Considerations for Establishing Q1/Q2 Sameness of Complex Formulations

Complex Generic Drug product Development Workshop

Session 3: Complex Formulations/Dosage Forms

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Definition of Q1/Q2

- Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the reference listed drug (RLD).
- Q2 (Quantitative sameness) means that concentrations of the inactive ingredient(s) used in the test product are within ±5% of those used in RLD.

Need for Q1 and Q2 sameness

- Per regulations [21 CFR 314.94(a)(9)(iii-iv)]:
  - parenteral, ophthalmic, otic
- Per OGD's product-specific guidances:
  - e.g., Q1/Q2 sameness may be recommended in a PSG for using alternative methods to demonstrate BE in lieu of in vivo BE studies

Q1/Q2 formulation assessment

- When Q1/Q2 sameness is required or recommended, applicant may submit a controlled correspondence to request for Q1/Q2 formulation assessment
  - Draft Guidance for Industry, Controlled Correspondence Related to Generic Drug Development https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm583436.pdf

PLGA-based drug products

- PLGA (poly(lactic-co-glycolic acid)) is used in FDA approved drug products for a variety of formulations
  - Microspheres, in situ forming gel, implants
  - 17 approved new drug products use PLGA excipient,
  - Currently, there are no approved generic products with PLGA excipient
- PLGA polymer is noncompendial excipient
- In vivo performance relies on the polymer properties
- Polymer properties could be altered by manufacturing processes

Example: formulation table

Name of ingredient	Function	RLD		Proposed Test product	
		Qty in % w/w	mg/unit	Qty in % w/w	mg/unit
Front chamber (microsphere powder)					
Leuprolide Acetate					
gelatin					
DL-lactic and glycolic acid copolymer					
D-mannitol					
Second chamber (diluent)					
CMC-Na					
D-mannitol					
Polysorbate-80					
Water for injection					

A composition table alone is NOT adequate to assess Q1/Q2 equivalence of a PLGA based formulation

Q1/Q2 assessment on generic PLGA products

- Provide comparative characterization data on PLGA polymer from the Generic and RLD
- Characterization should include, but is not limited to: composition (L/G ratio), molecular weight and molecular weight distribution, polymer structure (i.e., linear or star), inherent viscosity, glass transition temperature, and polymer end-cap
- Should characterize the branch frequency if it is a star polymer
- If there are differences, need to provide justification on why these differences would not impact the safety or efficacy of the generic drug as compared to the RLD

Example: polymer characterization data

Table1. the L:G ratio of the PLGA polymers determined by 1H-NMR

Sample	% (mol) of lactide	% (mol) of glycolide
Test product	75	25
RLD product	75	25

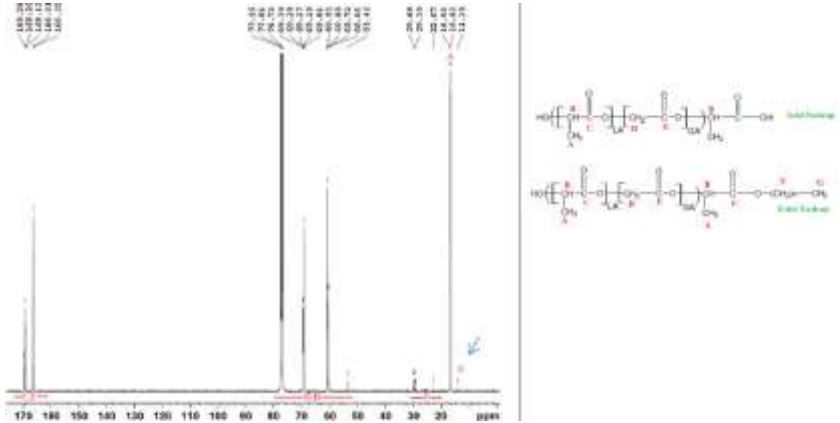
Table 2. Relative molecular weights measured by GPC

Sample	Mw	Mn	Mw/Mn
Test product	83000	49000	1.67
RLD product	82000	49000	1.67

Table 3. Average intrinsic viscosity (IV) of PLGA polymers

Sample	IV (dL/g)
Test product	0.50
RLD product	0.49

Characterization of polymer end cap using 13C-NMR



(International Journal of Pharmaceutics, 2015, 495:87-92)

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Common deficiencies

- Incomplete composition table (i.e., no information on diluent formulation provided)
- Lack of comparative PLGA characterization data from the Generic and the RLD product
- Incomplete or unacceptable polymer characterization data

For products containing microsphere and diluent

- If microsphere and diluent are copackaged, the Q1/Q2 sameness will be determined and commented on the whole product rather than individual component (i.e., diluent)
- Should provide the full formulation including both microsphere and diluent, if applicable
- One microsphere formulation and 3 diluent formulations will be considered as 3 formulations

Polymer characterization data

- Should provide comparative physicochemical data on PLGA polymers extracted from finished Test product and RLD
  - Not acceptable if using Certificate of Analysis from vendor
  - Not acceptable if characterizing raw polymer vs. polymer extracted from the RLD
  - Characterization should include, but 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

Summary

- In addition to composition table, comparative physicochemical characterizations on the PLGA polymer are needed to make assessment on Q1/Q2 sameness of PLGA-based products.

- Characterization should include, but 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.

- If microsphere and diluent are copackaged, the Q1/Q2 sameness will be determined and commented on the whole product rather than individual component (i.e., diluent).

- Applicant should provide sufficient validation data for methods used for polymer characterization in the ANDA submission.


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