Compositional Sameness for Complex Polymeric Excipients: Progress and Remaining Challenges

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Outlines

- Introduction to compositional sameness requirements
- Case studies: information requirements for complex polymeric excipients
- Conclusions

When is demonstration of compositional sameness needed?

- Regulation[1] requires that generic drugs with parenteral, ophthalmic, and otic routes of administration contain “the same inactive ingredients in the same concentration as the reference listed drug”.
- “same inactive ingredients” is referred as qualitative (Q1) sameness
- “in the same concentration” is referred as quantitative (Q2) sameness

[1] 21 CFR 314.94(a)(9)(iii) and (iv)

Other triggers for demonstration of compositional sameness

In some cases, compositional sameness is recommended to follow bioequivalence studies outlined in the Agency's product-specific guidances (PSGs).

Active Ingredient:	Levonorgestrel
Dosage Form:	System
Route:	Intrauterine
Strength:	19.5 mg
Recommended Studies:	One in vitro bioequivalence study with supportive comparative studies and one in vivo/ex vivo bioequivalence study

To be eligible for the bioequivalence studies recommended in this guidance, the test (T) product should contain no difference in inactive ingredients or in other aspects of the formulation relative to the reference listed drug (RLD) product that may significantly affect the local or systemic availability of the active ingredient. For example, the T product can be qualitatively (Q1) [1] and quantitatively (Q2) [2] the same as the reference standard (RS) to satisfy no difference in inactive ingredients. [3]

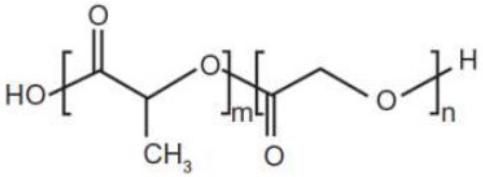
PSG on Levonorgestrel Intrauterine System (NDA 208224)

Q1Q2 evaluation of polymeric components

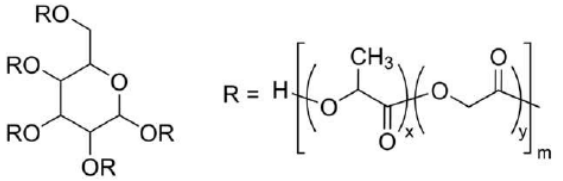
- Straightforward cases:
  - Polyethylene glycol (PEG)
  - Carboxymethylcellulose sodium
  - Ethylene vinyl acetate (EVA) copolymers
- Complex cases requiring additional information
  - Poly(lactide-co-glycolide) (PLGA)
  - Crosslinked hydrogel
  - Polydimethylsiloxane (PDMS) elastomer

Case#1: PLGA

- PLGA is a biodegradable copolymer composed of lactide and glycolide monomers that undergoes hydrolytic degradation in biological environments.
- PLGA functions as the primary rate-controlling excipient in more than 20 FDA-approved long-acting injectable and implantable drug products.
- Key polymer properties include molecular weight and weight distribution, molar ratio of lactide to glycolide, end group, inherent viscosity, glass transition temperature, polymer architecture (linear vs. branched), etc.
- Polymer characteristics can be altered during the manufacturing processes such as microencapsulation, extrusion and sterilization.



Linear PLGA

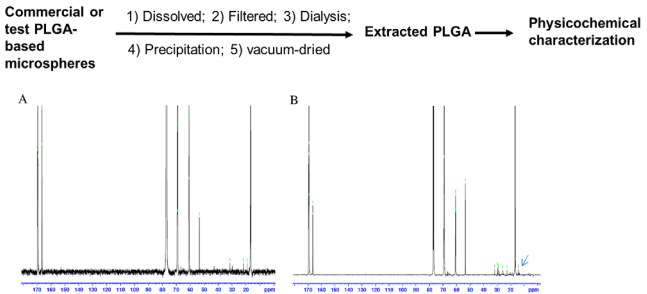


Glucose cored star shaped PLGA

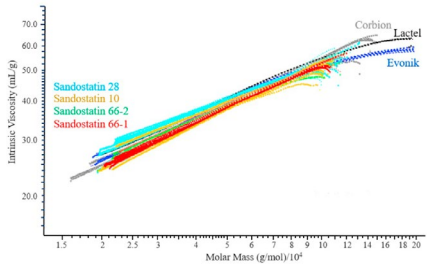
GDUFA research on PLGA characterization

GDUFA[1] research developed:

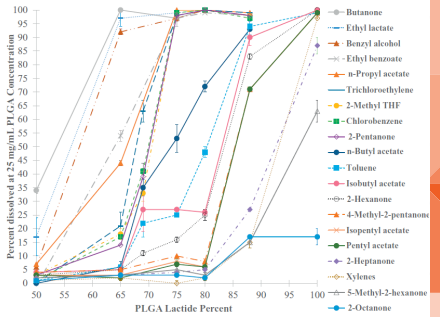
- Extraction and characterization protocol for PLGA analysis from finished drug products
- Advanced characterization methods for glucose-cored, star-shaped PLGA polymers
- Separation techniques for differentiating PLGAs based on different lactide-to-glycolide ratios



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



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



J. Control. Release 300 (2019) 174-184
Contract HHSF223201610091C

[1]Generic Drug User Fee Amendments (GDUFA)

Establish Q1 sameness for PLGA

- To support Q1 sameness of PLGA, provide comparative characterization data including polymer composition (molar ratio between glycolide and lactide), molecular weight and weight distribution, and PLGA architecture (e.g., linear or branched) on the PLGA polymer extracted from the test and the RLD products.
- Branch analysis should be provided for branched PLGA (e.g., glucose cored star shaped PLGA).
- For quality assessment, provide characterization on the extracted PLGA including but not limited to polymer end cap analysis, inherent viscosity, and glass transition temperature.
- For products using PLGA mixture, comparative characterization can be performed using PLGA mixture extracted from the finished products.

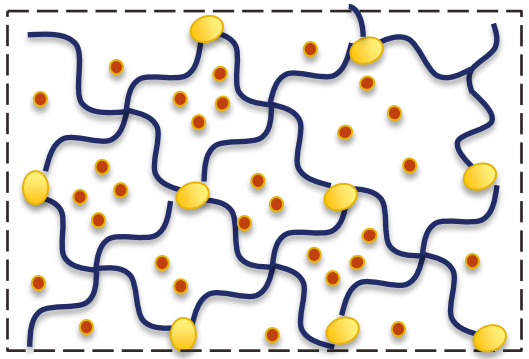
Remaining challenge of PLGA characterization

- Miniaturized drug products present significant practical challenges for reverse engineering and comparative characterization due to their limited material availability.
  - E.g., products such as DURYSTA and OZURDEX are extremely small (<1 mg) [1]
- To address these analytical limitations, GDUFA research is currently being conducted under Contract #75F40123C00192.
- More detailed updates on this research initiative will be presented at the upcoming FDA-CRCG Workshop: Visionary Standards: Advancing Science and Regulation in Generic Ophthalmic Products, November 19-20, 2025.

[1] *Mol Pharm.* 2025, 22(1):446-458

Case#2: Crosslinked hydrogel

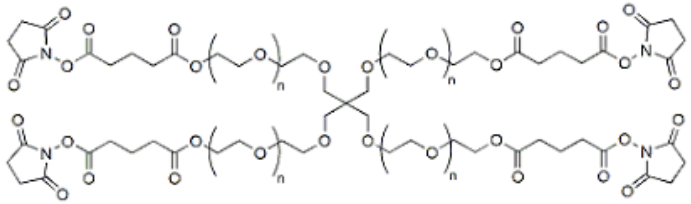
- Hydrogels are three-dimensional polymer networks characterized by high water content and the ability to absorb substantial amounts of aqueous solutions while maintaining their structural integrity.
- Chemical crosslinking methods create covalent bonds between polymer chains, resulting in the formation of stable hydrogel networks.



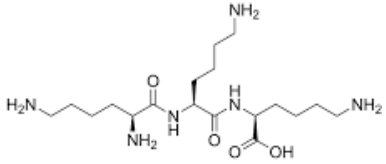
Bioeng Transl Med. 2020;5:e10158.

Example: DEXTENZA (dexamethasone ophthalmic insert)

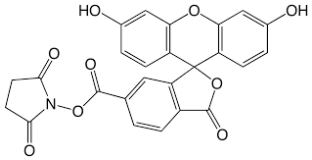
- DEXTENZA is a PEG-based hydrogel made of 4-arm polyethylene glycol (PEG) Nhydroxysuccinimidyl glutarate (20K), trilysine acetate, N-hydroxysuccinimide-fluorescein, sodium phosphate dibasic, sodium phosphate monobasic, water for injection[1].



4 arm PEG NHS



Trilysine



Fluorescein-NHS

- N-hydroxysuccinimde (NHS) ester reacts with primary amine, releasing N-hydroxysuccinimide as a leaving group.

[1]DEXTENZA drug labeling

Establish Q1Q2 sameness for crosslinked PEG-based hydrogel

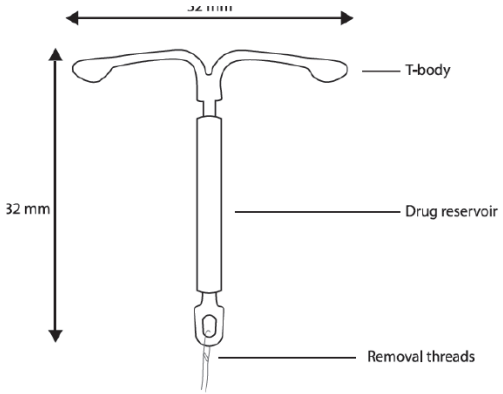
- It is noted that the crosslinked PEG polymers conjugated with fluorescein constitute the actual component in the finished product.
- To support Q1 assessment, applicants should provide detailed description on starting materials, ratios and concentrations of all starting materials and crosslinking method for producing the hydrogel.
- To support Q2 assessment, applicants should provide information on the amount of each starting material. Differences in Q2 could be justified by comparable mechanical properties. In addition, the amount of each starting material should not raise any potential safety concerns.
- An FDA internal research project was conducted to support product-specific guidance development on dexamethasone ophthalmic insert.
- Updates on this research and related regulatory considerations will be presented at the FDA-CRCG Workshop: Visionary Standards: Advancing Science and Regulation in Generic Ophthalmic Products (Nov 19-20, 2025)

Case#3 PDMS

- PDMS elastomers are commonly used as drug reservoir and release controlling excipients in intrauterine systems (IUS) and vaginal rings.
- PDMS is a crosslinked polymer formed by the curing of silicone prepolymers or copolymers and consisted of repeating structural backbone of (-Si-O-).
- Crosslinking methods:
  - Addition curing
  - Condensation curing
  - Peroxide curing
- Pre-polymers kit may contain addictive(s).

Int J Pharm. 612 (2022) 121383

Example: MIRENA (levonorgestrel-releasing intrauterine system)



- The reservoir is made of a mixture of levonorgestrel (LNG) and silicone (polydimethylsiloxane).
- The reservoir is covered by a semi-opaque silicone membrane, composed of polydimethylsiloxane and colloidal silica.

MIRENA drug labeling

GDUFA research relevant to PDMS compositional sameness

GDUFA research has developed scientific foundation necessary to evaluate PDMS compositional sameness.

- Development of analytical techniques to measure and characterize PDMS crosslinking density and related material properties
- Understanding of how PDMS crosslinking density affects drug release in IUS (Int J. Pharm. 612 (2022) 121383)
- Impact of curing chemistry (addition curing vs. condensation curing) and fillers on manufacturability and performance of LNG IUS (Int J. Pharm. 660 (2024) 124343)
- Impact of excipients (additives, fillers, lubricants) on formulation attributes and in vitro performance of LNG-IUSs (J Control Release. (2024) 370, 124-139)

Grant 1U01FD005443-01

Compositional sameness of PMDS-based IUS

- To support the Q1Q2 assessment, applicants should provide compositional information (e.g., PDMS chemistry, degree of crosslinking, quantity of each component), dimensional information (e.g., similar length, thickness of membrane) and mechanical properties.

Conclusion

- Demonstrating compositional sameness of a polymeric excipient is generally straightforward, but complex cases exist that require additional information such as comparative characterization to support sameness evaluation.
- In these complex cases, GDUFA-funded research has developed the analytical methods and scientific foundation necessary to support sameness evaluation.

Questions?

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