# Content and Format of Composition Statement and Corresponding Statement of Ingredients in Labeling in NDAs and ANDAs

## 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***DRAFT GUIDANCE***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 2024**
**Generic Drugs**

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

**April 2024**
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# Content and Format of Composition Statement and Corresponding Statement of Ingredients in Labeling in NDAs and ANDAs 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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 is intended to assist new drug application (NDA) and abbreviated new drug application (ANDA) applicants in submitting an accurate and complete composition statement in their applications and a corresponding statement of ingredients in the DESCRIPTION section of the prescribing information[2] and in other types of FDA-approved labeling (e.g., patient labeling, carton and container labeling) as applicable.[3] Throughout this guidance, the term *composition statement* refers to information submitted in a drug product's NDA or ANDA, and the term *statement of ingredients* refers to information contained in a drug product's DESCRIPTION section of its prescribing information and other types of FDA-approved labeling, as appropriate.

This guidance provides recommendations for the content and format of the composition statement in the application and the corresponding statement of ingredients in labeling. It provides recommendations for minimizing the number of assessment cycles and communications that are appropriate for approval, as well as ensuring that FDA-approved labeling contains the required qualitative (Q1) and quantitative (Q2) ingredient information. This guidance includes examples of common, recurring problems FDA has identified during its assessment of NDAs and ANDAs concerning the content and format of the composition statement in the application and the corresponding statement of ingredients in labeling, and this guidance provides applicants with recommendations on how to avoid these problems. This guidance also describes FDA's intent, when possible, to use the composition statement submitted in electronic common

[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 21 CFR 201.57(c)(12) and 21 CFR 201.80(a).

[3] 21 CFR 201.100 requires labeling for certain drug products to include information on inactive ingredients.

technical document (eCTD)[4] section 3.2.P.1 of NDAs and ANDAs as the statement of ingredients.[5]

This guidance does not include a comprehensive list of all potential problems in a composition statement or a statement of ingredients. FDA encourages applicants to review applicable FDA regulations and all applicable guidance documents for industry to understand FDA's current thinking on this topic.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

## II. BACKGROUND

Section 505(b)(1)(A) (21 U.S.C. 355(b)(1)(A)) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) requires, among other things, that an NDA include "a full list of the articles used as components of such drug" and "a full statement of the composition of such drug."[6] Further, 21 CFR 314.50(d)(1)(ii)(*a*) requires that an NDA contains a "list of all components used in the manufacture of the drug product (regardless of whether they appear in the drug product) and a statement of the composition of the drug product."

Section 505(j) of the FD&C Act, together with its implementing regulations, generally requires that an ANDA must contain information to demonstrate that the proposed drug product and the applicable reference listed drug (RLD) are the same with respect to active ingredient(s), dosage form, route of administration, strength, previously approved conditions of use, and, with certain exceptions, labeling.[7] An ANDA must also include sufficient information to demonstrate that the proposed drug product is bioequivalent to the RLD[8] and must demonstrate that the methods used in, or facilities and controls used for, the manufacture, processing, and packing of the drug are adequate to assure and preserve its identity, strength, quality, and purity.[9] An ANDA

[4] For more information on the eCTD format, see https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/electronic-common-technical-document-ectd.

[5] The statement of ingredients is the composition referred to in 21 CFR 314.50(d)(1)(ii)(*a*).

[6] Section 505(b)(1)(A)(ii) and (iii) of the FD&C Act.

[7] Sections 505(j)(2)(A) and 505(j)(4) of the FD&C Act, 21 CFR 314.94, and 21 CFR 314.127.

[8] Sections 505(j)(2)(A)(iv) and 505(j)(4)(F) of the FD&C Act and 21 CFR 320.21(b).

[9] Section 505(j)(4)(A).

applicant is also required to list all components used in the manufacture of the drug product and a statement of the composition of the drug product.[10]

The ANDA applicant is required to identify and characterize the inactive ingredients,[11] so FDA can determine whether such inactive ingredients affect the safety or efficacy of the proposed drug product.[12] Certain drug products (i.e., parenteral, ophthalmic, and otic routes of administration) must have the same inactive ingredients (i.e., Q1 sameness) in the same concentration (i.e., Q2 sameness), with exceptions, to ensure the inactive ingredients do not affect the drug product's safety or efficacy.[13] Certain drug products' bioequivalence (BE) may be deemed self-evident if the drug product has the same inactive ingredients in the same concentration as a drug product that is the subject of an approved NDA or ANDA.[14]

For drug products where Q1/Q2 sameness is not required by regulation, such as those intended for topical, nasal, or inhalation administration, FDA's guidances sometimes recommend specific BE approaches. These BE approaches may be suitable when the formulation components and composition of the proposed generic drug product meet specified criteria for sameness or for no significant difference relative to that of the reference standard, which ordinarily is the RLD.[15]

Additionally, ANDAs must contain information to show that the proposed labeling for the generic drug product is the same as the labeling for the RLD, with certain permissible differences.[16] With limited exceptions, 21 CFR 201.100(b)(5) requires that labeling for NDAs and ANDAs for nonoral drug products contain the names of all inactive ingredients.[17] The labeling of drug products administered by parenteral injection must also specify the quantity or proportion of all inactive ingredients, except those ingredients added to adjust the pH or to make

[10] 21 CFR 314.50(d)(1)(ii)(*a*).

[11] 21 CFR 314.94(a)(9)(ii).

[12] Ibid.

[13] 21 CFR 314.94(a)(9)(iii)–(v).

[14] 21 CFR 320.22(b)(1)(ii).

[15] See 21 CFR 314.94(a)(9)(v); see, e.g., the draft product-specific guidances (PSGs) on topical Doxepin Hydrochloride, the draft PSGs on Tazarotene, and the draft PSGs on Vancomycin Hydrochloride at. https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm. When final, these guidances will represent the FDA's current thinking on these topics.

[16] See sections 505(j)(2)(A) and 505(j)(4) of the FD&C Act, 21 CFR 314.94, and 21 CFR 314.127.

[17] FDA recommends including the name of inactive ingredients in the labeling of oral drug products. The established name of the inactive ingredients is required on the labels and labeling of drug products. See section 502(e)(1)(A)(iii) of the FD&C Act. Although 21 CFR 201.100(b) does not require the names of inactive ingredients for oral drug products, from a safety perspective, listing inactive ingredients allows for identification of ingredients that may potentially cause sensitivities or hypersensitivity reactions in some patients.

the drug isotonic, which may be declared by name and a statement of their effect; if the vehicle is water for injection, it need not be named.[18]

For FDA to efficiently assess whether ANDAs meet these requirements, it is vital for NDA and ANDA applicants to report their inactive ingredients clearly and accurately. Failing to do so leads to increased assessment time, assessment cycles, and FDA communication with NDA and ANDA applicants. Additionally, accurate and specific identification of inactive ingredients is instrumental to determine whether the different inactive ingredients may affect the drug product's safety or efficacy.

## III. SUBMITTING COMPOSITION STATEMENTS IN NDAs AND ANDAs AND INCLUDING CORRESPONDING STATEMENTS OF INGREDIENTS IN LABELING

### A. Consistency Between the Composition Statement in NDAs and ANDAs and the Statement of Ingredients in the Approved Labeling

Generally, the statement of ingredients in the approved labeling should be qualitatively and quantitatively consistent with the composition statement in section 3.2.P.1 of the eCTD. Applicants of nonoral use drugs must disclose the names of all inactive ingredients and, for certain drug products, the quantities in the labeling.[19] In addition, qualitative information required by 21 CFR 201.100(b)(5), such as the identity and effect of tonicity agents or pH adjusters, must be listed in the approved labeling. In these situations, applicants should declare the names of pH adjusters in the labeling statement per 21 CFR 201.100(b)(5)(iii).

Qualitative and quantitative information required by 21 CFR 201.100 should be reflected in the labeling with the same specificity as described in section III.C, Information on Inactive Ingredient Function, Hydration State, and Amount. In addition, when an inactive ingredient is added as part of a solution, applicants should report the amount of the inactive ingredient itself rather than the amount of the solution.

Generally, applicants should not round amounts in the statement of ingredients in the labeling. The number of significant figures (i.e., decimals) reported in the statement of ingredients in the labeling should be identical to the composition statement.

Additionally, applicants should include in the statement of ingredients in the labeling all pH adjusters that may be used to manufacture the drug product regardless of whether they were used to manufacture the batch(es) submitted in the application.

[18] 21 CFR 201.100(b)(5)(iii).

[19] 21 CFR 201.100(b)(5) and 21 CFR 314.94(a)(9)(iii)–(v).

## B. Consistency in Compositions Identified Within the Same Application

Applicants should ensure drug product composition statements are qualitatively and quantitatively consistent throughout the entire application. The composition statement submitted in section 3.2.P.1 is the composition that should be used throughout the application. Generally, any submission that has a composition statement (e.g., addition of new colors or flavors, modification of inactive ingredient levels, changes in inactive ingredient grades) that differs from the composition statement submitted in section 3.2.P.1 should be accompanied by a composition table in section 3.2.P.1, and FDA would consider this a change in formulation. Any supplements that discuss drug product composition should be identical to the submitted section 3.2.P.1 and contain a statement that section 3.2.P.1 has not changed. If an applicant does wish to submit changes to a composition statement, the applicant should submit an amendment to section 3.2.P.1.[20]

### *1. Consistency Between the Composition Statement and the Master Batch or Executed Batch Records*

Applicants should ensure drug product composition statements are qualitatively and quantitatively consistent throughout the application including, but not limited to, the composition table in section 3.2.P.1, batch formula in section 3.2.P.3.2, and the executed and master production (blank manufacturing) records in section 3.2.R.

**Example 1:** The drug product composition table in section 3.2.P.1 does not list any pH adjusters. However, the drug product batch formula in section 3.2.P.3.2 lists a strong acid and strong base as pH adjusters. The executed batch records also indicate the use of both types of pH adjusters. In this case, the composition statement in section 3.2.P.1 does not accurately reflect the drug product information, and the applicant should revise the composition statement to include the acid and base components.

**Example 2:** The drug product composition statement in section 3.2.P.1 lists a fixed amount for a certain inactive ingredient. However, the drug product batch formula in section 3.2.P.3.2 lists a quantum satis (q.s.) amount of the same inactive ingredient, or the manufacturing steps show that the inactive ingredient is added in a q.s. amount to hit a target specification. In this case, the composition statement in section 3.2.P.1 and the batch formula in section 3.2.P.3.2 are not consistent, and the applicant should revise the composition statement in section 3.2.P.1 to reflect the q.s. amount for that inactive ingredient.

### *2. Consistency in Composition Statements*

There may be instances where multiple composition statements exist in the same application. Composition statements in an application should be consistent.

[20] Applicants should use the correct modifying operator to identify the current composition statement in the application. See the guidance for industry *Providing Regulatory Submissions in Electronic Format—Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* (February 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.

For example, an applicant should submit one overarching, parent composition statement in the application in section 3.2.P.1 that accounts for any variability between different manufacturing facilities. If there is variability between different manufacturing facilities, the composition statement should include all possible ingredients and their levels.

**Example:** An applicant uses multiple drug product manufacturers that use different pH adjusters, and the applicant identifies different pH adjusters in separate composition statements for each facility. The applicant fails to identify a single, overarching composition for the drug product. Instead, the applicant should provide an overarching composition statement in section 3.2.P.1, listing all possible ingredients and their levels, which should be consistent with the statement of ingredients in the labeling.

### *3. Clear Identification of Components of Inactive Ingredients*

Applicants should clearly identify components of inactive ingredients. An example of a failure to clearly identify components is when an applicant does not include a drug master file (DMF) with a selected source that contains an active ingredient with multiple components. FDA encourages applicants to identify a DMF along with a letter of authorization to reference the DMF or provide the components of the mixture and their amounts in the application. References to DMFs should clearly identify the DMF number and location (e.g., page number) of the relevant component composition information. The DMF should contain information about components of inactive ingredient mixtures such as colorant, flavor, essence, or materials used in their preparation.[21]

A further example of when an inactive ingredient may not be clearly identified is when an inactive ingredient name or United States Pharmacopeia (USP)-National Formulary (NF) title in the composition statement does not identify a single substance but refers to a family or drug product line with different chemical structures (e.g., hypromellose). In such cases, the composition statement is incomplete unless the applicant specifies the inactive ingredient grade or type[22] that fully identifies the inactive ingredient composition (e.g., hypromellose 2910 (with specified millipascal second).[23]

### *4. Actual Amount or Concentrations of an Inactive Ingredient in the Drug Product*

The applicant should denote only the actual concentration for an inactive ingredient in the drug product in its composition statement. For example, the amount reported should not be the

[21] See 21 CFR 314.420(a)(4).

[22] Many USP-NF monographs for inactive ingredients specify *types* that indicate composition (e.g., stearic acid and hypromellose types and povidone K-values). Global Substance Registration System (GSRS) also uses the term *type*. For complete identification, these types should be included in the composition statement.

[23] FDA encourages applicants to provide the preferred term as it appears in FDA's GSRS as well as the USP-NF title to clearly identify the inactive ingredient and its grade. Refer to section III.C.4, Correct Nomenclature in Composition Statements in Applications and Statements of Ingredients in Labeling, of this guidance for further information on nomenclature.

amount dispensed in preparation for manufacturing, but rather the actual amount of the inactive ingredient used in the manufacturing.

**Example:** If an applicant prepares 6 milligrams (mg) of 1 molar of sodium hydroxide solution and adds that inactive ingredient to the drug product as a q.s. amount to a pH target, the reported amount on the composition statement should be q.s and not 6 mg.

*5. Units of Measure*

An applicant should clearly list units of measure for the quantity or concentration of inactive ingredients in a composition statement (e.g., weight per weight (w/w) percent; weight per volume (w/v) percent; volume per volume (v/v) percent). Applicants sometimes erroneously list quantities in composition statements in different units of measure without noting the change in units from the other inactive ingredients in the composition. Instead, FDA recommends that applicants use the same units of concentration for all inactive ingredients, where appropriate, and include additional information, such as ingredient and/or inactive ingredient density, used in the calculations to convert the inactive ingredient concentration units. Where applicable, applicants should show the calculations for such conversions. FDA recommends that applicants clearly denote the difference in concentration units for those inactive ingredients and any associated justification for the difference.

Additionally, if an inactive ingredient concentration is listed as a percentage, applicants should clearly indicate the units of measure used to calculate the percentage (i.e., w/w, w/v, or v/v).[24] Percentages for w/w and v/v should total 100 percent. Applicants should consider that when overage is included for the active or inactive ingredients, this should be clearly noted in the composition table as well as the justification for the overage.

*6. Nominal Amounts Listed for Inactive Ingredients in Composition Statement*

Applicants should list nominal amounts for inactive ingredients in composition statements. If a range is more appropriate than a nominal amount or concentration, applicants should clearly indicate the reason for providing a range in the composition statement.

### C. Information on Inactive Ingredient Function, Hydration State, and Amount

In the application, applicants should accurately identify inactive ingredient function, provide the hydration state for applicable inactive ingredients, and accurately list the amount (or provide a range if the ingredient is not used on a q.s. basis or fixed amount) for each inactive ingredient in the drug product. Moreover, if the listed amount of the ingredient may be sourced in multiple hydration states, applicants should clearly identify this in the composition table in the application and the corresponding statement of ingredients in labeling (where applicable).

[24] See 21 CFR 201.10(d)(2), which states that alcohol must be expressed as percent volume per volume in all labeling.

### *1. Information Regarding Equivalent Amounts of Inactive Ingredients Available in Different Hydrate Forms, Purity, and Grades*

FDA recommends all ingredients should be in the same units of amount and/or concentration, and any conversions should include the associated information used to calculate those conversions. A common, recurring problem is a lack of information regarding equivalent amounts of ingredients available in different hydrate forms, purity, and grade or type of an inactive ingredient.

Examples of inactive ingredients where FDA has observed discrepancies in hydration state, purity, and grade include: edetate disodium, alcohol, sorbitol, benzalkonium chloride, hydroxyethyl cellulose, hydroxypropyl methylcellulose, povidone, carboxymethyl cellulose, acetic acid, and carbomer.

Applicants should indicate in the composition table whether the amount or concentration listed for the inactive ingredient represents the anhydrous amount, where applicable (also sometimes known as the dehydrate (i.e., dried) amount). When using an anhydrous ingredient, applicants should refer to the ingredient as *anhydrous*, not *dehydrate*, to avoid confusion with the term *dihydrate*. Anhydrous and dihydrate terms are consistent with USP-NF monograph terminology. Additionally, applicants should specify which grade or type of the inactive ingredient is used, where applicable (see section III.C.4, Correct Nomenclature in Composition Statements and in Applications Statements of Ingredients in Labeling).

### *2. Listing the Primary Function*

If an applicant lists multiple functions for an inactive ingredient, the applicant should indicate the primary function of the ingredient in the proposed drug product in its application. Generally, FDA will consider the primary function of the ingredient for purposes of ANDA formulation comparisons.

### *3. Clarity Regarding Functionality of Inactive Ingredients*

Applicants should clearly identify the functionality of an inactive ingredient in their applications. The functionality of an inactive ingredient should describe the role of the ingredient in the formulation as opposed to the mechanistic action of the ingredient. For example, *chelating agent* describes the mechanism by which the ingredient binds metal ions, but does not describe the actual function, or role, such as preservative or antioxidant, of the ingredient in the formulation.

Applicants should refrain from using ambiguous terminology when identifying the functionality of inactive ingredients in their applications. Examples of ambiguous terminology include, but are not limited to, the following: *pH buffering agent*, *acidifying agent*, and *alkalizing agent*. Instead of *pH buffering agent*, applicants should simply use the term *buffering agent* when the ingredient acts with a conjugate acid or base to buffer the composition from changes to the pH. When the primary function of an inactive ingredient is to alter the pH of the formulation and is commonly a strong acid or base, the ingredient's primary function should be listed as a *pH adjuster*. When the primary function of an inactive ingredient is to increase the solubility of the

active ingredient, applicants should use the term *solubilizing agent*, instead of *acidifying agent* or *alkalizing agent*.

Applicants should also refrain from listing an inactive ingredient as a pH adjuster in the statement of ingredients in the labeling when it functions as an in situ converter (e.g., salt-forming agent). When one inactive ingredient is used for in situ conversion and pH adjustment, the composition table should indicate the amount used for in situ conversion.

#### *4. Correct Nomenclature in Composition Statements in Applications and Statements of Ingredients in Labeling*[25]

Applicants should use the Global Substance Registration System (GSRS) display name, which identifies the Unique Ingredient Identifiers for a particular inactive ingredient, in the composition statement. If the GSRS preferred term differs from the USP-NF monograph title, FDA recommends adding the USP monograph title with an asterisk below the composition statement for clarity and to demonstrate consistency with the labeled statement of ingredients. See Appendix for an example. Applicants should list the ingredients' hydration state(s) and provide additional relevant descriptive information, as appropriate.[26] Additionally, if the inactive ingredient has multiple hydration states and is the subject of a USP monograph, applicants should use a footnote to provide the inactive ingredient's USP monograph title and equivalent amount based on the monograph definition. Furthermore, when an inactive ingredient has multiple hydration states, the USP monograph definition explains how those quantities should be expressed. Where use of the inactive ingredient in a composition statement deviates from the USP monograph, applicants should provide a statement that describes the deviation.[27]

Applicants must list the established name of inactive ingredients in the statement of ingredients in a drug product's labeling.[28,29] The term *established name* is defined in section 502(e)(3) of the FD&C Act (21 U.S.C. 352) as an official name designated under section 508 of the FD&C Act (21 U.S.C 358). If no such official name has been designated, and the drug or ingredient is an article recognized in an official compendium (such as USP), then the established name is the official title described in such compendium.[30] If neither of the two options above applies, then the established name is the common or usual name of the drug.[31] FDA does not routinely

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[25] The principles and recommendations in this section are also relevant to biological products that are the subject of biologics license applications.

[26] If there is no Unique Ingredient Identifier for an ingredient, contact FDA-SRS@fda.hhs.gov.

[27] USP General Notices 3.20, *Indicating Conformance*.

[28] Section 502(e)(1)(A)(iii) of the FD&C Act.

[29] If an inactive ingredient has the grade or type as a part of the compendial name, this information should be included in the labeling.

[30] Section 502(e)(3)(B) of the FD&C Act.

[31] Section 502(e)(3)(C) of the FD&C Act.

designate official names under section 508 of the FD&C Act. Therefore, if there is a USP monograph for an inactive ingredient, the inactive ingredient's established name is the USP monograph title. Additionally, applicants should list inactive ingredients in alphabetical order in the statement of ingredients in labeling.[32] See Appendix for an example.

### D. Drug Product Compositions in Annual Reports

In an annual report, applicants may make minor editorial changes (e.g., correcting a typographical error) that do not affect the actual drug product composition, or they may delete or reduce an ingredient intended to affect only the color of the drug product.[33] Generally, changes to a composition statement that go beyond those listed at 21 CFR 314.70(d) would not fall into either of these categories. In these circumstances, applicants should submit updated composition statements in a submission after approval.

## IV. SUBMITTING UPDATED COMPOSITION STATEMENT IN AN APPLICATION AND CORRESPONDING STATEMENT OF INGREDIENTS IN LABELING FOR APPROVED NDAs AND ANDAs

The application holder of an approved NDA and ANDA should submit an updated composition statement and the corresponding statement of ingredients in labeling when applicable, consistent with the recommendations in this guidance in an appropriate submission after approval.[34]

[32] See USP General Chapter <1091> *Labeling of Inactive Ingredients*.

[33] 21 CFR 314.70(d)(1), 21 CFR 314.70(d)(2)(ii), and 21 CFR 314.97.

[34] See section 506A of the FD&C Act (21 U.S.C. 356), 21 CFR 314.70, and 21 CFR 314.97.

# APPENDIX — EXAMPLES OF COMPOSITION STATEMENT IN NDAs AND ANDAs AND CORRESPONDING STATEMENT OF INGREDIENTS IN LABELING

## Example 1: Composition Statement for Injectable Drug Product

Inactive ingredient functions clearly identified using nonambiguous terminology

Composition of Drugozide Injection 125 mg/5 mL (25 mg/mL) vial

| Component | Reference Quality Standard | Function | Quantity (% w/v) | Quantity (%w/w) | Quantity (mg) mg/mL | Quantity (mg) mg/vial |
|---|---|---|---|---|---|---|
| Sodium Drugozide[i] | USP | API | 2.73% | 3.00% | 27.3 | 136.5 |
| Sodium Chloride | USP | Tonicity | 0.25% | 0.28% | 2.5 | 12.5 |
| Trisodium Citrate Dihydrate[ii] | USP | Buffer | 0.10%[iii] | 0.11% | 1 | 5 |
| Citric Acid Monohydrate[iv] | USP | Buffer | 0.10% | 0.11% | 1 | 5 |
| Edetate Disodium Dihydrate[v][vi] | USP | Preservative | 0.06% | 0.06% | 0.554 | 2.77 |
| Sodium Metabisulfate | In-House | Antioxidant | 0.50% | 0.55% | 5 | 25 |
| Povidone K-17 | USP | Stabilizer | 0.10% | 0.11% | 1 | 5 |
| Sodium Hydroxide | NF | pH adjuster | q.s. | q.s. | q.s. | q.s. |
| Hydrochloric Acid (1M)[vii] | In-House | pH adjuster | q.s. | q.s. | q.s. | q.s. |
| Water for Injection | USP | Solvent | q.s. to 100% | q.s. to 100% | q.s. to 1 mL | q.s. to 5 mL |
| Nitrogen[viii] | NF | Processing Aid | - | - | - | - |

Units clearly identified

Hydration state clearly identified with footnotes for expressed quantities

Inactive ingredient grade clearly identified

- Identify any overages
- Clarify the corresponding quantities related to the hydration state
- Clarify when inactive ingredients are not present in the final drug product

[i] Factored to a 100% basis, equivalent to 25 mg/mL of drugozide
[ii] 1 mg trisodium citrate dihydrate is equivalent to 0.877 mg sodium citrate, USP (anhydrous)
[iii] Include hydration state. In this instance as dihydrate
[iv] 1 mg citric acid monohydrate is equivalent to 0.914 mg citric acid anhydrous
[v] 0.554 mg edetate disodium dihydrate is equivalent to 0.500 mg edetate disodium, USP (anhydrous)
[vi] Components are named by the USP Monograph Title
[vii] Ingredient prepared from USP grade Concentrated Hydrochloric acid and Ph. Eur. grade Purified water.
[viii]Nitrogen is used as a processing aid during the manufacturing process and is not present in the final drug product

mg = milligram; mL = milliliter; w/v = weight per volume; w/w = weight per weight; USP = United States Pharmacopeia; NF = National Formulary; API = active pharmaceutical ingredient; q.s. = quantum satis.

## Example 2: Composition Statement for Injectable Drug Product Using a Fixed Amount of a Strong Acid or Base for In Situ Salt Conversion

Inactive ingredient functions clearly identified using nonambiguous terminology

Composition of Drugozide Injection 125 mg/5 mL (25 mg/mL) vial

| Reference Quality Standard | Reference Quality Standard | Function | Quantity (% w/v) | Quantity (% w/w) | Quantity (mg) mg/mL | Quantity (mg) mg/vial |
|---|---|---|---|---|---|---|
| Drugozide[i] | USP | API | 2.50% | 2.75% | 25 | 125 |
| Sodium Chloride | USP | Tonicity | 0.25% | 0.28% | 2.5 | 12.5 |
| Trisodium Citrate Dihydrate[ii] | USP | Buffer | 0.10%[iii] | 0.11% | 1 | 5 |
| Citric Acid Monohydrate[iv] | USP | Buffer | 0.10% | 0.11% | 1 | 5 |
| Edetate Disodium Dihydrate[v][vi] | USP | Preservative | 0.05% | 0.06% | 0.55 | 2.75 |
| Sodium Metabisulfate | In-House | Antioxidant | 0.50% | 0.55% | 5 | 25 |
| Povidone K-17 | USP | Stabilizer | 0.10% | 0.11% | 1 | 5 |
| Sodium Hydroxide | NF | Salt-forming agent | 0.41% | 0.45% | 4.1 [vii] | 20.5 |
| Hydrochloric Acid (1M)[viii] | In-House | pH adjuster | q.s. | q.s. | q.s. | q.s. |
| Water for Injection | USP | Solvent | q.s. to 100% | q.s. to 100% | q.s. to 1 mL | q.s. to 5 mL |
| Nitrogen[ix] | NF | Processing Aid | - | - | - | - |

Units clearly identified

Hydration state clearly identified with footnotes for expressed quantities

Inactive ingredient grade clearly identified

Listed with the primary function

[i] Factored to a 100% basis, equivalent to 27.3 mg/mL of sodium drugozide
[ii] 1 mg trisodium citrate dihydrate is equivalent to 0.877 mg sodium citrate, USP (anhydrous)
[iii] Include hydration state. In this instance as dihydrate
[iv] 1 mg citric acid monohydrate is equivalent to 0.914 mg citric acid anhydrous
[v] 0.554 mg edetate disodium dihydrate is equivalent to 0.500 mg edetate disodium, USP (anhydrous)
[vi] Components are named by the USP Monograph Title
[vii] 4 mg for in-situ conversion of drugozide to sodium drugozide and 0.1 mg for pH adjustment.
[viii] Ingredient prepared from USP grade Concentrated Hydrochloric acid and Ph. Eur. grade Purified water.
[ix] Nitrogen is used as a processing aid during the manufacturing process and is not present in the final drug product

- Identify any overages
- Clarify the corresponding quantities related to the hydration state
- Indicate the amount used for in situ conversion and pH adjustment
- Clarify when inactive ingredients are not present in the final drug product

mg = milligram; mL = milliliter; w/v = weight per volume; w/w = weight per weight; USP = United States Pharmacopeia; NF = National Formulary; API = active pharmaceutical ingredient; q.s. = quantum satis.

**Example 3: Corresponding Statement of Ingredients for Example 1 and Example 2 in the DESCRIPTION Section of the Prescribing Information[1]**

**11 DESCRIPTION**

*[Include required information]*[2] . . . Each milliliter contains drugozide 25 milligrams (mg) (equivalent to 27.3 mg sodium drugozide) and the following inactive ingredients: citric acid monohydrate 0.914 mg,[3] edetate disodium 0.5 mg, povidone K-17 1 mg, sodium chloride 2.5 mg, sodium citrate 0.877 mg, sodium metabisulfate 5 mg, and water for injection. Hydrochloric acid and sodium hydroxide added to adjust pH.

[1] The tonicity adjuster information is not required by regulation but should be included. In Example 2, 4 milligrams (mg) of sodium hydroxide is listed for in situ conversion to form the active ingredient, and footnote vii indicates that additional (i.e., 0.1 mg) sodium hydroxide is added for pH adjustment. As such, sodium hydroxide should also be listed in labeling as a pH adjuster, consistent with the recommendations in section IV.C.3, Clarity Regarding Functionality of Inactive Ingredients.

[2] See 21 CFR 201.57(c)(12) and 21 CFR 201.80(a).

[3] See United States Pharmacopeia's definition of *citric acid monohydrate*. Citric acid monohydrate contains one molecule of water of hydration. It contains not less than 99.5 percent and not more than 100.5 percent of citric acid, calculated on the anhydrous basis.