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Research Article

A Two One-Sided Parametric Tolerance Interval Test for Control of Delivered Dose Uniformity—Part 3—Investigation of Robustness to Deviations from Normality

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Abstract. The robustness of the parametric tolerance interval test, which was proposed by the Food and Drug Administration for control of delivered dose uniformity in orally inhaled and nasal drug products, is investigated in this article using different scenarios for deviations from a univariate normal distribution. The studied scenarios span a wide range of conditions, the purpose of which is to provide an understanding of how the test performs depending on the nature and degree of the deviation from normality. Operating characteristic curves were generated to compare the performance of the test for different types of distributions (normal and non-normal) having the same proportion of doses in the tails (on one or both sides) outside the target interval. The results show that, in most cases, non-normality does not increase the probability of accepting a batch of unacceptable quality (i.e., the test is robust) except in extreme situations, which do not necessarily represent commercially viable products. The results also demonstrate that, in the case of bimodal distributions where the life-stage means differ from each other by up to 24% label claim, the test's criterion on life-stage means does not affect pass rates because the tolerance interval portion of the test reacts to shifting means as well.

KEY WORDS: bimodal; distribution; heavy-tailed; inhaler; skewed.

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ABBREVIATIONS: μ, population (batch) mean; σ, population (batch) standard deviation; $\overline{X}$, sample mean; ACPS, Advisory Committee for Pharmaceutical Science; BOU, beginning of unit; CMC, chemistry, manufacturing, and controls; DDU, delivered dose uniformity; DPI, dry powder inhaler; EOU, end of unit; IPAC-RS, International Pharmaceutical Aerosol Consortium on Regulation and Science; MDI, metered dose inhaler; OC, operating characteristic; OINDP, orally inhaled and nasal drug products; $Pmax_{TA}$, maximum allowable proportion of doses in a tail area (left or right) outside the target interval; PTI, parametric tolerance interval; LC, label claim; N, total sample size; N_1, sample size in the first tier; N_2, additional units tested in the second tier; s, sample standard deviation.

INTRODUCTION

In the previous two articles of this three-part series, a parametric tolerance interval test (PTI-TOST) proposed by Food and Drug Administration (FDA) at the 2005 Advisory Committee meeting was described and characterized. One of the main assumptions of the test is that the delivered dose uniformity (DDU) data in a given product are normally distributed. The DDU distribution for a typical product is studied during product development, and it may happen that the data are not strictly normal. For example, a local inhomogeneity of the active ingredient in a dry powder formulation or insufficient shaking of an MDI suspension may lead to a normal distribution with occasionally observed extreme values. As another example, if the beginning-of-unit (BOU) and end-of-unit (EOU) DDU measurements in a multi-dose product are sufficiently different, the distribution may appear bimodal. There could be several physical reasons for the change from BOU to EOU drug content, one being increasing drug concentration resulting from propellant evaporation due to the increase of the head-space volume in an MDI canister as the canister is being emptied. It is therefore of interest to study the properties of the test [e.g., using operating characteristic (OC) curves] over a wide range of deviations from normality to determine whether the test will perform appropriately under the expected conditions. This article investigates the effect of several types of deviations from normality on the PTI-TOST performance.

This study focuses on the "default" PTI-TOST parameters, as described in the first article of this series. Ideally, such a test should allow no more than 5% acceptance probability if either of the tail areas in the DDU distribution is 6.25% or greater. This article therefore focuses on the acceptance probability of two types of non-normal distributions—bimodal and normal with extreme values—when one of the tail areas approaches 6.25%.

MATERIALS AND METHODS

Studied Test and Distributions

The PTI-TOST studied here was described in detail in the first paper of this series and is briefly summarized below. The same assumptions and notations are used here as in part 1. For convenience, a general form of the "default" PTI-TOST is presented below.

Tier 1

Collect 20 doses from ten multi-dose orally inhaled and nasal drug products (OINDP) units (BOU and EOU from each unit). The 20 observations must pass the following criteria:

(1a) $T_{L1}=\overline{X}_1 - K_1\, s_1 \geq 80$ with $\text{Pmax}_{TA}=6.25\%$ and $\alpha_1=0.0226$, where K_1 is listed in Table I.
(1b) $T_{U1}=\overline{X}_1 + K_1\, s_1 \leq 120$ with $\text{Pmax}_{TA}=6.25\%$ and $\alpha_1=0.0226$, where K_1 is listed in Table I.
(1c) $85 \leq \overline{X}_{BOU,1} \leq 115$
(1d) $85 \leq \overline{X}_{EOU,1} \leq 115$

If the sample fails any of the criteria 1a–1d, the test proceeds to the second tier. In tier 2, collect an additional 40 doses and repeat the steps above with $N=60$ and K_2 substituted for K_1. In Table I, K_1 and K_2 are given for several sample size and Pmax_{TA} options when $\alpha_1=0.0226$ and $\alpha_2=0.0340$, which were recommended by the FDA based on the Pocock method (see the Appendix in the accompanying article by S. Novick, D. Christopher, M. Dey, S. Lyapustina, M. Golden, S. Leiner, B. Wyka, H.-J. Delzeit, C. Novak, and G. Larner, "A Two One-Sided Parametric Tolerance Interval Test For Control of Delivered Dose Uniformity—Part 1—Characterization of FDA Proposed Test") and match the K values of the FDA proposal (1).

For this study, datasets were simulated with four different types of non-normal distributions: skewed unimodal, symmetric unimodal with heavy tails, bimodal (bivariate normal), and univariate normal with non-repeating outliers (further details are included in the "Results" section). OC curves were generated using Monte Carlo simulation techniques to compare the probability of passing the PTI-TOST for each distribution to the probability of passing the test under a univariate normal distribution. Since the objective of the PTI-TOST is to ensure no more than the maximum allowable proportion of doses in each of the tail areas (Pmax_{TA}) outside the target interval, each distribution in this study was created with the same proportion of DDU observations in the tail area. Additionally, the effect of the non-parametric life-stage-means component of the PTI-TOST on bimodal data was evaluated with OC curves.

Approach to Studying Test Robustness

To study robustness, datasets with the univariate normal distribution were first created, with specified tail proportions above and below the FDA-recommended target interval [80, 120]. Three different cases were studied:

- "Tail=Left": tail proportions ranging from 0.001 to 0.0625 to the left of 80 and virtually zero proportion to the right of 120.
- "Tail=Right": tail proportions ranging from 0.001 to 0.0625 to the right of 120 and virtually zero proportion to the left of 80.
- Tail=Both": equal tail proportions ranging from 0.001 to 0.0625 to the left of 80 and to the right of 120. The tail proportions given for this scenario refer to the proportion in each tail.

Because the univariate normal distribution covers any interval with non-zero probability, it is not possible to create a scenario in which the area under the normal distribution curve outside the target interval is exactly zero. The value 10^{-10} was used to represent zero tail proportionality. The

Table I. K Coefficients for the PTI-TOST for Several Pmax_{TA} and Sample Sizes, with $\alpha_1=0.0226$ and $\alpha_2=0.0340$

Pmax_{TA}	$(100-2*\text{Pmax}_{TA})\%$	N_1	N_2	N (total)	K_1	K_2
8.75%	82.5%	10	20	30	2.816	1.933
7.5%	85.0%	10	20	30	2.957	2.037
6.25%	87.5%	10	20	30	3.119	2.155
5.0%	90.0%	10	20	30	3.310	2.294
3.75%	92.5%	10	20	30	3.545	2.464
8.75%	82.5%	20	40	60	2.203	1.734
7.5%	85.0%	20	40	60	2.317	1.830
6.25%	87.5%	20	40	60	2.448	1.940
5.0%	90.0%	20	40	60	2.601	2.068
3.75%	92.5%	20	40	60	2.791	2.226
8.75%	82.5%	30	60	90	2.000	1.656
7.5%	85.0%	30	60	90	2.106	1.749
6.25%	87.5%	30	60	90	2.227	1.855
5.0%	90.0%	30	60	90	2.369	1.979
3.75%	92.5%	30	60	90	2.544	2.132

mean and standard deviation for a univariate normal distribution can be exactly determined given left and right tail proportions.

To evaluate the performance of the test under deviations from normality, all distributions were generated with the same tail proportions outside the target interval. Acceptance probabilities for all the distributions were calculated for comparison to the univariate normal acceptance probabilities with the same tail proportions (or the same quality level, per PTI-TOST). These acceptance probabilities were plotted in the form of OC curves.

Characterization of Non-normal Distributions Used for Robustness Assessment

Asymmetric distributions exhibit a property called skewness. Skewness is technically defined as the quotient of the third central moment over the cube of the standard deviation. The univariate normal distribution (which is symmetric) has zero skew. Practically, skewness means that an asymmetric distribution is not symmetric with respect to the maxima of the distribution or one side of the distribution has a larger area than the other.

A heavy-tailed distribution exhibits a property called kurtosis, which is defined by the quotient of the fourth central moment over the square of the variance. The univariate normal distribution has a kurtosis value of three. Excess kurtosis is defined as the value (kurtosis-3.0), which is a measure of the heaviness of the tails relative to those of a univariate normal distribution. Kurtosis is generally only interesting for symmetric (not skewed) distributions.

Skewness and excess kurtosis values are immutable to the shifting and scaling of a random variable. Thus, the values for skewness and excess kurtosis for a random variable X are the same as the values for the random variable $\Delta+\lambda X$.

Table II shows the skewness and excess kurtosis values for the univariate normal and chi-square and T distributions with 5, 10, and 50 degrees of freedom. These distributions are used in the assessment of robustness of the PTI-TOST to skewness and heavy tails.

RESULTS

In this section, a series of figures is presented for each of the scenarios for deviation from normality. In each scenario (except univariate normal with non-repeating outliers), the first figure displays examples of the probability density function of the simulated datasets. This type of figure shows the distribution of data in comparison to the target interval, with one column per figure for each of the three cases described above: "Tail=Left," "Tail=Right," and "Tail=Both." These figures illustrate the changes in the distribution as the degree of the deviation from normality changes from high to medium to low. They also compare these distributions to the univariate normal.

The next two figures in each scenario represent a collection of OC curves for the sampling plans N_1/N_2=20/40 and N_1/N_2=30/60. Again, there are three columns per figure, one for each of the three cases for tail proportions. Each figure has two rows. The first row shows OC curves for the acceptance probabilities of the overall PTI-TOST, while the second row shows OC curves for just tier 1 of the PTI-TOST.

Within each figure, an individual OC curve is a plot of the acceptance probabilities of the test on the vertical axis against the tail proportion of the distribution outside the target interval on the horizontal axis. There is one OC curve for the univariate normal distribution and one for each of the non-normal distributions (with varying degrees of deviation). The OC curves may be compared to determine how robust the test is to deviations from normality. If the OC curves overlap or are similar, one can conclude that the test performs similarly regardless of the distribution of the data. If the OC curves for non-normal distributions are below or to the left of the normal OC curve, then the probability of passing the test is lower for the non-normal distributions. The opposite is true if the non-normal OC curves are above or to the right of the normal OC curve. The shape of a non-normal OC curve and its difference from that of the normal OC curve thus illustrate the *test's robustness* to a particular deviation from normality (i.e., similar or lower acceptance of batches at the borderline of unacceptable quality).

Table II. The Skewness and Excess Kurtosis Values for the Univariate Normal and Chi-Square and T Distributions with 5, 10, and 50 Degrees of Freedom

Distribution	Skewness	Excess kurtosis
Univariate normal	0	0
Chi-square with 5 degrees of freedom	1.26	2.4
Chi-square with 10 degrees of freedom	0.89	1.2
Chi-square with 50 degrees of freedom	0.40	0.24
T with 5 degrees of freedom	0	6
T with 10 degrees of freedom	0	1
T with 50 degrees of freedom	0	0.13

Robustness to Skewness

Figure 1 displays distributions for shifted and scaled chi-squared random variables with 5 degrees of freedom (high skew), 10 degrees of freedom (medium skew), and 50 degrees of freedom (low skew) and for the univariate normal distribution (no skew). In the panel "Tail=Left," the tail proportion to the left of 80 is 0.0625, and that to the right of 120 is 10^{-10}. In the panel "Tail=Right," the tail proportion to the left of 80 is 10^{-10}, and that to the right of 120 is 0.0625. In the panel "Tail=Both," the tail proportions to the left of 80 and to the right of 120 are 0.0625 each (or 0.125 together).

Figures 2 and 3 illustrate that, when the equal proportion of DDU results outside the target interval resides in both tails or in the left portion (opposite the skewness), the pass rates are lower for the non-normal distributions. The higher pass rates for the right tail case are most likely due to being slightly more on-target than the corresponding normal distribution, despite a larger standard deviation.

Robustness to Heavy Tails

Figure 4 displays distributions for shifted and scaled T random variables with 5 degrees of freedom (high excess kurtosis), 10 degrees of freedom (medium excess kurtosis),

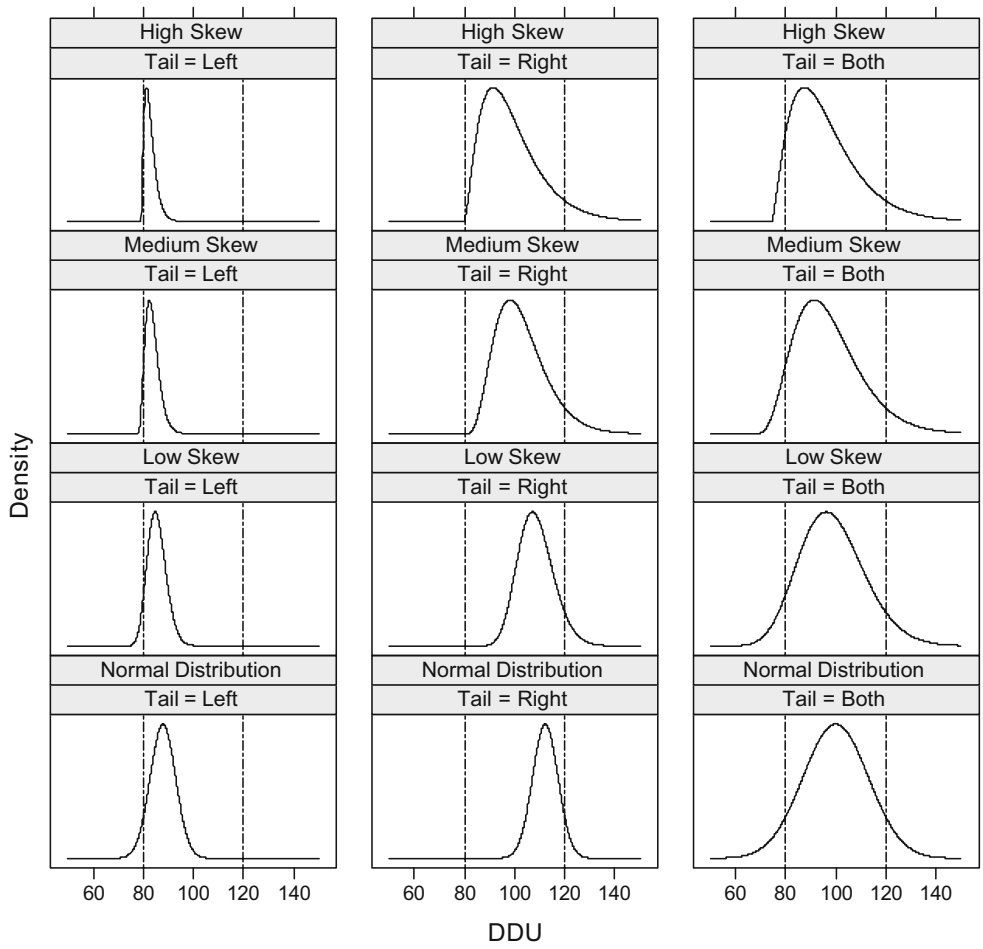

Fig. 1. Distributions for chi-squared random variables with tail proportion=0.0625 in each specified tail (skewed distributions). See text for other details

and 50 degrees of freedom (low excess kurtosis) and for the univariate normal distribution (no excess kurtosis). In the panel "Tail=Left," the tail proportion to the left of 80 is 0.0625, and that to the right of 120 is 10^{-10}. In the panel "Tail=Right," the tail proportion to the left of 80 is 10^{-10} and that to the right of 120 is 0.0625. In the panel "Tail=Both," the tail proportions to the left of 80 and to the right of 120 are 0.0625 each (or 0.125 together).

Figures 5 and 6 illustrate that, if the heaviness is in either tail, the pass rates are lower for the more extreme non-normal distributions (degrees of freedom=5 and 10). The low non-normal (degrees of freedom=50) and the normal distributions have nearly identical OC curves. The pass rates are slightly higher when both tails are heavy for the more extreme non-normal distributions.

Robustness to Bimodality

A more general distribution for BOU and EOU pairs taken from the same sampled unit is the bivariate normal with mean vector (μ_{BOU}, μ_{EOU}) and variance covariance matrix $V = \begin{pmatrix} \sigma_1^2 & \rho\sigma_1\sigma_2 \\ \rho\sigma_1\sigma_2 & \sigma_2^2 \end{pmatrix}$. This allows for different life-stage means, for different life-stage standard deviations, and for the (BOU, EOU) paired measurements to be correlated within a unit. It has been observed for many product types that $\mu_{\mathrm{BOU}} \neq \mu_{\mathrm{EOU}}$ and sometimes $\sigma_1 < \sigma_2$. The PTI-TOST assumes that $\mu_{\mathrm{BOU}} = \mu_{\mathrm{EOU}} = \mu$, $\sigma_1 = \sigma_2 = \sigma$, and $\rho = 0$. For this robustness study, the case where $\mu_{\mathrm{BOU}} = \mu - \Delta$ and $\mu_{\mathrm{EOU}} = \mu + \Delta$ will be considered with $\sigma_1 = \sigma_2 = \sigma$, and $\rho = 0$. Thus, the life-stage means differ from each other by 2Δ, the variance for both life stages are equal, and there is no correlation between beginning and end measurements within the same unit. As given in Everitt and Hand (2, page 30), so long as $abs(\mu_{BOU} - \mu_{EOU}) < 2\sigma$, the data will appear to be unimodal (and normally distributed); otherwise, the data will appear bimodal. Thus, when $\Delta > \sigma$ (i.e., the mean difference in life stages is greater than the standard deviation within each life stage), the data appear bimodal. Figure 7 displays plots of the bivariate normal distribution and the univariate normal distribution with the tail proportions=0.0625. In Fig. 7, distributions for bivariate normal distributions are displayed as random variable with means $\mu_{\mathrm{BOU}} = \mu - \Delta$ and $\mu_{\mathrm{EOU}} = \mu + \Delta$ for $\Delta = 0$, 3, 6, 9, and 12. The univariate normal distribution is given by $\Delta = 0$. In the panel "Tail=Left," the tail proportion to the left of 80 is 0.0625, and that to the right of 120 is 10^{-10}. In the panel "Tail=Right," the tail proportion to the left of 80 is 10^{-10} and that to the right of 120 is 0.0625. In the panel "Tail=Both," the tail proportions to the left of 80 and to the right of 120 are 0.0625 each (or 0.125 together).

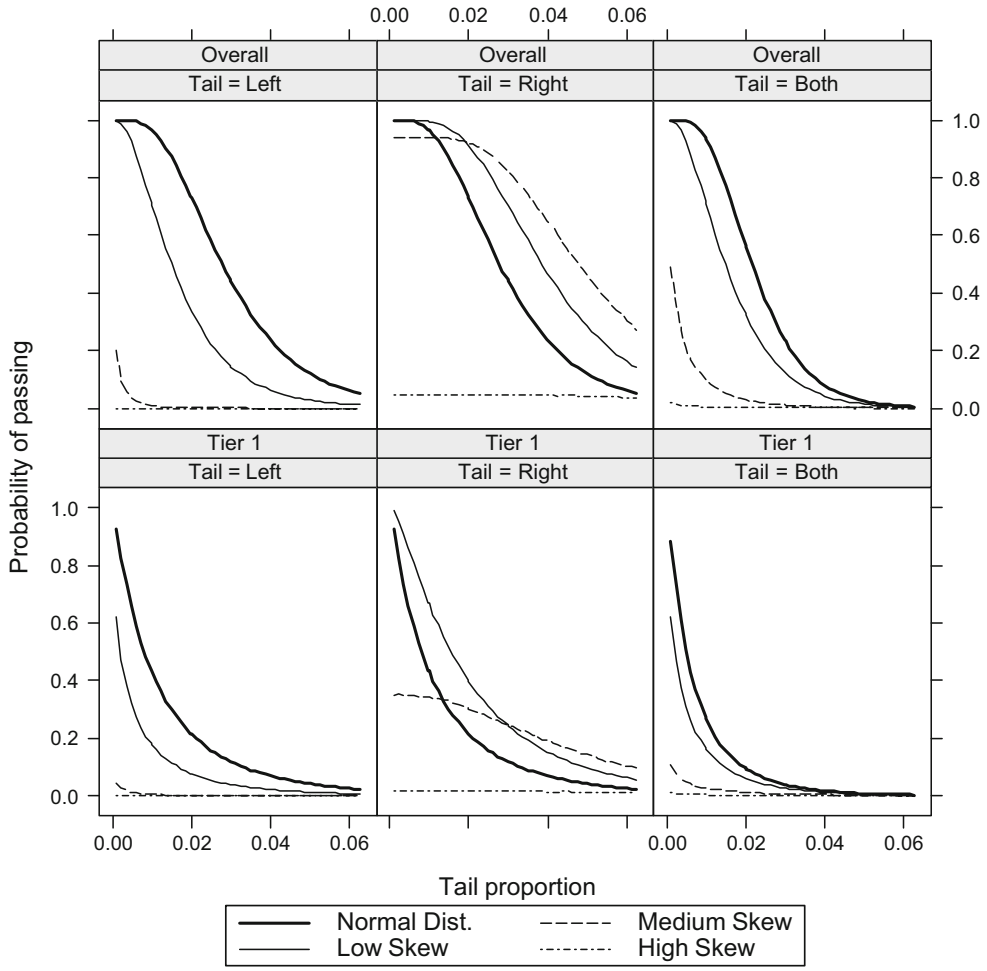

Fig. 2. OC curves for shifted and scaled chi-squared distribution for N_1/N_2=20/40

As Figs. 8 and 9 demonstrate, the pass rates for the bivariate normal distributions are all lower than the corresponding normal distribution, indicating that the PTI-TOST is fairly robust for these types of distributions.

Effect of Life-Stage Means Test when Data are Bivariate Normal

To investigate the effect of the life-stage means portion of the PTI-TOST on pass rates in the bimodal cases described above, the acceptance probabilities were re-computed for the bivariate normal scenario (see Figs. 7, 8, and 9) but without the life-stage means test. The results are presented in Figs. 10 and 11.

Figures 10 and 11 illustrate that the life-stage portion of the PTI-TOST does not impact the pass rates. When the life-stage test fails, the tolerance interval portion of the test also fails in either tier.

Robustness to Non-repeating Outliers

It has been observed for some products that the DDU observations appear to be univariate normal but with an occasional non-repeating large outlier value. To study this phenomenon, acceptance probabilities were estimated by creating univariate normal data sets with a small probability for a single outlier value in the first tier based on observed patterns from actual products. In tier 1, data were generated as univariate normal given specified tail proportions. With probability r, one outlier, a randomly chosen tier 1 observation, was replaced with a uniform random variable with limits (130, 170). No outliers were created for tier 2 data.

As Figs. 12 and 13 illustrate, the pass rates for the distributions containing outliers are similar to the corresponding normal distribution, indicating that the PTI-TOST is fairly robust for these types of distributions.

DISCUSSION

In this study, different scenarios for deviations from a univariate normal distribution have been examined to assess the robustness of the PTI-TOST. The scenarios considered here span a wide range of conditions and, in some cases, may *not* be representative of what is encountered in practice. The purpose of simulations in this study was to provide an understanding of how the PTI-TOST performs depending on the nature and degree of deviation from normality. OC curves were generated to compare the performance of the test for different types of non-normal distributions versus a

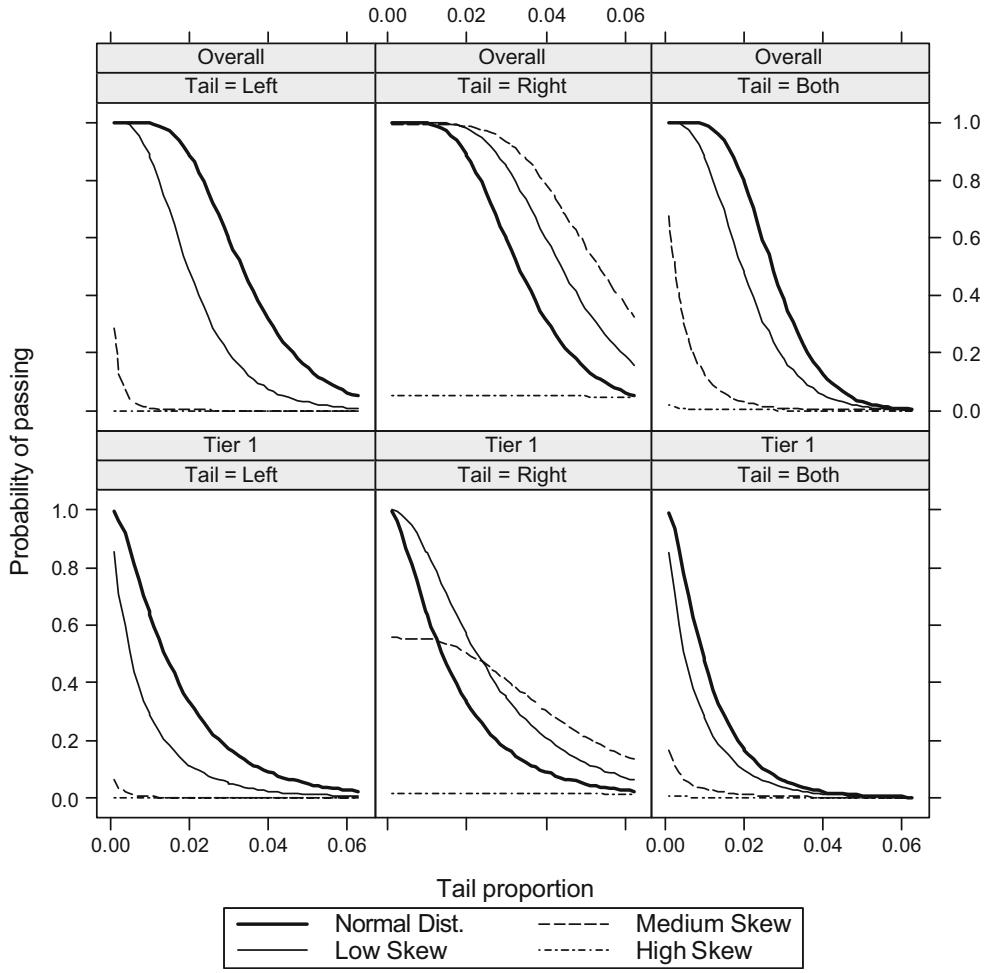

Fig. 3. OC curves for shifted and scaled chi-squared distribution for N_1/N_2=30/60

normal distribution with the same tail area outside the target interval.

Most deviations from normality that may occur for MDIs would generally increase the sample standard deviation. Since the PTI-TOST depends in part on the amount of delivered dose variability, larger standard deviations will likely cause lower pass rates. For most of the scenarios studied here, the OC curves for the non-normal distributions were similar to the corresponding normal distribution with the same tail area characteristics. A few instances resulted in slightly elevated pass rates: moderately skewed, but on-target distributions and distributions with slightly heavy tails on both sides. From the results presented in this article, it appears that the PTI-TOST is generally robust to non-normal distributions likely to be encountered in practice.

For the bivariate normal distributions studied in this paper, the life-stage portion of the test had no impact on the pass/fail disposition of the test for the BOU-to-EOU separations of up to 24% label claim (LC) because at least one tolerance interval portion of the test fails when the life-stage BOU or EOU portion of the test fails.

CONCLUSION

A systematic investigation of the PTI-TOST proposed by the FDA for control of DDU in OINDP has demonstrated that, in the case of bimodal, skewed, heavy-tailed, or normal with non-repeating outlier distributions, non-normality does not increase the probability of accepting a batch of unacceptable quality (i.e., the test is robust), except in extreme situations that do not necessarily represent commercially viable products. The results also demonstrate that, in the case of bimodal distributions where the life-stage means differ from each other by up to 24% LC, the test's criterion on life-stage means does not affect pass rates because the tolerance interval portion of the test reacts to shifting means as well.

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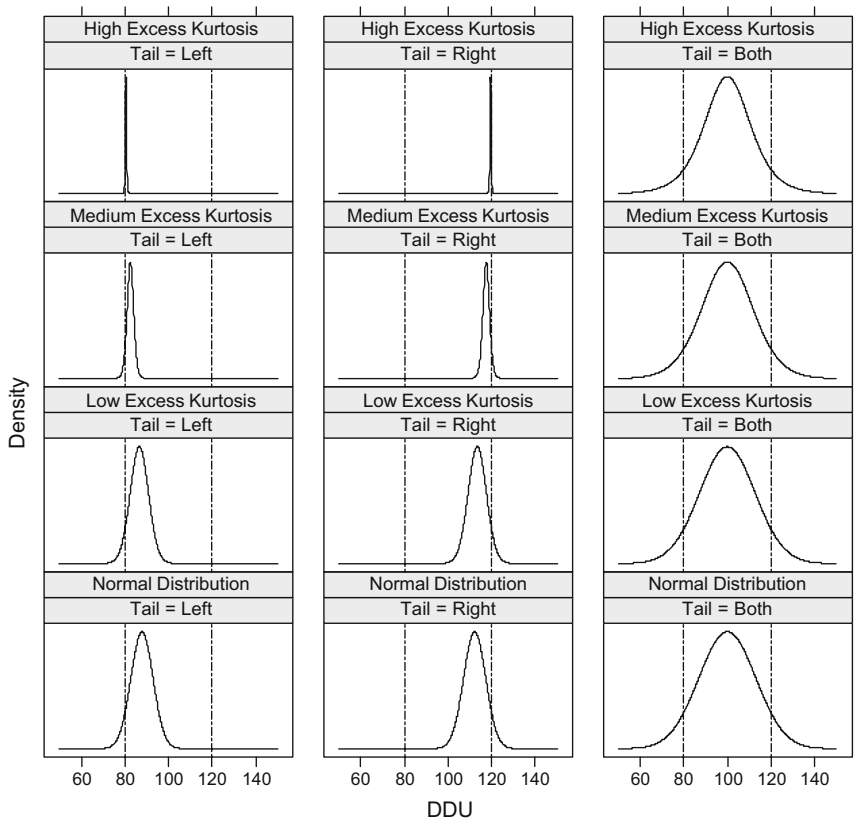

Fig. 4. Densities for *T*-distributed random variables with tail proportion=0.0625 in each specified tail (heavy-tailed distributions). See text for other details

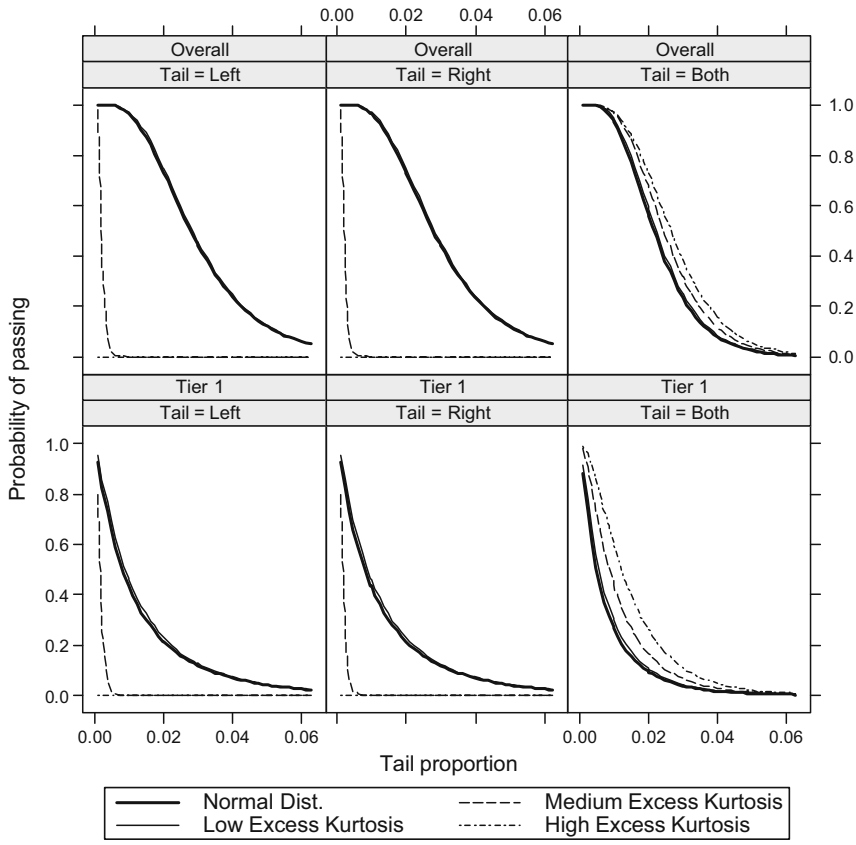

Fig. 5. OC curves for shifted and scaled T distribution for N_1/N_2=20/40

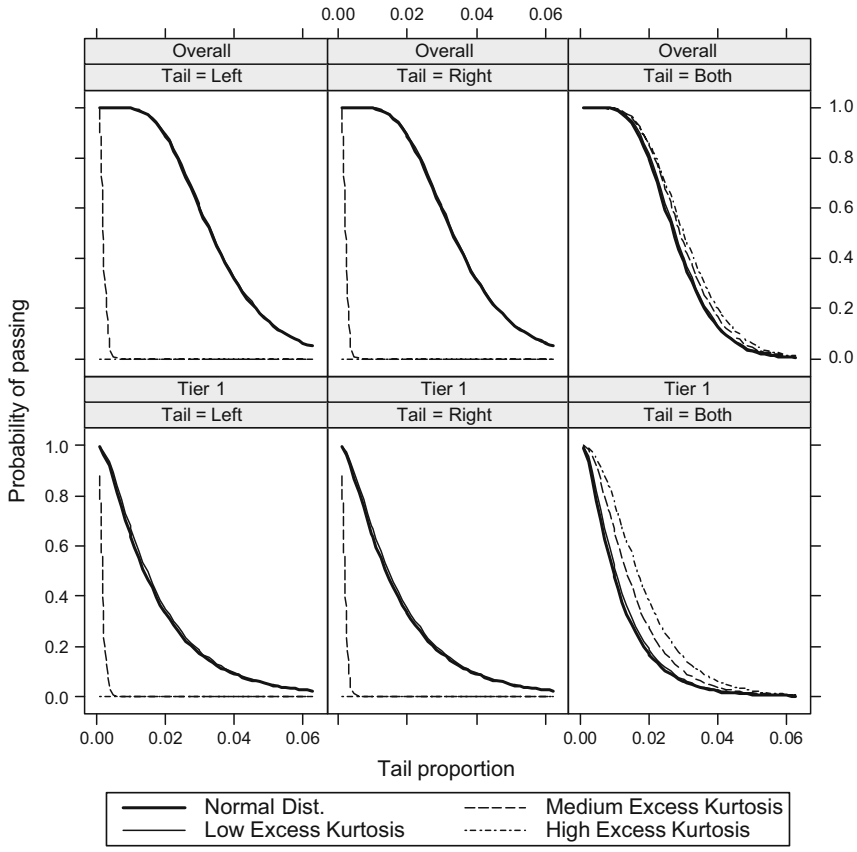

Fig. 6. OC curves for shifted and scaled T distribution for $N_1/N_2=30/60$

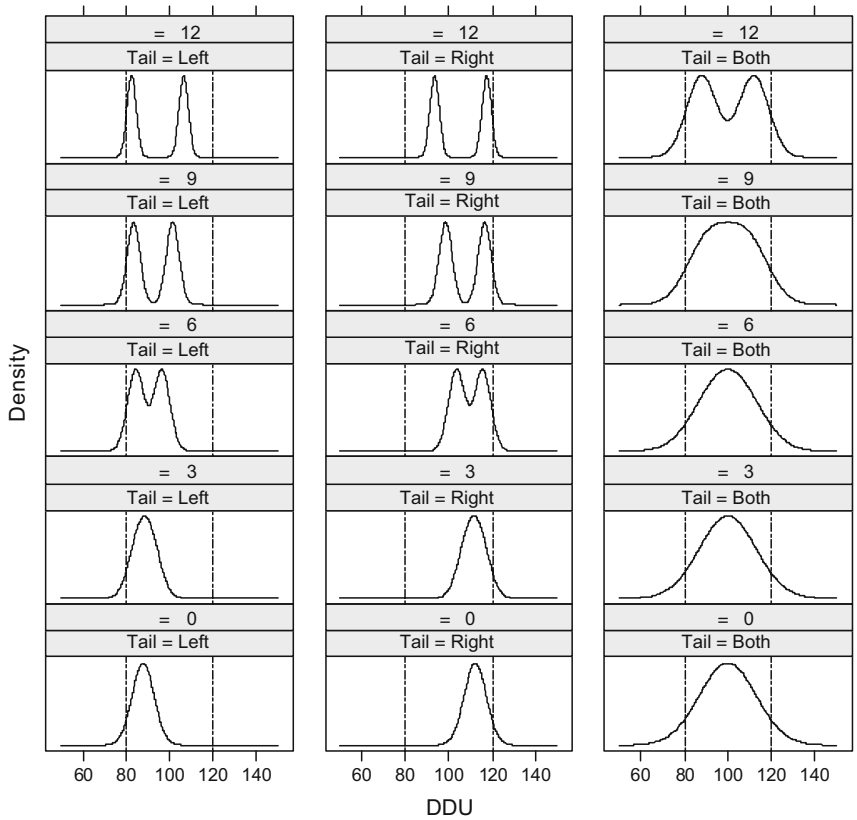

Fig. 7. Densities for bivariate normal random variables with tail proportion=0.0625 in specified tail(s) (bivariate normal distributions). See text for other details

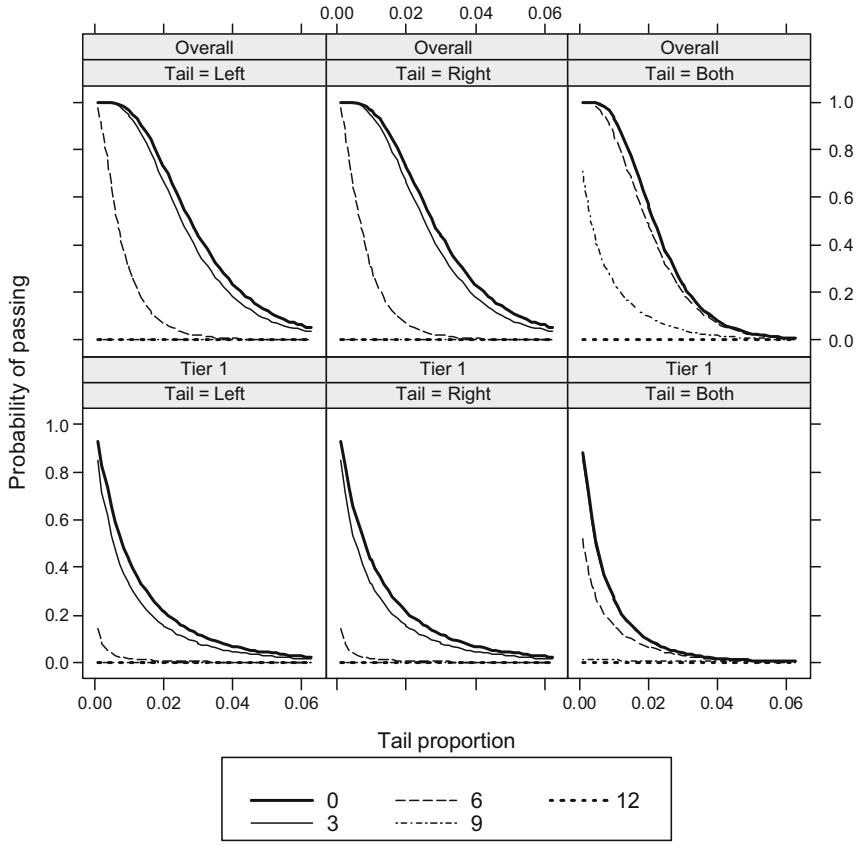

Fig. 8. OC curves for bivariate normal distribution for N_1/N_2=20/40. The legend box displays values for Delta

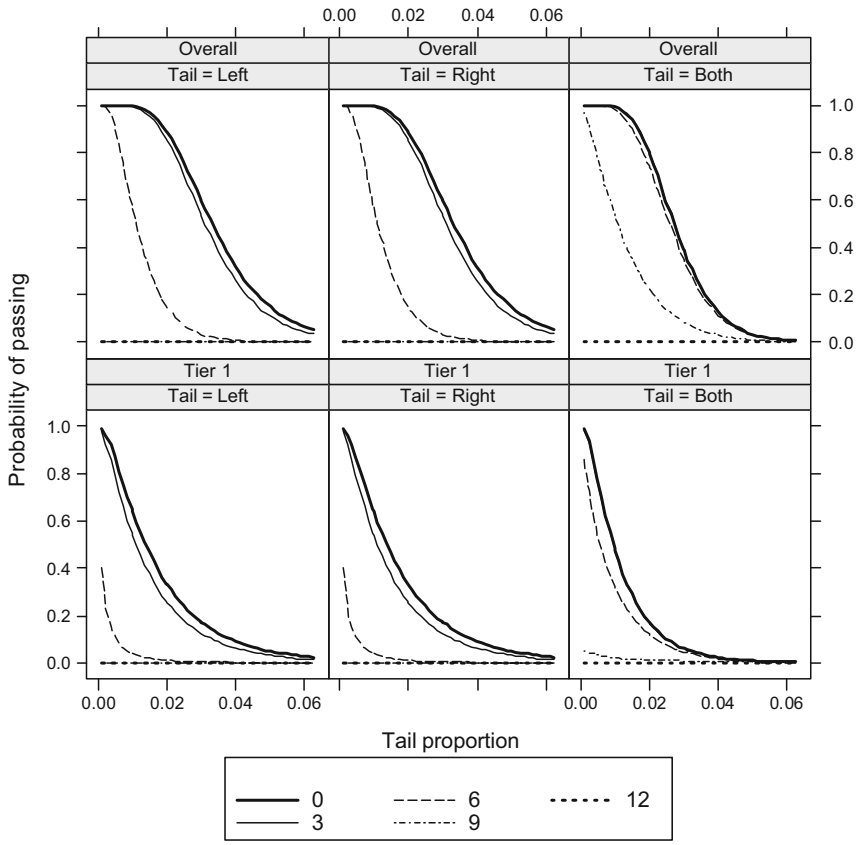

Fig. 9. OC curves for bivariate normal distribution for N_1/N_2=30/60. The legend box displays values for Delta

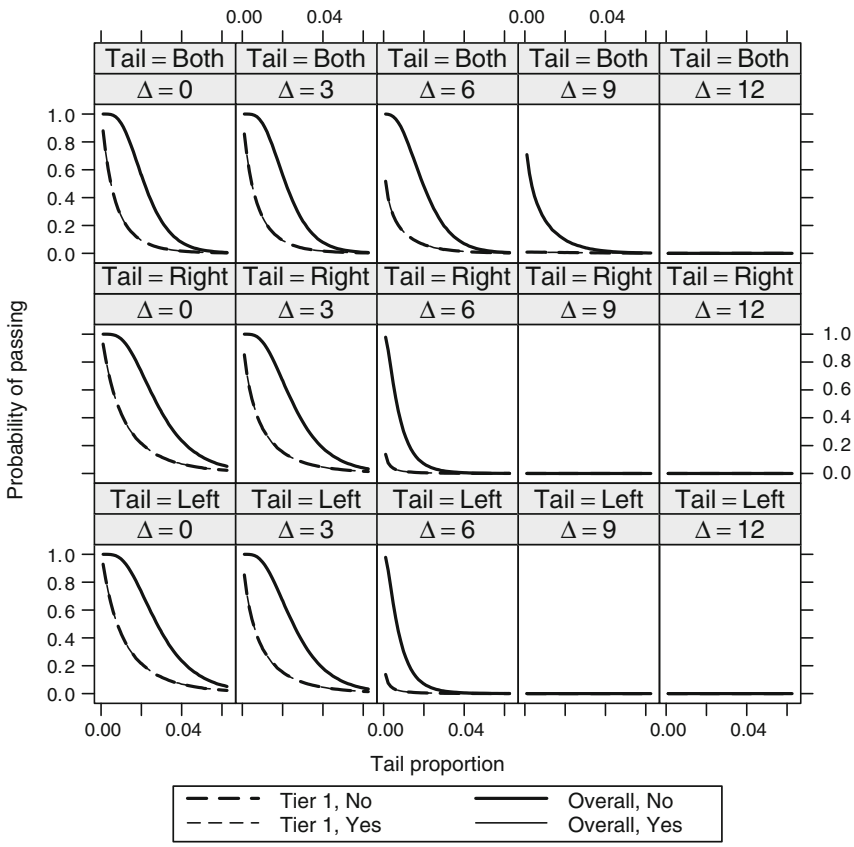

Fig. 10. OC curves for bivariate normal with and without life-stage means test for N_1/N_2=20/40. Yes and No in the legend box refer to the presence or absence of the life-stage-means portion in the test, respectively

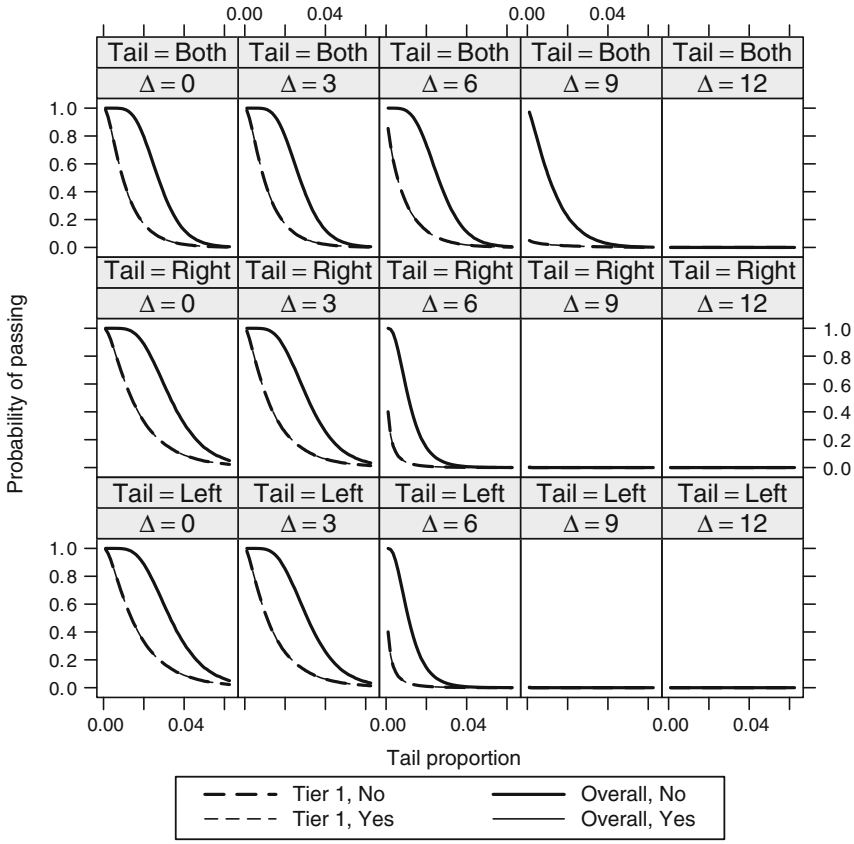

Fig. 11. OC curves for bivariate normal with and without life-stage means test for N_1/N_2=30/60. Yes and No in the legend box refer to the presence or absence of the life-stage-means portion in the test, respectively

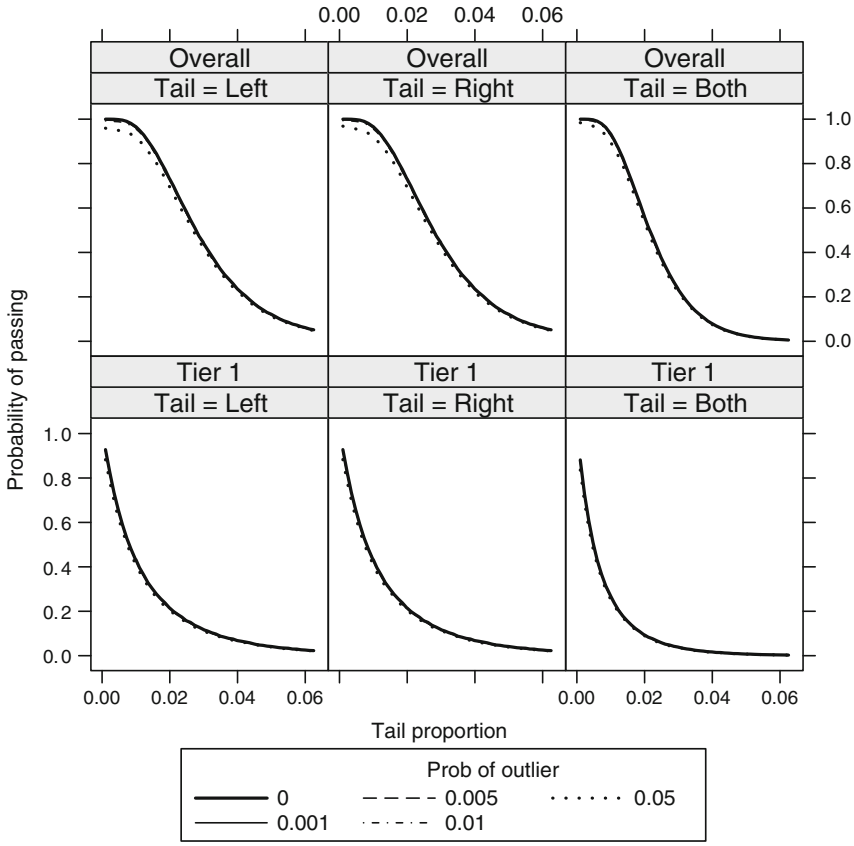

Fig. 12. OC curves for normal distribution with non-repeating outlier for N_1/N_2=20/40

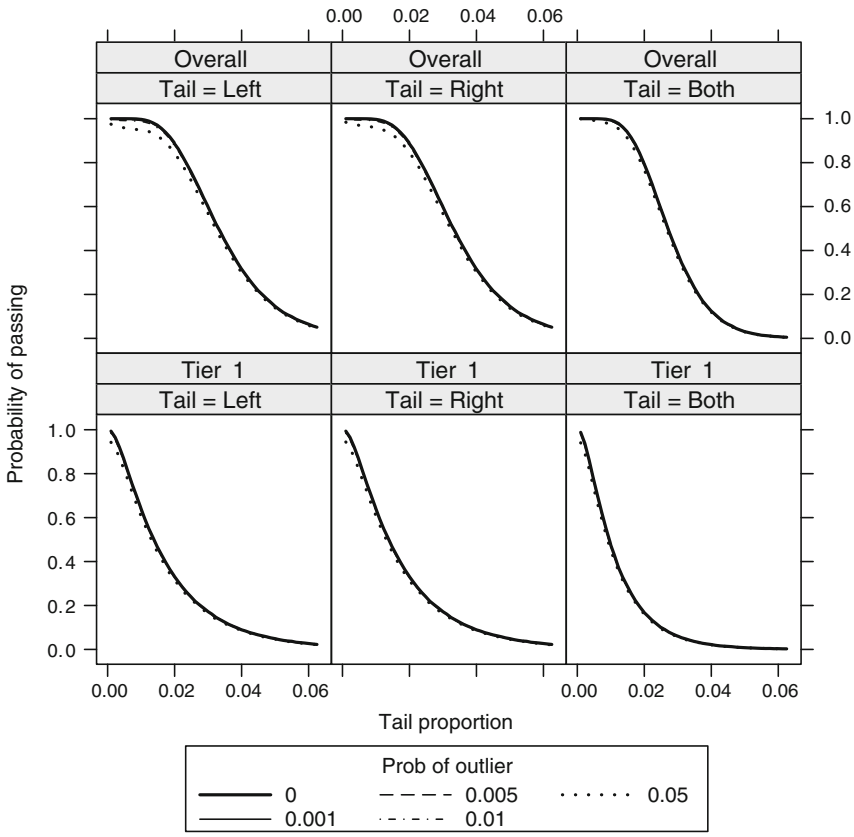

Fig. 13. OC curves for normal distribution with non-repeating outlier for N_1/N_2=30/60

Hauck for his original proposal to use parametric approaches for DDU testing, starting with his 1999 presentation at the Management Forum Conference on European/FDA Regulatory Issues in Oral Inhalation and Nasal Delivery. This article is part of a series that presents a factual description and analysis of the test proposed by the FDA and should not be construed as endorsement or advocacy by the authors or organizations with which they are affiliated.

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