POLICY AND PROCEDURES

OFFICE OF PHARMACEUTICAL QUALITY

Naming of Drug Products Containing Salt Drug Substances

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PURPOSE

This Manual of Policies and Procedures (MAPP) describes how the Center for Drug Evaluation and Research (CDER) will consistently apply the United States Pharmacopeia (USP) policy entitled, *Monograph Naming Policy for Salt Drug Substances in Drug Products and Compounded Preparations*[1] (the USP Salt Policy) to prescription drug products.[2] The USP Salt Policy became effective May 1, 2013 in accordance with CDER's guidance for industry[3] (Salt Guidance). This MAPP provides information to help reviewers determine when the USP Salt Policy's exceptions should be granted and outlines a process to be followed when reviewing the nonproprietary name of a prescription drug product that contains an active ingredient that is a salt.

BACKGROUND

As of May 1, 2013, CDER applied the USP Salt Policy to prescription drug products approved under section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

[1] The *Monograph Naming Policy for Salt Drug Substances in Drug Products and Compounded Preparations* is published in USP General Chapter <1121> *Nomenclature.* See www.usp.org for current policy

[2] This MAPP does not address the application of the USP Salt Policy to nonprescription drugs, biologic products, or the naming and labeling of compounded preparations.

[3] See guidance for industry *Naming of Drug Products Containing Salt Drug Substances* (June 2015).

The USP Salt Policy is a naming and labeling policy applicable to drug products that contain an active ingredient that is a salt.

A. The USP Salt 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 stipulates that USP will base the strength of the product on the active moiety. The policy allows for exceptions under specified circumstances.

B. The USP Salt Policy applies to all new drug product monographs that contain an active ingredient that is a salt. The names of drug product monograph titles published prior to May 1, 2013 should not change unless necessary for reasons such as safety.[4] USP and CDER agreed to coordinate regarding any retrospective name changes.

C. The USP Salt Policy affects the development of new drug products because a USP drug product monograph title, in most instances, serves as the nonproprietary name[5] of related drug products.[6] A product with a label or labeling that contains a nonproprietary name that is not consistent with the applicable monograph title risks being misbranded.[7]

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

1. USP Salt Policy[8]

A. 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., “drug-x tablets” instead of “drug-x hydrochloride tablets”).

B. The strength also will be expressed in terms of the active moiety (e.g., “100 mg drug-x,” rather than salt strength equivalent (e.g., “123.7 mg drug-x hydrochloride”).

[4] See guidance for industry *Naming of Drug Products Containing Salt Drug Substances* section C.
[5] For purpose of this guidance, *nonproprietary name* refers to the established name of a drug product.
[6] See section 502(e)(3) of the FD&C Act.
[7] See section 502(e)(1) of the FD&C Act. 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.
[8] USP General Chapter <1121> *Nomenclature.*

C. 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 CDER has determined proportion is more appropriate) of the active ingredient (e.g., salt) will appear elsewhere on the drug product label[9] and labeling.[10]

D. The USP Salt Policy provides for exceptions to the *active moiety* naming approach when the name of the salt conveys vital information from the clinical perspective. In these cases, the drug product monograph will include the name of the salt, and the strength of the drug product is expressed in terms of the salt form (active ingredient). In these cases, the label and labeling should include an equivalency statement to indicate the amount of active moiety related to the amount of active ingredient (salt).[9,10]

2. CDER Application of the USP Salt Policy

A. CDER published the Salt Guidance for industry, *Naming of Drug Products Containing Salt Drug Substances,* to help applicants understand how products with active ingredients that are salts may be affected by CDER's implementation of the USP Salt Policy.

B. CDER will apply the USP Salt Policy only to prescription drug products under development whose approval is sought under section 505 of the FD&C Act.

C. CDER's application of the USP Salt Policy, in conjunction with the application of other labeling policies and requirements, should help 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.

3. CDER Application of Exceptions

FDA, not the applicant, will determine whether the USP Salt Policy exceptions apply; early discussions with the applicant will assist the FDA in making this determination. As CDER applies the USP Salt Policy, additional grounds for exceptions may be identified.

A. When applying the USP Salt Policy's exception that the name of the salt may be retained if it conveys vital information from a clinical perspective, CDER

[9] See Attachment 2 for examples of equivalency statements on labels for prescription drug products that contain an active ingredient that is a salt.
[10] See USP General Chapter <7> Labeling.

has determined that the name of the salt could be retained if any of the following is true:

1) 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.

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

3) 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 include recommended daily intake of sodium in patients with heart failure or recommended daily intake of potassium in patients with chronic kidney disease.

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

B. In addition to the application of the exception specified in the USP Salt Policy, the name of the salt could be retained if any of the following safety or historical conditions are met:

1) 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 prior to May 1, 2013 included the salt in its nonproprietary name and the drug product's strength is based on the salt form, then the naming convention would not change for a new capsule dosage form with the same active ingredient (salt) that is approved after May 1, 2013.

2) There are relevant, documented safety reasons (e.g., documented medication errors related to name or strength) in a closely related product.

A drug product is named according to the USP Salt Policy (i.e., the name and strength of the product are based on the active moiety), and there are post-approval reports of medication errors or safety concerns. CDER will consider whether a retrospective name change is appropriate. 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 to have an existing USP monograph updated.

PROCEDURES

Within the Office of Pharmaceutical Quality (OPQ) it is the responsibility of Quality reviewers in the Office of New Drug Products (ONDP) to determine whether the USP Salt Policy applies to a new drug product.[11] The following procedures should be followed:

1. ONDP Quality reviewers will work with the applicant at the earliest stage possible (e.g., investigational new drug (IND) phase 2) 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:

    A. Determine whether the product contains an active ingredient that is a salt.

    B. Determine whether the product may qualify for an exception to the USP Salt Policy (see CDER Application of Exceptions in Background section).

    C. Refer the applicant of all new products that contain an active ingredient that is a salt to the Salt Guidance and the USP Salt Policy.

    D. Confer with OPQ labeling experts (and the CDER Labeling and Nomenclature Committee as needed) and members of the extended review team (e.g., Office of New Drugs, Office of Surveillance and Epidemiology) if:

        1) The ONDP Quality reviewer (in consultation with their management) thinks that a drug product qualifies for an exception to the USP Salt Policy; and/or
        2) The applicant asserts that their drug product qualifies for an exception to the USP Salt Policy.

2. If CDER determines 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 will use standard methods of communication to:

    A. Advise the sponsor of an IND application for a product that contains an active ingredient that is a salt that the nonproprietary name and strength will not include the name or strength, respectively, of the salt.

    B. Advise the applicant of a new drug application (NDA) of a product that contains an active ingredient that is a salt and is currently under review to

[11] For questions about CDER's application of the USP Salt Policy, contact the Division of Internal Policies and Programs (DIPAP) in the Office of Policy for Pharmaceutical Quality (OPPQ) in the Office of Pharmaceutical Quality.

apply the USP Salt Policy so that the nonproprietary name and strength will not include the name or strength, respectively, of the salt.

3. The ONDP Quality reviewer will confirm that the product's labeling is consistent with statutory and regulatory requirements as part of the discipline-specific review process. Specifically:

   A. The reviewer will verify that the label and labeling correctly display the nonproprietary names of both the drug product and active ingredient(s) as required by FDA statute or regulations.[12]

   B. 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 nonproprietary name and strength of the drug product.[13]

   C. Products that use the active moiety in the name and strength should include an equivalency statement on the container label, carton label, and other labeling to indicate the amount of active moiety related to the amount of active ingredient (salt).[14]

   D. 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.[15]

4. The ONDP Quality reviewer will evaluate the following in his/her labeling review of the prescribing information:

   A. Confirm that the nonproprietary name in the product title in the Highlights of Prescribing Information[16] is accurate.

   B. The DOSAGE FORMS AND STRENGTHS section[17] 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).

      Example #1 (when the USP Salt Policy applies):

      Tablets: 10 mg of drug-x

[12] See section 502(e)(1)(A)(ii) of the FD&C Act; 21 CFR 201.10.
[13] Section 502(e)(1)(A)(ii) of the FD&C Act.
[14] See Example 1 in Attachment 2.
[15] See Example 2 in Attachment 2.
[16] 21 CFR 201.57(a)(2).
[17] 21 CFR 201.57(a)(8), and 21 CFR 201.57(c)(4).

Example #2 (when an exception to the USP Salt Policy has been granted:

Tablets: 10.5 mg of drug-x hydrochloride

C. The DESCRIPTION section[18] 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. For example:

DRUG-X contains 100 mg of drug-x equivalent to 123.7 mg of drug-x hydrochloride

D. Confirm the nonproprietary name is consistently displayed throughout the prescribing information using the name of either the active moiety or active ingredient (salt), as appropriate.

5. The use of an active moiety in the nonproprietary name and in the expression of strength does not impact the need to meet other statutory and regulatory requirements related to the active ingredient. For example, an applicant for an abbreviated new drug application (ANDA) will still have to demonstrate that the generic product has the same active ingredient as the reference listed drug (RLD). The ONDP Quality reviewer will determine that other statutory and regulatory requirements related to the active ingredient have been met.

REFERENCES

1. Section 502 of the FD&C Act.
2. Section 505 of the FD&C Act.
3. 21 CFR 201.10.
4. 21 CFR 201.57.
5. 21 CFR 314.3(b).
6. 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*.
7. USP General Chapter <7> *Labeling.*

[18] 21 CFR 201.57(c)(12)(i).

DEFINITIONS

1. **Active ingredient** - Any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of humans. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect.[19]

2. **Active moiety** - The molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, 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.[20]

3. **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

Effective Date	Revision Number	Revisions
2/20/2013	Initial	n/a
12/7/2017	Rev. 1	Changes incorporate internal procedures to be consistent with the published Salt Guidance (June 2015)
12/2/2022	n/a	Recertified: no changes

[19] 21 CFR 210.3(b)(7).
[20] 21 CFR 314.3(b). Please note that the USP Salt Policy definition of an active moiety no longer includes "esters." See the USP40 General Chapter <1121>.

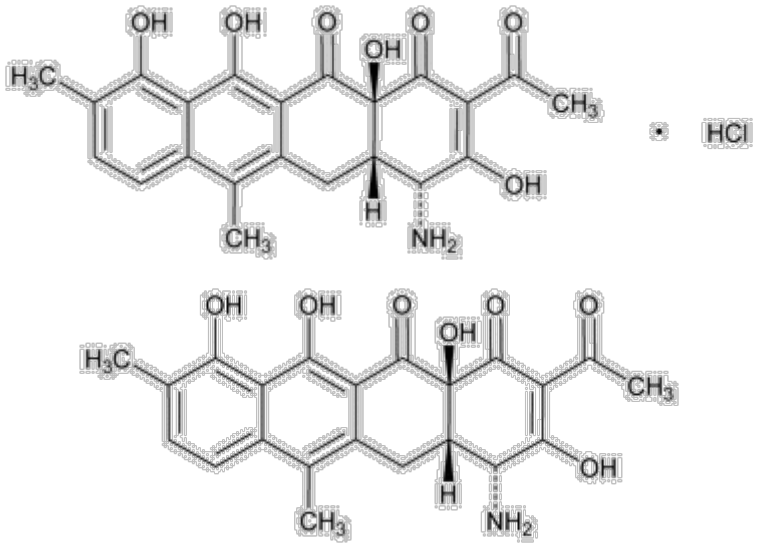
ATTACHMENT 1:

Monograph Naming Policy for Salt Drug Substances in Drug Products and Compounded Preparations[21]

The titles of USP monographs for drug products approved on or after May 1, 2013 and compounded preparations formulated with a salt of an acid or base use the name of the active moiety, unless there is an exception 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,[22] 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.

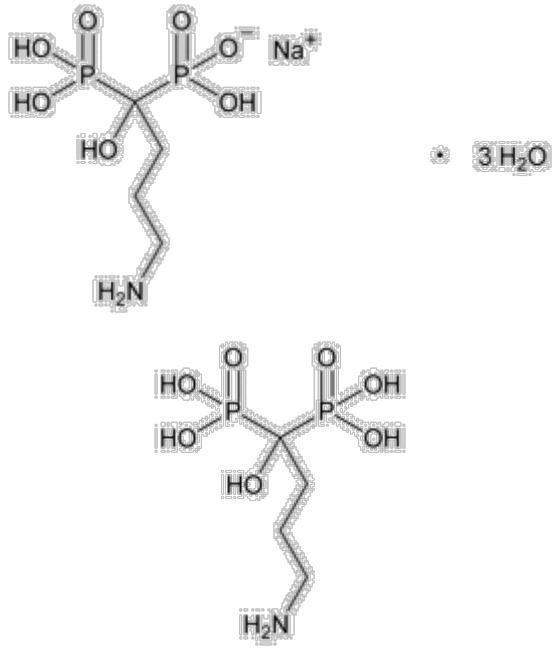
i. Example: Chelocardin Hydrochloride active moiety is Chelocardin



[21] See USP General Chapter <1121>.

[22] See 21 CFR 314.3(b). 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.

ii. Example: Alendronate Sodium active moiety is Alendronic 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.

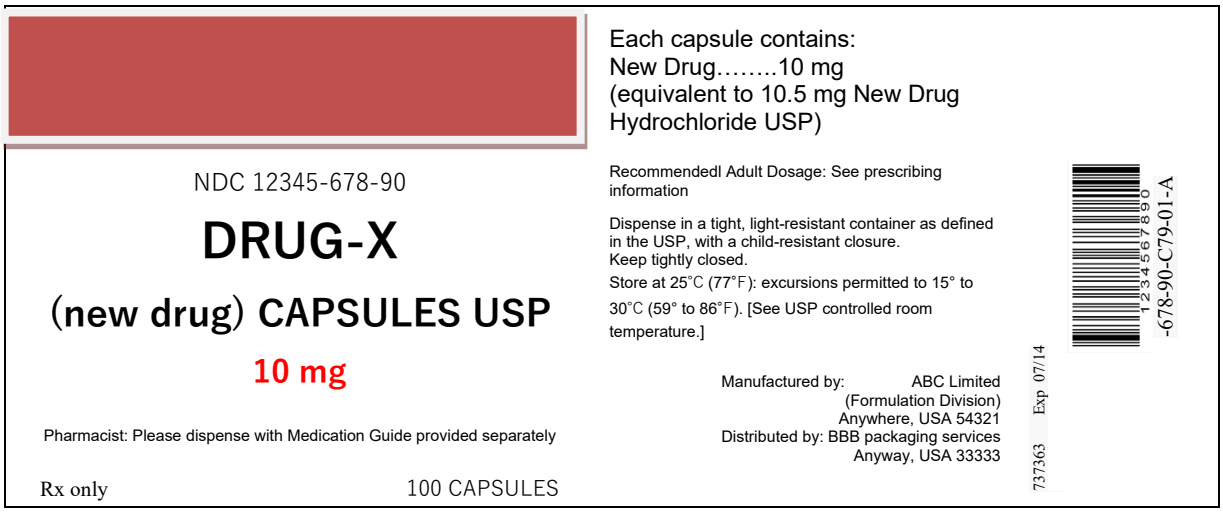
ATTACHMENT 2:

Sample Labels with Equivalency Statement Language and Formatting for Prescription Drug Products

Example 1: Preferred format. Label with name and strength based on active moiety. When possible, 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)

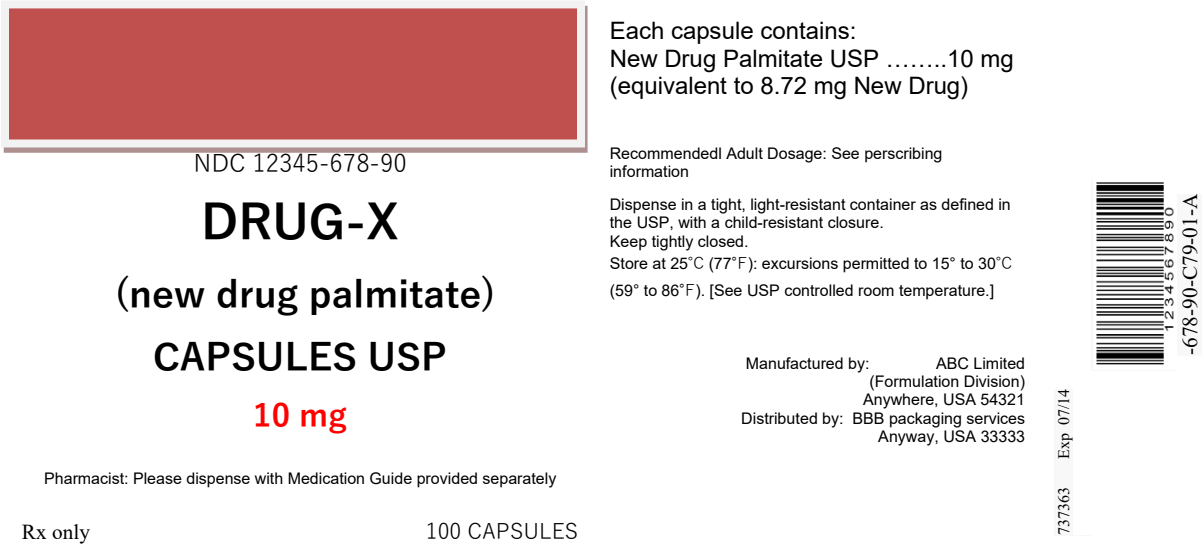


[24] Certain products with small container labels may be exempt from certain label requirements under 21 CFR 201.10(h)(2). To find out if the NDA or ANDA product under review is exempt from this regulation reviewer should consult with the DIPAP or CDER LNC to discuss appropriate labeling that satisfies the USP Salt Policy.

Example 2: For previously approved products or for those where exception was granted. Label with name and strength based on active ingredient (salt). When possible, 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] Ibid.