U.S. FOOD & DRUG ADMINISTRATION

# Session II:
# Characterization of Complex Excipients and Formulations

Yan Wang
Division of Therapeutic Performance
Office of Research and Standards
Office of Generic Drugs

# Goals of Section II

- Introduction: challenges to develop generic complex formulations
- Introduce GDUFA research priorities
- Research update

# Complex Formulations/Dosage Forms

- Complex formulations/dosage forms
  - Long-acting (LAI) parenteral drug products
    - Microparticles
    - Implants/inserts
    - Multivesicular liposomes
    - suspensions
  - Injectable drug products with nanotechnology
    - Nano size liposomes
    - Iron complex
    - Nano-suspensions
  - Semi-solids
    - Lotion
    - Ointments
    - Cream
  - Emulsions
  - Abuse deterrent formulations

# Challenges to Develop Generic Complex Formulations

- Demonstration of qualitative (Q1) and quantitative (Q2) sameness of excipients prior to conduct of bioequivalence (BE) studies of parenteral drug products

  21 CFR 314.94 (a)(9)(iii) – *Inactive ingredient changes permitted in drug products intended for parenteral use.*

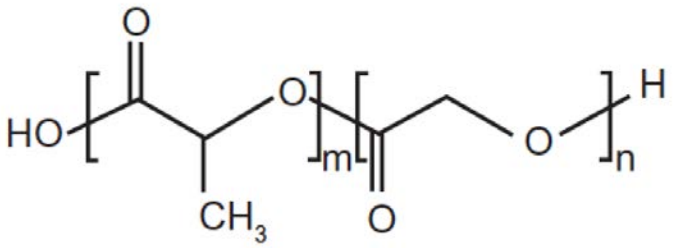
  Generally, a drug product intended for parenteral use shall contain the same inactive ingredients (qualitatively the same – "Q1") and in the same concentration (quantitatively the same – "Q2") as the reference listed drug.

  An applicant may seek approval of a drug product that differs from the reference listed drug in **preservative, buffer, or antioxidant** provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.

  A formulation which contains an excipient not contained in the RLD and not considered to be an "exception excipient" cannot be submitted as an ANDA.

# Challenges to Develop Generic Complex Formulations (Cont.)

- Complex inactive ingredients
  - **Poly(lactic-*co*-glycolic acid) (PLGA) copolymer**

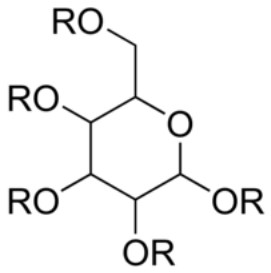


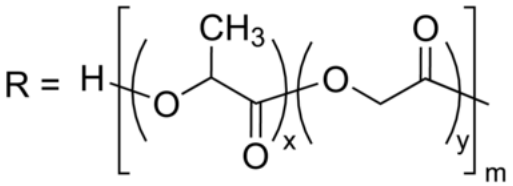

PLGA

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**

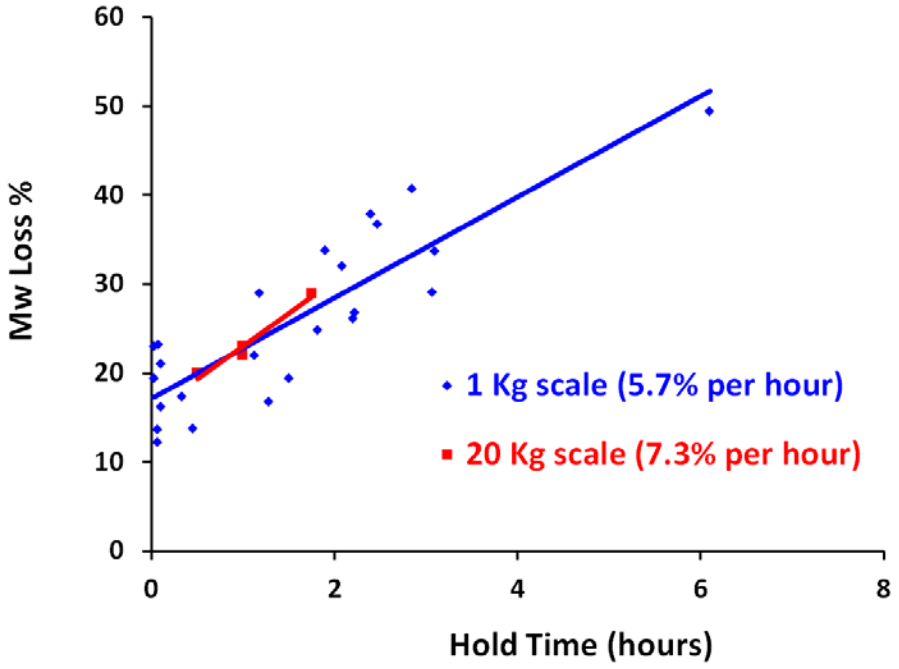



Sandostatin LAR depot
(octreotide acetate microsphere)

# Challenges to Develop Generic Complex Formulations (Cont.)

- Impact of manufacturing conditions on complex inactive ingredients (complex reverse engineering)

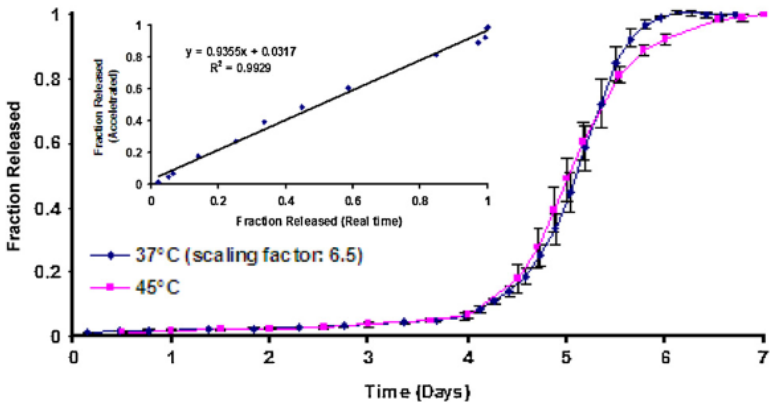



PLGA degradation during manufacturing of risperidone-PLGA microsphere

Alkermes, US 6,264,987 B1, 2001

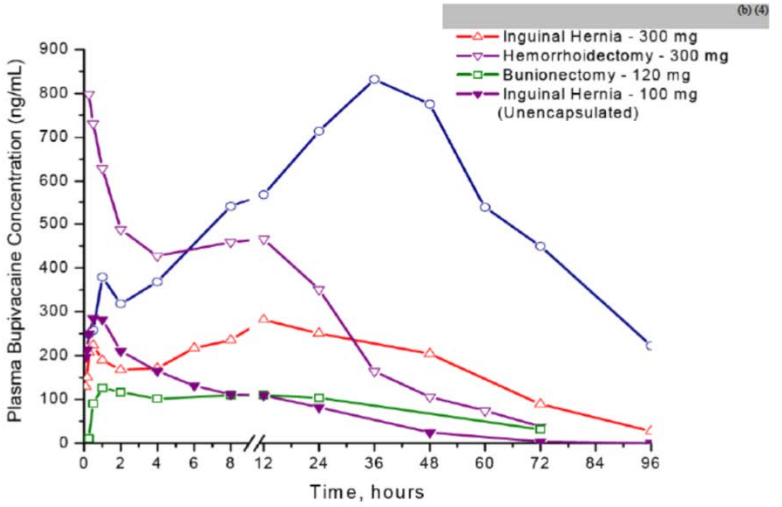
# Challenges to Develop Generic Complex Formulation (Cont.)

- Complicated multi-phasic in vitro drug release profiles and in vivo pharmacokinetics profiles




In vitro release profiles of Risperdal Consta 25 mg in 0.05 M PBS pH 7.4 at 37 °C and 45 °C

A. Rawat, U. Bhardwaj, D.J. Burgess. Comparison of in vitro–in vivo release of Risperdal® Consta® microspheres. (2012) Int J Pharm, 434(1-2), pp 115-121. http://dx.doi.org/10.1016/j.ijpharm.2012.05.006

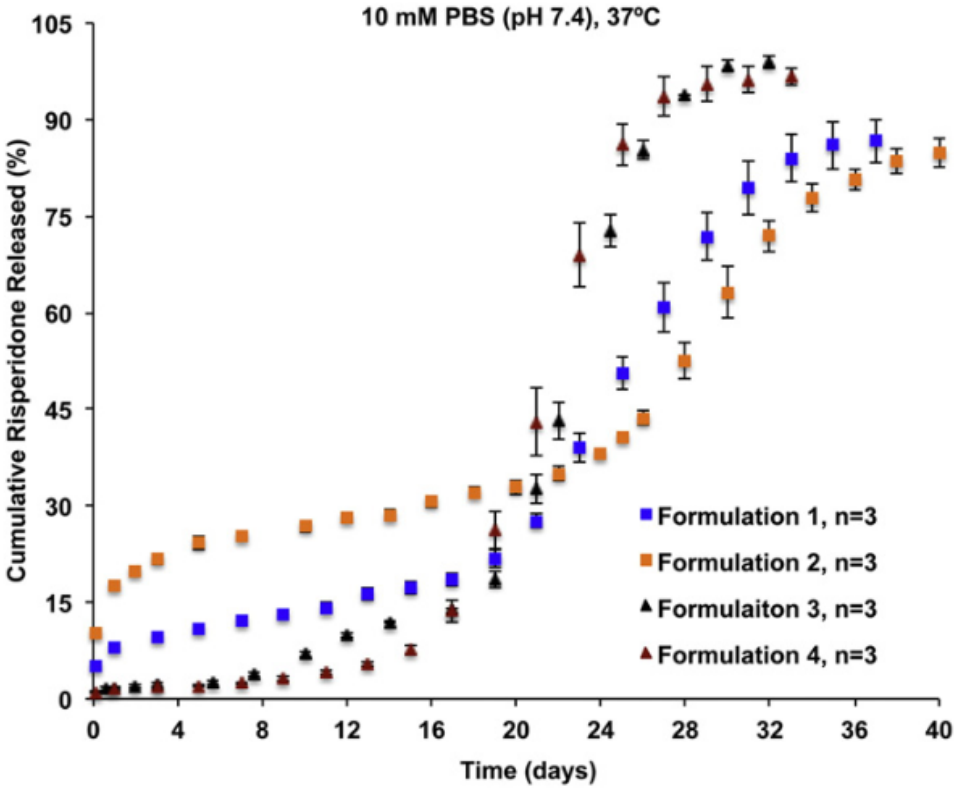



Mean plasma concentrations of bupivacaine after administration of single doses of Experal and Bupivacaine HCl (Un-encapsulated)

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022496Orig1s000ClinPharmR.pdf

# Challenges to Develop Generic Complex Formulations (Cont.)

- 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)

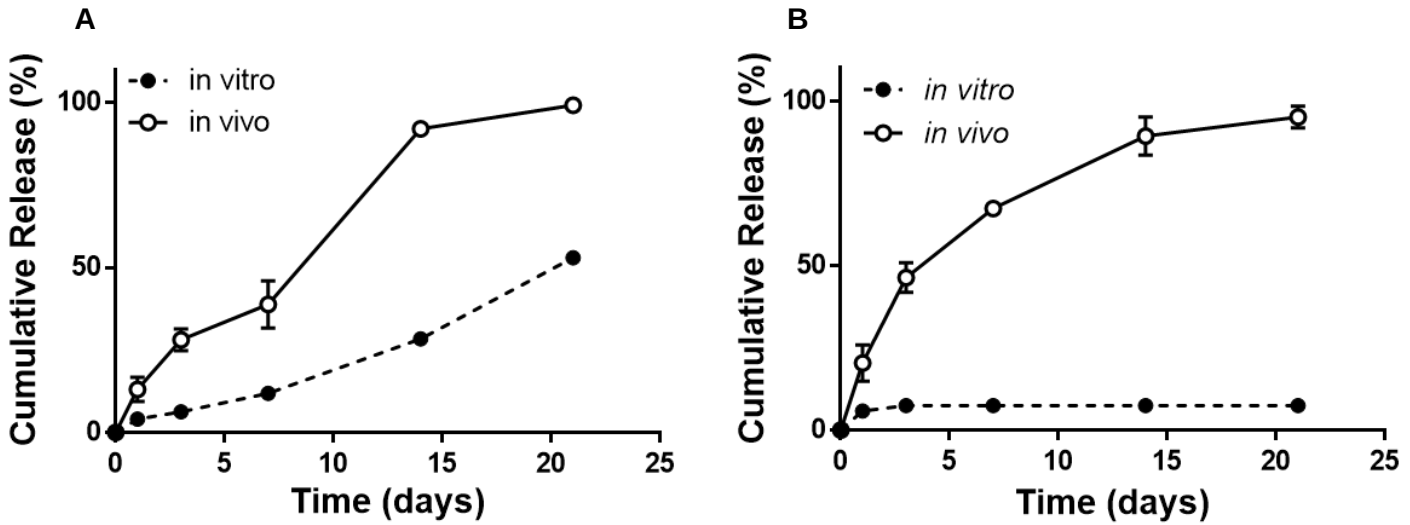
J. Shen, S. Choi, W. Qu, Y. Wang, D.J. Burgess. In vitro-in vivo correlation of parenteral risperidone polymeric microspheres. (2015) Journal of Controlled Release. 218, pp. 2-12 http://dx.doi.org/10.1016/j.jconrel.2015.09.051

# Challenges to Develop Generic Complex Formulations (Cont.)

- Complex bioequivalence study design, such as combination of in vitro and in vivo studies, or partial AUCs
  - Risperidone intramuscular injectable microspheres
    - In vitro drug release + In vivo, two period, crossover steady state in patients (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM201272.pdf)
  - Doxorubicin hydrochloride injectable liposome
    - Single dose, two way crossover in vivo + liposome size distribution and additional characterization (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM199635.pdf)

# Challenges to Develop Generic Complex Formulations (Cont.)

- Lack of compendial in vitro drug release testing methods, in vitro in vivo correlation, and complete understanding of drug release mechanisms




*Contrasting in vitro and in vivo release from triamcinolone acetonide_1 (A) and triamcinolone acetonide_2 (B) microspheres.*

Doty, A. C., Hirota, K., Olsen, K. F., Sakamoto, N., Wang, Y., Choi, S., Qu, W., Schwendeman, A. S. and Schwendeman, S. P., Validation of a cage implant for assessing in vivo performance of long-acting release microspheres, *Biomaterials*, 109, 88-96 (2016). http://ac.els-cdn.com/S0142961216303787/1-s2.0-S0142961216303787-main.pdf?_tid=9e506490-9caa-11e7-b96e-00000aab0f26&acdnat=1505764407_767d6cbf46bd78acfbbd0a00c9a8c685

# Challenges to Develop Generic Complex Formulations (Cont.)

- Duration of BE studies is much long compared to conventional dosage forms, which results in potential high drop out rate
- Different strengths may require separate BE studies due to difference in formulation composition and release characteristics

# Role of GDUFA Research

The GDUFA research priorities identified from 2012-2017:

- New analytical tools for characterizing complex excipients and formulations
- Investigation of drug release mechanisms from various complex formulations and development of discriminatory in vitro drug release methods
- Development of IVIVC
- Investigation on how manufacturing affects the critical quality attributes of complex formulations
- Development of new methods to measure PK of complex formulations

# Role of GDUFA Research (Cont.)

- GDUFA funded research on long acting drug products (15 grants/contracts):
  1) To obtain a better understanding of the impact of properties of PLGA polymers on product performance;
  2) To explore biorelevant IVIVCs for biodegradable injectable PLGA microspheres;
  3) To investigate dissolution methods for PLGA microsphere and implant drug products that can discriminate formulations with manufacturing differences;
  4) To investigate potential peptide PLGA interactions during product manufacturing and use;
  5) To develop modeling tools to facilitate development of generic LAI formulation development as well as bioequivalence guidances for LAI formulations;
  6) To develop discriminatory and predictive real time and accelerated drug release methods for IUS;
  7) To explore IVIVCs of long-acting periodontal drug products,
  8) To investigate release mechanisms of multivesicular liposomes.

# Role of GDUFA Research (Cont.)

- GDUFA funded research on long acting drug products (15 grants/contracts):
  1) To obtain a better understanding of the impact of properties of PLGA polymers on product performance;
  2) To explore biorelevant IVIVCs for biodegradable injectable PLGA microspheres;
  3) To investigate dissolution methods for PLGA microsphere and implant drug products that can discriminate formulations with manufacturing differences;
  4) To investigate potential peptide PLGA interactions during product manufacturing and use;
  5) To develop modeling tools to facilitate development of generic LAI formulation development as well as bioequivalence guidances for LAI formulations;
  6) To develop discriminatory and predictive real time and accelerated drug release methods for IUS;
  7) To explore IVIVCs of long-acting periodontal drug products,
  8) To investigate release mechanisms of multivesicular liposomes.

# Session II Speakers

10:30 – 11:00 am

***"Characterization of PLGA polymers"***
Kinam Park, Ph.D
Showalter Distinguished Professor of Biomedical Engineering & Professor of Pharmaceutics
Purdue University

11:00 – 11:30 am

***"In vitro release from complex parenterals and development of IVIVCs"***
Diane. J. Burgess, Ph.D
Board of Trustees Distinguished Professor & Professor of Pharmaceutics
University of Connecticut

11:30 – 12:00 pm

***"Mechanisms of release from PLGA microspheres"***
Steven Schewendeman, PhD
Chair and Ara G. Paul Professor of Pharmaceutical Sciences & Professor of Biomedical Engineering
University of Michigan