Add the following:

▲⟨1099⟩ LIMIT ON NUMBER OF LARGE DEVIATIONS WHEN ASSESSING CONTENT UNIFORMITY IN LARGE SAMPLES

INTRODUCTION

The uncertainty around the application of the zero tolerance criterion (ZTC) to sample sizes larger than 30 may inhibit the collection of uniformity data from large samples. This chapter provides a process for limiting the number of observed results that fall outside of the ZTC (c_2), as described in *Uniformity of Dosage Units* ⟨905⟩, when samples larger than 30 are collected. It should be noted that the criterion described in this chapter is not intended as a batch release test, nor as a replacement of or alternative to ⟨905⟩. It also is not intended as an extension to go beyond second tier testing in ⟨905⟩. The use is solely to help judging if a large data set is consistent with the ZTC element of ⟨905⟩; whether the large data set complies with the complete set of requirements in ⟨905⟩ must be decided by other means.

The ZTC in ⟨905⟩ states that no individual content of any dosage unit can be less than $[1 - (0.01)(L2)]M$ nor more than $[1 + (0.01)(L2)]M$, where $L2$ is 25.0% unless otherwise specified in the applicable monograph, and M, the “reference value”, depends on the sample mean, $\overline{X}$ (expressed as a percentage of the label claim), as follows:

M = 98.5% if $\overline{X}$ <98.5, M = 101.5% if $\overline{X}$ >101.5, and $M = \overline{X}$ otherwise, with a sample size (N) of 30

PROCEDURE

When a sample that includes the contents of more than 30 units has been collected, the following procedure can be used to confirm that the results in that sample are consistent with the ZTC of ⟨905⟩. The criterion is applicable both when the content is determined directly by assaying a number of units and when the content is determined indirectly by weighing the units in the situations allowing this as described in ⟨905⟩. The procedure is as follows:

1. Express individual results $x_1, x_2, ..., x_N$ as a percentage of the label claim
2. Calculate the mean ($\overline{X}$) of the contents of the N units in the sample
3. Calculate the reference value M: M = 98.5% if $\overline{X}$ <98.5, M = 101.5% if $\overline{X}$ >101.5, and $M = \overline{X}$ otherwise
4. Determine S_N, the number of sample results less than $[1 - (0.01)(L2)]M$ or more than $[1 + (0.01)(L2)]M$, where $L2$ = 25.0% unless otherwise specified in the applicable monograph
5. The sample is consistent with the ZTC of ⟨905⟩ if $S_N \leq c_2$, where c_2 depends on the sample size as detailed in *Table 1*

Table 1. Limit on Number of Observed Results Falling Outside of the ZTC Based on Sample Size

N	c_2
31–100	0
101–181	1
182–265	2
266–353	3
354–442	4
443–533	5
534–624	6
625–717	7
718–810	8
811–903	9
904–998	10
999–1092	11
1093–1187	12
1188–1283	13
1284–1379	14
1380–1475	15
1476–1571	16
1572–1667	17
1668–1764	18
1765–1861	19

Values of c_2 for other sample sizes (N) are determined as

$$c_2 = \max\left\{c: \sum_{i=0}^{c} \binom{N}{i} f^i (1-f)^{N-i} \leq 0.75\right\},$$

where $f = 1 - 0.75^{1/30} = 0.00954357$. The c_2 value can be calculated in a spreadsheet with a cumulative binomial function.▲ (Postponed on 1-Mar-2019)