DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 16(14), 2153-2166 (1990)

CONSTRUCTING ACCEPTANCE LIMITS FOR MULTIPLE STAGE TESTS

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ABSTRACT

Multiple stage tests are often used in the pharmaceutical industry (e.g., content uniformity, dissolution, disintegration). Acceptance limit methodology is given which assures that a future sample will have at least P% chance of passing a multiple stage test. For a given sample size, an associated acceptance region for the sample mean and standard deviation is found by (1) constructing a confidence region for the population mean and standard deviation, and (2) finding the probability of passing the test for each population mean and standard deviation in this confidence region. The acceptance region is the set of all sample means and standard deviations such that the probability of passing the test is greater than a specified P for all points in the confidence region.

INTRODUCTION

Two components of manufacturing a product are evaluation of the manufacturing process (process validation) and testing batches prior to distribution (release testing). Process validation provides assurance that the process does what it purports to do, whereas release testing provides evidence that all the units in a batch will meet certain specifications. A common approach to process validation or release testing is to obtain a single sample, test the attributes of interest, and if the

specification for the tested attribute is met, the process is validated or the batch is released. However, this does not guarantee, with a high level of assurance, that if the test was performed again that the test would have a high probability of meeting the specification. This paper shows one way to construct acceptance limits that guarantee that future samples from a batch will meet a given product specification a given percentage of the time. The type of specification discussed in this paper are multiple stage tests. Multiple stage tests consist of several stages with specific criteria at each stage. If the criteria for the first stage are met, the test is passed. If the criteria for the first stage are not met, then additional stages of testing are done. If the criteria at any stage are met, the test is passed. This paper provides an approach to constructing acceptance limits for a validation sample which assures that a future sample will have at least P% chance of passing a multiple stage test.

Assuming the underlying distribution for the data is normal, the following approach is used to construct acceptance limits. For a given sample size, an associated acceptance region for the sample mean and standard deviation is found by: (1) constructing a confidence region for the population mean and standard deviation, and (2) finding the probability of passing the multiple stage test for each population mean and standard deviation in the confidence region. The acceptance region is the set of all sample means and standard deviations such that the probability of passing the multiple stage test is greater than a specified P for all points in the confidence region. Thus, it is necessary to: (1) find a lower bound for the probability of passing a given test, and (2) construct a confidence region for the population parameters. A general lower bound, construction of a confidence region, and an example is given in the following subsections.

GENERAL LOWER BOUND

A general expression for the lower bound for passing a multiple stage test expressed in terms of individual criteria can be derived as follows:

Let S_i = event that i^{th} stage of k stage test is met

and

C_{ij} = event that j^{th} criterion for i^{th} stage ($j = 1, \ldots, m_i$) is met

then

$$P(\text{passing k stage test}) = P(S_1 \text{ or } S_2 \text{ or } \ldots \text{ or } S_k) \geq P(S_i) \text{ for each i, } i = 1, \ldots, k$$

so

$$P(\text{passing k stage test}) \geq \max \{P(S_1), P(S_2), \ldots P(S_k)\}.$$

Now

$$P(S_i) = P(C_{i1} \text{ and } C_{i2} \text{ and } \ldots \text{ and } C_{im_i}) \geq \max \left[\sum_{j=1}^{m_i} P(C_{ij}) - (m_i - 1), 0\right]$$

so a lower bound, LB say, for passing the multiple k stage test is

$$\max_i \left[\max \left\{\sum_{j=1}^{m_i} P(C_{ij}) - (m_i - 1), 0\right\}\right].$$

CONFIDENCE REGION

Suppose n results from each of L locations (a total of $N = nxL$) are performed. Let Y_{ij} denote the j^{th} assay result ($j = 1, 2, \ldots n$) from location i($i = 1, 2, \ldots, L$). The following one way random effects model is assumed.

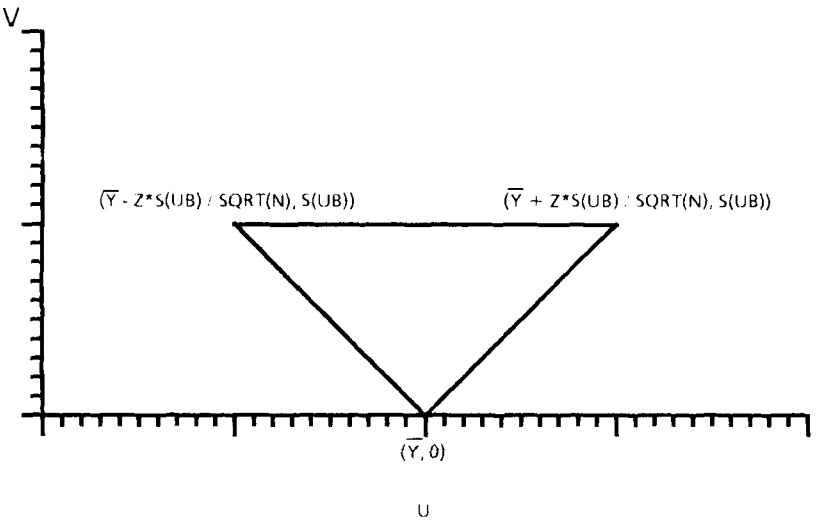
$$Y_{ij} = u + L_i + E_{ij}$$

where u is the population mean, E_{ij} is i.i.d. $N(0, V_E^2)$, and L_i is i.i.d. $N(0, V_L^2)$. E_{ij} and L_i are independent random variables. Note that $E(Y_{ij}) = u$ and $Var(Y_{ij}) = V_E^2 + V_L^2$. Denote $V_E^2 + V_L^2$ by V^2.

Confidence regions for u and V^2 are derived below for each of two sampling plans--Plan 1) one observation at each location, and Plan 2) more than one observation at each location.

Sampling Plan 1

Suppose one assay is performed at each of L locations (i.e., N = L). Then u is estimated by the sample mean and V^2 ($= V_E^2 + V_L^2$) is estimated by the sample variance. A simultaneous confidence region for u and V^2 is given in Lindgren[1] and is plotted in Figure 1.



WHERE
N = SAMPLE SIZE
$\overline{Y}$ = SAMPLE MEAN
Z = STANDARD NORMAL PERCENTILE
S(UB) = UPPER BOUND FOR SIGMA

FIGURE 1
Sampling Plan 1
Simultaneous Confidence Region
for U and V

Sampling Plan 2

Suppose that n assays ($n>1$) are performed at each of L locations. A simultaneous confidence interval for (u, V_E^2, V_L^2) can be constructed from $(\bar{Y}, S_E^2, S_L^2)$ of a sample where $\bar{Y}$ = overall mean, S_L^2 = mean square between locations, and S_E^2 = mean square error from a one way analysis of variance.

Let Z_k and $X^2_{m,w}$ denote k and m percentiles of the standard normal distribution and the chi-square distribution with w degrees of freedom, respectively. Given a confidence coefficient, α, choose p and q such that $\alpha=(1-2p)(1-q)(1-q)$. Let $E = V_E^2 + nV_L^2$, which is the expected value of S_L^2. Then

$$\text{Prob}([-Z_{1-p} < (\bar{Y}-u)/(E/N)^{\frac{1}{2}} < Z_{1-p}]$$
$$\text{and } [L(n-1)S_E^2/V_E^2 > X^2_{q,L(n-1)}]$$
$$\text{and } [(L-1)S_L^2/E > X^2_{q,L-1}])$$
$$= \text{Prob}(-Z_{1-p} < (\bar{Y}-u)/(E/N)^{\frac{1}{2}} < Z_{1-p})$$
$$* \text{Prob}(L(n-1)S_E^2/V_E^2 > X^2_{q,L(n-1)})$$
$$* \text{Prob}((L-1)S_L^2/E > X^2_{q,L-1})$$
$$= (1-2p)(1-q)(1-q) = \alpha$$

A simultaneous confidence region for (u, V_E^2, V_L^2) is therefore:

$$\bar{Y} - Z_{1-p}(E/N)^{\frac{1}{2}} < u < \bar{Y} + Z_{1-p}(E/N)^{\frac{1}{2}},$$

$$0 < V_E^2 < L(n-1)S_E^2/X^2_{q,L(n-1)},$$

and

$$0 < V_L^2 < (1/n)((L-1)S_L^2/X^2_{q,L-1} - V_E^2) \qquad \text{if } V_E^2 \leq (L-1)S_L^2/X^2_{q,L-1}$$
$$V_L^2 = 0 \qquad \text{otherwise.}$$

For each V_E^2 and V_L^2 contained in the confidence region, a value of V^2 (variance of Y_{ij}) and a range for u (expected value of Y_{ij}) can be computed.

EXAMPLE

The example given in this section provides specific details on construction of acceptance limits including confidence interval derivations for a multiple stage test used in the pharmaceutical industry to test for uniformity of tablets.

The USP XXI[2] test criteria for content uniformity of tablets is the two stage procedure given below:

STAGE 1:

Assay 10 tablets. Pass if both of the following criteria are met:

1) CV is less than or equal to 6.0%;

2) no value is outside 85% to 115% of claim.

Fail if one or more values are outside 75% to 125% of claim. Otherwise, go to Stage 2.

STAGE 2:

Assay 20 further tablets. Pass if, for all 30 tablets, the following criteria are met:

1) CV is less than or equal to 7.8%;

2) no more than one value is outside 85% to 115% of claim and no value is outside 75% to 125% of claim.

Otherwise, fail.

The remainder of this example is divided into two subsections. In the first subsection, a lower bound is found for the probability of passing the USP XXI content uniformity test for tablets given the population assay mean and variance. In the

second subsection, confidence intervals for the population assay mean and variance are found for each of two sampling plans.

Probability Bound

Let

C_{11} be the event that criterion 1 in stage 1 is met.

C_{12} be the event that criterion 2 in stage 1 is met.

C_{21} be the event that criterion 1 in stage 2 is met.

C_{22} be the event that criterion 2 in stage 2 is met.

Then Prob(passing USP) = Prob(first ten tablets meet USP stage 1 criteria or all thirty tablets meet the USP stage 2 criteria)

$\geq$ max {Prob(first ten tablets meet USP stage 1 criteria), Prob(all thirty tablets meet the USP stage 2 criteria)}

$\geq$ max {$\text{Prob}(C_{11}) + \text{Prob}(C_{12}) - 1$, $\text{Prob}(C_{21}) + \text{Prob}(C_{22}) - 1$}.

Therefore, by finding $\text{Prob}(C_{11})$, $\text{Prob}(C_{12})$, $\text{Prob}(C_{21})$, and $\text{Prob}(C_{22})$, we will have a lower bound, LB, on the probability of passing the USP test.

Let the content uniformity assay values, Y (expressed as a percent of claim), have a normal distribution with mean u and variance V^2 denoted $N(u,V^2)$. The sample c.v. after a suitable transformation (sample size/cv^2) has a non-central F distribution, whereas the $\text{Prob}(C_{11})$ and $\text{Prob}(C_{21})$ for a given u and V^2 can be computed as follows.

Let P_1 be the probability that an assay result is in the region from 85% to 115% of claim.

$P_1 = \text{Prob}(85 \leq Y \leq 115)$

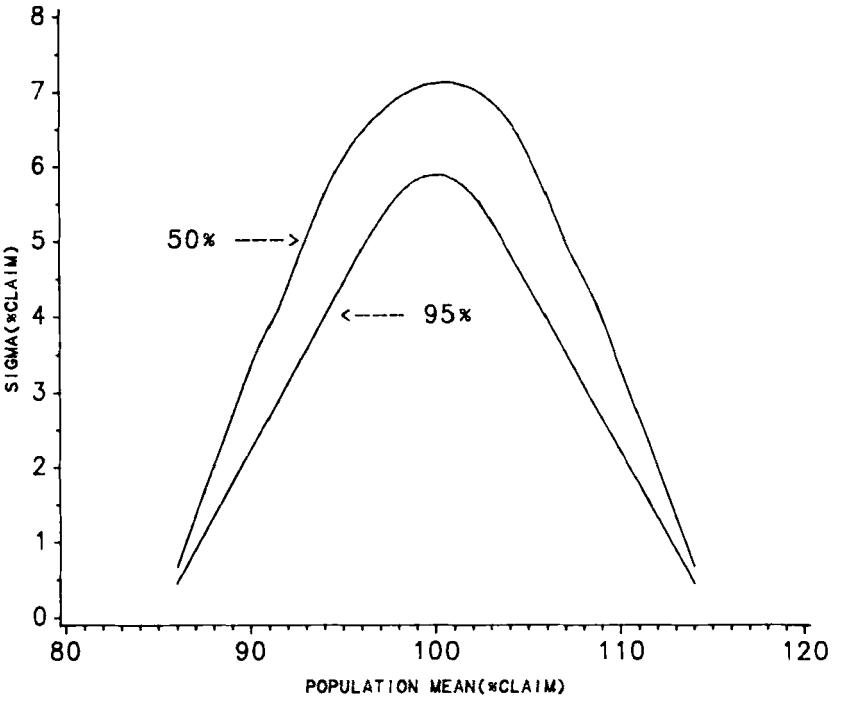


FIGURE 2

50% AND 95% LOWER BOUND CONTOURS FOR PASSING CONTENT UNIFORMITY TEST

Let P_2 be the probability that an assay result is in the region between 75% to 85% of claim or 115% to 125% of claim.

$$P_2 = \text{Prob}(75 \leq Y \leq 85) + \text{Prob}(115 \leq Y \leq 125)$$

Then,

$$\text{Prob}(C_{12}) = P_1^{10}$$

and

$$\text{Prob}(C_{22}) = P_1^{30} + 30\, P_1^{29}\, P_2.$$

So for a given u and V^2, LB can be calculated. The contours for LB equal to 50 and 95 are given in Figure 2. So, for example, if u is 94, and if V is less than 5.60, there

TABLE 1
Simulation Results
Lower Bound Vs. Simulated Results
(% Passing Test)

POPULATION MEAN	SIGMA 2		4		6	
	LOWER BOUND	SIMULATION RESULT	LOWER BOUND	SIMULATION RESULT	LOWER BOUND	SIMULATION RESULT
86	2.5	2.5	0.0	0.6	0.0	0.2
90	98.5	99.1	26.8	36.8	0.0	9.0
94	100.0	100.0	94.8	96.8	34.7	53.7
98	100.0	100.0	100.0	100.0	88.4	92.0
100	100.0	100.0	100.0	100.0	93.4	95.7
102	100.0	100.0	100.0	100.0	89.6	92.9
106	100.0	100.0	94.8	97.0	38.8	55.8
110	98.5	99.1	32.4	36.4	0.9	10.0
114	2.5	2.5	0.4	0.5	0.0	0.3

is at least a 50% chance of passing the USP test. For each u ($85 < u < 115$) as V decreases to zero, the probability of passing the content uniformity test increases so that for any (u, V) below any given LB contour, the probability of passing the content uniformity is greater than LB.

To evaluate how close the lower bound is to the actual probability of passing the content uniformity test, a simulation was performed. At various combinations of population mean and standard deviation values, 10,000 sets of random normal numbers were generated. Each set was evaluated against the USP criteria for tablet content uniformity. The percentage of sets passing the USP test was calculated as well as the lower bound. Results of the simulation are given in Table 1. The lower bound

is quite close to the simulated result for sigma equal 2. However, note that the difference between the lower bound and the simulated result tends to increase as the population standard deviation increases.

Suppose sampling Plan 1 is used. Construct the simultaneous confidence region. Recall that for a fixed u ($85 < u < 115$), the probability of passing the USP test increases as V goes to zero. Therefore, if $85 < A$ and $B < 115$ in Figure 1, than the point resulting in the lowest probability of passing the USP test would lie on the line segment AB. Since the LB contours are concave, the point resulting in the lowest probability is either point A or point B.

Using the methods described above, acceptance limits for the sample mean and standard deviation can be determined for a given sample size as follows. Select a value of LB (typically, this is the value of LB that would be considered 'unacceptable' (e.g., LB = 50). For each sample mean in the interval (85%, 115%), determine the sample standard deviation such that the point in the resulting confidence region with the lowest probability of passing specification is equal to LB. The standard deviation associated with each mean is the acceptance limit for that mean. The set of sample means and standard deviations constructed in this way defines an acceptance region. Given the population mean and standard deviation, this acceptance region can be evaluated numerically to determine the probability that a sample mean and standard deviation will fall inside the acceptance region. The sample size can be chosen so that if the probability of passing the specification is high (e.g., LB = 99), there is a high probability of meeting the acceptance limits.

Suppose sampling Plan 2 is used. A simultaneous confidence region is constructed as described in Section 3.2. However, only two points in the region need

be examined since these points always result in the smallest lower bound for the probability of passing the USP test. Appendix 1 gives the details as to which points result in this smallest possible probability.

Using the methods described above, acceptance limits for ($\bar{Y}$, S_E^2, S_L^2) can be determined for a given value of n and L as follows. Select a value of LB (typically, this is the value of LB that would be considered 'unacceptable' (e.g., LB = 50). For each $\bar{Y}$ in the interval (85%, 115%), select a value of S_L^2 and determine the value of S_E^2 such that the point in the resulting confidence region with the lowest probability of passing specification is equal to LB. The S_E^2 associated with each $\bar{Y}$ and S_L^2 pair is the acceptance limit for that pair. The set of sample means and standard deviations constructed in this way defines an acceptance region. Given (u, V_E^2, V_L^2), this acceptance region can be evaluated numerically to determine the probability that a sample mean and standard deviation will fall inside the acceptance region.

APPENDIX

CONFIDENCE REGION POINTS GIVING SMALLEST LB

Notice from the simultaneous confidence region for (u, V_E^2, V_L^2) that the mean, $\bar{Y}$, gives the center of each confidence interval for u. Each value of (V_E^2, V_L^2) in the confidence region gives a value of V^2 and determines the confidence interval width for u. Now, if the same value of (V_E^2, V_L^2), P_o say, results in the largest value of V^2 and the widest confidence interval for u, then the smallest lower bound for the probability of passing the USP is at one of the endpoints of the confidence interval for u associated with P_o. This is true since the LB contours are concave and for a given u, smaller values of V^2 increase the probability of passing the USP.

Let $L(n-1)S_E^2/X^2_{q',L(n-1)}$ be denoted by $S^2_{E(UB)}$

and $(L-1)S_L^2/X^2_{q',L-1)}$ be denoted by $S^2_{L(UB)}$.

Notice that these are the upper confidence bounds for V_E^2 and E, respectively.

Since the confidence regions for V_E^2 and V_L^2 do not depend on u, let us consider the confidence region in only the (V_E^2, V_L^2) plane. The shape of this confidence region depends on the magnitude of $S^2_{L(UB)}$ relative to $S^2_{E(UB)}$. If $S^2_{E(UB)}$ is less than $S^2_{L(UB)}$, then the confidence region has the shape given in Figure A1. If $S^2_{L(UB)}$ is greater than $S^2_{E(UB)}$, then the confidence region has the shape given in Figure A2.

The largest value of V^2 is determined from Figures A1 or A2 by plotting the line $V_E^2 + V_L^2 = C$ for various C ($C \geq 0$). Since the slope of this line is -1 and the slope of line connecting $(0, S^2_{L(UB)}/n)$ to $(S^2_{L(UB)}, 0)$ is -1/n, the (V_E^2, V_L^2) contained within the confidence region resulting in the largest C (i.e., the largest V^2) occurs at

$(S^2_{E(UB)}, [S^2_{L(UB)} - S^2_{E(UB)}]/n)$ in Figure A1

and

$(S^2_{E(UB)}, 0)$ in Figure A2.

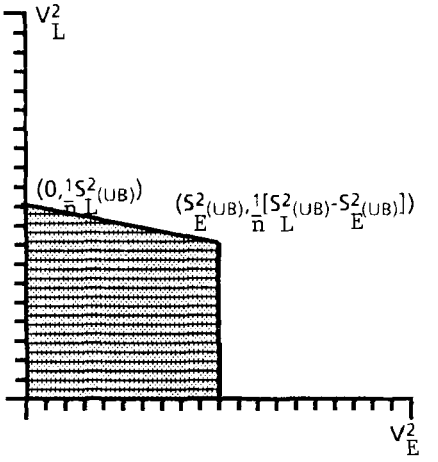


FIGURE A1
Confidence Region for (V_E^2, V_L^2)
When $S^2_{E(UB)} \leq S^2_{L(UB)}$

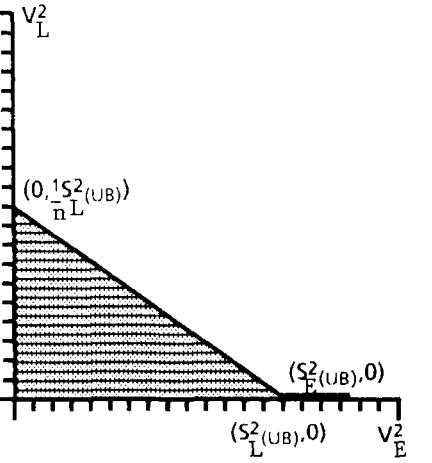


FIGURE A2
Confidence Region for (V_E^2, V_L^2)
When $S^2_{E(UB)} > S^2_{L(UB)}$

Therefore, the upper limit for V^2 is

$$(1-1/n)S^2_{E(UB)} + S^2_{L(UB)}/n \qquad \text{if } S^2_{E(UB)} < S^2_{L(UB)}$$

and

$$S^2_{E(UB)} \qquad \text{if } S^2_{E(UB)} \geq S^2_{L(UB)}$$

Since the width of the confidence interval for u depends only on E ($= V^2_E + nV^2_L$), the confidence interval width for u can be determined from Figures A1 or A2 by plotting the line $V^2_E + nV^2_L = C (C \geq 0)$. The slope of this line is -1/n which is the same as the slope of the line connecting $(0, S^2_{L(UB)}/n)$ to $(S^2_{L(UB)}, 0)$. So, in Figure A1, any point along the line connecting $(0, S^2_{L(UB)}/n)$ to $(S^2_{L(UB)}, 0)$ provides the widest confidence interval. In Figure A2, the point $(S^2_{E(UB)}, 0)$ provides the widest confidence interval. Notice that the points given above the largest value of V^2 are also on the line that provides the widest confidence interval. Therefore, the smallest lower bound for the probability of passing the USP test occurs at one of the endpoints of the confidence interval for u. The coordinates of these endpoints (u, V) are:

$$(\bar{Y} \pm Z_{1-p}(S^2_{L(UB)}/N)^{\frac{1}{2}}, ((1-1/n)S^2_{E(UB)} + S^2_{L(UB)}/n)^{\frac{1}{2}}) \qquad \text{if } S^2_{E(UB)} < S^2_{L(UB)})$$

$$(\bar{Y} \pm Z_{1-p}(S^2_{E(UB)}/N)^{\frac{1}{2}}, S_{E(UB)}) \qquad \text{if } S^2_{E(UB)} \geq S^2_{L(UB)})$$

ACKNOWLEDGEMENTS

The author wishes to thank Dr. Earl Nordbrock for his advice during the preparation of this manuscript and Donna Gifford for typing the manuscript so efficiently.

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