Scientific Challenges Related to Establishing Q1/Q2 Sameness—An Industry Perspective

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

December 6, 2022

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Introduction

This presentation focuses on scientific challenges related to establishing Q1/Q2 sameness as illustrated by parenteral-specific concerns.

21 CFR 314.94(a)(9)(iii) and (iv) and 314.127(a)(8)(ii)(B) and (C) specify (with certain permitted exceptions – *Preservative, Buffer or Antioxidant can be different, with justification*) that FDA will consider an inactive ingredient in, or the composition of, a generic drug product intended for parenteral, ophthalmic, or otic use to be unsafe unless it contains the same inactive ingredients (Q1/qualitative sameness) in the same concentration (Q2/quantitative sameness) as the RLD.

Outline

- Inconsistent or insufficient information in the RLD’s package insert
- Divergent opinions on Q1/Q2 sameness during CC vs ANDA review
- Disjointed Controlled Correspondence (CC) process
- Policy limitations

Inconsistent or insufficient information in the RLD's package insert

- The RLD package insert is a principal basis for generic parenteral formulation design.
- 21 CFR 201.100(b)(5)(iii) requires that label of a drug for administration by parenteral injection, shall disclose the quantity or proportion of all inactive ingredients, except that ingredients added to adjust the pH or to make the drug isotonic may be declared by name and a statement of their effect; and if the vehicle is water for injection, it need not be named.
- Instances when the information in RLD package insert is inconsistent or insufficient, creating scientific challenges for generic product development:
  - Mismatch in inactive ingredients between two sections of RLD PI
  - Chemical or technical grade disclosure of inactive ingredient (e.g., hydrate form, copolymer ratios).
  - Undisclosed ingredient listed late in RLD PI (seemingly hidden excipient within excipient)
  - Missing ingredient in RLD package insert (e.g., entrapment agent)
  - Qualitative listing, but no disclosure of quantitative levels

Divergent opinions on Q1/Q2 sameness during CC vs. ANDA review

- Agency's guidance about Q1/Q2 sameness during the CC process provides critical assurance to applicants.
- Significant time and resources are spent towards generation of CMC/BE data for submission of ANDA.
- Historically, in certain cases, compositions that were "cleared" as Q1/Q2 same by CC were later questioned/rejected during ANDA acceptance/review.
    - RTR issued for submitted ANDA
    - Q1/Q2 sameness questioned in under-review ANDA
    - Q1/Q2 sameness questioned in tentatively approved ANDA
    - Issuance of "revised" CC responses
- Improved CC process and real-time updates from Agency could prevent some Q1/Q2 sameness-related delays.

Disjointed CC process

- Per 21 CFR 201.100, pH adjusters at minimum need to be disclosed qualitatively in the RLD label.
- Q1/Q2 sameness CC proposals listing pH adjuster denied for several years. USRLD did not list pH adjuster; RLD brand in other health authorities and in patents listed pH adjuster.
- *Considerations for Waiver Requests for pH Adjusters in Generic Drug Products Intended for Parenteral, Ophthalmic, or Otic Use*; Draft Guidance for Industry (April 2022)
  - Provides some clarity on pH adjuster waivers
  - Needs to be further refined to address residual concerns about pH adjusters and other categories of inactive ingredients

Policy limitations

- Agency's existing CC review policy has limitations, e.g., limits vital communication with applicants.
- Publication of pH adjuster guidance addressed Q1/Q2 issues related to pH adjusters in a scientific way, e.g., a §314.99 waiver request.
- H.R. 7032, *Increasing Transparency in Generic Drug Applications Act,* requires the FDA to inform ANDA applicants of critical information about the identity of ingredient(s) that cause a proposed generic product not to be Q1/Q2 the same as the RLD and the direction of any identified deviation.

Summary

- RLD’s package insert with inconsistent or insufficient information and review discrepancies in CC process present scientific challenges in establishing Q1/Q2 sameness.
- Scientific challenges in establishing Q1/Q2 sameness amplify delays in patient access to generic medicines.
- Agency’s issuance of the “pH adjuster guidance” is a positive step.
- Agency’s current CC review policy has limitations.
- Policy changes, such as demonstrated in HR 7032, are in the right direction.