PURPOSE

This MAPP describes how CDER will apply the United States Pharmacopeia (USP) *Monograph Naming Policy for Salt Drug Substances in Drug Products and Compounded Preparations* (the USP Salt Policy) to prescription drug products to ensure consistent drug product naming when the USP Salt Policy becomes official on May 1, 2013. This MAPP also provides information to help reviewers determine when the USP Salt Policy’s exceptions should be granted.

BACKGROUND

1. 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 drug product monograph titles. The USP Salt Policy

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1 The *Monograph Naming Policy for Salt Drug Substances in Drug Products and Compounded Preparations* is published in USP General Chapter <1121> Nomenclature in USP 36-NF 31. See www.usp.org for current policy.
2 See Appendix A.
3 This MAPP does not address the application of the USP Salt Policy to the naming and labeling of compounded preparations.
stipulates that USP will base the strength of the product on the active moiety. The policy allows for exceptions under specified circumstances.

2. When the USP Salt Policy becomes official on May 1, 2013, USP will apply it only to new drug product monograph titles. The names of published drug product monograph titles should not change unless necessary for reasons such as safety. USP and FDA have agreed to coordinate on any retrospective name changes.

3. If there is an existing USP drug product monograph title, that title in most instances serves as the nonproprietary name of the related drug product. A product with a nonproprietary name that is not consistent with the applicable monograph title risks being misbranded.

A. USP Salt Policy

1. When an active ingredient in a drug product is a salt, the USP Salt Policy provides that the nonproprietary name of the drug product should 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 should be expressed in terms of the active moiety (e.g., “100 mg newdrug,” rather than salt strength equivalent (e.g., “123.7 mg newdrug hydrochloride”).

3. For drug products for which the name and strength are expressed in terms of active moiety, the full name and full strength (or proportion, if FDA has determined proportion is more appropriate) of the active ingredient (salt) also must appear elsewhere on the drug product labeling (see the Responsibilities and Procedures section for additional information related to the proper labeling of drug products that contain an active ingredient that is a salt).

4. The USP Salt Policy provides for an exception to the active moiety naming approach. Specifically, when the name of the salt conveys vital information from a clinical perspective, the name of the salt should be used in the name of the drug product and the strength of the drug product should also be in terms of the salt form (active ingredient).

B. CDER Application of USP Salt Policy

5 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. FDA will generally follow this naming structure for products approved prior to the creation of a USP monograph title.
7 USP General Chapter <1121> Nomenclature in USP 36-NF 31.
1. When considering whether to apply the USP Salt Policy, CDER formed a working group with representatives from several CDER offices and the Office of Chief Counsel. The working group reviewed potential benefits and concerns and recommended that CDER apply the USP Salt Policy. At a Center Director’s briefing, the CDER director determined that CDER should apply the USP Salt Policy now to ensure consistent application when the USP Salt Policy becomes official on May 1, 2013.

2. In this MAPP, CDER is applying the USP Salt Policy only to prescription drug products approved under section 505 of the Federal Food, Drug and Cosmetic Act (FD&C Act).8 CDER is separately considering the decision whether to apply the USP Salt Policy to over-the-counter (OTC) drug products,9 and to biological products licensed under the Public Health Service Act (PHS Act).10

3. CDER’s application of the USP Salt Policy should help to avoid medication errors that could result from a mismatch of nonproprietary name and strength (e.g., the name includes the salt but the strength is based on active moiety). In addition, the policy will make it easier for 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 will be based on the active moiety.

4. All uses of the nonproprietary name of a drug product containing a salt drug substance should be consistent with this MAPP.

C. CDER Application of Exceptions

1. When applying the USP Salt Policy’s exception that the name of the salt should be retained if it conveys vital information from a clinical perspective, CDER has determined that the name of the salt should be retained if any of the following is true:

   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.

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9 As identified in section 751 of the FD&C Act; 21 U.S.C. 379r.
10 Section 351 of the PHS Act; 42 U.S.C. 262.
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 such as 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 would 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 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. In addition to the application of the exception specified in the USP Salt Policy, CDER will make additional exceptions when retention of the name of the salt is appropriate for safety or historical reasons. CDER will apply the exception to the USP Salt Policy when:

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 was approved prior to May 1, 2013, with the name of the salt in the nonproprietary name and the salt form is used as the basis of strength of the drug product, then a capsule dosage form of that same active ingredient (salt) approved after May 1, 2013, would be permitted to continue to use the salt in the nonproprietary name and strength of the drug product.

b. There are documented medication errors in a closely related product.

c. There are reports of medication errors associated with the active moiety name or strength of the drug product. In keeping with the provision that a retrospective name change can be made for safety reasons after product approval, CDER may request such a change and will coordinate with USP if there is an existing USP monograph.

3. As CDER applies the USP Salt Policy, additional grounds for exceptions may be identified.
POLICY

CDER staff will now apply the USP Salt Policy as described herein.

RESPONSIBILITIES AND PROCEDURES

A. It is CDER’s responsibility to determine whether the name of a drug product that contains an active ingredient that is a salt should include the name of the active moiety or the name of the active ingredient (salt). CDER anticipates that most drug products containing active ingredients that are salts will be named using the active moiety.

1. CDER Salt Policy Working Group Tasks

   a. CDER's application of the USP Salt Policy includes, but will not be limited to, the following:

      i. Preparing guidance for industry explaining the USP Salt Policy and outlining CDER’s application of the USP Salt Policy (e.g., which products likely fall under one of the exceptions).

      ii. Amending relevant regulations, including the labeling and drug product-naming regulations, to clarify application of the USP Salt Policy (rulemaking does not need to occur prior to beginning to apply the USP Salt Policy).

      iii. Drafting CDER staff communications about application of this policy as necessary.

   iv. Providing staff training and education.

2. Office of New Drug Quality Assessment (ONDQA) Reviewer Tasks

   a. To apply the USP Salt Policy, ONDQA reviewers should work with a sponsor at the earliest stage possible in the development of a new product that contains an active ingredient that is a salt. During review of such a product, reviewers should take the following steps:

      i. Identify that the product contains an active ingredient that is a salt.

      ii. Identify whether the product may be considered for an exception (see CDER Applications of Exceptions in Background section).

      iii. Confer with the ONDQA supervisor and the application review team if:
b. If it is determined by CDER that an exception does not apply and the name of the salt should not be included in the name of the drug product, the reviewer should use standard methods of communication to:

i. Encourage the sponsor of an investigational new drug (IND) of a product that contains an active ingredient that is a salt to develop the product so that the nonproprietary name and strength will not include the name or strength, respectively, of the salt.

ii. Encourage the sponsor of a new drug application (NDA) of a product that contains an active ingredient that is a salt and is currently under review to apply the USP Salt Policy so that the nonproprietary name and strength will not include the name or strength, respectively, of the salt.

iii. Remind the sponsor of all new products that contain an active ingredient that is a salt that the USP Salt Policy is effective May 1, 2013. After that date, titles for new USP monographs will include only the name of the active moiety unless an exception applies. A product with a name inconsistent with a USP monograph title risks being misbranded.\(^{11}\)

c. Confirm that the product is labeled consistently with statutory and regulatory requirements as part of the discipline-specific review process.

i. The reviewer should verify that the labels\(^{12}\) and labeling correctly display the nonproprietary names of both the drug product and active ingredient(s) as required by FDA statute or regulations.

ii. 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 or regulation even when the active moiety is used in the nonproprietary name and strength of the drug product.\(^{13}\)

iii. Products that use the active moiety in the name and strength should include an equivalency statement on the container label to indicate the amount of active moiety related to the amount of active ingredient (salt). An equivalency statement would appear on the container label, carton labeling, and other labeling. See Example 1 in Appendix B.

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\(^{12}\) FDA notes that the USP Salt Policy requires the active ingredient information in the labeling. The FD&C Act requires such information to be on the label itself. Section 502(e)(1)(A)(ii) of FD&C Act; 21 U.S.C. 352(e)(1)(A)(ii). Accordingly, the active ingredient information must be on the product label itself.

iv. Products that include the name of the active ingredient (salt) in the nonproprietary 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. An equivalency statement should appear on the container label, carton labeling, and other labeling. See Example 2 in Appendix B.

v. The nonproprietary name of the drug product should be correctly displayed throughout the labeling.

d. The reviewer should pay attention to the inclusion of this language in the following locations in the prescribing information:

i. Confirm that the product title in the Highlights of Prescribing Information\textsuperscript{14} is accurate.

ii. The DOSAGE FORMS AND STRENGTHS section\textsuperscript{15} 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).

iii. The DESCRIPTION section\textsuperscript{16} 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, which can be accomplished with the use of an equivalency statement.

e. Use of the name of the active moiety in the nonproprietary name and in the expression of strength does not change other statutory and regulatory requirements related to “active ingredient.”

f. Continue to apply current practices with respect to naming and labeling of OTC products and biological products licensed under the PHS Act until a decision is made on whether and how to apply the USP Salt Policy to those products.

3. ONDQA Supervisors/Application Review Team Tasks

a. Contact the CDER Labeling and Nomenclature Committee (LNC) for an advisory opinion if the ONDQA supervisor/application review team believes the product qualifies for an exception. The LNC is assisting the CDER

\textsuperscript{14} 21 CFR 201.57(a)(2)
\textsuperscript{15} 21 CFR 201.57(a)(8), and 21 CFR 201.57(c)(4).
\textsuperscript{16} 21 CFR 201.57(c)(12)(i).
working group in gathering examples of reasons for granting an exception and may use this information for future policy changes.

b. The ONDQA supervisor/application review team also may consult with CDER’s Division of Medication Error Prevention and Analysis for assistance when determining whether a name change is warranted for safety reasons.

c. For questions about CDER’s application of the USP Salt Policy, contact Office of Pharmaceutical Science’s Immediate Office, ONDQA, Office of Generic Drugs, or Office of Biotechnology Products.

REFERENCES


- 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).


- Monograph Naming Policy for Salt Drug Substances in Drug Products and Compounded Preparations: The USP Salt Policy is published in USP 36-NF 31 in General Chapter <1121> Nomenclature.

- Section 351 of the Public Health Service Act (PHS Act); 42 U.S.C. 262: Regulation of Biological Products.
DEFINITIONS

- **Active moiety** - The molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester,\textsuperscript{17} 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.\textsuperscript{18}

- **Labeling and Nomenclature Committee (LNC)** - This committee is consulted within CDER for technical and regulatory advice on matters pertaining to the nomenclature and labeling of drug substances and drug products and how such nomenclature, including strength, dosage form, and route of administration should be captured in labeling. The LNC does not have regulatory decision making authority.

EFFECTIVE DATE

This MAPP is effective upon date of publication.

CHANGE CONTROL TABLE

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Revision Number</th>
<th>Revisions</th>
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\textsuperscript{17} The USP has announced plans to revise the USP Salt Policy definition of an active moiety so that it will no longer include “esters.” See the USP Pharmacopeial Forum 38 (1), published on January 2, 2012 (http://www.usp.org/usp-nf/pharmacopeial-forum).

\textsuperscript{18} 21 CFR 314.108.
APPENDIX A

Monograph Naming Policy for Salt Drug Substances in Drug Products and Compounded Preparations¹⁹

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 also is 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 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, without regard to the actual charged state of the molecule in-vivo.

For example, the active moiety of a hydrochloride salt of a base will be the free base and not the protonated form of the base. The active moiety of a metal acid salt will be the free acid.

i. Example: Chelocardin Hydrochloride active moiety is Chelocardin

ii. Example: Alendronate Sodium active moiety is Alendronic Acid

¹⁹ USP General Chapter <1121> (USP 36-NF 31).
²⁰ The USP has announced plans to revise the USP Salt Policy definition of an active moiety so that it will no longer include “esters.” See USP Pharmacopeial Forum 38(1).
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.

**Related Issues**

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

Exceptions— In those 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, where 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.
APPENDIX B

Sample Equivalency Statement Language and Formatting

**Example 1:** Label with name and strength based on active moiety. When possible, the information about the salt is included on the side panel.

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)

<table>
<thead>
<tr>
<th>NDC 12345-678-90</th>
<th>WONDER DRUG (NEW DRUG) CAPSULES USP</th>
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<tbody>
<tr>
<td></td>
<td>10 mg</td>
</tr>
<tr>
<td>Pharmacist: Please dispense with Medication Guide provided separately</td>
<td></td>
</tr>
<tr>
<td>Rx only 100 CAPSULES</td>
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</table>

Usual Adult Dose: See package insert
Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure. Keep tightly closed.
Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). [See USP controlled room temperature.]

Manufactured by: ABC Limited (Formulation Division) Anywhere, USA 54321
Distributed by: BBB packaging services Anyway, USA 33333

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21 This information may not be included on the side panel, to the extent that 21 CFR 201.10(h)(2) applies to products with a small container label.
**Example 2:** Label with name and strength based on active ingredient (salt). When possible, the information about the active moiety is included on the side panel.  \(^{22}\)

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)

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22 This information may not be included on the side panel, to the extent that 21 CFR 201.10(h)(2) applies to products with a small container label.