U.S. FOOD & DRUG ADMINISTRATION

Role of GDUFA research on resolving technical and regulatory challenges for complex generic drug development and approval

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Overview

- What are complex generic drug products and Generic Drug User Fee Amendments (GDUFA) commitments
- Leveraging GDUFA research and the product-specific guidance (PSG) program
- Example of studies conducted to support approvals of first generics
- Summary

What are Complex Drug Products

- GDUFA III Commitment Letter introduced what are complex products for generic drug development.
- The posted MAPP 5240.10 provides details and examples of how products are classified as complex. These products generally includes one or more of the following five features:

1. **A complex active ingredient**
   Heterogenous mixtures of different components (e.g., conjugated estrogen, omega-3 acid ethyl esters) or molecular weights (e.g., patiromer, pentosan polysulfate sodium); certain peptide products
2. **A complex route of delivery**
   Locally acting product (e.g., topical dermatological, local-GI)
3. **A complex dosage form or formulation**
   Formulations that have two or more discrete states of matter (e.g., emulsion, suspension, cream); generally, any non-solution products for routes other than oral administration
4. **A complex drug-device combination product**
   Device design may impact drug delivery to the site of action and/or absorption and labeling indicates that users should be trained by a healthcare provider
5. **"[C]omplexity or uncertainty concerning the approval pathway or [a] possible alternative approach [that] would benefit from early scientific engagement"**

Product-Specific Guidances (PSGs)

- Complexity is drug product specific, but the therapeutic performance of a complex drug product is typically expected to be dependent on the physicochemical properties of the drug product (e.g., formulation and critical quality attributes).
- PSGs outline FDA's current thinking on the studies and information that are recommended to demonstrate a proposed generic drug product is therapeutically equivalent to a specific reference listed drug (RLD).
- Scientific and/or regulatory challenges associated with developing and/or approval of complex generics are explored during development of PSGs.

Regulatory and Scientific Challenges for Complex Products

- Sameness of complex active ingredients
- Qualitative (Q1) sameness of certain inactive ingredients
- Impurity characterization of peptide and oligonucleotide drugs and immunogenicity risk evaluation
- Characterization of complex dosage forms for both bioequivalence and quality purposes
- In vitro and in vivo bioequivalence studies
- …..

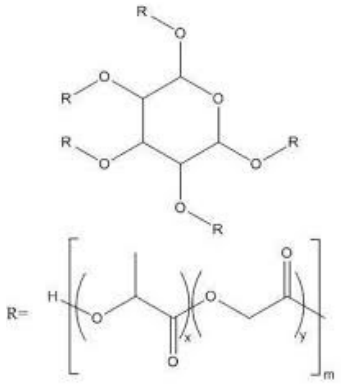
GDUFA Research

- GDUFA Research Program provides FDA with dedicated funds to address knowledge gaps to facilitate the development and approval of therapeutically equivalent generic drug products.
  - Main research focuses of the research program are
    - Analytical methods for supporting sameness of complex active ingredients and evaluating immunogenicity risk
    - The development of bioequivalence approaches for complex generic drug products.
    - Novel/new analytical methods for characterization of complex products to determine critical quality attributes
    - In vitro drug release testing and in vitro in vivo correlation
    - New tools for supporting pharmaceutical equivalence and bioequivalence (e.g., modeling and simulation)
  - Research priorities are set annually based on public feedback. Check GDUFA Research and Science webpage for updates.

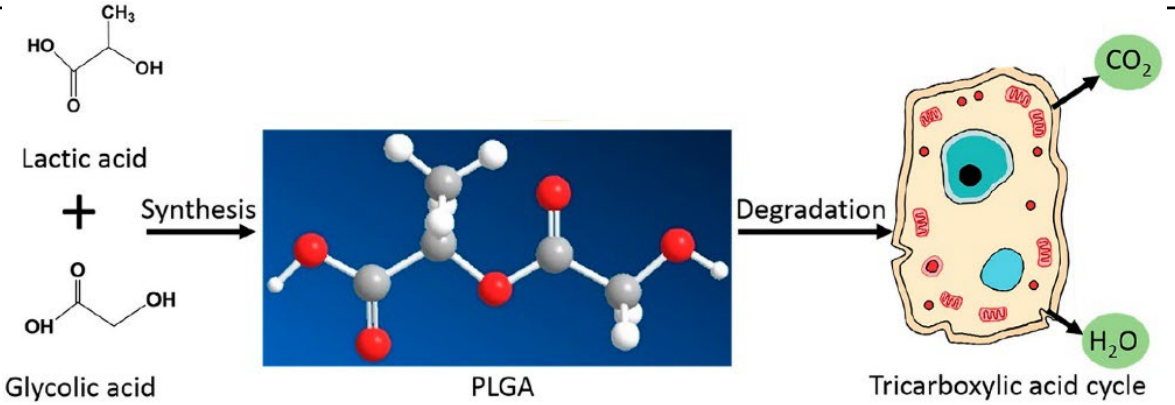
Three First Approvals of Generic Long Acting Injectable (LAI) Microsphere Products

- Three first generic LAI microsphere products were approved in 2023.

DP	Active Ingredient	LAI Technology Class	NDA Approval Year[a]	LOE[b]	Patent Expiry[b]	PSG[c]
Lupron Depot®	Leuprolide acetate	Polymer microsphere	1989	Expired	Expired	2014
Sandostatin® LAR	Octreotide acetate	Polymer microsphere	1998	Expired	Expired	2014
Risperdal Consta®	Risperidone	Polymer microsphere	2003	Expired	Expired	2016
Vivitrol®	Naltrexone	Polymer microsphere	2006	Expired	Expired[d]	2015
Somatuline Depot®	Lanreotide acetate	Other	2007	2024	Expired	2014
Invega® Sustenna®	Paliperidone palmitate	Suspended solid	2009	Expired	Expired[e]	2016
Exparel®	Bupivacaine	MVL	2011	2021	2021	2018
Bydureon®	Exenatide	Polymer microsphere	2012	2021	2025[f]	–
Abilify Maintena®	Aripiprazole	Suspended solid	2013	Expired	2025[g]	2014



Glucose-PLG polymer
Sandostatin LAR

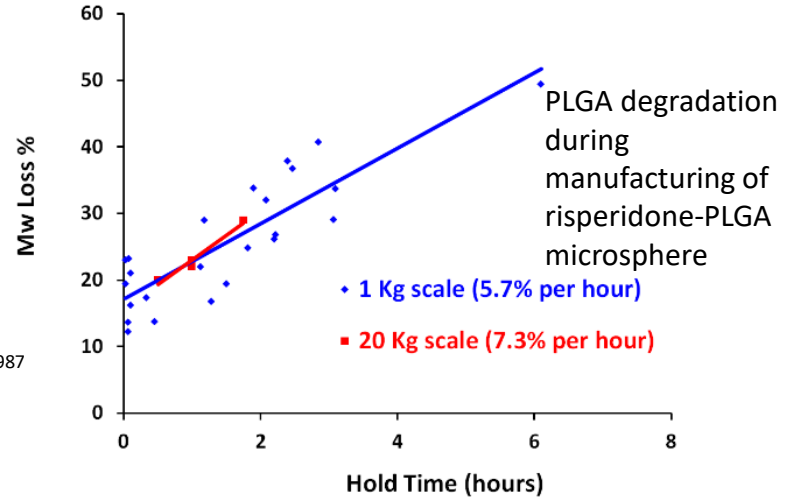


Linear PLGA polymer
Risperdione Consta; Vivitrol

Regulatory Challenge for PLGA based LAI Generics

- Per regulation, LAI generics need to be qualitative (Q1) and quantitative (Q2) the same as the reference listed drugs (RLDs). However, for complex polymeric excipients (i.e., PLGA), there was no exiting regulatory approaches/standards for assessing Q1Q2.
- PLGA are random co-polymers with inherent heterogeneity. Polymer characteristics can be sensitive to manufacturing conditions.

Impact of manufacturing conditions on PLGA molecular weight

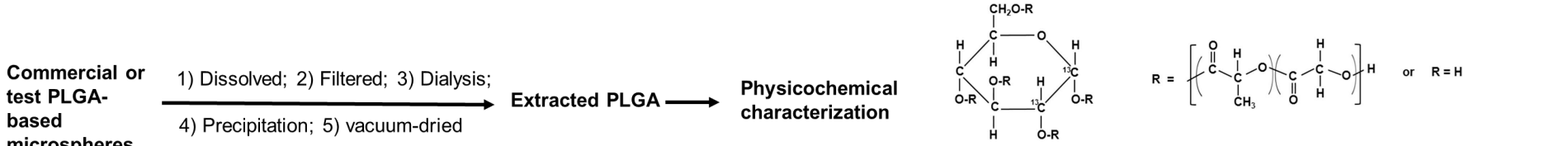


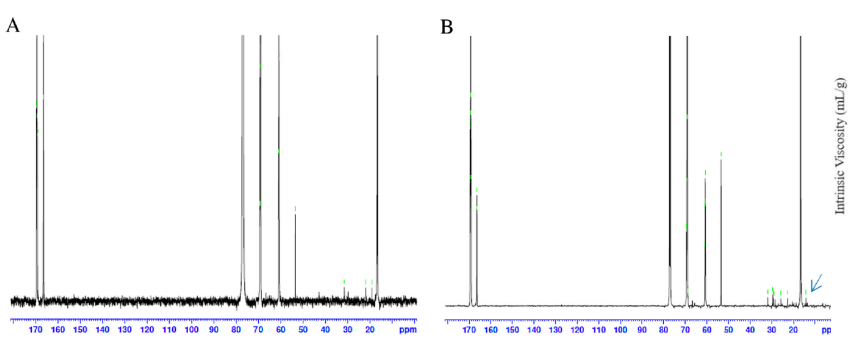
Alkermes, US 6,264,987 B1, 2001

Q1 Sameness of PLGA Polymers

Challenge: Complex reverse engineering as manufacturing process can change PLGA properties

GDUFA research: developed a protocol to extract PLGA from the finished product and developed characterization methods for PLGA.

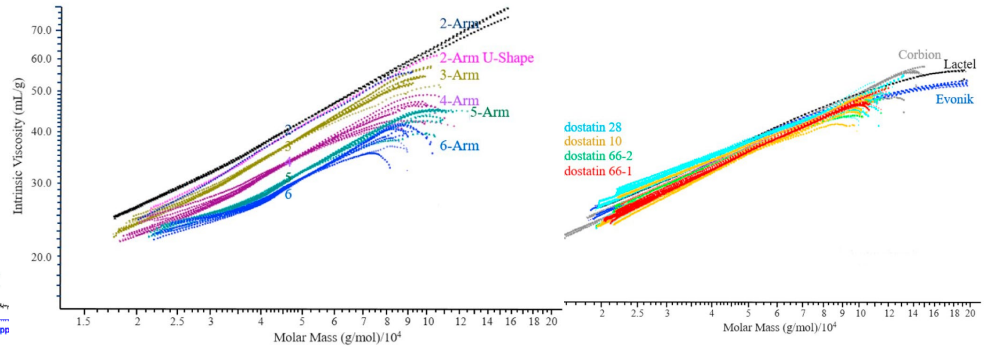




Int. J. Pharm. 495 (2015) 87–92
Grant U01FD05168

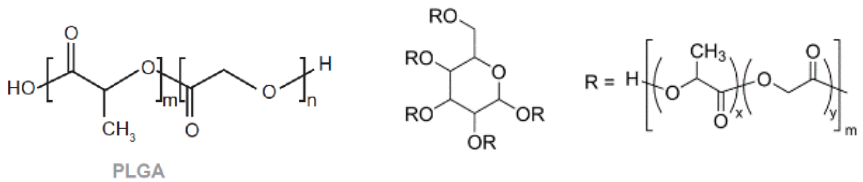
Challenge: No readily available method to characterize glucose cored, star-shaped PLGA

GDUFA research: developed characterization method to characterize glucose cored, star-shaped PLGA



J. Control. Release 204 (2019) 75-89
Contract HHSF223201710123C

Q1 Polymer Sameness Current Practice



PLGA

Garner 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.

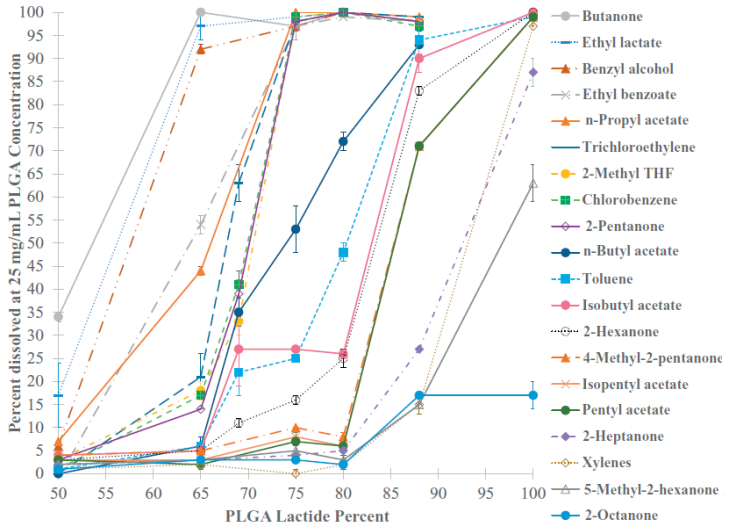
- Poly esters
  - PLG copolymers
  - PLA polymers

Should provide comparative physicochemical data on PLA/PLGA polymers extracted from the FINISHED Test product and the RLD

- Not acceptable to only use the Certificate of Analysis from the excipient vendor
- Not acceptable if characterizing raw polymer vs. polymer extracted from the RLD
- Characterization should include, but is not limited to: Composition (Lactide/Glycolide ratio), molecular weight and molecular weight distribution, polymer structure (i.e., linear or star), inherent viscosity, glass transition temperature, and polymer end-cap

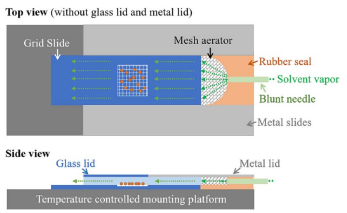
Q1 Polymer Sameness
Ongoing Efforts

Challenge: Difficult to characterize products containing more than one PLGA
GDUFA research: Semi-solvents were studied to develop method to separate PLGAs based on different lactide to glycolide ratio. SAVI showed potential to reveal composition of PLGA microspheres and to probe structural arrangement differences that arise from different manufacturing process.

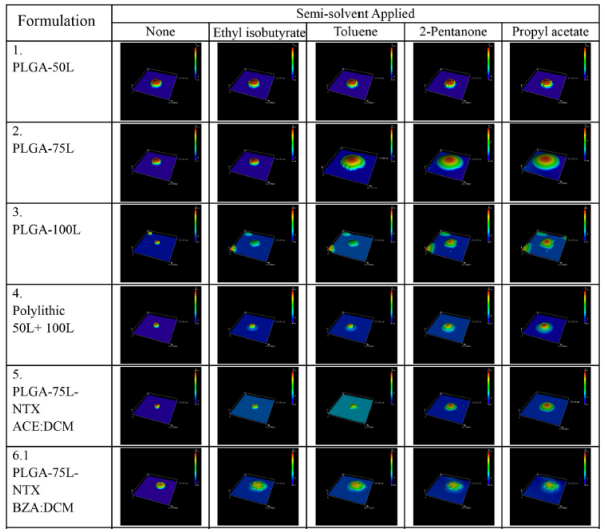


J. Control. Release 300 (2019) 174-184

Contract HHSF223201610091C



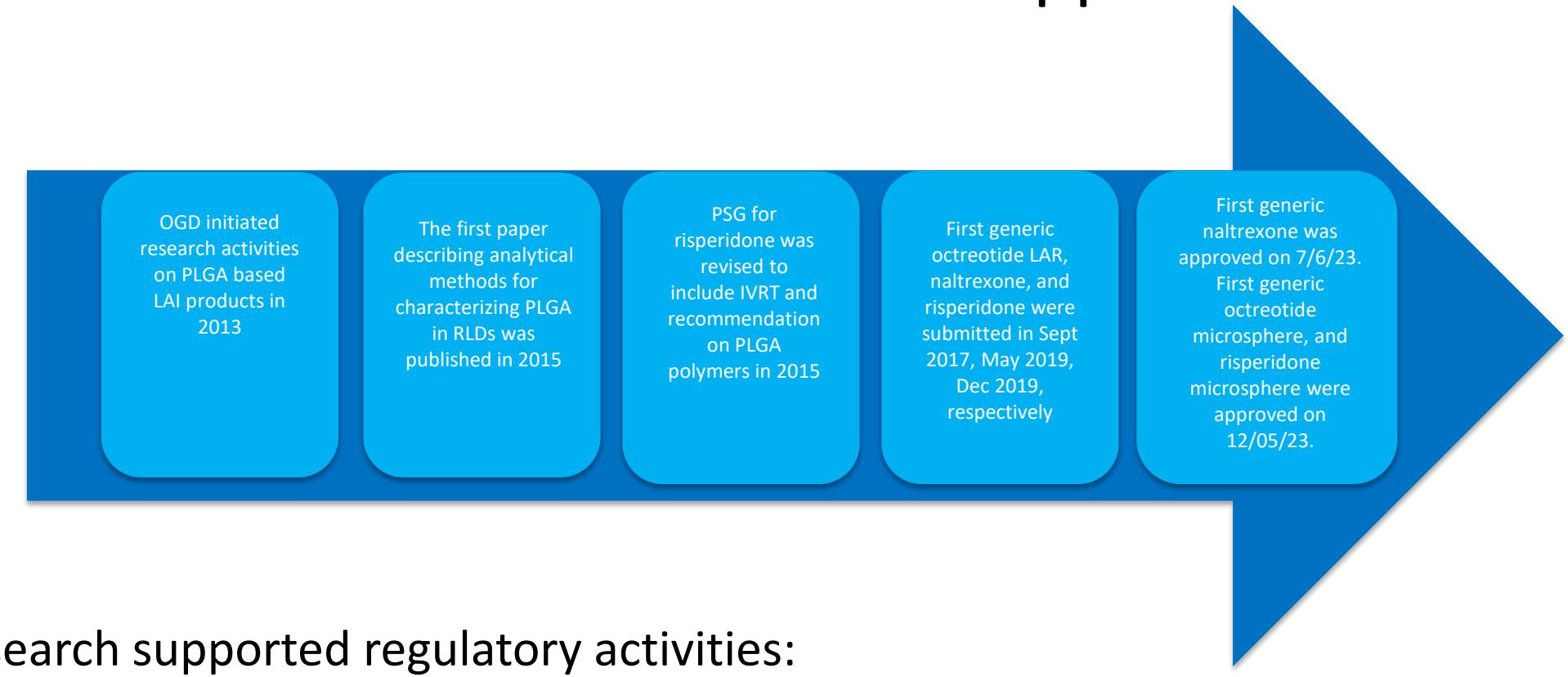
Surface analysis of sequential semi-solvent vapor impact (SAVI)



J. Control. Release 350 (2022) 600-612

Contract 75F40119C10096

GDUFA Research Translates to Approvals



Research supported regulatory activities:

- Controlled correspondences and pre-ANDA meeting requests
- Product-specific guidances
- FDA organized workshops
- Consults to support ANDA assessment

First Approval of Generic Multivesicular Liposome

- First generic bupivacaine multivesicular liposome was approved in 2024

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Lupron Depot®	Leuprolide acetate	Polymer microsphere	1989	Expired	Expired	2014
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Complexity of Bupivacaine MVL

- Lipid based microparticles with nano-sized inner structure
- Complex manufacturing process
- Locally acting
- Systemic pharmacokinetic profile is surgical site dependent

Scientific and Regulatory Efforts Supporting Generic Development and Approval

Research on better understanding formulation characteristics and drug release mechanism was initiated in 2017

Characterization of Exparel Bupivacaine Multivesicular Liposomes

Minzhi Yu[a,1], Wenmin Yuan[a,1], Ziyun Xia[a], Yayuan Liu[a,2], Yan Wang[b], Xiaoming Xu[c], Jiwen Zheng[d], Anna Schwendeman[a,e,*]

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[c]Division of Product Quality Research, Office of Testing and Research, Office of Pharmaceutical Quality, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD 20993, United States

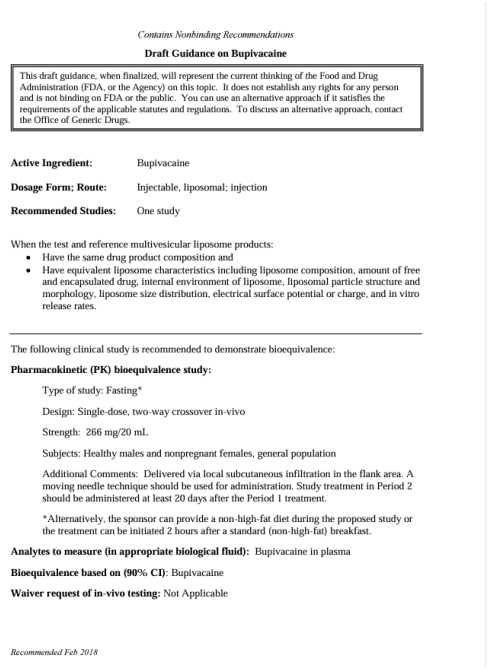
[d]Division of Biology, Chemistry and Materials Science, Office of Science and Engineering Laboratories, Center for Devices and Radiological Health, U.S. Food and Drug Administration, Silver Spring, MD 20993, United States

[e]Biointerfaces Institute, University of Michigan, Ann Arbor, MI 48109, United States

Abstract

Exparel is a bupivacaine multivesicular liposomes (MVLs) formulation developed based on the DepoFoam technology. The complex composition and the unique structure of MVLs pose challenges to the development and assessment of generic versions. In the present work, we developed a panel of analytical methods to characterize Exparel with respect to particle size, drug and lipid content, residual solvents, and pH. In addition, an accelerated *in vitro* drug release assay was developed using a rotator-facilitated, sample-and-separate experimental setup. The proposed method could achieve over 80% of bupivacaine release within 24 hours, which could potentially be used for formulation comparison and quality control purposes. The batch-to-batch variability of Exparel was examined by the established analytical methods. Four different batches of Exparel showed good batch-to-batch consistency in drug content, particle size, pH, and *in vitro* drug release kinetics. However, slight variation in lipid contents were observed.

A draft PSG was published in 2018 recommending an in vivo PK BE study in healthy subject with supportive characterization studies



Contains Nonbinding Recommendations

Draft Guidance on Bupivacaine

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Bupivacaine

Dosage Form; Route: Injectable, liposomal; injection

Recommended Studies: One study

When the test and reference multivesicular liposome products:

- Have the same drug product composition and
- Have equivalent liposome characteristics including liposome composition, amount of free and encapsulated drug, internal environment of liposome, liposomal particle structure and morphology, liposome size distribution, electrical surface potential or charge, and in vitro release rates.

The following clinical study is recommended to demonstrate bioequivalence:

Pharmacokinetic (PK) bioequivalence study:

Type of study: Fasting*

Design: Single-dose, two-way crossover in-vivo

Strength: 266 mg/20 mL

Subjects: Healthy males and nonpregnant females, general population

Additional Comments: Delivered via local subcutaneous infiltration in the flank area. A moving needle technique should be used for administration. Study treatment in Period 2 should be administered at least 20 days after the Period 1 treatment.

*Alternatively, the sponsor can provide a non-high-fat diet during the proposed study or the treatment can be initiated 2 hours after a standard (non-high-fat) breakfast.

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

Bioequivalence based on (90% CI): Bupivacaine

Waiver request of in-vivo testing: Not Applicable

Recommended Feb 2018

Research outcomes were used to support:

- Product-specific guidance
- Controlled correspondences
- Pre-ANDA Development Meeting requests

Summary

- Drug products may have multiple aspects of complexity that need to be considered when developing appropriate studies to support pharmaceutical equivalence and bioequivalence of the product.
- The GDUFA research program has played a critical role for developing PSGs and resolving regulatory challenges.
- Development and approval of generic complex products benefit from discussion, and research. Controlled correspondence and/or pre-ANDA meetings may be used to obtain feedback.
- FDA held public workshops may be used for feedback on priority areas where research or further guidance may be needed.

FY23 GDUFA Science & Research Report

GDUFA Research and Funding

- **Regulatory Research under GDUFA:**
  - Generic Drug Research-Related Guidances & Reports

- **GDUFA Research Outcomes**

- **Generic Drug Research Collaborations Opportunities**

Meetings with the FDA

- **All Generic Drug Development Stages:**
  - ❑ Model-Integrated Evidence (MIE) Industry Meeting Pilot Between FDA and Generic Drug Applicants

- **Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA Guidance for Industry**
  - ❑ Product Development Meeting (Pre-ANDA)
  - ❑ Post Complete Response Letter Scientific Meeting (Post-CRL)

- **FDA-EMA Parallel Scientific Advice (PSA) program**
  - ❑ Meetings for prospective applicants to engage with FDA and EMA concurrently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