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Dissolution Testing Strategies for Large Sample Sizes and Applications in Continuous Manufacturing

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ABSTRACT

The potential advantages of larger sample sizes for dissolution testing through surrogate modeling in the context of continuous manufacturing and process analytical technology is the motivation for development of a statistically based batch release acceptance criterion. A common approach in conventional batch release is to measure at most 24 tablets in three subsequent stages and evaluate the results against the acceptance criteria of the United States Pharmacopoeia (*USP* <711> Dissolution). We describe two approaches for a statistically based release testing strategy for immediate-release dosage forms with $N > 24$: 1) generalization of *USP* <711> three-stage acceptance criteria for any sample size greater than 24, and 2) a tolerance interval approach. Both approaches are based on a sample-size independent criterion ensuring a known probability of passing *USP* <711> acceptance criteria. The proposed criteria can be applied to the entire batch or segmented portions of a single batch run.

KEYWORDS: Release testing, continuous manufacturing, large N, tolerance intervals, dissolution

INTRODUCTION

In vitro dissolution is an important quality attribute of pharmaceutical solid oral formulations, such as immediate-release tablets. It requires a time consuming and complex laboratory measurement method. Hence, there is motivation to develop surrogate models capable of predicting dissolution based on process analytical technology (PAT) tools and process parameters, as PAT measurements can be available online with little extra cost and for larger sample sizes (*1*, *2*). Dissolution testing for batch release is typically performed by using a three-stage evaluation against the acceptance criteria of the harmonized dissolution chapter of the *United States Pharmacopoeia*, *European Pharmacopoeia*, and *Japanese Pharmacopoeia*, henceforth referred to as *USP* <711> acceptance criteria (*3*). This involves assessment of six tablets at the first stage, six additional tablets in the second stage, and 12 additional tablets at the third stage. At most, 24 tablets are evaluated, but in practice a typical product rarely goes beyond stage 1, where only six tablets are evaluated. Continuous manufacturing and PAT have enabled the ability to analyze larger numbers of dosage units compared to the traditional batch manufacturing process. The development of surrogate models for dissolution can support a full realization of real-time release (RTR) and reduce the time to market. For example, such models can predict the dissolution for an entire sample of tablets collected for content uniformity testing. This would lead to a substantial increase in the amount of dissolution data to interpret, higher than what is currently included in the *USP* <711> acceptance criteria. There are no default acceptance criteria for dissolution testing applicable to large sample sizes. Hence, companies need to propose the release test and its acceptance criteria based on knowledge built during the drug product development cycle, considering regulatory guidelines, the company's own risk control practices, and the commercial and clinical needs of the product.

In this study, the development of two acceptance criteria for dissolution release testing for sample sizes greater than 24 are presented along with an assessment of their statistical risk properties. One attractive feature of the proposed approaches is probability-based flexibility to accommodate variable risk levels in relation to meaningful batch quality requirements. Moreover, increased sample size leads to higher precision in enabling the right release test decision.

This study focuses on *USP* <711> acceptance criteria for immediate-release dosage forms as a basis for

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characterizing the release test performance using concepts developed by Garcia et al. and Bergum et al. for *USP* <905> testing of content uniformity (*4*–*6*). The aim is to develop an acceptance criteria rule that ensures a high probability of passing *USP* <711> acceptance criteria. The alternative approach directly assesses the desired quality level in a straightforward, interpretable way based on a tolerance interval approach. The risks and benefits for both approaches will be discussed.

USP <711>-BASED APPROACH

The evaluation of dissolution performance against *USP* <711> acceptance criteria can be understood as a demonstration test of quality. The inference applies only to the sample tested (*3*). Tablets are analyzed in stages, only moving to the next stage if the current stage fails. Success at any stage is considered to pass the overall acceptance criteria. Batch rejection only occurs if the dissolution results do not comply with the stage three acceptance criterion. Given the limitation on inference beyond the units tested with *USP* <711>, companies may develop their own dissolution test acceptance criteria, including the specification time point (Q-time point) and specification value (Q value). Internally developed acceptance criteria can be evaluated against the *USP* <711> test. Typically, we would expect to see company-developed acceptance criteria that afford greater protection against batch mean and variability shifts compared with the *USP* <711> test, partly as a consequence of larger sample sizes.

For immediate-release dosage forms, *USP* <711> acceptance criteria with a prespecified fixed Q value, expressed as a percentage of the labeled content of the dosage unit dissolved at a prespecified time point are as follows:

- Stage 1 (6 tablets): no tablet is less than Q + 5%
- Stage 2 (+6 tablets): mean of 12 tablets is equal or greater than Q, and no tablet is less than Q – 15%
- Stage 3 (+12 tablets): mean of 24 tablets is equal or greater than Q, not more than (NMT) two tablets are less than Q – 15%, and no tablet is less than Q – 25%.

Given that failure of Stage 1 and Stage 2 of *USP* <711> acceptance criteria do not result in batch rejection, the role of the first two stages is analogous to an 'early stopping rule', e.g., if the process is capable of producing product of such quality that all six samples are above Q + 5, then there is no need to further investigate the batch mean dissolution.

The probability of passing the *USP* <711> acceptance criteria can serve as a baseline to assess alternative company-developed acceptance criteria. As an example, probabilities of passing were calculated in relation to assumed true batch properties for a case where Q = 80%, including four levels of batch dissolution (mean % dissolved) across a broad range of standard deviation (SD). Figure 1 provides the operating characteristic curve for the four batch mean values (79%, 80%, 85%, and 90%) in relation to varying the magnitude of SD. A batch with a true mean of 79% and a low SD would generally fail *USP* <711> acceptance criteria; however, with a larger SD, the probability of passing is up to nearly 40%. This is mostly due to the stage 2 rule. A batch mean of 80%, equal to the Q value, has approximately 62% probability of passing *USP* <711> acceptance criteria when the SD is small (close to zero). This is a result of a 50% probability to pass the mean value criterion in stage 2 and an additional smaller probability to pass stage 3 (conditionally on failing stage 2). With increasing SD, the probability of rejection increases due to requirements on individual tablets. Finally, with a batch mean of 85% or above, there is a rather high probability of passing if SD is below 10%, and rapidly decreasing probability as SD increases above 10%.

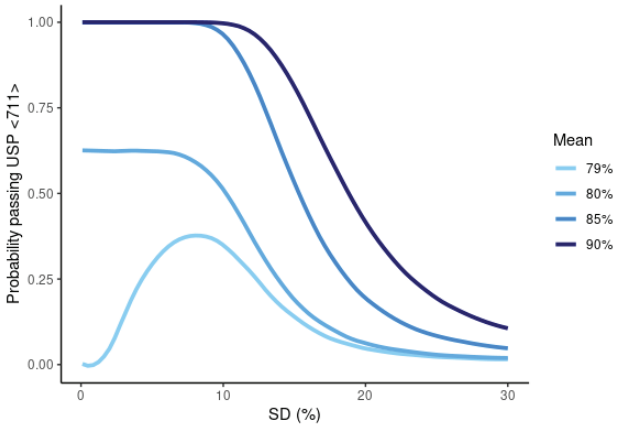

Figure 1. Probability of passing the USP <711> acceptance criteria depending on mean percent dissolved and standard deviation (SD), in an example where Q = 80%.

Extension of USP <711> Acceptance Criteria to Large Samples

Companies have commonly used *USP* <711> acceptance criteria as a release test, although the acceptance criteria were not designed with any probability-based assumption that permits risk calculations applicable to the batch being tested. However, the probability (i.e., assurance) of passing *USP* <711> acceptance criteria under given assumptions of batch quality can be used as a benchmark to evaluate competing acceptance criteria for large

sample sizes. Analogous discussions have been published in the context of *USP* <905> and content uniformity (*4*, *6*).

When extending acceptance criteria beyond $N = 24$, start with the stage 3 criterion of *USP* <711> (*3*):

1. *Sample Mean*: mean of 24 tablets (point estimate) is not less than Q;
2. *Individual Values at Q – 15*: NMT two tablets (function of *N*) are less than Q – 15%; and
3. *Individual Values at Q – 25*: no tablet is less than Q – 25%.

Condition 1: Sample Mean

Condition 1 of the *USP* <711> procedure imposes a requirement on the mean. It is a simple demonstration requirement and lacks any statistical claim of a known probability of meeting this requirement for some random batch at time of manufacture. It is reasonable to assume that the aim of *USP* <711> acceptance criteria is to ensure that the batch has a mean of at least Q.

In this regard, there are two approaches that can be followed. The first is to assess the point estimate of the mean directly against the threshold value. The second is to compare the lower confidence bound against the threshold. With increasing sample sizes, the two approaches are numerically close to each other, although the overall test performance of batches with true mean of percent dissolved close to the Q-value may be affected by the two approaches. The advantage of the confidence interval (CI) approach is that it effectively fails batches with true means of percent dissolved below Q. On the other hand, batches with means above Q have reduced probability to pass the criterion in comparison with a point estimate approach.

Condition 2: Individual Values at Q – 15%

To impose a requirement of high probability of compliance with *USP* <711> acceptance criteria, consider the proportion allowed below Q – 15% from stage 3 with $N = 24$, then generalize to larger sample sizes to arrive at a recommendation as described below. Note that variability is addressed on the SD scale rather than variance scale. The algorithm is given as follows.

1. Assume "worst-case mean" of Q. Note that a batch with a mean equal to Q has only 50% probability of passing the mean criterion. The following steps focus on the variability criterion only.
2. Calculate the probability under the normality assumption for various SDs to comply with Q – 15% criterion from *USP* <711> in stage 3 (see Fig. 2).
3. Choose the desired target probability p_1 to achieve as the baseline to calibrate against.
4. Find corresponding SD, denoted as SD_1, to achieve the target probability (e.g., $p_1 = 95\%$ gives $SD_1 = 8.275$; $p_1 = 90\%$ gives $SD_1 = 8.947$; see example below). SD_1 will be used to calibrate with stage 3 *USP* <711> acceptance criteria.
5. Select desired sample size (e.g., $N = 50$) and find the value of $k(N)$ (i.e., number of tablets < Q – 15%) such that p_1 for SD_1 is met for the chosen sample size.

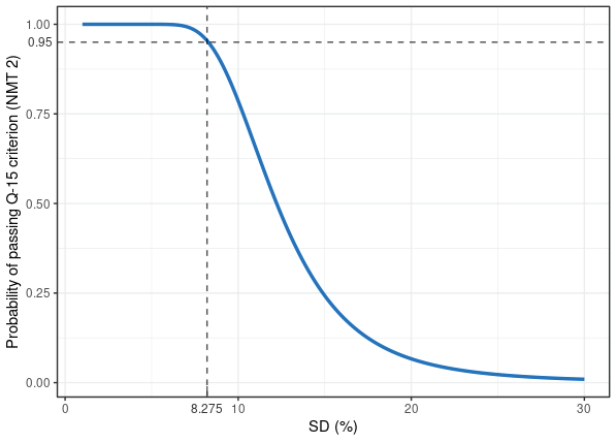

Figure 2. Probability of passing the condition that no more than (NMT) two measurements are below Q – 15% for a batch with mean percent dissolved of Q and standard deviation (SD) as on x-axis.

The following example is for a desired target probability to pass *USP* <711> acceptance criteria of 95% ($p_1 = 95\%$). The probability (*P*) to pass the criterion is simply $P(X \le 2)$, where the relevant binomial equation is given by $X \sim Binom\left(24, \Phi_{Q,sd}(Q-15)\right)$, where $\Phi_{Q,sd}(y)$ normal distribution function, *Q* is the mean, and *sd* is SD. Solve the binomial equation to find the highest SD, such that the $P(X \le 2) \ge 0.95$. As mentioned above, select $SD_1 = 8.275$ or lower to achieve ≥ 95%.

For a given sample size ($N = 50$) and SD_1, solve the binomial equation to obtain $k(N)$ where $P(X \le k) \ge 0.95$. The solution in this case is $k = 4$ tablets, i.e., allowing two extra tablets compared to standard *USP* <711> stage 3 acceptance criterion below Q – 15 (see supplemental table for tabulated values and instruction for use). Note that the solution is obtained assuming that the batch has a true mean equal to Q, as the calculation for $k(N)$ only aims at assessing variability. The mean check is part of condition 1.

Condition 3: Individual Values at Q – 25%

For condition 3, we can either assume the same criterion as for N = 24 (no individual value below Q – 25%) or consider an alternative analogous to condition 2: following the derivation of Q – 15% (condition 2), calculate how many values are allowed below Q – 25% as part of the acceptance criteria, denoted as $k_2(N)$. The acceptance criterion can be set as: NMT $k_2(N)$ below Q – 25%. In such case, the determination of $k_2(N)$ should be done directly from the normal distribution assumed for the condition 2 development to keep internal consistency of the acceptance criterion. However, to maintain a conservative approach and for simplicity, we suggest requiring no values less than Q – 25%, as a more stringent criterion.

Final criterion

In summary, the derivation described above leads directly to the formulation of the acceptance criterion for a sample size larger than 24. For given Q value, sample of size N has to fulfill:

1. *Sample Mean*: Mean of all tablets is above Q (point estimate or lower 95% confidence bound);
2. *Individual Values at Q – 15%*: $k(N)$ represents the number of tablets allowed below Q – 15% as a function of N; and
3. *Individual Values at Q – 25%*: no tablet can have a value below Q – 25%.

Drawbacks of Proposed Extension of USP <711>

The development of the *USP* <711> extension criterion has made multiple statistical as well interpretational assumptions either explicitly or implicitly. These assumptions are summarized below, and the drawbacks of this approach are discussed.

Normality Assumption

The normality assumption is necessary to derive rules to satisfy conditions 2 and 3. However, if the normal distribution is assumed and evaluated for N = 24 for *USP* <711> acceptance criteria, the same SD_1 is not derived for conditions 2 and 3 following the steps given previously (i.e., to achieve NMT two below for condition 2 and none below for condition 3). Because of this difference in SD_1 obtained by each condition, only condition 2 is used for SD_1 determination, whereas condition 3 is only used to safeguard against heavy-tailed distributions. Lack of clarity on which SD should be used for condition 3 led to the recommendation of no single value below Q – 25%, but the problem is more profound; it questions whether normality should be used for calibration or some other distribution.

At the same time, using larger sample sizes in the hundreds to thousands with the normality assumption would lead to decreasing probabilities to pass condition 3 with SD_1 for p_1 = 95%. With N = 200, the probability of passing condition 3 is only around 80% probability (if the batch mean is at Q%). In practice, such a large SD is not expected to be obtained, so the actual risk of failure due to condition 3 is expected to be very low. Still, it is a drawback of the statistical approach given.

Role of Q Value Selection

The developed framework assumes that the true (but unknown) batch mean percent dissolved is not too close to 100%. Note that an atypical dissolution readout can arise from two different causes: actual slower/faster dissolution properties of the tablet or off-target content. The latter can vary both below and above 100%, affecting proportionately of the percent dissolved at the defined Q time point, but the former results in skewed distribution of percent dissolved at Q time point at the tablet level, as there is more potential variability for slower dissolution than for faster dissolution, which is bounded by tablet content. The combination of these properties would cause issues with normality and affect the SD calculations needed to derive the table for Q – 15% criterion. For typical choices of immediate-release dosage forms with Q between 75–85%, with typical SD values, the proposed framework will work sufficiently well, but it needs to be clearly understood that it is an approximate solution that may not work with Q values closer to 100% (note that such large Q is unrealistic in practice).

Granularity and Choice of p_1

The p_1 target value is typically not achieved exactly, especially for smaller sample sizes with resulting $k(N)$ < 10 tablets. At various sample sizes, the actual overall properties of the criterion would differ somewhat.

For example, changing p_1 from 95% to 93% would have achieved same result for N = 50, i.e., $k(N)$ = 4 tablets due to the granularity of the criterion. The dependence of $k(N)$ on choice of p_1 is more pronounced for large sample sizes. For N = 1000 tablets, $k(1000)$ = 51 tablets for p_1 = 93%, or 45 tablets for p_1 = 95%. Thus, conformance to the chosen p_1 is sample size dependent.

The choice of p_1 allows a company the flexibility to set the acceptable risk level. Hence, it should not be chosen arbitrarily or according to a default strategy but based on scientific assessment and internal business practices.

Performance

The overall performance of the extended framework is shown in Figure 3. The black line represents the curve for $N = 24$ with $k(24) = 2$ tablet, and the dashed lines represent varying criteria based on sample size. The proposed criteria are more conservative than the traditional *USP* <711> criteria used directly. That is expected given that *USP* <711> is a demonstration test, whereas the extended criteria lead to a confidence level of passing the demonstration test. However, the resulting curves are rather far from the desired ideal curve (i.e., step function with respect to the black reference line: at probability of 1 when reference curve is above p_1 and immediately dropping to zero when the reference line crosses below p_1). Sample sizes well above 100 would be required to achieve performance close to the desired step function.

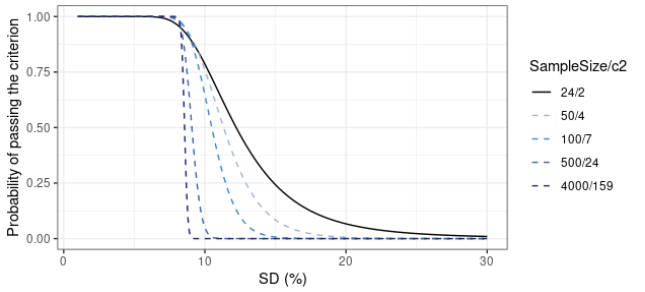

Figure 3. Probability of passing the various criteria: solid line refers to USP <711> acceptance criterion of stage 3 NMT than two values below Q – 15 with N = 24; dashed lines represent larger samples (N = 50, 100, 500, and 4000) with corresponding k(N) values (4, 7, 24, and 159, respectively). c2: condition 2 of respective criterion; NMT: not more than; SD: standard deviation.

DIRECT QUALITY (TOLERANCE INTERVAL) APPROACH

As shown in previous sections, building the criteria directly around *USP* <711> acceptance criteria is rather cumbersome. An alternative approach to large N criteria is to start from a patient-centric perspective and simplify criteria to a single threshold decision rule.

An approach based on tolerance intervals (TIs) can be employed to ensure that the quality of the product is above a required threshold with a prespecified degree of confidence. Analogous reasoning has been proposed for large sample considerations for *USP* <905> (*7*). A further simplification is that for dissolution, only a one-sided tolerance limit is needed.

There are several advantages of such an approach. Firstly, the tolerance limit implementation is relatively simple. Following Krishnamoorthy and Mathew, the *p*% content and (1 – α)% confidence lower tolerance bound, is calculated according to the equation (*8*): $\bar{x} - K \cdot s$, where *K* is the TI constant.

$$K = \frac{t_{n-1,1-\alpha,\ell}}{\sqrt{n}}.$$

K is equal to the (1 – α)% quantile of the non-central t-distribution with n-1 degrees of freedom and non-centrality parameter $\ell = z_p\sqrt{n}$ divided by $\sqrt{n}$; *n* is sample size; z_p is the p^{th} quantile of the standard normal distribution, $\bar{x}$ is the sample mean, and *s* is the sample SD.

Note that *K* is used in this section to distinguish TI constant from the lowercase *k*(*N*) used in the previous section.

The formula may be too complicated to be implemented for release in commercial manufacturing quality systems. However, given that for a single product, both α and p will be fixed, the *K* value can be precalculated for varying sample sizes. Then, the formula is given by $\bar{x} - K(N) \cdot s$, with *K*(*N*) denoting dependence of the constant K on the sample size *N*.

Finally, the calculated tolerance bound is compared with a certain threshold that defines the required quality. The criterion is single-stage, and the sample size is already considered in the calculation, so the acceptance criterion is independent of the sample size.

There are two TI-based approaches to consider, one is based on quality of individual values and the other is based on an extension of the *USP* <711> stage 3 acceptance criterion.

Individual Tablet Quality

Conceptually the simplest, yet the most stringent, approach to a direct quality assessment would be an individual tablet quality requirement. This approach is related to a known probability of compliance with the *USP* <711> acceptance criteria assuming the same Q value. A high proportion of the tablets being above the Q value implies high probability of compliance.

To show a concrete example, let Q = 80%, *p* = 95%, and 1 – α = 90%, and consider various levels of the true underlying dissolution mean and SD. Results for *N* = 50 are shown in Figure 4 and discussed in detail here; sample sizes of 24 and 200 are shown in supplemental figures. In contrast to *USP* <711> acceptance criteria shown in Figure 1, a criterion based on the TI limit has entirely different behavior: lower SD values and a certain distance above Q = 80 are needed for compliance (due to the inclusion of the lower bound as part of the criterion). Naturally, this is caused by the requirement of having individual tablet readouts above a certain threshold. Note that the curve shows a clear step-function-like behavior.

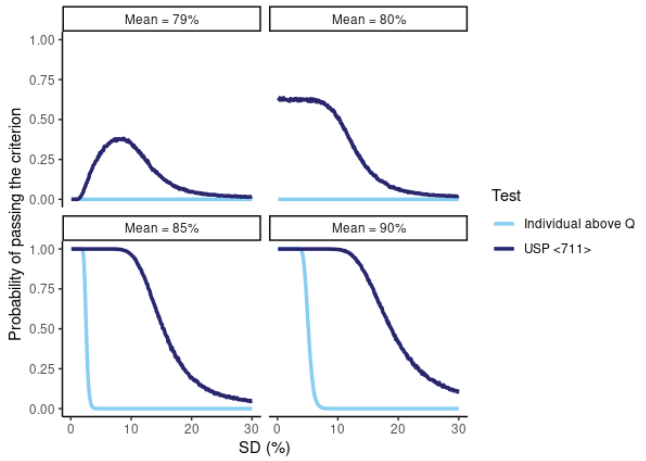

Figure 4: Comparison of the 90% confidence, 95% coverage tolerance interval above the Q = 80% mean value versus USP <711> acceptance criteria for batches of N = 50 across a range of mean values and standard deviation (SD). Sample sizes of 24 and 200 are shown in supplemental figures.

A drawback of this approach is considerable conservativeness of the criterion when compared to *USP* <711> acceptance criteria in the sense of rejecting batches that exhibit large probability of compliance with *USP* <711>. Hence, it can only be applied if there is a clear requirement for individual values to be above the Q value.

USP <711>-Based Quality

A variation of the direct quality approach is deriving the TI threshold and coverage directly from *USP* <711> acceptance criteria. The stage 3 criterion allows two out of 24 tablets to be below Q – 15%, which translates into 8.33% of tablets. Extrapolating this to the population using a threshold of Q – 15% with p = 92% content and $1 - \alpha$ = 95% confidence, TI would align with the properties of *USP* <711> acceptance criteria. To ensure a sufficiently large probability to pass *USP* <711> acceptance criteria for a batch passing TI criterion, the coverage needs to be increased above 92%. Empirically, p = 97.5% has been shown to provide good performance.

Note that when using Q – 15%, an additional acceptance criterion must be added. The population statement above Q – 15% does not guarantee the mean above Q, so the point estimate or the lower confidence bound of the mean value of the observed tablets must be above the Q value. Essentially, a use of confidence limit requirement instead of point estimate will eliminate the possibility of batches below Q passing the criterion in small samples and will penalize batches with a mean value just above the Q value.

Results for N = 50 are shown in Figure 5, including the point estimate and confidence interval for the mean value criterion (sample sizes of 24 and 200 are shown in supplemental figures). An SD of approximately 10% is the threshold where the batches start to occasionally fail *USP* <711> acceptance criteria. With a 95%/97.5% parametric one-sided TI, there is only a small probability for batches with SD > 10% to pass the criterion. At the same time, the criterion is much less conservative than the approach using Q = 80%, as discussed in previous sub-section.

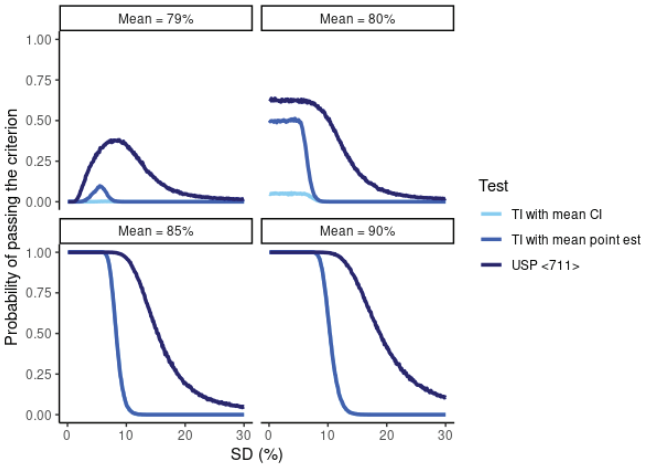

Figure 5: Comparison of the USP <711> acceptance criteria with a double criterion of 95% confidence, 97.5% coverage tolerance interval (TI) above Q – 15% and mean above Q. The plot shows batches of N = 50 across a range of mean values and standard deviation (SD). When only two lines are displayed, the point estimate and confidence interval (CI) based testing fully overlaps. Sample sizes of 24 and 200 are shown in supplemental figures.

DISCUSSION

This study presents two statistical approaches to developing acceptance criteria applicable to dissolution release testing of large sample sizes (N > 24). The first approach is an extension of the *USP* <711> acceptance criteria to large N sample sizes, including a strict requirement on individual tablets. The second approach is based on a TI criterion with two different options. The operating characteristic curves were compared in relation to *USP* <711> acceptance criteria, considering the practical implementation, ease of interpretation, and quality protection of both approaches.

The simplicity of the TI-based criterion is an advantage, and it has good small sample size properties when the true batch mean percent dissolved is close to the Q threshold. The most important criterion is the direct link to quality, unlike the fairly complex relationship for the approach based on an extension of *USP* <711> acceptance criteria. The TI-based approach is recommended as a practical release strategy, affording good product quality protection to the patient.

The TI-based option that requires individual tablet quality specifications looks at the problem from a strict individual tablet quality requirement perspective. This criterion is overly conservative and generally requires lower SD than the *USP* <711> test to be successful. Although there may be circumstances related to operational considerations and patient risk requirements where this option may be considered, this approach is generally not recommended.

The TI-based option that is based on extension of stage 3 *USP* <711> acceptance criteria has good calibration properties and is not overly conservative. Hence, it may generally be a good choice for an acceptance criterion rule for dissolution assessment of large samples. Additionally, such an approach is consistent with the development of content uniformity testing (*9*).

Immediate-release dosage forms were used in this study; however, the approaches can be adapted to testing of other dosage forms.

CONCLUSION

The proposed approaches contain a probabilistic metric that controls the risk level and can be applied to large sample sizes in applications such as continuous manufacturing. The first approach extends *USP* <711> acceptance criteria to a large sampling procedure, controlling the risk with parameter p_1. Risk control with respect to batch parameters for two TI-based approaches are maintained via the content and confidence parameters. Different values may be assessed to achieve a desired risk level and level of calibration against *USP* <711> acceptance criteria as appropriate for a given situation.

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DISCLOSURES

All authors are employees of Johnson & Johnson and the manuscript has been written as part of their employment. No other financial support or conflicts of interest have been declared by the authors.

SUPPLEMENTAL MATERIAL

Supplemental material is available for this article and may be requested by contacting the corresponding author.

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