U.S. FOOD & DRUG ADMINISTRATION

Scientific Challenges in the Development of Complex Injectables

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Advanced Manufacturing Technologies: Accelerating Injectable Product Development and Addressing Drug Shortages

Impact of Drug Shortages

- Drug Shortages have a significant impact on patient care
- Each year FDA prepares a drugs shortage report
  - CY 2022 report was releases 6/2023
  - https://www.fda.gov/media/169302/
- Covers notifications and FDA actions to mitigate drug shortages

Solution to Shortages

- Availability of multiple suppliers
- Adaptable manufacturing that can increase production in response to demand
- Robust supply chain that is not constrained
  - API
  - Excipients
  - Container Closure
  - Device Constituent Parts

Generic Drugs

- In the US, generic drugs provide over 90% of dispensed prescriptions!
- Generic drugs are the primary pathway to provide multiple suppliers of pharmaceutical products
- Any solution to drug shortages relies on a viable, stable and robust generic drug industry

FDA Commissioners Analysis

- The “fundamental problem,” to hear Califf tell it, is that “we essentially have two drug industries in the U.S.”
- There’s the “innovator industry,” where Califf said he thinks "the prices are too high,” and then there’s the generics industry, where “a lot of the prices are too low.”
- “What I mean by that is that the price has been driven down below the cost of manufacturing and distributing the drug,” he said. “And we have an industry which is continuing to leave the U.S. because it’s not viable to run the business.”
- August 2023
  - FDA Commissioner Robert Califf critiques low generic drug prices (fiercepharma.com)

Simple or Not?

- You might think that generic drugs are copies and what CDER's Office of Generic Drugs does is simple.
- CDER's new drug programs have the gold standard in clinical trials, but they can be so powerful for decision making that we don't need to know why a drug works.
- In the generic program, we use pharmaceutical science and clinical pharmacology to identify what needs to be the same
  - so, we do not have to repeat clinical trials to provide access to competition.

Office of Research and Standards (ORS) Purpose

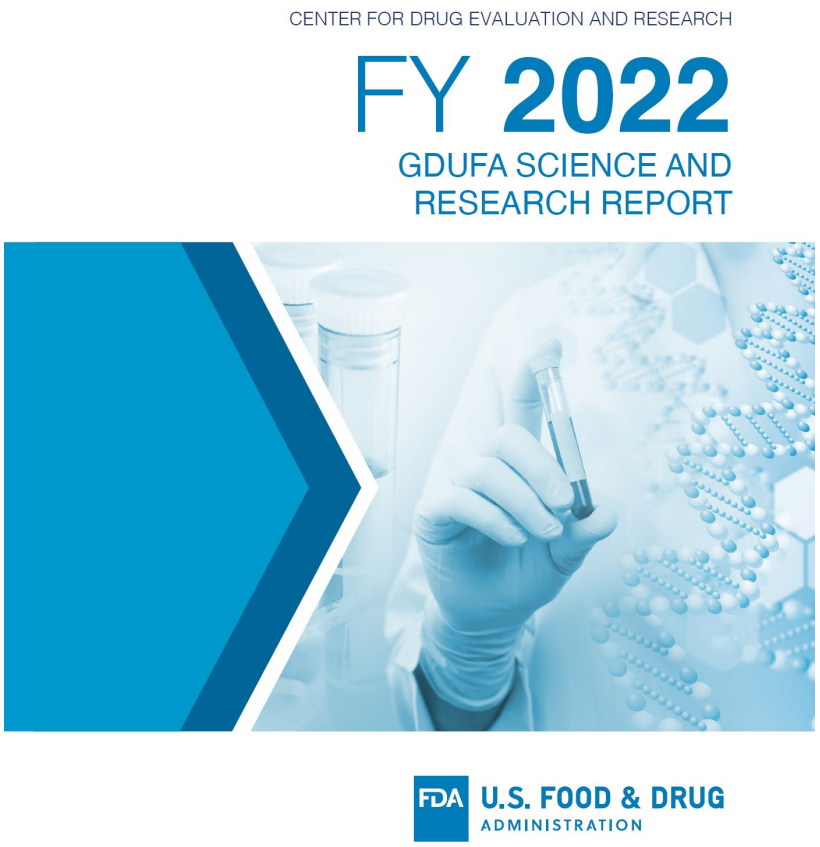
- We make bioequivalence studies for simple products more efficient.
- We spend significant efforts on establishing the possibility of generic competition for complex products (inhalation, dermal, long-acting injectable or drug-device combination products).
- We coordinate lab research to characterize complex products and build models to describe and predict what they do.

Unique Features of GDUFA Research

- Tight integration between research and scientific advice to generic applicants
  - Product-Specific Guidance (PSG)
    - Written by staff doing research
  - Pre-ANDA Meetings
    - Led by staff doing research
- Focus on complex generics

GDUFA Science and Research Report

- The FY2022 GDUFA Science and Research Report is available at: https://www.fda.gov/drugs/generic-drugs/fy-2022-gdufa-science-and-research-report
- It highlights the scope and impact of **all** GDUFA-supported research across FDA
- High transparency to the generic industry on what we use GDUFA resources for



Key Scientific Challenges for Generic Injectables

- Regulations around Q1 and Q2 sameness
- Sameness for complex injectables
  - Advances in analytical methods and in vitro BE
- Bioequivalence (BE) for long acting or locally acting products

Q1 and Q2

- FDA's regulations say that generic injectables must have the same active and inactive ingredients (Q1) in the same amounts (Q2) as their reference listed drug
  - Exception for buffers, antioxidants, and preservatives
  - FDA's interpretation is that +/- 5% difference is acceptable for non-exception excipients

Q1 and Q2

- What is a generic product uses a different amount of pH adjuster?
  - Many injectables are manufactured with QS for pH adjustment to the appropriate pH
    - QS for RLD and QS for generic are considered the same
    - If either uses a fixed amount => ???

pH Adjuster Guidance

- April 2022, FDA Guidance "Considerations for Waiver Requests for pH Adjusters in Generic Drug Products Intended for Parenteral, Ophthalmic, or Otic Use"
- Describes how to request a waiver of the Q1 Q2 requirement for changes in pH adjusters
  - A small step toward a better world!

Other non Q1-Q2?

- Applicants that want to manufacture a non Q1 Q2 product that is not covered by this guidance generally need to submit a new drug application (NDA)
  - Not a great use of the NDA process which is intended to evaluate new safety and efficacy data

Other Elements of Sameness

- Generics must have the same dosage form, route of administration and strength as their RLD
- Suitability Petitions allow a generic applicant to seek approval of a product that differs from the RLD

Suitability Petitions

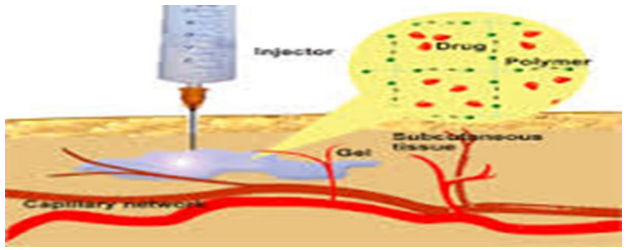
- Generally, FDA will only approve a suitability petition when no new clinical studies are needed
  - Pediatric study requests often attach to new dosage forms
- For injectables, suitability petitions that provide new strengths or container sizes are most common
  - These can provide flexible dosing and minimize waste

Complex Injectables

- Definition: Generally, all non-solution injectables are considered complex products by the GDUFA commitment letter

Long Acting Injectables

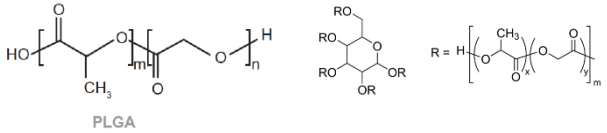
Brand	Drug	Route	Dosing frequency	Dosage Form	Local (L) or Systemic (S) action
RISPERDAL CONSTA	Risperidone	i.m.	2 weeks	Microsphere	S
VIVITROL	Naltrexone	i.m.	1 month	Microsphere	S
LUPRON DEPOT	Leuprolide	i.m.	1, 3, 4, 6 months	Microsphere	S
BYDUREON	Exenatide	s.c.	1 week	Microsphere	S
ZOLADEX	Goserelin	s.c.	1, 3 months	Implant	S
ELIGARD	Leuprolide acetate	s.c.	1, 3, 4, 6 months	In-situ gel	S
EXPAREL	Bupivacaine	s.c.	Single dose	Liposome	L
Mirena	Levonorgestrel	Intrauterine	5 years	Intrauterine device	L
Estring	Estradiol	Intravaginal	90 days	Ring	L
Sinuva	Mometasone furoate	Sinus	90 days	Implant	L



- Challenges for Generics
- Material Science of the Release Controlling Polymers
- PK study designs for month long dosing

Q1 Polymer Sameness

- Poly esters
  - PLG copolymers
  - PLA polymers



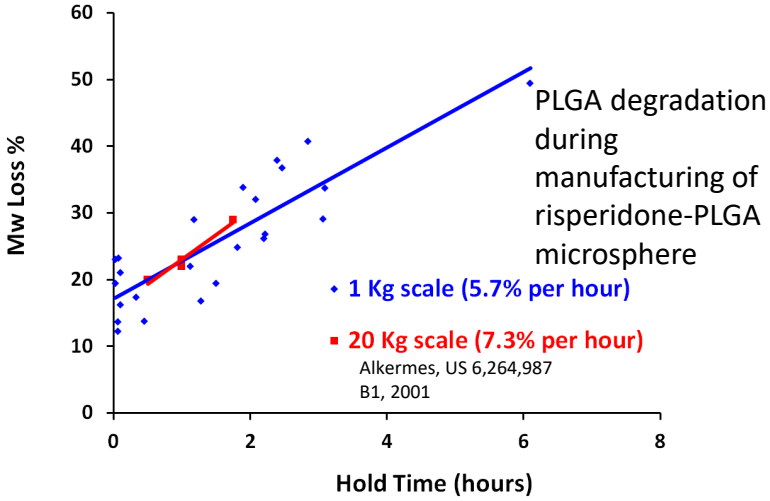
Should provide comparative physicochemical data on PLA/PLGA polymers extracted from the FINISHED Test product and the reference listed drug (RLD)

- 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

Garnera 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.

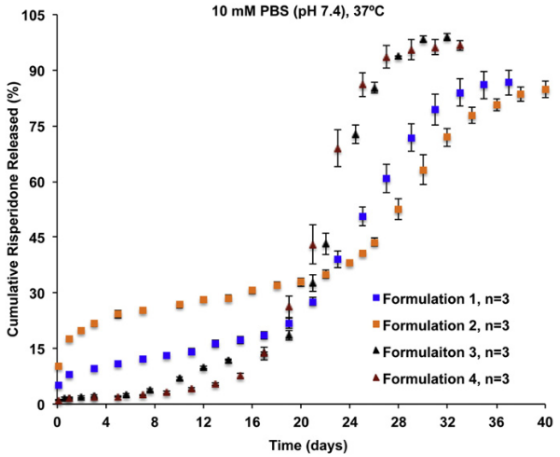
Q1 Polymer Sameness

- Impact of manufacturing conditions on complex inactive ingredients



PLGA degradation during manufacturing of risperidone-PLGA microsphere

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

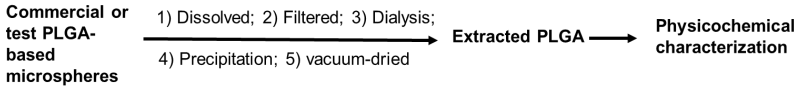


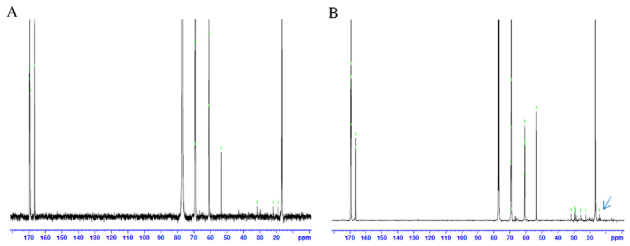
In vitro release profiles of the formulation composition equivalent risperidone microspheres with manufacturing differences obtained using USP apparatus 4 method at 37 °C in 10 mM PBS (pH 7.4)

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

Q1 Polymer Sameness

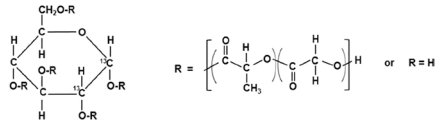
Challenge: Complex reverse engineering as manufacturing process can change PLGA properties
GDUFA research: developed a protocol to extract PLGA from the finished product and developed characterization methods for PLGA.

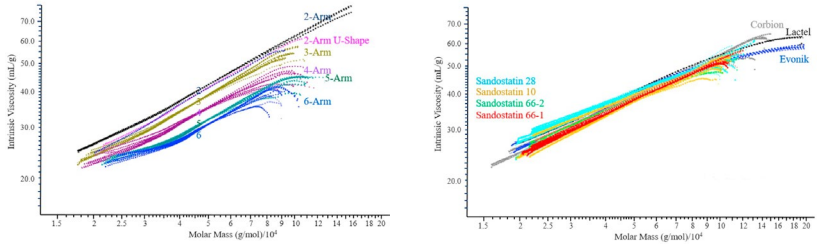




Int. J. Pharm. 495 (2015) 87–92
Grant U01FD05168

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

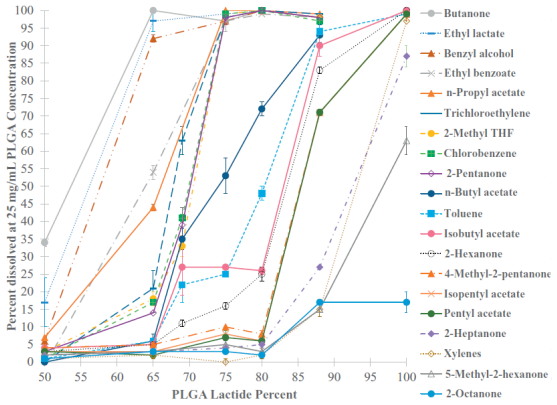




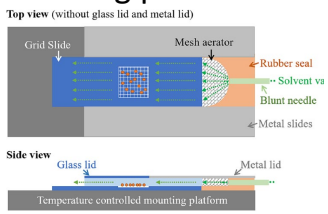
J. Control. Release 204 (2019) 75-89
Contract HHSF223201710123C

Q1 Polymer Sameness

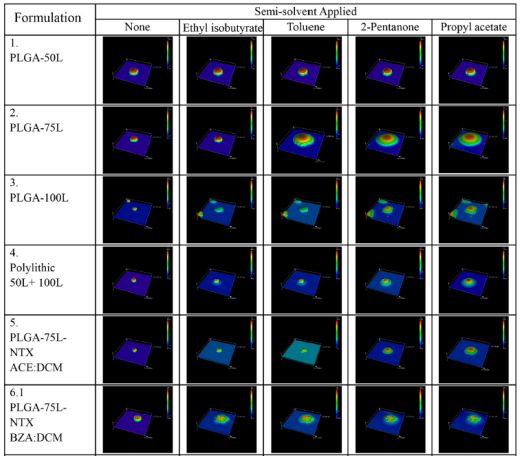
Challenge: Difficult to characterize products containing more than one PLGA
GDUFA research: Semi-solvents were studied to develop method to separate PLGAs based on different lactide to glycolide ratio. SAVI showed potential to reveal composition of PLGA microspheres and to probe structural arrangement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

Approval of PLGA based ANDA

- Three ANDA for PLGA based generics were approved in 2023!
  - *ANDA 213195 for Naltrexone for Extended-Release Injectable Suspension*
  - *ANDA 214068 for Risperidone for Extended-Release Injectable Suspension*
  - *ANDA 210317 for Octreotide Acetate for Injectable Suspension*
- The scientific foundation provided by GDUFA regulatory science program was essential

Lessons Learned

- A scientific investment program that is
  - directly focused on solving regulatory challenges
  - seeks constant stakeholder input
  - engages leading scientific experts
- Can impact drug product availability and introduce new technologies into the generic drug industry
- Can be a model for accelerating product development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