Two-Tier System for Setting Tolerances – (PVT vs Products)

USP introduces a new lot of 10 mg prednisone tablets for Performance Verification Testing (PVT), with the following Acceptance Values, as supplied with certificate (link).

Table 1 (*Abbreviated*): Performance Verification Test (PVT)
[Lot Q0H398 (New Lot), Lot P1I300 (Previous Lot)]

Apparatus	# of Vessels	Single-Stage		Two-Stage			
				1st Stage of Two Stages		2nd Stage of Two Stages	
		GM*	%CV*	GM*	%CV*	GM*	%CV*
1	6	54 - 72 56 - 75	12 10	57 – 69 60 - 71	9.2 7.7	54 -72 56 - 75	12 10
2	6	26 – 38 25 - 41	6.7 6.8	27 – 36 27 - 38	4.9 5.1	26 – 38 25 – 41	6.5 6.7

The current practice/approach of setting tolerances appears to be of questionable merit and may require reconsideration, because:

1. The tolerances for PVT are lot dependent, while tolerances for actual products for human use, according to <711>, are lot independent. Following the practice of developing tolerances for PVT, are the manufacturers allowed to adjust the tolerances of their products from lot to lot, say a *Q* value from 80 to 75 or 70 depending on the results obtained from the newly manufactured lot? If not, then why not? Is there a rationale for this two-tier approach?

2. In the USP general chapter <1092>, it is stated that the variability (%CV) of dissolution results should be less than 10%. However, the allowed variability for the current lot of PVT is 12%, even with 12 units. Is the USP considering relaxing the allowed variability for the tolerances for the products as well?

3. In addition, current PVT tolerances are based on the criteria of (a) %CV, and (b) ranges of means. It appears that %CV reflects variation within a run (6 or 12 units) while ranges of means reflect variability between runs, most likely between laboratories. This approach implies that it is possible that two laboratories/apparatuses can pass the PVT criterion of %CV, but, while remaining within the accepted range, the mean results from two or more laboratories/apparatuses can be significantly be different, as shown in the example below.

   Lab 1 (Paddle Apparatus) = (% Dissolved=27,28,27,30,29,28; Mean=28; %CV=4.2)
   Lab 2 (Paddle Apparatus) = (% Dissolved=38,34,35,35,36,37; Mean=36; %CV=4.1). PVT criteria met in both cases, but the results are significantly different between laboratories with a $p < 0.001$).

This shows that different apparatuses (within or between labs) will pass the PVT, but will provide significantly different results for products. Then, how should one address such a situation for comparing results of the same product between these two laboratories (method/apparatus/labs transfer)?