

USP General Notices and General Test Chapters Interpretations and Misinterpretations

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The authors dispel common misinterpretations of the *United States Pharmacopeia*.

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The United States Pharmacopeial Convention, Inc. (USPC) is an independent organization that sets the standards for determining the quality of pharmaceutical products marketed in the United States of America. The USPC is responsible for publishing the *United States Pharmacopeia* (*USP*), a legally recognized compendium used by the pharmaceutical industry. Established in 1820 as a collection of recipes for pharmacists, the *USP* has evolved into a collection of test methodologies and associated specifications used primarily by proprietary and generic pharmaceutical manufacturers. These standards govern the quality, strength, purity, and potency of excipients, active pharmaceutical ingredients (APIs), pharmaceutical dosage forms, and many of the reagents, solutions, and indicators used to test these materials. Because of the extensive industry applicability of *USP* methods, any pharmaceutical testing laboratory must be capable of using the technologies and performing the procedures described in this world-recognized compendium.

The Federal Food, Drug, and Cosmetic Act (FD&C Act) and the *Code of Federal Regulations* refer to the standards in the *USP* and mandate the recognition of those standards by the Food and Drug Administration (1–4). FDA does not offer any guidance, however, on how to interpret the compendium. This article clarifies some of the requirements contained in the “General Notices and Requirements” section and offers possible interpretations of the information contained in general test chapters, where little interpretive guidance is offered. The authors dispel common misinterpretations made when reviewing the *USP*.

The *USP* consists of various sections. The bulk of the book comprises monographs for excipients, APIs, and final products. In addition to those monographs, the compendium includes a “Guide to General Chapters,” which contains information about basic test procedures (“General Tests and Assays”), and broad-scope guidance advice (“General Information”). With few exceptions, general test chapters define the criteria for frequently used methods such as loss on drying or pH, which are independent of the material being tested. General Information chapters, numbered 1000 and above, describe the USPC’s philosophies about broad-scope issues such as the recommended requirements for validating compendial methods.

The “General Notices and Requirements” section at the beginning of the *USP* provides the overall guiding principles for using the monographs and General Chapters. The first paragraph of this section states, “The General Notices and Requirements ... provide in summary form the basic guidelines for interpretation and application of the standards, tests, assays, and other specifications of the *United States Pharmacopeia* ...” It is by referring to this section that common misinterpretations regarding information contained in the *USP* can be clarified for the reader. The following examples aim to clarify some of the most common misunderstandings attributed to the *USP*. All page numbers refer to *USP 27–NF 22* (5).

Misinterpretation: The word “about” in the *USP* always means $\pm 10\%$.

Clarification. This statement is true when referring to weights, volumes, and apparatus dimensions but does not apply to temperatures, times, or product specifications. The relevant statement in the “General Notices” section reads, “In stating the appropriate quantities to be taken for assays and tests, the use of the word ‘about’ indicates a quantity within 10% of the specified weight or volume. However, the weight or volume taken is accurately determined and the calculated result is based on the exact amount taken. The same tolerance applies to specified dimensions.” When a method specifies a time or temperature at which the analysis is to be performed, the tolerance range is

generally provided in the monograph or the applicable general test chapter. (See “General Notices and Requirements, Tests and Assays, Procedures,” p. 7.)

Misinterpretation: If no *USP* Reference Standard (RS) is available, then the product does not need to be tested according to the *USP* monograph requirements.

Clarification. This statement only applies to new monograph tests (e.g., an impurities method) that require using the specific RS. Other monograph tests not requiring the use of the RS are still applicable to the product being examined. The actual sentence reads, “The requirements for any new *USP* or *NF* standards, tests, or assays for which a new *USP* Reference Standard is specified are not in effect until the specified *USP* Reference Standard is available.” Should the *USP* run out of established reference standard material, companies should qualify an internal standard until the *USP* standard becomes available. This information is not stated in the *USP*, but FDA provided guidance in its September 1996 “GMP Notes” in response to a similar question regarding the unavailability of the prednisone dissolution calibrator tablets. In addition, companies are encouraged to contact the USPC regarding any concerns related to reference standards. (See “General Notices and Requirements, *USP* Reference Standards,” p. 5.)



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Misinterpretation: I can use alternative methods to USP methods.

Clarification. This statement is true under certain circumstances. Before you can use an alternative method to an official USP method you must validate the alternative method and prove it is equivalent to or better than the existing official method. In such cases, the company may need to update its regulatory filings to state the

test used. In the case of an inconsistency or dispute, however, only results generated using the official method are considered conclusive. The section addressing this issue reads, "Automated procedures employing the same basic chemistry as those assay and test procedures given in the monograph are recognized as being equivalent in their suitability for determining compliance. Conversely, where an

automated procedure is given in the monograph, manual procedures employing the same basic chemistry are recognized as being equivalent in their suitability for determining compliance." The section adds that "such alternative or automated procedures or methods shall be validated." This section of the USP goes on to state "where a difference appears or in the event of dispute, only the result obtained by the procedure given in this *Pharmacopeia* is conclusive." (See "General Notices and Requirements, Tests and Assays, Procedures," p. 7.)

Misinterpretation: The USP test for content uniformity gives 10 results because it uses 10 units.

Clarification. This statement is false. The user obtains only one result for the test even though 10 individual units are tested. The clarifying sentence in USP states, "Tests and Assays in this *Pharmacopeia* prescribe operation on a single specimen, that is, the singlet determination, which is the minimum sample on which the attributes of a compendial article should be measured. Some tests, such as those for dissolution and uniformity of dosage units, require multiple dosage units in conjunction with a decision scheme. These tests, albeit using a number of dosage units, are in fact the singlet determinations of those particular attributes of the specimen." (See "General Notices and Requirements, Tests and Assays, Test Results, Statistics, and Standards," p. 8.)

Misinterpretation: If a product is not labeled "USP," then USP monograph requirements are not applicable to the product.

Clarification. This statement is false. Even if a product is not labeled "USP," if an official USP monograph exists for that product, then the product must meet the specific monograph requirements. The applicable statements for this interpretation are provided in section 501(b) of the FD&C Act as well as the USP ("General Notices and Requirements," p. 3). The FD&C Act "deems an official drug (*i.e.*, a drug purported to be or represented as a drug, the name of which is recognized in an official compendium) to be adulterated if it fails to conform to compendial standards of quality, strength, or purity.



Compendial tests or assay methods are used when determining such conformance under 501(b). The standards are stated in individual monographs as well as in portions of the 'General Notices' section of the *USP-NF*. Standards and test methods have been established for such characteristics as potency, sterility, dissolution, weight variation, and content uniformity. If an official drug fails to conform to one or more compendial standards of strength, quality, or purity, but the label plainly states how it differs from the standard, then the drug is not deemed to be adulterated under Section 501(b)" (1).

Similarly, the *USP* states that "The designation *USP* in conjunction with the official title or elsewhere on the label of an article means that the article purports to comply with *USP* standards..." The *USP* also states that "standards apply equally to articles bearing the official titles or names derived by transposition of the definitive words of the official titles or transposition in the order of the names of two or more active ingredients in official titles, whether or not the added designation *USP* is used." Occasionally an approved pharmaceutical product will have requirements different from those contained in the monograph. The *USP* covers this scenario by declaring, "Where an article differs from the standards of strength, quality, and purity, as determined by the application of the assays and tests set forth for it in the *Pharmacopeia*, its difference shall be plainly stated on its label." (See "General Notices and Requirements, 'Official' and 'Official Articles,'" p. 3.)

Challenging examples

In some cases, the *USP* does not offer clear interpretations. For these situations, the user must review applicable information to draw a conclusion that is based on the data presented in the *USP*. The following two scenarios demonstrate how one might undertake the responsibility of supporting such a position. The reader should be warned that the following interpretations are not viewed as official positions by any standard or regulatory authority and are merely the opinion of the authors.

Example 1: The *USP* specifies an incubation time of 48 hours and the laboratory method specifies an incubation time of 2 days. Is the laboratory method in compliance with *USP*?

Interpretation. The answer depends on how the laboratory records incubation start and stop times. In general, the *USP* typically indicates incubation times in terms of hours for tests completed in 3 days and in terms of days for tests requiring 5 days or more incubation time. Therefore, the authors conclude that 2 days is not necessarily compliant with a 48-hour incubation time. We believe the *USP* requires 48 hours of incubation from the start of incubation time. However, recording 14 calendar days would be sufficient for a 14-day incubation period for a sterility test. This conclusion was determined by reviewing microbiological test incubation times in the *USP*. The information was tabulated and evaluated before the aforementioned general conclusion was made. Refer to the following *USP* General Tests and Assays chapters:

- <51> "Antimicrobial Effectiveness Testing"
- <55> "Biological Indicators—Resistance Performance Tests"
- <61> "Microbial Limits Tests"
- <71> "Sterility Tests."

Example 2: The second *Supplement* to *USP 24–NF 19* removed reference to using control standard endotoxins in the text of General Test Chapter <85>, "Bacterial Endotoxins Test" (BET). Does this mean only reference-standard endotoxins can be used when performing BET testing?

Interpretation. Control standard endotoxins may be used when performing BET testing. The information needed to make this determination incorporates information contained in the *Pharmacopeial Forum* (the USPC's journal of standards development and compendium revision), in addition to official information contained in the *USP*. The *Pharmacopeial Forum* briefing supporting this interpretation states, "The use of in-house standards shown to be equivalent to *USP* Reference Standards is permitted under the requirements for alternative methods in the 'General Notices.' The control standard endotoxin (CSE) has thus been deleted because in-house standards have to be shown to be equivalent to the *USP* Endotoxin RS" (6). The statement in the "General Notices" to which the briefing refers is contained in the same paragraph used in the third misinterpretation above: "Compliance may be determined also by use of alternative methods chosen for advantages in accuracy, sensitivity, precision, selectivity, or adaptability to automation or computerized data reduction or in other special circumstances. Such alternative or automated procedures or methods shall be validated." In this case, the authors are considering the use of CSEs as a special case.

Conclusion

Most misinterpretation of the *USP* can be clarified by reading the "General Notices and Requirements" section in its entirety. Other appropriate information contained in the text of the *USP* should be considered, if applicable. To determine a suitable interpretation when no clear statement is made, users should investigate the issue by referring to appropriate *Pharmacopeial Forum* proposals and related *USP* chapters. In addition, one can also contact USPC to ask questions (www.usp.org).

References

1. Federal Food, Drug, and Cosmetic Act (1938), section 501(b).
2. *Code of Federal Regulations, Title 21, Food and Drugs* (General Services Administration, Washington, DC, 1 April 1973), Part 20205.50(c).
3. *Code of Federal Regulations, Title 21, Food and Drugs* (General Services Administration, Washington, DC, 1 April 1973), Part 299.4(c), (d), and (f).
4. *Code of Federal Regulations, Title 21, Food and Drugs* (General Services Administration, Washington, DC, 1 April 1973), Part 11.194(a)(2).
5. *United States Pharmacopeia 27–National Formulary 22* (United States Pharmacopeial Convention, Rockville, MD, 2003).
6. *Pharmacopeial Forum*, **26** (1), 2000. **PT**

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