Considerations for the Qualitative Sameness Evaluation of a Proposed Generic Formulation

FDA-CRCG Webinar on Excipients and Formulation Assessments of Complex Generic Products: Best Practices and Lessons Learned

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What is Q1/Q2

- Q1/Q2 is a term referring to inactive ingredient assessments in abbreviated new drug applications (ANDAs)
- 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

When is Q1 and Q2 Sameness Assessed?

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

Q1 Assessment of Complex Polymeric Excipients (Case #1)

- Additional comparative characterization of the proposed excipient and that of the RLD may be requested to support Q1 assessment of complex excipients.
- For example, **poly (D,L lactide-co-glycolide) (PLG)** is a biodegradable random copolymer used as the rate controlling excipient in ~20 long-acting drug products.
  - Formulation: microsphere, in situ forming gel, solid implant
- Biodegradation depends on multiple factors:
  - e.g., Polymer properties, manufacture method (e.g., exposure to water)
- Comparative characterization data is needed for proper assessment on Q1 sameness because polymer characteristics can be altered during manufacturing.

Common Missing Information

- Lack of comparative PLG characterization data from the Generic and the RLD product
  - Certificate of Analysis from vendor or claim to having the same excipient supplier is not sufficient
  - Characterizing the raw polymer to be used in the proposed test formulation vs. the polymer extracted from the RLD is not appropriate
- Incomplete polymer characterization data
- Incomplete composition table (i.e., no information on diluent formulation provided)

Q1 Assessment of Complex Excipients (Cont.)

- Example of PLG characterization data and analytical methods

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

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

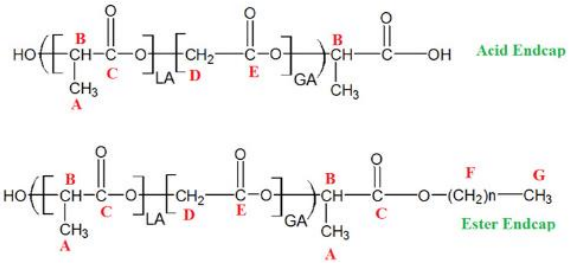
Table 2. Relative molecular weights measured by GPC

Sample	Mw	Mn	Mw/Mn
Test product	83000	49500	1.68
RLD product	82000	49000	1.67

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

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

Characterization of polymer L:G ratio, end cap, and structure



Outcomes from GDUFA Funded Research

J. Garner, et al. "A protocol for assay of poly (lactide-co-glycolide) in clinical products." *International Journal of Pharmaceutics* 495.1 (2015): 87-92.

S. Skidmore, et al. "Complex sameness: Separation of mixed poly (lactide-co-glycolide)s based on the lactide: glycolide ratio." *Journal of Controlled Release* 300 (2019): 174-184.

J. Hadar, et al. "Characterization of branched poly (lactide-co-glycolide) polymers used in injectable, long-acting formulations." *Journal of Controlled Release* 304 (2019): 75-89.

J. Hadar, et al. "Method matters: Development of characterization techniques for branched and glucose-poly (lactide-co-glycolide) polymers." *Journal of Controlled Release* 320 (2020): 484-494.

Consideration for Q1 Sameness of PLG-Based Products

- Provide comparative characterization data on PLG 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, provide justification on why these differences would not impact the safety or efficacy of the generic drug as compared to the RLD

Q1 Assessment of Complex Polymeric Excipients (Case #2)

- Additional comparative characterization of the proposed excipient and that of the RLD may be requested to support Q1 assessment of a novel and/or complex non-compendial excipients.
- For example, **silicone elastomer (Polydimethylsiloxane, PDMS)** is a non-biodegradable polymer used as the drug reservoir and/or rate controlling excipient in intravaginal rings (IVRs) and intrauterine systems (IUSs). Generic IVRs and IUSs do not need to establish Q1 and Q2 sameness per regulation. However, formulation similarity (no significant differences in excipients) may be recommended as part of a BE approach.

Supportive Data for Formulation Similarity

- Example polymer: **Silicone elastomer**

Name of ingredient	Function	RLD		Proposed Test product	
		Qty in % w/w	mg/unit	Qty in % w/w	mg/unit
Excipient 1					
Silicone elastomer					

A composition table alone is NOT adequate to assess formulation similarity of the proposed IVR or IUS as the PDMS can be made using different polymerization chemistry with various by-products which need additional evaluation.

Provide information on starting materials, polymerization chemistry of the test material and comparative physicochemical characterization data on both the silicone elastomer in the FINISHED test product and the RLD.

Q1 Assessment of Excipients with Various Grades

Some excipients are supplied with various grades.

- For example, is the grade of **hydroxypropyl methylcellulose (HPMC)** specified in the composition table subject to Q1 assessment?

- What if the grade of HPMC in the proposed test formulation is different from the grade of HPMC in the RLD? Will FDA receive or refuse to receive the ANDA?

Q1 Assessment of Excipients with Various Grades (Cont.)

- Is the grade of **HPMC** specified in the composition table subject to Q1 assessment?

- Yes, grade is part of the Q1 assessment. Accordingly, HPMC is Q1 same where the test uses the same grade of HPMC as the RLD.

Q1 Assessment of Excipients with Various Grades (Cont.)

- What if the grade of HPMC in the proposed test formulation is different from the grade of HPMC in the RLD? Will FDA receive or refuse to receive the ANDA?

- It may be acceptable for a proposed test formulation to use a different grade of HPMC provided that sufficient justification (e.g., the grade is appropriate for the route of administration) and supportive data are included in the ANDA (i.e., data showing comparable viscosity between the test and reference products). The final acceptability is determined during assessment of ANDA. It is not addressed during the filing stage. However, an applicant with a test formulation for a drug product that is required or recommended to be Q1/Q2 same as the RLD that contains a different grade HPMC should include in the ANDA justification for supporting the formulation difference. FDA will refuse to receive the ANDA if no justification is provided.

Q1 Assessment of Excipient Mixtures

- Some excipients are mixtures.
- For example, **microcrystalline cellulose (MCC) and carboxymethylcellulose sodium (CMC)** are two inactive ingredients that are incorporated as a mixture in some nasal spray products.

Q1 Assessment of Excipient Mixtures (Cont.)

- Could it be acceptable to add MCC and CMC separately into a proposed test nasal formulation?

- No. The formulations where MCC and CMC added separately are generally NOT considered Q1 the same as when the MCC/CMC are added as a mixture, since the excipient mixture is a co-processed formulation of MCC and CMC, and not just a physical blend of the two components. There is a monograph for the MCC/CMC mixture as well as the individual components.

Q1 Assessment of Excipients with Overlapping Properties

- Polymeric excipients with overlapping chemical composition and properties may be considered Q1 the same, with information to support sameness.

- For example, **polyethylene glycol (PEG)-n castor oil** (n=30, 35) may be considered Q1 the same based on:
  - Comparable structural identity
    - Such as chemical structure and molecular weight distribution
  - Comparable properties and functionality
    - Such as critical micelle concentration (CMC) and micelle size distribution

How to Ask Q1 Questions

To obtain FDA's feedback on formulation Q1/Q2 sameness, an applicant may submit a controlled correspondence (CC) to request a Q1/Q2 assessment for up to three proposed formulations.

- If co-packaged as drug formulation and diluent, a Q1/Q2 assessment is made on the entire drug product and not on the individual components.

- *When comparative data is provided to support Q1 sameness of a complex excipient, you may ask:*
  - *If the proposed comparative characterization tests are appropriate for supporting Q1 sameness of the excipient(s) in your proposed test formulation.*

- When the excipient in the proposed test formulation have overlapping properties/chemical composition, but may not be identical to the one used in the reference listed drug (e.g., PEG-n castor oil)
  - You should provide data/justification to support why the proposed test formulation should be considered Q1 the same as the reference listed drug.

Summary

- Qualitative (Q1) sameness refers to the same inactive ingredients (identity) to the RLD.
- A bioequivalence approach may depend on the formulation sameness/similarity of the generic product to the RLD. Take the BE approach into consideration when framing formulation assessment questions to the Agency.
- When manufacturing process can alter properties/composition of polymeric excipients, provide rationale and supportive data (e.g., comparative molecular weight/weight distribution) for Q1 assessment.
    - Critical attributes of some complex excipients (e.g., PLG polymers) and related analytical methods have been discussed in publications produced by GDUFA funded research, which may serve as resources/references for supporting generic development https://www.fda.gov/drugs/generic-drugs/generic-drug-research-publications-resources
- When supplied as a mixture of excipients, a physical mixture of the individual components may not be Q1 to the formulated mixture of excipients.
- When an excipient is supplied with various grades, grade is part of the Q1 assessment.
- An applicant who wishes to seek approval for a generic drug product that is required or recommended to be Q1/Q2 same as the RLD but with a formulation containing a different grade of an excipient compared to the RLD should include in its ANDA justification for supporting the formulation difference. FDA will refuse to receive an ANDA absent justification for the difference in grade.
- The acceptability of a particular grade of the excipient in a proposed test formulation is determined during assessment of the ANDA.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