Out Of Specification Test Results from the Statistical Point of View

- Attachment to the Article of the Same Title in PharmInd in 3 Parts -

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Personal request: Call for the submission of additional example data sets

As stated in Chapter 4.3 (Part 3), the rules for the treatment of especially low or high values are best specified in the form of example data sets to be uniformly evaluated by experts. Please send me such (if necessary disguised) data sets to: (see the address at the end of this article, or via e-mail: h.waetzig@tu-bs.de). These data sets could then be introduced to a larger readership for discussion in a follow-up article.

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6 Attachment

6.1 Additions to Chapter 2.1

6.1.1 Derivation of the equation (Equation 4)

In a random sample of size n, k values are WS and n-k values are OOS. If the probability of a WS result is equal to γ, then the possible values for k a binomial distribution with the parameters γ and n. The probability of k WS results among n values is:

$$P(k \mid \gamma, n) = \binom{n}{k} \gamma^k (1-\gamma)^{n-k} \quad k = 0,1,...n \qquad \text{(Equation 4.1)}$$

where

$$\binom{n}{k} = \frac{n \cdot (n-1) \cdot ...(n-k+1)}{1 \cdot 2 \cdot ...k} \qquad \text{(Equation 4.2)}$$

is the binomial coefficient n over k.

The null hypothesis $\gamma \leq \gamma_0$ is to be tested against the alternative $\gamma > \gamma_0$ for a given γ_0 in respect of the error probability α. This is done by specifying a threshold k_0. If the observed $k \geq k_0$ then the null hypothesis is rejected, otherwise it is accepted.

The probability for the rejection of the null hypothesis, if $\gamma = \gamma_0$ or is smaller, should equal α at the most. The following must thus apply for the threshold k_0:

$$\sum_{i=k_0}^{n} \binom{n}{i} \gamma_0^i (1-\gamma_0)^{n-i} \leq \alpha \qquad \text{(Equation 4.3)}$$

The smallest whole number k_0 for which this condition is true, is the sought threshold.

For values n that are not too small ($n\gamma_0 (1 - \gamma_0) > 1$ is to apply) the binomial distribution can be approximated via a normal distribution with the mean value $n\gamma_0$ and the variance $n\gamma_0 (1 - \gamma_0)$. The condition for k_0 is thus as follows:

$$1 - \Phi\left(\frac{k_0 - n\gamma_0}{\sqrt{n\gamma_0 (1-\gamma_0)}} \right) \leq \alpha \qquad \text{(Equation 4.4)}$$

where $\Phi(.)$ represents the standard normal distribution. From this it follows that k_0 is the smallest whole number for which the following is true:

$$k_0 \geq n\gamma_0 + z_{1-\alpha} \sqrt{n\gamma_0 (1-\gamma_0)}\ , \qquad \text{(Equation 4.5)}$$

where $z_{1-\alpha}$ is the $(1-\alpha)$ quantile of the standard normal distribution.

In order to achieve the test power 1-β for a value $\gamma_1 > \gamma_{0.}$ n must be high enough for

$$\sum_{i=k_0}^{n} \binom{n}{i} \gamma_1^i (1-\gamma_1)^{n-i} \geq 1-\beta \qquad \text{(Equation 4.6)}$$

to be true for the k_0 conforming to the condition cited above. With the normal approximation this condition is as follows:

$$\Phi\left(\frac{n\gamma_1 - n\gamma_1 - z_{1-\alpha}\sqrt{n\gamma_0(1-\gamma_0)}}{\sqrt{n\gamma_1(1-\gamma_1)}} \right) \geq 1-\beta. \qquad \text{(Equation 4.7)}$$

From this it follows that n is the smallest whole number for which the following is true:

$$n \geq \frac{(z_{1-\alpha}\sqrt{\gamma_0(1-\gamma_0)} + z_{1-\beta}\sqrt{\gamma_1(1-\gamma_1)})^2}{(\gamma_1 - \gamma_2)^2}. \qquad \text{(Equation 4)}$$

6.1.2 Calculation of the limits for the confidence interval

(Compare Chapter 2.1.2)

Of n independent random-sample values, k are WS and n - k are OOS. To be found are confidence intervals with the reliability 1-α for the probability γ of WS results.

The lower limit γ_{min} of a one-sided upper confidence interval for γ with a reliability 1-α (i.e. of an interval that contains the actual value of γ with a probability 1-α) must fulfill the following condition: For $\gamma=\gamma_{min}$, the probability for k or more WS results among n values is not greater than α; i.e.:

$$\sum_{i=k}^{n} \binom{n}{i} \gamma_{min}^i (1-\gamma_{min})^{n-i} \leq \alpha \qquad \text{(Equation 7.1)}$$

This means that for values γ that are either equal to γ_{min} or even smaller, k or more WS results among n values at a maximum can be expected with a probability α. If one asserts for such a result that γ is greater than γ_{min}, one can maximally err with the probability α and be right with the reliability 1-α.

Accordingly, the following must be true for the upper limit γ_{max} of a one-sided lower confidence interval for γ with the reliability 1-α:

$$\sum_{i=k}^{n} \binom{n}{i} \gamma_{max}^i (1-\gamma_{max})^{n-i} \geq 1-\alpha \qquad \text{(Equation 7.2)}$$

By means of the (1-α) quantiles $F_{1-\alpha,\ df1.\ df2}$ of the central F-distribution with df1 and df2 degrees of freedom, the two limits can be exactly calculated. The following applies:

$$\gamma_{min} = \frac{k}{k + (n - k + 1)F_{1-\alpha,2(n-k+1),2k}} \qquad \text{(Equation 7a)}$$

$$\gamma_{max} = \frac{(k+1)F_{1-\alpha,2(k+1),2(n-k)}}{n - k + (k+1)F_{1-\alpha,2(k+1),2(n-k)}} \qquad \text{(Equation 7b)}$$

The quantiles of the central F-distribution are cited in many publications of statistical tables (e.g. Dokumenta Geigy #) and can be found in statistical program systems such as SAS or SPSS as function macros.

6.1.3 Derivation of the equation k=n+1-(l+r)

(Compare Chapter 2.1.3)

Given is a random sample $x_{1.}$ $x_{2.}$ ... x_n of n independent and identically distributed values. The random-sample values are once arranged from the smallest to the greatest value and a second time from the greatest to the smallest. The rank of a value s in the order from the smallest to the greatest value is referred to as 'left' rank l and the rank in the order from the greatest to the smallest value as 'right rank r. The random-sample value with the left rank l is designated as $x_{[l]}$ and the random-sample value with the right rank r is designated as $_{(r)}$. The question is, how great is the probability (the percentage in the total population) γ for values that are greater than $x_{[l]}$ and smaller than or equal to $x_{(r)}$, i.e. that lie between l-smallest and r-greatest random-sample value?

Since the random-sample values constitute realizations of random variables, a prediction for this percentage can only be made with a calculated reliability 1-α. Sought is the value γ_{min}, of which it can be stated with the reliability 1-α that at a minimum this percentage lies between $x_{[l]}$ and $x_{(r)}$.

l random-sample values are smaller than or equal to $x_{[l]}$ and r-1 random-sample values are greater than $x_{(r)}$. The interval $x_{[l]}<x\leq x_{(r)}$ thus contains k=n+1-(l+r) values. A lower limit of the upper confidence interval for the probability γ with which values lie within the interval is therefore the γ_{min} described in Attachment 2, at a given n and 1-α for k=n+1-(l + r).

6.1.4 Required size n of the random sample to determine the decision threshold k_0

The null hypothesis is rejected if of n random-sample results fewer than k_0 are WS. A random-sample size n is required at a minimum to achieve for $\gamma=\gamma_1$ the test power 1-β (i.e. to be able to expect the rejection of the null hypothesis with the probability 1-β; Table 6).

6.1.5 Lower confidence limits

Lower confidence limits γ_{min} for the probability γ of WS results in the production unit if of n random-sample values k are WS:

A) γ_{min} at α=20%, reliability 1-α=80%: Table 7

B) γ_{min} at α=10%, reliability 1-α=90%: Table 8

C) γ_{min} at α=5%, reliability 1-α=95%: Table 9

D) γ_{min} at α=2.5%, reliability 1-α=97.5%: Table 10

6.1.6 Upper confidence limits

Upper confidence limits γ_{max} for the probability γ of WS results in the production unit if of n random-sample values k are WS:

A) γ_{max} at α=20%, reliability 1-α=80%: Table 11

B) γ_{max} at α=10%, reliability 1-α=90%: Table 12

C) γ_{max} at α=5%, reliability 1-α=95%: Table 13

D) γ_{max} at α=2.5%, reliability 1-α=97.5%: Table 14

6.1.7 Value of factor $t_{\gamma,n-1}\sqrt{1-\frac{1}{n}}$.

This factor is required for the calculation of the limits of tolerance intervals with normal distribution. For a one-sided upper tolerance interval the lower limit is: $\bar{x}$-s·factor; for a one-sided lower interval the upper limit is: $\bar{x}$+s·factor. For a two-sided tolerance interval the limits are: $\bar{x}\pm$s·factor.
The last line in the table (n=∞) indicates the quantiles z_γ of the normal distribution, which are to be used if the mean value μ and the standard deviation σ of the total population are known (Table 15).

6.1.8 Calculation of tolerance intervals for a normally distributed total population (addition to Chapter 2.1.3)

The literature also contains formulas for tolerance intervals of normally distributed measurement values. Since the distribution of the measurement values in the total population is unknown, and it cannot be reliably assumed that the measurement values are distributed normally, the use of this formula for OOS problems is not recommended. Moreover, the method has the disadvantage that the reliability with which this interval actually overlaps the percentage γ of the total population, cannot be stated. It is nevertheless dealt with here, as it is used in practice.

A normal distribution F(x) is fully defined by the mean value μ and the standard deviation σ. If $\Phi(z)$ indicates the standard normal distribution with a mean value 0 and the standard deviation 1, then it follows that: $F(x)=\Phi((x-\mu)/\sigma)$. The quantiles ξ_q of a normal distribution can be calculated, using the quantiles z_q of the standard normal distribution, by means of the formula: $\xi_q=\mu+z_q\sigma$. Because of the symmetry of the standard normal distribution around 0, it follows that: $z_q<0$ for $q<0.5$, $z_q=0$ for $q=0.5$ and $z_q>0$ for $q>0.5$. It further follows that: $z_q=-z_{1-q}$, so that it suffices to know the quantiles z_q for $q>0.5$.

A one-sided upper tolerance interval for normally distributed measurement values with a mean value μ and a standard deviation σ and containing the percentage γ (>0.5) of the total population, has a lower limit $x_u=\mu-z_\gamma\sigma$, a one-sided lower tolerance interval has the upper limit $x_o=\mu+z_\gamma\sigma$, and a two-sided tolerance interval has the lower limit $x_u=\mu-z_{(1+\gamma)/2}\sigma$ and the upper limit $x_o=\mu+z_{(1+\gamma)/2}\sigma$. If μ and σ are known, the limits of the tolerance intervals can be calculated by means of these formulas if the quantiles z_q are known (see Table 4, last line).

However, μ and σ are usually not known and are estimated by means of the arithmetic mean $\overline{x}$ and the standard deviation s of the random sample. This results in the determination of the tolerance limit becoming uncertain. This uncertainty is addressed with a correction link.

If only the mean value μ is replaced by $\overline{x}$, the necessary correction can be derived by means of a simple consideration. With normally distributed measurement values x, the arithmetic mean $\overline{x}$ is also distributed normally with the mean value μ and the standard deviation (standard error) $\sigma/\sqrt{n}$. The difference between an arbitrary measurement value x that is not included in the random sample and the arithmetic mean $\overline{x}$, is also distributed normally with the mean value 0 and the standard deviation $\sigma\sqrt{1+\frac{1}{n}}$. The share of measurement values x for which the difference to the mean value $\overline{x}$ is greater than $z_{1-\gamma}\ \sigma\sqrt{1+\frac{1}{n}} = -z_\gamma\sigma\sqrt{1+\frac{1}{n}}$, is γ. This results in a lower limit of a one-sided upper tolerance interval for the share γ of: $x_u=\overline{x}-z_\gamma\sigma\sqrt{1+\frac{1}{n}}$. But σ must also be replaced by the standard deviation s of the random sample. This means that the quantiles z_γ of the standard normal distribution are replaced by the quantiles $t_{\gamma,\,n-1}$ of a central t-distribution with n-1 degrees of freedom (which is the distribution of the quotient of $\overline{x}$ to the standard error $s/\sqrt{n}$ with μ=0). Table 4 contains, for different values of γ and n-1, the values of $t_{\gamma,n-1}\sqrt{1+\frac{1}{n}}$.

The lower limit of a one-sided upper tolerance interval for the share γ is:

$$x_u=\overline{x}-s\cdot t_{\gamma,n-1}\sqrt{1+\tfrac{1}{n}}\,, \qquad \text{(Equation 8a)}$$

The upper limit x_o of a one-sided lower tolerance interval for the share γ is:

$$x_u=\overline{x}+s\cdot t_{\gamma,n-1}\sqrt{1+\tfrac{1}{n}} \qquad \text{(Equation 8b)}$$

The lower and upper limits of a two-sided tolerance interval for the share γ is:

$$x_u, x_o = \bar{x} \pm s \cdot t_{(1+\gamma)/2,n-1}\sqrt{1+\tfrac{1}{n}}\ , \qquad \text{(Equation 8c)}$$

where the positive prefix yields x_o and the negative x_u.

In cases 1 to 3 in Figure 3, n, $\bar{x}$ and s are:

n	$\bar{x}$	**s**
5	0.4034	0.3037
10	0.3790	0.2160
30	0.4161	0.1937

Using the factors cited in Table 15, the following tolerance intervals result:

Lower limit of the one-sided upper Tolerance interval:

n	**γ=0.6**	**γ=0.7**	**γ=0.8**	**γ=0.9**	**γ=0.95**
5	x_u=0.313	x_u=0.214	x_u=0.090	x_u=-0.107	x_u=-0.306
10	x_u=0.320	x_u=0.256	x_u=0.179	x_u=0.066	x_u=-0.036
30	x_u=0.366	x_u=0.312	x_u=0.248	x_u=0.158	x_u=0.082

Upper limit of the one-sided lower tolerance interval:

n	**γ=0.6**	**γ=0.7**	**γ=0.8**	**γ=0.9**	**γ=0.95**
5	x_o=0.493	x_o=0.593	x_o=0.716	x_o=0.913	x_o=1.113
10	x_o=0.438	x_o=0.502	x_o=0.579	x_o=0.692	x_o=0.794
30	x_o=0.466	x_o=0.521	x_o=0.584	x_o=0.674	x_o=0.751

Limit of a two-sided tolerance interval:

n	γ	**0.6**	**0.7**	**0.8**	**0.9**	**0.95**
5	**x_u-x_o**	**0.090**-0.716	**0.007-0.799**	-0.107-0.913	-0.306-1.113	-0.520-1.327
10	**x_u-x_o**	0.179-0.579	0.130-0.628	0.066-0.692	-0.036-0.794	-0.133-0.891
30	**x_u-x_o**	0.248-0.584	0.208-0.624	0.158-0.674	0.082-0.751	0.013-0.819

For the random sample with n=5 it is to be expected that, for example, the percentage 0.6 of the total population is greater than 0.09 and that the percentage 0.7 of the total population lies between 0.007 and 0.799. Since the normal distribution presupposes that the value range stretches from -∞ to +∞, it is possible for negative lower limits or other limits outside the actual measurement range to occur. In such cases the tolerance interval based on the assumption of a normal distribution is not permissible.

For comparison, those shares of γ_{min} are cited that with a reliability of 90% can at a minimum be asserted for the tolerance interval formed with the smallest and greatest values of cases 1 to 3:

n	x_u	x_o	γ_{min}	Reliability
5	0.16	0.90	0.416	90%
10	0.09	0.69	0.663	90%
30	0.05	0.73	0.876	90%

Both the width of the tolerance intervals and the size of the share γ covered by it differ for the two methods. In cases 2 and 3 the tolerance intervals formed with the smallest and greatest random-sample values are greater than the intervals formed for the approximately equal share γ assuming a normal distribution.

For the tolerances formed in accordance with the formulas depicted above and assuming a normal distribution, it is not possible to state the percentage γ with reliability. It is only known that with frequent repeating of the method the percentage γ coincides in the mean with the actual share overlapped by the interval. For a concretely calculated interval, however, the actual share covered by this interval can significantly deviate from the value γ especially if the sizes of the random samples are small. In part because of the lack of reliability data, the tolerance intervals should not be calculated using the formulas cited above.

The production unit can be classified as WS if the tolerance interval for a share $\gamma>\gamma_0$ lies completely within the specification interval. The reliability with which this statement is true cannot be stated precisely.

6.2 Addition to Chapter 2.2 Data Number and Assessment Ability of Specifications

The more information is available on a data set the easier it is to arrive at decisions regarding:

- Whether or not normal distribution is given?
- Whether or not outliers are observed?
- WS or OOS?

In borderline cases in particular, a lot of information is needed for the evaluation. Here, information means: multiple measurements. Described in more detail in the following paragraphs is how multiple measurements affect the width of the intervals. Rules become apparent showing in which cases multiple measurements can indeed facilitate the making of decisions.

In order to meet the specification, the prediction interval must not exceed the target value. If a specific value is not to fall below a certain value, it means that the target value must be smaller than the lower limit of the prediction interval:

$$x_{soll} < prd_u(x) = \bar{x} - t_{\alpha, n_1+n_2-2} \cdot \hat{\sigma}_{ges} \cdot \sqrt{\frac{1}{n_1} + \frac{1}{n_2}} \qquad \text{(Equation 5.1)}$$

By conversion one obtains the following:

$$\frac{\bar{x} - x_{soll}}{\hat{\sigma}_{ges}} > t_{\alpha, n_1+n_2-2} \cdot \sqrt{\frac{1}{n_1} + \frac{1}{n_2}} \qquad \text{(Equation 5.2)}$$

If this condition is met, the examined batch conforms to specification. Equation 5.2 expressed in words means the following: Since the distance to the target limit may be small, either the standard deviation must be small or the data number n must be high. The t-factor and the value under the root depend on the data number. This relationship is depicted in the following table (Table 16).

Both the t-factor and the term under the root affect the size of the prediction interval. From n=2 to n=3, the width of the interval is halved. If n=9, the total value is smaller than 2. For data numbers greater than/equal to 9, this means that a distance of mean value and target value of 2 standard deviations suffices. For very high data numbers the total value does not become arbitrarily small, however. The t-distribution strives towards the normal distribution, the corresponding quantile of the normal distribution measures ca. 1.65. For very high data numbers, the root term strives towards 1. Therefore, the total term also strives towards 1.65. This produces an interesting result: If the distance between mean and target value, in relationship to the standard deviation ($(\bar{x} - x_{spec}) / \hat{\sigma}$), is smaller than 1.65, then the distance becomes too small in any case – and no number of multiple measurements can compensate for it. In other words: If mean value and target value are this close to each other, a considerable part of the single values will no longer meet the specification.

7 Literature

[1] U.S. Department of Health and Human Services, Food and Drug Administration (FDA), Center of Drug Evaluation and Research (CDER). Draft Guidance for Industry. Investigating Out of Specification (OOS) Test Results for Pharmaceutical Production. http://www.fda.gov/cder/guidance/1212dft.pdf* - [2] Häusler, H., Niehörster, M., Wörns, K.P., Zum Umgang mit Normdeviationen in der Laborpraxis, Pharm. Ind. 61. 935 (1999) -[3] Out-of-specification issues – report. Institute of Validation Technology. http://www.ivthome.com/products/publications/current/ivt0825.cfm?sid=84913&token=0* - [4] Schmidt, R.: FDA-/GMP-konforme Bearbeitung von OOS-Results. Vortrag zum Kurs Nr. 405 der Arbeitsgemeinschaft für Pharmazeutische Verfahrenstechnik (APV). http://www.apv-mainz.de - [5] Hartung, J., Statistik, Oldenbourg Verlag München, 8. Aufl. 1991 - [6] Wätzig, H., in: Nürnberg, E., Surmann, P. (Hrsg.), Hagers Handbuch der Pharmazeutischen Praxis, Springer Verl. Berlin/Heidelberg/New York 5. Aufl., 1991. Band 2. S. 1048-1084 - [7] Renger, B, Nicht spezifikationskonforme Analysenresults, Pharm. Ind. 61. 1053 (1999) - [8] Stewart, I., Irrfahrt zum Mean value , Spektrum der Wissenschaft, S. 112-114 (4/1999) – [9] R. Kringle, R. Khan-Malek, F. Snikeris, P. Munden, C. Agut, M. Bauer, Drug Information J. 35 (2001) 1271-1288 - [10] Baumann, K., Regression and calibration for analytical separation techniques. Part II: Validation, Weighted and Robust Regression, Process Control and Quality 10. 75-112 (1997) - [11] Rousseuw P.J., Leroy A., Robust regression and outlier detection, John Wiley & Sons, New York, 1987 - [12] Expert Group Pharmaceutical Analysis /Quality Control of the German Pharmaceutical Society. Comments and Suggestions Regarding the FDA/CDER Draft Guidance for Industry. Investigating Out of Specification (OOS) Test Results for Pharmaceutical Production, http://www.fda.gov/ohrms/dockets/dailys/040199/c000036.pdf*

*The author has copies of citations listed as Web addresses. If the Web page no longer exists, the documents can be requested from the author via e-mail.

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Glossary / Index of Symbols and Abbreviations

α	Probability of an error of the 1st kind, i.e. to discard the null hypothesis despite its applicability; producer risk
β	Probability of an error of the 2nd kind, i.e. to discard the alternative hypothesis despite its applicability; consumer risk
γ_0	Threshold value for the percentage of WS values in the production unit required to be reached at a minimum in order for the production unit to be considered to conform to specification
Outlier	(Extreme) values due to errors
Bias	Difference between the true value and the analysis result
Total population	All of the elements of a quantity to be examined, e.g. all tablets in a batch, number of all possible measurement values obtained by one method
k_0	Threshold value for the percentage of WS values in the random sample required to be reached at a minimum in order for the production unit to be considered to be within specification
Collective	See total population; term according to R. v. Mises
Confidence interval	See confidence range
Measurement range	Range from the lowest measured value to the highest measured value
n	Size of the random sample
N	Size of the total population
OOS result	Out-of-specification result; result lying outside the specification limits
Power	„Test power“ of a method; indicates the certainty with which an OOS result is recognized as such, $1-\beta$
Precision	Unit of measure for the spread and the congruence of the measurement values after the multiple performance of an analysis (within one measurement series)
Production unit	Production batch, lot; e.g. batch
Range	See measurement range
Robustness	Measure for the independence of the analysis results of a method after minor changes to the measuring system
Random sample	Measurement values obtained for a sample of the size n taken from a total population; $x_1, x_2,...x_n$
Test power	See power
Tolerance interval	Measurement range in which a specified percentage of the total population can be found
Confidence interval	Range in which the (unknown) value for the actual percentage of WS results in the total population can be found with the probability $1-\alpha$
Prediction interval	Range in which the mean value of a future random sample will lie with a certain probability $(1-2\alpha)$
WS values	Within-specification values; values lying within the specification limits
$z_{1-\alpha}$	$(1-\alpha)$ quantile of the standard normal distribution (mean value 0, variance 1)

Table 6: Required size n of the random sample and decision threshold k_0 for testing the null hypothesis $\gamma>\gamma_0$ against the alternative $\gamma\leq\gamma_0$ at a given probability α in respect of the erroneous rejection of the null hypothesis

Table 7: Lower confidence limits γ_{min} for the probability γ of WS results in the production unit if of n random-sample values, k are WS: γ_{min} at α=20%, reliability 1-α=80%

Table 8: As in Table 7, but γ_{min} at α=10%, reliability 1-α=90%

Table 9: As in Table 7, but γ_{min} at α=5%, reliability 1-α=95%

Table 10: As in Table 7, but γ_{min} at α=2.5%, reliability 1-α=97,5%

Table 11: Upper confidence limits γ_{max} for the probability γ of WS results in the production unit if of n random-sample values, k are WS:
γ_{max} at α=20%, reliability 1-α=80%

Table 12: As in Table 11, but γ_{max} at α=10%, reliability 1-α=90%

Table 13: As in Table 11, but γ_{max} at α=5%, reliability 1-α=95%

Table 14: As in Table 11, but γ_{max} at α=2.5%, reliability 1-α=97.5%

Table 15: Factor for calculating the limits of tolerance intervals with normal distribution

Table 16: Correlation between the t-factor and s-value under the root and the data number (compare Equation 5.2; n_1 = 1. n_2 = n, α = 0.1)

Table 6:

	α	β	n	k_0
γ_0=0.5 γ_1=0.9	20%	20%	3	3
	10%	20%	5	4
	10%	10%	7	6
	5%	20%	8	7
	5%	10%	10	8
	5%	5%	11	9
γ_0=0.6 γ_1=0.9	20%	20%	5	4
	10%	20%	9	8
	10%	10%	12	10
	5%	20%	13	11
	5%	10%	16	13
	5%	5%	19	15
γ_0=0.7 γ_1=0.9	20%	20%	11	9
	10%	20%	18	16
	10%	10%	24	20
	5%	20%	26	23
	5%	10%	33	28
	5%	5%	39	33
γ_0=0.8 γ_1=0.9	20%	20%	35	30
	10%	20%	59	52
	10%	10%	81	70
	5%	20	83	73
	5%	10%	109	95
	5%	5%	133	114

Table 7:

n	k = Number of WS Results									
	1	2	3	4	5	6	7	8	9	10
3	0.072	0.287	0.585							
4	0.054	0.212	0.418	0.669						
5	0.044	0.169	0.327	0.510	0.725					
6	0.037	0.140	0.269	0.415	0.578	0.765				
7	0.031	0.120	0.228	0.350	0.483	0.629	0.795			
8	0.028	0.104	0.199	0.303	0.416	0.538	0.670	0.818		
9	0.024	0.093	0.176	0.268	0.366	0.471	0.582	0.702	0.836	
10	0.022	0.083	0.158	0.239	0.327	0.419	0.516	0.619	0.729	0.851

Table 8:

n	k = Number of WS Results									
	1	2	3	4	5	6	7	8	9	10
3	0.035	0.196	0.464							
4	0.026	0.143	0.320	0.562						
5	0.021	0.112	0.247	0.416	0.631					
6	0.017	0.093	0.201	0.333	0.490	0.681				
7	0.015	0.079	0.170	0.279	0.404	0.547	0.720			
8	0.013	0.069	0.147	0.240	0.345	0.462	0.594	0.750		
9	0.012	0.061	0.130	0.210	0.301	0.401	0.510	0.632	0.774	
10	0.010	0.055	0.116	0.188	0.267	0.354	0.448	0.550	0.663	0.794

Table 9:

n	k = Number of WS Results									
	1	2	3	4	5	6	7	8	9	10
3	0.017	0.135	0.368							
4	0.013	0.098	0.249	0.473						
5	0.010	0.076	0.189	0.343	0.549					
6	0.009	0.063	0.153	0.271	0.418	0.607				
7	0.007	0.053	0.129	0.225	0.341	0.479	0.652			
8	0.006	0.046	0.111	0.193	0.289	0.400	0.529	0.688		
9	0.006	0.041	0.098	0.169	0.251	0.345	0.450	0.571	0.717	
10	0.005	0.037	0.087	0.150	0.222	0.304	0.393	0.493	0.606	0.741

Table 10:

n	k = Number of WS Results									
	1	2	3	4	5	6	7	8	9	10
3	0.008	0.094	0.292							
4	0.006	0.068	0.194	0.398						
5	0.005	0.053	0.147	0.284	0.478					
6	0.004	0.043	0.118	0.223	0.359	0.541				
7	0.004	0.037	0.099	0.184	0.290	0.421	0.590			
8	0.003	0.032	0.085	0.157	0.245	0.349	0.473	0.631		
9	0.003	0.028	0.075	0.137	0.212	0.299	0.400	0.518	0.664	
10	0.003	0.025	0.067	0.122	0.187	0.262	0.348	0.444	0.555	0.692

Table 11:

n	k = Number of WS Results									
	0	1	2	3	4	5	6	7	8	9
3	0.415	0.713	0.928							
4	0.331	0.582	0.788	0.946						
5	0.275	0.490	0.673	0.831	0.956					
6	0.235	0.422	0.585	0.731	0.860	0.963				
7	0.205	0.371	0.517	0.650	0.772	0.880	0.969			
8	0.182	0.330	0.462	0.584	0.697	0.801	0.896	0.972		
9	0.164	0.298	0.418	0.529	0.634	0.732	0.824	0.907	0.976	
10	0.149	0.271	0.381	0.484	0.581	0.673	0.761	0.842	0.916	0.978

Table 12:

n	k = Number of WS Results									
	0	1	2	3	4	5	6	7	8	9
3	0.536	0.804	0.965							
4	0.438	0.680	0.857	0.974						
5	0.369	0.584	0.753	0.888	0.979					
6	0.319	0.510	0.667	0.799	0.907	0.893				
7	0.280	0.453	0.596	0.721	0.830	0.921	0.985			
8	0.250	0.406	0.538	0.655	0.760	0.853	0.931	0.987		
9	0.226	0.368	0.490	0.599	0.699	0.790	0.871	0.939	0.988	
10	0.206	0.337	0.450	0.552	0.646	0.733	0.812	0.884	0.945	0.990

Table 13:

n	k = Number of WS Results									
	0	1	2	3	4	5	6	7	8	9
3	0.632	0.865	0.983							
4	0.527	0.751	0.902	0.987						
5	0.451	0.657	0.811	0.924	0.990					
6	0.393	0.582	0.729	0.847	0.937	0.991				
7	0.348	0.521	0.659	0.775	0.871	0.947	0.993			
8	0.312	0.471	0.600	0.711	0.807	0.889	0.954	0.994		
9	0.283	0.429	0.550	0.655	0.749	0.831	0.902	0.959	0.994	
10	0.259	0.394	0.507	0.607	0.696	0.778	0.850	0.913	0.963	0.995

Table 14:

n	k = Number of WS Results									
	0	1	2	3	4	5	6	7	8	9
3	0.708	0.906	0.992							
4	0.602	0.806	0.932	0.994						
5	0.522	0.716	0.853	0.947	0.995					
6	0.459	0.641	0.777	0.882	0.957	0.996				
7	0.410	0.579	0.710	0.816	0.901	0.963	0.996			
8	0.369	0.527	0.651	0.755	0.843	0.915	0.968	0.997		
9	0.336	0.483	0.600	0.701	0.788	0.863	0.925	0.972	0.997	
10	0.309	0.445	0.556	0.652	0.738	0.813	0.878	0.933	0.975	0.997

Table 15:

n	γ					
	0.6	**0.7**	**0.8**	**0.9**	**0.95**	**0.975**
2	0.3979	0.8898	1.6857	3.7694	7.7327	15.5619
3	0.3333	0.7127	1.2247	2.1773	3.3717	4.9683
4	0.3093	0.6534	1.0940	1.8311	2.6311	3.5581
5	0.2966	0.6229	1.0308	1.6795	2.3353	3.0414
6	0.2886	0.6043	0.9932	1.5941	2.1765	2.7765
7	0.2831	0.5916	0.9682	1.5392	2.0773	2.6159
8	0.2791	0.5824	0.9504	1.5008	2.0095	205081
9	0.2761	0.5755	0.9370	1.4724	1.9601	2.4307
10	0.2737	0.5700	0.9265	1.4505	1.9226	2.3726
11	0.2718	0.5656	0.9182	1.4332	1.8931	2.3272
12	0.2702	0.5620	0.9113	1.4191	1.8692	2.2909
13	0.2688	0.5590	0.9056	1.4074	1.8496	2.2611
14	0.2677	0.5564	0.9007	1.3976	1.8331	2.2362
15	0.2667	0.5542	0.8965	1.3891	1.8191	2.2151
16	0.2658	0.5522	0.8929	1.3819	1.8070	2.1971
17	0.2651	0.5505	0.8897	1.3755	1.7965	2.1814
18	0.2644	0.5490	0.8869	1.3699	1.7873	2.1676
19	0.2638	0.5477	0.8844	1.3650	1.7791	2.1555
20	0.2633	0.5465	0.8822	1.3605	1.7718	2.1447
30	0.2599	0.5390	0.8683	1.3331	1.7272	2.0790
40	0.2583	0.5353	0.8615	1.3198	1.7058	2.0478
50	0.2573	0.5331	0.8575	1.3120	1.6932	2.0296
60	0.2566	0.5316	0.8548	1.3068	1.6850	2.0176
70	0.2561	0.5306	0.8529	1.3032	1.6791	2.0091
80	0.2558	0.5298	0.8515	1.3004	1.6747	2.0029
90	0.2555	0.5292	0.8504	1.2983	1.6714	1.9980
100	0.2553	0.5287	0.8495	1.2966	1.6687	1.9941
∞	0.2534	0.5244	0.8416	1.2816	1.6449	1.9600

Table 16:

n	$t_{\alpha, n-1}$	$\sqrt{1+1/n}$	$t * \sqrt{}$
2	6.3137	1.2247	7.7327
3	2.9200	1.1547	3.3717
4	2.3534	1.1180	2.6311
5	2.1318	1.0954	2.3353
6	2.0150	1.0801	2.1765
7	1.9432	1.0690	2.0773
8	1.8946	1.0607	2.0095
9	1.8595	1.0541	1.9601
10	1.8331	1.0488	1.9226
15	1.7613	1.0328	1.8191
20	1.7291	1.0247	1.7718
30	1.6991	1.0165	1.7272
40	1.6849	1.0124	1.7058
50	1.6766	1.0100	1.6932
60	1.6711	1.0083	1.6850
lim $n \to \infty$ (NV)	1.6449	1.0000	1.6449