Considerations for Waiver Requests for pH Adjusters in Generic Drug Products Intended for Parenteral, Ophthalmic, or Otic Use – Guidance Implementation in Q1/Q2 Assessment

CRCG 2022: Excipients and Formulation Assessments of Complex Generic Products: Best Practices and Lessons Learned

Session 4: Scientific Challenges and Considerations During Formulation Development

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- This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Outline

- General overview of scientific thinking on the role of pH adjusters
- Hypothetical examples of pH adjuster Q1/Q2 assessment
- Will deny or may deny situation
- Supportive information for pH adjuster change

Regulatory Background

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

- Q1 - Same inactive ingredients
- Q2 - Same concentration
  - OGD interprets Q2 sameness to mean a concentration that is within 95-105% of the reference listed drug (RLD) concentration

Regulations permit differences in certain inactive ingredients for drug products intended for parenteral, ophthalmic, or otic use, commonly referred to as “exception excipients,” if the ANDA contains sufficient information to demonstrate that any differences do not affect the safety or efficacy of the drug product

- pH adjuster is not one of the exception excipients for drug products intended for parenteral, ophthalmic, or otic use. However, a waiver of the inactive ingredient requirements in 314.94(a)(9)(iii)-(iv) for a difference in pH adjuster in a generic drug product intended for parenteral, ophthalmic, or otic use may be appropriate (See draft guidance, *Considerations for Waiver Requests for pH Adjusters in Generic Drug Products Intended for Parenteral, Ophthalmic, or Otic Use* (April 2022)).

Role of pH Adjusters

Role of pH Adjuster

1. pH Adjuster Acts Alone

- A pH adjuster is commonly an acid or base which is used to change the equilibrium concentration of hydronium ions [H_3O^+] in solution (i.e., the pH). Therefore, the pH value is routinely used to control the amount of pH adjuster added. For example,

$$HCl + H_2O \rightleftharpoons H_3O^+ + Cl^-$$

- Drug products express the quantity of pH adjuster used as:

  - Fixed amount
  - *quantum satis* (*q.s.*), which means the quantity added is as much or as little (which may be none) as necessary to achieve a specified pH range for any given batch of drug product. Thus, this specified pH range of the drug product is the primary aim, and the amount of pH adjuster used to achieve the pH of the drug product is adjusted accordingly.

Role of pH Adjuster

2. pH Adjuster Acts as Part of a Buffer

- A buffer is an aqueous solution of either a weak acid and its conjugate base or a weak base and its conjugate acid, which is resistant to changes in pH upon addition of an acidic or basic component.

- Because a buffer contains at least one conjugate acid/base pair, when a pH adjuster is added to shift the equilibrium between the conjugate acid/base pair, **the pH adjuster becomes part of the buffer**, for example:

$$NaOH + HOAc \rightleftharpoons NaOAc + H_2O$$

NaOH addition to an acetic acid-sodium acetate buffer converts some acetic acid to sodium acetate.

Role of pH Adjuster

3. pH Adjuster Acts as an in-situ Converter

- In achieving its intended purpose (i.e., adjusting the pH), a pH adjuster may also interact with components in the formulation to form a salt. For example, a simple neutralization reaction as shown below can occur where a base inactive ingredient (XOH) is neutralized by adding hydrochloric acid (HCl), which may also be used as a pH adjuster, to form the salt of the inactive ingredient (XCl) and water:

$$HCl + XOH \rightarrow XCl + H_2O$$

- To the extent a pH adjuster is used to convert the active pharmaceutical ingredient (API) to form the API salt (i.e., in-situ converter), the pH adjuster is not included in the Q1/Q2 assessment because it becomes part of the *active ingredient*. If excess pH adjuster is used, that excess amount is generally considered an *inactive ingredient* subject to the Q1/Q2 assessment.

Hypothetical Case Studies

- In next few slides, hypothetical examples are provided to highlight some of FDA's considerations for evaluating a 314.99(b) waiver request during the scientific assessment of the ANDA.
- Examples are intended to illustrate instances when a 314.99(b) waiver may be acceptable in an ANDA, but do not constitute "grant" scenarios.
- A decision to grant a waiver request is based on scientific evaluation of the specific facts of an individual ANDA, including the supporting documentation and justification submitted for the specific waiver request.

Hypothetical Scenarios For pH Adjuster Q1 Difference

Use of pH Adjuster		Q1 Same?
RLD Product	**Test Product**	
Used pH adjuster	Not used	No
Not used	Used pH adjuster	No
Used pH adjuster A	Used pH adjuster B	No

- Possible Q1 differences:
  - Use of a different pH adjuster
  - Omission of a pH adjuster in the test product
  - Addition of a pH adjuster in the test product

Hypothetical Scenarios
For pH Adjuster Q2 Difference

pH Adjuster Amount		Q2 Same?^
RLD Product	**Test Product**	
q.s.	q.s.	Yes
q.s.	Fixed	Yes
Fixed	q.s.	No
Fixed	Fixed	Yes (based on % difference*)
		No (based on % difference*)

* % difference = [(Test-RLD)/RLD * 100%]
^Quantitative sameness generally is interpreted by OGD to mean a concentration that is within 95-105% of the RLD concentration.

A proposed drug product with a formulation that contains more than a 5% difference in concentration of a pH adjuster compared to the RLD is considered not Q2 the same to the RLD

- Fixed vs q.s.
- Fixed vs Fixed

Hypothetical Example 1: Q1 Difference Injectable Suspension

Ingredient[&]	RLD	Proposed Test
Inactive Ingredient - 1	A	A
pH Adjuster	Hydrochloric Acid (q.s.)	--
	0.1 N Sodium Hydroxide (q.s.)	0.1 N Sodium Hydroxide (q.s.)

& Only critical information shown and not full formulation

- pH adjuster is not an exception excipient under 21 CFR 314.94(a)(9)(iii) for Injectable suspensions.
- May be acceptable to waive the inactive ingredient requirement, if scientifically justified.
- Possible supporting data: Comparable physicochemical data (e.g., pH, osmolality, and other properties as appropriate) between Test and Reference Standard products.

Hypothetical Example 2: Q1 Difference Injectable Solution

Ingredient[&]	RLD	Proposed Test
Inactive Ingredient - 1	A	A
Inactive Ingredient - 2	B	B
Citric Acid, Anhydrous	--	X mg/mL

& Only critical information shown and not full formulation

- Test formulation contains citric acid anhydrate and listed as a buffer by the applicant.
- Citric acid is not a buffering agent if there is no citrate salt or conjugate base added to the test formulation or defined at a level to form a buffering system with citric acid. The main function of citric acid in this case is a pH adjuster.
- Once citric acid function is correctly identified as a pH adjuster, may be acceptable to waive the inactive ingredient requirement, if scientifically justified.
- Possible supporting data: Comparable physicochemical data (e.g., pH, osmolality, and other properties as appropriate) between Test and Reference Standard products; supportive information with respect to the safety of the proposed qualitative difference in pH adjuster.

Hypothetical Example 3, Q2 Difference Injectable Solution

Ingredient[&]	RLD	Proposed Test	% Difference*
Inactive Ingredient - 1	A	A	0
Inactive Ingredient - 2	B	B	0
pH Adjuster	0.1 N Sodium Hydroxide (X mg/mL)	0.1 N Sodium Hydroxide (q.s.)	> 5

& Only critical information shown and not full formulation; *Difference (%) = (Test-RLD)/RLD x 100

- pH adjuster, Sodium Hydroxide, is not Q2 the same as RLD.
- pH adjuster is not an exception excipient under 21 CFR 314.94(a)(9)(iii) for Injectable solutions.
- May be acceptable to waive the inactive ingredient requirement, if scientifically justified.
- Possible supporting data: Comparable physicochemical data (e.g., pH, osmolality, and other properties as appropriate) between Test and Reference Standard products; supportive information with respect to the safety of a proposed quantitative difference in pH adjuster.

Will Deny and May Deny Situations

Will Deny Situations

- FDA will deny a waiver request under 21 CFR 314.99(b) when the difference in pH adjuster is not acceptable for an ANDA. For example, if the difference in pH adjuster causes the final product to contain:
  - A different form of the API than the RLD in the final product
  - A novel inactive ingredient in the final product that has not been used in an FDA-approved drug product, the safety of which cannot be established without clinical testing

May Deny Situations

- FDA may deny a waiver request if the difference in pH adjuster impacts physical or chemical properties critical to the performance of the product or where those property changes raise potential safety concerns.
    - ANDA uses a different pH adjuster compared to RLD, and that difference gives rise to either a new counter-ion species not present in RLD or a different concentration of counter-ion species than the RLD.
    - Additionally, a change in counter-ion concentration or species may impact the physicochemical properties of complex formulations, which may alter performance of the drug product in ways that may not be appropriate for approval in an ANDA (e.g., final pH is different from the pH listed by the RLD).

Supportive information for pH adjuster change

Supportive Information for pH Adjuster Changes

Justifications for the difference in pH adjuster may include but are not limited to:

- Information, including reference to the Inactive Ingredients Database, that demonstrates the difference does not affect the safety of the proposed drug product
  - Use of proposed pH adjuster in FDA approved drug products for the same route of administration
  - Amount of pH adjuster can be considered safe based on the amount of this pH adjuster in FDA approved drug products for the same route of administration
  - Concentration of newly formed salt or acid/base species of the buffer does not affect the safety of the proposed drug product

- Physicochemical characterization information (pH, buffer capacity, osmolality, viscosity, electrophoretic mobility, etc., where applicable)

- Other relevant data or information
  - Differences in the amount of pH adjuster, the number or identity of pH adjusters, or both does not affect bioequivalence. For example, pharmacokinetic data from in vivo BE studies for non-solution products or in vitro release testing data from in vitro BE studies.

Reference

- Draft Guidance for Industry: Considerations for Waiver Requests for pH Adjusters in Generic Drug Products Intended for Parenteral, Ophthalmic, or Otic Use https://www.fda.gov/media/157655/download

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Questions?

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