

# CDER Implementation of: The United States Pharmacopeia (USP) <1121> *Monograph Naming Policy for Salt Drug Substances in Drug Products*

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# Outline

- Background on the USP Salt Policy
- USP Implementation
- CDER Implementation
- Examples
- Frequently Asked Questions (FAQs)
- Conclusions

# Background

- Early 1990's, USP initiated policy to:
  - Delete salt from title of existing dosage form monographs
  - Change the expression of strength to the active moiety
- FDA objected & reached compromise with USP, creating exception for clinical reasons
- 1995 – USP published policy in *General Notices* **stating that name and strength should match**
- 2006 – USP published for comment in *Pharmacopeial Forum* **a policy emphasizing that the naming of drug products containing salts should be based on the active moiety**
- May 1, 2013 the policy becomes official

# The USP Salt Policy

- *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 **[neutral species] active moiety**....*
- *The **strength** of the product or preparation also is expressed in terms of the **[neutral species] active moiety**....*
- *The names and strengths of both the active moiety and specific salt form (where applicable) are provided in the labeling.*
- **Esters are excluded from this policy**

# The USP Salt Policy

- **The policy includes exceptions** that allow retaining the salt form in the name AND strength if any of the following apply:
  - The active ingredient is a simple salt such as lithium carbonate
  - Scientific evidence demonstrates that the specific salt form affects absorption. Distribution, metabolism, or excretion (ADME)
  - Clinically significant amounts of salt ions such as sodium accompany the active moiety in the drug product.
  - Other safety or historical reasons to lessen the potential for medication errors.
  - Within CDER, exception requests within this policy are decided as a **review issue**.

# USP Implementation

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

# Why is this important?

- Drug product labels that do not reflect the Policy will be misbranded once USP designates the title of the related drug product monograph that reflects the Policy
- Therefore, it is important that new drug product labeling reflect this policy at initial approval before the monograph stage to avoid having to rename an approved drug product.

# FDA Implementation

- The Agency agrees to fully implement on May 1<sup>st</sup>, 2012
- The Agency has been working with IND sponsors and NDA applicants to encourage adherence to this policy for some years through the meeting and review process.
- Development of appropriate MAPP (final stage) and Guidance (mid-stage) are in process
- Agency Training (CDER) is in progress



# FDA Implementation

- CDER review staff identify salt / strength mismatches
  - If in early IND, request that sponsor design posology (the determination of dose) to align with USP policy.
  - If at late IND or NDA stage, encourage sponsor to align with USP to avoid potential misbranding issues or the need to change the label later on.
  - If an exception request is warranted to allow the salt to be part of the name (review decision), then the strength is to be expressed *as that salt* and will include an equivalency statement to indicate the amount of active moiety present (see examples).

# Conforming Sample Labels

## USP Policy\*

**PANACEBO<sup>®</sup>**

**(newdrug)**

**TABLETS 100 mg\***

\*Each tablet contains 100 mg of newdrug equivalent to 123mg of newdrug hydrochloride

\*Name and strength match to active moiety and the mass of drug substance is also captured.

## Allowed USP exception case\*

**PANACEBO<sup>®</sup>**

**(newdrug hydrochloride)**

**TABLETS 123 mg**

\*Name and strength still match. In exception cases, the salt counter ion is determined to be clinically relevant.

# Nonconforming Sample Labels

## Prohibited Mismatch

**PANACEBO®**

(newdrug)

TABLETS **123 mg\***

\*Each tablet contains **123 mg of newdrug hydrochloride** equivalent to **100 mg of newdrug**

Here the name is as the active moiety but the strength is expressed as the salt

## Prohibited Mismatch

**PANACEBO®**

(newdrug hydrochloride)

TABLETS **100 mg\***

\*Each tablet contains **123 mg of newdrug hydrochloride** equivalent to **100 mg of newdrug**

Here the name is as the salt but the strength is expressed as the active moiety.

## Example – USP Policy

- The label for “Oxycodone and Aspirin Tablets” does not include the name of the salt(s). However, the salts are still listed on the container’s label and in the insert labeling.
  - According to the USP Monograph: Oxycodone and Aspirin Tablets, can be formulated with either oxycodone hydrochloride or a mixture of oxycodone hydrochloride and oxycodone terephthalate.
  - The monograph also has the following labeling requirement: *“Label the Tablets to state both the content of the oxycodone active moiety and the content or contents of the salt or salts of oxycodone used in formulating the article.”*

## Example - Exception

- The title for drug products, such as “Penicillin G Sodium for Injection,” includes the name of the salt for clinical use.
  - According to the general precautions in the drug labeling, the salt in penicillin is listed on the label: *“Penicillin G Sodium for Injection, USP given by the intravenous route in high doses (above 10 million units) should be administered slowly because of the potential adverse effects of electrolyte imbalance from the sodium content of the penicillin. Penicillin G Sodium for Injection, USP contains 1.68 mEq of sodium per million units of penicillin G.”*

# FAQs

- My product in development is a salt. How can I avoid confusing dosing numbers (e.g., 123.4 mg) in the labeling when named according to the active moiety?
  - Act early in development. Design clinical trial posology which reflects active moiety content in clinical trial drug products; not salt content.

# FAQs

- If my product in development is a salt, will two USAN names be needed?
  - Yes; one for the salt and one for the active moiety because both names will appear in the labeling. USAN has a 50% fee reduction for the second name.

# FAQs

- How do I seek an exception request to the USP Salt Policy?
  - Act as soon as you are confident that you have a scientifically supportable case.
  - Contact the appropriate CDER Project Manager with a meeting request.
  - Provide a specific and appropriately detailed meeting package.
  - CC [NewDrugCMC@fda.hhs.gov](mailto:NewDrugCMC@fda.hhs.gov), alert Rik Lostritto and Michael Folkendt in ONDQA



## FAQs

- Will generic drug products still have to comply with current “Q&Q” composition requirements?
  - Yes, the Orange book will link ratings to the specific salt of the RLD product.

# FAQs

- How will multiple (approved) salt forms of the same dosage form be distinguished?
  - Brand name
  - Orange Book
  - NDC number
  - Prescription written for a specific salt
  - Not many such cases expected. Usually multiple salt forms of the same active moiety refer to different dosage forms

# FAQs

- The USP Salt Policy will appear as <1121>. Therefore, it is informational. Do I have to follow it?
  - This chapter covers salt nomenclature aspects of how USP develops monograph titles
  - USP monographs are mandatory for FDA under the FD&C Act.
  - Therefore it behooves FDA and the regulated industry to follow <1121> to avoid changing drug product names post-approval after a monograph is created.

# FAQs

- I have other questions about this policy. Who do I contact?
  - For general questions about the policy, email: [NewDrugCMC@fda.hhs.gov](mailto:NewDrugCMC@fda.hhs.gov)
  - For product specific questions (pre-IND, IND, NDA) contact the corresponding CDER Project Manager

# Conclusions

- The USP Salt Policy becomes effective May 1, 2013.
  - Non proprietary name uses the active moiety (neutral) form
  - Strength is linked to the active moiety
  - The salt form is captured in labeling as well
  - An exception clause exists to retain the salt in name and strength when necessary
  - Allowing exceptions is a CDER review issue.
- It will still be feasible to distinguish between approved salt forms
- Generic equivalents will still have to match the salt form in the reference listed drug (RLD)

# Conclusions

- **CDER is applying the policy now whenever feasible.**
  - Following the policy avoids misbranding when the approved drug product becomes a USP monograph
  - **Design posology in consideration of this policy**
  - Discuss exception requests with Agency early
  - The Agency will continue to work with the regulated industry and other stakeholders to facilitate compliance with this policy.

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*Thank you*