Bioequivalence Assessment for Long-acting Injectables (LAIs) - FDA Regulatory Perspectives

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Wenlei Jiang, Ph.D.
Senior Science Advisor

Office of Research and Standards (ORS)
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)
U.S. FDA

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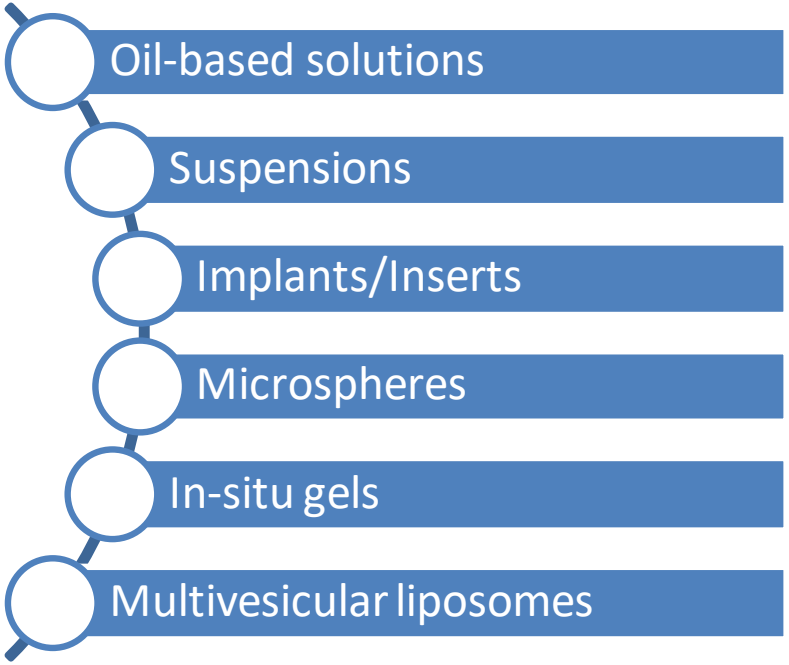
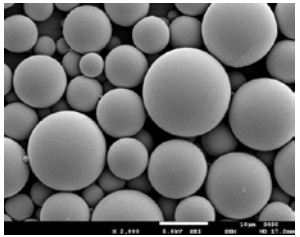
Long-acting Injectables (LAIs)

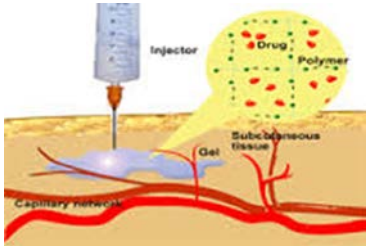
- Achieve extended drug release action from days to years when administered via intramuscular (IM) or subcutaneous (SC) routes
- Improve patient compliance with a better therapeutic option



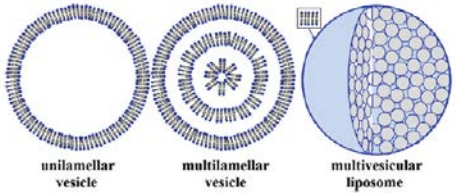
Example LAI Products

Brand	Drug	Route	Dosing frequency/duration	Dosage Form	Local (L) or Systemic (S) delivery
HALDOL	Haloperidol decanoate	IM	Monthly	Oil solution	S
ARISTADA	Aripiprazole lauroxil	IM	Every month, 6 weeks, 2 months	Suspension	S
EXPAREL	Bupivacaine	SC	Single dose	Liposomes	L
RISPERDAL CONSTA	Risperidone	IM	2 weeks	Micospheres	S
VIVITROL	Naltrexone	IM	1 month	Micospheres	S
LUPRON DEPOT	Leuprolide	IM	1, 3, 4, 6 months	Micospheres	S
BYDUREON	Exendatide	SC	1 week	Micospheres	S
ZOLADEX	Goserelin	IM	1, 3 months	Implant	S
ELIGARD	Leuprolide acetate	SC	1, 3, 4, 6 months	In-situ gel	S

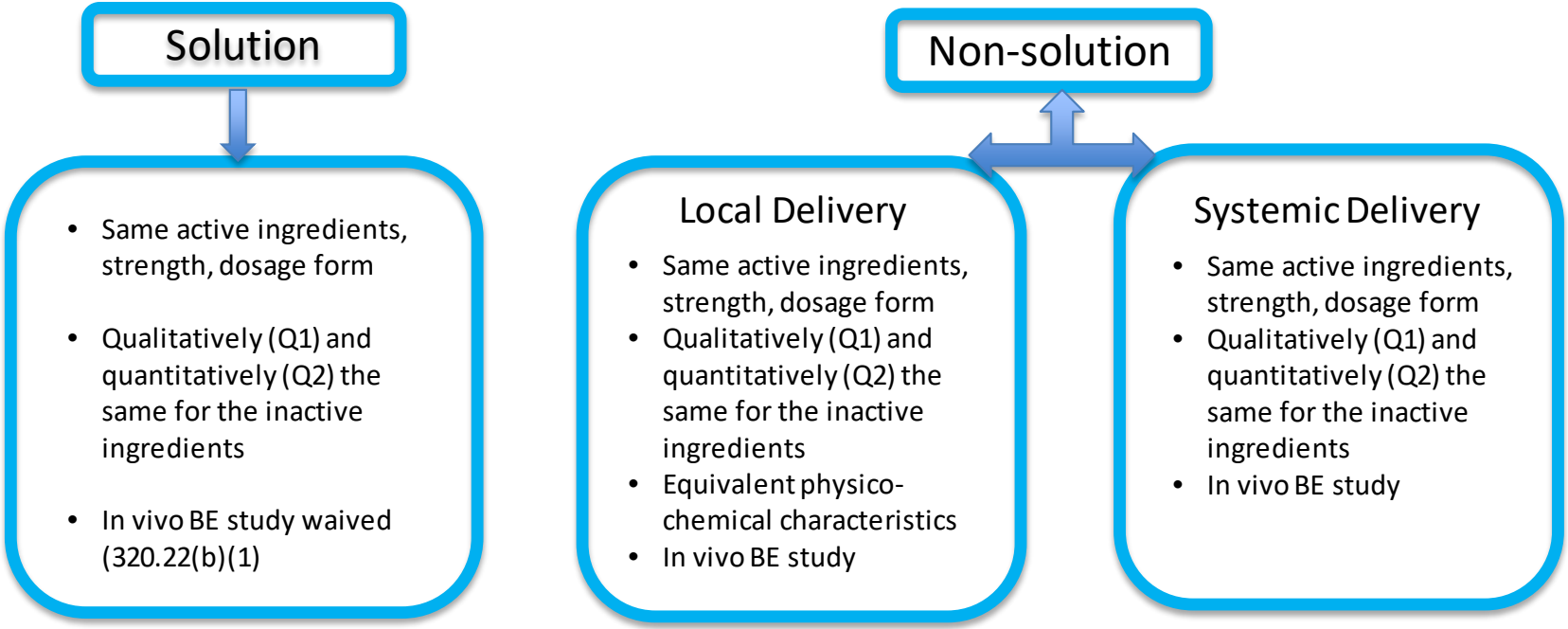




Complex Product



Current FDA Thinking on Generic LAIs to Demonstrate Therapeutic Equivalence



Generic Complex LAIs Landscape

Generic Available

- MEDROXYPROGESTERONE ACETATE Injection

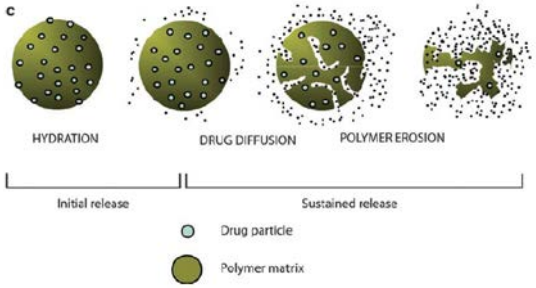
PSG Published

- MEDROXYPROGESTERONE ACETATE Injection
- GOSERELIN ACETATE Implant
- ARIPIPRAZOLE Suspension
- LEUPROLIDE ACETATE Injection
- LEUPROLIDE Implant
- LEUPROLIDE ACETATE Depot, NORETHINDRONE ACETATE Tablet
- NALTREXONE Injection
- OCTREOTIDE ACETATE Injection
- OLANZAPINE PAMOATE Injection
- PALIPERIDONE PALMITATE Injection
- RISPERIDONE Injection
- TRIPTORELIN PAMOATE Injection
- Naltrexone Injection
- BUPIVACAINE Liposome Injection

https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drug-development

Challenges to Demonstrate Therapeutic Equivalence of Complex LAIs

- **Formulation sameness**
  - Demonstrate Q1 and Q2 sameness of the polymeric excipients
- **Discriminative in vitro release within reasonable timeframe**
- **In vivo bioequivalence studies**
  - Long duration
  - Determination of steady state
  - Difficulty to enroll patients
  - Conventional BE matrix may not be sufficient to capture multiphasic in vivo drug release



Product-specific Guidances for LAIs (1)

Drug	Route	Dosage Form	BE Recommendation	BE Study Population	BE Study Strength	PK Metrices for Statistical Analysis
Aripiprazole	IM	Suspension	Steady state, crossover	Patients who are already receiving a stable regimen of aripiprazole extended-release injection via the intramuscular route	400 mg/vial for in vivo study. 300 mg/vial can be waived	AUC and C_{max}
Medroxyproges-terone acetate	IM	Suspension	Single-dose, parallel	Healthy non-pregnant females	150 mg/ml	Not specified
Medroxyproges-terone acetate	IM	Suspension	Single-dose, parallel	Healthy non-pregnant females	400 mg/ml	Not specified
Olanzapine Pamoate	IM	Suspension	In vivo multiple-dose, steady-state, parallel or crossover	Patients with schizophrenia who are on maintenance dose of olanzapine pamoate	405 mg/vial for in vivo study, 210 mg and 300 mg/vial waived	AUC and Cmax
Paliperidone Palmitate	IM	Suspension	In vivo multiple-dose, steady-state, parallel or crossover	Patients with schizophrenia who are receiving stable regimen of paliperidone palmitate	156 mg/ml for in vivo study, 39 mg/0.25 ml, 78 mg/0.5 ml, 117 mg/0.75 ml, and 234 mg/1.5 ml waived	AUC and Cmax

https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drug-development

Product-specific Guidances for LAIs (2)

Drug	Route	Dosage Form	BE Recommendation and In Vivo Study Design	BE Study Population	BE Study Strength	PK Metrices for Statistical Analysis
Triptorelin Pamoate	IM	Microgranules	Single-dose, parallel	Advanced prostate cancer male patients	3.75 mg, 11.5 mg, 22.5 mg/vial	Log-transformed AUC_{7-t}, AUCt, $AUC_{0-\infty}$, and Cmax
Octreotide Acetate	IM	Microspheres	Single-dose, parallel	Healthy males and non-pregnant females, general population	30 mg/vial for in vivo study, 10 mg and 20 mg/vial waived	Log-transformed AUC_{0-28}, AUC_{28-56}, AUCt, $AUC_{0-\infty}$, and Cmax
Leuprolide Acetate	IM	Microspheres	Single-dose, parallel	Prostatic carcinoma patients undergoing initial therapy	30 mg/vial for in vivo study, 11.25 mg/vial-3 month and 22.5 mg/vial can be waived for in vivo study	Log-transformed AUC_{7-t}, AUCt, $AUC_{0-\infty}$, and Cmax
Leuprolide Acetate	IM	Microspheres	Single-dose, parallel	Prostatic carcinoma patients undergoing initial therapy	7.5 mg/vial for in vivo study. 3.75, 11.25, and 15 mg/vial can be waived.	Log-transformed AUC_{7-t}, AUCt, $AUC_{0-\infty}$, and Cmax

https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drug-development

Product-specific Guidances for LAIs (3)

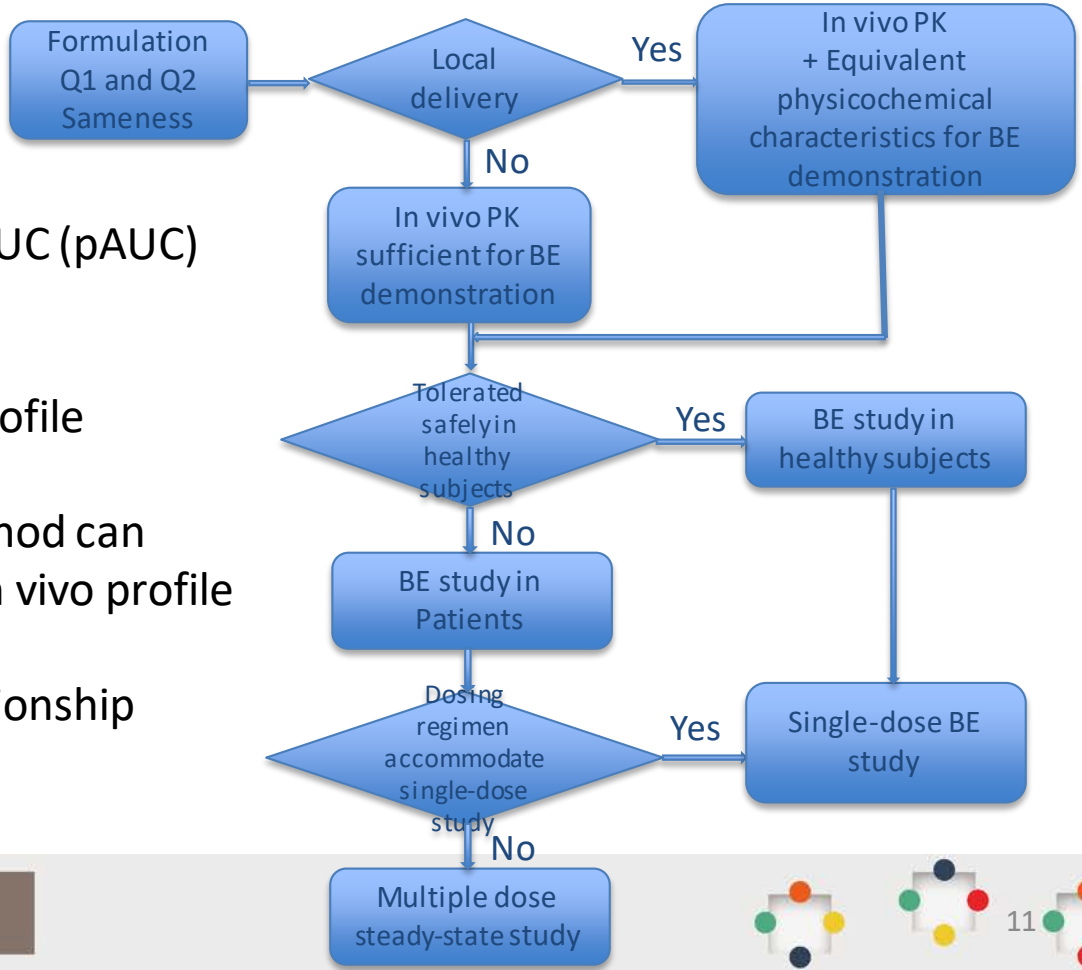
Drug	Route	Dosage Form	BE Recommendation and In Vivo Study Design	BE Study Population	BE Study Strength	PK Metrices for Statistical Analysis
Bupivacaine	SC	Liposomes	Single-dose, two-way crossover Equivalent liposome characteristics	Healthy males and nonpregnant females, general population	266 mg/20 ml	Not specified
Naltrexone	IM	Microspheres	Single-dose, parallel	Healthy males and non-pregnant females, general population	380 mg/vial	Cmax, AUC_{1-10}, AUC_{10-28}, and $AUC_{0-\infty}$
Risperidone	IM	Microspheres	2-period, crossover steady-state Equivalent in vitro drug release	Patients who are already receiving a stable regimen of risperidone LAIs	25 mg/vial for in vivo study, other strengths 12.5, 37.5, and 50 mg/vial waived	AUC and Cmax

https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drug-development

General Considerations for In Vivo BE Study Design for Complex LAIs

Considerations for partial AUC (pAUC) recommendation

- Multiphasic in vivo PK profile
- Whether an in vitro method can predict or characterize in vivo profile
- Exposure-response relationship

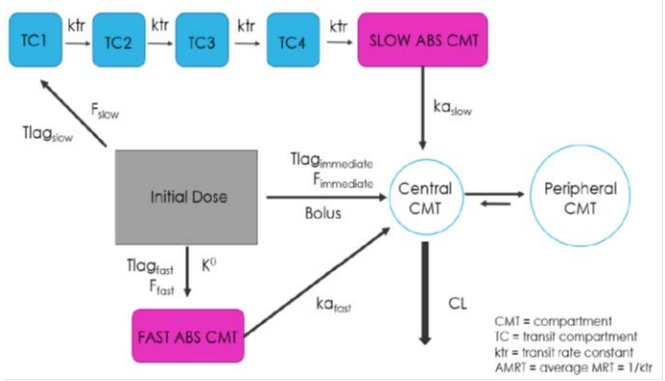


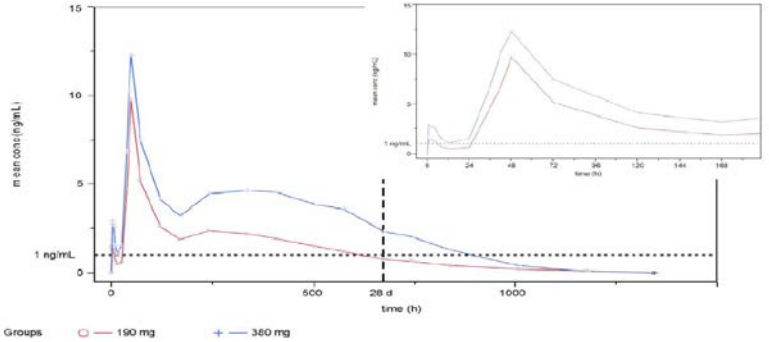
Pharmacokinetic Modeling and Simulation to Support pAUC Selection

Vivitrol

- Naltrexone PLGA (75:25) microspheres
- Indicated for alcohol dependence
- Every **4 weeks or once a month** via IM
- Therapeutic plasma concentration: **>1 ng/ml**

PopPK model developed by Alkermes





Metric combinations:

- 'Traditional': Cmax, AUC0-∞, and AUC0-t
- 'trad_mf2': 'traditional' + modified f2test
- 'trad_10_28': 'traditional' + AUC_{10-28}
- 'trad_1_28': 'traditional' + AUC_{1-10} + AUC_{10-28}
- 'minusAUCt': remove AUC0-t from 'trad_1_28'

The inclusion of AUC_{1-10} and AUC_{10-28} reduces false positive rate and the pAUCs have less intersubject variability than Cmax.

Babiskin, A, et al. Pharmacokinetic modeling and simulation of naltrexone for extended-release injectable suspension to derive alternative BE metrics. 2015 ACoP

Considerations on Steady-state Study Design

Appropriate determination of steady state is challenging.

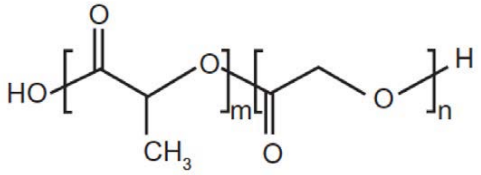
FDA recommends Abbreviated New Drug Application (ANDA) applicants

- Develop model-based approaches for steady-state simulation or other innovative study design
- Seek input about approaches to determine steady-state via controlled correspondences and/or pre-ANDA meeting requests

Considerations on PLGA Sameness

- **Characterization of PLGA**
  - Polymer composition (L to G ratio)
  - Molecular weight and weight distribution
  - Polymer architecture (linear vs star-shaped)
  - Intrinsic viscosity
  - Glass transition temperature
  - Polymer end-cap
  - Crystallinity

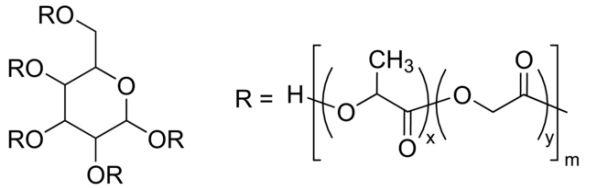
Poly(lactic-*co*-glycolic acid) (PLGA) copolymer



PLGA

m = number of units of lactic acid
n = number of units of glycolic acid
- Ratio of lactic acid to glycolic acid
- Molecular weight ~5kDa -100kDa

Glucose star polymer, D,L-lactic and glycolic acids copolymer



Garnera J et al. A protocol for assay of poly(lactide-co-glycolide) in clinical products. International Journal of Pharmaceutics 495 (2015) 87–92.
This work was supported by FDA grant U01FD05168.

Discriminative In Vitro Release Method for Risperidone Suspension

Risperidone Product-specific Guidance

Active Ingredient: Risperidone

Dosage Form; Route: Injectable; intramuscular

Recommended Studies: Two studies: in vitro and in vivo

1. Type of study: In vitro drug release
   Strength: 25 mg/vial
   Medium: Dissolution medium (pH 7.4) prepared as indicated below
   Volume: 400 mL (200 mL for each temperature)
   Apparatus: Cylinder bottle
   Temperature: 37 °C and 45 °C (water bath)
   Sampling Times: Day 1 and Day 21 for 37 °C
   Multiple time points from Days 0 to 8 for 45 °C. Two sampling time points, that bracket $T_{50\%}$ (which is defined as the time of 50% drug release), are to be linearly interpolated to determine $T_{50\%}$.

Parameters to measure: Cumulative drug release at Days 1 and 21 at 37 °C, cumulative drug release at Day 8 at 45 °C, and $T_{50\%}$ at 45 °C.

Bioequivalence based on (90% CI): $T_{50\%}$. The 90% confidence interval of the test/reference ratio of $T_{50\%}$ should be within 80-125%.

Summary

- Complex LAIs have unique complexity and challenges for generic product development
- FDA has developed product-specific guidances for majority of LAIs
- BE study design of LAIs should consider the following:
  - ✓ Local or systemic delivery
  - ✓ Tolerability in healthy subjects
  - ✓ Dosing regimen
  - ✓ In vivo pharmacokinetic profiles
  - ✓ In vitro and in vivo relationship
- Discuss alternative BE approaches and steady-state determination via controlled correspondences or pre-ANDA program

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Thank You!

Any question?

wenlei.jiang@fda.hhs.gov