Decoding the Guidance: *Considerations for Waiver Requests for pH Adjusters in Generic Drug Products Intended for Parenteral, Ophthalmic, or Otic Use**

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* Will be referred to as the “Guidance” throughout the presentation.

Presentation Outline	Presenter
▪ Objectives ▪ Regulatory Background ▪ Aim and scope of the Guidance	Amanda Jones, PhD
▪ Role of pH adjusters ○ pH adjuster acts alone ○ pH adjuster acts as part of a buffer ○ pH adjuster acts as an in-situ converter ▪ Supportive information to justify the difference in pH adjuster	Darby Kozak, PhD
▪ Will deny and may deny situations ▪ Hypothetical examples ▪ Recommendations for assessing primary safety concerns with pH adjuster difference(s) ▪ Content of 314.99(b) waiver request ▪ Timing and process for submission; decision on acceptability of waiver request ▪ Effect on eligibility to use certain approaches to show bioequivalence (BE) ▪ Mechanism to receive feedback from the Agency	Hee Sun Chung, PhD

Q&A and Panel Discussion		
Speakers and Panelists	Brittany Avaritt, PhD Bing Cai, PhD Melissa Mannion, PharmD, JD	Utpal Munshi, PhD Truong-Vinh (Vinh) Phung, PharmD

Objectives

- Provide an overview of the draft Guidance
- Describe the rationale for the Agency's recommendations for applicants requesting 21 CFR 314.99(b) waivers for qualitative (Q1) and quantitative (Q2) differences in pH adjuster between the proposed and reference listed drug (RLD) formulations
- Discuss examples of data which may be considered in support of 314.99(b) waiver requests
- Discuss timeline and process for submission and mechanism to receive feedback on waiver request from the Agency

Regulatory Background
Aim and Scope of the Guidance

Regulatory Background

- Section 505(j)(4)(H) of the FD&C Act prohibits approval of an ANDA if (i) the inactive ingredients are unsafe for use under the conditions prescribed, recommended, or suggested in the labeling proposed for the drug, or (ii) the type or quantity of inactive ingredients included or the manner in which the inactive ingredients are included is unsafe for use under such conditions.
  - Permits FDA to deny approval of an ANDA if "there is a reasonable basis to conclude that one or more of the inactive ingredients of the proposed drug or its composition raises serious questions of safety or efficacy." (21 CFR 314.127(a)(8)(ii)(A))
  - “FDA may identify changes in inactive ingredients or composition that may adversely affect a drug product's safety or efficacy" based on the Agency's "experience with reviewing inactive ingredients, and from other information available to it." (314.127(a)(8)(ii)(A))
- 21 CFR 314.94(a)(9)(iii) and (iv), and 314.127(a)(8)(ii)(B) and (C), further specify 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 (with certain listed exceptions) in the same concentration as the *RLD*.
  - Same inactive ingredients (qualitative sameness, Q1)
  - Same concentration (quantitative sameness, Q2)

Aim and Scope of the Guidance

- Assist ANDA applicants that reference an RLD intended for parenteral, ophthalmic, or otic use but are seeking approval of a drug that is Q1 or Q2 different from the RLD with respect to a pH adjuster(s)

- Share the Agency's scientific considerations for why certain Q1 or Q2 differences in pH adjuster(s) relative to the RLD may be acceptable in an ANDA

- Enable flexibility in the inactive ingredient requirements for pH adjuster differences via 314.99(b) waiver provision to help remove some barriers to the development and approvability of drugs intended for parenteral, ophthalmic, and otic use, where scientifically appropriate

When to Consider Submitting a 314.99(b) Waiver Request for pH Adjuster Difference: Q1 Difference

Use of pH Adjuster		Q1 Same?	Submission of a 314.99(b) waiver request necessary?
RLD Product	**Test Product**		
Used pH adjuster A	Not used	No	Yes
Not used	Used pH adjuster A	No	Yes
Used pH adjuster A	Used pH adjuster B	No	Yes

- To the extent a pH adjuster is used to convert the API to form the API salt (e.g., in-situ converter, solubilizing agent), 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.

When to Consider Submitting a 314.99(b) Waiver Request for pH Adjuster Difference: Q2 Difference

A proposed drug product with a formulation that contains more than a 5% difference in concentration of a pH adjuster compared to the RLD will need a 314.99(b) waiver request.

pH Adjuster Amount		Q2 Same?^	Submission of a 314.99(b) waiver request necessary?
RLD Product	Test Product		
q.s.	q.s.	Yes	No
q.s.	Fixed	Yes	No
Fixed	q.s.	No	Yes
Fixed	Fixed	Yes (based on % difference*)	No
		No (based on % difference*)	Yes

* % 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.

What the Guidance Does

- Describes the scientific principles regarding the role of pH adjusters in formulations that underlie FDA's current thinking on why certain pH adjuster differences may be acceptable in an ANDA
- Describes how FDA intends to evaluate a request for a waiver of inactive ingredient requirements for a Q1 or Q2 difference in pH adjuster
- Includes recommendations on the type of information that applicants should consider submitting with their waiver request, and the format and process for submitting such waiver requests
- Makes clear that waiver requests will be evaluated on a case-by-case basis to determine whether a particular difference in pH adjuster is scientifically acceptable and appropriate in an ANDA
  - Evaluating a waiver request is a fact-specific assessment within the context of a specific application and a specific 314.99(b) waiver request

Role of pH Adjusters & Supportive Information to Justify Difference in pH Adjuster

Role of pH Adjusters

General overview of scientific thinking on the role of pH adjusters and considerations for the scientific justification to support a waiver request.

- When a pH adjuster acts alone
- When a pH adjuster acts as part of a buffer
- When a pH adjuster acts as an in-situ converter

pH Adjuster Acts Alone

Role of pH Adjusters

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,

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

The amount of hydrochloric acid (HCl) pH adjuster added generates an equivalent amount of hydronium and chloride ions. Therefore, a measure of the hydronium ion concentration (i.e., pH) is correlated to the amount of HCl added.

Role of pH Adjusters

- Drug products often express the quantity of pH adjuster used as *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.
  - Possible Q1 differences:
    - Use of a different pH adjuster
    - Omission of a pH adjuster in the test product
    - Addition of a pH adjuster
  - Possible Q2 differences:
    - Fixed vs q.s.
    - Fixed vs fixed

Supportive Information for pH Adjuster Changes

- Identify any Q1 and/or Q2 differences in pH adjusters used.

- Provide justification in 314.99(b) waiver request for the difference in pH adjuster. Examples may include:
  - Information from Inactive Ingredients Database (IID)
    - Use of proposed pH adjuster in previously 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
  - Physicochemical characterization information (pH, osmolality, viscosity, etc.)
  - Other relevant data or information

pH Adjuster Acts as Part of a Buffer

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- 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.
  - Buffer is an exception excipient under 314.94(a)(9)(iii) & (iv) and OGD has approved generics with buffer differences.
  - A difference in buffer could change both counter ion and pH of the system, similar to what a pH adjuster does.

pH Adjuster Acts as Part of a Buffer

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

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

  - NaOH addition to a sodium phosphate monobasic-sodium phosphate dibasic buffer converts some sodium phosphate monobasic to sodium phosphate dibasic.

$$NaOH + H_2PO_4^- \rightleftharpoons HPO_4^{2-} + H_2O + Na^+$$

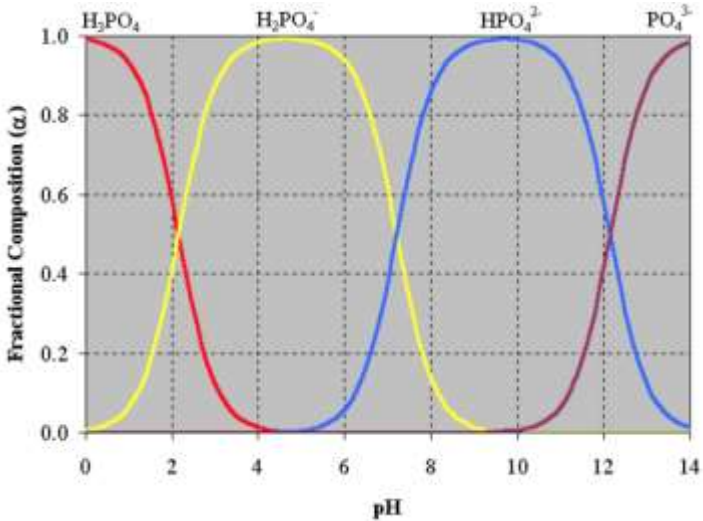
Buffer Chemistry Example

$$H_3PO_4 \overset{k_1}{\rightleftharpoons} H^+ + H_2PO_4^- \overset{k_2}{\rightleftharpoons} 2H^+ + HPO_4^{2-} \overset{k_3}{\rightleftharpoons} 3H^+ + PO_4^{3-}$$

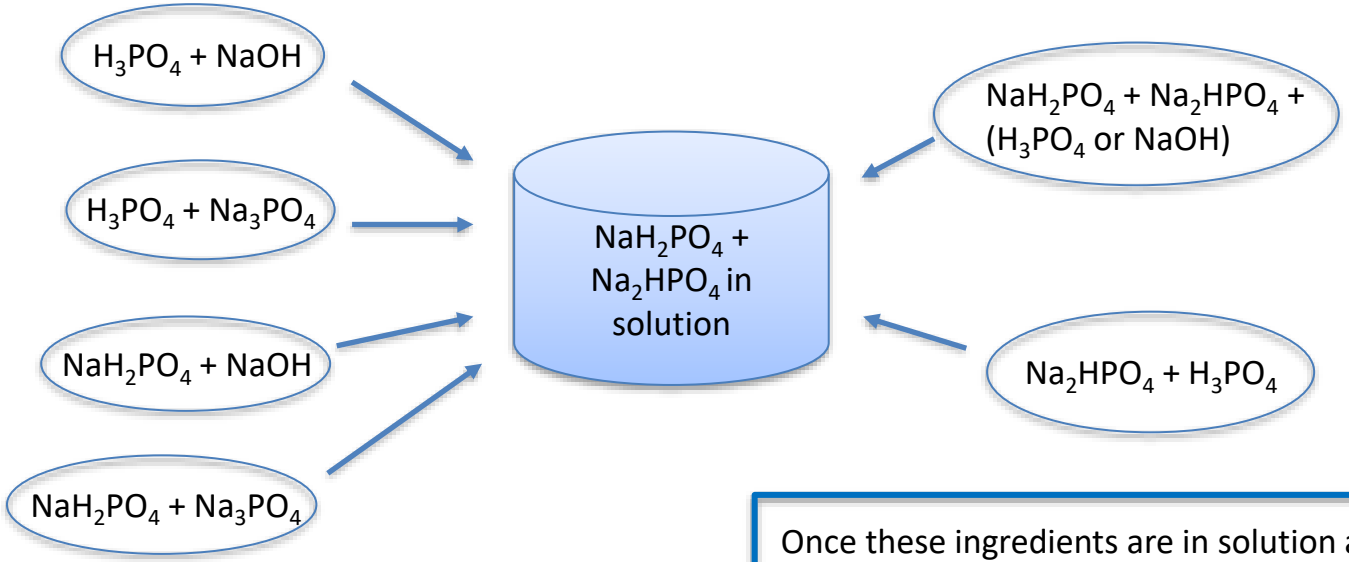
$$pH = pK_2 + \log \frac{[HPO_4^{2-}]}{[H_2PO_4^-]} \quad \text{or} \quad \frac{[HPO_4^{2-}]}{[H_2PO_4^-]} = 10^{pH-pK_2}$$

(called the "Henderson Hasselbalch Equation")

- ✓ No matter what the starting amounts are for the dibasic and monobasic sodium phosphate, at a fixed pH, the molar ratio (which is also the amount ratio) of $[HPO_4^{2-}]/[H_2PO_4^-]$ is fixed;
- ✓ If the total phosphate amount in generic formulation is the same to that of the RLD, then at a known pH in solution, each individual phosphate (dibasic and monobasic) amount would be the same.



There Are Many Ways to Make the Same Buffer



Same phosphate buffer:

- Same total phosphate concentration* (molar amount)
- Same pH of the buffer solution

*phosphate salts with different hydration states can be converted to same molar equivalent of anhydrous phosphate salts

Once these ingredients are in solution at a specific pH they are no longer the starting material. They are in equilibrium (e.g., mono and dibasic) that relative ratio is based on the pH of the solution. The important thing is the amount of phosphate (buffer capacity and tonicity) and pH of the solution.

Example of pH Adjuster Changes with Buffers

$$NaOH + H_2PO_4^- + Na^+ \rightleftharpoons HPO_4^{2-} + H_2O + 2Na^+$$

- Potential pH adjuster differences: phosphate buffer example
  - **Q1 change:**
    1) Exclusion of pH adjuster: sodium hydroxide
    2) Inclusion of pH adjuster with same ion(s) as the buffer: phosphoric acid
    3) Inclusion of pH adjuster with different ion(s) from the buffer: e.g., Potassium Hydroxide or Hydrochloric acid
  - **Q2 change:**
    1) Differences in pH adjuster amounts used: fixed vs q.s.

Example of Other Buffer Systems

- This principle can also be applied to other buffer systems.
- Examples:
  - Acetate buffer (acetic acid/sodium acetate)
    - Acetic acid + Sodium acetate = Acetic acid + NaOH = Acetic acid + NaOH + Sodium acetate
  - Citrate buffer (citric acid/sodium citrate)
    - Citric acid + trisodium citrate = Citric acid + NaOH =sodium citrate monobasic+ NaOH = Sodium citrate dibasic + citric acid

Supportive Information for pH Adjuster Changes with Buffers

- Identify any Q1 and/or Q2 differences in pH adjusters used.

- Provide justification in 314.99(b) waiver request for the difference in pH adjuster. Examples may include:
  - Information from IID
    - Concentration of newly formed salt or acid/base species in the buffer, vs IID limits
  - Physicochemical characterization information (pH, buffer capacity, osmolality, viscosity, etc.)
  - Other relevant data or information

pH Adjuster Acts as an in-situ Converter

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:

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

- Notably, the same chemical composition can be achieved through different routes (e.g., in the prior example, the same result could also be achieved by adding XCl to H_2O).

In-situ Converter Examples

- A pH adjuster might be used to generate the salt form of an *inactive ingredient** (same/similar to change in buffer salt form). In general, the pH adjuster should be a strong acid or base and used on an equal molar amount to the ingredient being converted. For example:
  - NaOH acts as an in-situ converter of oleic acid to form sodium oleate.

$$NaOH + \text{oleic acid} \rightarrow \text{sodium oleate} + H_2O$$

* To the extent a pH adjuster is used to convert the API to form the API salt (e.g., in-situ converter, solubilizing agent), 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.

Supportive Information for pH Adjuster Changes as In-situ Converter

- Identify any Q1 and/or Q2 differences in pH adjusters used.

- Provide justification in 314.99(b) waiver request for the difference in pH adjuster. Examples may include:
  - Information from IID
    - Use of proposed pH adjuster in previously 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
  - Physicochemical characterization information (pH, osmolality, viscosity, etc.)
  - Other relevant data or information

Will Deny and May Deny Situations

Will Deny Situations

- FDA will deny a waiver request 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 active ingredient than the RLD or
  - A novel inactive ingredient 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.
  - Example: 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.
  - 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).

Hypothetical Examples

Disclaimer Related to Examples

- 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 Example 1, Q2 Difference: Ophthalmic Solution

Ingredient[&]	Function	% Difference*
Drug Substance	Active Ingredient	--
0.1 N Sodium Hydroxide	pH Adjustment	-8
Water for injection	Continuous Phase	--

& 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)(iv) for ophthalmic products.
- May be acceptable to waive the inactive ingredient requirement, if scientifically justified.
- Possible supporting data: Comparable physicochemical data (e.g., pH, viscosity, specific gravity, osmolality, buffer capacity, and other properties as appropriate) between Test and Reference Standard products.

Hypothetical Example 2, Q1 Difference: Injection

Components	Test		RLD	
	Quantity per mL	Function	Quantity per mL	Function
Drug Substance	1.00 mg	API	1.00 mg	Drug Substance
Sodium Chloride	8.6 mg	Tonicity Adjuster	8.6 mg	Tonicity Agent
Citric Acid, Anhydrous	0.5 mg	Buffer	--	--
Hydrochloric Acid	as required	pH Adjuster	as required	pH Adjuster
Water for Injection	q.s. to 1 ml	Diluent	q.s. to 1 ml	Solvent

- Test formulation contains citric acid monohydrate, function listed as buffer.
- Without conjugate base, citric acid monohydrate is not considered buffer, but a pH adjuster.
- Test product applicant should correct the function of citric acid monohydrate.
- Once citric acid monohydrate function updated to pH adjuster, may be acceptable to waive the inactive ingredient requirement, if scientifically justified.
- Possible supporting data: supportive information from IID and comparable pH between Test and Reference Standard products.

Key: Accuracy of excipient function matters.

Recommendations for Addressing Primary Safety Concerns with pH Adjuster Difference(s)

Recommendations for Addressing Primary Safety Concerns with pH Adjuster Difference(s)

- Inactive ingredient concerns
  - 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 (will deny scenario)
  - Inactive ingredient found in IID but not for same route of administration (may deny scenario)
  - Concentrations above limits described in IID including when the concentration is Q2 same as RLD

- Supportive information
  - Provide supportive information from IID, and or other information as needed.
  - IID reference should be for the same context of use (i.e., route of administration, dosage form, level and duration of exposure, patient population, indication(s) for use).
  - Scientific principles around inclusion of buffer in a formulation may support justification for difference in pH adjuster.

Content of 314.99(b) Waiver Request

Content of a 314.99(b) Waiver Request

- Waiver request must be submitted (with supporting documentation) in an ANDA submission.
- Under the applicable regulations, a waiver request must contain at least one of the following:
  1) An explanation why the applicant's compliance with the requirement is unnecessary or cannot be achieved;
  2) A description of an alternative submission that satisfies the purpose of the requirement; or
  3) Other information justifying a waiver

Content of a 314.99(b) Waiver Request

- Information to be included in the cover letter:
  - Relevant RLD, including application number, proprietary (brand) name, NDA holder, active ingredient, dosage form, and strength(s)
  - Statement describing the Q1 or Q2 difference in pH adjuster for which the applicant is requesting waiver of the applicable regulatory requirement
  - Summary of type of information submitted to support the waiver request, and
  - Identification of the module, section, and subsection of the ANDA submission that contains the waiver request and the information submitted to support the waiver request

Timing and Process for Submission

Decision on Acceptability of Waiver Request

Timing and Process for Submission:
Process and Format for Requesting a Waiver

- Agency recommends that an ANDA applicant submit a controlled correspondence (control) requesting an evaluation of the proposed formulation and the RLD.
- An ANDA applicant might consider submitting a 314.99(b) waiver request to support the pH adjuster difference in its ANDA submission if:
  - Response to the control indicates that the proposed formulation does not meet the inactive ingredient requirements applicable to the product, and
  - ANDA applicant believes that this failure to meet such requirements is due to a difference in pH adjuster(s).
- If an ANDA applicant chooses to submit its ANDA without utilizing the control process and believes its formulation may not meet the inactive ingredient requirements in 314.94(a)(9)(iii) or (iv) with respect to one or more pH adjusters, FDA recommends such ANDA applicant submit a 314.99(b) waiver request with the ANDA.

Timing and Process for Submission:
Consideration of a 314.99(b) Waiver Request

- A 314.99(b) waiver request and its supporting documentation must be submitted in an ANDA, or in an amendment or supplement to an ANDA where appropriate (e.g., an amendment or supplement seeking to change the drug product formulation).
- Agency will refuse to receive an ANDA for a proposed product intended for parenteral, ophthalmic, or otic use that contains a Q1 or Q2 difference in pH adjuster compared to its RLD but does not include a waiver request and its supporting documentation.
- An inquiry about a waiver request via control or pre-ANDA meeting request does not constitute a waiver request.
- Agency will not consider a waiver request unless the request and the accompanying documentation are included in an ANDA submission, consistent with the requirements of 314.90 and 314.99(b).

Decision on Acceptability of Waiver Request

- Acceptability of a waiver request will be determined during the scientific review of an ANDA.
- FDA will inform an applicant of the Agency's decision regarding a waiver request when FDA acts on the ANDA containing the waiver request.

Effect on Eligibility to Use Certain Approaches to Show BE

Effect on Eligibility to Use Certain Approaches to Show BE: 320.22(b)(1)

- Where an applicant seeks a 314.99(b) waiver of inactive ingredient requirements at 314.94(a)(9)(iii) or (iv) for a Q1 or Q2 difference in pH adjuster compared to its RLD, then that ANDA product necessarily does not contain the same inactive ingredients in the same concentration as the RLD for BE to be considered "self-evident" under 21 CFR 320.22(b)(1).

Effect on Eligibility to Use Certain Approaches to Show BE:
Where PSG Recommends Q1/Q2 Sameness for Particular BE Approach

- Product-specific guidance (PSG) may recommend that an ANDA product be Q1/Q2 the same as its RLD to use a particular approach recommended in the PSG to demonstrate BE.

PSG Recommendation

Recommended Study: Two options: in vitro or in vivo study

I. In vitro option:

To qualify for the in vitro option for this drug product all of the following criteria should be met:

i. The test and reference listed drug (RLD) formulations are qualitatively (Q1)[1] and quantitatively (Q2)[2] the same[3].

Example Drug Products (list not comprehensive)

Cyclosporine Ophthalmic Emulsion
Prednisolone Acetate Ophthalmic Suspension/Drop
Loteprednol Etabonate Ophthalmic Gel
Timolol Maleate Ophthalmic Solution/Drops
Propofol Injection

Effect on Eligibility to Use Certain Approaches to Show BE:
Where PSG Recommends Q1/Q2 Sameness for Particular BE Approach

- Recommendations in a PSG are not binding, and applicants may use an alternative approach if it satisfies the statutory and regulatory requirements.

- Scientific principles described in this guidance that provide support for a waiver of the inactive ingredient requirements under 314.94(a)(9)(iii) and (iv) for a difference in pH adjuster may, in some cases, also provide support for an applicant's scientific justification for use of a particular BE approach.

Requesting Waiver of Evidence of in vivo BE

- Waiver under 314.99(b) ≠ waiver under 21 CFR Part 320 (e.g., 320.22)
  - 314.99(b) waiver request permits an applicant to seek waiver of requirements under 314.92 through 314.99, including the inactive ingredient requirements at 314.94(a)(9)(iii) and (iv) (i.e., Q1/Q2 difference in pH adjuster of a parenteral, ophthalmic or otic drug).
  - The requirements for BE are governed by the regulations set forth in 21 CFR Part 320. Thus, a waiver of evidence of in vivo BE (e.g., 320.22(b)(1)) is different from a waiver under 314.99(b), and a waiver under 314.99(b) does not also waive the requirement to submit evidence of in vivo BE.

- We encourage an applicant who plans to submit a waiver request under 314.99(b) for a difference in pH adjuster and use an in vitro approach to establish BE to contact the Agency to discuss the particular approach to establish BE for that drug product.

Mechanism to Receive Feedback from Agency

Mechanism to Receive Feedback from Agency

- Controls
  - Use to request a Q1/Q2 sameness evaluation of a proposed formulation against the RLD.
  - Agency will respond to indicate whether the proposed formulation would or would not likely be refused to receive.

- Pre-ANDA Product Development Meeting
  - Use to get feedback on proposed information and rationale that may support a 314.99(b) waiver request, where appropriate, for a difference in pH adjuster for a parenteral, ophthalmic, or otic product.

Questions?