Designation: D 7077 – 04

Standard Test Method for Evaluation of Drop Size by weight of Solutions and Suspensions[1]

This standard is issued under the fixed designation D 7077; the number immediately following the designation indicates the year of original adoption or, in the case of revision, the year of last revision. A number in parentheses indicates the year of last reapproval. A superscript epsilon (ε) indicates an editorial change since the last revision or reapproval.

1. Scope

1.1 This standard test method uses a simulated in-use study to measure the drop size by weight and to determine the number of drops per container for solutions and suspensions contained in a package system designed to deliver product drop-wise through a controlled size orifice by squeezing or compressing the package.

1.2 *This standard does not purport to address all of the safety concerns, if any, associated with its use. It is the responsibility of the user of this standard to establish appropriate safety and health practices and to determine the applicability of regulatory limitations prior to use.*

2. Terminology

2.1 *Definitions:*

2.1.1 *Average drop size per dosing interval*—The average weight of a drop of product dispensed from a given package within a given dosing interval.

2.1.2 *Average drop size per package*—The average weight of a drop of product dispensed from a given package considering all dispensed doses.

2.1.3 *Controlling orifice*—A dispensing plug which fits snuggly enough in the mating bottle to form a seal, thereby forcing all fluid exiting the package to travel through the plug.

2.1.4 *Dosing interval*—The time period between product dosings. Testing may be performed "as per label directions," which means testing is performed at time intervals defined by label directions (for example, once daily). Alternatively, testing may be performed "continuously," meaning that a shorter time period between dosing intervals is used in order to expedite testing.

2.1.5 *Drop size*—The weight of a single drop of product dispensed from a package designed to deliver product through a controlling orifice.

2.1.6 *Unsolicited drops*—An amount of product that comes from the container without the user squeezing the container.

2.1.7 *Variable*—Different plugs, closures, bottles, or formulations.

2.1.8 *Volcanoing*—Spewing forth of the product upon initial opening of the container/closure system.

3. Summary of Test Method

3.1 Drop size tends to be highly subjective given all the potential variables, however, it is an essential element in describing the dosage delivered from a specific package. This test method is structured to mimic patient use of an solution or suspension that is delivered through a controlling orifice to determine an average drop size for the product. The average number of drops per container will then be calculated from the data collected.

4. Significance and Use

4.1 This test method may be used to measure the drop size and the number of drops per container for solutions and suspensions in a specific package system.

5. Apparatus

5.1 For drop size testing solutions and suspensions, the following equipment is required:

5.1.1 *Analytical balance*—accurate to ± 0.0001 gram.

6. Reagents and Materials

6.1 Bottles, plugs, and closures that are representative of the desired package system under investigation.

6.2 It is strongly recommended that actual product be used for this test. However, it is recognized that in some instances actual product may not be available. In this case a fluid that has similar viscosity and dispensing characteristics as the product under investigation should be used.

7. Hazards

7.1 Any remaining test product should be disposed of in a responsible manner.

7.2 The disposal requirements of the available MSDS for the product, or key ingredients of the product, or both should be observed in disposal.

8. Sampling, Test Specimens, and Test Units

8.1 Ten test samples are recommended for testing. A test sample is defined as a complete unit consisting of the bottle, plug, and closure intended for use; and the package should be

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filled with the appropriate fluid. The fill level should be consistent with the level intended for market. Unless otherwise specified, samples are to be unopened and unused at the beginning of the test.

8.2 The test samples should be labeled with the product label and adhesive intended for marketing. The label will add stiffness, or a more durable gripping surface, or both; therefore, it could potentially impact the "squeezability" of the finished package.

8.2.1 Number all test samples sequentially.

8.2.2 Prepare each test sample by removing all tamper-evident features, (i.e., shrink bands, tamper-evident ring).

9. Preparation of Apparatus

9.1 Ensure the balance weigh pan is clean and free from debris.

10. Calibration and Standardization

10.1 Ensure the unit is properly calibrated according to the user's existing procedures.

11. Conditioning

11.1 The materials to be tested should be at room condition before the testing is initiated, unless the product labeling indicates otherwise. If the label indicates the product will be stored in the refrigerator during the package use period then the test conditions should be altered accordingly.

12. Procedure

Part A – Drop Size Determination

12.1 Weigh each test sample individually and record this value as the "initial weight".

12.2 Product may be dispensed at a 45°, 60°, 75° or 90° angle from horizontal. Record the angle at which drops will be dispensed. The angle of dispensing will vary the drop size.

NOTE 1—It is not realistic in most instances to anticipate a patient will hold a bottle absolutely perpendicular to the delivery site while dosing (i.e. 90°) therefore, alternate angles should be considered. Typically, the smaller the angle the larger the drop size.

12.3 Obtain a weigh boat or other suitable container and place it in the center of the weigh pan of the balance.

12.4 Tare the balance.

12.5 Select Sample No. 1 and shake the product, if required.

12.6 Remove the closure, recording any occurrence of volcanoing.

12.7 Holding the test sample at the angle recorded in Step 12.2., dispense one drop onto the weigh boat.

12.8 Record the Sample Number and the weight of the drop to the nearest 0.1 mg.

12.9 If the product requires more than one drop per dose, tare the balance and repeat steps 12.7 and 12.8, according to the number of drops required per dosing interval, recording the weight of each drop dispensed.

NOTE 2—Drops should be dispensed from the test samples in compliance with the dosing regimen defined for the product. As an example, if the labeling indicates one drop in the affected eye, and we assume both eyes are affected, then two drops would be individually weighed and measured and then the closure returned to the closed position and the bottle returned to the upright position. This action comprises one dose for this product.

12.10 Replace the closure and store the test sample in an upright position until the next dosing interval.

12.11 Repeat steps 12.1-12.10 for each of the remaining test samples. Calculate the average drop size dispensed from each package per each dosing interval. Record any unusual occurrences, e.g., multiple drops, unsolicited drops, bubbling, foaming, and so forth.

12.12 Continue testing until the data indicate no significant trends in the average drop size per dosing interval per package, or until product is exhausted, whichever occurs first. A minimum of forty drops is recommended to evaluate the data for significant trends in drop size.

12.13 *Dosing Intervals*—The interval or period of time allowed between product dosings for a given package may be either "as per label directions," or "continuously". For example, for a product used once daily, the drop size testing interval will be once each day if performed "as per label directions". Alternatively, testing may be performed "continuously," meaning that a shorter time period between dosing intervals is used in order to expedite testing. For instance, ten samples may be tested in rotation during a single day. It is recommended that each of the ten bottles should be dispensed before returning to the first sample to begin again. Each test bottle should be placed upright and re-closed between doses of drops. For suspension products the product should be resuspended by shaking if so indicated by the labeling. The manner of dosing should be recorded as either "according to product labeling" or "continuous".

Part B – Product Fill, Product Loss, Doses/Container Determination

12.14 After completing the drop size evaluation in accordance with 12.12, select the two test samples with the highest and lowest average drop size and the two test samples with the highest and lowest initial weight. In the event that a single test sample qualifies on more than one of the criteria above, e.g., the test sample with the lowest initial weight also produces the lowest average drop size, select the next qualified test sample. Obtain a weigh boat or other suitable container and place it in the center of the weigh pan of the balance and tare the balance.

12.15 Select one of the four test samples from 12.13. Remove the closure. Holding the test sample at the angle recorded in 12.2, dispense drops equivalent to a dose per product labeling. Replace the closure and return the bottle to upright. If the product is a suspension it should be shaken between doses if shaking is recommended in the product labeling.

12.16 Repeat step 12.15 until the container is empty. Record the number of drops required to completely empty the test sample and the cumulative weight of the product dispensed.

12.17 Repeat steps 12.14-12.16 for the remaining three samples.

12.18 For each of the four empty samples weigh and record the weight. This weight will be designated as "final weight (empty)".

12.19 Clean and dry the four empty test samples to remove all residual product and weigh and record the weight of the cleaned test samples. This weight will be designated as "final weight (cleaned)".

13. Calculation or Interpretation of Results

Part A

13.1 Using the data collected in Part A, calculate the overall drop size average and standard deviation for the entire data set (all packages, all doses dispensed).

13.2 Using the data collected in Part A, calculate the average drop size and standard deviation for each container.

Part B

13.3 Calculate the total fill volume for each of the four test samples used in Part B by subtracting the final weight (cleaned) (step 12.19) from its initial weight (step 12.1).

13.4 Calculate the total product loss for the four test samples used in Part B by subtracting the total product dispensed (step 12.16) from the total fill (step 13.3).

13.5 Calculate the average total number of drops per container for each of the samples tested in steps 12.16 and 12.17.

14. Report

14.1 The report is to contain the overall average drop size with standard deviation per package population (step 13.1), the average drop size with standard deviation per test sample (step 13.2), the average total number of drops per container (step 13.5), the total fill volume for samples tested (step 13.3), and the total product loss (step 13.4).

14.2 The report should also contain the necessary information to describe the test samples components. This information may include but is not limited to: part number, material reference, and lot number.

14.3 The dispensing angle, dosing interval, and any special observations related to product dispensing characteristics are to be recorded.

15. Precision and Bias

The precision of this method has not yet been determined. A method of determining bias is not available for this test method.

16. Keywords

16.1 dose; drop size