Lot Acceptance Procedure Criteria

Providing Statistical Confidence to Pass

BY JAMES BERGUM

Q. Lots are released based on comparing test results from a sample to lot acceptance procedure criteria. If a set of test results meets the lot acceptance procedure criterion, how can I be assured that another sample from the lot would also pass the criterion?

A: Companies use lot acceptance procedures to release a lot. Test results from a sample are evaluated against lot acceptance procedure criteria, and if the criteria are met, the lot is released. However, since test results are subject to variability, another sample from the same lot may not meet the criteria. If units from a lot fail after release, there can be significant cost to the company (e.g., a lot recall). ASTM E2709, Practice for Demonstrating Capability to Comply with an Acceptance Procedure, provides a general statistical approach that can be used to make a statement such as this one: "With 95 percent confidence, there is a 95 percent chance that another sample taken from the lot will pass the lot acceptance procedure."

ACCEPTANCE PROCEDURES AND CRITERIA

Lot acceptance procedures might consist of a single or multiple stages. Each stage may have single or multiple criteria that must be met. For example, a single stage test (taken from ASTM E2709) might be the following.

- Sample five units at random from the lot and measure a numerical quality characteristic of each unit.
- Criteria: Pass if all five individual units are between 95 and 105 percent of target.
- Otherwise, fail the lot.

A multiple stage test might be based on a product specification of 90 to 100 percent of target.

- *Stage 1*: Sample five units at random from the lot and measure a numerical quality characteristic of each unit.
- Criteria: Pass if all five individual units are between 95 and 105 percent of target.
- Otherwise go to Stage 2.
- *Stage 2*: Randomly sample five additional units from the lot and measure a numerical quality characteristic of each unit.
- Criteria: Pass if the average of the ten test results is between 97 and 103 percent of target and all 10 individual results are between 90 and 110 percent of target.
- Otherwise fail.

STRATEGIES TO MEET LOT ACCEPTANCE PROCEDURE CRITERIA

To reduce the risk of releasing a lot that cannot meet the lot acceptance criteria, companies may use tighter in-house limits with the assumption that if the tighter limits are met, then the lot acceptance procedure criteria will be met. For example, for the above single stage test, the in-house limit might be that all five results must be between 97 and 103 percent of target instead of 95 to 105 percent of target. An alternative approach to tightening the lot acceptance procedure itself would be to use a strategy where *n* individual units are selected from the lot according to a specific sampling plan. The test results from these units would then be used to ensure with a high level of confidence that if the lot acceptance procedure were applied, there would be a high probability of passing the lot acceptance procedure criteria. In this approach, the sampling plan and acceptance limits are different from the lot acceptance procedure. However, passing the acceptance limits for this alternative approach assures passing the lot acceptance procedure. The details for the general methodology have been published[1-4] and appear in ASTM E2709.

A specific application of the methodology is given in ASTM E2810 for the U.S. Pharmacopeial Convention Uniformity of Dosage Units test used to release lots in the pharmaceutical industry. The uniformity test is used to show that individual dosage units contain similar amounts of the active ingredient. To apply the ASTM E2709 methodology requires a specified lot acceptance procedure such

as the multiple stage lot acceptance procedure given above. A sampling plan is required to collect the units to test. There are three common sampling plans that are used: 1) completely random; 2) systematic, where one unit is tested from equally spaced intervals throughout the lot and 3) systematic, where more than one unit is tested from equally spaced intervals throughout the lot. The advantage of the third method is that the between and within interval variability can be estimated, which can be very useful to determine how much of the total variability in the test results is due to interval to interval.

For the rest of this article, assume that the first or second sampling plan is used to collect the units for testing. Once the units are tested, sample statistics are calculated such as the sample mean and standard deviation, and these compared to upper limits given in an acceptance limit table. The acceptance limit table is the same for both the first and second sampling plans. Details of how to construct the table are given in ASTM E2709. Mathematics and generally a computer program are required to develop the table for a given lot acceptance lot procedure. Constructing the table requires the user to choose a level of confidence (usually 90 or 95 percent), the desired probability (called coverage) of passing the lot acceptance procedure (usually 90 or 95 percent), and a sample size.

EXAMPLE

Suppose that the sampling plan is to test 30 units (*n*) either randomly taken from the lot or at equally spaced intervals throughout the lot. Suppose that the sample mean is 98 percent of target and the standard deviation is 0.358 percent of target. Suppose that the prespecified level of confidence and the desired probability of passing the lot acceptance procedure (coverage) are both 95 percent. The associated acceptance limit table using the lot acceptance procedure and criteria given above is given in Table 1 – Acceptance Limits.

For possible sample means, the acceptance table provides the upper limit on the sample standard deviation. In our example, the upper limit of an acceptable standard deviation for a mean of 98 percent is 0.819. Since the found sample standard deviation is 0.358 percent of target, the sample meets the acceptance limit table criterion. Note that the acceptance limit criteria and sample sizes are not the same as actual lot acceptance procedure criteria. However, by passing the acceptance limit table criteria, the following statement can be made: With 95 percent confidence, there is at least a 95 percent chance of passing the lot acceptance procedure.

Table 1 – Acceptance Limits[1]

Mean (% Target)	Standard Deviation (% Target)
97.0	0.546
98.0	0.819
99.0	1.599
100.0	2.240
101.0	1.599
102.0	0.819
103.0	0.546

1. 95 percent confidence interval; 95 percent coverage

REFERENCES

1. Bergum, J.S., "Constructing Acceptance Limits for Multiple Stage Tests," *Drug Development and Industrial Pharmacy*, Vol. 16, No. 14, 1990, pp. 2153-2166.
2. Bergum, J.S., and Utter, M.L., "Process Validation," *Encyclopedia of Bio-Pharmaceutical Statistics*, 3rd ed., Informa Health, New York, NY, 2010, pp. 1070-1082.
3. Bergum, J.S., and Utter M.L., "Statistical Methods for Uniformity and Dissolution Testing," *Pharmaceutical Process Validation*, 3rd ed., Robert A. Nash and Alfred H. Wachter, Eds., Marcel Dekker, New York, NY, 2003, pp. 667-697.
4. Bergum, J.S., and Li, H., "Acceptance Limits for the New ICH USP 29 Content Uniformity Test," *Pharmaceutical Technology*, October 2007, pp. 90-100.

JAMES BERGUM, *Ph.D., is a statistical consultant and president of BergumSTATS, LLC, Howell, N.J., and a member of ASTM International Committees E11 on Quality and Statistics and E55 on Manufacture of Pharmaceutical Products.*

DEAN V. NEUBAUER, *Corning Inc. Corning, N.Y. is an ASTM fellow; he serves as chairman of Committee E11 on Quality and Statistics, chairman of E11.90.03 on Publications and coordinator of the DataPoints column.*

snonline

Get more tips for ASTM standards development at www.astm.org/sn-tips.

Find other DataPoints articles at www.astm.org/standardization-news/datapoints.