
- Reserve sample retention

Example Deficiencies Found in ANDAs for LAIs

Carry-over effect:

- Insufficient number of doses between treatments in the crossover steady-state study, i.e., insufficient washout.

Dropouts:

- The number of subjects not balanced in terms of injection sites (gluteal and deltoid) and treatments (Test and Reference) due to a high dropout rate. Applicant did not evaluate the impact of these imbalances on the study outcome.

Example Deficiencies Found in ANDAs for LAIs - continued

Safety profile:

- Difference in the rate of serious adverse events (SAE) between Reference and Test treatments

Concomitant medications:

- Applicant did not demonstrate the lack of interference from the concomitant medications on the analytical method used to measure the analyte and the possible impact on the PK profiles

Clinical center effect:

- Applicant did not provide evaluation of the clinical center effect on the BE statistical analysis

Key Takeaways for In Vivo PK Study Design and Conduct for LAIs

- Overall BE study design for LAIs should account for the formulation design (i.e., release-controlling mechanism), dosing regimen/frequency, and the study population
- The appropriate number of doses to achieve steady state should be determined and balanced by the need to minimize the study duration
- Consideration of dropout rate in sample size estimation
- Appropriate sampling scheme to accurately capture PK parameters
- Sufficient pre-study method validation examining interference of concomitant medications
- Appropriate safety monitoring
- Appropriate statistical approach for evaluation of clinical center effect and injection site effect, as needed

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