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Brief/Technical Note

Acceptance Probability (P_a) Analysis for Process Validation Lifecycle Stages

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Abstract. This paper introduces an innovative statistical approach towards understanding how variation impacts the acceptance criteria of quality attributes. Because of more complex stage-wise acceptance criteria, traditional process capability measures are inadequate for general application in the pharmaceutical industry. The probability of acceptance concept provides a clear measure, derived from specific acceptance criteria for each quality attribute. In line with the 2011 FDA Guidance, this approach systematically evaluates data and scientifically establishes evidence that a process is capable of consistently delivering quality product. The probability of acceptance provides a direct and readily understandable indication of product risk. As with traditional capability indices, the acceptance probability approach assumes that underlying data distributions are normal. The computational solutions for dosage uniformity and dissolution acceptance criteria are readily applicable. For dosage uniformity, the expected AV range may be determined using the s_{lo} and s_{hi} values along with the worst case estimates of the mean. This approach permits a risk-based assessment of future batch performance of the critical quality attributes. The concept is also readily applicable to sterile/non sterile liquid dose products. Quality attributes such as deliverable volume and assay per spray have stage-wise acceptance that can be converted into an acceptance probability. Accepted statistical guidelines indicate processes with C_{pk}>1.33 as performing well within statistical control and those with C_{pk}<1.0 as "incapable" (1). A C_{pk}>1.33 is associated with a centered process that will statistically produce less than 63 defective units per million. This is equivalent to an acceptance probability of >99.99%.

KEYWORDS: acceptance probability; FDA guidance; GMP and statistics; pharmaceutical quality statistics; process validation lifecycle stages.

INTRODUCTION

In January of 2011, the FDA issued "Process Validation: General Principles and Practices" (the 2011 FDA Guidance). Process validation (PV) is defined in this guidance as follows:

> "the collection and evaluation of data, from the process design stage through commercial production which establishes scientific evidence that a process is capable of consistently delivering quality product." (2)

Grace E. McNally of the FDA indicated in her 2011 presentation "Process Validation: A Lifecycle Approach" that the use of statistical methods and tools will facilitate for a science and risk based decision making on the ability of the process to consistently produce quality products (3). The PV guidance stresses that the pharmaceutical industry should develop and use tools that can infer and predict future batch performance. Such predictive ability based on generated data sets can be deemed as important as determining if an individual batch passes specification requirements.

Critical process parameter (CPP) is established during the process design stage (stage 1). The CPPs are verified at the process performance qualification stage (stage 2). Quality attributes (in-process and finished product) and parameters are continually monitored during routine manufacturing (stage 3). Statistical process control (SPC) techniques are often applied to determine process capability. The capability of a process is defined in ICH as the ability of a process to realize a product that will fulfill the requirements of that product (4–6). ICH Q10 calls for analysis tools that measure quality attributes and parameters identified in the control strategy to verify continued operation within a state of control to meet the product acceptance criteria. Widely accepted quantitative capability measures include C_p, C_{pk}, P_p, and P_{pk}. Per ICH guidelines, a process is considered stable and capable if the results consistently fulfill the established quality attribute specification limits (4–6). It is a current practice to demonstrate process stability using various types of process control charts and test data normality before applying capability analysis.

Unlike in other industries, the acceptance criteria for pharmaceutical products are typically multi-level. Because of the more intricate acceptance criteria, traditional SPC strategies and capability measures may give erroneous indications

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or fall short in providing a suitable assessment of product risk. A more applicable analysis method is required to provide a reliable understanding of the ability of the product to fulfill the requirements for the quality attributes. For example, dosage uniformity and dissolution testing in pharmaceutical analysis uses multiple tested units and follows a stage-wise acceptance criterion as prescribed by monographs such as USP. Because of these unique acceptance criteria, traditional process capability (C_{pk}) measures fall short in providing reliable assessment of the ability of the product to meet the acceptance criteria.

This paper describes an improved and innovative statistical approach of probability of acceptance (P_a) that provides a scientifically unbiased approach towards understanding how variation impacts the likelihood that a manufacturing process will produce product that meets the required quality attribute acceptance criteria. The probability of acceptance concept provides a clear measure that adheres to the 2011 FDA Industry guidance—"Process Validation: General Principles and Practices," Quality by Design (QbD) requirements and provides a direct and clear indication of a product acceptance and risk.

P_A

Stage-wise criteria are prevalent in many USP monographs (Dissolution, Dosage Uniformity, etc.) (7,8). If a traditional capability index is directly applied to dosage uniformity data, it will provide an indication of the probability that a "single" future produced unit will meet the desired specification limits. The USP <905> uniformity of dosage criterion for acceptance value (AV) primarily assesses the variability from the analyses of no less than ten tablets (7). The performance of a single unit, while important, is largely unrelated to the product ability to meet the AV requirements.

A similar limitation exists for the application of the capability indices for USP <711> dissolution, which describes a three-stage acceptance criteria (8). Traditional capability computations on individual unit dissolution data give an indication that a single unit will meet the entered specification. The stage-wise criteria are based on both single unit and the average of multiple unit requirements. A calculation that accommodates the non-standard/complicated/complex acceptance of the USP is warranted to accurately predict the ability of the product to meet specifications.

An "improved" concept, described herein as the P_a, provides a clear measure of assurance and risk based on presently measured statistics. This measure can be tailored to provide an assessment of the probability that the product will meet any quality attribute requirement. The analysis addresses the 2011 FDA Guidance requirement of using objective measures (statistical metrics) to achieve adequate assurance. In contrast to C_{pk}, which typically provides information about a future single unit, the improved concept, P_a, is designed to provide the probability that a future produced batch will meet the specification acceptance criteria. The resultant P_a outcome is considerably more distinctive than capability indices. It is challenging to understand the implications of a process with a C_{pk}=1.28. However, the meaning of a 99.93% probability that a future batch will meet the requirements is easily understood. P_a is designed to directly relate to the assurance that a future batch will meet the required specification.

PREREQUISITE OF ENSURING DATA NORMALITY

As with traditional capability indices, the acceptance probability approach assumes that underlying data distributions are normal. Non-normal or skewed distributions should be approached with more sophisticated statistical modeling techniques. There is also an implied assumption that maintaining the current manufacturing and raw material controls, future batches shall behave as per the modeled data, which is the fundamental concept for process validation. It is required that the normality of the data is to be examined (such as using Anderson Darling normality test) before proceeding with further analysis.

This new statistical approach using probability of acceptance will readily support the scientific and risk-based decision making process as recommended in the FDA guidance. The following sections provide detailed computational examples of the basic approach for a few select example quality attributes.

EXAMPLE I: DOSAGE UNIFORMITY—DETERMINING PROBABILITY OF ACCEPTANCE AND EXPECTED OPERATING RANGE FOR USP <905> AV

This is an example that illustrates how much applicable P_a can be when dealing with a complicated stage-wise acceptance criteria where C_{pk} calculation is unable to properly demonstrate the future risk of the product. USP <905> "Uniformity of Dosage Units" describes the currently accepted methodology to assess the consistency of dosage units within a given batch of product (7). The current USP <905> monograph instructs how to calculate an AV that incorporates a two-stage acceptance criteria (L1=15.0; L2=25.0). Also, there is additional requirement that no individual tablet result is outside 0.75*M to 1.25*M as per the stage 2 (L2) instructions, where M is a reference value depending on the calculated batch DU average (7). Since this criterion (individual tablet result is outside 0.75*M to 1.25*M) is applying to an individual unit, the probability of acceptance can be deciphered from the C_{pk} calculation which is described in the later section "Comparison: Capability Indices and Acceptance Probability". On the contrary, due to the complexity of the stage-wise acceptance criteria, the probability of passing AV criteria cannot be properly represented by C_{pk} indices.

Thus, this particular example will focus on describing the mathematical strategy to determine the probability that a future batch passing the dosage uniformity AV based on the past sampled and measured performance of the process.

USP <905> describes multiple cases depending on the measured mean of the sampled units. The general form of the AV equation is as follows:

$$AV = |M - \bar{x}| + ks$$

where $\bar{x}$ is the batch average result, and M, k, and s are defined in Table I as per USP <905> "Uniformity of Dosage Units" (7).

Note that while USP <905> provides more details, this report only investigates examples where the target dosage

Table I. Definition of Terms Used in Acceptance Value (AV) Calculation (7)

		If n=10, then k=2.4	
k	Acceptability constant	If n=30, then k=2.0	
s	Sample standard deviation		$\left[\frac{\sum_{i=1}^{n}(X_i-\overline{X})^2}{n-1}\right]^{\frac{1}{2}}$
M (case 1) to be applied when $T \le 101.5$	Reference value	*If* $98.5\% \le \overline{x} \le 101.5\%$, then	$M = \overline{X}(\mathrm{AV} = ks)$
		If $\overline{x} < 98.5\%$, then	$\mathrm{M} = 98.5\%\ (\mathrm{AV} = 98.5 - \overline{X} + ks)$
		If $\overline{x} > 101.5\%$, then	$M = 101.5\%\ (\mathrm{AV} = \overline{X} - 101.5 + ks)$
M (case 2) to be applied when T≤101.5	Reference value	*If* $98.5 \le \overline{x} \le T$, then	$M = \overline{X}\ (\mathrm{AV} = ks)$
		If $\overline{x} < 98.5\%$, then	$M = 98.5\%\ (\mathrm{AV} = 98.5 - \overline{X} + ks)$
		If $\overline{x} > T$, then	$M = T\%\ (\mathrm{AV} = \overline{X} - T + ks)$

value (noted as "T" in Table I) is ≤101.5% as the T for almost all solid dose products is 100.0%.

USP <905> describes testing 10 units at stage L1 (k=2.4) and 30 units at stage L2 (k=2.0). There are three cases each to consider for both the L1 and L2 acceptance:

The AV critical limit for stage 1 is NMT 15 and for stage 2 it is NMT 25. Note that using these values, one can work backwards to determine the required or limiting standard deviation (S_{lim}) to pass the USP <905> dosage uniformity test for each case. For instance, in case A, the S_{lim} for passing L1 can be back calculated as follows: $(\overline{x} - 98.5 + 15) / 2.4 = \overline{x} / 2.4 - 34.79$, whereas for case A L2, S_{lim} is $(\overline{x} - 98.5 + 25) / 2.0 = \overline{x} / 2.0 - 36.75$. Case B and C can be calculated in similar manner. These solutions are provided in Tables II and III.

The upper confidence limit for the standard deviation is described by a chi-square distribution. Placing the limiting standard deviation into the equation permits an assessment of the probability that a measured standard deviation will exceed the limiting standard deviation.

$$s_{hi} = s\sqrt{\frac{n-1}{X^2_{\left(n-1,\frac{\alpha}{2}\right)}}}$$

Substituting s_{hi} with S_{lim} and solving for χ^2 provides the following:

$$X^2_{\left(n-1,\frac{\alpha}{2}\right)} = \frac{(n-1)s^2}{s^2_{\mathrm{lim}}}$$

Thus, one can assess α, the probability that a test will exceed the AV limit for each case from the chi-square distribution and the measured dosage uniformity data. The probability of acceptance (P_{a}) is equivalent to (1−α). This P_{a} value provides an estimate of the chance that a future batch will meet the AV requirements as long as the entered statistics remain descriptive of the process population (i.e., the process remains consistent and stable as observable results).

The example of application of P_{a} for USP acceptance criteria demonstrates how future product risk can be measured on a consistent and readily understandable basis. P_{a} can provide an understanding of the product probability of meeting both stage 1 and stage 2 criteria. Since USP <905> allows for reduced number of tablets to be analyzed if it meets stage 1 criteria, this determination will help making an informed decision to decide whether to go directly with testing 30 dosage units or start with testing 10 units, which will potentially help to eliminate excessive sample testing cycles.

Expected AV Range for Future Batches

Another statistic of interest is the expected AV range for future batches. In essence, this range can be used to predict the future batch performance for this critical finished product quality attribute. This range can be determined from the following equations:

$$s_{lo} = s\sqrt{\frac{n-1}{X^2_{\left(n-1,1\frac{\alpha}{2}\right)}}}$$

$$s_{hi} = s\sqrt{\frac{n-1}{X^2_{\left(n-1,\frac{\alpha}{2}\right)}}}$$

If the mean dosage uniformity value is not between 98.5 and 101.5, the mean assay value becomes important in the overall equation and should be included as illustrated in Table II. An estimate of the "worst case" scenario (as described below) should be made using the

Table II. Summary of the Three Cases Described as per USP <905> "Uniformity of Dosage Units"

Case	Mean	L1	L2
Case A	$98.5\% > \overline{x}$	AV=98.5−$\overline{x}$+2.4 s	AV=98.5−$\overline{x}$+2.0 s
Case B	$98.5\% \le \overline{x} \le 98.5\%$	AV=2.4 s	AV=2.0 s
Case C	$\overline{x} > 101.5\%$	AV=$\overline{x}$−101.5+2.4 s	AV=$\overline{x}$−101.5+2.0 s

Table III. Calculations for the Limiting Standard Deviation (S_{lim}) for the Three Cases at Both Stage L1 and L2 Based on USP <905> "Uniformity of Dosage Units"

Case	Mean	L1	L2
Case A	98.5%>$\bar{x}$	$S_{lim}=x/2.4-34.79$	$S_{lim}=x/2.0-36.75$
Case B	98.5%≤$\bar{x}$≤98.5%	$S_{lim}=6.25$	$S_{lim}=12.5$
Case C	$\bar{x}$>101.5%	$S_{lim}=48.54-x/2.4$	$S_{lim}=63.25-x/2.0$

following formulation for estimating confidence intervals of the mean.

$$\mu = \bar{x} \pm t_{\left(\frac{\alpha}{2}, n-1\right)} \frac{s}{\sqrt{n}}$$

Specifically, when the mean is greater than 101.5%, AV shall be calculated using the upper confidence interval of the mean as the $\bar{x}$ in Table II to represent the "worst case" scenario; when the mean is smaller than 98.5%, AV shall be calculated using the lower confidence interval of the mean as the $\bar{x}$ in Table II to represent the "worst case" scenario.

The expected AV range may be determined using the s_{lo} and s_{hi} values along with the worst case estimates of the mean. An alpha value of 0.05 can be used for the t and chi distribution to indicate 95% confidence interval of the expected AV range for future batches.

EXAMPLE II: DISSOLUTION—DETERMINING PROBABILITY OF ACCEPTANCE FOR USP ≤711≥ IMMEDIATE RELEASE DISSOLUTION (8)

As in dosage uniformity, dissolution testing uses multiple tested units and follows a stage-wise acceptance criterion. Because of this, traditional process capability (C_{pk}) measures fall short in providing reliable assessment of the ability of the product to meet the acceptance criteria. Acceptance criteria for dissolution testing follow rules outlined in USP General Chapter <711> dissolution. The USP rules for immediate release dosage forms are indicated in Table IV.

These acceptance criteria rules are inter-related and become quite complicated to solve analytically. However, the probability of meeting the acceptance criteria (P_a) for a future batch at a particular stage can be estimated by comparing the pooled dissolution statistics (average and standard deviation) of the measured batches against with data derived from a Monte Carlo simulation of the USP acceptance criteria guidelines with defined batch averages and variability. More detail of this approach and other similar strategies are described by Bergum (9–12) and other publications (13–15).

Table IV. USP Rules for Immediate Release Dosage Forms

Stage	Number of units	Acceptance criteria
1	6	• Each unit is not less than Q+5%
2	6	• Average of 12 units (S1 and S2) is ≥Q • No unit is less than Q−15%
3	12	• Average of 24 units (S1, S2, and S3) is ≥Q • Not more than two units are less than Q−15% • No unit is less than Q−25%

Conceptually, the Monte Carlo are a broad class of computational algorithms that use repeated random sampling to obtain the distribution of an unknown probabilistic entity. Monte Carlo simulation is often useful when it is challenging to obtain a closed-form expression such as the probability of passing a multi-stage testing. Its simulation can provide a "virtual" manufacturing plant that produces "units" that are defined by a normal distribution of dissolution results with a mean and standard deviation described by the historical batch sample results (13,14). A flow chart outlining the form of the Monte Carlo for the USP <711> stage-wise IR acceptance criteria is provided in Fig. 1 (13,14). In this process, a simulated batch is initiated and tablets are generated with normal distribution characteristics based on the measured analytical results from the validation batches. The USP criteria are applied to the simulated tablets to assess if the specific batch meets the USP criteria. The number of tablets that pass a given stage criteria are compared to the total number of tablets produced to provide the probability that a batch with the defined normal distribution characteristics will be accepted. For instance, stage 1 criterion is passed if all six units tested are ≥Q+5%. This probability can be calculated as P{Pass S1}=p^6, where p is the probability of a single unit result is greater than Q+5%. For the samples that fail S1, a new sample of 6 is then generated, combined with the first 6 units and tested against S2 criteria. Similarly, more units can be generated accordingly to test against S3 criteria.

Lower 95% confidence limits are generated by repeating the assessment with the lower 95% confidence level of the mean and the upper 95% confidence level of the standard deviation. This provides the lower bound to the acceptance probability determination.

This simulation process may be altered with a new set of Normal Distribution characteristics and the process repeated to generate tables of acceptance probabilities for each characteristic.

Charts or the "operating curves" were developed from the tabular data that provide the Probability of Acceptance (P_a) for various virtual plant population means and standard deviations. These general charts are shown for each dissolution acceptance stage in the Figs. 1 and 2 (14,15).

Rather than deriving analytical equations that estimate the probability, such as CuDAL approach by Bergum (11,12), Monte Carlo simulation generates these "operating curves" that provide solution to the complex stage-wise equation (14,15). This solution is as precise as the number of iterations used in the Monte Carlo simulation. More simulation iterations provide a higher precision to the actual solution.

In order to assess, P_a, the computed mean and standard deviation of the validation batches are located on the charts. For example, if the dissolution results from the campaign for a product are 90% with a standard deviation of 4% and the dissolution acceptance criterion is Q=80% at the specified Q

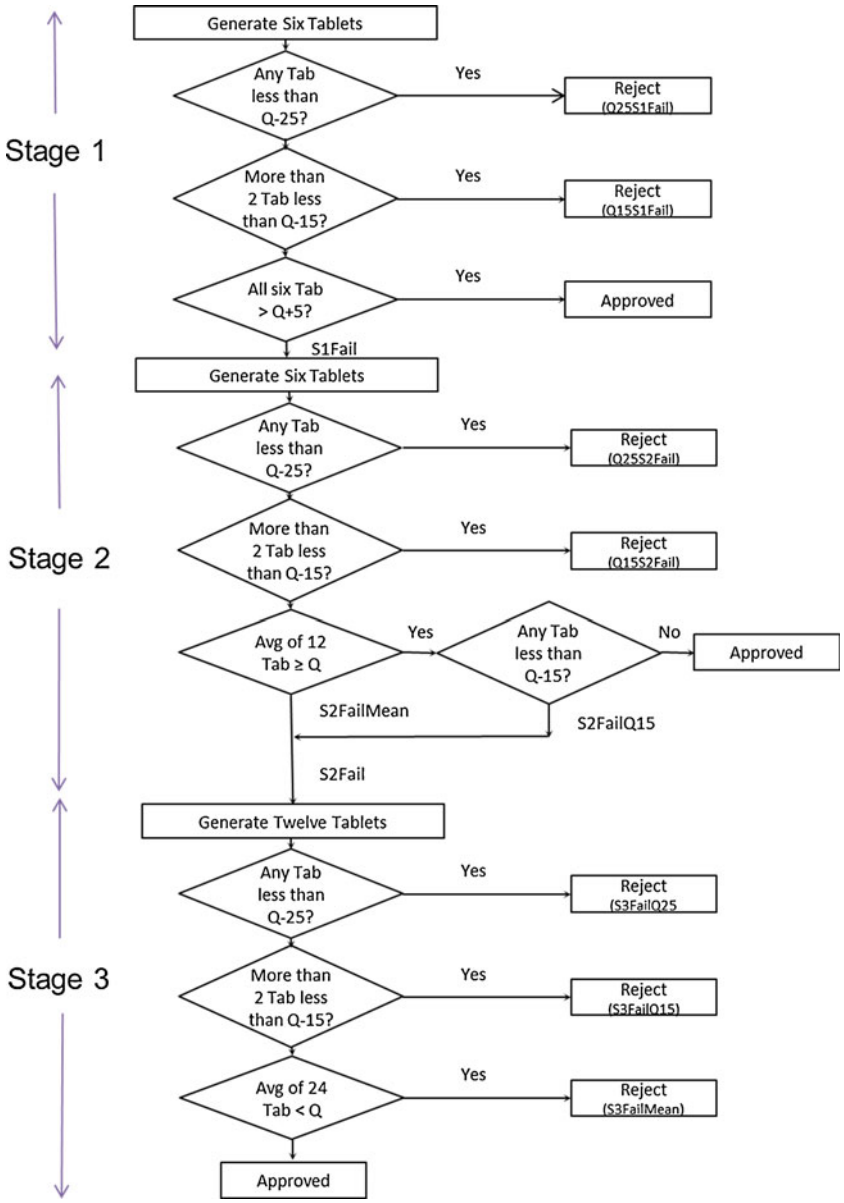

Fig. 1. Flow chart for immediate release dissolution test simulation

time, then the stage 1 probability of acceptance is 0.50 (i.e., there is a 50% chance that a future batch of product will pass the stage 1 criterion). There is >99.99% probability that a future product batch will meet the stage 2 and stage 3 criteria. Confidence limits are used to indicate how well the determined dissolution capability is known. The probability of meeting each particular stage acceptance criteria and the associated lower 95% confidence limits (see equations 1 and 2 above) can be determined for each stage by assessing the "worst-case" intervals for both the mean and standard deviation as accomplished above.

EXAMPLE III: IN PROCESS MEASURES—HARDNESS, THICKNESS, UNIT WEIGHT

In-process examinations often assess multiple units. For example, five (5) tablets may be removed at a regular interval from the process and individually tested for hardness. If any single tested tablet in the examined group does not meet the hardness specification criteria, the examination fails and a corrective action taken on the process. As with dosage uniformity and dissolution, assessing multiple units for each examination complicates a proper computation of process capability. The probability of acceptance (P_a) for a specific examination is dependent on the number of units tested (n) and the probability that a single unit (P_{su}) will pass the specification criteria.

$$P_a = (P_{su})^n$$

As with previous measures, confidence limits may be assessed that depend on the number of samples acquired.

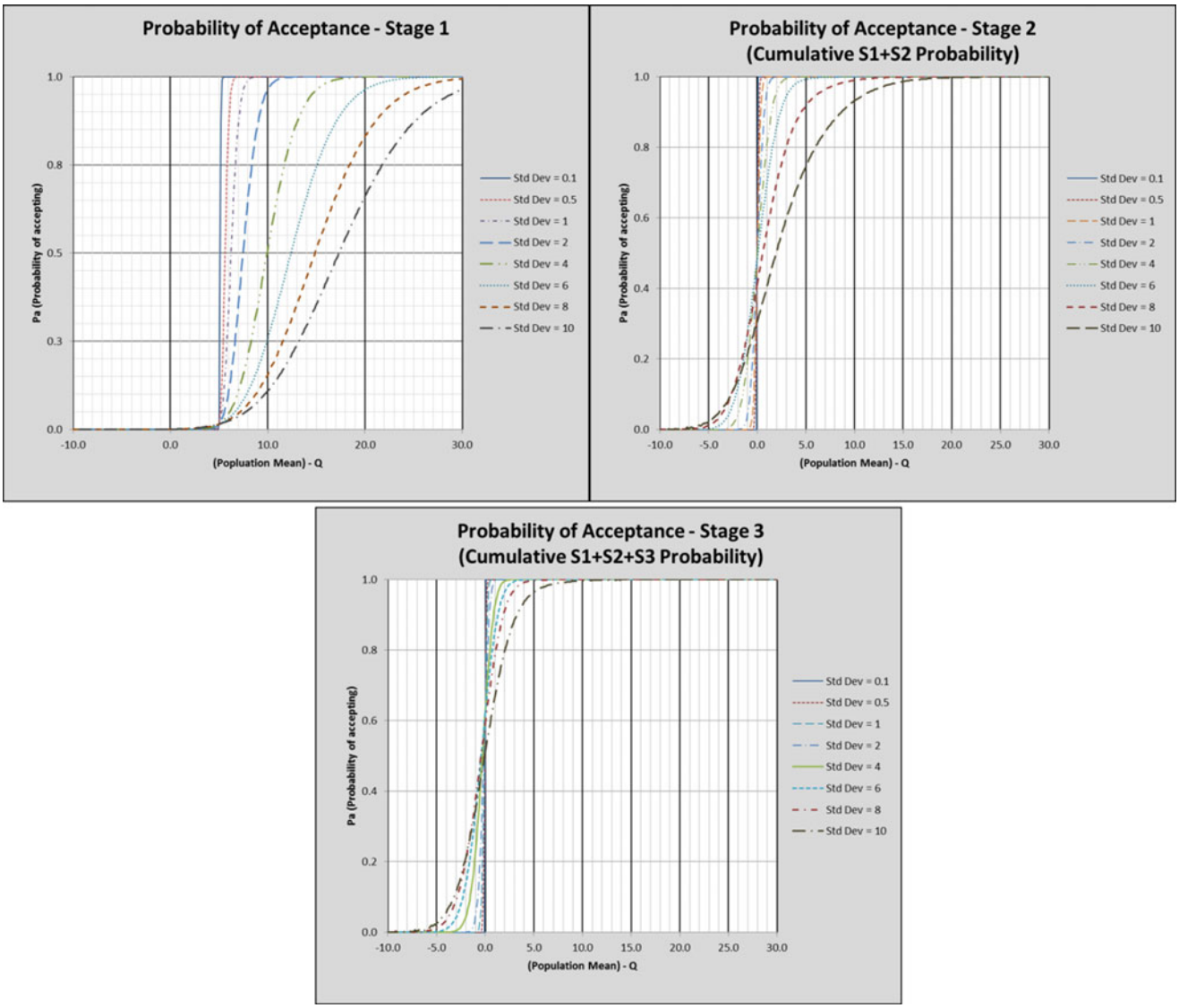

Fig. 2. Plot of probability of acceptance of immediate release dissolution test at stage 1, stage 2 and stage 3 as a function of percent of individual results greater than Q

OTHER EXAMPLES

With a bit of thought and understanding of the specific process parameter acceptance criteria, along with the fundamental equations and confidence interval statistics, one can apply the P_a concept to any quality attribute.

The concept is also readily applicable to sterile/non sterile liquid dose products. Quality attributes such as deliverable

Table V. Correlation Between C_{pk}, Sigma Level, Acceptance Probability, and Fraction Defects (20–22)

Process capability (C_{pk})	Sigma level[a]	Acceptance probability (P_a)[b]	Fraction defects (ppm)[b]
0.33	1	30.8537533%	691,462
0.67	2	69.1462467%	308,537
1.00	3	93.3192771%	66,807
1.33	4	99.3790320%	6210
1.67	5	99.9767327%	233
2.00	6	99.9996599%	3.4

[a] Sigma level=number of standard deviation that is between the process mean and nearest specification limit
[b] The acceptance probability and corresponding fraction defects is determined using the sigma level and a normal distribution with a 1.5 sigma shift which is a general industrial practice (20–22)

volume and assay per spray have stage-wise acceptance that can be converted into an acceptance probability.

COMPARISON: CAPABILITY INDICES AND ACCE PTANCE PROBABILITY

Process capability indices were developed as part of traditional statistical process control strategies to denote the ability of a process to produce output within specifications limits. Table V provides a correlation between C_{pk} values, the sigma level, anticipated acceptance probability, and the expected level of defects.

Commonly accepted statistical guidelines indicate processes with C_{pk}>1.33 as performing well within statistical control and those with C_{pk}<1.0 as "incapable" (1,16). A C_{pk}>1.33 is associated with a centered process that will statistically produce less than 63 defective units per million. This is equivalent to an acceptance probability of >99.99%. A C_{pk}<1.0 is associated with a process that will statistically produce more than one defective unit per thousand. Note that there is variability in C_{pk} estimation, and often times computing the confidence interval of the C_{pk} will help to evaluate the uncertainty of the capability analysis, as described in various publications and by international standards (17–19). The C_{pk} confidence interval computation is dependent on the sample size and can be noticeably wide for sample size under 100. For instance, 95% confidence interval for a C_{pk} of 1.33 with sample size of 30 is 1.02 to 1.76 (18). These process capability concepts are well applied to processes wherein individual units are assessed and compared to defined specification limits and are readily applicable to many non-pharmaceutical industry applications.

CONCLUSION

This paper introduces an innovative statistical approach that helps to understand how variation impacts the acceptance criteria of quality attributes. Because of more complex stage-wise acceptance criteria, traditional process capability measures are inadequate for general application in the pharmaceutical industry. The P_a concept provides a clear and more precise measure, derived from specific acceptance criteria for each quality attribute. In line with the 2011 FDA guidance, this approach systematically evaluates quality attribute data and scientifically establishes evidence that a process is capable of consistently delivering quality product. The probability of acceptance provides a direct and readily understandable indication of product risk.

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