
Everyone deserves confidence
in their *next* dose of medicine.
Pharmaceutical quality
assures the
availability,
safety,
and efficacy
of *every* dose.

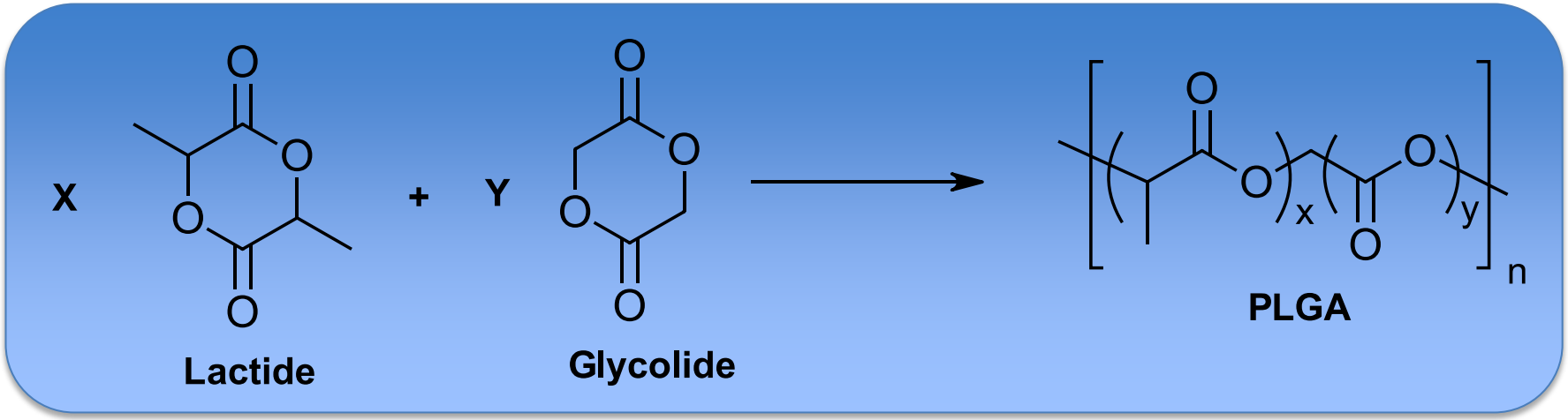
Long-Acting Injectable Drug Products Containing Poly(lactic-co-glycolic acid) (PLGA)

Vasiliy Korotchenko, Ph.D.

Division of Pharmaceutical Quality Assessment IV
Office of Product Quality Assessment I (OPQA I)
Office of Pharmaceutical Quality
Center of Drug Evaluations and Research, U.S. FDA

Presentation Objectives

- ✓ To share FDA expectations regarding comparative characterization studies for generic PLGA-based drug products
- ✓ To facilitate the development of generic PLGA-based drug products



- Poly(lactic-co-glycolic acid) (PLGA) is a polyester copolymer of lactide and glycolide with variable ratio of components.
- PLGA is biocompatible and biodegradable, making it a suitable vehicle for the controlled delivery of active ingredients (small molecules, peptides, macromolecules).
- For example, parenteral drugs formulated with active ingredient entrapped in a PLGA matrix, form a subcutaneous or intramuscular depot upon dosing.
- Active ingredient is slowly released from this depot by hydrolysis-mediated degradation of PLGA.
- The drug release profile can be modulated in wide interval by modifying the PLGA polymer properties.
- Frequency of administration for approved drug products ranges from once per week (e.g., BYDUREON® (Exenatide extended-release) to once per several months (e.g., ELIGARD (Leuprolide Acetate) for injectable suspension).

Regulatory Challenges for Development of Generic PLGA-Based Injectables

- There are about twenty approved brand PLGA-based injectables, and some of them approved more than 30 years ago.
- To demonstrate bioequivalence, generic injectable products need to be qualitatively (Q1) and quantitatively (Q2) the same to the corresponding RLD (with exception of preservative, buffer, or antioxidant).
- However, the characterization of the PLGA excipient in comparison to that of the RLD can be challenging and may require extensive testing.
- Furthermore, PLGA properties in the finished drug formulation may be different from those of PLGA itself, because of changes that occur during the manufacturing of the drug product. Therefore, it is not sufficient to characterize PLGA excipient prior to using it in the drug product.
- Comparative characterization of the finished generic drug product and the RLD, as well as characterization of the PLGA extracted from the drug product, represents a significant challenge in the development of generic PLGA-based products.
- Because of the challenges in sameness demonstration, there are only three approved PLGA-based injectables generics to date.

Approved Generic PLGA-Based Products

Drug Product	Active Ingredient	Dosage Form / Route of Administration	PLGA Characteristics Described in Product Labeling	Frequency of administration
Vivitrol	Naltrexone	Microsphere / Intramuscular	L/G = 75/25	Every 4 weeks
Risperdal Consta	Risperidone	Microsphere / Intramuscular	L/G = 75/25	Every 2 weeks
Sandostatin LAR Depot	Octreotide acetate	Microsphere / Subcutaneous	Glucose star polymer. L/G ratio is not provided in the Labeling	Every 4 weeks

Factors Affecting PLGA Degradation and Active Ingredient Release

- **PLGA composition (Lactide to Glycolide ratio): per Labeling, Lactide to Glycolide ratio (L/G) ranges from 50/50 to 85/15 in the approved drug products**
- **Initial molecular weight of the polymer and molecular weight distribution**
- **Crystallinity or glass transition temperature (Tg)**
- **Viscosity**
- **End-group functionalization**
- **Polymer structural shape (linear or branched)**
- **Drug concentration (ratio of API to PLGA)**

References:

Polymers (Basel), 2011, 3 (3): 1377–1397

International Journal of Pharmaceutics, 2020, 585, 119441

Expert Opinion on Drug Delivery, 2022, 19 (5), 559–576

Polymers, 2024, 16, 2606

Recommended Tests for Comparative Characterization of PLGA

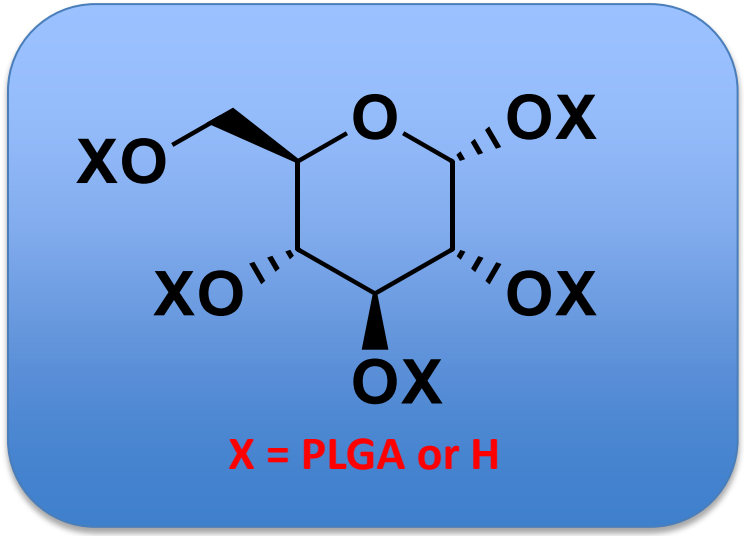
Parameters	
• Polymer composition: Lactide/Glycolide ratio	• Radius of gyration (Rg)
• Characterization of the end group	• Hydrodynamic radius (Rh)
• Molecular weight, including number-average molecular weight (Mn), weight average molecular weight (Mw), polydispersity (PDI)	• Crystallinity - Glass Transition Temperature (Tg)
• Inherent Viscosity	• Intrinsic Viscosity

- **It is recommended that these tests be performed on PLGA excipient prior to formulation and on PLGA extracted from the formulation (RLD and generic product).**
- **To capture the batch-to-batch variation of the PLGA properties, it is recommended that exhibit batches of the drug product be manufactured using multiple lots of PLGA.**

References

International Journal of Pharmaceutics, 2015, 495 (1), 87-92
Molecular Pharmaceutics, 2021, 18 (1), 18-32.
The AAPS Journal, 2021, 23: 92

Glucose Star PLGA



- For Glucose Star PLGA, several PLGA arms (typically 3-4) are polymerized from the central glucose core.
- For ANDAs referencing RLDs that include this class of PLGA in their formulation, it is recommended the same type of PLGA (star-branched) be used in the proposed generic product.

Additional characterization tests recommended for Star-PLGA
Presence of glucose. Distribution of PLGA arms and glucose core
Degree of branching (number of the branch units per molecule of Glu-PLGA
Heterogeneity of PLGA arms on a glucose core (Standard deviation of number of arms per core)

References:

Journal of Controlled Release, 2019, 304, 75-89

Expert Opinion on Drug Delivery, 2022, 19 (5), 559–576

Comparative Characterization of the Finished Product (for PLGA-Based Microspheres)

Parameters	
✓ Molecular weight	✓ API Assay
✓ Particle Size Distribution	✓ Water content
✓ Surface morphology of the microparticles	✓ API-related impurities
✓ Microsphere Porosity (specific surface area, pore size distribution)	✓ Content uniformity
✓ Distribution of the API in the polymer matrix	✓ Residual solvents from the drug product manufacturing process
✓ In Vitro drug release	✓ Extractables and leachables from the container closure system
✓ API crystallinity in the drug product, as applicable	✓ Potential leachables or impurities from unknown sources, trapped in the PLGA microspheres.

References

Molecular Pharmaceutics, 2020, 17 (11), 4141-4151

Journal of Controlled Release, 2021, 329, 1150-1161

The AAPS Journal, 2021, 23: 92

Advanced Drug Delivery Reviews, 2023, 198, 114857

Summary

- **The drug release profile of PLGA-based long acting injectables is affected by the properties of PLGA excipient.**
- **Comprehensive characterization of the PLGA and of the finished drug product is recommended for PLGA-based generic injectables.**

Acknowledgements

Cameron Smith

Young Jhon