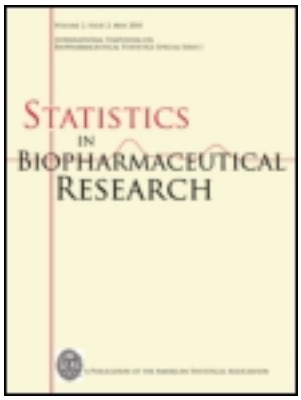

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Evaluating Two PTI Test Procedures for Control of Delivered Dose Uniformity for Aerosol Products

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Evaluating Two PTI Test Procedures for Control of Delivered Dose Uniformity for Aerosol Products

Yan LAN, C. Thomas LIN, and Hongyuan CAO

IPAC-RS developed a two-sided PTI test procedure in 2001 in response to the FDA draft guidance tests (FDA/CDER 1998; FDA/CDER 1999) for delivered dose uniformity for aerosol products. Subsequently, FDA proposed a two one-sided PTI test procedure (2005) to replace the original guidance test. The latter procedure was recently characterized and evaluated by Novick et al. (2009). The two procedures control product quality using different algorithms. In this article we evaluate the performance of these two procedures by simulations for different scenarios of parameter settings (mean, standard deviation, and sample size). Operating characteristic curves and contour plots for acceptance (or rejection) regions are generated to describe the consumer risk and the producer risk under each scenario. We apply the two procedures to batches produced under realistic simulated production situations and to mixtures of normally distributed DDU (delivered dose uniformity) data from simulated multidose products to illustrate the utility of these methods and assess their performance for control of delivered dose uniformity. Under the same parameter setting, the FDA two one-sided PTI procedure is consistently more conservative than the IPAC-RS two-sided PTI procedure. However, when dealing with products with low quality or products with contamination, the FDA PTI test exhibits a more desirable performance characteristic than the IPAC-RS PTI test. We found that the performance of the FDA two one-sided PTI test can be markedly improved by using the exact K value of the tolerance factor used in the construction of its PTI test.

Key Words: Consumer risk; Contour plot; Operating characteristic curve; Parametric tolerance interval; Producer risk.

1. Introduction

A two-sided parametric tolerance interval (PTI) test procedure developed by the International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS; IPAC-RS 2001), referred to in this article as IPAC-RS two-sided PTI test procedure, was proposed in 2001 as a replacement for the unit dose uniformity tests (between container and through container life) recommended by the U.S. Food and Drug Administration (FDA) in draft Guidances for Industry (FDA/CDER 1998; FDA/CDER 1999).

The FDA guidance test is a nonparametric attribute (counting) test with preset limits beyond which no individual sample result is allowed (i.e., "zero tolerance" limits) for control of delivered dose uniformity (DDU) for orally inhaled and nasal drug products (OINDP). In contrast, the two-sided PTI test procedure controls product quality through controlling the coverage of batches within the target interval. It processes information obtained from samples more efficiently than the FDA guidance test and thereby offers improved protection in con-

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trolling levels of both consumer and producer risks.

Subsequently, in 2005, FDA proposed a two one-sided PTI test procedure (referred to in this article as the FDA TOST PTI test procedure) to replace the previous guidance test. This procedure was recently characterized and evaluated by IPAC-RS (Novick et al. 2009). The TOST PTI test procedure controls the quality through controlling the maximum allowable tail area of the batch distribution outside the target interval, which is different from that of the IPAC-RS two-sided PTI test procedure.

Since IPAC-RS two-sided PTI test procedure and FDA TOST PTI test procedure are based on different hypotheses and other criteria (e.g., coverage of distribution vs. tail area of distribution), we focus on comparing the operating characteristics of these two testing algorithms instead of comparing traditional statistical test of hypotheses such as Type I error and power.

We compare the performance of these two parametric tolerance interval test procedures by simulations for different scenarios of parameter settings. Operating characteristic curves and contour plots for acceptance (or rejection) regions are generated to describe the consumer risk and the producer risk under each scenario. We apply the two procedures to batches produced under realistic simulated production situations and to mixtures of normally distributed DDU (delivered dose uniformity) data from simulated multidose products to illustrate the utility of these methods and assess their performance for control of delivered dose uniformity. We also evaluate the impact of using the exact K value of the tolerance factor in the FDA TOST PTI test on its performance.

The remainder of the article is organized as follows. In Section 2, we describe the concepts of tolerance interval test and the acceptance criteria for both procedures. In Section 3, we present the simulation plans for both single-dose and multidose products and the corresponding results. Finally, some concluding remarks are given in Section 4.

2. Parametric Tolerance Interval Tests

A tolerance interval is constructed to describe a specified proportion (i.e., coverage) of a population with a stated confidence level. The structure of a tolerance interval is similar to that of a confidence interval. All tolerance interval related discussions throughout this article are under the normality assumption. Let $X_1,\ldots,X_n$ be random samples from $N(\mu,\sigma^2)$ and write $\mathbf{X}=(X_1,X_2,\ldots,X_n)$. The coverage and confidence level are denoted by p and $1-\alpha$, respectively.

A $(p,1-\alpha)$ two-sided normal tolerance interval $(L(\mathbf{X}),U(\mathbf{X}))$ satisfies the condition

$$P_{\mathbf{X}}\{P_X(L(\mathbf{X})\le X\le U(\mathbf{X})|\mathbf{X})\ge p\}=1-\alpha.$$

We usually define $L(\mathbf{X})=\overline{X}-ks$ and $U(\mathbf{X})=\overline{X}+ks$, where $\overline{X}$ is the sample mean of $\mathbf{X}$ and s is the sample standard deviation. The tolerance factor k depends on the coverage p, the confidence level $1-\alpha$, and the sample size n. Referring to Krishnamoorthy and Mathew (2009), the exact tolerance factor can be obtained from various sources or can be computed using a computer. Krishnamoorthy and Mathew pointed out a simple and satisfactory approximation for k. However, in the IPAC-RS two-sided PTI procedure, the tolerance factor k is determined differently, which will be discussed later.

Similarly, a one-sided normal tolerance interval of the form $(-\infty,U(\mathbf{X}))$ is constructed such that

$$P_{\mathbf{X}}\{P_X(X\le U(\mathbf{X})|\mathbf{X})\ge p\}=1-\alpha,$$

where $U(\mathbf{X})=\overline{X}+k^*s$. And the one-sided tolerance factor $k^*=\sqrt{1/n}T^{-1}_{n-1,1-\alpha}(\sqrt{n}Z_p)$, where Z_p is the pth quantile of the standard normal distribution and $T^{-1}_{n-1,1-\alpha}(\sqrt{n}Z_p)$ is the $(1-\alpha)$th quantile of a noncentral T distribution with $n-1$ degrees of freedom and noncentrality parameter $\sqrt{n}Z_p$. We write the one-sided tolerance interval of the form $(L(\mathbf{X}),\infty)$ as $(\overline{X}-k^*s,\infty)$.

In a two-sided PTI test procedure, the constructed tolerance limits (denoted as $(\hat{L},\hat{U})$) from the sample of an acceptable batch should be within the target interval (denoted as (LL,UL)). Otherwise, the batch should be rejected if either tolerance limit is outside of the target interval. Figure 1 illustrates the general idea of the PTI test by a two-sided procedure. Both IPAC-RS two-sided and FDA TOST PTI test procedures use a two-tiered approach. N_1 observations are collected at tier 1. If not accepted, additional N_2 observations are collected and all N_1+N_2 observations are used to construct the tolerance limits at tier 2.

2.1 IPAC-RS Two-Sided PTI Test Procedure

For the IPAC-RS two-sided PTI test procedure, an 85% coverage of the 75–125% delivered dose label claim (LC) target interval defines the minimum quality standard, below which level there is a low probability of acceptance ($<5\%$). With high confidence (95%), an accepted batch will have 85% or more of the doses within the specified target interval. Let s_1 be the overall sample standard deviation, m_1 be the overall sample mean of N_1 doses, and $m_{\mathrm{LS},1}$ be the life stage sample mean for each of the life stages tested in tier 1. The acceptance criteria for multi-dose products at tier 1 are:

- The overall sample standard deviation cannot exceed a predetermined, sample-size dependent, maximum value, that is, $s_1\le 25\%\ \mathrm{LC}f/k_1$;
- The acceptance value $|100\%\mathrm{LC}-m_1|+k_1s_1$ cannot exceed a fixed limit, that is, $|100\%\mathrm{LC}-m_1|+$

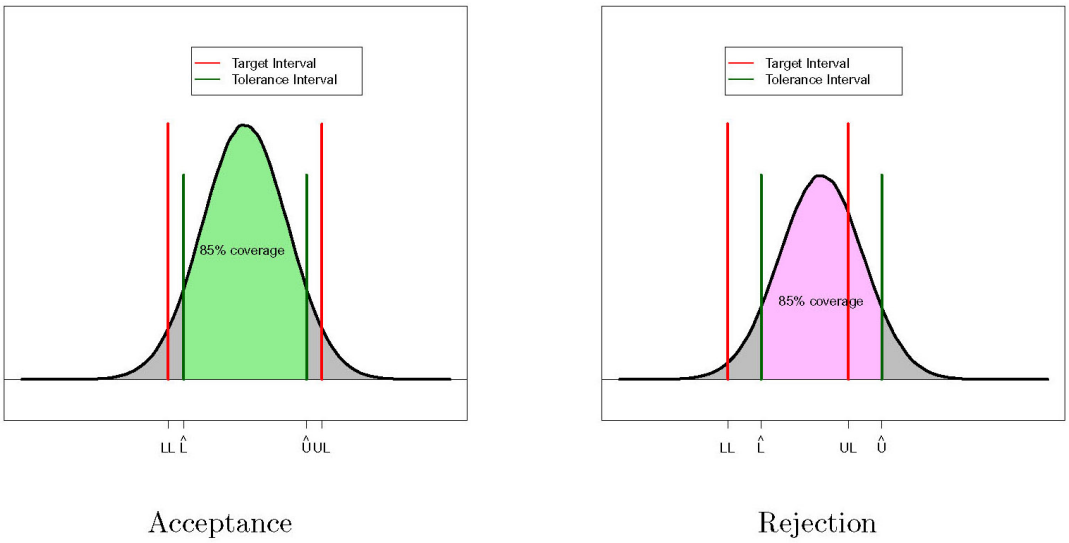


Figure 1. Tolerance limits of accepted batch and rejected batch from a two-sided PTI test.

$k_1 s_1 \leq 25\%\text{LC}$;

- The sample mean of each tested life-stage is within $(100 \pm 15)\%$ LC, that is, $|100\%\text{LC} - m_{\text{LS},1}| \leq 15\%$ LC.

If not accepted, additional N_2 doses are collected and the batch will be accepted if:

- $s_2 \leq 25\%\ \text{LC} f/k_2$;
- $|100\%\text{LC} - m_2| + k_2 s_2 \leq 25\%$ LC;
- $|100\%\text{LC} - m_{LS,2}| \leq 15\%$ LC;

where s_2 is the overall sample standard deviation of $N_1 + N_2$ doses, m_2 is the overall sample mean of $N_1 + N_2$ doses and $m_{\text{LS},2}$ is the life stage sample mean (including samples from both tier 1 and tier 2) for each life-stage. The coefficients (k_1, k_2, f) are varied with the sample size to ensure that the level of consumer risk is not greater than 5%. IPAC-RS (2001) provided an algorithm and SAS code to calculate these coefficients for different sample sizes via simulations.

2.2 FDA TOST PTI Test Procedure

As mentioned earlier, FDA TOST PTI test procedure controls the quality through controlling the maximum allowable tail area ($P_{\max_{\text{TA}}}$) of the batch distribution outside the target interval. Eighty to 120% of the label claim has been defined as the target interval for this procedure. Two one-sided tolerance limits (which are directly related to the tail areas of the distribution), lower limit and upper limit, with $(1-\alpha)100\%$ confidence, are constructed and compared to the lower and upper target limits, respectively. If both one-sided tolerance limits are inside the target interval, the batch passes the test. In a complete two-tiered FDA TOST PTI test procedure, following the same notation as used in the IPAC-RS two-sided PTI test procedure, the batch is accepted for multidose products at tier 1 if

- $m_1 - K_1 s_1 \geq 80\%$ LC with $P_{\max_{\text{TA}}} = 0.0625$;
- $m_1 + K_1 s_1 \leq 120\%$ LC with $P_{\max_{\text{TA}}} = 0.0625$;
- $|100\%\text{LC} - m_{\text{LS},1}| \leq 15\%$ LC.

Similar acceptance criteria are defined in the second tier test if the batch is not accepted at the first tier:

- $m_2 - K_2 s_2 \geq 80\%$ LC with $P_{\max_{\text{TA}}} = 0.0625$;
- $m_2 + K_2 s_2 \leq 120\%$ LC with $P_{\max_{\text{TA}}} = 0.0625$;
- $|100\%\text{LC} - m_{\text{LS},2}| \leq 15\%$ LC,

where

$$K_1 = \sqrt{1/N_1}\, T^{-1}_{N_1-1,1-\alpha_1}(\sqrt{N_1} Z_{P_{\max_{\text{TA}}}}),$$

and

$$K_2 = \sqrt{1/(N_1+N_2)}\, T^{-1}_{N_1+N_2-1,1-\alpha_2}(\sqrt{N_1+N_2} Z_{P_{\max_{\text{TA}}}}).$$

The significance levels α_1 and α_2 for tier 1 and tier 2, respectively, are chosen by the Lan and DeMets (1983) approach using the Pocock-alpha spending function.

Table 1. Some coefficients used in the simulation studies

	FDA TOST PTI procedure		IPAC-RS two-sided PTI procedure		
Sample size (N_1/N_2)	α_1	α_2	k_1	k_2	f
10/20	0.0226	0.034	2.09	1.59	0.839
20/40	0.0226	0.034	1.67	1.40	0.805
30/60	0.0226	0.034	1.52	1.32	0.787
30/30	0.0309	0.0296	1.54	1.38	0.800

3. Evaluation of Two PTI Test Procedures

To evaluate the performance of these two PTI test procedures, we conducted simulation studies with different parameter settings. The target (delivered dose label claim) of the simulated products is set as 100. We made a small modification to the FDA TOST PTI test procedure by setting its target interval the same as that of the IPAC-RS two-sided PTI test procedure, that is, [75%LC, 125%LC]. For multidose products, values are taken at the beginning and the end of the canister life. We assume batch mean (m) on-target or off-target (from 1% off target to 15% off target by an increment of 1%). The within-batch standard deviation s changes from 1% to 20% of LC. Four sets of sample size (N_1/N_2) combinations were studied: 10/20, 20/40, 30/30, and 30/60. For the simulation studies, the coefficients k_1, k_2, and f generated from the algorithm provided by IPAC-RS and values of α_1 and α_2 for FDA TOST PTI test procedure are listed in Table 1. We follow Hauck and Shaikh (2001) to get the values of α_1 and α_2 for $N_1/N_2 = 30/30$.

3.1 Simulation Plans

Simulate multidose products

To simulate the multidose products for each parameter setting $\{m, s, N_1, N_2\}$:

1. Select a specific batch L from a normal distribution with a batch mean (m) and batch-to-batch standard deviation (4% LC) to get a true mean for this batch, denoted as μ.

2. Generate $N_1/2$ cans from a normal distribution with mean μ and standard deviation s to obtain N_1 observations. The simulation assumes no change in the performance between the beginning and the end of the canister life.

3. Construct two-sided or two one-sided tolerance intervals.

4. If the tolerance intervals, the sample standard deviation (for IPAC-RS two-sided PTI procedure), and the sample mean of each life stage pass the test under tier 1 criteria, then this run will be recorded as "succeed at tier 1".

5. Otherwise, generate additional N_2 observations and construct tolerance intervals for those $(N_1 + N_2)$ observations. If they pass the test under tier 2 criteria, then this run will be recorded as "succeed at tier 2", otherwise it will be treated as "failure".

6. Repeat Steps 2 through 5 1000 times and get 1000 results.

7. Calculate the probability of acceptance at tier 1 and overall probability of acceptance based on 1000 results in Step 6.

8. Repeat Steps 1 through 7 1000 times and get 1000 probabilities of acceptance at tier 1 and 1000 overall probabilities of acceptance.

9. Calculate the average probability of acceptance at tier 1 and the average overall probability of acceptance from Step 8.

Simulate Single-Dose Products

The simulation plan for single-dose product is the same as above, except for a slight modification of Step 2 and Step 4 as given below in 2* and 4*:

2*. Generate N_1 cans from a normal distribution with mean μ and standard deviation s to obtain N_1 observations.

4*. If the tolerance intervals, the sample standard deviation (for IPAC-RS two-sided PTI procedure), and the sample mean pass the test under tier 1 criteria, then this run will be recorded as "succeed at tier 1".

3.2 Operating Characteristic Curve

Considering the probability of acceptance as a function of the batch mean and the within-batch standard deviation is a conventional way of describing the operating

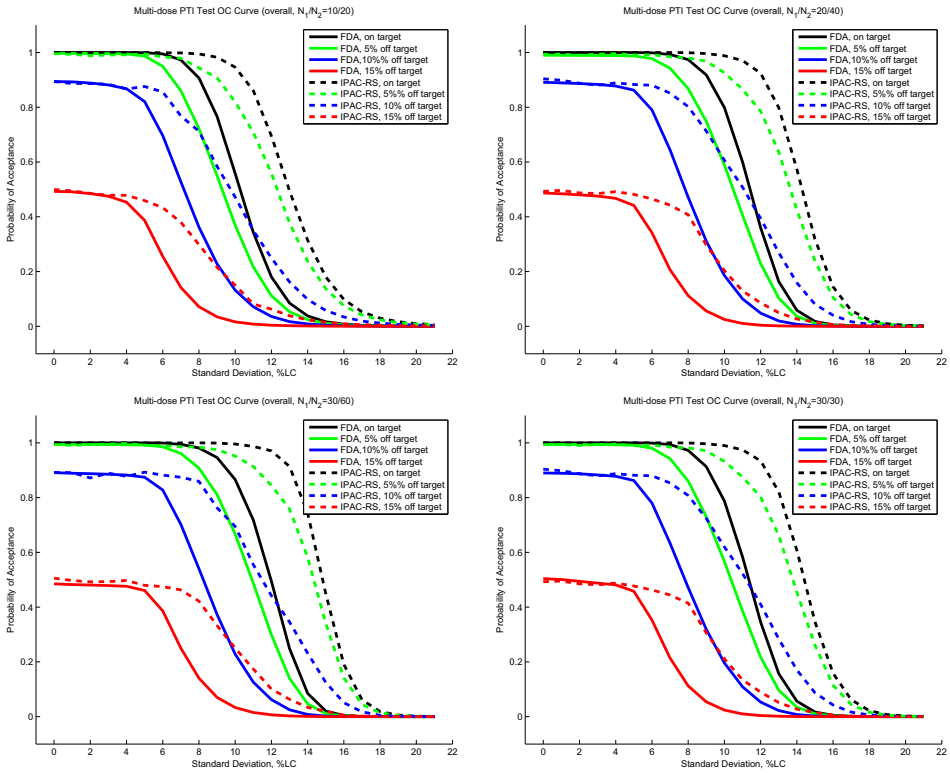


Figure 2. Top panels: OC curves of the simulated multidose products for $N_1/N_2 = 10/20$ (left) and 20/40 (right). Bottom panels: OC curves of the simulated multidose products for $N_1/N_2 = 30/60$ (left) and 30/30 (right).

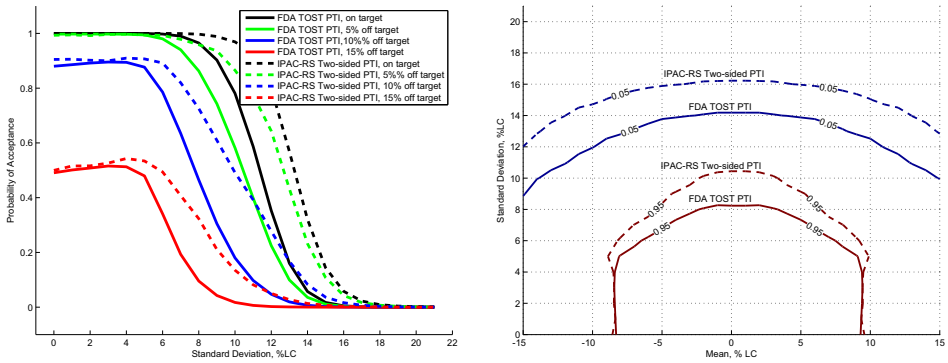
characteristic of a given sampling plan for a testing algorithm. This type of curves is known as the operating characteristic (OC) curve.

As shown in Figure 2, for multidose products, the FDA TOST PTI test procedure (solid lines) is consistently more conservative (with lower probability of acceptance) compared to the IPAC-RS two-sided PTI test (dashed lines) under the same condition (N_1, N_2, mean, and standard deviation). The OC curves become steeper as sample sizes increase. When $N_1 + N_2 = 60$, the overall pass rates are similar for $N_1/N_2 = 20/40$ and $N_1/N_2 = 30/30$. However, in practice, we would prefer the former setting since only 20 samples are required at tier 1.

For single-dose products, similar OC curves could be generated (left panel of Figure 3). A contour plot (right panel of Figure 3) for the acceptance region is an alternative graphical tool used to describe the consumer risk and the producer risk. Figure 3 exhibits the 95% (brown) and 5% (blue) acceptance regions for single-dose products when tested by both procedures (for $N_1/N_2 = 20/40$). The contour plot can be generated using the average probabilities of acceptance obtained from the simulation with their corresponding means and standard deviations. We use function *contour* in Matlab to obtain contour lines but we only plot 0.05 and 0.95 lines here for illustration.

3.3 Exact K Value for FDA TOST PTI Test Procedure

Owen (1964) proposed an acceptance sampling plan in which the hypothesis testing is framed in the same manner as the hypothesis testing in the FDA TOST PTI test. Solving the integral equation derived by Owen (1964), we can obtain the exact K value for this type of hypothesis test. It is noted that the FDA procedure uses the K value determined for a one-sided tolerance interval for each tail area to construct the TOST PTI test. This one-sided K value was actually used by Krishnamoorthy and Mathew (2009) in their computer program as the initial value for searching the exact solution of the integral equation for K. The K value used in the construction of the FDA TOST PTI test thereby was an approximation to the exact K value. It is of interest to know if using the exact K value results in an improvement for the performance of the FDA TOST PTI test. As shown in Table 2, the computed exact tolerance factors K_1 and K_2 are consistently smaller than the approximated values. Thus, we expect that the FDA TOST PTI procedure will have increased acceptance rates (see dash-dotted lines in Figure



OC Curve *Acceptance Region*

Figure 3. Left panel: OC curves of the simulated single-dose product for $N_1/N_2 = 20/40$. Right panel: acceptance region of the simulated single-dose product for $N_1/N_2 = 20/40$.

4) using the exact K values. For notation, the K value used in the construction of the FDA TOST PTI test (as in Novick et al. 2009) is referred to as "the approximated K value" in the remainder of the article.

3.4 Simulated Multidose Products under Production Situation

To illustrate the performance of the two test procedures under the realistic production situation, we simulate multidose products with high quality and low quality separately. For each situation, 10000 batches are generated. We define the high-quality product as having batch mean 100% LC and batch standard deviation 10% LC, whereas the low-quality products have 85% LC batch mean and their batch standard deviation is $15\% * 85\%$ LC.

As we know, the true quality of batches varies. We follow the same procedure as in IPAC-RS (2001) to simulate the batches. For each simulated batch i, a true mean μ_i was randomly drawn from a normal distribution with mean $\tilde{\mu}$ ($\tilde{\mu} = 100\%$ LC for high-quality products and $\tilde{\mu} = 85\%$LC for low-quality products) and a standard deviation of 4.5% LC. Similarly, for each batch the true within-batch standard deviation σ_i was randomly drawn from a normal distribution $N(10\%\text{LC}, 1.5\%\text{LC})$ for high-quality products (or $N(15\%*85\%\text{LC}, 1.5\%\text{LC})$ for low-quality products). In other words, the overall batch mean is 100% LC for high-quality products (or 85% LC for low quality products) and the standard deviation of the batch means is 4.5% LC. The overall within-batch standard deviation is 10% LC for high-quality products (or $15\%*85\%$ LC for low-quality products) and the variability of the within-batch standard deviation is 1.5% LC.

We first look at the products with high quality. Similar to Figure 2, four sets of sample sizes are selected. As shown in Table 3, the acceptance rate increases with increasing sample size for both procedures as expected since the batches are considered of good quality. The FDA TOST PTI procedure is conservative and accepts only a relatively small portion of high-quality batches while the IPAC-RS two-sided PTI procedure has a much higher acceptance rate. We also calculate the acceptance rates of FDA TOST PTI procedure using exact K values as listed in Table 3. Those values are higher than those of FDA TOST PTI procedure using approximated K values, but still lower than those of IPAC-RS two-sided PTI procedure. For 20/40 sample size (see Figure 5), the majority of the batches are accepted by the IPAC-RS two-sided PTI procedure, whereas a significant portion of the batches are rejected by the FDA TOST PTI procedure. As shown in Figure 5, we present a range of batch means from 75% LC to 125% LC by increment 1% LC. At each batch mean μ, we search the corresponding standard deviation σ to satisfy that 85% of the population $N(\mu, \sigma^2)$

Table 2. Approximated and exact tolerance factor K in the FDA TOST PTI procedure

Sample size (N_1/N_2)	α_1	α_2	Approx. K_1	Exact K_1	Approx. K_2	Exact K_2
10/20	0.0226	0.034	3.120	2.485	2.155	1.877
20/40	0.0226	0.034	2.448	2.067	1.940	1.755
30/60	0.0226	0.034	2.227	1.933	1.855	1.707
30/30	0.0309	0.0296	2.172	1.890	1.955	1.766

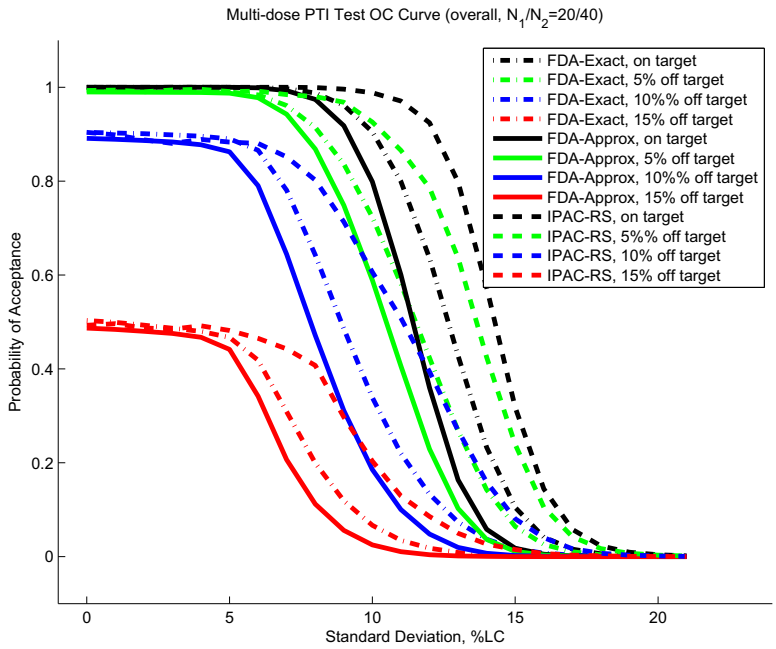


Figure 4. Comparison of OC curves for simulated multidose products for $N_1/N_2 = 20/40$.

Table 3. Probability of acceptance from the simulated products with high quality

Sample size (N_1/N_2)	Probability of acceptance		
	FDA TOST PTI Procedure (using approximated K)	FDA TOST PTI Procedure (using exact K)	IPAC-RS two-sided PTI Procedure
10/20	51.63%	73.66%	87.24%
20/40	69.41%	83.36%	96.02%
30/30	69.83%	82.76%	96.49%
30/60	77.27%	87.25%	97.88%

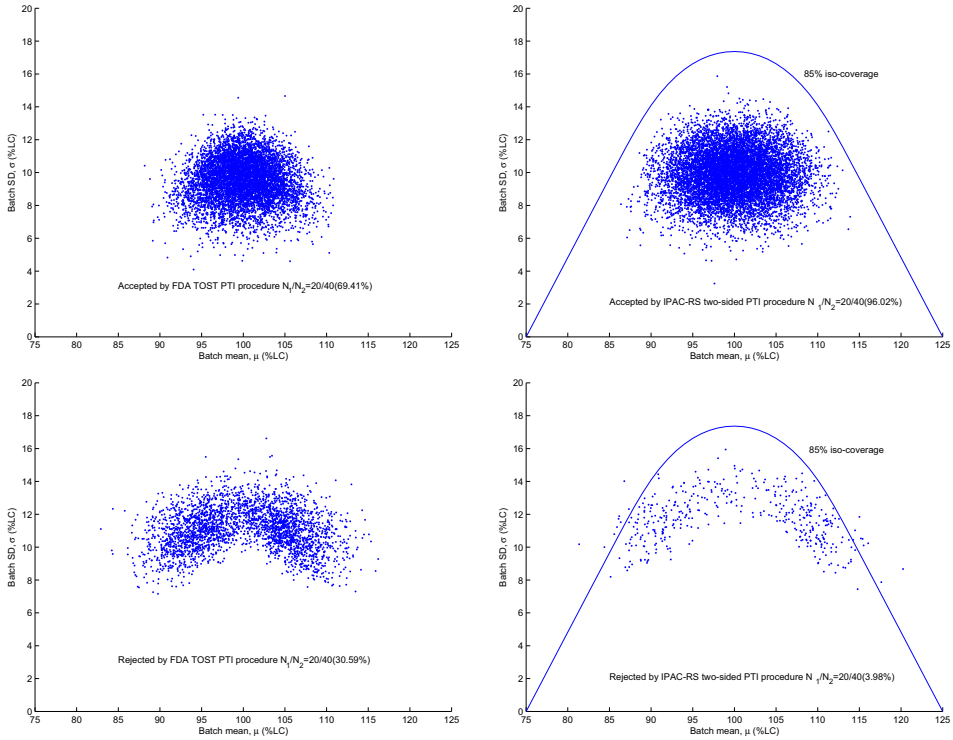


Figure 5. Top panels: accepted batches of high-quality products by FDA TOST PTI procedure using approximated K values (left) and IPAC-RS two-sided PTI procedure (right). Bottom panels: rejected batches of high-quality products by FDA TOST PTI procedure using approximated K values (left) and IPAC-RS two-sided PTI procedure (right).

are within the target interval. These pairs are used to generate the 85% iso-coverage curve by plotting σ against μ. Recall that the FDA TOST PTI procedure controls the quality through controlling the maximum allowable tail area of the batch distribution outside the target interval. There is no direct translation between $P_{\max_{TA}}$ and the requirement on coverage. Therefore, we did not add the iso-coverage curve on the graphs for the FDA TOST PTI procedure (using approximated K values). The overall probabilities of acceptance for $N_1/N_2 = 20/40$ and $N_1/N_2 = 30/30$ are very close (less than 1% difference) as long as the total sample size is the same ($N = 60$ no matter $N_1/N_2 = 20/40$ or 30/30).

Table 4 gives a summary of the characteristics of accepted batches and rejected batches. For each batch, the coverage of that batch within the target interval was calculated for both procedures. The percentiles statistics of those coverages are summarized for accepted batches and rejected batches separately under each test procedure. We note that the coverage of accepted or rejected batches

Table 4. Coverage statistics of the target interval for simulated products with high quality

	Coverage statistics of the target interval of the accepted batches (%)						Coverage statistics of the target interval of the rejected batches (%)					
	Median		5th percentile		95th percentile		Median		5th percentile		95th percentile	
N_1/N_2	IPAC-RS	FDA	IPAC-RS	FDA	IPAC-RS	FDA	IPAC-RS	FDA	IPAC-RS	FDA	IPAC-RS	FDA
10/20	98.29	98.95	94.44	96.24	99.84	99.91	94.48	96.54	87.68	90.90	97.62	98.95
20/40	98.11	98.68	93.86	96.04	99.82	99.88	91.90	95.57	83.88	90.08	95.56	98.08
30/30	98.08	98.66	93.90	95.97	99.81	99.86	91.87	95.67	85.06	90.35	95.28	98.22
30/60	98.06	98.51	93.62	95.83	99.81	99.96	90.02	94.96	82.90	89.35	94.14	97.47

FDA denotes FDA TOST PTI procedure using approximated K;
IPAC-RS denotes IPAC-RS two-sided PTI procedure.

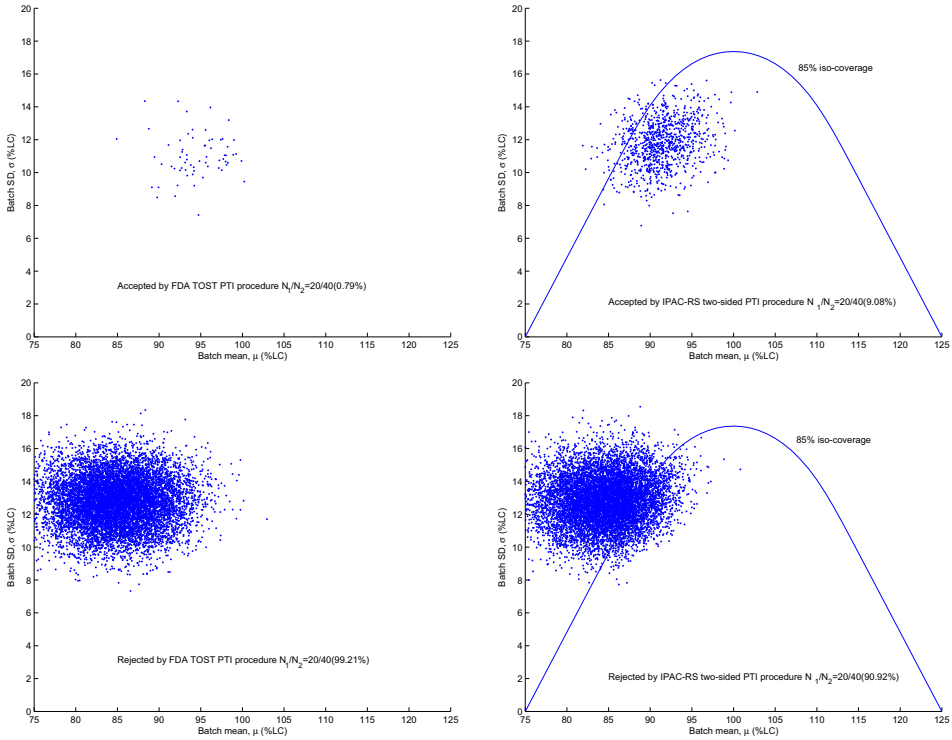


Figure 6. Top panels: accepted batches of low-quality products by FDA TOST PTI procedure using approximated K values (left) and IPAC-RS two-sided PTI procedure (right). Bottom panels: rejected batches of low-quality products by FDA TOST PTI procedure using approximated K values (left) and two-sided PTI procedure (right).

does not change significantly with respect to the sample size. The coverages of accepted batches are very close for the two procedures. Similar results hold for rejected batches. Therefore, we cannot use the coverage of target interval as a criteria to differentiate the two procedures. The coverage statistics under FDA TOSI PTI procedure using exact K values are similar to above two procedures too (results not presented).

Similar graphs and summary tables for low-quality products are shown in Figure 6 and Tables 5 and 6. We note that the probability of acceptance using the IPAC-RS two-sided PTI procedure increases with sample size increases, which is not desired for testing bad batches. On the contrast, the FDA TOST PTI procedure (using either approximated K or exact K values) provides preferred consistent low acceptance rates over a range of varied sample sizes. Therefore, the FDA TOST PTI procedure performs better when testing products with low quality.

3.5 Products with Contamination

Doses may come from different normal distributions under some production conditions. We consider a mixture of normal distributions by mixing a certain percentage of off-target normal distribution with the on-target normal distribution having the same standard deviation.

The simulations were performed as follows: for different standard deviations, a value was randomly drawn from the on-target mean normal distribution. With a certain probability, this value was then disturbed by the addition of a randomly drawn value from an off-target mean normal distribution. We consider 5%, 10%, 15% off-target mean and increasing contamination level ($q = 5, 10, 15\%$) for the two procedures. Therefore, the mixture normal distribution can be expressed as $N(100\%LC + b \times d, \sigma^2)$, where $b \sim \text{Bernoulli}(q)$, $d = 5\%\text{LC}, 10\%\text{LC}, 15\%\text{LC}$, and $q = 0.05, 0.10, 0.15$.

We use Figure 7 to illustrate simulation results. Solid lines represent the FDA TOST PTI procedure using approximated K values, dash-dotted lines represent the FDA TOST PTI procedure using exact K values and dashed lines represent the IPAC-RS two-sided PTI procedure. Lines in black correspond to batches without contamination. The colors green, blue, and red denote batches contaminated from normal distribution with mean 5%, 10%, and 15% off-target, respectively. At the low contamination level (top panel of Figure 7), the acceptance rates are slightly smaller for contaminated batches than batches without contamination and the acceptance rates under FDA TOST PTI procedure using

Table 5. Probability of acceptance from the simulated products with low quality

Sample size (N_1/N_2)	Probability of acceptance		
	FDA TOST PTI procedure (using approximated K)	FDA TOST PTI procedure (using exact K)	IPAC-RS two-sided PTI procedure
10/20	0.71%	2.57%	6.81%
20/40	0.79%	2.06%	9.08%
30/30	0.92%	1.89%	9.14%
30/60	0.70%	2.34%	11.12%

exact K values are very close to those under IPAC-RS two-sided PTI procedure. As the contamination level increases (middle and bottom panels of Figure 7), the acceptance rates decrease as the off-target means increase. The OC curves for the FDA TOST PTI procedure (using either approximated K or exact K) seem more sensitive to off-target mean compared to those for the IPAC-RS two-sided PTI procedure.

The results are presented in another way by fixing the off-target mean of the contamination sample distribution. As shown in Figure 8, when the off-target mean of the contaminated sample distribution is small or moderate (top and middle panels of Figure 8), the OC curve does not change much even at high levels of contamination for any procedure. However, when the off-target mean of the contaminated sample distribution is large, the acceptance rate from the FDA TOST PTI procedure (using either approximated K or exact K) decreases noticeably with increasing level of contamination. The colors blue, red, and green represent the contamination level 5%, 10%, and 15%, respectively.

In general, both FDA TOSI PTI and IPAC-RS two-sided PTI procedures have lower acceptance rates when the batches are contaminated as would be expected for use in practice. The FDA TOST PTI procedure (using either approximated K or exact K) is more sensitive to levels of contamination in batches compared with the IPAC-RS two-sided PTI procedure.

4. Summary and Discussion

We evaluated the performance of two parametric tolerance interval test procedures for control of the delivered dose uniformity by several simulation studies. As stated previously, the IPAC-RS two-sided PTI test procedure controls the coverage of the target population within the target interval, whereas the FDA TOST PTI test procedure controls the maximum tail area of values outside the target interval. Under the same parameter setting, the FDA TOST PTI procedure is consistently more conservative than the IPAC-RS two-sided PTI procedure. However, when dealing with low-quality products or products with contamination, the FDA PTI test yields a much lower probability of batch acceptance than the IPAC-RS PTI test. Maximum sample standard deviation is controlled in the IPAC-RS two-sided PTI procedure and simulation is required to generate the coefficients (k_1, k_2, f) in the test, which renders this procedure difficult to implement in situations when coverage and target intervals are different from the default settings.

We evaluated these two procedures by following their criteria exactly except setting the target interval as $[75\%\ \text{LC}, 125\%\ \text{LC}]$ for both procedures. The original target interval defined in the FDA TOST PTI procedure

Table 6. Coverage statistics of the target interval for simulated products with low quality

	Coverage statistics of the target interval of the accepted batches (%)						Coverage statistics of the target interval of the rejected batches (%)					
	Median		5th percentile		95th percentile		Median		5th percentile		95th percentile	
N_1/N_2	IPAC-RS	FDA	IPAC-RS	FDA	IPAC-RS	FDA	IPAC-RS	FDA	IPAC-RS	FDA	IPAC-RS	FDA
10/20	91.32	94.10	82.31	84.05	96.77	98.56	77.41	78.05	57.69	57.79	90.14	91.52
20/40	91.28	95.99	83.46	89.80	96.47	98.50	77.09	78.07	56.98	57.55	89.02	91.53
30/30	91.46	95.91	84.98	90.90	96.29	98.68	77.11	78.05	58.00	57.79	88.94	91.46
30/60	91.36	96.44	84.86	91.32	96.43	98.78	76.70	78.17	57.19	58.16	88.20	91.59

FDA denotes FDA TOST PTI procedure using approximated K;
IPAC-RS denotes IPAC-RS two-sided PTI procedure.

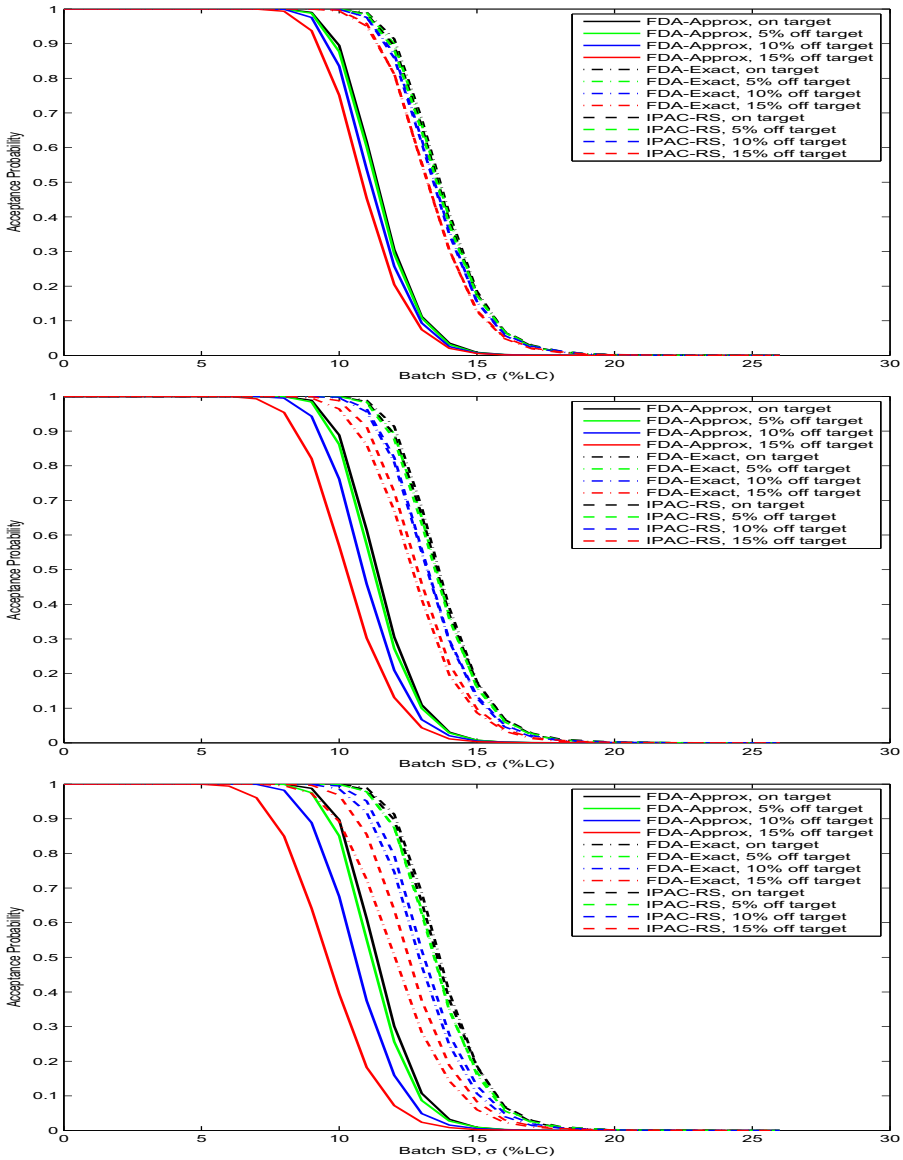


Figure 7. OC curves for products with contamination level 5% (top), 10% (middle), and 15% (bottom).

(Novick et al. 2009) is narrower than that in the IPAC-RS two-sided PTI procedure, which will contribute to a lower acceptance rate for the TOST PTI test. Nevertheless, as shown here, even when setting the target interval the same for both procedures, we still get more conservative results from the FDA TOST PTI procedure. The nominal coverage for a TOST PTI test procedure is at least $1 - 2P_{\max_{TA}}$ (Novick et al. 2009), while the exact coverage depends on the batch mean as well as the standard deviation. The greater the deviation from the target mean, the higher is the coverage requirement for the FDA TOST PTI test procedure. Hence, it is almost impossible to find an exact value of $P_{\max_{TA}}$ to match the 85% coverage requirement in the IPAC-RS two-sided PTI test procedure for a given set of DDU data from a batch. This issue underscores the difficulty to define equivalent acceptance criteria for both procedures.

Our investigation on the influence of the exact K value of the tolerance factor for the FDA TOST PTI procedure suggests an improved performance of the test procedure with the exact K value. The FDA TOST PTI procedure using exact K value is comparable with that of the IPAC-RS two-sided PTI procedure when dealing with products with a low level of contamination or a small off-target mean of the contaminated sample distribution, but is more discriminatory than the IPAC-RS two-sided PTI procedure when dealing with low-quality products or products with high levels of contamination.

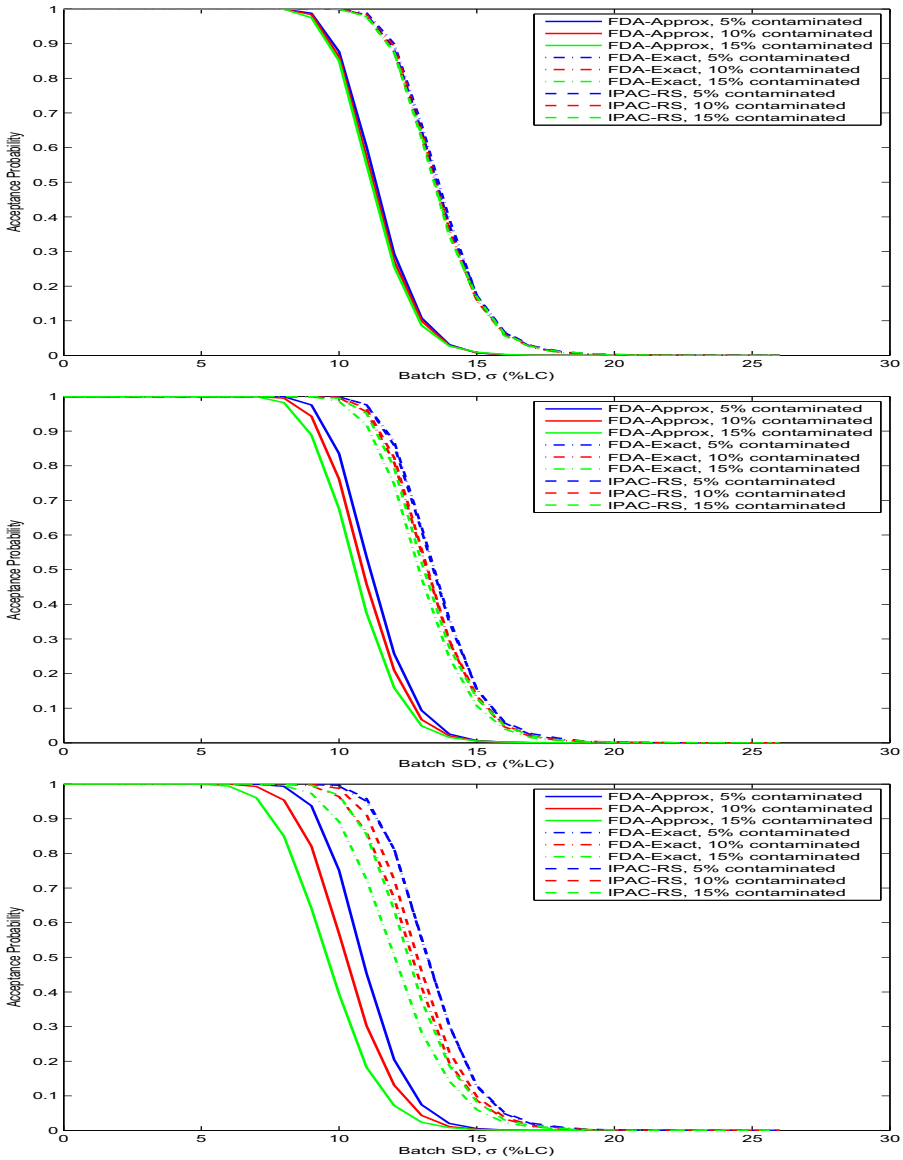


Figure 8. OC curves for products with contamination which has 5% off target mean (top), 10% off target mean (middle), and 15% off target mean (bottom).

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