Supporting Information for Dissolution / Drug Release / Disintegration Tests in USP Monographs

1. Why do 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 reasons 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 biopharmaceutics classification system (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, co-crystallization, complexation, etc.) Consequently, specific performance test conditions may be necessary in each case.

b – **Polymorphs**: the drug substance has several polymorphic forms with different solubilities. As the polymorphic forms profile depends on the manufacturing process, specific performance test conditions may be necessary.

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 applies to other dosage forms, 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. It was later 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. In 2000, the statement was modified 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/regulatory-information/search-fda-guidance-documents/orally-disintegrating-tablets) and for chewable tablets (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/quality-attribute-considerations-chewable-tablets-guidance-industry), 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 should 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 are available in the Orange Book (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 information do I need to submit to USP for inclusion of a new a dissolution test?

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

In the submission to USP, the sponsor should provide FDA-approved conditions and tolerances. Please follow the Checklist for required documentation and the Revision Request Form provided at https://www.usp.org/get-involved/usp-donations-program/submission-guidelines. If the product is pending FDA approval, the sponsor should follow the procedure and submission requirements described in the Pending Monograph Guideline at https://www.uspnf.com/pending-monographs.

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 in some cases, 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 general 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, and material of construction. If the modified apparatus or non-compendial apparatus is commercially available, include a 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. Information about 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 specifications should be included. If unusual sinkers are used (generally those made in-house), 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, 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 Checklist* 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 of the applicable monograph. 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). If the proposal is received during the public comment period for a new monograph, its receipt will be noted in the Commentary (see https://www.uspnf.com/official-text/proposal-statuscommentary) and addressed in a timely manner.

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. Proposals which have been approved for potential adoption are published on the Compendial Notices section of the USP-NF website at https://www.uspnf.com/pending-monographs/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, package insert, and carton. Most companies will display the information about the dissolution / drug release / disintegration test in the package insert, 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 noted above, the tests are numbered in the order in which they were approved and became official. In 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 information on how to handle multiple tests for products marketed in other regions, consult with the applicable local regulatory authority.

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), accessible at http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. This site is a useful source of information about the market status of products in the U.S. (RX – by prescription only, OTC – over the counter, DISCN – discontinued). For veterinary products, the information is available in the FDA Green Book, accessible 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