Naming of Drug Products Containing Salt Drug Substances

Guidance for Industry

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

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Labeling

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Naming of Drug Products Containing Salt Drug Substances

Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not create 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 for industry is intended to help you, the sponsor, understand how products with active ingredients that are salts may be affected by CDER's implementation of the United States Pharmacopeia (USP) policy entitled, *Monograph Naming Policy for Salt Drug Substances in Drug Products and Compounded Preparations*[2] (the USP Salt Policy). Your involvement with the implementation of this policy helps to ensure drug product naming that is consistent with the USP Salt Policy, which became effective on May 1, 2013.

This guidance addresses prescription drug products approved under the Federal Food, Drug, and Cosmetic Act (FD&C Act).[3] This guidance does not address implementation of the USP Salt Policy for nonprescription drug products[4] or biological products licensed under the Public Health Service Act (PHS Act).[5]

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

The USP Salt Policy is a naming and labeling policy applicable to drug products that contain an active ingredient that is a salt. The policy stipulates that USP will use the name of the active moiety, instead of the name of the salt, for such a drug product when creating a drug product

[1] This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] The *Monograph Naming Policy for Salt Drug Substances in Drug Products and Compounded Preparations* is published in USP General Chapter <1121> *Nomenclature.* Please see Appendix 1.

[3] See section 505 of the FD&C Act. This guidance does not address naming and labeling of compounded preparations.

[4] See 21 CFR 201.66.

[5] See section 351 of the PHS Act.

monograph title. The USP Salt Policy also states that USP will base the strength of the product on the active moiety. The policy allows for exceptions under specified circumstances.

The USP Salt Policy became effective on May 1, 2013, and USP is now applying it to all new drug product monographs for products that contain an active ingredient that is a salt. It affects the development of new drug products, because a USP monograph title for a new drug product, in most instances, serves as the nonproprietary or "established" name of the related drug product.[6] A drug product with a label or labeling that contains a name that is inconsistent with the applicable monograph title risks being misbranded.[7]

The USP Salt Policy only applies to the monograph titles for drug products. The policy will not apply to the titles of monographs for drug substances (active ingredients). Accordingly, the names of active ingredients (e.g., salts) will not be affected.

A. USP Salt Policy Overview[8]

The USP Salt Policy provides the following:

1. When an active ingredient in a drug product is a salt, the drug product monograph title will contain the name of the active moiety (or neutral form), and not the name of the salt (e.g., "newdrug tablets" instead of "newdrug hydrochloride tablets").

2. The strength also will be expressed in terms of the active moiety (e.g., "100 mg newdrug") rather than the salt strength equivalent (e.g., "123.7 mg newdrug hydrochloride").

3. If the name and strength of a drug product are expressed in terms of the active moiety, the full name and full strength (or proportion, if CDER has determined proportion is more appropriate) of the active ingredient (e.g., salt), will appear elsewhere on the drug product label and labeling.[9]

4. The USP Salt Policy provides for exceptions to the "active moiety" naming approach, when the name of the salt conveys vital information from a clinical perspective. In these cases, the drug product monograph title will include the name of the salt, and the strength of the drug product also is expressed in terms of the salt form (active ingredient).

5. USP does not anticipate changing existing monograph titles, unless necessary for safety. USP and CDER have agreed to coordinate regarding any necessary retrospective name changes.

B. How CDER is Applying the USP Salt Policy

We are applying the USP Salt Policy to prescription drug products under development for which approval is sought under section 505 of the FD&C Act.

[6] See section 502(e)(3) of the FD&C Act.
[7] See section 502(e)(1)(A)(i) of the FD&C Act.
[8] See USP General Chapter <1121> *Nomenclature*.
[9] See section III.B. for additional information related to the labeling of products that are salts.

CDER's application of the USP Salt Policy should help avoid medication errors that could result from a mismatch of established name and strength (e.g., the name includes the salt but the strength is based on active moiety). In addition, we anticipate that the policy will make it easier for healthcare practitioners to calculate an equivalent dose when transferring patients from one dosage form to another (e.g., calculating dose from an injection to a tablet), even if the products contain active ingredients that are different salts, because the strengths and names both will be based on the active moiety.

We recommend you consistently use the established name of the drug product as determined under the USP Salt Policy in all contexts in which a product's established name is used.

C. How CDER is Applying Exceptions

We anticipate that most drug products containing active ingredients that are salts will be named using the active moiety, in accordance with the USP Salt Policy. To facilitate implementation of the policy and its exceptions, we have developed the procedures described below that we generally intend to follow when considering whether an exception to the USP Salt Policy is appropriate. To help determine if your product meets one of the exceptions listed below, contact the review division for your specific drug product and request a meeting. Early communication for a potential exception (at Pre-IND or Phase I) is important because it could affect how the product could be developed so that the name and dosing is based on the active moiety or the salt. The Agency, not the sponsor, will determine whether USP Salt Policy exceptions apply, and early discussions will help us decide. As we apply the USP Salt Policy, we may identify additional grounds for exceptions.

1. The name of the salt could be retained if any of the following conditions are met:

    a. The active ingredient is a relatively simple salt and administration of the entire salt is therapeutically important. Examples include: lithium carbonate; iron sulfate, and other oral and intravenous iron salts; calcium gluconate and other calcium salts; potassium chloride; magnesium sulfate; sodium or potassium phosphate; and sodium citrate.

    b. Scientific evidence demonstrates the salt form affects the absorption, distribution, metabolism, and/or excretion (ADME) of the drug in a manner that influences the clinician's product selection.

    c. Clinically significant amounts of cations (e.g., sodium, potassium, magnesium or calcium) accompany the active moiety of a drug product. Clinical significance may be related to the recommended maximum daily amount of an electrolyte intake in special patient populations. Examples include: recommended daily intake of sodium in patients with congestive heart failure or recommended daily intake of potassium in patients with chronic kidney disease.

    d. There is a significant evidence-based safety concern that the counter-ion part of the salt could cause acid-base disturbances, hepatic, renal or other organ damage, or hypersensitivity reactions.

2. The name of the salt could be retained if any of the following safety or historical conditions are met:

    a. The name of the salt is necessary to maintain consistency with other dosage forms of the same active ingredient (salt). For example, if a tablet dosage form that was approved before May 1, 2013 included the salt in its established name and the drug product's strength is based on the salt form, the naming convention would not change for a new capsule dosage form with the same active ingredient (salt) that is approved after the effective date.

    b. We identify that the USP Salt Policy should not be applied because there are relevant, documented safety reasons (e.g., documented medication errors related to name or strength) in a closely related product.

    c. If we name a drug product according to the USP Salt Policy (e.g., the name and strength of the product are based on the active moiety) and, postapproval, there are safety concerns, we will consider whether a retrospective name change is appropriate. CDER and USP have agreed to coordinate any retrospective name changes.

III. HOW TO IMPLEMENT THE USP SALT POLICY

A. Product Development

When developing a drug product that may be affected by the USP Salt Policy, we encourage you to do the following:

1. Consider whether the USP Salt Policy applies to your product. Does your product contain an active ingredient that is a salt?

2. If you think your product qualifies for an exception, contact CDER for preliminary feedback on whether the USP Salt Policy or one of its exceptions applies to your product. You should provide data to support your position.

3. Develop your product so the name and strength match and are defined in accordance with the USP policy or CDER feedback.

B. Labels and Labeling Information

Application of the USP Salt Policy does not affect existing statutory and regulatory requirements for drug products.

1. You should create labels and labeling with the following in mind:

    a. The name of the active ingredient in a drug product is not subject to or affected by application of the USP Salt Policy. This means that the established name of the drug product may be different than the established name of the active ingredient (e.g., the active ingredient in "new drug tablets" will remain "newdrug hydrochloride"). The name and the amount of the active ingredient (salt) should appear on the container label, carton

labeling, and other labeling as required by statute and regulation even when the active moiety is used in the established name and strength of the drug product.[10]

b. Products that use the active moiety in the name and strength should include an equivalency statement to indicate the amount of active moiety related to the amount of active ingredient (salt). This equivalency statement should appear on the container label, carton labeling, and other labeling.[11]

c. Products that include the name of the active ingredient (salt) in the established name of the drug product, because they qualify for an exception, also should include an equivalency statement indicating the strength in terms of the active moiety. The equivalency statement should appear on the container label, carton labeling, and other labeling.[12]

d. The established name of the drug product and the active ingredient should be correctly displayed throughout the labeling.

2. You should pay careful attention to the language used in the following locations in the prescribing information:

a. Confirm that the product title in the Highlights section of the Prescribing Information[13] is accurate.

b. Confirm that the Dosage Forms and Strengths section[14] clearly states the product contents in a manner that allows the reader to understand whether the strength is based on the active moiety or active ingredient (salt).

c. Confirm that the Description section[15] for drug products containing an active ingredient that is a salt clearly identifies the active ingredient (salt), the active moiety, and the strengths of each. This can be accomplished with the use of an equivalency statement.

C. USP Salt Policy Does not Impact Statutory or Regulatory Requirements Related to Active Ingredients

Using the name of the active moiety in the established name and in the expression of strength does not implicate or change other statutory and regulatory requirements related to "active ingredient." For example, an applicant for an abbreviated new drug application will still have to demonstrate that the company's proposed generic product has the same active ingredient as the reference listed drug.[16] The *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations* will continue to provide listings based on the active ingredient.

[10] See section 502(e)(1)(A)(ii) of the FD&C Act.
[11] See Appendix 2, Example 1.
[12] See Appendix 2, Example 2.
[13] See 21 CFR 201.57(a)(2).
[14] See 21 CFR 201.57(a)(8), and 21 CFR 201.57(c)(4).
[15] See 21 CFR 201.57(c)(12)(i).
[16] See sections 505(j)(2)(A)(ii) and 505(j)(4)(C) of the FD&C Act.

IV. PRODUCTS THAT FAIL TO FOLLOW THE USP SALT POLICY RISK BEING MISBRANDED

The USP Salt Policy became effective on May 1, 2013. After that date, we anticipate that titles for new USP drug product monographs[17] will not include the active ingredient (salt) unless an exception applies. A product with a name that is inconsistent with a USP monograph title[18] risks being misbranded under the FD&C Act.[19]

V. REFERENCES

Section 502 of the FD&C Act: Misbranded Drugs and Devices

Section 505 of the FD&C Act: New Drugs

Section 751 of the FD&C Act: National Uniformity for Nonprescription Drugs

21 CFR 201.10: Drugs; Statement of Ingredients

21 CFR 201.57: Specific Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products Described in Section 201.56(b)(1)

21 CFR 314.108(a): New Drug Product Exclusivity; Definitions

Monograph Naming Policy for Salt Drug Substances in Drug Products and Compounded Preparations: The USP Salt Policy is published in General Chapter <1121> *Nomenclature.*

Section 351 of the PHS Act; Regulation of Biological Products

VI. DEFINITION

Active moiety - The molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester,[20] salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.[21]

[17] After May 1, 2013, the date the USP Salt Policy became effective, the names of already published drug product monograph titles should not change unless necessary for safety reasons.

[18] USP uses the following as the general format when creating a drug product monograph title: [DRUG][ROUTE OF ADMINISTRATION][DOSAGE FORM]. See USP General Chapter <1121> *Nomenclature.* CDER will generally follow this naming structure for products approved before the creation of a USP monograph title.

[19] See section 502(e)(1)(A)(i) of FD&C Act.

[20] The USP Salt Policy definition of an active moiety does not include "esters." See USP General Chapter <1121> *Nomenclature*. Consequently, esters should be named as the entire existing covalent entity.

[21] See 21 CFR 314.108(a).

APPENDIX 1: Monograph Naming Policy for Salt Drug Substances in Drug Products and Compounded Preparations[22]

The titles of USP monographs for drug products and compounded preparations formulated with a salt of an acid or base use the name of the active moiety, as defined below. The strength of the product or preparation is also expressed in terms of the active moiety.

An active moiety is the molecule or ion, excluding those appended portions of the molecule that cause the drug to be a salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule. The active moiety is responsible for the physiological or pharmacological action of the drug substance, without regard to the actual charged state of the molecule in vivo. For example, the active moiety of a hydrochloride salt of a base is the free base and not the protonated form of the base. The active moiety of a metal salt of an acid is the free acid.

This policy is followed by USP in naming drug products and compounded preparations that are newly recognized in the USP. Revising existing monographs to conform to this policy is not intended, except where the USP Council of Experts determines that, for reasons such as safety, a nomenclature change is warranted.

Labeling: The labeling clearly states the specific salt form of the active moiety that is present in the product or preparation because this information may be useful to practitioners and patients. The names and strengths of both the active moiety and specific salt form (when applicable) are provided in the labeling.

Exceptions: In rare cases in which the use of the specific salt form of the active moiety in the title provides vital information from a clinical perspective, an exception to this policy may be considered. In such cases, when the monograph title contains the specific salt form of the active moiety, the strength of the product or preparation also is expressed in terms of the specific salt form.

[22] See USP General Chapter <1121>.

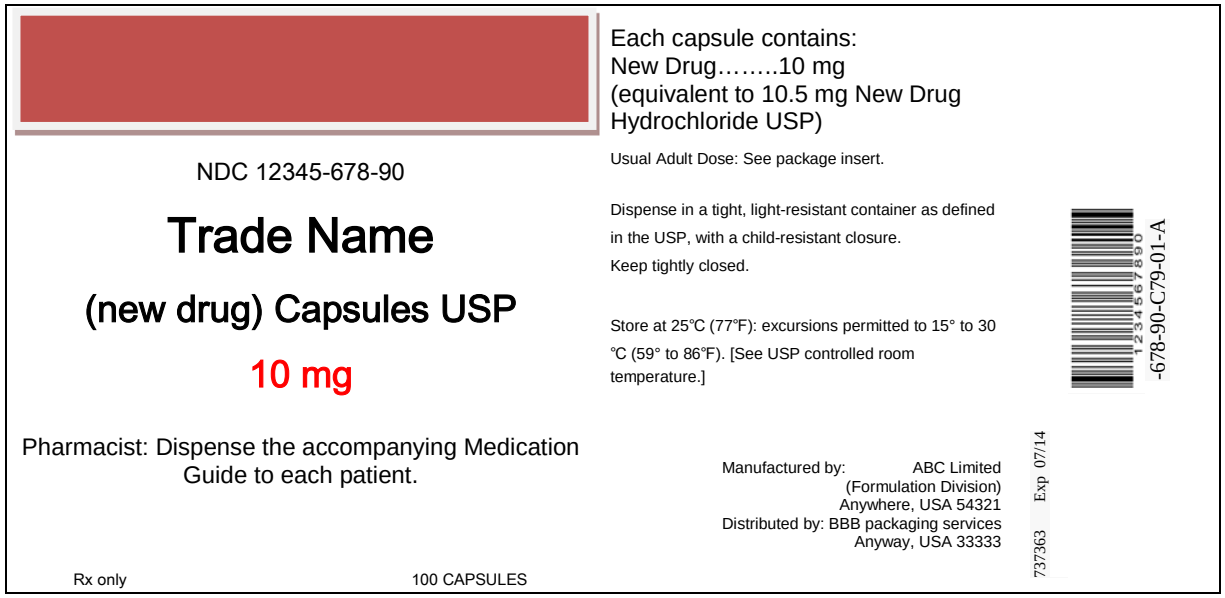
APPENDIX 2: Sample Labels with Equivalency Statement Language and Formatting for Prescription Drug Products[23]

We've created the following examples to help you design labels for products subject to the USP Salt Policy.

Example 1: Label with name and strength based on active moiety. The information about the salt is included on the side panel.[24]

The new language adds the information about the salt in parentheses with "equivalent to."

Each capsule contains:
New Drug…..10 mg
(equivalent to 10.5 mg New Drug Hydrochloride USP)



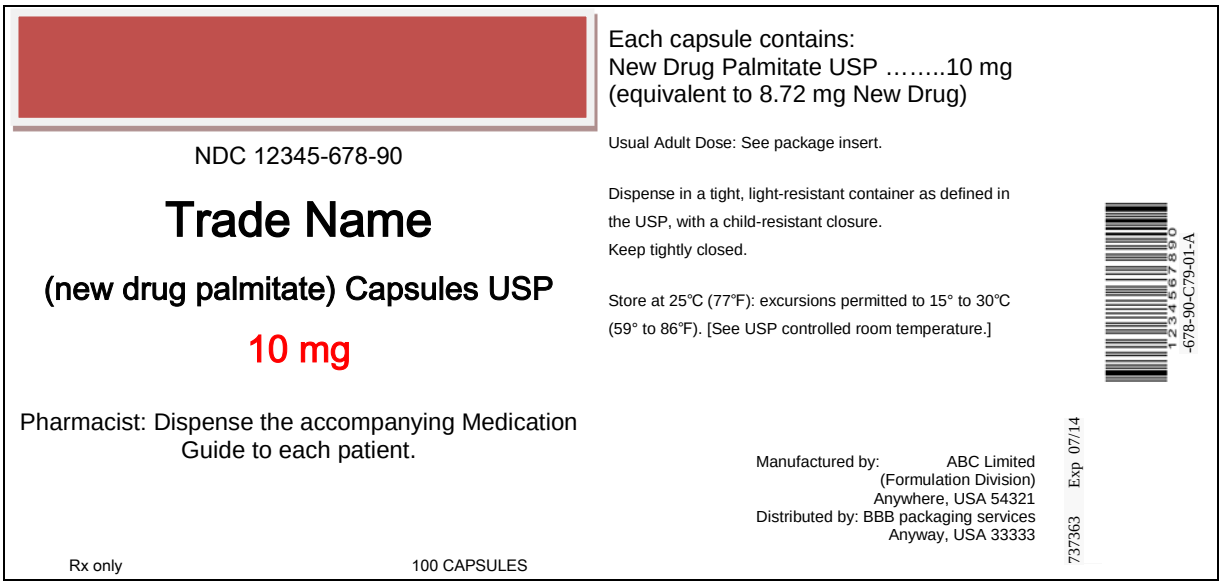
[23] The sample labels are included to only show the addition of an equivalency statement and changes to the name and strength that are necessary to implement the USP Salt Policy and its exceptions.

[24] Certain products with small container labels may be exempt from certain label requirements under 21 CFR 201.10(h)(2). To find out if your product is exempt from this regulation, you should contact the agency to discuss appropriate labeling that satisfies the USP Salt Policy.

Example 2: Label with name and strength based on active ingredient (palmitate salt). The information about the active moiety is included on the side panel. [25]

The new language adds the information about the active moiety in parentheses with "equivalent to."

Each capsule contains:
New Drug Palmitate USP…..10 mg
(equivalent to 8.72 mg New Drug)



[25] See footnote 24.