# Quantitative Labeling of Sodium, Potassium, and Phosphorus for Human Over-the-Counter and Prescription Drug Products

## 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***DRAFT GUIDANCE***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)**
**Center for Biologics Evaluation and Research (CBER)**

**September 2022**
**Labeling**

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# Quantitative Labeling of Sodium, Potassium, and Phosphorus for Human Over-the-Counter and Prescription Drug Products 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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 provides recommendations for quantitative labeling of sodium, potassium, and phosphorus present in human prescription and nonprescription (commonly referred to as over-the-counter (OTC)) drugs.[2] This guidance addresses sodium, potassium, and phosphorus when present as constituents of active or inactive drug ingredients[3] (e.g., sodium as a constituent of the inactive ingredient *anhydrous trisodium citrate*, phosphorus as a constituent of the inactive ingredient *dibasic calcium phosphate*, or sodium as a constituent of the active ingredient *naproxen sodium*). Products within the scope of this guidance's recommendations are orally ingested products and injectable medications containing an amount of 5 mg or more of sodium, potassium, or elemental phosphorus per maximum single dose. Individuals or entities responsible for drug product labeling are encouraged to engage with FDA for advice on specific cases.

This guidance restates the legal requirements set forth in current regulations regarding quantitative information for sodium and potassium in labeling of OTC products. (See 21 CFR 201.64 and 201.72.) It provides additional information to manufacturers who seek to include quantitative information for sodium, potassium, and phosphorus in labeling for prescription drug products and for phosphorus in labeling for OTC drugs.

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[1] This guidance has been prepared by the Office of Medical Policy in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research at the Food and Drug Administration.

[2] This guidance applies to drugs, including biological products that are regulated as drugs. For the purposes of this guidance, the terms *drug product* or *drug* or *product* are used to refer to human OTC and prescription drug and biological products that are regulated as drugs.

[3] As provided for in 21 CFR 201.10(b), "The term *ingredient* applies to any substance in the drug, whether added to the formulation as a single substance or in admixture with other substances."

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 guidances means that something is suggested or recommended, but not required.

## II. DISCUSSION

This guidance provides information and recommendations concerning the quantification of sodium, potassium, and phosphorus in drug product labeling because (1) these substances are common constituents of ingredients that can be present in drug products in amounts that may represent a significant portion of an individual's total daily intake and (2) dietary restriction of these constituents is often recommended for various diseases that affect a substantial number of patients in the U.S. population.

Sodium, potassium, and phosphorus may be present in drug products as constituents of active or inactive ingredients.[4,5] The amount of these constituents can vary among drug products, including drugs with the same active ingredient, depending on factors such as the manufacturer, the formulation, or the dosage form. For example, the amount of sodium, potassium, or phosphorus may differ between a reference listed drug[6] (RLD) and a generic version of the drug or between different generic drugs with the same RLD.

Health care providers generally recommend that patients with certain clinical conditions—such as heart failure, hypertension, or chronic kidney disease—restrict dietary intake of sodium, potassium, and/or phosphorus. Quantifying these constituents in drug product labeling would

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[4] See FDA's database Inactive Ingredient Search for Approved Drugs (available at https://www.accessdata.fda.gov/scripts/cder/iig/).

[5] See the *Orange Book: Approved Drug Products With Therapeutic Equivalence Evaluations* (available at https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm) to search for FDA-approved drugs containing sodium, potassium, or phosphate as a constituent of an active ingredient.

[6] The term *reference listed drug* is defined in 21 CFR 314.3(b) as "the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA [abbreviated new drug application]." The term *listed drug* is defined in 21 CFR 314.3(b) as "a new drug product that has been approved under section 505(c) of the Federal Food, Drug, and Cosmetic Act for safety and effectiveness or under section 505(j) of the Federal Food, Drug, and Cosmetic Act, which has not been withdrawn or suspended under section 505(e)(1) through (5) or section (j)(6) of the Federal Food, Drug, and Cosmetic Act, and which has not been withdrawn from sale for what FDA has determined are reasons of safety or effectiveness." Listed drug status is evidenced by a drug product's identification in the current edition of FDA's publication *Approved Drug Products With Therapeutic Equivalence Evaluations* (commonly referred to as the Orange Book) as an approved drug. A drug product is deemed to be a listed drug on the date of approval for the new drug application (NDA) or ANDA for that drug product.

provide health care providers and patients with information that will help them account for the amounts of these constituents present in a patient's daily drug regimen when determining an individual's total daily intake. Quantifying these constituents in drug product labeling as recommended in this guidance may also allow health care providers and patients to select drug products with lower amounts of these constituents when such alternatives are available.

## III. LABELING RECOMMENDATIONS

This section provides recommendations on the description and placement of the quantitative information in labeling for sodium, potassium, and phosphorus.

### A. Clarifying What Should Be Quantified in Drug Labeling

For simplicity and consistency with existing OTC regulations (see section III.E of this guidance), FDA recommends that drug labeling include certain information about the total amounts of sodium, potassium, and phosphorus in a drug product, expressed in milligrams (mg). For sodium and potassium, this guidance pertains to sodium and potassium ions. For phosphorus, however, this guidance pertains to the calculated equivalent amount of elemental phosphorus from all the phosphorus-containing components. Although the terms phosphorus (chemical element, P) and phosphate ($PO_4^{3-}$) are often used interchangeably in the clinical literature, they are not synonymous. Notably, when expressed in milligrams, phosphate values are approximately three times the phosphorus values. Although phosphorus is typically present in nature and in many drugs as phosphate, expressing drug content in terms of equivalent phosphorous content is in accordance with dietary intake recommendations and values reported for food and therefore allows for easier comparisons of quantities of phosphorus in foods and in drugs.

The drug labeling should state the total amount of the constituent, regardless of whether the constituent is present as part of an active or inactive ingredient. The amount of sodium, potassium, or phosphorus in a drug product should be determined from the drug product's formulation information. For example, if a drug product contains both naproxen sodium and trisodium citrate, the total amount of sodium in the drug product from both compounds should be stated. The amount of sodium present in 1 gram (g) of trisodium citrate, for instance, is 267 mg as determined stoichiometrically according to its molecular formula ($Na_3C_6H_5O_7$). Similarly, 1 g of anhydrous dibasic calcium phosphate ($CaHPO_4$) contains 228 mg of phosphorus.

### B. Thresholds Below Which FDA Does Not Recommend or Require Quantification in Labeling

FDA does not recommend or require quantitative information in labeling for sodium, potassium, or phosphorus if the amount in a maximum single dose of the drug product is less than 5 mg. The presence of sodium, potassium, and phosphorus in quantities less than 5 mg is not expected to be clinically significant relative to dietary intake, even in patients taking several nonprescription and prescription drugs. For example, if the maximum single dose of a drug product is two tablets at one time and that total dose contains 4 mg of sodium (2 mg of sodium

per tablet), FDA does not recommend or require quantitative information in the labeling regarding the sodium content of the drug product. In this case, manufacturers may elect to include a statement in labeling that the product contains "less than 5 mg of sodium per tablet." If the maximum single dose is two tablets at one time and the total dose contains 8 mg of sodium (4 mg of sodium per tablet), however, FDA would recommend quantitative information in labeling for sodium content for the drug.

### C. Clarifying Quantities Per Dosage Unit

For consistency across products and for simplicity and ease of determination, FDA recommends that manufacturers provide quantitative information on a *per dosage unit* basis. The dosage unit should be consistent with the primary expression of potency strength on the container label. For oral solids, the amount per tablet, capsule, etc., should be used regardless of how many tablets/capsules a patient might take at one time or per day as stated in the labeling. For oral liquids (or products reconstituted to make an oral liquid), if the strength is expressed as the amount of drug/mL or amount of drug/5 mL, for the purposes of reporting sodium, potassium, or phosphorus, the dosage unit will be 1 mL or 5 mL, respectively.

For injectable dosage forms, the dosage unit will be 1 mL, unless the net quantity in the container is less than 1 mL, in which case the dosage unit will be the net quantity in the container.

For injectable drug products provided as solids intended to be reconstituted to yield an injectable solution or suspension, FDA recommends that the quantitative information for sodium, potassium, and phosphorus be stated as the amount per milliliter (e.g., 5 mg/mL) or per dosage unit (e.g., 5 mg/0.5 mL) after reconstitution if the labeling provides for the use of a specific amount of diluent for which the quantitative information for sodium, potassium, or phosphorus is known.

If you have questions, contact the appropriate FDA review division for guidance.

### D. Rounding

As stated previously, this guidance restates the legal requirements set forth in current regulations regarding quantitative information in labeling for sodium and potassium for OTC products intended for oral ingestion. For simplicity and consistency with existing OTC regulations (see section III.E of this guidance), FDA recommends (1) that labeling of quantitative information regarding the total amounts of sodium present in a drug product be stated in milligrams and rounded to the nearest whole number per dosage unit and (2) that potassium be rounded to the nearest 5 mg per dosage unit (or expressed in the nearest tenth of a gram if present above 1 g per dosage unit). FDA recommends rounding the total amounts of phosphorus present in a drug product to the nearest 5 mg per dosage unit. In some cases, doing so will allow for a single statement in labeling to apply to more than one available strength of a drug product (e.g., "Each tablet contains 20 mg of phosphorus"). See Appendix A for examples.

## E. OTC and Prescription Drug Product Labeling

### *1. OTC Drug Products*

FDA regulations currently require labeling of certain OTC drugs to include quantitative information for sodium (21 CFR 201.64) and potassium (21 CFR 201.72). Specifically, the regulations state that the labeling of OTC drug products intended for oral ingestion must contain the sodium content per dosage unit (e.g., per tablet, per 5 mL), if the sodium content of a single maximum recommended dose of the product (which may be one or more dosage units) is 5 mg or more. The same standard applies for potassium. This information is captured under the ***Other information*** heading of the Drug Facts labeling.[7]

FDA's labeling recommendation in this guidance for phosphorus in OTC drug products aligns with the existing regulations for sodium and potassium in OTC drug products intended for oral ingestion.[8] For orally ingested OTC drugs, FDA recommends (1) including the amount of phosphorus in the Drug Facts labeling under the heading ***Other information*** and (2) labeling the phosphorus content per dosage unit (e.g., per tablet) if the phosphorus content of a single maximum recommended dose of the product (which may be one or more dosage units) is 5 mg or more. See Appendix B for examples regarding this section.

### *2. Prescription Drug Products*

When quantitative information on sodium, potassium, and phosphorus content is included in prescription drug labeling, it should be presented per dosage unit in the DESCRIPTION section of labeling, following the list of inactive ingredients. See Appendix A for examples regarding this section.

We note that for some biological products, such as cellular therapy products, quantification may be difficult. In such cases, we recommend that manufacturers considering including information about these substances discuss with the appropriate FDA review division how to quantify these substances.

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[7] See 21 CFR 201.64 and 201.72, respectively. See also 21 CFR 201.66(c)(7)(i).

[8] See 21 CFR 201.64 (sodium), 201.72 (potassium), and 331.11 (listing of specific active ingredients). FDA has also issued the guidance for industry *Labeling OTC Human Drug Products — Questions and Answers* (December 2008). We update guidances periodically. To ensure that you have the most recent version of a guidance, check FDA's guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

### F. Considerations for Generic Drugs Approved Under Section 505(j) of the Federal Food, Drug, and Cosmetic Act

Generally, drug product labeling for a drug approved under an abbreviated new drug application (ANDA) is required to be the same as the labeling for the RLD, with certain permissible labeling differences because the ANDA and the RLD are produced or distributed by different manufacturers. Permissible differences include, for example, differences in labeling made to comply with current FDA labeling guidelines or other guidance (see section 505(j)(2)(A)(v) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355)) and 21 CFR 314.94(a)(8)(iv)).

An ANDA or a supplement to an ANDA that proposes to include quantitative information in its proposed labeling for sodium, potassium, and/or phosphorus, as recommended in this guidance, or proposes to omit such quantitative information, even if the inclusion or omission of such information differs from how such information is reflected in the labeling for the RLD, may be acceptable, provided the requirements for approval are met.

## IV. SUBMISSION AND ADOPTION RECOMMENDATIONS AND REQUIREMENTS

This section describes recommendations and requirements for manufacturers on how to submit labeling that includes quantitative information about sodium, potassium, and/or phosphorus for a drug product.

### A. Drug Products With New or Pending Applications

An applicant submitting a new drug application (NDA), an ANDA, or a biologics license application (BLA) that elects to include quantitative information on sodium, potassium, or phosphorus in product labeling must ensure that the labeling statement is accurate and is supported by information related to the drug product's ingredients.[9] Support for the quantitative information regarding the amounts of constituents of ingredients that are described in labeling should be submitted in the chemistry, manufacturing, and controls section of the application, under the heading DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT. Manufacturers with pending applications may add this information when they propose changes to their draft labeling during the application review process.

### B. Drug Products With Approved Applications

If a drug product's labeling already includes information on the constituents discussed in this guidance, manufacturers should review this guidance and determine whether they should revise their labeling to meet the current content and format recommendations.

[9] See section 502(a) of the FD&C Act (21 U.S.C. 352(a)).

When an NDA, ANDA, or BLA holder plans to add or revise quantitative information about sodium, potassium, and phosphorus in drug product labeling without changes to the approved product formulation—and the change is not combined with another change that requires submission of a supplement—the application holder may revise labeling at any time. Pursuant to 21 CFR 314.70(a)(3) and 21 CFR 601.12(a)(3), FDA recommends that application holders provide notification and supporting information in an annual report when drug product labeling is changed to include the quantities of sodium, potassium, and/or phosphorus without other changes to the product or its labeling that would require submission of a supplement.

## APPENDIX A: EXAMPLES OF PRESCRIPTION DRUG LABELING

This appendix provides examples of quantitative labeling statements for prescription drugs containing sodium, potassium, and phosphorus as constituents of prescription drug ingredients in products with single or multiple strengths and for products with different dosage forms.[1] The Food and Drug Administration (FDA) recommends that these constituents be listed in alphabetical order when more than one is quantified in labeling.

1. For prescription drug products available in a single strength, state the amount of each constituent present in the product. For example:

   "Each [insert DRUG name] tablet contains 5 mg of potassium and 9 mg of sodium."

   "Each [insert DRUG name] tablet contains 7 mg of sodium."

2. For prescription drug products available in multiple strengths containing multiple constituents, these data may be presented in a concise and readable manner (e.g., in a table). For example:

**Table 1. Phosphorus, Potassium, and Sodium Constituents for [insert DRUG name]**

| Tablet Strength Per Dosage Unit | Phosphorus Content | Potassium Content | Sodium Content |
|---|---|---|---|
| **50 mg tablet** | 20 mg | 10 mg | 43 mg |
| **100 mg tablet** | 40 mg | 35 mg | 50 mg |
| **150 mg tablet** | 60 mg | 50 mg | 62 mg |

3. For prescription drug products available in multiple strengths with similar constituent content, the information may be more efficiently presented in a sentence or two rather than a table. For example:

   "All strengths of [insert DRUG name] tablets contain less than 5 mg each of phosphorus and potassium per tablet. The 5 mg and 15 mg [insert DRUG name] tablets each contain 7 mg of sodium. The 30 mg tablet contains 12 mg of sodium."

   "The 5 mg and 15 mg [insert DRUG name] tablets each contain 5 mg of phosphorus. The 30 mg tablet contains 10 mg of phosphorus."

   "The 5 mg and 15 mg [insert DRUG name] tablets each contain 5 mg of potassium and sodium. The 30 mg tablet contains 10 mg each of potassium and sodium."

[1] The examples in this appendix are for illustrative purposes only and should not be considered exhaustive. Alternative wording can be proposed for FDA's consideration, as appropriate.

4. For drug products supplied as solutions or suspensions for injection, FDA recommends that quantitative information for sodium, potassium, and phosphorus be stated as the amount per milliliter (e.g., 10 mg/mL). For example:

   "Each 1 mL of [insert DRUG name] injection contains 33 mg of sodium and less than 5 mg each of phosphorus and potassium."

   Alternatively, for oral drug products supplied as solutions or suspensions or as solids intended to be reconstituted to yield oral solutions or suspensions, FDA recommends that quantitative information for sodium, potassium, and phosphorus be stated for the most commonly administered dosage unit of volume. For example:

   "Each 5 mL of [insert DRUG name] oral solution contains 100 mg of potassium, 47 mg of sodium, and less than 5 mg of phosphorus."

5. For drug products containing less than 5 mg of sodium, potassium, or phosphorus in the maximum recommended single dose, applicants may include this information in labeling. For example:

   "Each [insert DRUG name] capsule contains less than 5 mg each of sodium, potassium, and phosphorus."

## APPENDIX B: EXAMPLES OF OTC DRUG LABELING

This appendix provides examples of statements to include in the labeling of nonprescription (commonly referred to as over-the-counter (OTC)) drug products containing sodium, potassium, and phosphorus as constituents of the product's ingredients.[1]

If manufacturers choose to include the recommended phosphorus content within the Drug Facts labeling, it should be included in alphabetical order within the required list of constituents under the heading ***Other information***. Although a statement of phosphorus content would be considered *additional information*,[2] phosphorus should be included in alphabetical order within the list of required constituents, to avoid confusion.

If applicable, the first bulleted statement under this heading must include calcium (21 CFR 201.70), magnesium (21 CFR 201.71), potassium (21 CFR 201.72), and sodium (21 CFR 201.64) to read as follows:

> [in bold type] **Each (insert appropriate dosage unit) contains:** [in non-bold type, insert name(s) of ingredient(s) and quantity of each ingredient].

**Example 1: Labeling statement when maximum single dose (which may be one or more dosage units) contains *5 mg or more of* constituent (i.e., sodium, potassium, and phosphorus):**

> ***Other information***
>
> **Each tablet contains:** calcium 20 mg, magnesium 10 mg, phosphorus 5 mg, potassium 5 mg, and sodium 13 mg
>
> [bullet] Phenylketonurics: Contains phenylalanine 10 mg per tablet
>
> [bullet] [insert storage conditions]
>
> [bullet] [insert tamper-evident statement]

[1] The examples in this appendix are for illustrative purposes only and should not be considered exhaustive. Alternative wording can be proposed for FDA's consideration, as appropriate.

[2] See also 21 CFR 201.66(c)(7).

**Example 2: Labeling statement when maximum single dose contains *less than 5 mg* of constituent (i.e., sodium, potassium, and phosphorus):**

If firms choose to include the statement for phosphorus, potassium, and sodium in the Drug Facts labeling when the maximum single dose contains less than 5 mg of constituent (i.e., sodium, potassium, and phosphorus), this information should appear as the last statement under the subheading ***Other information***. Placement of such statements should not interfere with the required information in the labeling.

***Other information***

[bullet] Phenylketonurics: Contains phenylalanine 10 mg per tablet

[bullet] [insert storage conditions]

[bullet] [insert tamper-evident statement]

[bullet] [insert relevant constituent; for example, "contains less than 5 mg sodium per tablet"]