Complex Injectable and Implantable Drug Products: Bioequivalence Considerations

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Rockville, MD

Disclaimer: The views expressed in this presentation are those of the speaker and not necessarily those of the Food and Drug Administration (FDA).
Parenteral Drug Products

• Injections and implanted drug products
  - Injected through the skin or other external boundary tissue
  
  - Implanted within the body to allow the direct administration of the active drug substances into blood vessels, organs, tissues, or lesions

• Routes of administration
  intravenous (i.v.), intramuscular (i.m.), subcutaneous (s.c.), intraventricular, intra-arterial, intra-articular, intrathecal, intracisternal, and intraocular
Parenteral Drug Products

Injections /infusions
- Sterile liquids
  - Small volume parenterals
  - Large volume parenterals
- Sterile solids
  - Lyophilized solids
- Dry powder fill
- Sterile disperse system

Implanted products
- Implants
- Microspheres
- In-situ gel
- Drug-eluting stents
Bioequivalence (BE) Approaches

**Approaches to Determining Bioequivalence (21 CFR 320.24)**
- In vivo pharmacokinetic comparison
- In vivo pharmacodynamic comparison
- In vivo clinical comparison
- In vitro comparison
- Any other approach deemed appropriate by FDA

**Parenteral solution**
- Same active ingredients, strength, dosage form
- Qualitatively (Q1) and quantitatively (Q2) the same for the inactive ingredients
- In vivo BE study waived (320.22(b)(1))

**Tablets/capsules**
- Same active ingredients, strength, dosage form
- Can have different inactive ingredients/design/release mechanisms
- Pharmacokinetic study preferred to demonstrate bioequivalence

Bioequivalence approaches for complex injectable and implantable products?

www.fda.gov
Bioequivalence Demonstration of Complex Injectable and Implantable Drug Products

- Product complexity
- Current FDA approaches for BE demonstration
- Recent scientific and regulatory advances with the support of GDUFA funding

GDUFA: Generic Drug User Fee Amendment

GUDFA regulatory science
https://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/GenericDrugs/ucm567695.htm
www.fda.gov
Injectable Emulsion Drug Products

<table>
<thead>
<tr>
<th>Trade name</th>
<th>Active Ingredient</th>
<th>Route</th>
<th>Initial Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>RESTASIS</td>
<td>Cyclosporine</td>
<td>Ophthalmic</td>
<td>10/10/2003</td>
</tr>
<tr>
<td>DIPRIVAN</td>
<td>Propofol</td>
<td>Intravenous</td>
<td>10/02/1989</td>
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<tr>
<td>CINVANTI</td>
<td>Aprepitant HCl</td>
<td>Intravenous</td>
<td>11/9/2017</td>
</tr>
<tr>
<td>VARUBI</td>
<td>Rolapitant HCl</td>
<td>Intravenous</td>
<td>10/25/2017</td>
</tr>
</tbody>
</table>

**Emulsion**: Dispersion made up of two immiscible liquid phases which are mixed using mechanical shear and stabilized with surfactant.

**Types of Emulsions**:
- Oil in Water (O/W)
- Water in Oil (W/O)
- Water-in-Oil-in-Water (W/O/W)
- Oil-in-Water-in Oil (O/W/O)

**Complexity**
- Complex formulation
- Some products intended for local action

www.fda.gov
Injectable Emulsion Drug Products Bioequivalence Demonstration

### In vitro option
- Formulation qualitatively (Q1) and quantitatively (Q2) the same
- Acceptable comparative physico-chemical characterization
- Acceptable comparative in vitro release

### In vivo option
- Permissible non-Q1/Q2 formulation (21CFR 314.94(b)(9)(iii))
- In vivo pharmacokinetic BE study or comparative clinical endpoint BE study

### Challenges
- Emulsion globule size comparison
- Development of discriminative in vitro release method
- Insensitive clinical endpoint
Product-Specific Guidance for Propofol Emulsion

Active Ingredient: Propofol
Dosage Form; Route: Injectable; injection
Strength: 10 mg/mL
Recommended Study: Two options: In vitro or In vivo studies

I. In vitro option:
To qualify for the in vitro option for this drug product pursuant to 21 CFR 320.24 (b)(6), under which “any other approach deemed adequate by FDA to measure bioavailability or establish bioequivalence” may be acceptable for determining the bioavailability or bioequivalence (BE) of a drug product, all the following criteria should be met:

i. The Test and Reference Listed Drug (RLD) formulations are qualitatively and quantitatively the same (Q1/Q2).

ii. Acceptable comparative physicochemical characterization of the Test and RLD formulations. The comparative study should be performed on at least three exhibit lots of both Test and Reference products.

Parameters to measure: Globule size distribution, viscosity profile as a function of applied shear, pH, zeta potential of the formulation and at physiological pH, osmolality, free acid concentration, and amount of propofol partitioned in the aqueous and oil phases.

The sponsor should also demonstrate that the test product is stable when diluted with 5% Dextrose Injection USP, according to label instructions.

Bioequivalence based on (95% upper confidence bound): Population bioequivalence (PBE) based on D50 and SPAN (alternatively harmonic intensity weighted average particle diameter and polydispersity index derived from cumulant analysis of the intensity size distribution) for the globule size distribution only

iii. Acceptable comparative in vitro drug release rate tests from 12 units of each of the test and RLD formulations.

An in vivo pharmacokinetic bioequivalence study is requested for any generic propofol injection, 10 mg/mL that has a different inactive ingredient from the RLD4 or unacceptable data from in vitro comparative studies.

II. In vivo option:
Type of study: Fasting
Design: Single-dose, two-way crossover in vivo
Strength: 10 mg/mL
Dose rate: 30 mcg/kg/min
Subjects: Healthy males, non-pregnant and non-lactating females, general population 18 to 55 years of age

 Analytes to measure (in appropriate biological fluid): Propofol in plasma

Bioequivalence based on (90% CI): Propofol


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Statistic Method for a Whole Profile Analysis of Emulsion Globule Size

Research Article

Equivalence Testing of Complex Particle Size Distribution Profiles Based on Earth Mover's Distance

Meng Hu,1 Xiaohui Jiang,1 Mohammad Absar,1 Stephanie Choi,1 Darby Kozak,1 Meiyu Shen,2 Yu-Ting Weng,2 Liang Zhao,1,3 and Robert Lionberger4

Received 27 December 2017; accepted 28 February 2018; published online 12 April 2018

Abstract. Particle size distribution (PSD) is an important property of particulates in drug products. In the evaluation of generic drug products formulated as suspensions, emulsions, and liposomes, the PSD comparisons between a test product and the branded product can provide useful information regarding in vitro and in vivo performance. Historically, the FDA has recommended the population bioequivalence (PBE) statistical approach to compare the PSD descriptors D50 and SPAN from test and reference products to support product equivalence. In this study, the earth mover's distance (EMD) is proposed as a new metric for comparing PSD particularly when the PSD profile exhibits complex distribution (e.g., multiple peaks) that is not accurately described by the D50 and SPAN descriptor. EMD is a statistical metric that measures the discrepancy (distance) between size distribution profiles without a prior assumption of the distribution. PBE is then adopted to perform statistical test to establish equivalence based on the calculated EMD distances. Simulations show that proposed EMD-based approach is effective in comparing test and reference profiles for equivalence testing and is superior compared to commonly used distance measures, e.g., Euclidean and Kolmogorov–Smirnov distances. The proposed approach was demonstrated by evaluating equivalence of cyclosporine ophthalmic emulsion PSDs that were manufactured under different conditions. Our results show that proposed approach can effectively pass an equivalent product (e.g., reference product against itself) and reject an inequivalent product (e.g., reference product against negative control), thus suggesting its usefulness in supporting bioequivalence determination of a test product to the reference product which both possess multimodal PSDs.

KEY WORDS: earth mover's distance; equivalence test; particle size distribution; profile comparison.
Pulsatile Microdialysis (PMD) for Dissolution of Emulsion Drug Products

Fig. 1. A schematic diagram of a microdialysis probe.

Shah, KB et al., Int J Pharm 468 (2014) 64-74.
In Vitro Release Testing of Cyclosporine Emulsion Formulations

Q1/Q2 cyclosporine ophthalmic emulsions containing 50%, 100%, 150% drug load relative to the RLD (left), or 100% drug load relative to the RLD (right). The x-axis corresponds to resting time, and the y-axis is the amount of cyclosporine released from the PMD probe window per area. The receiver medium was either (A) kept at 35 °C or (B) varied between 20 °C, 32 °C, and 35 °C. Data points represent the average from three replicates ± standard deviation. Courtesy of Robert Bellantone, Physical Pharmaceutica, LLC.

This work was partially funded by FDA Contract HHSF223201610105C.

www.fda.gov
Liposome Drug Products

<table>
<thead>
<tr>
<th>Trade name</th>
<th>Active Ingredient</th>
<th>Route</th>
<th>Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOXIL</td>
<td>Doxorubicin HCl</td>
<td>Intravenous</td>
<td>11/17/1995</td>
</tr>
<tr>
<td>DAUNOXOME</td>
<td>Daunorubicin Citrate</td>
<td>Intravenous</td>
<td>4/8/1996</td>
</tr>
<tr>
<td>AMBISOME</td>
<td>Amphotericin B</td>
<td>Intravenous</td>
<td>08/11/1997</td>
</tr>
<tr>
<td>DEPOCYT</td>
<td>Cytarabine</td>
<td>Intrathecal</td>
<td>04/01/1999</td>
</tr>
<tr>
<td>VISUDYNE</td>
<td>Verteporfin</td>
<td>Intravenous</td>
<td>04/12/2000</td>
</tr>
<tr>
<td>DEPODUR</td>
<td>Morphine Sulfate</td>
<td>Epidural</td>
<td>05/18/2004</td>
</tr>
</tbody>
</table>

**Complexity**

- Complex formulation and lipid excipients
- Complex manufacturing process
- Scale up challenges
- Complex in vivo behavior

**Liposome**: Microvesicle composed of a bilayer and/or a concentric series of multiple bilayers separated by aqueous compartments formed by amphipathic molecules such as phospholipids that enclose a central aqueous compartment.
# Injectable Liposome Drug Products Bioequivalence Demonstration

## In Vitro Option
- Formulation Q1 and Q2 the same
- Acceptable comparative physico-chemical characterization

For Immediate-Release Liposomes, e.g., verteporfin liposomes

For Non Immediate-Release Liposomes, e.g., doxorubicin HCl liposomes

## In Vivo Option
- Formulation Q1 and Q2 the same
- Equivalent physico-chemical characteristics
- In vivo pharmacokinetic BE study

## Challenges

Lack of standard in-vitro release method

In vivo pharmacokinetic BE studies
- Total drug alone is insufficient to demonstrate BE
- Limited number of patients for BE study
- Intensive pharmacokinetic sampling not feasible for certain physiological sites, e.g., cerebrospinal fluid (CSF).

www.fda.gov
Product-Specific Guidance for Doxorubicin HCl Liposome Injection

Active Ingredient: Doxorubicin hydrochloride

Dosage Form; Route: Injectable, liposomal

Recommended Studies: Two studies: in vivo and in vitro

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

- Qualitatively (Q1)\(^1\) and quantitatively (Q2)\(^2\) the same as the Reference Listed Drug (RLD)
- Manufactured by an active liposome loading process with an ammonium sulfate gradient
- At least one batch of the Test product should be produced by the commercial scale process and be used in the in vivo bioequivalence study
- Equivalent liposome characteristics including liposome composition, state of encapsulated drug, internal environment of liposome, liposome size distribution, number of lamellar, grafted PEG at the liposome surface, electrical surface potential or charge, and in vitro leakage rates comparable to the Reference Standard (RS).

In Vivo Study:

Type of study: Fasting\(^*\)
Design: Single-dose, two-way crossover in vivo
Strength: 50 mg/vial or 20 mg/vial
Dose: 50 mg/m2
Subjects: Ovarian cancer patients whose disease has progressed or recurred after platinum-based chemotherapy and who are already receiving or scheduled to start therapy on doxorubicin hydrochloride (liposomal).

In Vitro Study:

1. Type of study: Liposome Size Distribution

Design: In vitro bioequivalence study on at least three lots of both Test and RS product. At least one lot of the Test product should be produced by the proposed commercial scale manufacturing process.
Product-Specific Guidance for Doxorubicin HCl Liposome Injection

- In vitro leakage under multiple conditions: In vitro drug leakage testing to characterize the physical state of the lipid bilayer and encapsulated doxorubicin should be investigated to support a lack of uncontrolled leakage under a range of physiological conditions and equivalent drug delivery to the tumor cells. Below are some examples of proposed conditions.

<table>
<thead>
<tr>
<th>In Vitro Drug Leakage Condition</th>
<th>Purpose</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 37°C in 50% human plasma for 24 hours</td>
<td>Evaluate liposome stability in blood circulation.</td>
<td>Plasma mostly mimics blood conditions.</td>
</tr>
<tr>
<td>At 37°C with pH values 5.5, 6.5, and 7.5 for 24 hours in buffer</td>
<td>Mimic drug release in normal tissues, around cancer cells, or inside cancer cells</td>
<td>Normal tissues: pH 7.3, Cancer tissues: pH 6.6, Insider cancer cells (endosomes and lysosomes): pH 5-6 (Endosome and lysosomes of cancer cells may be involved in liposome uptake and induce drug release).</td>
</tr>
<tr>
<td>At a range of temperatures (43°C, 47°C, 52°C, 57°C) in pH 6.5 buffer for up to 12 hours or until complete release</td>
<td>Evaluate the lipid bilayer integrity</td>
<td>The phase transition temperature (Tm) of lipids is determined by lipid bilayer properties such as rigidity, stiffness and chemical composition. Differences in release as a function of temperature (below or above Tm) will reflect small differences in lipid properties.</td>
</tr>
<tr>
<td>At 37°C under low-frequency (20 kHz) ultrasound for 2 hours or until complete release</td>
<td>Evaluate the state of encapsulated drug in the liposome.</td>
<td>Low-frequency ultrasound (20 kHz) disrupts the lipid bilayer via a transient introduction of pore-like defects and will render the release of doxorubicin controlled by the dissolution of the gel inside the liposome.</td>
</tr>
</tbody>
</table>
USP Apparatus 4-Flow Through Cell Dissolution for Liposome Drug Products

Selection of Dissolution Media for Amphotericin B Liposomes

An addition of 5% w/v of γ-cyclodextrin to the release media of 5% sucrose, 10 mM HEPES, and 0.01% NaN3 (pH = 7.4) prevented Amp B precipitation and facilitated drug release.

Fig. 1. The effect of solubilizer addition to the release media on Amp B release from AmBisome® in the single-unit vial-based IVR assay at 45 °C, including 5% HP-CD (a), 10% IPA (b), 0.25% SDS (c) or 5% γ-CD (d). Lines represent: A. AmBisome® in Float-A-Lyzer® (●); B. Free Amp B solution in Float-A-Lyzer® (■); C. Free Amp B in release medium (▲). The final Amp B concentration in the release media is 10 µg/mL for all the groups.


This work was supported by FDA grant U01FD005249-01.
In Vitro Drug Release from Different Amphotericin B Drug Products

Fig. 5. The cumulative release of different commercial Amp B formulations on Sotax® at 55 °C. 5% γ-CD was added into media, and total Amp B concentration is 10 µg/mL for all the groups based on reported package insert drug concentrations.

Fig. 6. The cumulative release of different liposomal Amp B formulations prepared by extrusion and homogenization from Z1P on Sotax® at 55 °C. 5% γ-CD was added into media, and total Amp B concentration is 10 µg/mL for all the groups.


This work was supported by FDA grant U01FD005249-01.
Challenges and Solutions for In-Vivo Bioequivalence Study of Cytarabine Liposomes

**Generic Name:**
Cytarabine liposome injection

**Indication and Regimen:**
50 mg, administered intrathecally (intraventricular or lumbar puncture) every 14 days for treatment of lymphomatous meningitis

There is sustained release of cytarabine from the liposomes and the terminal half-life of free cytarabine was prolonged in cerebrospinal fluid (CSF).

**Bioequivalence Study Challenges**
- Difficult to enroll patients
- Intensive PK sampling from CSF is not feasible
- High inter- and intra-individual variability

**Parameter Definition**
- $F_{encap}$: Fraction of encapsulated cytarabine in the formulation
- $k_{rel}$: Release rate constant from encapsulated cytarabine
- $V_{encap}$: Volume of distribution of encapsulated cytarabine mL
- $V_{free}$: Volume of distribution of free cytarabine mL
- $CL_{free}$: Clearance of free cytarabine mL/h
- $CR_{encap}$: Conversion rate between encapsulated cytarabine (readily available form) and the depot mL/h

**Population PK Modeling of Encapsulated and Free Cytarabine**
Model-based Bioequivalence Method for Cytarabine Liposomes

The model-based BE evaluation method with a minimal 20 subjects and a widened BE limit of 60.00–166.67% provided reasonable statistical power and type-I error rate.

# Long-acting Polymeric Microspheres, In-Situ Gels, and Implants

<table>
<thead>
<tr>
<th>Brand</th>
<th>Drug</th>
<th>Route</th>
<th>Dosing Frequency</th>
<th>Dosage Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperdal CONSTA</td>
<td>Risperidone</td>
<td>IM</td>
<td>2 weeks</td>
<td>Micospheres</td>
</tr>
<tr>
<td>Sandostatin LAR DEPOT</td>
<td>Octreotide</td>
<td>IM</td>
<td>1 month</td>
<td>Micospheres</td>
</tr>
<tr>
<td>Vivitrol</td>
<td>Naltrexone</td>
<td>IM</td>
<td>1 month</td>
<td>Micospheres</td>
</tr>
<tr>
<td>Lupron Depot</td>
<td>Leuprolide</td>
<td>IM</td>
<td>1, 3, 4, 6 months</td>
<td>Micospheres</td>
</tr>
<tr>
<td>Bydureon</td>
<td>Exendatide</td>
<td>SC</td>
<td>1 week</td>
<td>Micospheres</td>
</tr>
<tr>
<td>Zoladex</td>
<td>Goserelin</td>
<td>IM</td>
<td>1, 3 months</td>
<td>Implant</td>
</tr>
<tr>
<td>Eligard</td>
<td>Leuprolide acetate</td>
<td>SC</td>
<td>1, 3, 4, 6 months</td>
<td>In-situ gel</td>
</tr>
</tbody>
</table>

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

**Complexity**

- Complex formulation and polymeric excipients ingredients
- Complex manufacturing process
- Scale up challenges
- Long residence in vivo
Long-acting Polymeric Microspheres Bioequivalence Demonstration

**In Vivo Option**

- Formulation Q1 and Q2 the same
- In vivo pharmacokinetic BE study

**Equivalence Challenges**

**Formulation sameness**
- Demonstrate Q1 and Q2 sameness of the polymeric excipients

**Discriminative in vitro release within reasonable timeframe**

**Bioequivalence studies**
- Long duration
- Conventional BE matrix may not be sufficient to capture multiphasic in vivo release

www.fda.gov
Product-Specific Guidance for Risperidone Suspension

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%.

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.

Analytes to measure (in appropriate biological fluid): Risperidone in plasma

Bioequivalence based on (90% CI): Risperidone
Consideration 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

\[
\begin{align*}
\text{PLGA} & \quad m = \text{number of units of lactic acid} \\
& \quad n = \text{number of units of glycolic acid}
\end{align*}
\]

• Ratio of lactic acid to glycolic acid
• Molecular weight ~5kDa -100kDa

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


This work was supported by FDA grant U01FD05168.
# FDA Recommended Dissolution Methods for Microspheres

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosage Form</th>
<th>USP Apparatus</th>
<th>Speed (RPMs)</th>
<th>Medium</th>
<th>Volume (mL)</th>
<th>Recommended Sampling Times (minutes)</th>
<th>Date Updated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triptorelin Pamoate</td>
<td>Intramuscular Suspension</td>
<td>II (Paddle)</td>
<td>75</td>
<td>50 mL of methanol to 950 mL of water</td>
<td>950</td>
<td>1, 8, 24, 96, and 168 hours</td>
<td>11/16/2017</td>
</tr>
<tr>
<td>Triptorelin Pamoate</td>
<td>Injectable Suspension</td>
<td>II (Paddle)</td>
<td>200</td>
<td>Water-Methanol (95:5); Reconstitute vial in 2 mL Water for Injection, add to 500 mL medium at 37°C</td>
<td>500</td>
<td>1, 6, 12, 23, 48, and 72 hours</td>
<td>07/14/2008</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>Injectable Suspension</td>
<td></td>
<td></td>
<td>Phosphate buffered saline with 0.02% Tween 20 and 0.02% Sodium azide, pH 7.4 (final osmolality should be 270 ± 20 mOsm), or any other appropriate medium, at 37°C.</td>
<td></td>
<td></td>
<td>09/01/2011</td>
</tr>
<tr>
<td>Octreotide</td>
<td>Injectable Suspension</td>
<td></td>
<td></td>
<td>Develop a dissolution method using USP IV (Flow-Through Cell), and, if applicable, Apparatus II (Paddle) or any other appropriate method, for comparative evaluation by the Agency</td>
<td></td>
<td></td>
<td>12/23/2010</td>
</tr>
</tbody>
</table>

https://www.accessdata.fda.gov/scripts/cder/dissolution/
In Vitro-In Vivo Correlation (IVIVC) of Parenteral Risperidone Polymeric Microspheres

Intramuscular administration of the prepared risperidone PLGA microspheres at a single dose of 1.92 mg/kg in rabbits. (mean±SD, n = 6)

Deconvoluted In-vivo Release in Rabbits

Deconvoluted using the Loo-Riegelman method

In-vitro Drug Release

USP apparatus 4 method at 37°C in 10 mM PBS (pH 7.4) (n=3).

Level A IVIVC


This work was supported by FDA (1U01FD004931-01).
Drug Release from Implants

**FIG. 1.** Cumulative release of dexamethasone from 1-piece and 3-piece dexamethasone intravitreal implants (DEX implants) *in vitro*. Results are expressed as mean percentage ± standard deviation based on 6 replicates per time point.

**FIG. 2.** Cumulative release of dexamethasone in the vitreous humor of rabbits after implantation of 1-piece or 3-piece DEX implants in the posterior segment of opposing eyes. Results are expressed as mean percentage ± standard deviation based on 6 replicates per time point. *P* = 0.025 at day 1, but not significant at any other time point.

Intact implants vs. Fragmented implants


www.fda.gov
Equivalence Demonstration of Complex Injectable and Implantable Drug Products

- Formulation qualitatively (Q1) and quantitatively (Q2) sameness
- Physico-chemical properties
- Comparative in-vitro drug release
- Pharmacokinetic equivalence

**Formulations:**
- Emulsion
- In-situ gel
- Implants

**Examples:**
- Liposomes
- Microspheres
Summary

• Complex injectable and implantable drug products have unique complexity and challenges for generic development

• In vitro and/or in vivo options are recommended for bioequivalence demonstration of complex injectable and implantable drug products

• Significant progress made in bioequivalence demonstration of these products with the support of GDUFA research funding
  – In vitro release testing method development
  – Statistic method development for particle size profile comparison
  – Model-based bioequivalence method
  – Excipient sameness consideration
  – IVIVC development
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  – Dr. Kinam Park (Purdue University)
  – Dr. Diane Burgess (University of Connecticut)
Thank You!

Any question?
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