Considerations for Waiver Requests for pH Adjusters in Generic Drug Products Intended for Parenteral, Ophthalmic, or Otic Use

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

April 2022
Generic Drugs

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Considerations for Waiver Requests for pH Adjusters in Generic Drug Products Intended for Parenteral, Ophthalmic, or Otic Use Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance describes how FDA (the Agency, or we) intends to evaluate a request for a waiver, with regard to a pH adjuster, under 21 CFR 314.99(b) (hereinafter waiver) of the requirement in 21 CFR 314.94(a)(9)(iii) and (iv) that a drug product intended for parenteral, ophthalmic, or otic use generally "must contain the same inactive ingredients and in the same concentration as the reference listed drug identified by the applicant." This guidance also provides recommendations regarding the timing and process for requesting such a waiver of the requirement in § 314.94(a)(9)(iii) and (iv) (waiver request).

This guidance is intended to assist abbreviated new drug application (ANDA)[2] applicants that reference a reference listed drug (RLD) intended for parenteral, ophthalmic, or otic use but are seeking approval of a drug that is qualitatively (Q1) different or quantitatively (Q2) different[3] from the RLD with respect to a pH adjuster(s).[4] This guidance is intended to identify the type of information FDA may generally consider in evaluating a waiver request for pH adjusters in generic drug products intended for parenteral, ophthalmic, or otic use and provide recommendations to ANDA applicants regarding the submission and content of such a waiver request.

[1] This guidance has been prepared by the Office of Generic Drugs in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] See section 505(j) of the FD&C Act.

[3] OGD interprets *quantitative sameness* to mean a concentration that is within 95-105% of the reference listed drug concentration. That is, sameness as discussed herein does not suggest an exact value, but rather a range of values.

[4] There may be circumstances where a proposed difference in pH adjuster is not acceptable in an ANDA. Examples of such circumstances are discussed further in section III.B. below.

The recommendations in this guidance are limited to inactive ingredients in ANDAs that adjust the pH of a drug product intended for parenteral, ophthalmic, or otic use, and do not apply to other inactive ingredients.[5]

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in FDA guidance means that something is suggested or recommended, but not required.

II. BACKGROUND

The Drug Price Competition and Patent Restoration Act of 1984, commonly referred to as the "Hatch-Waxman Amendments," created a statutory ANDA pathway by amending section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355).[6] To obtain approval, the ANDA applicant generally must show, among other things, that the proposed generic drug product (1) has the same active ingredient(s), dosage form, route of administration, strength, conditions of use, and, with certain exceptions, labeling as the RLD; and (2) is bioequivalent to the RLD.[7]

A. Statutory and Regulatory Provisions Regarding Inactive Ingredients in ANDAs

The FD&C Act does not require an ANDA product to have the same inactive ingredients as the RLD.[8] Section 505(j)(4)(H) of the FD&C Act does, however, state that an ANDA shall not be approved:

> . . . if information submitted in the application or any other information available to the Secretary shows (i) the inactive ingredients of the drug are unsafe for use under the conditions prescribed, recommended, or suggested in the labeling proposed for the drug, or (ii) the composition of the drug is unsafe under such conditions because of the type or quantity of inactive ingredients included or the manner in which the inactive ingredients are included.[9]

The Agency has interpreted section 505(j)(4)(H) of the FD&C Act as permitting the Agency to deny approval of an ANDA "if there is a reasonable basis to conclude that its inactive ingredients or composition raise serious questions about the drug's safety."[10] In its implementing

[5] The scientific principles described in this draft guidance may be relevant, in certain circumstances, to requests to use an in vitro approach to demonstrate bioequivalence (BE) for a proposed generic product intended for parenteral, ophthalmic, or otic use that is not Q1 or Q2 the same as the RLD. FDA encourages an applicant who proposes such a product that is not Q1 or Q2 the same as the RLD with respect to a pH adjuster(s), to contact the Agency to discuss its proposed approach to establish BE for its proposed drug product.

[6] Public Law 98-417 (Sept. 24, 1984).

[7] See generally, 21 CFR 314.94(a).

[8] See section 505(j)(2)(A) of the FD&C Act (setting forth the required contents of an ANDA).

[9] Section 505(j)(4)(H) of the FD&C Act.

[10] 21 CFR 314.127(a)(8)(ii); 54 FR 28871 at 28903 (July 10, 1989).

regulations, FDA explicitly noted that "FDA may identify changes in inactive ingredients that may adversely affect a drug product's safety or efficacy" based on the Agency's "experience with reviewing inactive ingredients and other information available to it."[11] In its regulations, the Agency has also provided non-exhaustive examples of changes in inactive ingredients in proposed generic drug products that may raise serious questions of safety,[12] including, for example:

- A change in an inactive ingredient so that the product does not comply with an official compendium;[13]
- A change in composition to include an inactive ingredient that has not been previously approved in a drug product for human use by the same route of administration;[14]
- A change in the composition of a parenteral drug product to include an inactive ingredient that has not been previously approved in a parenteral drug product;[15]
- A change in composition of a drug product for ophthalmic use to include an inactive ingredient that has not been previously approved in a drug for ophthalmic use;[16] and
- A change in composition to include a significantly greater content of one or more inactive ingredients than previously used in the drug product.[17]

The regulations at § 314.94(a)(9)(iii) and (iv), with parallel provisions in the approval regulations at 21 CFR 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 and will refuse to approve the ANDA unless the generic drug product contains the same inactive ingredients (with certain listed exceptions) in the same concentration as the RLD.[18] These regulations also identify permissible 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; for example:

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[11] 21 CFR 314.127(a)(8)(ii)(A).

[12] See 54 FR 28871 at 28902 (discussing FDA's interpretation of section 505(j)(3)(H) (now 505(j)(4)(H)) of the FD&C Act in the context of proposed rule 314.127 on the refusal to approve ANDAs).

[13] 21 CFR 314.127(a)(8)(ii)(A)(*1*).

[14] 21 CFR 314.127(a)(8)(ii)(A)(*2*).

[15] 21 CFR 314.127(a)(8)(ii)(A)(*3*).

[16] 21 CFR 314.127(a)(8)(ii)(A)(*4*).

[17] 21 CFR 314.127(a)(8)(ii)(A)(*6*).

[18] In evaluating drug product formulation and inactive ingredients, an ANDA applicant should compare its proposed generic drug to the RLD's formulation, not the formulation of the reference standard (where the reference standard is not the RLD). See FDA guidance for industry *Referencing Approved Drug Products in ANDA Submissions* (October 2020). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

- Drug products intended for parenteral use generally must contain the same inactive ingredients in the same concentration as the RLD; however, an applicant may seek approval of a drug product intended for parenteral use that differs from the RLD in preservative, buffer, or antioxidant provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.[19]

- Drug products intended for ophthalmic or otic use generally must contain the same inactive ingredients in the same concentration as the RLD; however, an applicant may seek approval for a drug product intended for ophthalmic or otic use that differs from the RLD in preservative, buffer, substance to adjust tonicity, or thickening agent provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.[20]

When proposing these regulations, the Agency provided a brief discussion for its reasoning in implementing the inactive ingredient requirements for drug products intended for parenteral, ophthalmic, or otic use:

> [E]ach parenteral, ophthalmic, and otic drug product represents an individual pharmaceutical system with its own characteristics and requirements. In the formulation of parenteral drug products, certain added substances are used to maintain solubility, stability, sterility, and to increase patient comfort (i.e., by adjusting toxicity[sic] and reducing tissue irritation). Added substances selected for parenteral drug products *must be known to be of the highest quality, must be known to not interfere with the therapeutic effectiveness of the product and must be known to be nontoxic in the quantities used*. The sensitivity of inactive ingredients in parenteral drug products is reflected in regulations under 21 CFR 201.100 which require that certain added substances and their concentrations be listed on the label of the product. Similarly, added substances are used in the formulation of products intended for ophthalmic and otic use such as buffers, antimicrobial preservatives, chemicals to adjust toxicity [sic], and thickening agents.[21]

B. Waiver of Certain Regulatory Requirements for ANDAs

When FDA updated its new drug regulations in the 1980s, the Agency promulgated a waiver provision "intended to give applicants flexibility to seek alternative ways of complying with the statutory standards for drug approval."[22] FDA has since codified a waiver provision applicable to ANDAs at 21 CFR 314.99(b),[23] under which "an applicant may ask FDA to waive under this

[19] See 21 CFR 314.94(a)(9)(iii); see also 21 CFR 314.127(a)(8)(ii)(B).

[20] See 21 CFR 314.94(a)(9)(iv); see also 21 CFR 314.127(a)(8)(ii)(C). The regulations also specify that for products intended for ophthalmic use, an applicant may not change a buffer or substance to adjust tonicity for the purpose of claiming a therapeutic advantage over or difference from the RLD. See 21 CFR 314.94(a)(9)(iv).

[21] See 54 FR 28872 at 28883 (July 10, 1989) (emphasis added). Both references to "adjusting toxicity" appear to be an inadvertent error for "adjusting tonicity."

[22] See 47 FR 46622 at 46637-38 (Oct. 19, 1982).

[23] See 54 FR 28872 at 28889 (Jul. 10, 1989) (proposing "to retain the current requirement under § 314.90 under which an applicant may obtain a waiver of requirements for the submission of information in an application. The

section any requirement that applies to the applicant under 314.92 through 314.99." As described in § 314.99(b), the applicant must comply with the requirements for a waiver under 21 CFR 314.90 and FDA may grant a waiver if it finds one of the following:

> (1) The applicant's compliance with the requirement is unnecessary for the agency to evaluate the [A]NDA or compliance cannot be achieved;
>
> (2) The applicant's alternative submission satisfies the requirement; or
>
> (3) The applicant's submission otherwise justifies a waiver.[24]

Even if FDA grants a waiver of a requirement in § 314.92 through § 314.99 in a particular application, the application still must meet all applicable statutory requirements for approval.[25] If FDA grants the applicant's waiver request with respect to a requirement under § 314.92 through § 314.99, the waived requirement will not constitute a basis for refusal to approve an ANDA under § 314.127.[26]

III. WAIVERS FOR pH ADJUSTERS IN GENERIC DRUGS INTENDED FOR PARENTERAL, OPHTHALMIC, OR OTIC USE MAY BE APPROPRIATE IN CERTAIN CIRCUMSTANCES

Over time there has been increased interest in and questions about waivers of the applicable inactive ingredient requirements for pH adjusters in ANDAs. FDA's current thinking is that pH adjusters function in such a way that, in some circumstances, a waiver of the inactive ingredient requirements in § 314.94(a)(9)(iii)-(iv) for a pH adjuster in a generic drug product intended for parenteral, ophthalmic, or otic use may be appropriate. In particular, how pH adjusters function or react in some formulations support the possibility that there may be circumstances where certain differences in pH adjusters in an ANDA as compared to the RLD may be scientifically appropriate and acceptable in an ANDA, as described in more detail below.

Accordingly, FDA believes that permitting such differences to pH adjusters through a waiver under § 314.99(b), as appropriate, is one way the waiver provision may enable flexibility in how a particular applicant meets the statutory standards for approval. Determining whether a particular difference in pH adjuster as compared to the RLD is scientifically acceptable and

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applicable sections are those set forth under new proposed Subpart C. FDA may not, however, waive statutory requirements").

[24] See 21 CFR 314.99(b) (citing 21 CFR 314.90(b)).

[25] For example, when an ANDA applicant seeks approval for a parenteral formulation that is the same as that previously (but not currently) marketed for the RLD, FDA has determined that, in appropriate circumstances, pursuant to 21 CFR 314.99(b), it may waive the requirement in the regulation that the inactive ingredients in a parenteral drug product approved under an ANDA be the same as those in the RLD (except for preservatives, buffers, and antioxidants), as long as the statutory requirement regarding safety of inactive ingredients has been met. See section 505(j)(4)(H) of the FD&C Act. In determining whether to grant such a waiver, the Agency considers, among other things, whether the previously marketed formulation was discontinued for reasons of safety or effectiveness. See, e.g., letter from Janet Woodcock to Steven H. Sklar and Peter O. Safir (November 7, 2012), Docket Nos. FDA2011-P-0339 and FDA-2012-P-0507.

[26] See 21 CFR 314.99(b).

appropriate in an ANDA is a fact-specific assessment within the context of a specific application and a specific § 314.99(b) waiver request. As noted in the preceding section, an application for which FDA grants a waiver must still meet all applicable requirements for approval.

A. The Role of pH Adjusters

The primary function of a pH adjuster, which is commonly an acid or base, is to change the equilibrium concentration of hydronium ions in solution (i.e., the pH). In general, the greater the concentration of hydronium ions in solution, the lower the pH value, which is measured on a logarithmic scale. For example, in an aqueous solution (H_2O), the balance of hydronium ions (H_3O^+) and hydroxide ions (OH^-) determines whether the pH of the solution is acidic ($[H_3O^+] > [OH^-]$), basic ($[H_3O^+] < [OH^-]$), or neutral ($[H_3O^+] = [OH^-]$). As the pH adjuster role is to change the equilibrium concentration of hydronium ions in solution, the pH value is routinely used as a surrogate to control the amount of pH adjuster added. For example, the amount of hydrochloric acid (HCl) pH adjuster added to an aqueous solution 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:

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

In FDA's experience reviewing applications for drug products intended for parenteral, ophthalmic, or otic use, pH adjusters are typically used on an as-needed basis to achieve a specified pH range in the drug product. These 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.

In cases where a formulation contains other ingredients that may act as a buffer, pH adjusters react with and may function as part of the buffer system to control the pH. In general, a buffer system is composed of a weak acid that is in equilibrium with its conjugate base, or vice versa. A buffer can be created in various ways; for example, by adding defined ratios of the weak acid and conjugate base or by adding a pH adjuster to convert some of the weak acid into the conjugate base. Thus, a pH adjuster can become an indistinguishable part of the buffer. For example, an acetic acid (CH_3COOH) sodium acetate (CH_3COONa) buffer may be created by mixing a ratio of these two ingredients in solution or by adding a sodium hydroxide (NaOH) pH adjuster to acetic acid. In solution, the buffer component species (i.e., acetic acid and sodium acetate) and pH adjuster (i.e., sodium hydroxide) are not "distinguishable" species, but the ionic species (i.e., sodium ion) and the buffer system containing the weak acid (i.e., acetic acid) and its conjugate base (i.e., acetate) are. Regardless of the components used in creating the buffer, the equilibrium of these species in the solution is dependent on the pH of the drug product:

$$CH_3COONa + H_2O \leftrightharpoons Na^+ + CH_3COO^- + H_2O$$

$$Na^+ + CH_3COO^- + H_2O \leftrightharpoons CH_3COOH + Na^+ + OH^-$$

Buffers are considered "exception excipients" in drug products intended for parenteral, ophthalmic, or otic use, meaning that a Q1 or Q2 difference is permitted, provided that the ANDA applicant identifies and characterizes the difference and provides information demonstrating that the difference does not affect the safety or efficacy of the proposed drug product.[27] In some instances, where a drug product intended for parenteral, ophthalmic, or otic use lists a pH adjuster separate from a buffer, the pH adjuster may act as part of the buffer system, but will nonetheless be treated as a pH adjuster, a non-exception excipient.

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:

$$HCl + XOH \leftrightharpoons XCl + H_2O$$

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).[28]

B. A Q1 or Q2 Difference in pH Adjuster May Be Appropriate in an ANDA in Certain Circumstances

The Agency's experience with pH adjusters, coupled with the specific role pH adjusters generally play in drug formulations, support the conclusion that in certain circumstances it may be appropriate for FDA to consider a waiver to permit a Q1 or Q2 difference in a pH adjuster(s) in a generic drug product intended for parenteral, ophthalmic, or otic use.

The Agency has approved many new drug applications for RLDs intended for parenteral, ophthalmic, or otic use where the applicant specifies the amount of pH adjuster used as q.s. Where an RLD is approved with a q.s. amount of pH adjuster, it is possible for a relative amount of pH adjuster added to a specific batch of the RLD to differ from batch to batch, based on the amount of pH adjuster needed to achieve the specified pH or pH range for a particular RLD batch. In approving an application under these circumstances, the Agency has determined as a scientific matter that the acceptability of the finished product (containing the as-needed amount of the pH adjuster) is assured by controlling the drug product's physicochemical characteristics (e.g., pH, osmolality, viscosity). In some instances, the use and amount of pH adjuster between batches of the RLD may exceed 5% while not changing the drug product's final attributes in an unacceptable manner (e.g., changing the pH or physicochemical characteristics that may be critical to the drug product's performance) or affecting the safety or efficacy of the RLD. Thus,

[27] See 21 CFR 314.94(a)(9)(iii), (iv); see also 21 CFR 314.127(a)(8)(ii)(B), (C).

[28] An ingredient that solely acts to convert an active ingredient (e.g., from a base form to a salt form) during manufacturing of the drug product is not considered an inactive ingredient (because it becomes part of the active ingredient) and is therefore outside of the intended scope of this guidance, which concerns the requirements for inactive ingredients in drug products intended for parenteral, ophthalmic, or otic use.

wide ranges in the amount of pH adjuster may be acceptable provided that the drug product's final attributes are adequately controlled.

Applying these scientific principles to instances where the RLD is approved with a fixed amount of pH adjuster, FDA has also concluded that there may be circumstances where an ANDA applicant can establish that a greater than 5% difference in the amount of pH adjuster in an ANDA product compared to the RLD would not change the proposed drug product's final attributes in an unacceptable manner (e.g., changing the pH or physicochemical characteristics that may be critical to the drug product's performance) or cause the drug product to not meet the statutory standards for approval of an ANDA.[29] For example, an ANDA applicant may choose to submit, and the Agency will review and consider, a waiver request to use an amount of a pH adjuster that is more than 5% higher than the amount contained in the RLD. In such a circumstance, a waiver request under § 314.99(b) should include supportive information to scientifically justify the difference in pH adjuster. For instance, with respect to the safety of a proposed quantitative difference in pH adjuster, an applicant may include supportive information from the Inactive Ingredients Database (IID),[30] and/or other information as needed, as part of its scientific justification for the difference in pH adjuster.

It is also notable that RLD application holders for drug products intended for parenteral, ophthalmic, or otic use may elect to include in their composition tables one or multiple pH adjusters, which are used on an as-needed basis. Thus, although included in the composition table, a pH adjuster(s) may, or may not, be present in a given RLD batch. For example, an RLD application holder may indicate in a composition table that pH adjuster A "and/or" B may be used q.s. Under this scenario, only pH adjuster A, only pH adjuster B, both pH adjusters, or neither pH adjuster may be included in any given RLD batch.

The scientific principle underlying this practice for an RLD may also support the conclusion that the omission or addition of a pH adjuster in an ANDA product referencing such an RLD, like the omission or addition of an exception excipient enumerated in § 314.94(a)(9)(iii) and (iv), may, in certain circumstances, not change the ANDA's final attributes in an unacceptable manner (e.g., change the pH or physicochemical characteristics that may be critical to the drug product's performance). In such case, such a change might be permissible in an ANDA if a waiver is requested and granted and as long as the drug product meets the standards for approval of an ANDA.[31] For example, an ANDA applicant may choose to submit, and the Agency will review and consider, a waiver request to use a pH adjuster that has been previously used in an approved drug product for the same route of administration[32] but that is not used in the RLD. In such a circumstance, a waiver request under § 314.99(b) should include supportive information to scientifically justify the difference in pH adjuster. For instance, with respect to the safety of a proposed qualitative difference in pH adjuster, an applicant may include supportive information

[29] See *infra* Part IV (providing recommendations on the type of information that can be submitted to support a waiver request, including information showing that the Q1 or Q2 difference does not affect safety or efficacy).
[30] See id; see also FDA's draft guidance for industry *Using the Inactive Ingredient Database* (July 2019). When final, this guidance will represent FDA's current thinking on this topic.
[31] See *infra* Part IV (discussing the type of information that can be submitted to support a waiver request, including information showing that the Q1 or Q2 difference does not affect safety or efficacy).
[32] See, e.g., 21 CFR 314.127(a)(8)(ii)(A)(2), (3), (4).

from the IID, and/or other information as needed, as part of its scientific justification for the difference in pH adjuster.

It is important to note, however, that determining the acceptability of any particular difference in pH adjuster is a fact-specific inquiry based on the circumstances of a particular application. There are differences that will likely not be acceptable for an ANDA and thus FDA would deny a waiver request submitted for such differences. For instance, FDA will deny a waiver request if the difference in pH adjuster: forms a different form of the active ingredient than the RLD in the final product; or uses or forms 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. These types of pH adjuster differences are not appropriate for an ANDA. In addition, FDA may deny a waiver request if the difference in pH adjuster impacts the physical or chemical properties critical to the performance of the product or where those property changes raise potential safety concerns. For example, there may be potential safety concerns where an ANDA uses a different pH adjuster to the RLD, and that difference gives rise to either a new counter-ion species not present in the RLD or a different concentration of the 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 the 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).

IV. INFORMATION FDA MAY CONSIDER WHEN EVALUATING A REQUEST FOR WAIVER FOR A pH ADJUSTER IN AN ANDA

As described above, in certain cases, a proposed Q1 or Q2 difference in a pH adjuster(s) in a generic drug product intended for parenteral, ophthalmic, or otic use may be acceptable in an ANDA. The general principles discussed in Section III above regarding the role pH adjusters play may support a waiver of the Q1 requirement when an ANDA applicant seeks to omit a pH adjuster, add a pH adjuster, or use a different pH adjuster compared to the RLD; and/or a waiver of the Q2 requirement when the RLD has specified a fixed quantity for a pH adjuster and an ANDA applicant seeks to use a different quantity. If an ANDA applicant believes it is appropriate to seek approval for a product with such a difference from its RLD, the ANDA applicant should submit a waiver request under § 314.99(b) to support the proposed difference.[33] However, as noted above, there may be instances where certain differences in pH adjuster may not be appropriate in an ANDA. To assist FDA in evaluating whether a waiver request for a pH adjuster in an ANDA intended for parenteral, ophthalmic, or otic use is appropriate, FDA recommends that applicants provide certain information, described below.

To support a waiver request, FDA recommends that applicants submit information about a proposed product's physicochemical characterization. Physicochemical characterization

[33] Where an RLD denotes the pH adjuster quantity used as q.s., the Agency has determined that the RLD is safe and effective despite the fact that the amount of pH adjuster used may vary, as needed, from batch to batch. Under FDA's current practice, an ANDA that relies on such an RLD can propose to use a q.s. or a fixed amount of the same pH adjuster, which FDA will generally consider to be Q2 same with respect to the pH adjuster, such that a waiver request with respect to that pH adjuster would not be necessary.

information might be included in an ANDA generally to identify essential physical and chemical properties of a product that may be critical to its performance. Physicochemical characterization information may also be submitted in support of a § 314.99(b) waiver request. Scientific advances have enhanced the accuracy and sensitivity of physicochemical characterization, and such characterization may be useful in evaluating the effect, if any, of a difference in pH adjuster on the performance of a proposed generic drug product compared to its RLD.

For example, as discussed above, comparative pH can be used to support similar hydronium concentrations between the RLD and generic drug product, which helps to ensure a similar physicochemical environment including any protonation and/or deprotonation of other ingredients in the formulation. In addition, comparative buffer capacity can be used to support similar capacities to resist changes in pH between the RLD and generic drug product, which helps to ensure that the generic drug product has a similar physicochemical environment as the RLD, and that drug product stability for the proposed generic drug product is not affected. Comparative osmolality can be used to support similar total solute concentrations between the RLD and generic drug product, which helps to ensure the safety and stability of the drug product. Further, for some complex formulations, comparative viscosity[34] and electrophoretic mobility can be used to support similar concentrations of charged species between the RLD and generic drug product, which helps to ensure drug product quality. Similarly, in vivo or in vitro studies showing comparable active ingredient release rates between the RLD and generic drug product can be used to support a waiver concluding that differences in type or amounts of pH adjuster between the RLD and generic drug product will not preclude approval of the proposed product in an ANDA.

In addition to information regarding physicochemical characterization, other information regarding the safety of a proposed difference in pH adjuster may be relevant to assess whether a waiver for a pH adjuster difference in an ANDA would be appropriate. For example, if the generic drug product proposes to contain a different pH adjuster or a higher amount of pH adjuster than that used in the RLD, then the Agency recommends that the ANDA applicant, at a minimum, include in support of its waiver request information showing that (1) the proposed pH adjuster has been used in drug products previously approved by FDA for the same route of administration, and (2) the amount of pH adjuster used can be considered safe based on the amount of that pH adjuster in previously approved drug products for the same route of administration.

In summary, the Agency recommends applicants consider submitting the following types of information for the proposed generic drug product and its RLD to assist FDA in evaluating a waiver request for a difference in pH adjuster in a proposed ANDA intended for parenteral, ophthalmic, or otic use (more or less information may be necessary depending on the proposed difference):[35]

[34] Because viscosity may be an important attribute that governs availability of the drug at the site of action, comparable viscosity can support a showing that differences in pH adjuster between the generic drug product and its RLD should not affect BE.

[35] For example, in general, the information that would be recommended to support a waiver request for a solution may be less extensive than the information recommended to support a waiver request for a suspension, gel, or emulsion.

- Comparative pH, buffer capacity, or both (where applicable).

- Comparative osmolality.

- Comparative viscosity.

- Comparative electrophoretic mobility.

- Comparative concentration of the pH adjuster ingredient being reacted with to form the new salt or free base/acid species,[36] including data or information that demonstrates that the new salt or free base/acid species does not affect the safety of the proposed drug product, for example, reference to the IID.

- Other comparative physicochemical data (e.g., which may support the use of pH adjusters in concentrations greater than ±5% of the amount used in the RLD).

- Data or information that demonstrates that the difference in the amount of pH adjuster, the number or identity of pH adjusters, or both (as applicable) between the proposed drug product and its RLD does not affect the safety of the proposed drug product, including, for example, reference to the IID.

- Data or information that demonstrates that the difference in the amount of pH adjuster or the number or identity of pH adjusters between the proposed drug product and its RLD does not affect bioequivalence (BE). For example, pharmacokinetic data from in vivo BE studies for non-solution products or in vitro release testing data from in vitro BE studies.

V. TIMING AND PROCESS FOR SUBMISSION AND FDA CONSIDERATION OF A 314.99(b) WAIVER REQUEST

A. Process and Format for Requesting a Waiver

FDA recommends that an ANDA applicant developing a proposed drug product intended for parenteral, ophthalmic, or otic use submit a controlled correspondence[37] requesting an evaluation of the proposed formulation and the RLD. If the response to the controlled correspondence indicates that the proposed formulation does not meet the inactive ingredient requirements applicable to the product, and the ANDA applicant believes that this failure to meet such requirements is due to a difference in pH adjuster(s), the ANDA applicant may consider submitting a § 314.99(b) waiver request to support the pH adjuster difference in its ANDA submission.

[36] The formation of a new salt or free base/acid species discussed here does not include a new salt or free base/acid species of the active ingredient(s).

[37] See FDA's guidance for industry *Controlled Correspondence Related to Generic Drug Development* (December 2020).

If an ANDA applicant chooses to submit its ANDA without utilizing the controlled correspondence process and believes its formulation may not meet the inactive ingredient requirements in § 314.94(a)(9)(iii)-(iv) with respect to one or more pH adjusters, FDA recommends such ANDA applicant submit a § 314.99(b) waiver request with the ANDA.

In accordance with § 314.99(b) (by reference to 21 CFR 314.90(a)), the waiver request and its supporting documentation must be submitted in an ANDA, or in an amendment or supplement to an ANDA (hereinafter referred to as an "ANDA submission") where appropriate (e.g., an amendment or supplement seeking to change the drug product formulation). The 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.[38] In addition, FDA does not consider an inquiry about a waiver request via controlled correspondence or pre-ANDA meeting request to constitute a waiver request. FDA 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).

FDA recommends that an ANDA submission containing a waiver request prominently identify in the cover letter to the submission in Module 1 of the Common Technical Document that a waiver request is included.[39] FDA recommends that applicants submit the waiver request in the module, section, and subsection of the ANDA submission that would otherwise address the regulatory requirement for which the waiver request is being submitted.[40] For additional recommendations about the information that should be ordinarily submitted in the applicable modules, sections, and subsection of ANDA submissions, please consult FDA's guidance for industry *ANDA Submissions—Content and Format* (June 2019).

B. Content of a Waiver Request

As noted above, a waiver request must be submitted (with supporting documentation) in an ANDA submission.[41] 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.[42]

[38] See 21 CFR 314.94(a)(9)(iii), (iv); see also FDA's guidance for industry *ANDA Submissions—Refuse-to-Receive Standards* (December 2016) at Part V.A.2. (discussing product quality deficiencies for changes to non-exception inactive ingredients in drug products intended for parenteral, ophthalmic, or otic use).

[39] See FDA's revised guidance for industry *Providing Regulatory Submissions in Electronic Format—Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* (January 2019) for more information on the contents of Module 1 of the Common Technical Document.

[40] Id.

[41] See 21 CFR 314.99(b) (referencing 314.90(a)).

[42] See 314.90(a).

To ensure the Agency is clear on which information in the ANDA submission is intended to support the waiver request, FDA recommends applicants include the following information in the ANDA submission cover letter in the section that specifically discusses the waiver request:

- Relevant RLD(s), as applicable, including application number, proprietary (brand) name, manufacturer, 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 the 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.

C. Waiver Request Outcome

The Agency may grant a waiver request if it finds one of the following:

(1) The applicant's compliance with the requirement is unnecessary for the Agency to evaluate the ANDA or compliance cannot be achieved;

(2) The applicant's alternative submission satisfies the requirement; or

(3) The applicant's submission otherwise justifies a waiver.[43]

The acceptability of a waiver request will be determined during the scientific review of an ANDA. FDA will inform applicants of the Agency's decision regarding a waiver request when FDA acts on the ANDA containing the waiver request.[44]

D. Effect on Eligibility to Use Certain Approaches to Show Bioequivalence

FDA recognizes that where an ANDA applicant wishes to seek a waiver of the inactive ingredient requirements at § 314.94(a)(9)(iii) or (iv) for a Q1 or Q2 difference in pH adjuster compared to its RLD, that applicant might also seek to utilize an in vitro approach to demonstrate BE. However, if FDA grants a waiver for an ANDA's Q1 or Q2 difference in pH adjuster, then that ANDA product necessarily does not contain the same inactive ingredients in the same concentration as its RLD. Thus, such an ANDA product would not be eligible under 21 CFR 320.22(b)(1) for a waiver of evidence of in vivo BE. Under 21 CFR 320.24(b)(6), however, an approach "deemed adequate by FDA to … establish bioequivalence" may be utilized to establish BE of a drug product where scientifically appropriate. FDA encourages an applicant who submits a waiver of the inactive ingredients requirement at § 314.94(a)(9)(iii) or (iv) for a

[43] See 21 CFR 314.90(a).

[44] See GDUFA Reauthorization Performance Goals and Program Enhancements, Fiscal Years 2018-2022, available at https://www.fda.gov/media/101052/download ("Act on an application – means FDA will either issue a complete response letter, an approval, a tentative approval, or a refuse-to-receive action.").

difference in pH adjuster and who also seeks to use an in vitro approach to demonstrate BE, to contact the Agency to discuss the particular approach to establish BE for that particular drug product.

Similarly, FDA's product specific guidances (PSG) may recommend that an ANDA product contain the same inactive ingredients in the same concentration as its RLD to use a particular approach recommended in the PSG to demonstrate BE. Recommendations in PSGs are not binding, and applicants may use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. The 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. As noted above, FDA encourages an applicant, who submits a waiver of the inactive ingredients requirement at § 314.94(a)(9)(iii) or (iv) for a difference in pH adjuster and who also seeks to use an in vitro approach to demonstrate BE, to contact the Agency to discuss the particular approach to establish BE for that particular drug product.