Some properties of the equivalence testing procedure for log-normal data

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In order to test whether two entities are equivalent with respect to some certain characteristics, in the pharmaceutical field the two one-sided test procedure is often used. For instance, the two one-sided test procedure is used to test equivalence in blood concentration×time profiles for different formulations of a pharmaceutical product. In equivalence testing the null hypothesis states, that tested entities are different by prespecified amount referred to as the equivalence margin. Parameters of concentration — time curve to be tested are supposed to be log-normally distributed (e.g., area under the curve, AUC). Thus, null hypothesis and alternative can be written in terms of ratio of log-normally distributed $AUCs$:

$$H_0 : \frac{\mu_T}{\mu_R} \leq \theta_1 \text{ or } \frac{\mu_T}{\mu_R} \geq \theta_2 \text{ vs}$$

$$H_A : \theta_1 < \frac{\mu_T}{\mu_R} < \theta_2,$$

or in terms of difference of normally distributed $\ln AUC$ after logarithmic transformation:

$$H_0^{'} : \mu_T' - \mu_R' \leq \ln\theta_1 \text{ or } \mu_T' - \mu_R' \geq \ln\theta_2 \text{ vs}$$

$$H_A^{'} : \ln\theta_1 < \mu_T' - \mu_R' < \ln\theta_2,$$

where μ_T and μ_R are the expectations of $AUCs$ for the test and reference formulations, μ_T' and μ_R' are the expectations of $\ln AUCs$ for the test and reference formulations, θ_1 and θ_2 are the lower and upper equivalence margins respectively (for details, see [1,2]).

Let's suppose, that random variable AUC for either formulation can be represented as a sum of a random part — partial $AUC_{partial}$ — and a constant c:

$$AUC = AUC_{partial} + c.$$

Adding constant does not change the fundamental statistical characteristics of any random variable, so $AUC_{partial}$ is also a log-normally distributed random variable with expectations $\mu_T^{partial} = \mu_T - c$ and $\mu_R^{partial} = \mu_R - c$ for

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the test and reference formulations respectively. For simplicity let's suppose, that $\mu_T^{partial} > \mu_R^{partial}$. It can be shown that:

$$0 < \ln \frac{\mu_T}{\mu_R} = \ln \frac{\mu_T^{partial} + c}{\mu_R^{partial} + c} < \ln \frac{\mu_T^{partial}}{\mu_R^{partial}},$$

and this follows by:

$$\ln \theta_2 < \ln \frac{\mu_T}{\mu_R} < \ln \frac{\mu_T^{partial}}{\mu_R^{partial}}.$$

This means, that the partial AUC test has larger hypothesis acceptance region χ_0 and smaller hypothesis rejection region χ_a, and, in this sense, is more sensitive to detect difference.

This approach can be of value in case of missingness in the equivalence trial data. Earlier it was shown, analytically and via simulations, that missing data can lead to increase in type I error [3, 4]. Additionally, in the latter paper it was noted, that missing values happened 'late' in the concentration — time curve has a very damaging effect on the study conclusions. Assuming that the 'late' part of concentration — time curve does not depend on absorption mainly, it can be treated as constant in our approach to control the level of the test.

Acknowledgements: this work was supported by the Moscow Center Fundamental and Applied Mathematics.

References

1. SC. Chow, JP. Liu, *Design and Analysis of Bioavailability and Bioequivalence Studies*, Chapman and Hall/CRC, New York, 2008.

2. M. A. Dranitsyna, T. V. Zakharova, R. R. Niyazov, Svojstva procedury dvuh odnostoronnih testov dlya priznaniya bioekvivalentnosti lekarstvennyh preparatov, emphRemedium. Zhurnal o rynke lekarstv i medicinskoj tekhniki **3** (2019) 40–47.

3. T. V. Zakharova, A. A. Tarkhov, Evaluation of the significance level in Schuirmanns test for checking the bioequivalence hypothesis in missing data conditions, *Informatics and Applications* **13** (2019) 58–62.

4. A. Donner, W. W. Hauck, G. Zou, The impact of missing values in the concentration-time curve on the assessment of bioequivalence, *Pharmaceutical Statistics* **4** (2005) 91–99.