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Simultaneous Fiducial Generalized Confidence Intervals for Ratios of Means of Lognormal Distributions

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Abstract: In this paper, we construct Fiducial Generalized Confidence Intervals (FGCI) for ratio of means of two lognormal distributions based on independent observations from the two distributions. We compared the proposed method with another method, the Z-Score method. A simulation study showed that the FGCI method performs much better than the Z-Score method, especially for small and medium samples. We also prove that the confidence intervals constructed using FGCI method have correct asymptotic coverage. In this paper we propose a new method for constructing simultaneous confidence intervals for all pairwise ratios of means of lognormal distributions. Our approach is based on Fiducial Generalized Pivotal Quantities (FGPQ) for vector parameters. Simulation studies show that the constructed confidence intervals have satisfactory small sample performance. We also prove that they have correct asymptotic coverage. The result has applications in bioequivalence studies for comparing three or more drug formulations.

Keywords: Fiducial Generalized Pivotal Quantity (FGPQ), Fiducial Generalized Confidence Interval (FGCI), Asymptotic Properties, Simultaneous Intervals, Bioequivalence.

1 Introduction

Fisher (1935) introduced the method of Fiducial Inference as an alternative to Bayesian inference in order to circumvent the step of selecting prior distributions for parameters. He illustrated the method by considering testing and interval estimation problems for situations where exact methods were unavailable. The simplest such problem where the fiducial method yielded a new solution at the time is the so called Behrens-Fisher problem. See Behrens (1929) and Fisher (1939). In this problem, one is interested in a confidence interval for $\mu_1 - \mu_2$ based on independent random samples X_i, $i = 1, \dots, m$ from $N(\mu_1, \sigma_1^2)$ distribution and Y_j, $j = 1, \dots, n$ from $N(\mu_2, \sigma_2^2)$ distribution. Fiducial inference was the subject of considerable debate and skepticism during the period from 1935 to 1980. Many published papers noted that fiducial confidence intervals were not exact in the frequentist sense. The end result was that fiducial inference fell into disrepute well before the end of the 20th century.

Tsui and Weerahandi (1989) introduced the method of generalized P-values for deriving approximate tests of hypotheses for problems where exact frequentist tests were unavailable. Subsequently, Weerahandi (1993) introduced the concept of a generalized pivotal quantity (GPQ) for a scalar parameter θ, using which he constructed approximate confidence intervals for problems where pivotal quantities, in the usual sense, are unavailable. He referred to such intervals as generalized confidence intervals (GCI). Hannig et al. (2005) identified an important subclass of GPQs, called Fiducial Generalized Pivotal Quantities (FGPQ). They proved a theorem to the effect that, under fairly general conditions, GCIs obtained from FGPQs, called Fiducial Generalized Confidence Intervals (FGCI), have correct asymptotic coverage. They also noted the essential equivalence between fiducial inference and generalized inference. In particular, their asymptotic results apply to fiducial intervals as well.

Abdel-Karim (2005) used FGPQs for vector parameters to construct simultaneous confidence intervals for all pairwise differences of means of k normal distributions. She showed via simulation studies that the intervals had satisfactory coverage in most situations. In this paper we use a similar approach to construct simultaneous confidence intervals for all pairwise ratios of means of k lognormal distributions.

More specifically, suppose $Y_{i1}, \ldots, Y_{in_i}$ is a random sample from $LN(\mu_i, \sigma_i^2)$, $i = 1, \ldots, k$, where $LN(\mu, \sigma^2)$ refers to a lognormal distribution with parameters μ, σ^2, i.e., $ln(Y_{ij}) \sim N(\mu_i, \sigma_i^2)$. We are interested in obtaining simultaneous confidence intervals for all pairwise ratios $\theta_{rs} = \theta_r/\theta_s$ $(1 \leq r < s \leq k)$ where θ_r is the mean of $LN(\mu_r, \sigma_r^2)$. In particular, $\log\theta_r = \mu_r + \sigma_r^2/2$. This is equivalent to the problem of obtaining simultaneous CIs for all pairwise differences of the form

$$\delta_{rs} = \log(\theta_r) - \log(\theta_s) = (\mu_r - \mu_s) + \frac{1}{2}(\sigma_r^2 - \sigma_s^2)\,.$$

Zhou et al. (1997) discuss comparing two lognormal means using a likelihood approach and also a bootstrap approach. Krishnamoorthy and Mathew (2003) proposed generalized confidence intervals for comparing lognormal means. Lidong, Hannig, and Iyer (2005) considered interval estimation for the ratio of two lognormal means.

To our knowledge there is no previous work on simultaneous inference on ratios of lognormal means. We consider it in this paper for two reasons. First, this problem provides us the backdrop for illustrating the construction of simultaneous FGCIs starting from a vector FGPQ, and second, this is an important problem in some applications as will become clear from the next paragraph.

Simultaneous confidence intervals for certain lognormal parameters are useful in pharmaceutical statistics. In bioequivalence studies comparing a test drug to a reference drug, it is of interest to compare the mean responses of the two drugs to ensure that they are (more or less) equally effective. With this in mind the U.S. Food and Drug Administration (FDA) requires the lab submitting an approval request to demonstrate that certain *equivalence criteria* are satisfied. One such criterion is called the average bioequivalence criterion which requires the ratio $\theta = \mu_T/\mu_R$ to be sufficiently close to 1, where μ_T denotes the mean response to a test formulation of a drug and μ_R denotes the mean for the reference formulation of the drug. A confidence interval for the ratio $\theta = \mu_T/\mu_R$ is useful in this situation. A key response variable in such studies is called AUC which is the area under the curve relating the plasma drug concentration in a patient to the elapsed time after the drug is administered. As per the FDA guidelines, the analysis of AUC is to be carried out using the log scale. This is because the distribution of AUC is typically modeled well by a log-normal distribution. So the parameter of interest is the ratio of means of two log-normal distribution. This approach is termed bioequivalence and involves the calculation of the confidence interval for the ratio of the average of test and reference products.

The experimental design of choice in bioequivalence studies comparing two or more formulations of a drug is a crossover design with adequate washout periods to minimize carryover effects. However, a parallel design is more appropriate when the half lives of drugs being tested are very long and this is recognized in the U.S. Food and Drug Administration (2001). The two-group parallel design was considered by Lidong et al. (2005) who derived FGCIs for the ratio of means of two Log-normal Distributions.

Some bioequivalence studies consider one or more reference drugs (for instance, the same drug in different forms – tablets, capsules, caplets, liquid, etc) and one or more test drugs. In such studies one is often interested in all pairs of ratios of means to help assess mutual bioequivalence of all formulations. We propose a solution to this problem by applying the method introduced in Abdel-Karim (2005) for constructing simultaneous confidence intervals based on FGPQs. The performance of the proposed method is assessed using a statistical simulation study.

The paper is organized as follows. In the next section we describe the notation and terminology used in this paper and exhibit simultaneous Fiducial Generalized Confidence Intervals for ratios of lognormal means. The performance of these intervals is assessed by statistical simulation which is described in Section 3. A proof of the asymptotic correctness of the proposed intervals is given in Section 4. Some concluding remarks are presented in Section 5.

2 Simultaneous Fiducial Generalized Confidence Intervals for Ratios of Log-Normal Means

In this section we show how one may construct simultaneous confidence intervals for parameters of interest based on a vector FGPQ. First we give the definition of a Generalized Pivotal Quantity (GPQ).

Definition 1. Let $\mathbb{S} \in \mathbb{R}^k$ denote an observable random vector whose distribution is indexed by a (possibly vector) parameter $\xi \in \mathbb{R}^p$. Suppose we are interested in making inferences about $\theta = \pi(\xi) \in \mathbb{R}^q$ ($q \geq 1$). Let $\mathbb{S}^\star$ represent an independent copy of $\mathbb{S}$. We will use s and $\mathrm{s}^\star$ to denote realized values of $\mathbb{S}$ and $\mathbb{S}^\star$, respectively. A generalized pivotal quantity for θ, denoted by $\mathcal{R}_\theta(\mathbb{S}, \mathbb{S}^\star, \xi)$ (or simply $\mathcal{R}_\theta$ or $\mathcal{R}$, when there is no ambiguity) is a function of $(\mathbb{S}, \mathbb{S}^\star, \xi)$ with the following properties.
(GPQ1) The conditional distribution of $\mathcal{R}_\theta(\mathbb{S}, \mathbb{S}^\star, \xi)$, conditional on $\mathbb{S} = \mathrm{s}$, is free of ξ.
(GPQ2) For every allowable $\mathrm{s} \in \mathbb{R}^k$, $\mathcal{R}_\theta(\mathrm{s}, \mathrm{s}, \xi)$ depends on ξ only through θ.

This definition is essentially the same as the definition given in Weerahandi (1993) but we use a slightly different notation which eventually facilitates a rigorous mathematical treatment of properties of confidence intervals obtained using GPQs.

Property GPQ2 implies that $\mathcal{R}_\theta(\mathrm{s}, \mathrm{s}, \xi) = f(\mathrm{s}, \theta)$ for some function f. It turns out that the subclass of GPQs for which $f(\mathrm{s}, \theta)$ is a function of θ only, say $f(\mathrm{s}, \theta) = f(\theta)$, has a special connection with fiducial inference. Generalized confidence regions obtained using such GPQs are not guaranteed to be intervals unless the function $f(\theta)$ is invertible. In this case, one may assume, without loss of generality, that $f(\theta)$ is identically equal to θ. Such GPQs exist in practically every application we have considered. Hannig et al. (2005)

refer to this subclass of GPQs as Fiducial Generalized Pivotal Quantities (FGPQ). They have shown that, if $\mathcal{R}_\theta$ is a FGPQ for θ then frequentist probability intervals associated with the distribution of $\mathcal{R}_\theta$ have a corresponding interpretation as fiducial probability intervals associated with the parameter θ.

Given a FGPQ for θ, a Fiducial Generalized Confidence Interval (FGCI) for θ may be written as $L \leq \theta \leq U$ where L is the $\alpha/2$ percentile and U is the $1-\alpha/2$ percentile of the distribution of $\mathcal{R}_\theta(\mathrm{s}, \mathbb{S}^\star, \xi)$, where s is the observed data. Except in some simple problems these percentiles are estimated by Monte-Carlo methods.

2.1 Proposed Method for Simultaneous Intervals

For $i = 1, \ldots, K$, suppose $Y_{ij} \overset{iid}{\sim} N(\mu_i, \sigma_i^2)$, for $j = 1, \ldots, n_i$. Then $\exp(Y_{ij})$, $j = 1, \ldots, n_i$ is an iid sample from a lognormal distribution with mean $\theta_i = \exp(\mu_i + \sigma_i^2/2)$. The problem of constructing simultaneous confidence intervals for $\theta_{ij} = \theta_i/\theta_j$ for all $i \neq j$ is equivalent to the problem of constructing simultaneous confidence intervals for the parameters $\delta_{ij} = \log(\theta_{ij}) = (\mu_i + \sigma_i^2/2) - (\mu_j + \sigma_j^2/2)$.

We first observe that a FGPQ for δ_{ij} is given by

$$\mathcal{R}_{\delta_{ij}}(\mathbb{S}, \mathbb{S}^\star, \xi) = \mathcal{R}_{\mu_i} - \mathcal{R}_{\mu_j} + \frac{1}{2}(\mathcal{R}_{\sigma_i^2} - \mathcal{R}_{\sigma_j^2})$$

where

$$\mathcal{R}_{\mu_p} = \bar{Y}_p - \frac{S_p}{S_p^\star}(\bar{Y}_p^\star - \mu_p)$$

and

$$\mathcal{R}_{\sigma_p^2} = \frac{S_p^2}{S_p^{\star 2}} \sigma_p^2$$

for $p = 1, \ldots, K$. Here $\bar{Y}_p$ denotes the mean and S_p^2 is the sample variance of Y_{pj} for $j = 1, \ldots, n_p$ and $\bar{Y}_p^\star$, $S_p^{\star 2}$ are independent copies of $\bar{Y}_p$, S_p^2.

Define

$$\mathcal{D}(\mathbb{S}, \mathbb{S}^*, \xi) = \max_{i \neq j} \left| \frac{(\overline{Y}_i + (1/2)S_i^2) - (\overline{Y}_j + (1/2)S_j^2) - \mathcal{R}_{\delta_{ij}}(\mathbb{S}, \mathbb{S}^*, \xi)}{\sqrt{V_{ij}}} \right| \tag{1}$$

where V_{ij} is a consistent estimator of the variance of $(\overline{Y}_i + (1/2)S_i^2) - (\overline{Y}_j + (1/2)S_j^2)$, i.e.,

$$V_{ij} = \frac{S_i^2}{n_i} + \frac{S_i^4}{2(n_i - 1)} + \frac{S_j^2}{n_j} + \frac{S_j^4}{2(n_j - 1)} \,. \tag{2}$$

Then $100(1-\alpha)\%$ two-sided simultaneous FGCIs for pairwise ratios θ_{ij}, $i \neq j$ of means of more than two independent lognormal distributions are $[L_{ij}, U_{ij}]$ where

$$L_{ij} = \exp(\overline{Y}_i - \overline{Y}_j + (1/2)S_i^2 - (1/2)S_j^2 - d_{1-\alpha}\sqrt{V_{ij}}) \tag{3}$$

$$U_{ij} = \exp(\overline{Y}_i - \overline{Y}_j + (1/2)S_i^2 - (1/2)S_j^2 + d_{1-\alpha}\sqrt{V_{ij}}) \tag{4}$$

and d_γ denotes the 100γ-percentile of the conditional distribution of $\mathcal{D}(\mathbb{S}, \mathbb{S}^*, \xi)$ given $\mathbb{S} = \mathbf{s}$.

Table 1: Classification of sample size and proportions of empirical coverage within limits of simulation error for each class (three populations).

Size	Combination	Proportion
small	(5 5 5) (5 5 25) (5 25 25) (5 5 125)	13.09%
medium	(25 25 25) (5 25 125) (5 125 125) (25 25 125) (25 125 125)	39.28%
large	(125 125 125)	62.86%

Remark 1. Let $\boldsymbol{\delta}$ denote a vector of parameters whose components are δ_{ij}, $1 \leq i < j \leq K$. It is instructive to note that the confidence region for $\boldsymbol{\delta}$ resulting from the proposed simultaneous intervals for δ_{ij} are one of the many possible ways in which to construct a generalized confidence region for $\boldsymbol{\delta}$. We begin with the vector FGPQ $\mathcal{R}_{\boldsymbol{\delta}}$ and obtain a confidence region for $\boldsymbol{\delta}$ that has a prespecified shape. For details the reader may refer to Hannig (2005) and Hannig et al. (2005).

In the next section we examine the performance of these simultaneous intervals in small sample situations as well as large sample situations. Section 4 contains a theorem describing the asymptotic behavior of these intervals.

3 Simulation Study and Discussion of Results

3.1 Details of Simulation Study

Simultaneous FGCIs for all pairwise ratios of means of three independent lognormal distributions were considered in the simulation study. The simulations were done using 5000 independently generated datasets for each of a number of scenarios covering different parameter settings. For each simulated dataset the 95% simultaneous generalized confidence intervals were estimated using 10000 realizations of the random variable $\mathcal{D}(\mathbb{S}, \mathbb{S}^*, \xi)$ defined in (1). Without loss of generality, it was assumed that all μ_i's, $i = 1, 2, 3$, are equal to 0. The values used for sample sizes were 5, 25 and 125. Five levels of σ_1^2 were used – 0.01, 0.1, 1, 10 and 100. For each level of σ_1^2, σ_2^2 values were set at $2^l\sigma_1^2$, and σ_3^2 values were set at $2^m\sigma_1^2$,where l and m are integers and $0 \leq l \leq m \leq 3$. Table 1 gives a classification of the various sample size combinations considered in the simulation study into small sample cases, medium sample cases and large sample cases. The last column of Table 1 gives the proportion of the simulation settings for which the empirical coverage probability is not significantly different from the target coverage rate of 0.95.

Several scenarios with combinations of very large sample sizes and extreme variances were also included in the study to judge how soon the asymptotics take effect (see Section 4). The parameter settings for these large sample cases are given in in Table 2. The last column in Table 2 gives the empirical coverage probability for the particular simulation setting considered.

Table 2: Empirical coverage associated with 95% FGCIs for combinations of very large sample size and extreme variances (three populations).

n_1	n_2	n_3	σ_1	σ_2	σ_3	Empirical Coverage
125	125	125	0.01	0.01	0.01	0.9531
625	625	625	0.01	0.01	0.01	0.9490
1000	1000	1000	0.01	0.01	0.01	0.9491
2000	2000	2000	0.01	0.01	0.01	0.9498
125	125	125	100	800	1600	0.9509
625	625	625	100	800	1600	0.9488
1000	1000	1000	100	800	1600	0.9513
2000	2000	2000	100	800	1600	0.9484

3.2 Discussion

The results of the simulation study are also classified into three categories according to the combination of sample sizes – small samples, medium samples, and large samples. See Table 1. Figure 1 shows histograms of empirical coverage probabilities for each of these three cases and also for all of the cases combined. It is seen that the empirical coverage rates are in the range from 0.94 to 1.0 and hence the proposed interval procedure is conservative. The results also show that most of the empirical coverages bigger than 0.98 occur with the combination of very small samples and large variances.

As the sample size increases, the empirical coverage approaches the claimed coverage and the proportion of empirical coverage within the binomial simulation error bounds increases. Table 2 shows that empirical coverages approach the claimed coverage as sample sizes increase even for very large variances. The convergence appears to be slower for scenarios with large variances than scenarios with small variances.

4 Asymptotic Behavior of Simultaneous FGPQs for Ratios of Lognormal Means

We continue to use the notation of the previous section. We now prove the following theorem

Theorem 1. *Let all $n_1, \dots, n_K$ approach infinity in such a way that $r_j = \lim n_j/(n_1 + \cdots + n_K)$ exists and $0 < r_j < 1$. Then the $100(1-\alpha)\%$ two-sided simultaneous confidence intervals have asymptotically $100(1-\alpha)\%$ frequentist coverage, i.e.,*

$$P(L_{ij} \le \theta_{ij} \le U_{ij}\,, \textit{for all } i, j) \to 1 - \alpha\,.$$

Proof. Set $n = n_1 + \cdots + n_K$. Define a vector $\mathbf{m} = (\mu_1, \dots, \mu_K, \sigma_1^2, \dots, \sigma_K^2)$, and a diagonal matrix

$$D = \operatorname{diag}\left(\frac{\sigma_1}{\sqrt{r_1}}, \dots, \frac{\sigma_K}{\sqrt{r_K}}, \frac{\sigma_1^2\sqrt{2}}{\sqrt{r_1}}, \dots, \frac{\sigma_K^2\sqrt{2}}{\sqrt{r_K}}\right)\,.$$

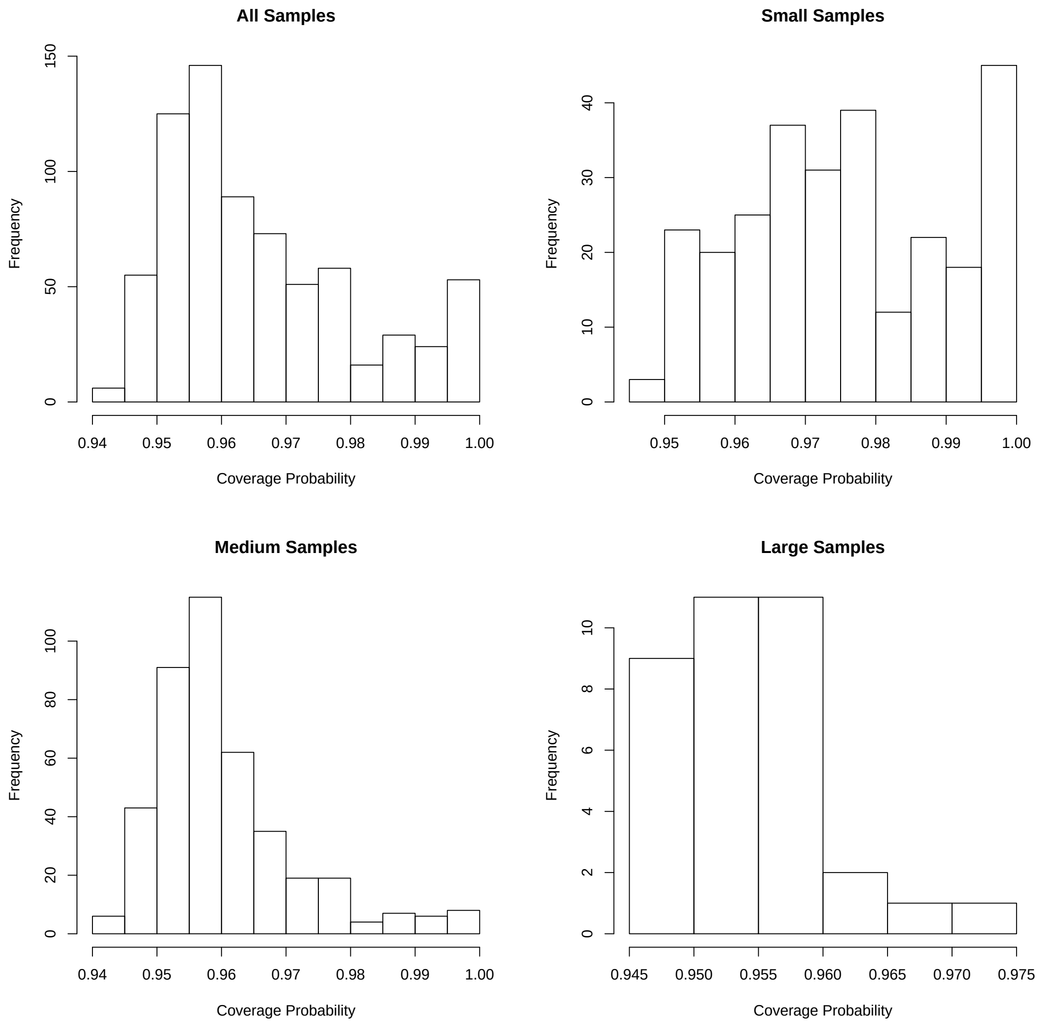

Figure 1: Histograms of empirical coverage (three populations)

The central limit theorem implies that $\sqrt{n}(\mathbb{S}_n - \mathbf{m}) \xrightarrow{\mathcal{D}} D\mathbb{Z}$ where $\mathbb{Z} = (Z_1, \dots, Z_{2K})$ are i.i.d. N(0,1) variables. By Skorokhod's theorem (see Billingsley (1995)) we can find a sequence $\bar{\mathbb{S}}_n$ independent of $\mathbb{S}^*$ such that $\bar{\mathbb{S}}_n$ has the same distribution as $\mathbb{S}$ and $\sqrt{n}(\bar{\mathbb{S}}_n - \mathbf{m}) \to D\mathbb{Z}$ almost surely. In what follows we can therefore assume without loss of generality that

$$\sqrt{n}(\mathbb{S}_n - \mathbf{m}) \to D\mathbb{Z} \quad \text{a.s.} \tag{5}$$

It follows from the Slutsky's theorem that as $n \to \infty$

$$\mathcal{D}(\mathbb{S}, \mathbb{S}^\star, \xi) \to \max_{i \neq j} \left| \frac{Z_i^\star \frac{\sigma_i}{\sqrt{r_i}} + Z_{i+K}^\star \frac{\sigma_i^2}{\sqrt{2r_i}} - Z_j^\star \frac{\sigma_j}{\sqrt{r_j}} - Z_{j+K}^\star \frac{\sigma_j^2}{\sqrt{2r_j}}}{\left(\frac{\sigma_i^2}{r_i} + \frac{\sigma_i^4}{2r_i} + \frac{\sigma_j^2}{r_j} + \frac{\sigma_j^4}{2r_j} \right)^{1/2}} \right| \quad \text{a.s.} \tag{6}$$

Here the a.s. comes from the a.s. convergence in (5).

Recall the definition of the percentile $d_\gamma(\mathbf{s})$ above. Since the limiting distribution in (6) is continuous, we have by the definition of convergence in distribution

$$d_\gamma(\mathbb{S}) \to q_\gamma\,, \tag{7}$$

where q_γ is the the 100γ-percentile of the limiting distribution in (6).

Finally, realize that (5) implies

$$\frac{\overline{Y}_i - \overline{Y}_j + (1/2)S_i^2 - (1/2)S_j^2 - \delta_{ij}}{\sqrt{V_{ij}}} \to \frac{Z_i\frac{\sigma_i}{\sqrt{r_i}} + Z_{i+K}\frac{\sigma_i^2}{\sqrt{2r_i}} - Z_j\frac{\sigma_j}{\sqrt{r_j}} - Z_{j+K}\frac{\sigma_j^2}{\sqrt{2r_j}}}{\left(\frac{\sigma_i^2}{r_i} + \frac{\sigma_i^4}{2r_i} + \frac{\sigma_j^2}{r_j} + \frac{\sigma_j^4}{2r_j}\right)^{1/2}} \quad \text{a.s.}$$

This, together with (7) and some algebra gives

$$\begin{aligned}
&P(L_{ij} \le \theta_{ij} \le U_{ij},\ \text{for all } i,j) \\
&= P\left(\max_{i\neq j}\left|\frac{\overline{Y}_i - \overline{Y}_j + (1/2)S_i^2 - (1/2)S_j^2 - \delta_{ij}}{\sqrt{V_{ij}}}\right| \le d_{1-\alpha}\right) \\
&\to P\left(\max_{i\neq j}\left|\frac{Z_i\frac{\sigma_i}{\sqrt{r_i}} + Z_{i+K}\frac{\sigma_i^2}{\sqrt{2r_i}} - Z_j\frac{\sigma_j}{\sqrt{r_j}} - Z_{j+K}\frac{\sigma_j^2}{\sqrt{2r_j}}}{\left(\frac{\sigma_i^2}{r_i} + \frac{\sigma_i^4}{2r_i} + \frac{\sigma_j^2}{r_j} + \frac{\sigma_j^4}{2r_j}\right)^{1/2}}\right| \le q_{1-\alpha}\right) \\
&= 1-\alpha
\end{aligned}$$

as $n \to \infty$. □

5 Conclusion

In this paper we proposed a new method to construct simultaneous confidence intervals for all pairwise ratios of means of more than two lognormal distributions based on a Fiducial Generalized Pivotal Quantity (FGPQ). We verified by means of a simulation study that these intervals perform satisfactorily in small samples. We also proved that the constructed confidence intervals have correct asymptotic coverage. The role of such intervals in bioequivalence studies was also discussed.

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References

Abdel-Karim, A. (2005). *Applications of Generalized Inference*. Unpublished doctoral dissertation, Colorado State University, Fort Collins, Colorado.

Behrens, W.-V. (1929). Ein Beitrag zur Fehlerberchnung bei wenigen Beobachtungen. *Landwirtschaftliches Jahrbuch*, *LXVIII*, 807-837.

Billingsley, P. (1995). *Probability and Measure* (3rd ed.). New York: J. Wiley.

Fisher, R. A. (1935). The fiducial argument in statistical inference. *Annals of Eugenics*, *VI*, 91-98.

Fisher, R. A. (1939). Samples with possibly unequal variances. *Annals of Eugenics*, *IX*, 174-180.

Hannig, J. (2005). *On multidimensional fiducial generalized confidence intervals* (Tech. Rep. No. 2005/1). Colorado State University.

Hannig, J., Iyer, H. K., and Patterson, P. L. (2005). Fiducial generalized confidence intervals. *Journal of the American Statistical Association*, to appear.

Krishnamoorthy, K., and Mathew, T. (2003). Inferences on the means of lognormal distributions using generalized p-values and generalized confidence intervals. *Journal of Statistical Planning and Inference*, *115*, 103-121.

Lidong, E., Hannig, J., and Iyer, H. K. (2005). *Fiducial Generalized Confidence Intervals for Functions of Lognormal Means and Variances* (Tech. Rep.). Colorado State University, Fort Collins, Colorado.

Tsui, K. W., and Weerahandi, S. (1989). Generalized p-values in significance testing of hypotheses in the presence of nuisance parameters. *Journal of the American Statistical Association*, *84*(406), 602-607.

U.S. Food and Drug Administration. (2001). Guidance to industry - statistical approaches to establishing bioequivalence. *U.S. Department of Health and Human Services, Food and Drug Administration*.

Weerahandi, S. (1993). Generalized confidence intervals. *Journal of the American Statistical Association*, *88*(423), 899-905.

Zhou, X. H., Gao, S., and Hui, S. L. (1997). Methods for comparing the means of two independent log-normal samples. *Biometrics*, *53*(3), 1129-1135.

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