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GlaxoSmithKline

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Food and Drug Administration  
HFA-305  
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**Re: Docket Number 2003D-0493**

**Draft Guidance for Industry on Powder Blends and Finished Dosage Units - Stratified In-Process Dosage Unit Sampling and Assessment**

Dear Madam or Sir:

Enclosed please find comments from GlaxoSmithKline, including general and specific comments, for the Draft Guidance for Industry on Powder Blends and Finished Dosage Units - Stratified In-Process Dosage Unit Sampling and Assessment. These comments are presented for consideration by the FDA. The general comments are presented first, with the specific comments presented in order by section and line number in the draft guidance. An appendix with the statistical rationale to support our comments is also included.

GlaxoSmithKline appreciates the opportunity to provide feedback and suggestions for this draft guidance. I am submitting this guidance both electronically (Dockets Management, Electronic Comment Submission Form) and by hardcopy. Therefore, you will receive a paper copy of this letter with two copies of the comments through the USPS.

If you have any questions about these provided comments, please do not hesitate to contact me at (919) 483-5857. Thank you for your consideration.

Sincerely,

A handwritten signature in cursive script that reads "Mary Faye S. Whisler".

Mary Faye S. Whisler, Ph.D.  
Assistant Director  
New Submissions, North America

2003D-0493

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**Draft Guidance for Industry on Powder Blends and Finished Dosage Units -  
Stratified In-Process Dosage Unit Sampling and Assessment**

**GENERAL COMMENTS**

The criteria for blend homogeneity have been carried forward and are applied to uncoated tablet cores. FDA's premise for tighter in-process controls for blend homogeneity was that there are additional processes between the blending stage and the compression stage that could lead to further segregation (transfer of blend into hopper of the rotary compression press, within the hopper and feed chute of the rotary compression press, etc). However, there are no processing stages between tablet cores and coated tablets that can impinge on the homogeneity of the finished product (only coating), and therefore there should be no difference in the testing criteria of tablet cores and coated tablets, with respect to homogeneity.

The relative standard deviation (RSD) criteria for readily pass (not more than 4%, or NMT 4%) or marginally pass (NMT 6%) for the uncoated tablets are much more stringent than the existing USP counterparts: USP I (NMT 6%) or USP II (NMT 7.8%). There is a reasonably high chance (ca. 60%) of batches with high RSDs failing the new in-process stage 2 criteria, but passing the existing USP II criteria. This guidance should provide for criteria that are consistent the USP criteria. (See statistical rationale for support in Appendix 1.)

The number of samples specified in this guidance is excessive, and should be correlated with the batch size and/or the use of a well-designed study that would incorporate significant events into the 20 "planned locations" to lessen the burden of additional testing. The number of samples should be based on good science and be defined by the needs for statistical analysis of the data.

There is no consideration provided for tablets that are not film-coated; uncoated tablet batches can fail the tighter in-process requirements of these new guidelines, but would pass the existing USP I/II criteria.

There is no consideration provided for blends and tablets that are greater than 50% drug substance by weight. There should be a statement that these blends and tablets are excluded from this guidance.

Limited information is included in the guidance pertaining to sampling thieves/probes. A statement is needed to define various types and the need for a separate guidance on this topic.

## **SPECIFIC COMMENTS**

### **Section IV. B. Correlation of Powder Mix Uniformity with Stratified In-Process Dosage Unit Data and Section VI. A. In-Process Dosage Unit Sampling and Analysis**

Lines 150 and 254: The number of samples (20) required seem random; a well-designed study would provide information to support the number and locations of samples.

### **Section V. EXHIBIT/VALIDATION BATCH POWDER MIX HOMOGENEITY**

Lines 220-223: If powder blend is shown not to be a predictor of in process dosage form uniformity and efforts to ID a source of error in blend sampling cannot be identified, then blend sampling should be eliminated for a given product.

### **Section VI. B. Criteria to Meet the *Readily Pass* Classification**

Lines 278-281: In these rows, use the mean of the data with a range, instead of the target strength/label claim. (In the beginning of the document there is a comment that this guidance is about uniformity, not potency. If FDA wants to address uniformity, now is a great opportunity to separate the content assay from the CU assay.)

### **Section VIII. A. Applications Not Yet Approved**

Line 430: The correct reference for Drug Product Specification in the CTD is 3.2.P.5.1.

## APPENDIX 1

### COMPARISON OF ACCEPTANCE PROBABILITIES FOR DIFFERENT CRITERIA AND SAMPLING SCHEMES

#### SAMPLING SCHEMES AND OPERATING CHARACTERISTIC CURVES TO COMPARE THE CRITERIA WITHIN EACH SCHEME

Operating characteristic (OC) curves for a given sampling plan, allow an assessment of the probability of acceptance when applied to a batch with a given level of quality. The plots below show how the probability of acceptance is related to the standard deviation. These curves plot the true standard deviation on the horizontal axis and the probability of acceptance on the vertical axis.

N.B. For the purposes of this exercise, the terms standard deviation (sd) and relative standard deviation (rsd) are interchangeable (see also the 'assumptions' section at the end of this document).

#### **In-process Readily Pass Classification (IP 1):**

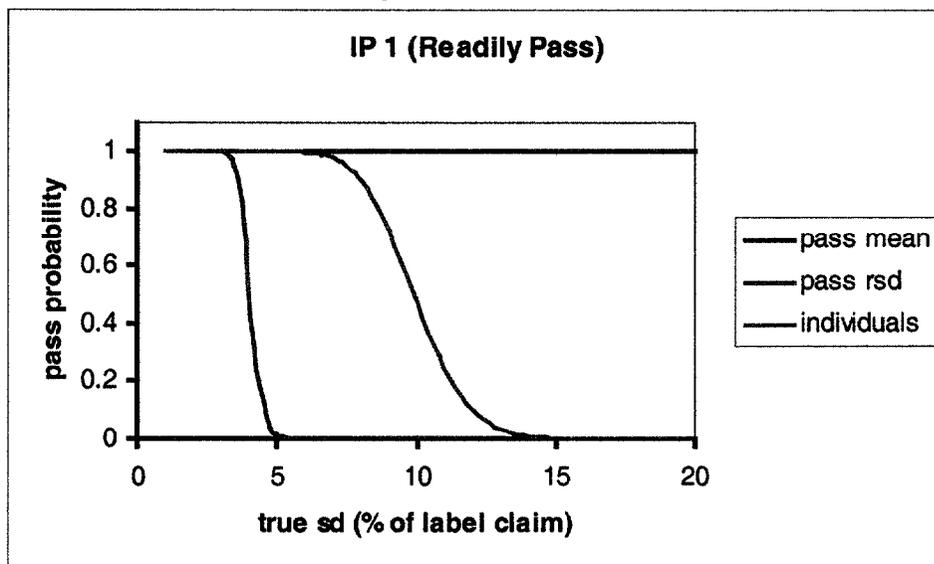
Sample 140 dosage units and test 60 dosage units (N=60).

Limits:

Mean is within 90-110%

RSD < or = to 4%

All individual results are within range of 75 to 125% of label claim



The criteria for the mean will almost certainly be met. The criteria for the rsd are the most challenging.

**In-process Marginally Pass Classification (IP 2):**

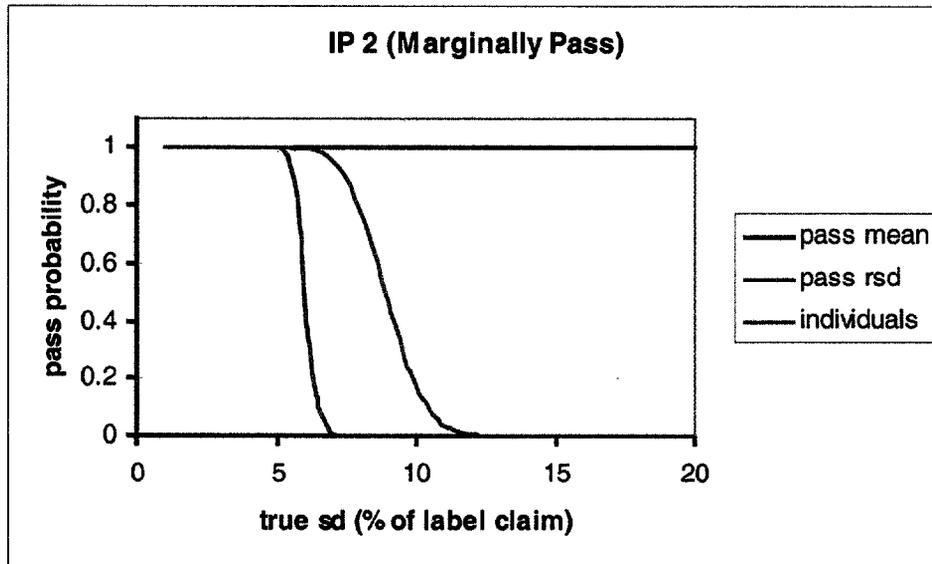
Sample 140 dosage units and test 140 dosage units (N=140).

Limits:

Mean is within 90-110%

RSD < or = to 6%

All individual results are within range of 75 to 125% of label claim



The criteria for the mean will almost certainly be met. The criteria for the rsd are the most challenging.

**Finished product at USP I stage testing (USP 1):**

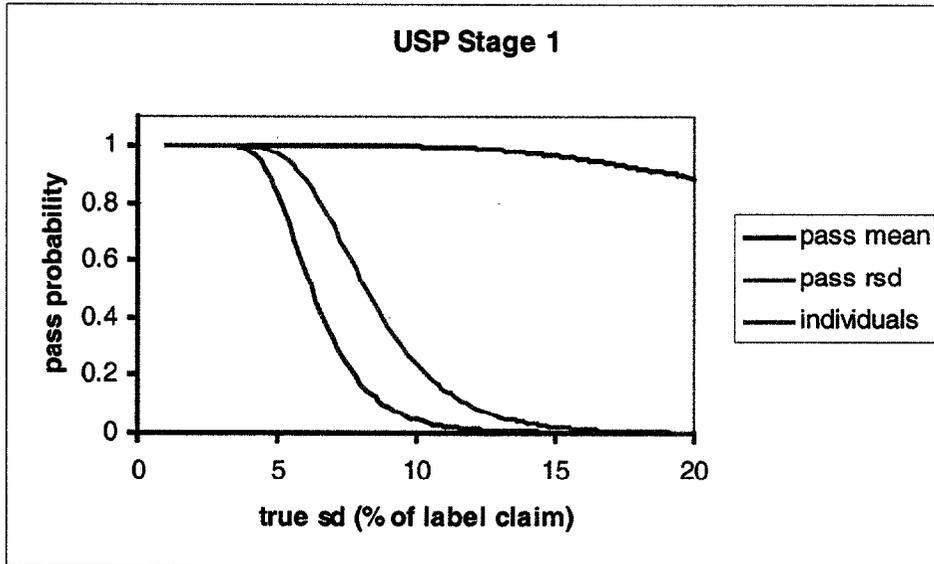
Sample 30 units and test 10 (N=10)

Limits:

Mean is within 90-110%

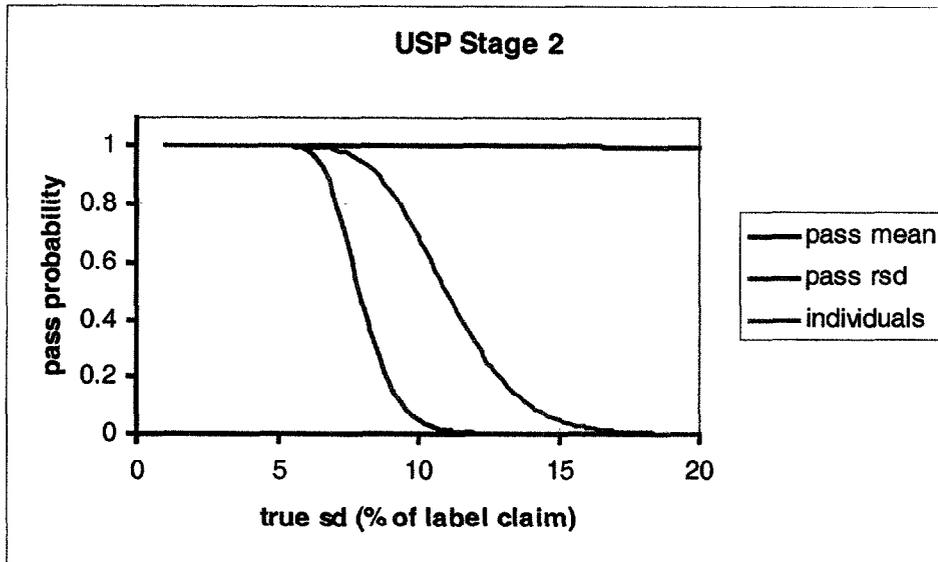
RSD < or = to 6%

All individual results are within range of 85 to 115% of label claim



The criteria for the mean will almost certainly be met. The criteria for the rsd are the most challenging.

**Finished product at USP II stage testing (USP 2):**  
 Sample 30 units and test 30 (N=30)  
 Limits:  
 Mean is within 90-110%  
 RSD < or = to 7.8%  
 All individual results are within range of 75 to 125% of label claim



The criteria for the mean will almost certainly be met. The criteria for the rsd are the most challenging.

The criteria for the four schemes are summarised in the table below:

	IP 1 (readily pass)	IP 2 (marginally pass)	USP 1	USP 2
sample size	60	140	10	30
limits for individuals	+/-25%	+/-25%	+/-15%	+/-25%
limits for mean	+/-10%	+/-10%	+/-10%	+/-10%
limits for rsd	<4%	<6%	<6%	<7.8%

It can be seen that for all of the schemes, the probability of passing the criteria for the mean is virtually certain until the standard deviation approaches 15% of label claim, and if that were the case, then it would be similarly certain that either the criteria for the rsd or for individuals would be not be met.

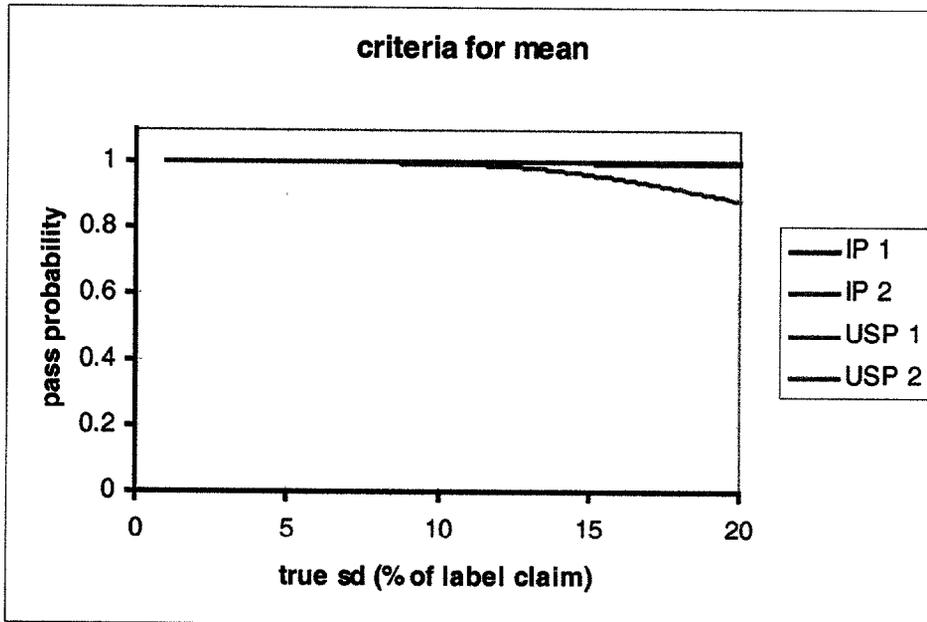
The criteria for the mean are therefore relatively unimportant when comparing the power of the different schemes.

It can further be seen that in general, the criteria for the rsd is more discriminating than the criteria for individuals.

Therefore it is the criteria on the rsd that are most likely to be decisive for batch acceptance.

**OPERATING CHARACTERISTIC (OC) CURVES TO COMPARE THE CRITERIA  
ACROSS THE SCHEMES**

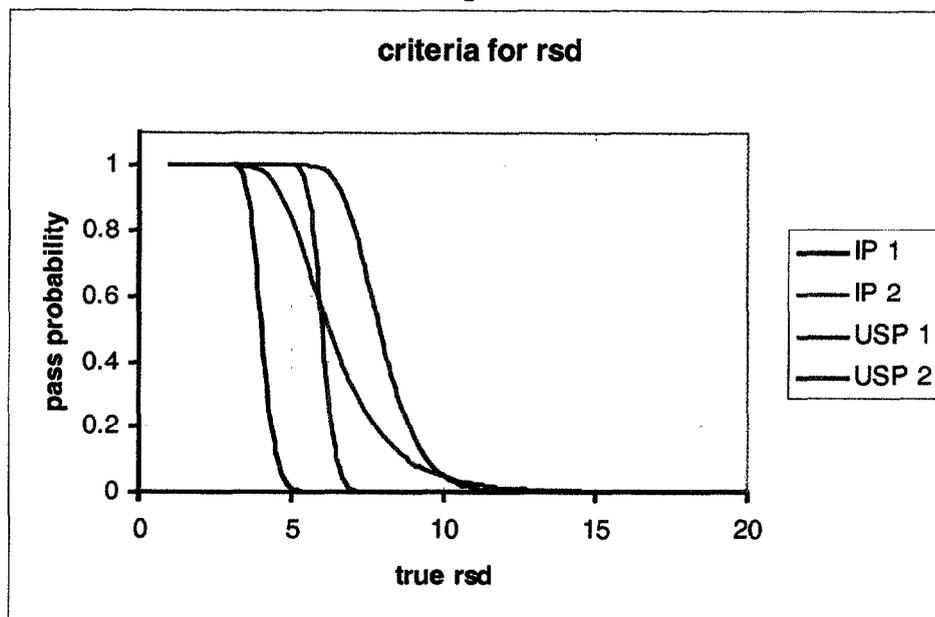
**OC curves for the criteria on sample mean**



It can be seen that for all of the schemes, the probability of passing the criteria for the sample mean is virtually certain until the standard deviation approaches 15% of label claim, and if that were the case, then it would be similarly certain that either the criteria for the rsd or for individuals would be not be met.

The criteria for the sample mean are therefore relatively unimportant when comparing the power of the different schemes.

**OC curves for the criteria on sample relative standard deviation**

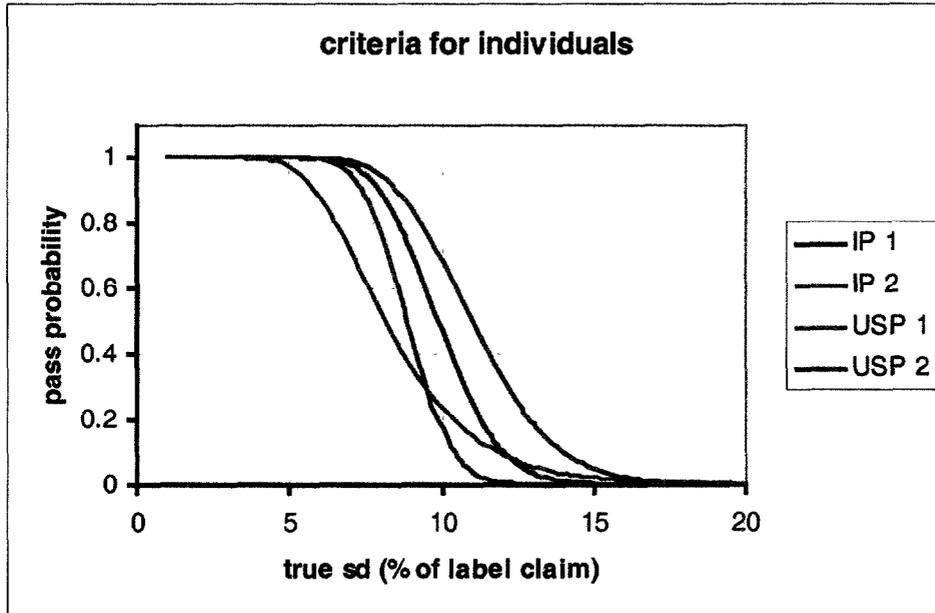


When the variability is low, the discriminating power for rsd is in the order IP 1, USP 1, IP 2 and USP 2.

If variability increases, both USP schemes lose power relative to the IP schemes.

N.B. In general, the criteria for the rsd are the most important, since they generally offer the greatest opportunity for batch rejection in each of the schemes.

**OC Curves for the criteria on individual results**

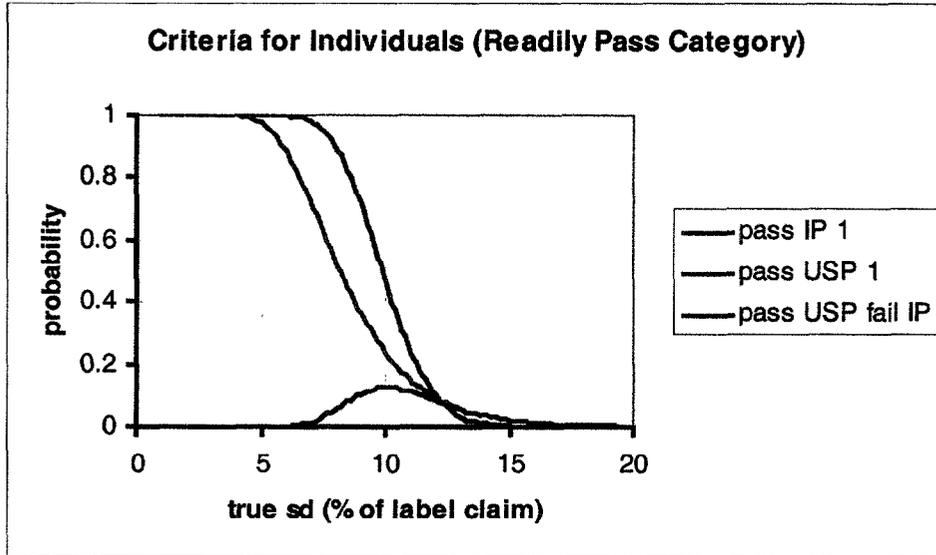


When the variability is low, the discriminating power for individuals is in the order USP 1, IP 2, IP 1 and USP 2.

As variability increases, USP 1 diminishes in power relative to the other schemes.

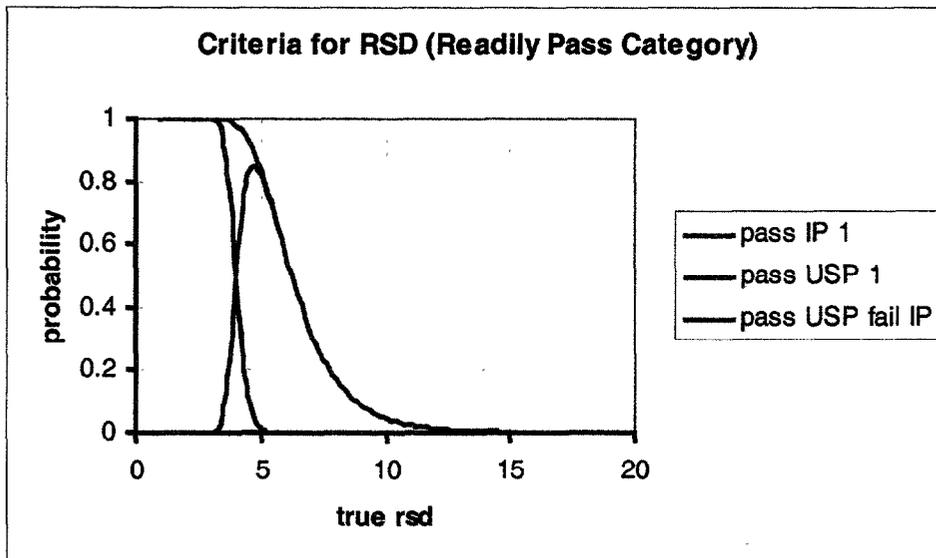
**OPERATING CHARACTERISTIC (OC) CURVES TO COMPARE THE PROBABILITY OF A BATCH FAILING WOULD PASS THE USP CRITERIA BUT WOULD BE REJECTED ON THE IP CRITERIA**

**For individual results (Readily Pass Category and USP 1 criteria)**



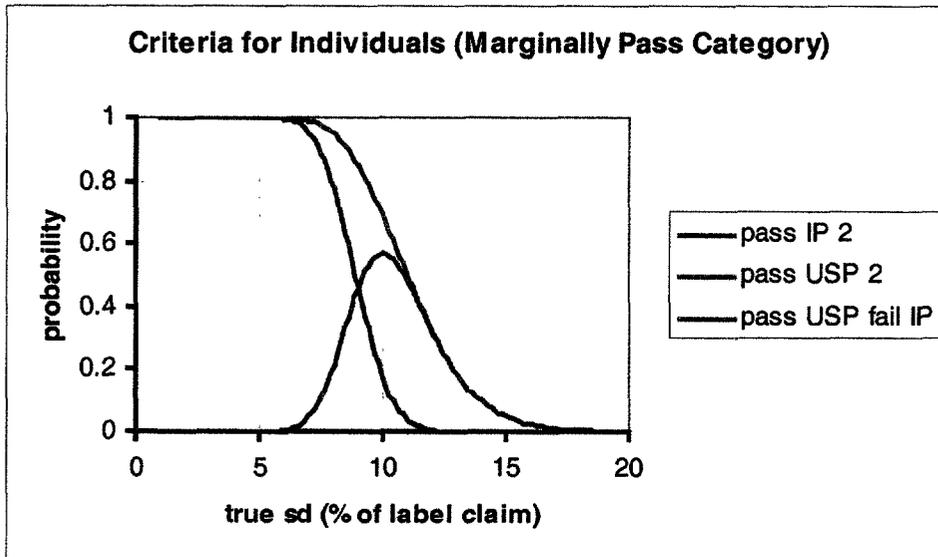
The USP criteria are generally more discerning, so the probability of failing IP but passing USP is low.

**For RSD (Readily Pass Category and USP 1 criteria)**



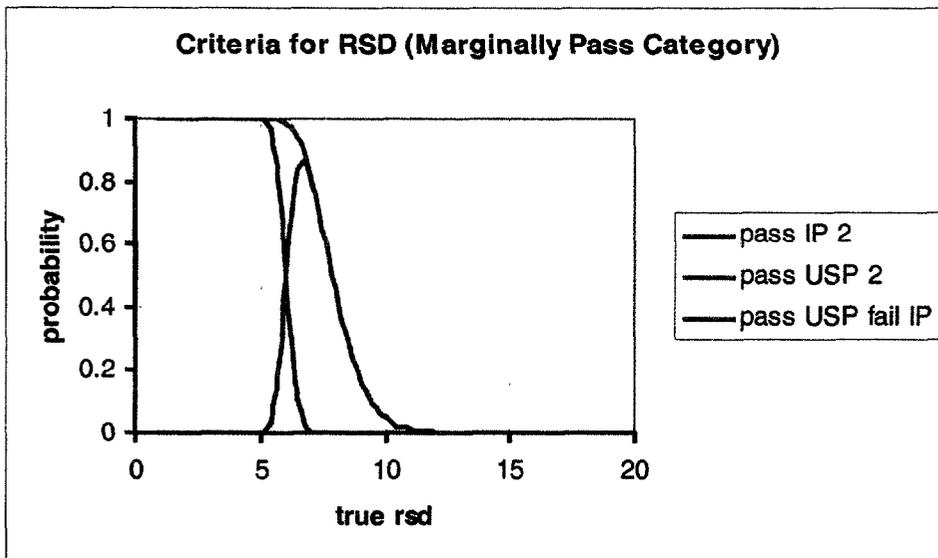
The IP criteria are generally more discerning, so the probability of failing IP but passing USP can be fairly high especially if the rsd is around 5%.

**For individual results (Marginally Pass Category and USP 2 criteria)**



The IP criteria are generally more discerning, so the probability of failing IP but passing USP can be fairly high especially if the rsd is around 10%.

**For RSD (Marginally Pass Category and USP 2 criteria)**



The IP criteria are generally more discerning, so the probability of failing IP but passing USP can be fairly high especially if the rsd is around 7%.

## ASSUMPTIONS:

### Probability of passing on individual results:

Assume a normal distribution centred at 100% of label claim with standard deviation  $\sigma$ . The probability of passing is the proportion of individual results within the spec limits raised to the power of  $n$  (the number of individuals tested).

$$Pa_{indiv} = \left( \int_{L_i}^{U_i} \phi(100, \sigma) \right)^n$$

$U_i$  and  $L_i$  are the upper and lower specification limits for individuals, and  $\phi(100, \sigma)$  is a normal variate, with mean = 100 and standard deviation =  $\sigma$ .

### Probability of passing on sample mean:

Assume a normal distribution centred at 100% of label claim with standard deviation  $\sigma/\sqrt{n}$ , where  $n$  is the number of individuals used to estimate the mean.

$$Pa_{mean} = \int_{L_m}^{U_m} \phi(100, \sigma/\sqrt{n})$$

$U_m$  and  $L_m$  are the upper and lower specification limits for a sample mean.

### Probability of passing on sample relative standard deviation:

Assume that the sample variance,  $s^2$ , follows a chi-square distribution with  $(n-1)$  degrees of freedom, multiplied by the true variance,  $\sigma^2$ , divided by  $n-1$ .

$$\frac{(n-1)s^2}{\sigma^2} \sim \chi_{n-1}^2$$

Therefore, the probability of meeting the rsd criteria is:

$$Pa_{rsd} = \Pr(s \leq U_{rsd}) = \Pr\left(\frac{(n-1)U_{rsd}^2}{\sigma^2} \geq \chi_{n-1}^2\right)$$

N.B. Strictly, this calculation applies to the sample standard deviation. The sample relative standard deviation is also a function the sample mean. However, since it has been assumed that the population mean, is 100% (of label claim), then for simplicity of calculation, the assumption has been made that the standard deviation is approximately equal to the relative standard deviation, i.e.

$$rsd = \frac{s}{m} \times 100 \approx s$$

Provided the true relative standard deviation is reasonably small, say a few percent of the sample mean, this approximation should be adequate for the purposes of this exercise.