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Bioequivalence of Polymeric Long Acting Drugs

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Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies

Outline

- Background
  - Examples of common polymeric long acting (LA) drugs
- Bioequivalence (BE) approaches for polymeric long-acting drugs
  - Regulatory and scientific challenges and approaches
  - Generic Drug User Fee Amendments (GDUFA) regulatory science program
  - Future direction
- Summary

Long Acting Drugs

Advantages

- Achieve more continuous extended drug release from days to years, compared to other formulations
- Improve patient compliance with a better therapeutic option

Route of Administration	Dosage Form/Formulation	Release Rate Controlling Polymeric Excipient(s)
Subcutaneous (SC)	• Suspension • **Implant** • Pellet • **In-situ forming gel/implant** • **Multivesicular liposome** • **Microsphere**	• No • **Yes** • No • **Yes** • **Yes** • **Yes**
Intramuscular (IM)	• **Microsphere** • Oil solution	• **Yes** • No

Long Acting Drugs (Cont.)

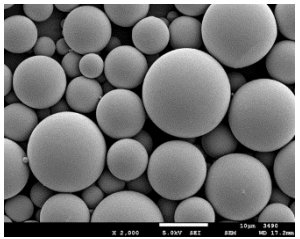
Route of Administration	Dosage Form/Formulation	Release Rate Controlling Polymeric Excipient(s)
Ophthalmic	• **Implant**	• **Yes**
Nasal	• **Implant**	• **Yes**
Intrauterine	• **Intrauterine device**	• **Yes**
Intravaginal	• **Ring**	• **Yes**
Periodontal	• **Microsphere** • **Insert**	• **Yes** • **Yes**

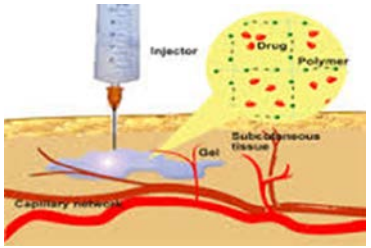
➢ Polymeric long acting (LA) drugs are considered by OGD to be complex drugs[1]

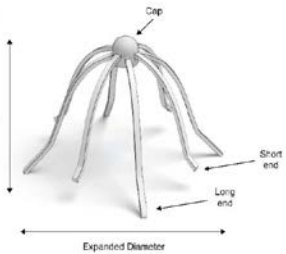
1. GDUFA II Commitment Letter https://www.fda.gov/media/101052/download

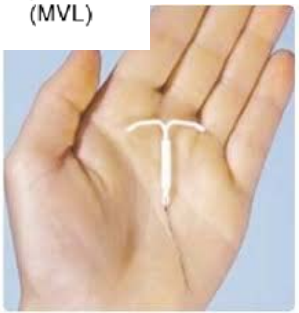
Examples of Polymeric LA Drugs

Brand Name	Drug	Route	Dosing frequency	Dosage Form	Local (L) or Systemic (S) action
RISPERDAL CONSTA	Risperidone	IM	2 weeks	Microsphere	S
VIVITROL	Naltrexone	IM	1 month	Microsphere	S
LUPRON DEPOT	Leuprolide	IM	1, 3, 4, 6 months	Microsphere	S
BYDUREON	Exenatide	SC	1 week	Microsphere	S
ZOLADEX	Goserelin	SC	1, 3 months	Implant	S
ELIGARD	Leuprolide acetate	SC	1, 3, 4, 6 months	In-situ gel	S
EXPAREL	Bupivacaine	SC	Single dose	Liposome	L
Mirena	Levonorgestrel	Intrauterine	5 years	Intrauterine device	L
Estring	Estradiol	Intravaginal	90 days	Ring	L
Sinuva	Mometasone furoate	Sinus	90 days	Implant	L



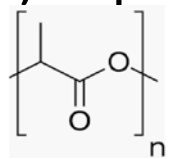


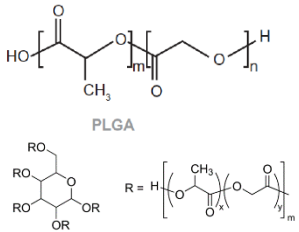




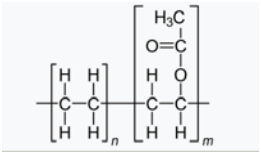
Rate Controlling Polymeric Excipients

- Poly esters
  - Poly(D,L-lactic and glycolic acid) (PLGA) copolymers
  - Poly(D,L-lactic acid) (PLA) copolymers

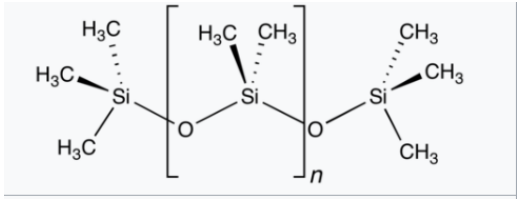




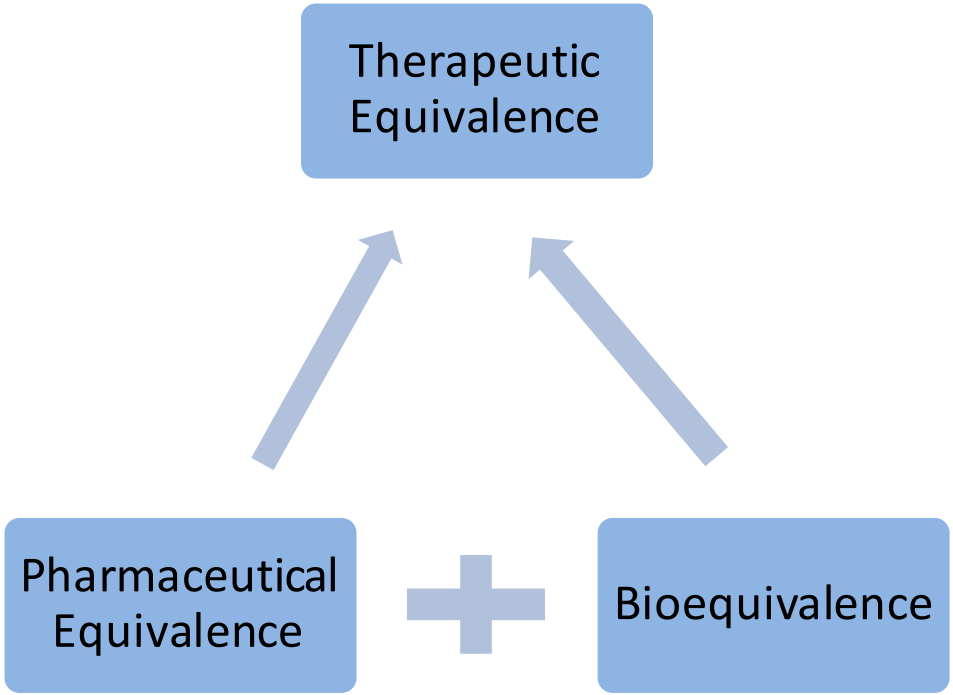
- Poly (ethylene-vinyl acetate) (EVA)



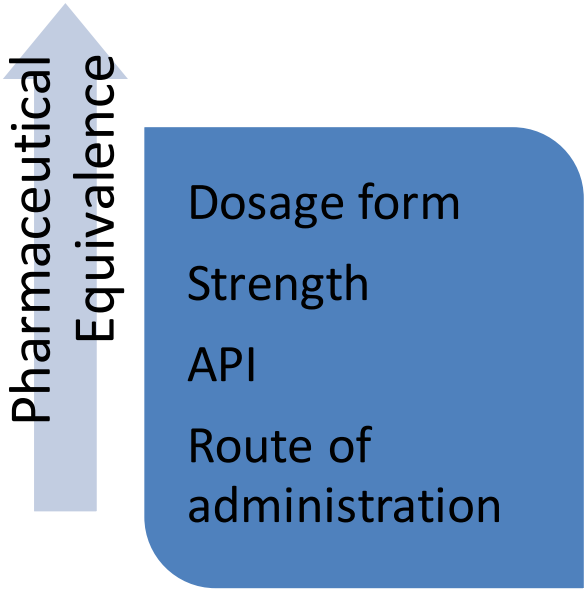
- Polydimethylsiloxane (PDMS)



Therapeutic Equivalence of Polymeric LA Drugs



For ALL polymeric LA drugs



Therapeutic Equivalence of Polymeric LA Drugs (Cont.)

Regulatory requirements for inactive ingredient(s), as per 21 CFR 314.94(a)(9):

For parenteral and ophthalmic drugs

Generally, a generic product shall contain the **SAME** inactive ingredients (qualitatively the same – "**Q1**") and in the same concentration (quantitatively the same – "**Q2**") as the reference listed drug.

Exception excipients:

For parenteral drugs: preservative, buffer, or antioxidant

For ophthalmic drugs: preservative, buffer, or viscosity/tonicity agent

Bioequivalence of Polymeric LA Drugs

General considerations, as per 21 CFR 320.24:

Should be the most accurate, sensitive, and reproducible approach for detecting potential formulation difference(s).

For polymeric LA drugs

- In vivo BE study with pharmacokinetic endpoints (systemic/local action)
- In vivo BE study with comparative clinical endpoints (local action)
- In vitro BE studies in combination with in vivo BE study (systemic/local action)

Generic Polymeric LA Drugs Landscape

PSG Published

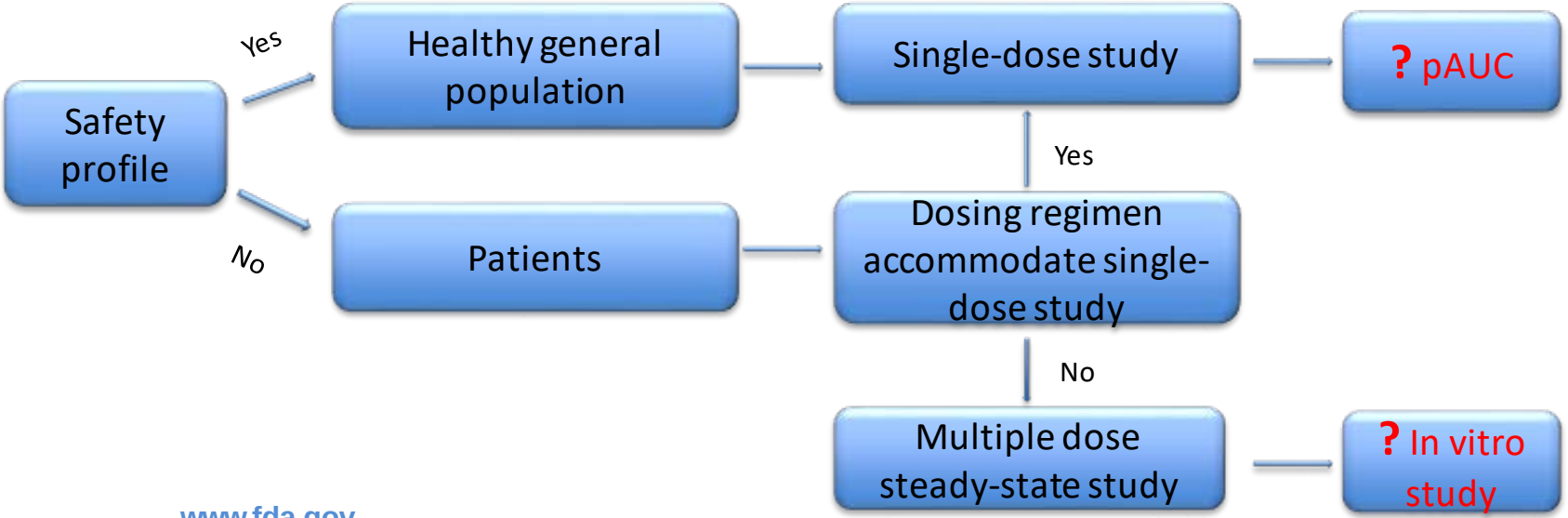
1. Goserelin acetate implant
2. Leuprolide acetate injection
3. Leuprolide implant
4. Leuprolide acetate depot, Norethindrone acetate tablet
5. Naltrexone injection
6. Octreotide acetate injection
7. Risperidone injection
8. Triptorelin pamoate injection
9. Naltrexone injection
10. Bupivacaine liposome injection

Generic Competition

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

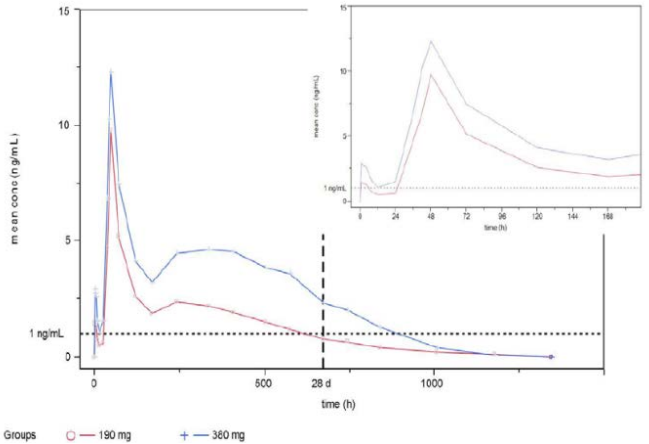
Bioequivalence Considerations for Systemically Acting LA Drugs

- In vivo BE study with pharmacokinetic endpoints
  - Subjects: healthy subjects vs. patients
  - Study design: single-dose vs. steady-state



In Vivo BE Study with PK Endpoints (pAUC)

- Example product: **Vivitrol** (Naltrexone PLGA (75/25) microspheres)
  - Indicated for alcohol dependence
  - Every **4 weeks or once a month** intramuscularly
  - Therapeutic plasma concentration: **>1 ng/ml**
  - Variability in Cmax
  - Multi-phasic in vitro and in vivo release profiles



Active Ingredient: Naltrexone

Dosage Form; Route: Extended-release suspension; intramuscular

Recommended Studies: One study

1. Type of study: In vivo single-dose fasting
   Design: Parallel
   Strength: 380 mg/vial (dose: 380 mg)
   Subjects: Healthy males and nonpregnant females, general population
   Additional comments: The 90% confidence intervals of the geometric mean test/reference (T/R) ratios for the metrics (C_{max}, AUC_{1-10}, AUC_{10-28}, and $AUC_{0-\infty}$) should fall within the limits of 80-125%

The inclusion of AUC_{1-10} and AUC_{10-28} reduces false positive rate and the partial AUCs have less inter-subject variability than Cmax.

In Vivo BE Study with PK Endpoints in Combination with In Vitro Study

- Example product: **Risperdal® Consta®** (Risperidone PLGA microspheres)
  - Indicated for schizophrenia, bipolar I disorder
  - Every **2 weeks** via IM
  - Multi-phasic in vitro and in vivo release profiles

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 $T_{50\%}$.

2. Type of study: In vivo, two-period, crossover steady-state
Strength: 12.5 mg/vial, 25 mg/vial, 37.5 mg/vial, 50 mg/vial
Subjects: Male and nonpregnant female patients with schizophrenia or bipolar I disorder who are already receiving a stable regimen of risperidone long-acting injection via the intramuscular route. Patients who are receiving any dosage regimen of risperidone long-acting injection every two weeks would be eligible to participate in the study by continuing their established maintenance dose.
Additional comments: FDA recommends that studies not be conducted using healthy subjects or patients on a different antipsychotic treatment. 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.

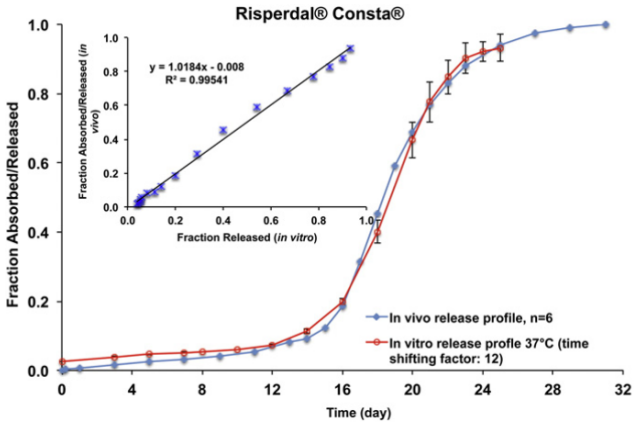


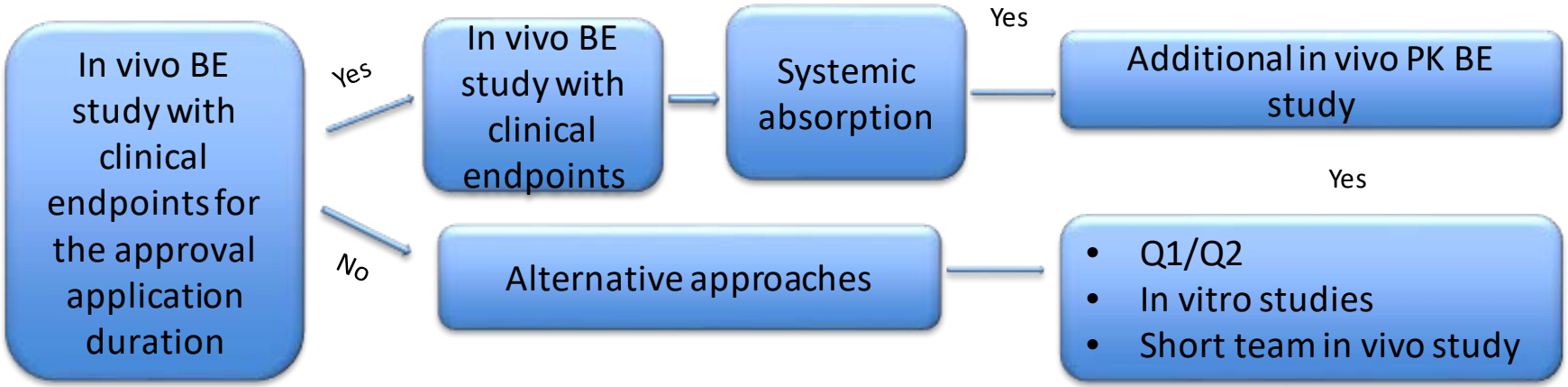
Fig. 6. *In vivo* absorption/release and *in vitro* release (time shifting factor: 12) profiles in 10 mM PBS (pH 7.4) at 37 °C of Risperdal® Consta®. Inserted figure shows linear correlation between fractions released *in vitro* (37 °C) and fraction absorbed/released *in vivo*.

In vitro release testing is included to assess equivalence of the initial release phase and the lag phase.

Shen J, et al. In vitro-in vivo correlation of parenteral risperidone polymeric microspheres. 2015 Journal of Controlled Release

Bioequivalence Considerations for Locally Acting LA Drugs

- In vivo BE study with comparative clinical endpoints
- In vivo BE study with comparative clinical endpoints + In vivo BE study with PK endpoints
- Alternative approaches



In Vivo BE Study with Comparative Clinical Endpoints

- Example product: **Arestin** (Minocycline hydrochloride PLGA microspheres)
  - Dental powder (no Q1Q2 per regulation)
  - No fixed dose nor dosing frequency
  - Local action

Active Ingredient: Minocycline hydrochloride (HCl)

Dosage Form; Route: Powder, extended-release (ER); dental

Recommended Studies: One study

Type of study: Bioequivalence (BE) study with clinical endpoint
Design: Randomized, double-blind, parallel, three-arm, vehicle-controlled in vivo
Strength: Equivalent (EQ) 1 mg base (administered to all initial and new periodontal pockets with mean pocket depth (PD) of ≥ 5 mm)
Subjects: Male and nonpregnant female adults with generalized, moderate-to-advanced periodontitis
Additional comments: Specific recommendations are provided below

Combination Approaches for Local LA Drugs

- Example product: **Mirena** (Levonorgestrel intrauterine system/device)

Dosage Form; Route: Intrauterine Device; intrauterine

Strength: 52 mg

Recommended Studies: Two studies: in vitro and in vivo/ex vivo

To be eligible for the bioequivalence studies recommended in this guidance, the test product should meet the following criteria:

- Qualitatively (Q1) and quantitatively (Q2) the same as the Reference Listed Drug (RLD).
- Equivalent physicochemical and mechanical characteristics including 1) particle size and size distribution of the active pharmaceutical ingredient (API); 2) Degree of crosslinking of poly(dimethylsiloxane) elastomer (PDMS) used in the drug reservoir and the drug rate controlling membrane; 3) Mechanical properties of the drug reservoir and the drug rate controlling membrane; 4) Appearance, memory, mechanical properties of the T-body; and 5) Breaking force of the removal thread comparable to the Reference Standard (RS).
- Same dimensions with respect to each component as the RS.

A. Comparative in vitro drug release

Acceptable comparative in vitro drug release of levonorgestrel from the test and RS products throughout the intended period of product use (5 years). Any accelerated dissolution method that correlates to the real-time drug release behavior may be submitted for the Agency's consideration through either a controlled correspondence or as part of a pre-ANDA meeting request.

B. In vivo/ex vivo clinical study

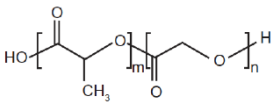
Type of study: In vivo/ex vivo study of residual levonorgestrel and serum levonorgestrel
Design: One year, single-dose, randomized, parallel in vivo study
Strength: 52 mg
Subjects: Healthy premenopausal, nonpregnant females, ages 18 to 45 years (inclusive), who are not using other hormonal contraceptive. The enrolled population should include a sufficient number of nulliparous women.

Comparative characterization data on PDMS polymers in the FINISHED test and reference products are recommended to support Q1 assessment

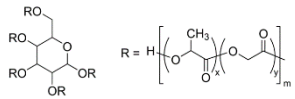
Remaining Scientific BE Challenges for Polymeric LA Drugs

Q1 Sameness of Polymeric Excipients

- Poly esters
  - Poly(D,L-lactic and glycolic acid) (PLGA) copolymers
  - Poly(D,L-lactic acid) (PLA) copolymers



PLGA



Should provide comparative physicochemical data on PLA/PLGA polymers extracted from the FINISHED Test product and the reference product to support Q1 sameness

- Insufficient to rely solely on the Certificate of Analysis from excipient vendor
- Insufficient to characterize stock excipient polymer used to polymer extracted from the RLD final product
- Polymer characterization should include, but not limited to: Composition (e.g., Lactide/Glycolide ratio), molecular weight and molecular weight distribution, polymer structure (e.g., linear or star), inherent viscosity, glass transition temperature, and polymer end-cap chemistry

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.

Comparative In Vitro Studies

- In vitro drug release testing
  - Discriminative ability with reasonable time frame
  - Accelerated vs Real time in vitro drug release testing
    - Correlation between accelerated and real time in terms of drug release mechanisms

- Physiochemical Characterization
  - Particle size measurement and related data analysis

Multi-dose Steady-state Study Design

- Appropriate determination of steady-state PK is challenging
  - Statistical methods
  - Exploring model-based approaches for steady-state simulation or other innovative study design

In Vivo BE Study with Comparative Clinical Endpoints

- High variability and low sensitivity → Large sample size

Are there alternative approaches?

Considerations for In Vitro Approaches to Demonstrate BE

- For local polymeric LA drugs:

Example: Minocycline HCl dental powder

Potential in vitro approach:

- Q1/Q2
- Similar manufacturing procedure
- Comparative physicochemical characterizations
- Comparative in vitro drug release testing

Considerations for In Vitro Approaches to Demonstrate BE (cont.)

- For systemic drugs polymeric LA drugs
  - Risks:
    - Indication(s): e.g., antipsychotic treatments
    - Long term use for chronic diseases: potential dose accumulation effect
  - In vitro in vivo correlation:
    - Drug release mechanisms in vitro and in vivo
    - Effects of physicochemical characteristics on product in vivo performance
    - Better understanding of impact of manufacturing on product performance

Future Directions

- Investigating in vitro in vivo correlation to support developing in vitro BE approach for systemic polymeric LA drugs
  - Developing novel in vitro drug release testing methods
  - Exploring new analytical tools for characterizing polymeric excipients and formulations
- Developing new modeling and simulation tools to improve BE study design

GDUFA Regulatory Science Program

GDUFA-funded research projects focusing on:

- Novel analytical tools for characterizing PLGA polymers
- In vivo in vitro corrections (IVIVCs) for LA drugs
- Impact of raw materials and manufacturing on product performance
- Emerging technologies for formulation characterization
- Modeling tools to facilitate development of generic LA drugs

Summary

- Polymeric LA drugs have unique complexity and challenges for generic product development and approval
- The BE study design for LA drugs 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 meeting requests

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Any questions?

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