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CDER's Application of the USP Salt Policy

As of May 1, 2013, CDER applied the United States Pharmacopeia (USP) Monograph Naming Policy for Salt Drug Substances in Drug Products and Compounded Preparations (which we refer to as the USP Salt Policy) to prescription drug products approved under section 505 of the Federal Food, Drug and Cosmetic Act (FD&C Act). CDER is separately considering the decision whether to apply the Policy to over-the-counter and biological products.

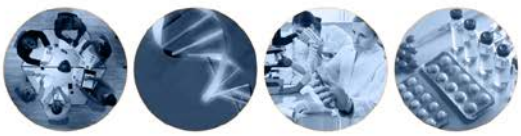
What is the USP Salt Policy? The USP Salt Policy is a naming and labeling policy applicable to drug products that contain an active ingredient that is a salt. The policy states:

- 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) rather than the name of the salt (e.g., "new drug tablets" instead of "new drug hydrochloride tablets") when creating drug product monograph titles.
- The strength will be expressed in terms of the active moiety (e.g., "100 mg new drug") rather than salt strength equivalent (e.g., "123.7 mg new drug hydrochloride").
- 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 (salt) also must appear elsewhere on the drug product labeling. Note that generic equivalents will still have to match the salt form in the reference listed drug (RLD).

How is CDER applying the USP Salt Policy and its Exceptions? The USP Salt Policy allows for exceptions under specified circumstances. Specifically, the name of the salt will be retained if it conveys vital information from a clinical perspective.

CDER further elucidated the exceptions and determined that the name of the salt should be retained if any of the following is true:

- The active ingredient is a relatively simple salt and administration of the entire salt is therapeutically important (e.g. lithium carbonate.)
- Scientific evidence demonstrates the salt form affects the absorption, distribution, metabolism, and/or excretion of the drug in a manner that influences the clinician's product selection.
- Clinically significant amounts of cations 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. (e.g. the recommended daily intake of sodium in patients with congestive heart failure)
- 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.
- Retention of the name of the salt is appropriate for safety or historical reasons; more examples of the application of this exception are included in FDA's Manual of Policy and Procedures.



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Within CDER, exception requests in this policy are decided as a review issue. As CDER applies the USP Salt Policy, CDER will make additional exceptions when retention of the name of the salt is appropriate for safety or historical reasons. Sponsors should request exceptions early, as soon as they believe their product qualifies for an exception. The sponsor should contact the appropriate CDER Project Manager with a meeting request and provide a specific and appropriately detailed meeting package, copying NewDrugCMC@fda.hhs.gov on the email request.

If CDER grants an exception to allow the salt to be part of the product's name, then the strength will be expressed ***as that product's salt*** and the labeling will include an equivalency statement to indicate the amount of active moiety present.

How will this benefit public health? 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 even if the products contain active ingredients that are different salts, because the strengths and names will be based on the active moiety.

How will this apply to products that already have a published drug product monograph? The names of USP 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. 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.

Therefore, it is important that new drug product labeling reflect this policy at initial approval to avoid having to change the name of the approved drug product at a later date when a USP monograph for that product is created.

How will CDER Apply the USP Salt Policy during Review? CDER review staff will identify salt / strength mismatches, determine if the policy is being appropriately applied, and recommend labeling changes if they believe a change is necessary. When the product is in the early stages of an investigational new drug application (IND), CDER may request that the sponsor design posology (the determination of dose) to align with USP policy. The sponsor should act early in development, and design clinical trial posology which reflects the active moiety (rather than salt) content in clinical trial drug products unless an exception to the policy applies.

If the application of the USP Salt Policy is determined for a product that is later in development, CDER may encourage the sponsor to align with USP to avoid potential misbranding issues. CDER recommends that the USP Salt Policy be applied earlier in development to avoid the need to change the label later on, which can lead to confusion.

Remember that a product risks being deemed misbranded if the name on the label is not consistent with the USP monograph title, if one exists. Therefore it is recommended that FDA and the regulated industry follow the USP Salt Policy to avoid changing drug product names post-approval after a monograph is created. The Agency will continue to work with the USP, the regulated industry and other stakeholders to facilitate compliance with this policy.

You may read more about CDER's application of the USP Salt Policy in FDA's Manual of Policy and Procedures. For general questions about CDER's application of the USP Salt Policy, you may email: NewDrugCMC@fda.hhs.gov. For product specific questions, please contact the corresponding CDER Project Manager.

Cheers,

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CDER Small Business Assistance

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