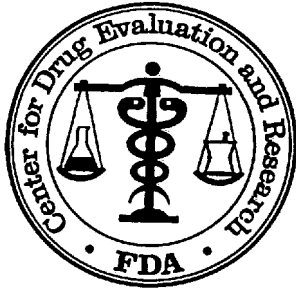


**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**209604Orig1s000**

**STATISTICAL REVIEW(S)**



US Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Translational Sciences  
Office of Biostatistics

## STATISTICAL REVIEW AND EVALUATION

### New Drug Application

#### Biometrics Division: VI

<b>NDA No.:</b>	209604
<b>DATE RECEIVED BY OB:</b>	10/13/2016
<b>DRUG NAME:</b>	Gemcitabine Injection
<b>INDICATION:</b>	
<b>SPONSOR:</b>	Accord Healthcare Inc
<b>REVIEW FINISHED:</b>	06/08/2017
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# **1 STATISTICAL REVIEW AND EVALUATION OF EVIDENCE**

## **1.1 Purpose of this review**

On April 17, 2017, Office of New Drug (OND) requests CMC statistics team in the Office of Biostatistics (OB) to evaluate adequacy of the sponsor's sample size in pharmacokinetic Bioequivalence study 311-13.

## **1.2 Sponsor's study design**

This was a multicentre, randomized, open label, two-period, two-treatment, two-way crossover, single dose bioequivalence study comparing Gemcitabine Injection 100 mg/mL (10 mL) (Manufactured by: Intas Pharmaceuticals Ltd.) to the reference listed drug Gemzar 1g/vial (Gemcitabine for Injection 1g/vial, Lilly USA, LLC, Indianapolis, IN 46285, USA) in patients with Pancreatic or Ovarian Cancer.

The study was planned to be conducted on 44 patients with pancreatic or ovarian cancer. However, due to the issue of the date of expiry of the reference medicinal product, and the subsequent advice received from the USFDA on the matter, the sponsor carried out equivalence evaluation using 30 patients.

## **1.3 Reduced sample size issue**

Office of Clinical Pharmacology expressed the concern on the power reduction due to sample size reduced from 44 to 30 and further concern on validity of BE Study 311-13. In order to under the power and consumer's risk for a bioequivalence study, we first have to set up an appropriate hypothesis tests. Let  $\mu_T$  be the population mean of AUC of Gemcitabine for patients treated with

Gemcitabine Injection 100 mg/mL (10 mL) (Manufactured by: Intas Pharmaceuticals Ltd.). Let  $\mu_R$  be the population mean of AUC of Gemcitabine for patients treated with the reference listed drug Gemzar 1g/vial. The sponsor proposed the following hypothesis for the bioequivalence study comparing ratio of two means.

$$\begin{aligned} H_0 : \mu_T / \mu_R \leq \theta_1 \text{ \textit{or} } \mu_T / \mu_R \geq \theta_2 \\ H_a : \theta_1 < \mu_T / \mu_R < \theta_2 \end{aligned} \quad (1)$$

Here  $\theta_1$  and  $\theta_2$  are pre-specified constants, also called equivalence margins, and  $\theta_1 < \theta_2$ . Here  $\theta_1 = 0.8$  and  $\theta_2 = 1.25$ .

The null hypothesis,  $H_0$ , states that  $\mu_T$  and  $\mu_R$  are not equivalent. The alternative hypothesis,  $H_a$ , states that they are equivalent. The alternative hypothesis representing equivalence,  $H_a$ , is the intersection of the two one-sided parameter regions,  $\{ \theta_1 < \mu_T - \mu_R \}$  and  $\{ \mu_T - \mu_R < \theta_2 \}$ . We conclude the test product is bioequivalent to the reference product if  $H_0$  is rejected.

We can calculate sample sizes provided that the ratio of means and variability are known from previous experience and the type I and type II error rates are specified assuming that  $\log(\text{AUC})$  is a normal variable.

For equivalence hypothesis tests in (1), the power to reject the  $H_0$  (not equivalent) under  $H_a$  (equivalent) will decrease due to smaller number of subjects. The producer's risk (type II error rate) is 1-power. So the producer's risk will increase due to smaller number of subjects. On other hand, the type I error rate is the probability of rejecting  $H_0$  under  $H_0$  (not equivalent). Under the intersection-union hypothesis testing, the type I error rate is controlled at the significance level,  $\alpha$ . The consumer's risk is type I error rate. Hence the consumer's risk of having not-equivalent

product is fixed at  $\alpha$ . In other words, smaller number of subjects will not increase the consumer's risk.

#### **1.4 Conclusion and recommendation**

For equivalence hypothesis tests in (1), the power to reject the  $H_0$  (not equivalent) under  $H_a$  (equivalent) will decrease due to smaller number of subjects. The producer's risk (type II error rate) is 1-power. So the producer's risk will increase due to smaller number of subjects. On other hand, the type I error rate is the probability of rejecting  $H_0$  under  $H_0$  (not equivalent). Under the intersection-union hypothesis testing, the type I error rate is controlled at the significance level,  $\alpha$ . The consumer's risk is type I error rate. Hence the consumer's risk of having not-equivalent product is fixed at  $\alpha$ . In other words, smaller number of subjects will not increase the consumer's risk.

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/s/  
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06/08/2017

YI TSONG  
06/08/2017