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Research Article

Challenges and Opportunities in Implementing the FDA Default Parametric Tolerance Interval Two One-Sided Test for Delivered Dose Uniformity of Orally Inhaled Products

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Abstract. The goal of this article is to discuss considerations regarding implementation of the parametric tolerance interval two one-sided test (PTI-TOST) for delivered dose uniformity (DDU) of orally inhaled products (OIPs). That test was proposed by FDA in 2005 as an alternative to the counting test described in the 1998 draft FDA guidance for metered dose inhalers and dry powder inhalers. The 2005 PTI-TOST, however, still has not found much use in practice despite the general desirability of parametric approaches in modern pharmaceutical quality control. A key reason for its slow uptake is that it rejects, with high probability, batches whose quality is considered acceptable by all other published regulatory and pharmacopeial standards as well as by the DDU specifications for many approved OIPs. Manufacturers therefore continue using nonparametric counting tests for control of DDU. A simulated case study presented here compares the consequences of the PTI-TOST compared to the counting test. The article discusses three possibilities that would help increase the uptake of the PTI-TOST approach, namely: product-specific quality standards, a different default standard suitable for the majority of OIPs, and integration of the PTI-TOST with a continuous verification control strategy rather than using it as an isolated-batch (transactional) end-product testing. In any of these efforts, if a parametric test is used, it is critical *not* to set the target quality close to, or at the boundary of the process/product capabilities, because PTI tests are designed to reject with high probability the identified target quality.

KEY WORDS: delivered dose uniformity; inhaled drug products; parametric tolerance interval; quality control; two one-sided test.

INTRODUCTION

Orally inhaled products (OIPs) deliver medication to the respiratory tract in the form of an aerosol generated from a solution, suspension, or dry-powder formulation when the OIP device is actuated. The delivered dose uniformity (DDU) is an important quality attribute that measures the amount of active pharmaceutical ingredient (API) delivered per minimum therapeutic dose from the mouthpiece of an inhaler into the collection cup of a pharmacopeial apparatus (1). DDU is an *in vitro* measure and is not equivalent to the amount of drug actually reaching the patient's lungs or other target deposition sites along the respiratory tract. This "patient-deposited" drug amount, in addition to the delivered dose, depends, for example, on the fine particle fraction of the dose as well as on many factors beyond quality controls or "chemistry, manufacturing and controls" (CMC). Such factors, which cannot be controlled by the producer but may influence the ultimate drug delivery, include: the geometry of the individual patient's respiratory tract, state of disease, inspiratory flow rate, inhalation pattern, patient's handling and storage of the device, and environmental conditions during use. Due to this complexity, the link between clinical (*in vivo*) outcomes and *in vitro* DDU characteristics of an OIP is currently not understood to the degree that would allow clinically based acceptance criteria for proper dosing reproducibility (or variability) to be deduced. Admittedly, the target for emitted dose is based on dose-ranging studies and therefore linked to clinical experience, but that relationship is not rigorous due to the notoriously flat dose–response curves or the customary setting of the target delivered dose at the

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plateau of a dose–response curve. In contrast, for acceptance limits on reproducibility or variability of the delivered dose, there is no quantitative basis. Therefore, this article discusses DDU strictly as an *in vitro* quality characteristic.

FDA specifications for DDU of metered dose inhalers (MDIs) and dry powder inhalers (DPIs) were first published in the 1998 draft CMC guidance (2). That test is based on counting the number of observations in a sample that are within pre-specified limits and is usually referred to as "counting" test. By contrast, "parametric" tests use the sample's statistics to estimate batch parameters such as mean and standard deviation.

One of the more challenging aspects of the 1998 test was the requirement that none of the observations in a sample be outside the interval 75–125% label claim (LC) — a so-called "zero tolerance" requirement, which increased chances of failure with increasing sample size regardless of product quality (3). In 2005, FDA presented a parametric tolerance interval test (4), which does not have a zero tolerance requirement and allows increased sample sizes, yet is even more restrictive than the tests in the 1998 CMC guidance (5).

The quality standard implied by the 1998 FDA counting test is more stringent than that implied by other published standards, such as the USP (1) and EP (6) combined with the European guideline's (7) requirement, as reflected in the operating characteristic curves (OCCs) in Fig. 1. These tests are described in the Appendix. In Fig. 1, the operating characteristic curve for the PTI-TOST is the farthest to the left. This illustrates that PTI-TOST requires the lowest standard deviation for a given batch mean and has the lowest probability of passing when compared with generally well established tests previously required by FDA and pharmacopeias. For all tests in Fig. 1, the OCCs shift to the left to various extents when the batch mean moves off target (off 100% LC).

Moreover, the databases collected through industry collaborations indicated that the exact DDU specifications in the 1998 guidance are more restrictive than capabilities of most marketed and in-development OIPs (8) and more restrictive than many FDA-approved specifications for OIPs (9) that had been found safe and effective based on the preponderance of evidence underpinning their approval (see Fig. 2, adapted from (10)). The approved specifications generally lie to the right of the FDA counting test for multi-dose products.

The formal reasons for the 2005 PTI-TOST being much stricter than all previously used tests are: (1) the test's two one-sided construction and (2) the default acceptance criteria, as explained in previous articles (11–13). In summary, those articles demonstrated that:

- The PTI test proposed by FDA in 2005 is a two one-sided parametric tolerance interval test (PTI-TOST), which controls the maximum allowable proportion in each tail of the DDU distribution (i.e., left (lower) and right (upper) areas outside the target interval) tested separately. Two one-sided tests have different properties than a two-sided (direct) coverage test, which controls the proportion inside the target

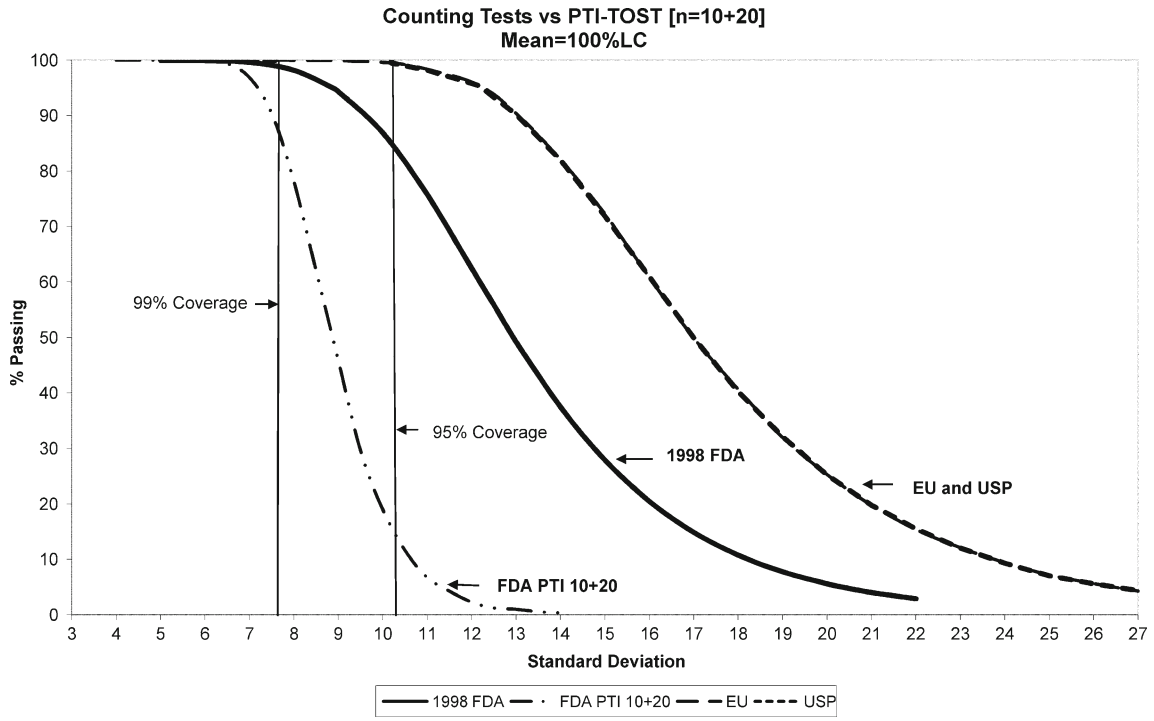

Fig. 1. Operating Characteristic Curves for the FDA counting test per the FDA 1998 draft guidance, (labeled "1998 FDA" in the figure), the USP and European pharmacopeial tests (overlapping), and the default FDA PTI-TOST ("FDA PTI 10+20"). See Appendix for tests' details. Reference lines for 99% and 95% coverage of the 80–120% LC interval are shown in *gray*

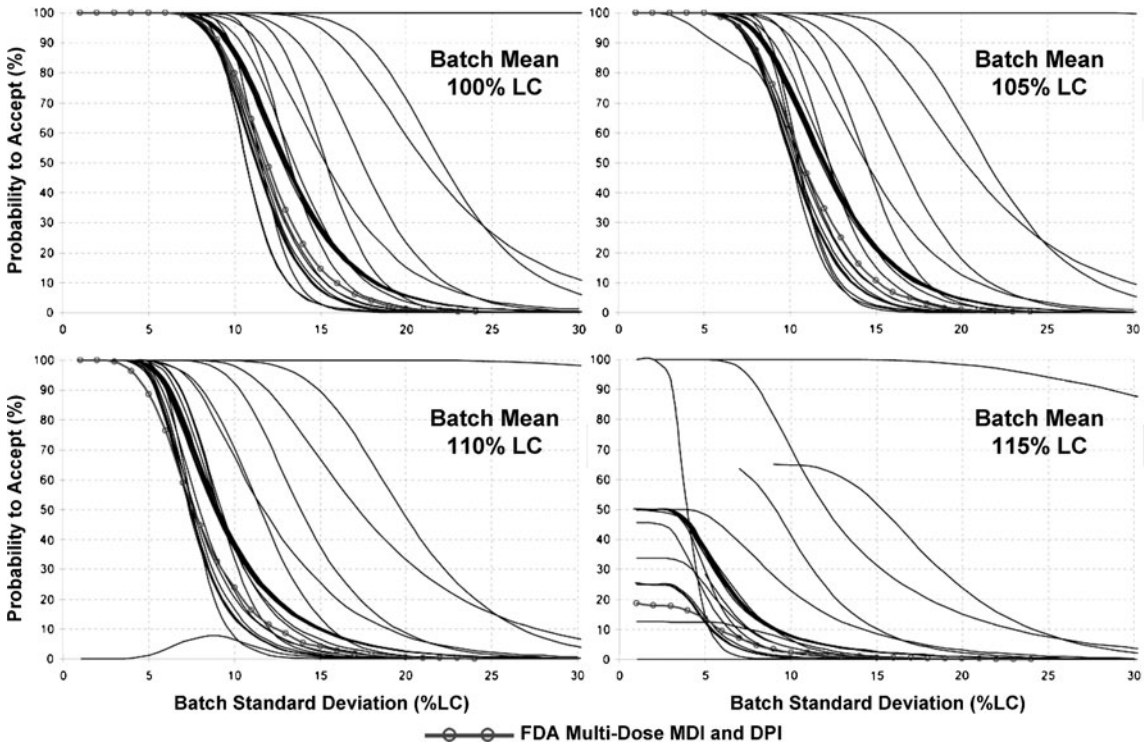

Fig. 2. Operating Characteristic Curves for 24 specifications approved by FDA in 1999–2003 for multi-dose MDIs and DPIs (*thin lines*, *some are overlapping*) compared to the OCC for the combined dose-content-uniformity and through-container-life uniformity test in the draft FDA 1998 guidance (*line with circles*). Adapted from (10)

interval and which is used, for example, in the harmonized pharmacopeial DDU test for solid oral dosage forms (14). For the default acceptance criteria set forth by FDA, that "maximum allowed single-tail proportion" is 6.25%, and the target interval is 80–120% LC (FDA did not specify a default sample size for PTI-TOST, leaving that decision to each sponsor). One of the practical consequences of a TOST construction is that the required batch coverages (i.e., proportion inside the target interval) are higher than may be assumed from the test's title ("87.5% coverage"). The probability of accepting a batch with 87.5% coverage is less than 1%. Batch coverages of 99% or greater are needed to have acceptance probability of 98% or greater.

- The minimal coverage required for passing the 2005 PTI-TOST with any given probability depends on the batch mean. Off-target means increase the minimal coverage requirement with that test.
- Test coefficients K1 and K2, used to calculate acceptance values for the test, do not depend on the target interval. K1 and K2 are computed to ensure that no more than a specified proportion of the DDU distribution lies outside the target interval at a specified level of confidence. K1 and K2 do change with tier-1 and tier-2 sample sizes and the required confidence level to which conformance with the quality standard needs to be demonstrated.
- For batches with acceptance probability less than 100% but more than 0%, the probability of acceptance for a given mean and standard deviation increases with sample size, target interval, and maximum allowable tail area.
- The only acknowledged flexibility possible for the FDA-proposed PTI-TOST so far is the ability to choose a sample size; however, sample sizes do not affect the required quality standard (which is a characteristic of the entire population).
- The 2005 PTI-TOST appears generally robust to common types of non-normal distributions (skewed, heavy-tailed, bimodal, and "normal with non-repeating extreme values").
- The life-stage mean requirement has minimal effect on the pass/fail rate because the PTI portion of the test reacts to shifting life means sooner.

When routinely testing production batches, the PTI-TOST is essentially a statistical test that assumes a batch has too high a proportion of delivered doses outside the 80–120% target interval (the null hypothesis). Like for all statistical tests, the observed data evidence must be overwhelmingly against the hypothesized presumption in order to reject the premise and accept the alternative. In order to "prove" a batch is not unfit for use, the delivered dose characteristics of the batch must be far better than the implied quality standard.

A review of several "Product Summary Basis of Approval" available at Drugs@FDA (15) reveals that several companies developing and manufacturing OIPs have considered and attempted to apply a PTI-TOST in recent years. Those

companies had proposed alternative PTI tests to FDA based on their submitted product-specific data but were unable to obtain approval for the modified tests that were different from the 2005 FDA PTI-TOST default and therefore reverted to the 1998 counting test.

In 2009, the International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS) conducted DDU Seminars in order to discuss with member companies industry's experiences with the PTI-TOST. During that discussion, it became clear that the scientific approach for parametric testing was valid and supported by the industry. However, it was also clear that based on individual companies' interactions with FDA, the industry viewed the specific quality standard required by the default PTI-TOST acceptance criteria as too stringent to be implemented in development or even in many commercial products, thus leading to unnecessary rejection of fit-for-purpose batches. By "fit for purpose," we mean batches that would have met the quality requirements of other well-established OIP uniformity standards (solution-based nasal sprays were acknowledged as a possible exception because their delivered doses are well within the default PTI-TOST standards). Furthermore, from direct interactions with FDA, companies had developed a perception that there was no flexibility for modifying the default PTI-TOST quality standard based on product-specific data (either during development or for the final commercial test); therefore, the industry was unlikely to apply the PTI-TOST to OIPs. By contrast, using the counting test allowed product-specific quality standards. Fortunately, a presentation by a group of FDA authors at the 2009 Non-Clinical Biostatistics Conference (16) indicated that one of the defaults responsible for the acceptance criteria "can be modified for products with large variability," signaling possible openness to consider modifications to the default PTI-TOST. More recently, another FDA presenter emphasized at the 2011 IPAC-RS Conference (17) that Quality-by-Design (QbD) principles should in general be used for inhaled products, concluding with a statement "Time is right to apply QbD approaches for efficacy and safety assessment based on product's clinical use and risk," which could be interpreted as another indication of a possible opening for discussing DDU specifications based on each product's data rather than based on a relatively arbitrary default. If those presenters' opinion reflects a movement within the agency, it could represent a welcome next step in the effort to bring advanced science into quality management of inhaled products.

In this article, we contrast the consequences of the 1998 counting test with those of the default PTI-TOST and suggest some ways to develop a DDU control strategy that would be more comprehensive and also more consistent with the existing consensus standards such as ISO, ANSI, and QbD approaches.

To prepare for that discussion, we need first to distinguish between the declared quality level (DQL) and the acceptance rules used to accept or reject a batch. Essentially, DQL sets the minimum characteristics for batches, above which batches are deemed fit for purpose and below which they are deemed not fit for purpose. The PTI-TOST was explicitly constructed to ensure meeting a specified DQL (i.e., "no more than 6.25% of the distribution in either tail outside of 80–120% LC"). In contrast, the counting test, at least historically, was not based on any explicit DQL but only described sample acceptance rules, from which a DQL might be inferred.

DQL is also distinct from other terms used in acceptance sampling, such as rejectable quality limit or level, as well as limiting quality level or standard, which all include the maximum probability of acceptance in their definition. The distinction between DQL and sample acceptance rules is illustrated in Table I.

After presenting the results of comparing the consequences of the PTI-TOST and counting tests, this article discusses a possible transition to, or development of a PTI-TOST for DDU for an OIP, in order to utilize the key scientific advantages of parametric testing such as: (1) better power to discriminate between fit-for-purpose batches and ones that are not and (2) improved ability to make correct decisions with increased sample size. Modifying DQLs and bringing them more in line with the quality of currently approved products or products under development will retain these advantages of parametric testing and would still be driven by the consumer assurance level (i.e., the modifications would be anchored on the lower end of the operating characteristic curves). Alternatively, PTI-TOST could be incorporated in a more advanced approach focused on process control and using existing information rather than relying on end-product isolated-batch (transactional) testing. Such changes could finally open the door to applying PTI-TOST in practice.

RESULTS

The key challenge with the 2005 default PTI-TOST is that the test uses a different and much stricter declared quality level than the 1998 counting test. The strictness comes from a number of the test's features: the relatively narrow target interval (80–120% LC *vs* 75–125% LC for the zero-tolerance requirement in the 1998 guidance or the 65–135% LC in the US pharmacopeia); the chosen default coverage (corresponding to 6.25% maximum allowed proportion in either tail of a DDU distribution); the two one-sided construction, and the fact that it is an equivalence test that seeks to reject the artificial null hypothesis that the batch under consideration is different from similarly produced batches.

The example worked out below illustrates the considerations for developing PTI-TOST criteria that are appropriate for OIPs.

Simulated Case Study of PTI-TOST Application

To demonstrate the different underlying (declared) quality level of the PTI-TOST, simulated batches were created with varying average doses but always with a within batch standard deviation of 6% LC, since it has previously been indicated that a 6% RSD would be fairly typical for an OIP (19). After generating one million doses for a batch assuming a normal distribution, doses were tallied in the 80–120% LC range, below 80% LC, and above 120% LC. The characteristics of the batch are known, including

Table I. Distinction between DQL and Sample Acceptance Rules

	Declared quality level	Acceptance rules
Defines requirements for	Population (a batch)	Sample
Depends on sample size?	No	Yes
Purpose	Sets the minimum acceptable characteristics for batches to be deemed fit for purpose.	Acceptance rules determine if a given batch adheres to the DQL with a desired confidence level based on evaluation of a sample.
Is derived from	Ideally, DQL should be derived from clinical considerations. In practice, DQL have been proposed based on somewhat arbitrary or historical considerations (e.g., by back-calculating from traditionally used acceptance rules).	Acceptance rules should be derived from the pre-set DQL and from the required confidence level for demonstrating compliance of a given batch with the DQL. (Historically, acceptance rules have evolved to manage quality without explicit definition of the underlying DQL).
Specifies	Target interval and the proportion of the population inside or outside that target interval	Sample size, statistical method used, mechanics of the test, accept/reject criteria, etc.
Relation to OC curve	None	Acceptance rules are the algorithm to construct an OC curve, which also take into account distributional assumptions. For a given test/implementation, the DQL is represented by a point on the lower side of the OC curve (e.g., at 5% acceptance probability for a test with 95% confidence).
Cautions	From quality perspective, batches at or above the DQL are all fit-for-purpose, by definition.	Acceptance rules (a test) are designed such that any batch at, or close to the DQL will fail the acceptance criteria with very high probability. Therefore any commercially viable operation must routinely produce batches with quality far above the DQL. This concept underpins the existing consensus standards that have been used in other contexts for many years (18).
Example	No more than 6.25% of doses are outside the 80–120% label claim interval in either tail of the distribution.	To demonstrate the quality standard in the example on the left, with 95% confidence, for Tier 1 Collect 20 doses (from 10 device-metered multi-dose OIP units, one each from the Beginning and End of Unit (BOU and EOU) measurement from each unit). Calculate $\overline{X}_1$ and S_1 as the mean and standard deviation of these N_1 observations. For multi-dose OIPs, calculate means for BOU and EOU ($\overline{X}_{BOU,1}$ and $\overline{X}_{EOU,1}$). The 20 observations must pass the following criteria. $T_{L1} = \overline{X}_1 - K_1 s_1 \geq 80$ with P_{maxTA}=6.25% and α_1=0.0226 where K_1=2.448. $T_{U1} = \overline{X}_1 + K_1 s_1 \leq 120$ with P_{maxTA}=6.25% and α_1=0.0226 where K_1=2.448. $85 \leq \overline{X}_{BOU,1} \leq 115$ $85 \leq \overline{X}_{EOU,1} \leq 115$ (This example is based on (11), which also contains information for tier-2, for a total sample size of 20+40=60)

whether it meets any declared quality level. Samples were taken to apply the counting test and PTI test 10,000 times; 10 in the first tier, followed by additional 20 in the second tier if necessary. This 10+20 sample size was chosen to provide a fair comparison between a PTI-TOST and the 1998 counting test (the complete dose uniformity test in the draft FDA 1998 guidance requires, in addition to the 10+20 dose content uniformity test, a through-container-life test for MDIs and multi-dose DPIs, with the sample size of 9+18 (2,20)). Each dose was taken from a different inhaler in a batch. The subsequent pass rates, percentage of tier-2 sampling, and average sample sizes are summarized in Table II.

From batches with means from 100% LC down to 94% LC, at least 99% of the doses fall in the 80–120% LC interval; well above the PTI-TOST declared quality level (of 87.5%). These batches are fit for purpose and a correspondingly high pass rate should therefore be expected from either test. The pass rates for the two tests, however, begin to diverge early in the comparison. For example, if a batch mean is at 94% LC, PTI-TOST has over a one in four chance of failing it, while the counting test has a 99.3% chance of passing it. The rest of the table clearly illustrates that the PTI-TOST is controlling to a different quality level. For a batch mean of 89% LC, the proportion in the tail exceeds 6.25%, and the PTI-TOST does what it is designed to do: it passes the batch at less than a 5% rate. Figures 2 and 3 illustrate the passing rates for the two tests. The simulation shows that not only will fit-for-purpose batches fail at a higher rate when using the PTI-TOST but more sampling will also be required. The table shows that the PTI-TOST will quite often require tier-2 testing and in general require twice the sampling resources and always have a higher likelihood of rejecting a batch.

Table II also illustrates the implications of being off-target. Each row represents the expected performance of the two tests for single batches, but what are the implications, long term, for a specific product? Our previous work (10,12) suggests that a 4% between-batch standard deviation may be typical, even for a well-controlled commercial product. Examples were explored for a hypothetical but realistic product with the following typical characteristics: normally distributed with an overall average of 98% LC, a between-batch standard deviation of 4%, and a within-batch standard deviation of 6%. This slightly off-target mean (with respect to the label claim) was selected to reflect the reality that targets are set early in the product life cycle. A product/process with these characteristics will produce fit for purpose batches 98–99% of the time. We showed previously (12) that this product would have a non-conformance rate of approximately 14% (86% passing) and implement tier-2 sampling about 64% of time. Meanwhile, the counting test would pass batches approximately 99% of the time and rarely advance to tier-2. The last row in Table II reflects the long-term performance of the two tests for a process with the stated characteristics. Rejecting fit-for-purpose batches and using more sampling resources make it difficult for manufacturers to implement the PTI-TOST.

Table II. 1998 Counting *vs* PTI-TOST Performance Comparison $n \leq 30$

	Batch characteristics (proportion in the indicated interval)			1998 Counting			PTI (10+20)		
Mean	<80% LC	80–120% LC	>120% LC	Pass	Going to tier-2	Average sample size	Pass	Going to Tier 2	Ave. sample size
100	0.04%	99.92%	0.04%	100.0%	0.0%	10.0	99.9%	45.5%	19.1
99	0.08%	99.90%	0.02%	100.0%	0.0%	10.0	99.9%	47.5%	19.5
98	0.13%	99.85%	0.01%	100.0%	0.0%	10.0	99.3%	53.4%	20.7
97	0.23%	99.77%	0.01%	99.9%	0.0%	10.0	97.8%	59.6%	21.9
96	0.39%	99.61%	0.00%	99.8%	0.1%	10.0	94.6%	67.1%	23.4
95	0.61%	99.38%	0.00%	99.5%	0.1%	10.0	86.6%	74.7%	24.9
94	0.97%	99.03%	0.00%	99.3%	0.4%	10.1	73.7%	81.0%	26.2
93	1.53%	98.47%	0.00%	98.5%	0.7%	10.1	56.8%	85.9%	27.2
92	2.30%	97.70%	0.00%	97.4%	1.7%	10.3	37.1%	90.9%	28.2
91	3.38%	96.62%	0.00%	95.4%	3.5%	10.7	21.9%	94.1%	28.8
90	4.81%	95.19%	0.00%	91.4%	5.5%	11.1	10.9%	96.0%	29.2
89	6.69%	93.31%	0.00%	84.7%	9.2%	11.8	4.2%	98.3%	29.7
88	9.11%	90.89%	0.00%	74.4%	13.5%	12.7	1.6%	98.9%	29.8
87	12.17%	87.83%	0.00%	58.5%	16.1%	13.2	0.5%	99.6%	29.9
86	15.80%	84.20%	0.00%	43.1%	15.8%	13.2	0.3%	99.7%	29.9
Long term expected for typical product: mean 98% LC, between batch 4%, within batch 6%				99.0%	0.5%	10.1	86.1%	63.8%	22.8

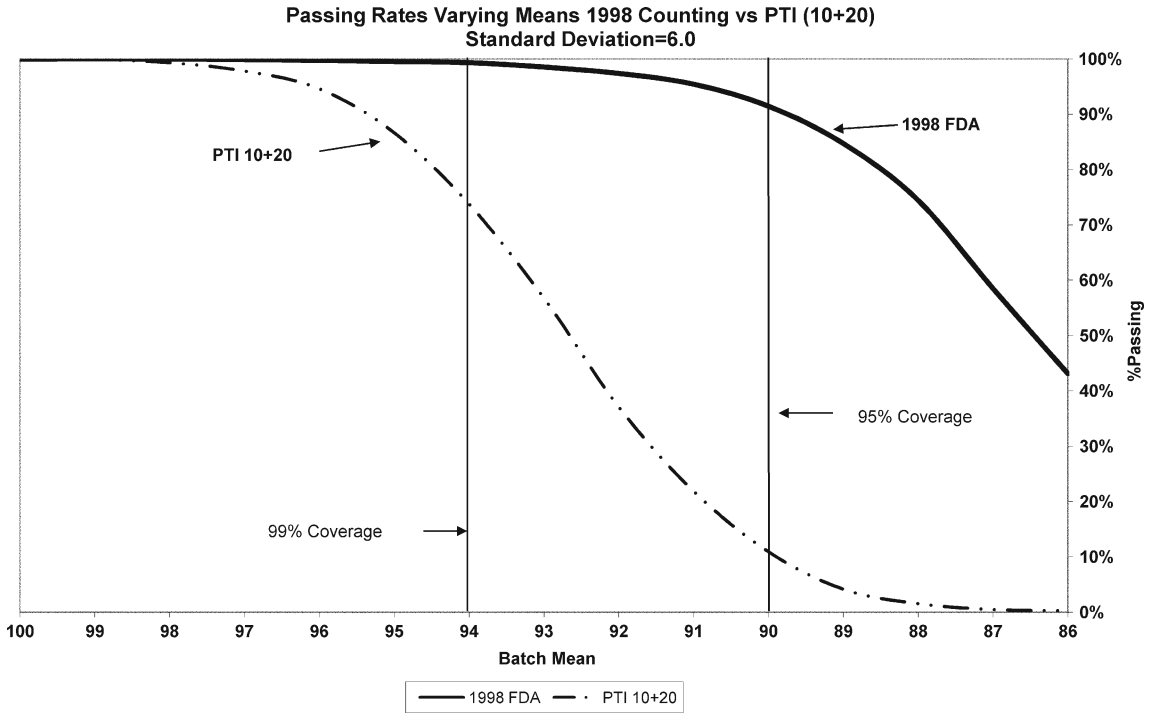

Fig. 3. Passing Rates for Varying Means with the FDA Counting test (1998 draft guidance) and the default PTI-TOST (with sample size 10 + 20)

The previous work (11–13) demonstrated that changing the parameters of the PTI-TOST can influence the corresponding pass rates of the test. For the presented hypothetical realistic product, how much would a 20+40 sampling scheme improve the fit for purpose decision? How about a 30+60 sampling scheme? How much would the maximum allowed proportion in the tail area (P_{maxTA}) need to change from 6.25% to improve the chance of passing for fit-for-purpose batches? Can the 80–120% LC target interval be widened to reduce the high rate of false rejections and still accomplish their purpose? Table III shows the pass rate and relative sample size comparison for a 20+40 PTI-TOST, 30+60 PTI-TOST, P_{maxTA}=12.5%, and 75–125% LC target interval. Pass rates, as expected, are higher for all the suggested modifications of the PTI-TOST. The long-term expected performance for the typical product is added as the last row and offers a concise numerical comparison of the alternatives. The resulting OCCs are illustrated in Fig. 4. All the modified PTI-TOSTs reduce the false rejections of acceptably fit-for-purpose batches. The target-interval adjustment offers a fairly simple change to the default PTI-TOST without changing the K1 and K2 constants (mentioned in Table I for one specific example).

The default PTI-TOST will assure that only batches with a much higher proportion of doses than 87.5% within the 80–120% LC range are passed. The consequences of this change in quality will likely increase the sampling effort at least two-fold, and many more batches that are truly fit-for-purpose will be rejected, benefiting no one. By contrast, product-specific modifications to the PTI-TOST could reduce the false rejection rate while still protecting against falsely accepting a truly unfit for purpose batch.

DISCUSSION

PTI-TOST or Counting Test?

In general, industry, regulatory agencies, and pharmacopeias are moving towards parametric tests for quality control because such tests represent a more statistically sound approach and allow hypothesis testing of a DQL. However, a direct-coverage (not TOST) approach is usually used. Among advantages of a parametric test, including a PTI-TOST, compared to a counting test are the following:

- PTI test can more effectively deal with non-repeating extreme values (“flyers”).
- There are fewer random failures during extended testing (e.g., process validation).
- Unlike counting test, PTI test rewards rather than penalizes more testing and hence more information about the product. This may be important for validation and stability studies or for post-approval changes.

Disadvantages of a PTI-TOST include:

- The test is less used/less familiar to industry and regulators of OIPs.
- Implementation requires thorough knowledge of the product and process variability (hence, upfront investment in extensive testing).

Table III. 1998 Counting *versus* Modified PTI-TOST Performance Comparison

	1998 Counting		PTI-TOST (10+20) P_{maxTA}=6.25 80–120%		PTI-TOST (20+40) P_{maxTA}=6.25 80–120%		PTI-TOST (30+60) P_{maxTA}=6.25 80–120%		PTI-TOST (10+20) P_{maxTA}=12.5 80–120%		PTI-TOST (10+20) P_{maxTA}=6.25 75–125%	
	Pass	*N*	Pass	*N*	Pass	*N*	Pass	*N*	Pass	*N*	Pass	*N*
100	100.0%	10.0	99.9%	19.1	100.0%	21.7	100.0%	30.1	100.0%	12.7	100.0%	12.6
99	100.0%	10.0	99.9%	19.5	100.0%	22.2	100.0%	30.3	100.0%	12.9	100.0%	12.7
98	100.0%	10.0	99.3%	20.7	100.0%	24.1	100.0%	30.6	100.0%	13.7	100.0%	13.3
97	99.9%	10.0	97.8%	21.9	100.0%	27.1	100.0%	32.1	100.0%	15.0	100.0%	14.2
96	99.8%	10.0	94.6%	23.4	100.0%	31.5	100.0%	35.5	100.0%	16.7	100.0%	15.3
95	99.5%	10.0	86.6%	24.9	99.5%	36.7	100.0%	41.9	99.8%	18.6	100.0%	16.9
94	99.3%	10.1	73.7%	26.2	97.0%	42.5	99.7%	51.3	98.9%	20.5	99.9%	18.4
93	98.5%	10.1	56.8%	27.2	87.1%	47.9	96.9%	62.3	95.9%	22.7	99.4%	20.0
92	97.4%	10.3	37.1%	28.2	64.2%	52.9	82.0%	73.4	88.8%	24.4	97.7%	21.9
91	95.4%	10.7	21.9%	28.8	35.4%	56.0	49.0%	81.6	73.0%	26.2	94.4%	23.3
90	91.4%	11.1	10.9%	29.2	14.8%	58.0	18.0%	86.4	53.2%	27.4	86.6%	24.9
89	84.7%	11.8	4.2%	29.7	3.7%	59.3	3.5%	88.9	31.9%	28.4	73.2%	26.1
88	74.4%	12.7	1.6%	29.8	0.9%	59.7	0.4%	89.8	15.0%	29.0	56.2%	27.3
87	58.5%	13.2	0.5%	29.9	0.2%	59.9	0.1%	90.0	5.3%	29.5	37.5%	28.1
86	43.1%	13.2	0.3%	29.9	0.1%	60.0	0.0%	90.0	1.9%	29.8	21.3%	28.8
Long-term typical product	99.0%	10.1	86.1%	22.8	93.2%	31.7	94.9%	40.4	96.6%	16.7	98.8%	15.6

N average sample size

– It is more complex: the effect of changing a parameter (e.g., test coefficients K's) is less obvious than changing a criterion in the counting test.

These disadvantages might be among the reasons for the observed reluctance on the part of regulators to adjust or modify the default PTI-TOST.

By contrast, counting tests for control of DDU in OIPs are more familiar to industry and regulators, and regulators therefore may be more amenable to adapting the requirements to develop more appropriate product-specific specifications. The main disadvantages of the current counting DDU test are: (1) the failure rate increases with sample size regardless of product quality due to the zero tolerance component; (2) there is no explicit quality standard for the batch. Nevertheless, there is no indication that current commercial products controlled by counting tests are in any way deficient in safety or efficacy.

Considerations for a Practical PTI Test

Faced with the impracticality of the current default DQL (which is the key "challenge" in this article's title), and yet recognizing the inherent advantages of an appropriately configured PTI test, one may consider three types of solutions for moving forward ("opportunities"):

1. Companies develop and are allowed to use a product specific DQL.
2. Agency sets a different default standard DQL for all OIPs (e.g., in a guidance).
3. Companies develop and implement a well-defined acceptance sampling system based on the principles of existing consensus standards to serve as part of the DDU control strategy.

These three options are discussed in more detail below.

Companies Develop and Use a Product-Specific DQL

For a commercial product, DDU data are available from a large number of batches (e.g., 10–20 or more) representative of the material, process, and testing variability. This amount of data provides information needed for justifying an alternative to the default PTI-TOST, if necessary. These data should be used to understand any deviations from normality associated with container-life effects or non-repeating extreme values. It is also advisable to assess the analytical method variability *versus* the variability of the product itself, both of which contribute to the measured within-inhaler, within-batch, and between-batch variability. If such information is available for a development product, it could be used in the initial submission to justify a modification to the FDA default PTI-TOST criteria; otherwise, these specifications would have to be the subject of a post-approval supplement.

If the product DDU distribution is bimodal (e.g., due to through-life trends, as in an MDI where the headspace and consequently API concentration increase as the canister is emptied), then two separate PTI-TOSTs might be needed, especially if the criteria allow very little

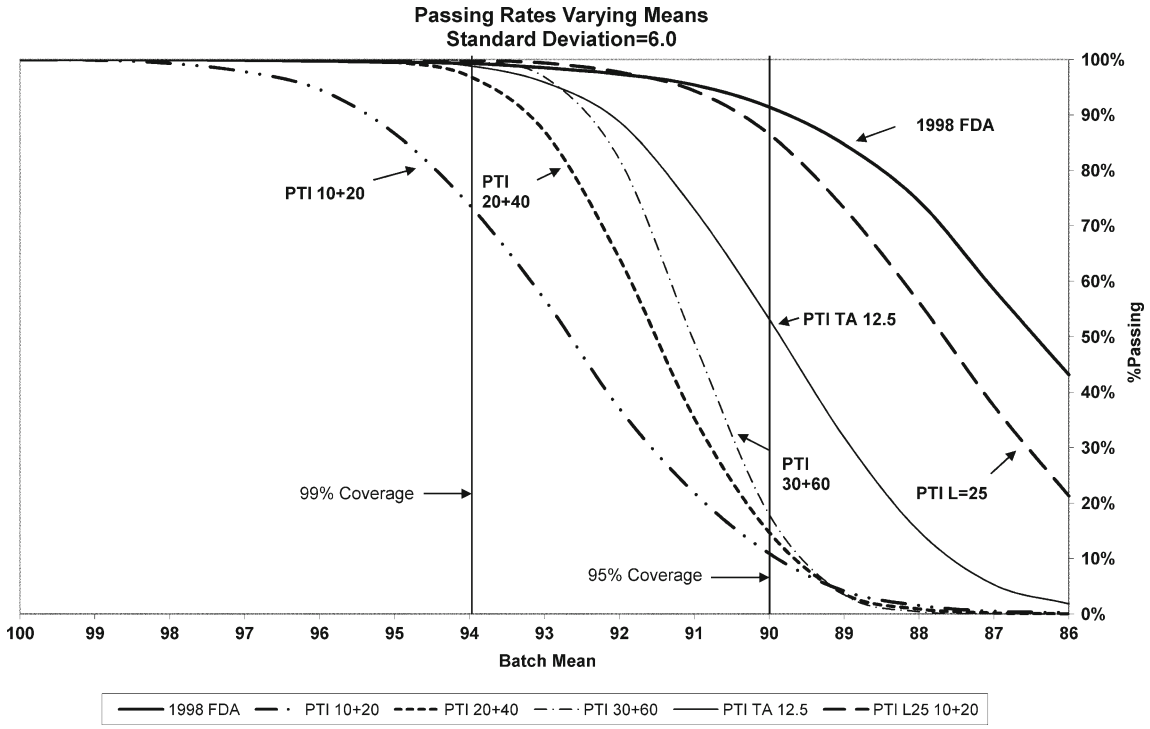

Fig. 4. Passing Rates for Varying Means with the FDA Counting test (1998 draft guidance) and PTI-TOST modifications "PTI 12.5" refers to the default PTI-TOST except that $P_{\max TA}=12.5\%$ (sample size 10+20). "PTI L25" is the default PTI-TOST except that the target interval is 75=125% (sample size 10+20). The other *three lines* labeled PTI refer to the default PTI-TOST with the sample sizes as indicated

variation in the mean. Alternatively, if a single PTI-TOST is preferred, such a test should have a target mean set in the middle between the two averages (beginning-of-unit and end-of unit content), as well as a sufficient allowance for the overall variability.

Changing the target interval might be more straightforward than other aspects of the PTI-TOST because K values would not change, whereas changing the maximum allowed tail proportion would require different K values in the formulas for PTI-TOST. Once the quality standard is set, changing the sample size would further control a product's failure rate. Caution: it is not advisable to use the range of the observed data to set the target interval because, in the PTI approach, 95% of the batches with quality at that DQL will fail. Thus, the target interval must be substantially wider than the range of the observed data, due to the nature of tolerance intervals. To guide the development of an alternate DQL, OCCs might be helpful. Some guidance was provided in the previous articles (11–13) and a recent presentation (21). To develop product-specific DQL, one must look at the population of batches that are fit-for-purpose and design a test that declares such batches acceptable at least 99.99% of the time.

In principle, specifically designed dose-ranging studies that show no change in response over a certain range might be helpful to justify a wider target interval. However, ethical considerations (e.g., institutional review board approval) and the additional resources for such studies would likely present insurmountable challenges. To set the target interval and other criteria (e.g., maximum allowed proportion in the tails) without clinical studies exploring a variety of DDU distributions, a company may attempt to use a combination of business objectives and common sense.

A company may also conduct simulations similar to those presented in this paper but based on their product's characteristics, showing the failure rates for different versions of the PTI test.

In any of these efforts, if a PTI test is used (in any implementation), it is critical to *not* set the quality target (DQL) at the boundary of the process data, because PTI tests are designed to reject with high probability the quality identified as DQL.

An Alternative Default Standard DQL

For a development product with little historical data, a practical solution would be to use a less restrictive declared quality limit. There is a precedent for using less restrictive acceptance criteria in the IND phase of a product's lifecycle because the final dose, drug product formulation, production method, and analytical methods have not been established, and the range of doses is typically multiples of the lowest strength. A PTI test that would have OC curves similar to those of the EP counting test (6) would be appropriate in early development. Such a test would require acceptance criteria on the mean (e.g., per the joint Canadian/European guidance (7)) and separate acceptance criteria on variability relative to the mean (rather than to the label claim), possibly

with widened acceptance limits. This way, manufacturers could realize the benefits of parametric testing even for the clinical trial material (better understanding of the batch quality, possibility of increased sample size without penalty, etc.). When all aspects of the product, process, methods, as well as chemistry, manufacturing and controls are well established, the manufacturer would transition to the tests, and specifications more commonly applied to commercial products.

Alternatively, a single applicable standard could be possible if technological capabilities of the majority of approved (and hence safe and efficacious) OIPs are used to derive such a standard and if consideration is given to business aspects. For example, to be economically viable, acceptance rates should be at least 99.5% for fit-for-purpose batches of approved products with established safety and efficacy and for batches used in pivotal clinical trials. Such a standard could be established by changing some aspects of the current default PTI-TOST, e.g., target interval and/or K's and/or confidence levels, and/or the TOST construction *versus* the classical coverage-based construction. As mentioned above, the DQL should not be set at the current limits of process capability, because any PTI tests will reject that target DQL quality with high probability.

Setting a more generous test as a default has a precedent because the Agency allows relatively wider limits for some other dosage forms that are inherently more capable and less variable, such as tablets. For a distribution of tablets, typical RSDs are 1–2%, and the 85–115% target interval therefore provides adequate flexibility even with a PTI-TOST. The large difference between the width of the target interval and the width of the data distribution is needed because PTI tests are designed to routinely reject the quality declared as target.

Companies Develop and Implement throughout the Product-Lifecycle, a Well-Defined Acceptance Sampling System Based on the Principles of Existing Consensus Standards to Serve as Part of the DDU Control Strategy

A product control strategy is a "comprehensive plan for ensuring that the final product meets critical requirements and therefore, the needs of the patient" (22). As described in ICH Q8(R2) (23), control strategy approaches can range from minimalistic approaches that rely heavily on intermediate and end-product testing to more enhanced QbD approaches where the "quality controls are shifted upstream" with real-time release and "reduced end-product testing" possible. Any testing (i.e., end-product, in-process, real-time release) that uses information from a sample in conjunction with acceptance rules to accept or reject manufactured product is an acceptance sampling test. The acceptance sampling plans provided in consensus standards such as, ISO 3951, ISO 2859 Series, BS 6002, ANSI/ASQ Z1.9, and ISO 7966 were designed to provide appropriate discriminatory power for rejecting a lot with unacceptable dose uniformity characteristics by assessing the individual lot in isolation or by assessing the individual lot in respect to the performance of the relevant series of lots from a process (lot-by-lot acceptance testing) (24) (in this article, we will use "lot" and "batch" interchangeably, because the former term is used widely in consensus-standards literature, while the latter term is typically used in the pharmaceutical industry).

Typically, lot-by-lot acceptance sampling is constructed to have at least a 95% probability of accepting batches from a *process* whose true quality (i.e., average process characteristics) is at or less than a pre-defined acceptance quality limit (AQL). Isolated lot acceptance sampling is constructed to have at least a 95% probability of rejecting any *batch* whose true quality (i.e., batch characteristics) is at or above a pre-defined limiting quality limit. The inspection process is considered to be part of an acceptance sampling scheme when lot-by-lot testing is performed with strict adherence to additional rules for switching to other sampling plans with more consumer protection (tightened acceptance sampling criteria or criteria for discontinuation of production until corrective action is in place) if deterioration in quality occurs. Switching to a sampling plan with less producer risk is allowed if the demonstrated process quality is exceptionally better than the AQL.

Counting tests, direct coverage parametric tolerance interval tests, and PTI-TOST tests are all acceptance sampling plans (i.e., tests) that can be implemented for use as part of the OINDP control strategy for DDU. All acceptance sampling testing currently conducted for DDU is applied as isolated lot acceptance testing and therefore is transactional in nature. Transactional testing implies that only the information obtained from the sample is used to infer whether or not a batch meets its critical requirements (i.e., does the batch meet the DQL at which the DDU characteristic is fit-for-patient purpose?). Transactional testing, or isolated-lot testing, does not allow for the use of prior process knowledge or the appropriate use of relevant historical process data. As inferred in the consensus standards, the use of sampling schemes and systems which mandate the use of switching rules provides the most benefit to the patient and manufactures by accumulating relevant process performance knowledge when making batch acceptance decisions—because all relevant information is used when making a decision about a sampling result.

The PTI-TOST was explicitly constructed to ensure meeting a specified DQL (i.e., "no more than 6.25% of the distribution in either tail outside of 80–120% LC") by essentially performing an equivalence hypothesis test with at least 95% confidence. Equivalence tests are designed with a null hypothesis that assumes the batch characteristics do not meet the DQL (i.e., are different) while seeking to demonstrate by rejecting the null hypothesis, that the batch characteristics meet the DQL (i.e., are equivalent). The PTI-TOST construction automatically sets the limiting quality level to the DQL and implies at least a 95% false reject rate for product defined as fit-for-purpose. As illustrated via the case study, the false reject rate is extremely high, even for batches that far exceed the DQL. For example, batches with no more than 1% of the distribution in either tail outside the 80–120% LC are rejected with greater than 20% probability. The sampling plans described in the consensus standards such

Table IV. Example of DDU Acceptance Sampling System

Type of acceptance sampling plan	Statistical objective of acceptance sampling plan	Sampling test	Possible lifecycle use
Isolated lot acceptance sampling	Individually demonstrate with 95% confidence that the true DDU properties of each batch do not exceed the DQL.	PTI-TOST	Development Validation Investigation
Lot-by-lot acceptance sampling test on a pre-specified number of batches. Product batches not eligible for release until data from all batches has been assessed collectively.	Assess each batch individually using criteria that minimize the false rejection rate of each individual batch that meets the DQL requirements. Demonstrate series of lots are from a reasonably robust process. Assess the process by assessing the batches collectively to provide a high level of consumer protection against manufacturing batches that do not meet the DQL.	Apply Variables Sampling Plan with Unknown Standard Deviation for Lot-by-Lot to individual Lots. Apply PTI-TOST to combined lots for process acceptance.	Development (Continuous Verification Validation)
Lot-by-lot acceptance sampling	Assess each batch individually using criteria that minimizes the false rejection rate of each individual batch that meets the DQL requirements. Trend rules would minimize false acceptance rate of batches not fit for purpose.	Variables Sampling Plan with known standard deviation. PTI-TOST with a 1% false rejection rate for the process average. Trending with rules to detect process changes. Acceptance Control Charts to accept lots on a routine basis. ISO 7966	Process control

as the variables sampling plans, ISO 3951, have a similar construction to the PTI-TOST in the sense that they control for the percentage of product in the tails of the distribution; however, they do not do it using an equivalence hypothesis structure. Equivalence tests are more appropriate in a bioequivalence context, when a new product is compared to an existing product.

Consensus standards recommend implementation of acceptance sampling schemes for routine release in order to maximize consumer protection (avoid false acceptance of batches not fit for purpose) while minimizing producer risk (avoid false rejection of batches fit-for-purpose) for routine end product testing. Consensus standards do not recommend application of transactional acceptance sampling plans, (i.e., isolated-lot acceptance testing) to a continuing series of lots from a consistent well-defined process. Transactional acceptance sampling plans are to be applied to isolated lots where very little process knowledge exists, where suspected problems have arisen or where atypical manufacturing events have occurred. Transactional or isolated-lot acceptance sampling plans are not process-focused. As stated in Military Standard 1916, the emphasis is on the process where the ultimate goal is having "effective product and process design and control activities" that have demonstrated consistent manufacture of fit-for-purpose product. Therefore, the emphasis of an effective control strategy should be on the process not just on the acceptance of a single lot (batch).

An acceptance sampling system that integrates the PTI-TOST construction with the principles of acceptance sampling plans and switching rules into the product lifecycle control strategy for OIPs promotes process knowledge and understanding in the dispositioning of batches. A high-level proposal on how to integrate the PTI-TOST with the existing, well-developed consensus standards is provided in Table IV.

CONCLUSION

Both the parametric tolerance interval tests and counting tests can serve as suitable methods for control of dose uniformity. An analysis of the consequences of applying the current default PTI-TOST demonstrates that a substantial proportion of fit-for-purpose batches are rejected and, therefore, modified approaches need to be considered (e.g., product-specific DDU standards, a different default standard suitable for the majority of OIPs, or integration of the PTI-TOST with a continuous verification control strategy). If the challenges of the current PTI-TOST can be overcome, then the inherent advantages of a parametric approach can be realized. For best efficiency, approaches should be considered with more focus on process control and using existing information to release batches and relying less on transactional end-product testing.

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APPENDIX. UNIFORMITY TESTS USED IN COMPARISONS

For an appropriate comparison of operating characteristic curves, the same sample sizes (10+20, in the first and second tier) were used in this article (the complete dose uniformity test in the draft FDA 1998 guidance requires, in addition, a through-container-life test for MDIs and multi-dose DPIs, with the sample size of 9+18, which results in further tightening of the overall dose uniformity test for these multi-dose products (2,20)). Each dose is taken from a different inhaler.

Table V. Uniformity Tests Used in Comparisons

	1998 Guidance (2)	USP <601> (1)	EU (6,7)	Default PTI-TOST (4) 10+20
	"%" is relative to label claim	"%" is relative to label claim	"%" is relative to sample average except where noted otherwise	"%" is relative to label claim
Tier 1 Sample Size	10	10	10	10
Passing Criteria Tier 1	≥9 within 80–120% (a) 0 outside 75–125% (b) 85%≤$\overline{X}$ ≤115% (c)	≥9 within 75–125% (a′) 0 outside 65–135% (b′)	≥9 within 75–125% (a″) 0 outside 65–135% (b″) 85%≤$\overline{X}$ ≤115% LC (c″)	$\overline{X}$ −3.12 s≥80 AND $\overline{X}$ +3.12 s≤120 85%≤$\overline{X}$ ≤115%
Fail in Tier 1	>3 outside 80–120% 1 or more outside 75–125% $\overline{X}$ <85% or $\overline{X}$ >115%	>3 outside 75–125% 1 or more outside 65–135%	>3 outside 75–125% 1 or more outside 65–135% $\overline{X}$ <85% or $\overline{X}$ >115% LC	
Conditions for Going to Tier 2	If conditions (b, c) are met AND ≥7 within 80–120%, go to tier-2 Otherwise, test failed	If condition (b′) is met AND ≥7 within 75–125%, go to tier-2 Otherwise, test failed	If condition (b″) is met AND ≥7 within 75–125%, go to tier-2 Otherwise, test failed	If tier 1 is not passed, go to tier-2
Tier 2 Sample Size	+20 (Total 30)	+20 (Total 30)	+20 (Total 30)	+20 (Total 30)
Passing Criteria Tier 2	≥27 within 80–120% 0 outside 75–125% 85%≤$\overline{X}$ ≤115%	≥27 within 75–125% 0 outside 65–135%	≥27 within 75–125% 0 outside 65–135% 85%≤$\overline{X}$ ≤115% LC	$\overline{X}$ −2.16 s≥80 AND $\overline{X}$ +2.16 s≤120 85%≤$\overline{X}$ ≤115%
Fail in Tier 2	>3 outside 80–120% 1 or more outside 75–125% $\overline{X}$ <85% or $\overline{X}$ > 115%	>3 outside 75–125% 1 or more outside 65–135%	>3 outside 75–125% 1 or more outside 65–135% $\overline{X}$ < 85% or $\overline{X}$ > 115% LC	$\overline{X}$ −2.16 s<80 OR $\overline{X}$ +2.16 s>120 $\overline{X}$ < 85% or $\overline{X}$ > 115%

$\overline{X}$ sample average, s sample standard deviation, LC label claim

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