1. Why Some USP Monographs Have Multiple Dissolution / Drug Release / Disintegration Tests

The dissolution, drug release, or disintegration tests in any USP monograph are the dosage form performance tests for products that were approved by FDA to be marketed in the United States. Because the dosage form performance may be formulation-dependent, a single test may not be suitable for all products covered by the USP monograph.

There are several general reasons why multiple performance tests (dissolution, drug release or disintegration) may be necessary in USP monographs:

a – **Solubility**: the drug substance has low solubility in aqueous systems. These drug substances belong to the BCS class 2 or 4. Each manufacturer will use different process strategies to try to increase the solubility of the drug substance, e.g., micronization, utilizing different particle shape, cocrystallization, complexation, etc. Consequently, specific performance test conditions may be necessary in each case.

b – **Polymorphs**: the drug substance has several polymorphic forms, each form with different solubility. As the polymorphic forms profile depends on the manufacturing process, specific performance test conditions may be necessary depending on the polymorphs profile of the drug substance being evaluated.

c – **Dosage form release mechanism**: dosage forms use different mechanisms to achieve a delayed- or extended-release profile. Some examples are tablets in layers, osmotic pump tablets, erosion tablets, functionally coated tablets or capsules, etc. Different dissolution / drug release / disintegration test conditions may be required depending on the release mechanism of the dosage form. The same principle is applicable for dosage forms other than tablets and capsules, such as transdermal systems, stents, suspensions, implants, etc.

Background Information

In 1996 the FDA and the USP Dissolution, Bioequivalence, and Bioavailability Subcommittee developed a mechanism to address multiple release tests in a compendial monograph. Initially, this mechanism was developed only for extended-release dosage forms but later was extended to all dosage form monographs that may have multiple dissolution tests. A labeling statement was established to indicate the number of the dissolution or drug release test the product complied with. Until late 1999, this labeling statement was used with all products that must comply with a particular USP monograph. In 2000 the statement was modified upon request from pharmaceutical companies to indicate that when more than one dissolution/drug release test is given, the labeling states the Dissolution test used only if Test 1 is not used. This change was made to avoid unnecessary expenses in changing packaging materials for products that were already on the market using the only test stated in the USP monograph when other tests were subsequently included in such monograph.

More recently, with the publication of the FDA guidances for orally disintegrating tablets (https://www.fda.gov/downloads/Drugs/.../Guidances/ucm070578.pdf) and for chewable tablets

(https://www.fda.gov/downloads/Drugs/Guidances/UCM507098.pdf), the same strategy has been applied for multiple disintegration tests in USP monographs. Most companies display this information in the leaflet or insert that goes in the product packaging. This labeling statement is valid only for products marketed in the United States. For other countries, the appropriate regulatory body needs to be contacted.

Within the *USP* monograph, the multiple tests are numbered in the order in which they were approved and became official. Consequently, Test 1 is not necessarily the test used by the Reference Listed Drug product. See additional information below under *Labeling and Test Numbering.*

The fact that a *USP* monograph has multiple performance tests does not imply that all the products meeting the requirements stated in the monograph are bioequivalent or interchangeable. FDA decisions on bioequivalence and interchangeability can be checked in the Orange Book at http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm.

This background information is reproduced in part from the article, USP and Dissolution—20 Years of Progress. (2014, August), *Dissolution Technologies,* retrieved from http://www.dissolutiontech.com/DTresour/201408Articles/DT201408_A05.pdf. For more information, please see *Useful References and Websites* below.

2. What Do I Need to Submit a Dissolution Test to USP?

In the submission to USP, the sponsor should provide FDA-approved conditions and tolerances. The procedure for submitting a request for revision to USP and the checklist for required documentation is provided in the *Submission Guideline for Chemical Medicine*s at http://www.usp.org/sites/default/files/usp/document/get-involved/submission-guidelines/chemical_medicines_rfr_guideline_-28apr16.pdf. If the product is pending FDA approval, the sponsor should follow the procedure and submission requirements described in the Pending Monograph Program at https://www.uspnf.com/pending-monographs and the detailed Guideline at https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/pending-monograph-guideline.pdf

The information below provides details for Dissolution tests, but is generally applicable for Drug Release and Disintegration tests as well.

Dissolution procedures submitted to USP must include sufficient details related to critical test parameters such as *Medium, Apparatus, Sampling time points and Tolerances* and the *Quantitative method* which are necessary to successfully perform the procedure and evaluate the results. Justification for unusual dissolution conditions should be provided as well. The following list suggests some of the details that should be included for a typical dissolution procedure.

a. Medium

- Composition: in the case of buffers, the preferred approach is to reference the USP Buffer Solutions section. However, other instructions may be described in the sponsor's documentation.
- pH: specify when applicable
- Deaeration: specify when necessary, including the deaeration procedure used
- Volume

Typically, for delayed-release (and for some examples for extended-release) dosage forms two different media may be used, e.g., for acid and buffer stages. When multiple dissolution media are required for the test, such as when the pH of the medium is adjusted partway through testing or when the medium is completely exchanged for a new medium, the same level of detail should be provided for each medium, along with a description of how and when the adjustment or exchange is to be carried out.

b. Apparatus

- Type: Any of the apparatus mentioned in the USP chapters (<711>, <724>, etc.).
  - If modification of any of the USP apparatus or use of a non-compendial apparatus is required, include drawings, blue-prints, measurements, material of construction. If the modified apparatus or non-compendial apparatus is commercially available, include a Note with catalog number and possible supplier.
- Agitation rate: Rotation speed, Dip rate or Flow rate (as applicable)
- Temperature: Required if different from standard conditions, 37 ± 0.5° for *Dissolution* or *Disintegration*.

Any specialized accessories needed for the test, i.e., accessories not defined in a USP general chapter, should be fully described. The information of a possible supplier will be included in a monograph as a Note.

Sinkers are available on the dissolution equipment marketplace. If commonly marketed sinkers are used, their description or specification should be included. If unusual sinkers are used (generally, in-house made), include a drawing with measurements and material of construction. This information will be included in a monograph under the description of the Apparatus.

c. Sampling time points and Tolerances

The sampling time point(s) refers to the specific time (or times for multiple sampling events) when samples are to be withdrawn from the medium for analysis. For each sampling time point(s), the specification should state the associated tolerances, i.e., acceptance range or acceptance limit. In the cases when multiple dissolution media are required for the test, the specification should clarify how the amount released in the first/acid stage is taken into account in the tolerances / acceptance criteria for subsequent dissolution stages, when applicable.

The interpretation of results will be assumed to follow the relevant Acceptance Table from the applicable USP general chapter, unless otherwise specified. Sponsors with regulatory approval

for a unique interpretation approach must submit their approved Acceptance Table for inclusion in the monograph.

Some sponsors may use the term (Q) as part of their specification statement. This term can help to facilitate the interpretation of dissolution results at advanced stages of testing, when it is used in conjunction with an Acceptance Table that also utilizes a (Q) term. When (Q) is included in the statement of the Tolerance, one of the following conditions must be met:

- Interpretation of results follows "Acceptance Table 1" in the General Chapter <711> Dissolution (applicable to Immediate-Release Dosage Forms)
- Interpretation of results follows "Acceptance Table for a Pooled Sample" in the General Chapter <711> Dissolution (applicable to Immediate-Release Dosage Forms, Pooled Sample)
- Interpretation of results follows "Acceptance Table 4" in the General Chapter <711> Dissolution (applicable to Delayed-Release Dosage Forms, reflecting a point in the dissolution profile where the dose is fully released.)
- The sponsor has provided details (possibly through a unique Acceptance Table) describing how results are to be interpreted. The interpretation utilizes a '(Q)' term.

d. Quantitative method

Complete details related to the method of quantitation, e.g., chromatographic, spectrophotometric, or other analytical techniques, must be provided. Refer to the *Submission Guideline for Chemical Medicines* for additional information on the documentation required to support the specific method of quantitation being employed. In addition, the procedure should include detailed calculations reflecting the method of execution for the test. This is particularly critical for dissolution profiles with multiple sampling times, where the calculation should reflect practices such as media replacement, volume correction (i.e., without media replacement) and accounting for drug lost to prior samples.

3. How Will USP Process My Submission for a New Dissolution / Drug Release / Disintegration Test?

If the test is a part of a new monograph submission, a complete monograph proposal will be published in Pharmacopeial Forum (*PF*) as an In-Process Revision for public comment.

Sponsors whose products have been approved by FDA with dissolution / drug release / disintegration test conditions and/or tolerances which are different from the ones(s) in an official monograph or in a published proposal should submit a request for revision. USP will notify the sponsor about the test number assigned to their test (see the *Labeling and Test Numbering* below).

The inclusion of a new test is typically done via an Accelerated Revision process (see https://www.uspnf.com/official-text/accelerated-revision-process). In some cases, if the proposal is received during the public comment period for a new monograph, it might be considered by an Expert Committee for inclusion at the ballot. This information will be included in the Commentary (see https://www.uspnf.com/official-text/proposal-statuscommentary).

If a request pertains to an application pending FDA approval, refer to the information about the Pending Monograph Program at https://www.uspnf.com/pending-monographs and the detailed Guideline at https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/pending-monograph-guideline.pdf. Proposals which have been approved for potential adoption are published on the Compendial Notices section of the USP-NF website under *Notices of Intent to Revise: Pending Monograph Program.*

4. Labeling and Test Numbering

Labeling in the U.S. constitutes any printed packaging material used with pharmaceutical products, such as the label, leaflet and carton. Most companies will display the information about the dissolution / drug release / disintegration test in the leaflet, typically under the description of the product.

The test numbers are assigned when the dissolution / drug release / disintegration test is going to be incorporated in the monograph. As noticed above, the tests are numbered in the order in which they were approved and became official. n most cases, these assigned test numbers reflect the order the submissions are received by USP. However, exceptions may occur when the documentation received is incomplete.

The numbering of the dissolution / drug release / disintegration tests and the associated labeling requirements are applicable only for products marketed in the U.S. For products marketed in other regions, the local regulatory agency needs to be consulted on how to handle multiple tests in that particular region/market.

As product label claims in other regions can differ from the product label claim in the U.S., users should verify the label claim of the product approved for marketing in the U.S. prior to testing a non-U.S. product according to the USP monograph. This information is available in the FDA Orange Book (for human use products) at http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. This site is a useful source of the information on the market status of the product in the USA (RX – by prescription only, OTC – over the counter, DISCN – discontinued). For veterinary products, the information is available in the FDA Green Book, access at https://www.fda.gov/animalveterinary/products/approvedanimaldrugproducts/

5. Useful References and Websites

U.S. FDA Orange Book (human use products)
https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm

U.S. FDA Green Book (veterinary products)
https://www.fda.gov/animalveterinary/products/approvedanimaldrugproducts/

U.S. FDA Guidances
https://www.fda.gov/RegulatoryInformation/Guidances/default.htm

U.S. FDA Dissolution Methods database
https://www.accessdata.fda.gov/scripts/cder/dissolution/

USP Dissolution Methods database
https://www.usp.org/resources/dissolution-methods-database

Dissolution Technologies journal
www.dissolutiontech.com