Standardizing Characterization Test Methods Supporting Bioequivalence and Product Quality: PLGA/PLG (LG Polymer) Nomenclature and Quality Test Methods

Peng Zhang, Ph.D. Principal Scientist-excipients

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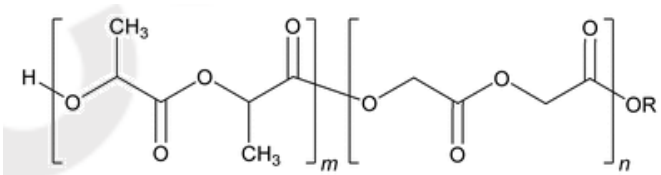
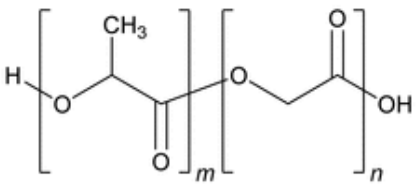
PLGs/PLGAs (LG Polymers): Critical Building Blocks to Building Quality Innovator and Generic Medicines

- Lactide-glycolide and lactic acid-glycolic acid polymers (PLGs and PLGAs, collectively referred as LG polymers) are biodegradable polyesters derived from these monomers and used in controlled-release formulations with varying drug-release periods.
  - Two main synthesis routes for this type of polymers (ring opening and polycondensation).





LG polymers
Traditionally annotated as PLGA (figure above), PLG (figure below), PLA, PL, Polyesters

Why are LG polymers preferred in drug formulations?

- Increases the therapeutic effect
- Improves biocompatibility
- Enhances biodegradability
- Tailored and controlled release: days to months
- High mechanical strength
- Reduces dosing frequency
- Minimizes side effects
- Improves patient convenience and compliance

- In 1989, FDA approved Lupron Depot, the first LG polymer-based drug product in the US.[1]
- So far, FDA has approved **28 LG polymer-based branded drugs[1]** and **6 LG Polymer-based generic drugs[2].**

[1]Park H, Otte A, Park K. Evolution of drug delivery systems: From 1950 to 2020 and beyond. J Control Release. 2022 Feb;342:53-6;
[2]ANDA #s 213195, 214068 , 210317, 218586, 211220, and 216589.

USP is Working to Address Bioequivalence and Product Quality Challenges: LG polymer Nomenclature and Quality Test Methods

Challenges

- lack of consistent nomenclature,
- variability, both batch-to-batch and manufacturer-to-manufacturer, due to lack of standardized methods and reference materials,
- limited eligibility of LG polymer products for compendial development.

- **In Feb 2017,** FDA and USP held a workshop on excipients. FDA emphasized the importance of advancing the science of excipient quality testing and selection and encouraged drug product innovation underlining the value of excipient function to drug product performance and equivalence.[1]
  - Several presentations from the FDA in the workshop covered PLG/PLGA polymer-based drugs.
  - **FDA noted that drug manufacturers encountered significant challenges in developing PLG/PLGA-based generic drugs due to inconsistent nomenclature of PLGs/PLGAs and complexities in PLG/PLGA characterization, consequently, FDA faced challenges in evaluating them.[2,3]**
  - **USP has been working towards addressing the challenges faced by drug manufacturers and regulators by developing advanced quality testing methods and monographs for complex excipient selection and regulatory evaluation.[4]**

[1]Dr. Robert Lionberger's opening presentation, 2017 FDA-USP Excipient Workshop, USP Rockville, MD.
[2]Wang Y, et al. American Pharmaceutical Review 2016 May-June: 14-21. [3]Wang Y, et al. The AAPS Jounal 2021: 23:92.
[4]Development of USP Compendial Standards for LG Polymers, poster, P. Zhang, H. Wang, C. Sheehan, CRS 2023, Jul. 2023 (Las Vegas, NV).

FDA Updated the Names of the 16 LG Polymers (in purple) Following the Naming System Proposed by USP's LG Polymer Stimuli Article

PLG/PLGA in FDA's Global Substance Registration System (GSRS)* in March 2024

No	Type	Item name before Sept 2022	Item name after Sept 2022[and]	UNII	FDA CDER IID listed (Yes/No)
1		POLY(DL-LACTIC-CO-GLYCOLIC ACID), (50:50; 12000 MW)	DL-Lactide and Glycolide (50:50) Copolymer 12000 Acid	WE369X5600	Yes
2		POLY(DL-LACTIC-CO-GLYCOLIC ACID), (50:50; 15000 MW)	DL-Lactide and Glycolide (50:50) Copolymer 15000 Acid	C329FPO0UC	No
3		POLY(DL-LACTIC-CO-GLYCOLIC ACID), (50:50; 30000 MW	DL-Lactide and Glycolide (50:50) Copolymer 30000 Acid	U5MPH5YWJ9	No
4		POLY(DL-LACTIC-CO-GLYCOLIC ACID), (50:50; 46000 MW)	DL-Lactide and Glycolide (50:50) Copolymer 46000 Acid	LQ35R50VR1	No#
5		POLY(DL-LACTIC-CO-GLYCOLIC ACID), (50:50; 63000 MW)	DL-Lactide and Glycolide (50:50) Copolymer 63000 Acid	QD923V64H3	Yes
6	PLGA (50:50)	POLY(DL-LACTIC-CO-GLYCOLIC ACID), ETHYL ESTER TERMINATED, (50:50; 7500 MW)	DL-Lactide and Glycolide (50:50) Copolymer 7500 Ethyl Ester	M5MB55C36J	No
7		POLY(DL-LACTIC-CO-GLYCOLIC ACID), ETHYL ESTER TERMINATED, (50:50; 12000 MW)	DL-Lactide and Glycolide (50:50) Copolymer 12000 Ethyl Ester	7SVE964630	No#
8		POLY(DL-LACTIC-CO-GLYCOLIC ACID), LAURYL ESTER TERMINATED, (50:50; 22000 MW)	DL-Lactide and Glycolide (50:50) Copolymer 22000 Lauryl Ester	RIU41B2XDV	No
9		POLY(DL-LACTIC-CO-GLYCOLIC ACID), LAURYL ESTER TERMINATED, (50:50; 64000 MW)	DL-Lactide and Glycolide (50:50) Copolymer 64000 Lauryl Ester	YK5TFZ8PC3	No
10	PLGA (55:45)	POLY(DL-LACTIC-CO-GLYCOLIC ACID), (55:45; 70000 MW)	DL-Lactide and Glycolide (55:45) Copolymer 70000 Acid	HFB0YWNRAP	No
11		POLY(DL-LACTIC-CO-GLYCOLIC ACID), (75:25;9500 MW)	DL-Lactide and Glycolide (75:25) Copolymer 9500 Acid	SJN700Q87A	No
12		POLY(DL-LACTIC-CO-GLYCOLIC ACID), (75:25; 20000 MW)	DL-Lactide and Glycolide (75:25) Copolymer 20000 Acid	58X445TH30	Yes
13	PLGA (75:25)	POLY(DL-LACTIC-CO-GLYCOLIC ACID), (75:25; 140000 MW)	DL-Lactide and Glycolide (75:25) Copolymer 140000 Acid	1SIA8062RS	No
14		METHYL POLY(DL-LACTIC-CO-GLYCOLIC ACID), (75:25;9500 MW)	DL-Lactide and Glycolide (75:25) Copolymer 9500 Methyl Ester	I8DU4QS1I2	No
15	PLGA (80:20)	POLY(DL-LACTIC-CO-GLYCOLIC ACID), (80:20; 27000 MW)	DL-Lactide and Glycolide (80:20) Copolymer 27000 Acid	K6S9F6373P	No
16	PLGA (85:15)	POLY(DL-LACTIC-CO-GLYCOLIC ACID), (85:15; 23000 MW)	DL-Lactide and Glycolide (85:15) Copolymer 23000 Acid	93PPD1S477	No
17	Polyglactin (poly(L-lactide-co-glycolide))	POLYGLACTIN 370	POLYGLACTIN 370	USA36U2P3T	No
18		POLYGLACTIN 910	POLYGLACTIN 910	51L8Z461QZ	No
19		POLYLACTIDE	POLYLACTIDE	459TN2L5F5	Yes
20		POLYLACTIDE (14000 MW)	POLYLACTIDE (14000 MW)	9J7G894K2M	Yes
21	Poly(D,L-lactide)	POLYLACTIDE (23000 MW)	POLYLACTIDE (23000 MW)	E14P5SD3J4	No
22		POLYLACTIDE (0.4 DL/G)	POLYLACTIDE (0.4 DL/G)	7B01B0FN51	No
23		LAURYL POLYLACTIDE (14000 MW)	LAURYL POLYLACTIDE (14000 MW)	AOA7A18GO2	No
24	Poly(L-lactide)	POLYLACTIDE, L-	POLYLACTIDE, L-	W92NDP347A	No

*https://gsrs.ncats.nih.gov/ginas/app/beta/home #FDA has no objections on developing its monograph.

Advance and Standardize Characterization Methods for LG Polymers

- USP LG Polymer Monographs include viscosity tests to differentiate among LG polymers, but stakeholders requested more advanced methods for comprehensive characterization.
- To address stakeholder feedback, USP excipient group, in collaboration with external sponsors and internal labs, have developed advanced methods via USP standalone general chapters and technical notes.

Item #	Publish time	PF	Title	Released or Proposed new USP Reference Standard (RS)	Comments
1	2024/09	50 (5)	<315> Nuclear Magnetic Resonance Spectroscopy Number-average Molecular Weight Determination for Lactide-Glycolide Polymers with Ester End Groups.	NA	Prospectus: https://www.uspnf.com/notices/gc-315-prospectus-20231229; **Currently official**
2	2024/09	50 (5)	<316> Size Exclusion Chromatography Molecular Weight and Polydispersity Determination for Lactide-Glycolide Polymers using Universal Calibration.	NA	Prospectus: https://www.uspnf.com/notices/gc-316-prospectus-20231229; **Currently official**
3	2025/07	51 (4)	<318> Nuclear Magnetic Resonance Spectroscopy Monomer Ratio Determination for Lactide-Glycolide Polymers	NA	Prospectus: https://www.uspnf.com/notices/318-gc-prospectus-20241025
4	2026/03	52 (2)	<319> Nuclear Magnetic Resonance Spectroscopy Block Length Determination for Lactide-Glycolide Polymers	NA	Prospectus: https://www.uspnf.com/notices/gc-319-prospectus-20251031
5	TBD	TBD	<324> Size Exclusion Chromatography Molecular Weight and Polydispersity Determination for Lactide-Glycolide Polymers	6 50:50 LG polymer calibrants and 7 75:25 LG polymer calibrants	In development

Advance and Standardize Characterization Methods for LG Polymers (cont'd)

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USP's characterization of commercial poly(lactic-co-glycolic acid) utilizing SEC-Multi-Angle Light Scattering and Refractive Index techniques via Absolute Method approach

Yixin Ren [a], Leo Liu [b], Yang Liu [c], Weidong Zhao [a], Peng Zhang [d], Hong Wang [d], Catherine Sheehan [d], Michael Ambrose [a]

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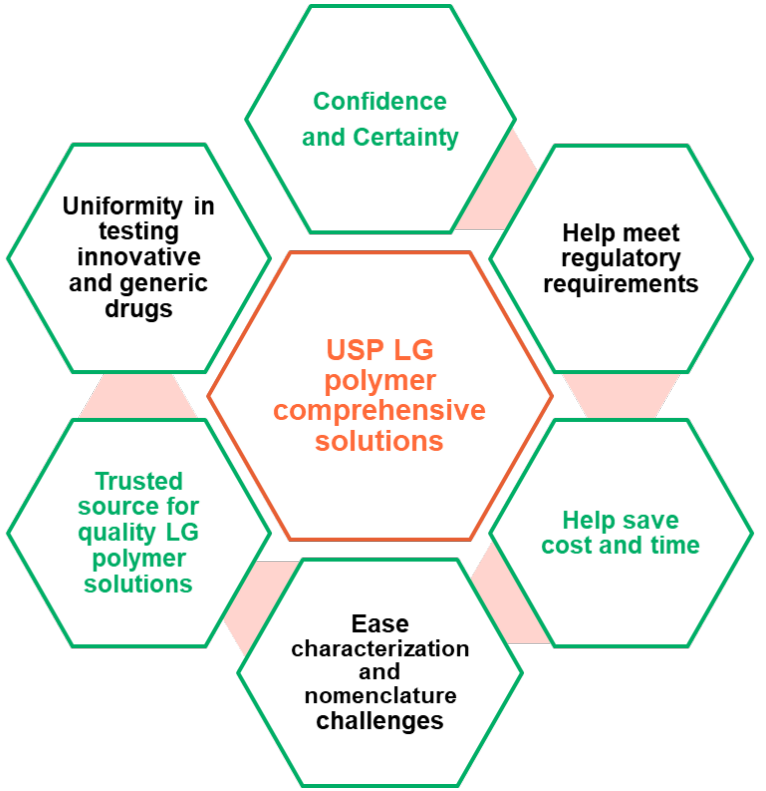
USP is developing a technical note based on this article, with a planned launch in Jun 2027

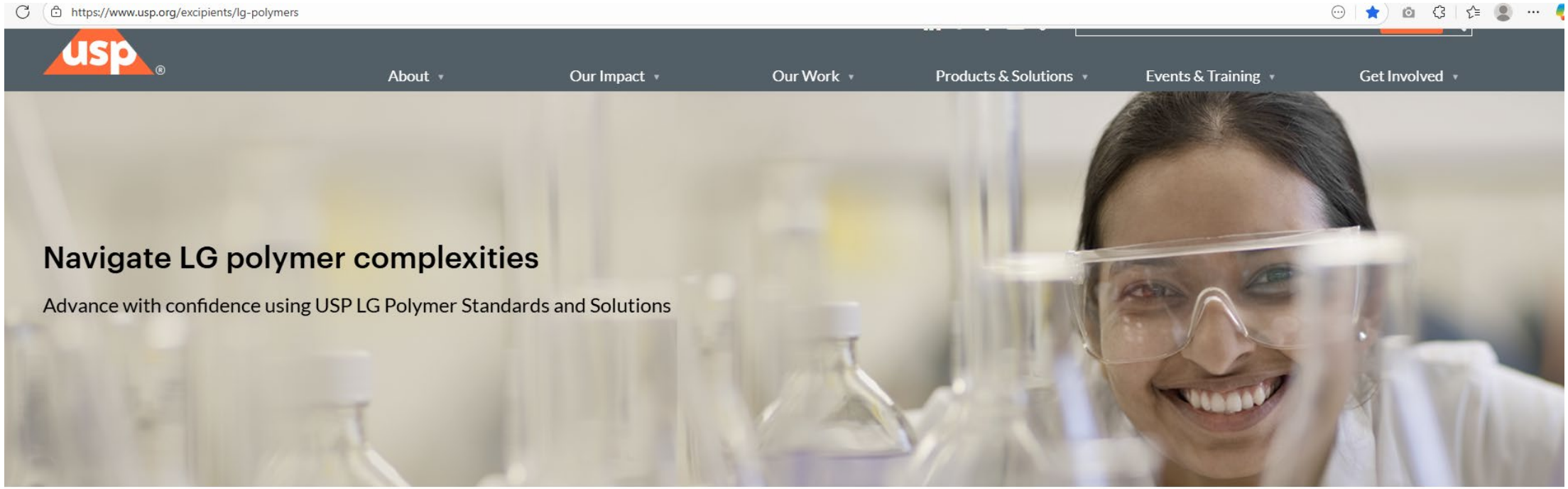
Simplify LG Polymer Nomenclature and Characterization Methods with USP's Suite of LG Polymer Tools

Monographs	USP Reference Standards	Stimuli article to address nomenclature challenges	General Chapters
DL-Lactide and Glycolide (50:50) Copolymer 12000 Acid, **Official**	USP DL-Lactide and Glycolide (50:50) Copolymer 12000 Acid RS **Cat No.1224300**	A Practical Approach to Compendial Nomenclature and Testing for Lactide and Glycolide Polymers and Related Polymeric Excipients, **PF 48 (2)**	<315> Nuclear Magnetic Resonance Spectroscopy Number-average Molecular Weight Determination for Lactide-Glycolide Polymers with Ester End Groups. **Official**
DL-Lactide and Glycolide (50:50) Copolymer 12000 Ethyl Ester, **Official**	USP DL-Lactide and Glycolide (50:50) Copolymer 12000 Ethyl Ester RS **Cat No.1224311**	USP Responses to Comments on Stimuli Article: "A Practical Approach to Compendial Nomenclature and Testing for Lactide and Glycolide Polymers and Related Polymeric Excipients ", **PF 49 (6)**	<316> Size Exclusion Chromatography Molecular Weight and Polydispersity Determination for Lactide-Glycolide Polymers using Universal Calibration. **Official**
DL-Lactide and Glycolide (50:50) Copolymer 46000 Acid, **Official**	USP DL-Lactide and Glycolide (50:50) Copolymer 46000 Acid RS **Cat No.1224322**		<318> Nuclear Magnetic Resonance Spectroscopy Monomer Ratio Determination for Lactide-Glycolide Polymers **PF 51 (4)**
DL-Lactide Homopolymer 14000 Acid, **Official**	USP DL-Lactide Homopolymer 14000 Acid RS **Cat No.1224333**		<319> Nuclear Magnetic Resonance Spectroscopy Block Length Determination for Lactide-Glycolide Polymers **PF 52 (2)**
DL-Lactide and Glycolide (50:50) Copolymer 63000 Acid **PF 51 (4)**		Analytical Reference Material (ARMs)	Case study, peer-reviewed journal article, education course, etc.
DL-LG (75:25) Copolymer 20000 Acid **PF 51 (4)**		**19 LG polymer ARMs of different ratios, molecular weights, and end group, with 8 already launched.**	**Available on USP LG Polymer Webpage**
DL-Lactide and Glycolide (85:15) Copolymer 23000 Hexanediyl Ester **PF 52(3)**			

Technical expertise derived from USP's years of quality standards development



USP LG Polymer Webpage: Featured resources like Flyers, Case Studies, Toolkits, USP Education Courses and more



USP / Our Work / Excipients

Lactide-glycolide or lactic acid-glycolic acid (LG) polymers

(Poly (lactic-co-glycolic acid), (PLGA) polymers, Polylactic acid (PLA) polymers, Poly (lactide-co-glycolide) (PLG) polymers, and Polylactide (PL) polymers)

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