Session II: Characterization of Complex Excipients and Formulations

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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


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
    
    \[ \text{PLGA} \]
    
    \[ m = \text{number of units of lactic acid} \]
    \[ n = \text{number of units of glycolic acid} \]
    
    • Ratio of lactic acid to glycolic acid
    • Molecular weight \( \sim 5\text{kDa} - 100\text{kDa} \)

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

    \[ R = H\left[\begin{array}{c}
    \text{CH}_3 \\
    \text{O}
    \end{array}\right]_{x}\left[\begin{array}{c}
    \text{O}
    \end{array}\right]_{y}\left[\begin{array}{c}
    \text{O}
    \end{array}\right]_{m}
    \]

    Sandostatin LAR depot (octreotide acetate microsphere)
Challenges to Develop Generic Complex Formulations (Cont.)

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

![Graph showing PLGA degradation during manufacturing of risperidone-PLGA microsphere.](image)

*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

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)](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
  – Doxorubicin hydrochloride injectable liposome
    • Single dose, two way crossover in vivo + liposome size distribution and additional characterization
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.

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.
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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