The Journey of First Approvals of Complex Generic Long-acting Injectable Products

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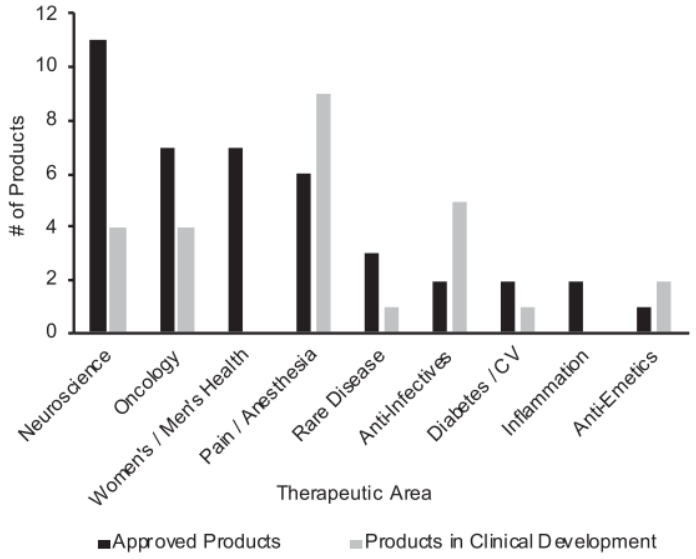
Advancing Generic Drug Development: Translating Science to Approval – September 25, 2024

Learning Objectives

- Describe on different long-acting injectable (LAI) products
- Recognize regulatory and scientific challenges for developing generic complex LAI products
- Identify example product-specific guidances (PSGs) on complex LAI products
- Summarize GDUFA research supporting first approvals of complex generic LAI products

Long-Acting Injectable (LAI) Products

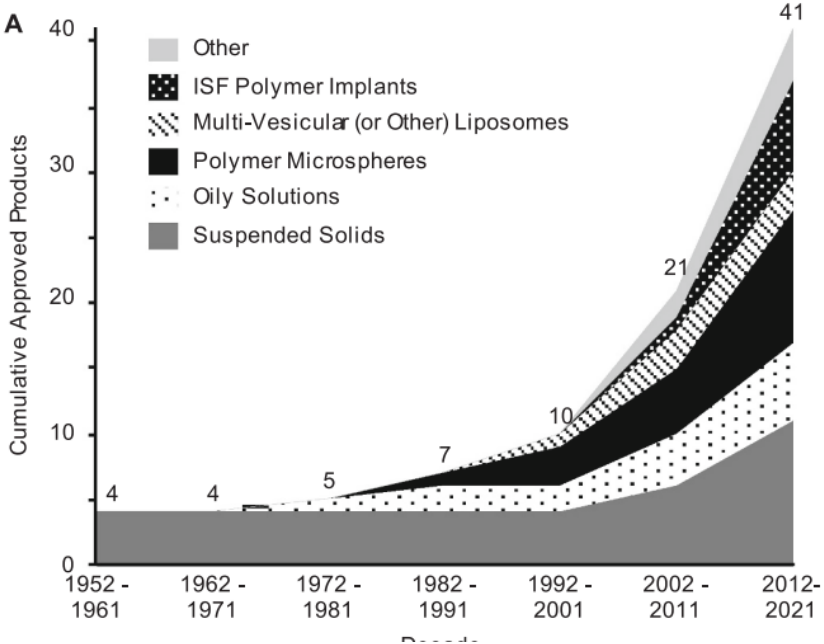
- Long-acting injectables (LAIs) are drug products that are designed to provide controlled/sustained release for days to months.
- Number of LAI products that had been approved by the FDA via NDA pathway (N = 41) or that are in clinical development (n = 26) as of May 2021

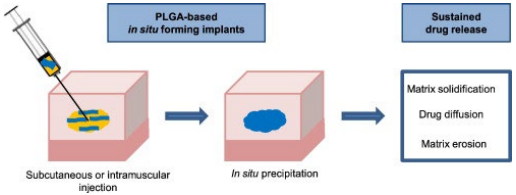


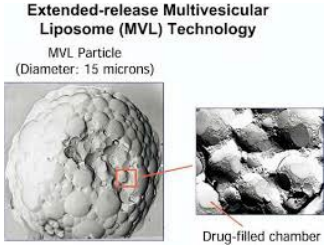
M.S. O'Brien et al., Challenges and opportunities in the development of complex generic long-acting injectable drug products, Journal of Controlled Release 336 (2021) 144-158 https://doi.org/10.1016/j.jconrel.2021.06.017

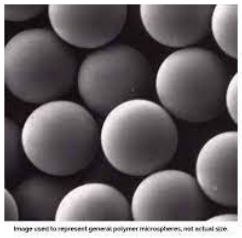
Dosage Forms of LAI Products

- Dosage forms

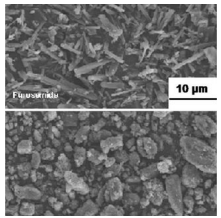








PLGA microspheres



Drug substance suspensions without rating controlling excipients

M.S. O'Brien et al., Challenges and opportunities in the development of complex generic long-acting injectable drug products, Journal of Controlled Release 336 (2021) 144-158 https://doi.org/10.1016/j.jconrel.2021.06.017

Generic Long-Acting Injectable Products

- High revenue LAI products eligible for generic competition with no generics as of May 2021

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

[a] Based on Drugs@FDA website.
[b] LOE or patent expiry year; Based on the U.S. FDA Orange Book listed patents as of April 2021.
[c] Year of most recently issued PSG, based on the U.S. FDA's PSG website [63].
[d] All U.S. FDA Orange Book listed DP patents expired. One remaining method of treatment patent expires in 2029.
[e] All U.S. FDA Orange Book listed DP patents expired. One remaining method of treatment patent expires in 2031.
[f] Additional U.S. FDA Orange Book listed non-DP patents extend out to 2028.
[g] Additional U.S. FDA Orange Book listed non-DP patents extend out to 2034.

M.S. O'Brien et al., Challenges and opportunities in the development of complex generic long-acting injectable drug products, Journal of Controlled Release 336 (2021) 144-158 https://doi.org/10.1016/j.jconrel.2021.06.017

First Approvals of Complex LAI Products

Three First Approvals of Generic LAI Microsphere Products

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

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Lupron Depot®	Leuprolide acetate	Polymer microsphere	1989	Expired	Expired	2014
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Risperdal Consta®	Risperidone	Polymer microsphere	2003	Expired	Expired	2016
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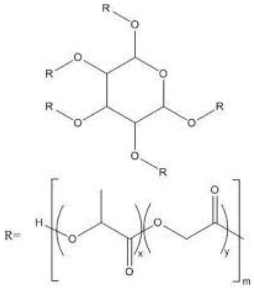
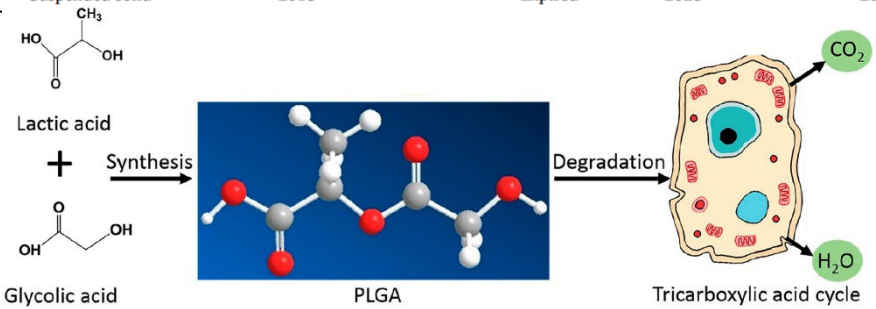




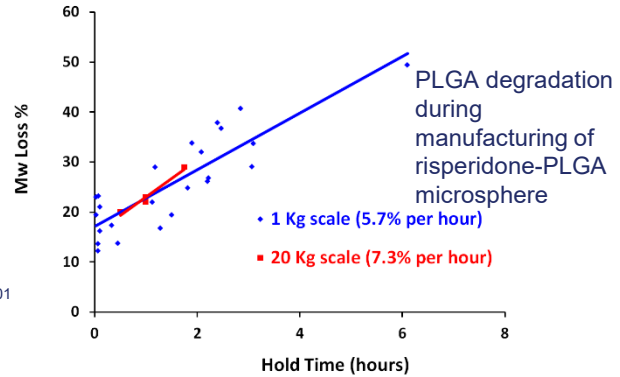
Glucose-PLG polymer
Sandostatin LAR

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

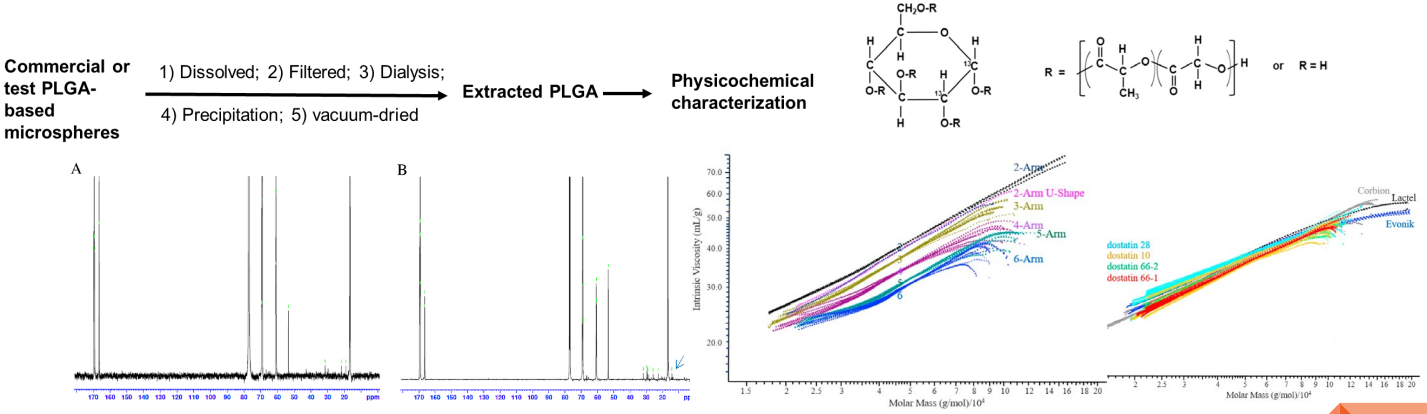


Alkermes, US 6,264,987 B1, 2001

Scientific Challenge 1
Q1 Polymer Sameness

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.

Challenge: No readily available method to characterize glucose cored, star-shaped PLGA
GDUFA research: developed characterization method to characterize glucose cored, star-shaped PLGA

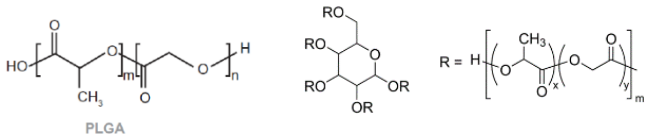


Int. J. Pharm. 495 (2015) 87–92
Grant U01FD05168

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

Q1 Polymer Sameness Current Practice

- Poly esters
  - PLG copolymers
  - PLA polymers



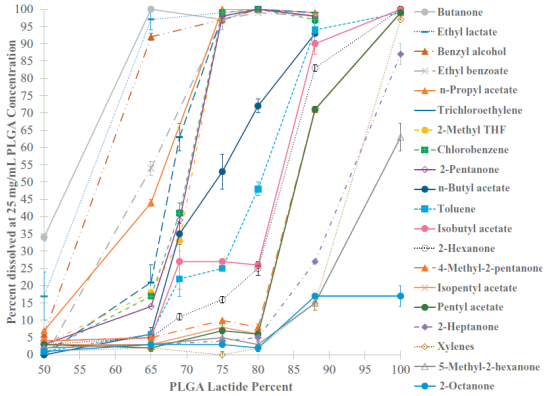
Garner J et al. A protocol for assay of poly(lactide-co-glycolide) in clinical products. International Journal of Pharmaceutics 495 (2015) 87–92.
This work was supported by FDA grant U01FD05168.

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

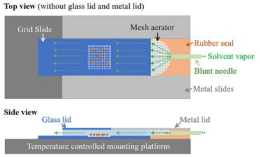
- Not acceptable to only use the Certificate of Analysis from the excipient vendor
- Not acceptable if characterizing raw polymer vs. polymer extracted from the RLD
- Characterization should include, but is not limited to: Composition (Lactide/Glycolide ratio), molecular weight and molecular weight distribution,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

Q1 Polymer Sameness Ongoing Efforts

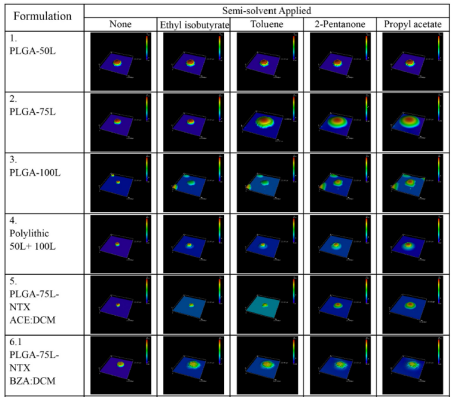
Challenge: Difficult to characterize products containing more than one PLGA
GDUFA research: Semi-solvents were studied to develop method to separate PLGAs based on different lactide to glycolide ratio. SAVI showed potential to reveal composition of PLGA microspheres and to probe structural arrangement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



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



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



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

Contract HHSF223201610091C

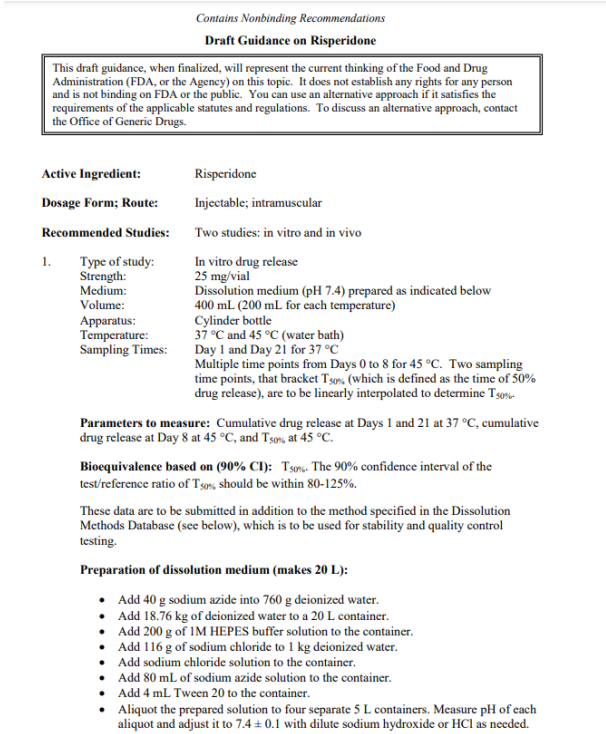
Contract 75F40119C10096

Scientific Challenge 2
In Vitro Drug Release Testing (IVRT)

- Development and validation of IVRT can be complex
- Two methods may need to be developed
  - Real time: Drug release evaluated through the intended period of product use
  - Accelerated: time/cost efficient to achieve complete drug release

GDUFA Research:

- Important tool for better understanding impact of formulation and manufacturing parameters on drug release
- Explore novel BE approaches
  - Totality of evidence in vitro approach
  - IVRT in combination with in vivo BE study



Contains Nonbinding Recommendations

Draft Guidance on Risperidone

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: 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%.

These data are to be submitted in addition to the method specified in the Dissolution Methods Database (see below), which is to be used for stability and quality control testing.

Preparation of dissolution medium (makes 20 L):

- Add 40 g sodium azide into 760 g deionized water.
- Add 18.76 kg of deionized water to a 20 L container.
- Add 200 g of 1M HEPES buffer solution to the container.
- Add 116 g of sodium chloride to 1 kg deionized water.
- Add sodium chloride solution to the container.
- Add 80 mL of sodium azide solution to the container.
- Add 4 mL Tween 20 to the container.
- Aliquot the prepared solution to four separate 5 L containers. Measure pH of each aliquot and adjust it to 7.4 ± 0.1 with dilute sodium hydroxide or HCl as needed.

Scientific Challenge 3
Bioequivalence (BE) Study

General considerations:

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

For PLGA based LA drugs

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

Example Product Specific Guidance PK BE study with pAUC

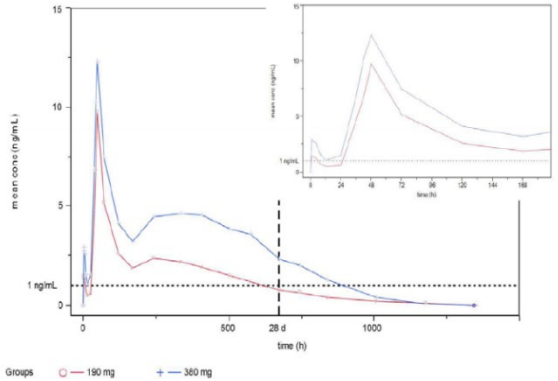
- Example product: **Vivitrol** (Naltrexone PLGA (75/25) microspheres)
  - Indicated for alcohol dependence
  - Every **4 weeks or once a month** via IM
  - Therapeutic plasma concentration: **>1 ng/ml**
  - Variability in Cmax
  - Multi-phasic in vitro and in vivo release profiles

Active Ingredient: Naltrexone

Dosage Form; Route: Extended-release suspension; intramuscular

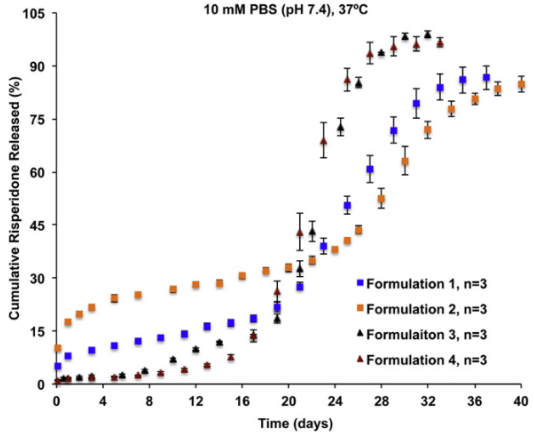
Recommended Studies: One study

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%



Scientific Challenge 4 Formulation Characterization and In Vitro and In Vivo Correlation (IVIVC)

- In vitro and in vivo drug release profiles are sensitive to manufacturing differences

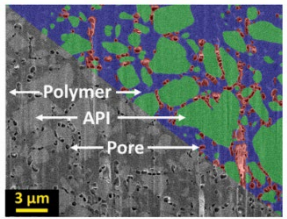


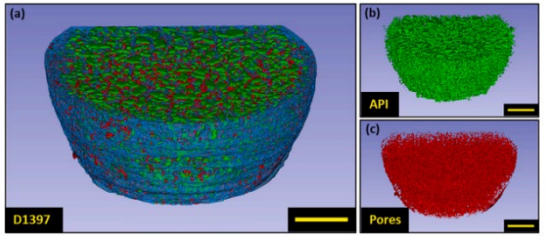
In vitro release profiles of the formulation composition equivalent risperidone microspheres with manufacturing differences obtained using USP apparatus 4 method at 37 ° C in 10 mM PBS (pH 7.4)

J. Shen, S. Choi, W. Qu, Y. Wang, D.J. Burgess. In vitro-in vivo correlation of parenteral risperidone polymeric microspheres. (2015) Journal of Controlled Release. 218, pp. 2-12 http://dx.doi.org/10.1016/j.jconrel.2015.09.051

GDUFA research:

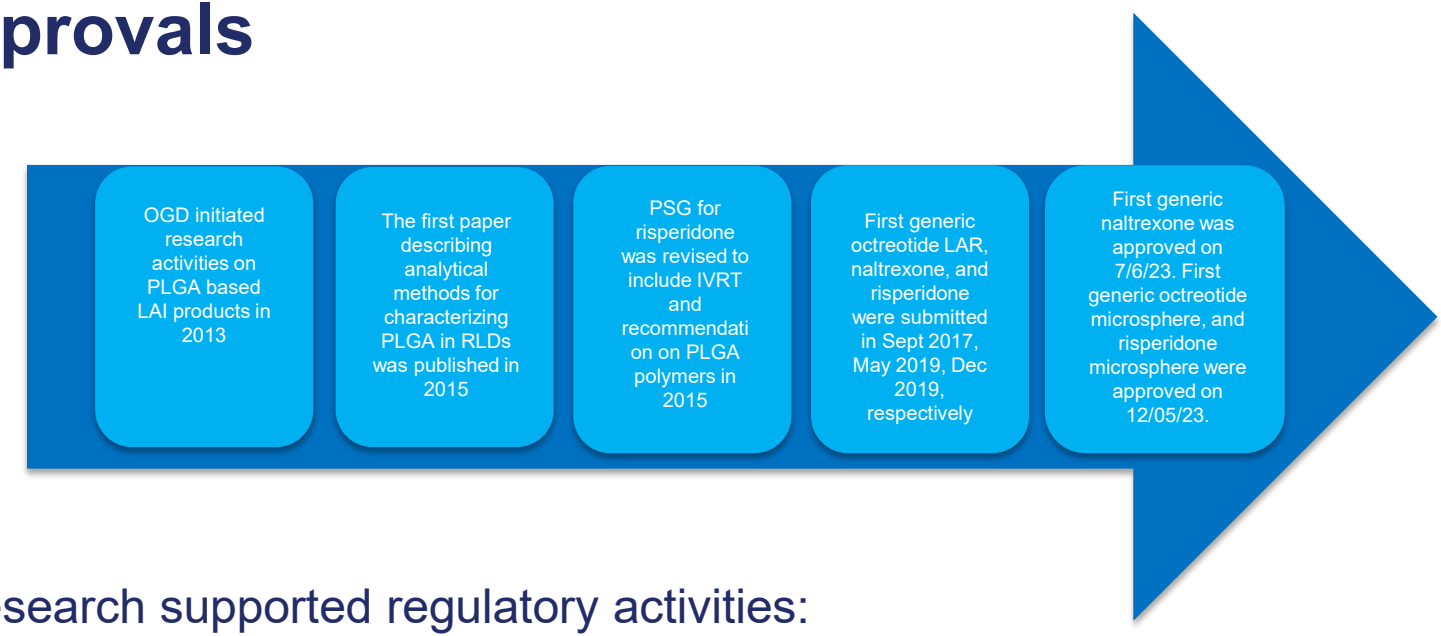
- Advanced imaging techniques and artificial intelligence-based image data analysis to assess microstructural critical quality attributes of PLGA based formulations to explore IVIVC
- Modeling efforts to develop PBPK models





A.G. Clark, R. Wang, Y. Qin, Y. Wang, A. Zhu, J. Lomeo, Q. Bao, D. J. Burgess, J. Chen, B. Qin, Y. Zou, S. Zhang, Assessing microstructural critical quality attributes in PLGA microspheres by FIB-SEM analytics, Journal of Controlled Release (2022)

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

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
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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

Complexity of Bupivacaine MVL

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

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Scientific and Regulatory Efforts Supporting Generic Development and Approval

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

COVER STORY

Probing the mechanism of drug release from liposomes

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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[b]Division of Therapeutic Performance 1, Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD 20993, United States

[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

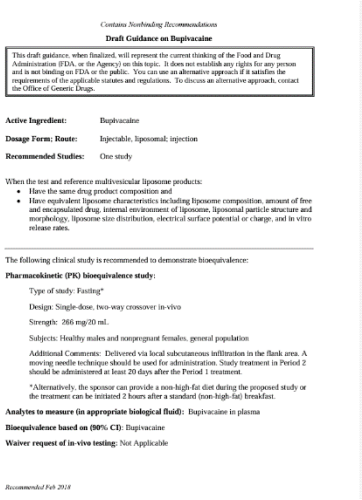
[d]Division of Biology, Chemistry and Materials Science, Office of Science and Engineering Laboratories, Center for Devices and Radiological Health, U.S. Food and Drug Administration, Silver Spring, MD 20993, United States

[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

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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

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Publications Produced by GDUFA Research

For PLGA based formulations, GDUFA research published 42 peer-reviewed research papers since 2015.

1. X. Wang, Q. Bao, R. Wang, T. Li, Y. Wang, B. Qin, Q. Li, D.J Burgess, In vivo characterization of Perseris and compositionally equivalent formulations, International Journal of Pharmaceutics (2023)
2. R. Schutzman, N. Shi, K.F Olsen, R. Ackermann, J. Tang, Y.Y Liu, J. KY Hong, Y. Wang, B. Qin, A. Schwendeman, S.P Schwendeman, Mechanistic evaluation of the initial burst release of leuprolide from spray-dried PLGA microspheres (2023)
3. A.G Clark, R. Wang, J. Lomeo, Y. Wang, A. Zhu, M. Shen, Q. Bao, D.J Burgess, B. Qin, S. Zhang, Investigating structural attributes of drug encapsulated microspheres with quantitative X-ray imaging, Journal of Controlled Release (2023)
4. X. Wang, Q. Bao, R. Wang, B. Wan, Y. Wang, B. Qin, D.J Burgess, Reverse engineering of Perseris and development of compositionally equivalent formulations, International Journal of Pharmaceutics (2023)
5. J. Zhou, R. Schutzman, N.Shi, R. Ackermann, K. Olsen, Y. Wang, S.P Schwendeman, Influence of encapsulation variables on formation of leuprolide-loaded PLGA microspheres, Journal of Colloid and Interface Science (2023)
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Challenge Question #1

All long-acting drug products considered as complex products.

A. True

B. False

Summary

- Polymer- or lipid-based microparticle are complex LAI products.
- GDUFA research projects helped to improve understanding on complex LAI products which are used to develop PSGs and address regulatory inquiries for facilitating generic development and approval.
- OGD continues to improve PSGs based on updated understanding obtained through communications with generic industry via workshop, CCs, pre-ANDA meeting requests and GDUFA funded research.
- Generic applicants are encouraged to leverage from GDUFA research outcomes and engage with the Agency early during development.

Questions?

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