國立臺灣大學生物暨農學院農藝學研究所

生物統計學組碩士論文

Division of Biometry Graduate Institute of Agronomy

College of Bioresources and Agriculture

National Taiwan University

Master thesis

生物相似性藥品之設限資料對等性評估的研究

A Study for Application of the Parallel-line Assay to Evaluation of Biosimilar Drug Products Based on Censored Data

張育誠

Yu-Cheng Chang

指導教授：劉仁沛 博士

Advisor: Jen-Pei Liu, PH.D.

中華民國 102 年 6 月

June, 2013

國立台灣大學碩士學位論文
口試委員會審定書

生物相似性藥品之設限資料對等性評估的研究

A Study for Application of the Parallel-line Assay to Evaluation of Biosimilar Drug Products Based on Censored Data

本論文係 張育誠 君（學號 R00621209）在國立台灣大學農藝所生物統計組完成之碩士學位論文，於民國 102 年 6 月 28 日承下列考試委員審查通過及口試及格，特此證明

口試委員：

國立台灣大學公共衛生學系與預防醫學研究所教授
季瑋珠 博士 季瑋珠

私立長庚大學臨床資訊與醫學統計研究中心助理教授
林志榮 博士 林志榮

國立台灣大學農藝學系(所)教授(指導教授)
劉仁沛 博士 劉仁沛

謝辭

首先誠摯的感謝指導教授劉仁沛博士，老師悉心的教導使我得以一窺統計於製藥領域的深奧，不時的討論並指點我正確的方向，使我在這兩年中獲益匪淺。老師對學問的嚴謹更是我輩學習的典範。

本論文的完成得感謝張智熙學長與林亞靚學姐的大力協助。因為有兩位的幫忙，使得本論文能夠更完整而嚴謹。兩年裡的日子，實驗室里共同的生活點滴，學術上的討論、言不及義的閒扯、因為睡太晚而遮遮掩掩閃進教室.....，各位的陪伴讓兩年的研究生活變得絢麗多彩。感謝志榮學長、姜杰學長不厭其煩的指出我研究中的缺失，且總能在我迷惘時為我解惑，也感謝亭甄同學、松林同學、智揚同學的幫忙，恭喜我們順利走過這兩年。實驗室的楊宇晴學妹、姚力維學弟與黃証群學弟當然也不能忘記，你/妳們的幫忙及搞笑我銘感在心。

最後要再次謝謝劉仁沛老師，你的處處諒解真的讓我十分感動，我一直是個有話不敢說的人。很多時候自己內心無法給自己答案，就會想要放棄一切。在我最低落的時候總會感受到老師的幫助，雖然我不常找老師聊天，但是在各種小地方上都可以感受到老師對我們的照顧，我非常感動。除了感謝外我也必須道歉，我真的一直給老師添麻煩了。

張育誠

台灣大學農藝所生物統計組

民國 102 年 6 月

English Abstract

In recent years, biologics market of biological drug increases rapidly, but the development costs are also very high. Therefore, after the patent of biological products expires, many pharmaceutical companies have invested in the development of biosimilar products. But, biological products, with process specificity, are different from traditional small molecule drug products. Therefore the methods for assessment of biosimilar products are also different from that of chemical generic products. Current regulations indicate that the clinical trials for assessment can be waived on a case-by-case basis, but a pharmacovigilance is necessary. However, if the requirement for clinical trials cannot be waived, the development cost of biosimilar products will be the same as that of the innovators. It cannot achieve the goal of cost reduction, and deny of access of biological drug products to needed patients.

In this thesis, we propose to apply the parallel-line assay to test whether the approval of the biosimilar products should require clinical trials. We developed the statistical testing procedure to evaluate the equivalence between the biosimilar drug product and innovator's biological procedure when the primary endpoint is a censored variable which follows an exponential distribution. The results of size and power from the simulation studies are presented. A numerical example is used to illustrate the application of the

proposed method

Keywords: Biological products, Biosimilar, Censored endpoints, Exponential distribution.

中文摘要

生物製劑的市場近年來逐漸增加，但是所需的開發成本仍然很高，所以在生物製劑的專利到期以後，許多藥廠紛紛投入生物相似性藥品的研發。不同於一般的化學分子學名藥，生物製劑具有製程專一的特性，所以評估生物相似性藥品必須與化學分子學名藥有所不同。現行法規中，生物相似性藥品需依個案，適度的減免臨床試驗，才能被核准上市，成本並不小於開發新的生物製劑，無法降低成本，達到造福病患之目的。

當療效指標為設限資料時，本篇論文以對數風險率回歸檢定法評估生物製劑相似性藥品與原廠生物製劑是否為相似，以評估是否需要執行完整臨床試驗，模擬所提出方法之第一型錯誤機率、檢定力和覆蓋率，並以數值例子來介紹方法之應用。

關鍵字: 生物製劑，生物製劑相似性藥品，設限資料，指數分佈。

Contents

List of Tables

List of Figures

Chapter 1 Introduction

1.1 Background and Motivations

Biologics are therapeutic moiety manufactured by a living system or organism, such as human, plants, animals or microorganisms, and they are used for medical, prevention and cure of human diseases. It can be applied to cancer, diabetes mellitus, growth impairment, and many other diseases. Furthermore, biologics include a wide range of medicinal products such as vaccines, blood and blood components, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins created by biological processes. Biologics are important life-saving drug products for patients with insufficiently medical needs. The worldwide sales of biologics in 2008 reached US $125 billion dollars which accounts about 20% of the pharmaceutical industry.

In addition, unlike the chemical drug products, biological products, which are much larger molecular weights, can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues. In short words, biological products are organic compounds made of amino acids, which possess primary, secondary, tertiary and quaternary structures. Biologic products are sensitive to heat, light, and shock, and it can easily be contaminated by manufacturing

process changes. Therefore, the manufacture of biological agents has to be noted, such as types of bacteria, the cells to create the protein and the quality of production equipments. Therefore the biological products are very expensive and can reach up to US $ 120,000 per patient per year. This high cost denies the accessibility of most of patients to the most of life-saving biological products. (Webber, 2007, Wikipedia, Biosimilar and Biologic, 2011.04)

Many best-selling biological products will face patent expiration in recent years. Table 1.1 shows that several biological products have reached the end of their patent protection. Therefore, generic reproductions of the innovator's biological products can be made available. These generic reproductions of the innovator's biological products are called biosimilar products by the European Union and follow-on biologics in the United States. In 2008, the US Congressional Budget Office predicted a savings of US $25 billion dollars in the next 10 years. Because of reduction of unnecessary drug testing and clinical trials, the price of the biosimilar drug products can be reduced and become affordable for most needed patients.

Biosimilars or follow-on biologics are not like the common small-molecule chemical drugs. Biologics generally exhibit high molecular complexity and may be quite sensitive to manufacturing process changes. Table 1.2 provides comparisons of the differences between small-molecule chemical generics and biosimilar products. Therefore,

assessment of biosimilar products may also be different. The innovators of the biological products suggest that biosimilar products should not be approved without data from large clinical trials. However if approved of biosimilar products requires clinical trials, then development cost of biosimilar products will be the same as that of the innovators. As a result, it cannot achieve the goal of cost reduction to benefit the patients.

Liu and Chow (2010) suggest that applying the method of parallel line assay to verify whether the clinical trials are required for approval of the biosimilar products and to assess the equivalence between the innovator and biosimilar products if validated characteristics of the drug products are reliable predictors of clinical responses. 林亞靚 (2010) proposed to apply the parallel line assay to the quantitative and continuous responses, 張志熙 (2011) proposed to apply the parallel line assay to the binary responses. Simulation results of both methods can adequately control the size.

1.2 Bioequivalence and Regulations

For small molecular chemical compounds, measures of bioavailability include the peak concentration (C_{max}) and the area under the concentration – time curve (AUC). The assessments of traditional chemical generic drugs are based on pharmacokinetics measures and the approval of traditional chemical generic drugs is based on the following Fundamental Bioequivalence Assumption (Chow and Liu, 2010)

When two drug products are equivalent in the rate and extent to which the active drug ingredient or therapeutic moiety is absorbed and becomes available at the site of drug action, it is assumed that they will be therapeutically equivalent and can be used interchangeably.

Next, we briefly review the regulations for approval of the traditional chemical generic drug products of small molecules.

Europe

According to the European regulations, two medicinal products are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and if their bioavailability after administration in the same molar dose is similar to such a degree that their effects, with respect to both efficacy and safety, will be essentially the same. This can be demonstrated if the 90% confidence intervals of the means ratios between the two preparations based on C_{max} and AUC lie in the range of (0.80, 1.25) or (-0.2231, 0.2231) for the log-transformed data. (EMEA, 2001)

United States

The FDA considers two products are bioequivalent if based on C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$, the 90% CI of the ratio of the means of the test (e.g. generic formulation) to the reference (e.g. innovator brand formulation) is within 80.00% to 125.00%. (US FDA, 2001 and 2003)

Taiwan

The Department of Health of Taiwan also has similar regulations for approval of generic products with respect to C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ based on the logarithm scale. If the 90% confidence interval of the mean ratio between generic and innovator of products is within (0.8, 1.25), then the generic drug product is claimed to the bioequivalent to the innovator's drug product. (TFDA, Taiwan, 2009)

Since approval of the traditional chemical generic drugs does not require conducting expensive and large clinical trials, the costs of chemical generic drugs are quite inexpensive, usually 1/5 to 1/2 of the innovator products. Therefore many chemical generic drugs become affordable to many needed patients. On the other hand, the biological products and traditional generic drug are fundamentally different.

In the United States, based on the regulations of Public Health Service Act 351(K) and Patient Protection and Affordable Care Act Title VII, there are two stages to approve the follow-on products. First, the follow-on products need to provide the evidence of the highly similarity of quality and to implement clinical trials, which can be waived by FDA. Second, for assessing interchangeability, follow-on products need to conduct switching studies. And, same as biologics, the US FDA requires follow-on products to conduct Risk Evaluation and Mitigation Strategies (REMS).

The Biologic Price Competition and Innovation Act of 2009 (BPCI Act) creates an abbreviated approval pathway for biological products shown to be biosimilar on

interchangeable with an FDA-licensed reference biological product. Based on the BPCI Act of 2009, the US FDA issued a series of guidance regarding the biosimilar drug products (FDA 2012a, 2012b, 2012c). According to the US FDA drug guidance on scientific considerations, biosimilarity is defined as "the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components" and as "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product".

On the other hand, European Medicine Agency (EMEA 2006a, 2006b, 2006c, 2006d) also approved the biosimilar products on a product-by- product basis.

In Taiwan, the Department of Health issued 藥品查驗登記審查準則－生物相似性藥品之查驗登記 in November, 2010. Though non-clinical trials and clinical trials can be waived by the data of the reference product, they still need to be implemented.

1.3 Aims of the study

Due to the differences between the biosimilar drug products of the chemical generic drugs of small molecules, the Fundamental Bioequivalence Assumption is no longer valid for biosimilar drug products. Chow and Liu (2010) proposed the following Fundamental Biosimilar Assumption (FDA).

When a biosimilar product is claimed to be biosimilar to an innovative's product based on some well-defined product characteristic, it is considered therapeutically equivalent provided that the well-defined product characteristics are validated and reliable prediction of safety and efficacy of the product.

Based on the fundamental biosimilarity assumption, 林亞靚 (2010) applied the parallel-line assay to evaluate equivalence of biosimilar product to its innovative biologic product based on the continuous endpoint. On the other hand, 張志熙 (2011) and Lin, et al. (2013) used the same method for the binary responses. In this thesis, with the same design we develop a statistical inference procedure to assess equivalence between the biosimilar drug and its reference product based on a censored endpoint which follow an exponential distribution and for which the relationship between the log-hazard and the well-defined drug characteristic is linear.

Chapter 2 provides literature review on interval hypotheses for assessment of equivalence, and the biological assay including the parallel-line assay. The proposed method for the censored data based on the parallel-line assay is introduced in Chapter 3. A numerical example is given in Chapter 4. The results of simulation studies for coverage probability, size and power are presented in Chapter 5. Chapter 6 gives the discussion and conclusion.

Table1.1: Patent status of leading biopharmaceuticals

Product	Trade Name	Patent Expiration (Year)	
		EU	USA
Epoetin Alfa	Epogen	expired	2012
Interferon Beta-1a	Avonex	2012	2008, 2013
G-CSF	Neupogen	expired	2013
IL-2	Proleukin	expired	2012
TNFR-Fc	Embrel	2010	2009
Anti TNFα Antibody	Remicade	2010, 2011, 2012	2011
Anti CD20 Antibody	Rituxan	2013	2015
Anti HER2 Antibody	Herceptin	2014	2014
Anti EGFR Antibody	Erbitux	2010	2015
Anti VEGF Antibody	Avastin	2019	2017

Source: Thomson Database of Pharmaceutical Invention (2007)

Table1.2: The differences between small-molecule generics and biosimilar products.

	Small molecule generics	Biosimilars
Product characteristics	• Small molecules • Often very stable • Mostly without a device	• Large, complex molecules • Stability requires special handling • Device is often a key differentiator
Production	• Produced by chemical synthesis	• Produced in living organisms • Highly sensitive to manufacturing changes • Often comparatively high costs
Regulation	• Abbreviated registration procedures in Europe and US • Usually enjoy "substitutability" status	• Regulatory pathway now defined by EMEA • "Comparability" status • No pathway yet in US under BLA
Marketing	• No or limited detailing to physicians • Key role of wholesalers and payers • Market substitution in pharmacies • High price discounts	• Detailing to (specialist) physicians required • Pharmacists may not substitute • Price discounts smaller; price sensitivity is product specific

Chapter 2 Literature Review

2.1 Interval Hypotheses

The assessment of average bioequivalence is based on the comparison of bioavailability profiles between formulations. Actually, no two formulations will have exactly the same bioavailability profiles. So, we accept the profiles of the two formulations may be considered equivalent if the profiles of the two formulations differ by less than a (clinically) meaningful limit. Following this concept, Schuirmann (1987) first introduced the use of interval hypotheses for assessing average bioequivalence.

Let μ_T be the average bioavailability of the test (T) formulation and μ_R the average bioavailability of the reference (R) formulation. The interval hypotheses for average bioequivalence on the log-scale can be formulated as

$$\begin{aligned} &H_0\colon\ \mu_T - \mu_R \le \theta_L \ \text{ or } \ \mu_T - \mu_R \ge \theta_U \\ &\text{vs.} \\ &H_a\colon\ \theta_L < \mu_T - \mu_R < \theta_U \end{aligned} \tag{2.1}$$

Where $\theta_L = -\theta_U = -0.2231$ are some clinically meaningful limits. The concept of interval hypotheses Eq. (2.1) is to show average bioequivalence by rejecting the null hypothesis of inbioequivalence.

Schuirmann's Two One-Sided Tests Procedure (TOST)

The interval hypotheses Eq.(2.1) can be divided into two sets of one-sided hypotheses,

$$H_{01}: \mu_T - \mu_R \le \theta_L \text{ vs. } H_{a1}: \mu_T - \mu_R > \theta_L$$
$$\text{and} \qquad (2.2)$$
$$H_{02}: \mu_T - \mu_R \ge \theta_U \text{ vs. } H_{a2}: \mu_T - \mu_R < \theta_U.$$

The first set of hypotheses is to verify that the average bioavailability of the test formulation is not too low, whereas the order set of hypotheses is to verify that the average bioavailability of the test formulation is not too high. A relatively low (or high) average bioavailability may refer to the concern of efficacy (or safety) of the test formulation. If one concludes that $\theta_L < \mu_T - \mu_R$ (i.e., reject H_{01}) and $\mu_T - \mu_R < \theta_U$ (i.e., reject H_{02}), then it can be concluded that

$$\theta_L < \mu_T - \mu_R < \theta_U,$$

and μ_T and μ_R, thus, are equivalent. The rejections of H_{01} and H_{02}, which leads to the conclusion of average bioequivalence, are equivalent to rejecting H_0 in Eq.(2.1). Schuirmann (1981, 1987) first introduced the two one-sided tests (TOST) procedure based on Eq.(2.2) for assessing average bioequivalence between formulations. The proposed TOST procedure suggests the conclusion of equivalence of μ_T and μ_R at the level of significance if and only if, H_{01} and H_{02} in Eq.(2.2) are rejected at a predetermined a level of significance. Under the normality assumptions, the two sets of one-sided hypotheses can be tested with ordinary one-sided t tests. We conclude that μ_T and μ_R are average equivalent at the α significance level if

$$T_L = \frac{(\bar{Y}_T - \bar{Y}_R) - \theta_L}{\hat{\sigma}_d \sqrt{\frac{1}{n_R} + \frac{1}{n_T}}} > t(\alpha, n_R + n_T - 2) \quad (2.3)$$

and

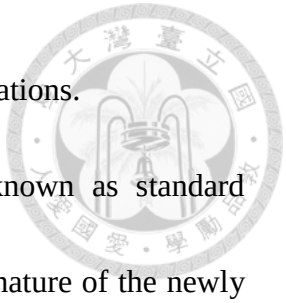
$$T_U = \frac{(\bar{Y}_T - \bar{Y}_R) - \theta_U}{\hat{\sigma}_d \sqrt{\frac{1}{n_R} + \frac{1}{n_T}}} < -t(\alpha, n_R + n_T - 2), \quad (2.4)$$

where $\bar{Y}_T, \bar{Y}_R$ and $\hat{\sigma}_d$ are the least squares estimator of the test and reference means and square root of error mean square.

The two one-sided t tests procedure is operationally equivalent to the classic (shortest) confidence interval approach; that is, if the classic (1-2α)100% confidence interval for μ_T and μ_R is within (θ_L, θ_U), then both H_{01} and H_{02} are also rejected at the α level by the two one-sided t tests procedure (Chow and Liu, 2010).

2.2 Biological Assay

Bioassay (commonly used shorthand for biological assay), or biological standardization is a type of scientific experiment. Bioassays measure the effects of a substance on a living organism, and they are essential in the development of new drugs. It is the procedure to determine the nature, concentration of purity or the potency of the preparation by the reaction of subjects. The preparation added to the subject can have a single dose level, or several different dose levels, and therefore the subjects produce a response value or multiple response values. We can test the potency of the preparation by



these values, and compare the relative potency of two or more preparations.

So, we always take a common nature of the preparation known as standard preparation (reference preparation), while the other is the unknown nature of the newly developed preparation, referred to as test preparation. The two preparations produce the difference between response values in the same dose, i.e., for inference of the potency of the test preparation. Generally we use the indirect assay, because it is easier to apply. Indirect assay consists of quantitative responses and qualitative responses. Lin (2010) suggested to apply the parallel line assay for evaluation of the similarity of biosimilar products which is the indirect assay with quantitative responses.

2.3 Parallel Line Assay to Evaluation of the Similarity of Biosimilar Products

Liu and Chow (2010) refer to group means of a well-defined product characteristic can be computed for each dose level for the biosimilar and innovator's product respectively. Using the group means of the well-defined characteristic as the independent variable, a simple linear regression equation can be fitted to the primary efficacy endpoint for the biosimilar and innovator's biological products respectively. It follows that the concept of relative potency in the parallel-line bioassay can be then employed to investigate extrapolability of equivalence in product characteristic to equivalence in

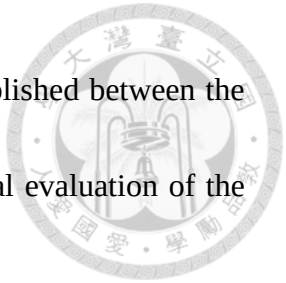
efficacy.

Design (a) in Figure 2.1 proposed by Liu and Chow (2010) consists of two dose-response trials, one for the biosimilar product and one for the innovator's biological product, each with at least three dose levels with a placebo group. Eligible patients are first randomized into biosimilar or innovator groups. Within each group, patients are randomized again to receive one of the dose levels for the respective products. Well-defined product characteristics and primary efficacy endpoints are evaluated for all patients at their respective dose levels. Suppose that after a statistically significant relationship as represented by a simple linear regression equation can be established between the well-defined product characteristics and the primary efficacy endpoint through dose levels for the innovator's product, maybe after a suitable transformation.

For design (a) Liu and Chow (2010) suggest that the standard statistical method for analysis of parallel line assays can be used to construct the $(1-2\alpha)100\%$ confidence interval for the relative potency in the following steps:

Step 1: Fit a linear regression equation to the primary efficacy endpoint with the group mean of the product characteristics at each dose level as the independent variable separately for the biosimilar and innovator's biological products. This may be done after a suitable transformation.

Step 2: If the estimate of the slope of any one product is not significant at the pre-



defined level, then conclude that no simple relationship can be established between the product characteristic and primary endpoint and hence, a full clinical evaluation of the biosimilar product is required. Otherwise, go to Step 3.

Step 3: Test whether the two estimated simple linear regressions are parallel at the predefined significance level. If the two estimated linear regressions are not parallel, then further clinical evaluation of the biosimilar product is warranted. Otherwise, proceed to Step 4.

Step 4: Compute estimated relative potency and its corresponding $(1-2\alpha)100\%$ confidence interval. If the $(1-2\alpha)100\%$ confidence interval for the relative potency is within the predefined margins (δ_L, δ_U**),** then equivalence in the product characteristic can be extrapolated to equivalence in the primary efficacy endpoint at the α significance level. Otherwise, further clinical investigation of the biosimilar product is needed.

Lin (2010), Chang (2011) and Lin et al. (2013) have applied the above procedure to continuous and binary responses. This thesis will consider the situation where the primary endpoint is a censored endpoint which follow an exponential distribution. Next section provides a brief review of survival analysis in terms of the exponential distribution with a right and random censored mechanism.

2.4 Survival Analysis

The following review is based on books by Lawless (2002) and Kleinbaum (1998).

Survival analysis involves the modeling of time to event data. The problem of analyzing time to event data arises in a number of applied fields, such as medicine, biology, public health, epidemiology, engineering, economics, and demography. Although the statistical tools we shall present are applicable to all these disciplines, our focus is on applying the techniques to biology and medicine. The definition of lifetime includes a time scale and time origin, as well a specification of the event (e.g., failure or death) that determines lifetime. A common feature of these data sets is they contain censored. Censored data arises when an individual's life length is known to occur only in a certain period of time. Possible censoring schemes are right censoring, where all that is known is that the individual is still alive at a given time, left censoring when all that is known is that the individual has experienced the event of interest prior to the start of the study, or interval censoring, where the only information is that the event occurs within some interval. Type I censoring occurs if an experiment has a set number of subjects or items and stops the experiment at a predetermined time, at which point any subjects remaining are right-censored. Type II censoring occurs if an experiment has a set number of subjects or items and stops the experiment when a predetermined number are observed

to have failed; the remaining subjects are then right-censored. Random (or non-informative) censoring is when each subject has a censoring time that is statistically independent of their failure time. The observed value is the minimum of the censoring and failure times; subjects whose failure time is greater than their censoring time are right-censored. In this thesis we only consider the right and random censoring mechanism.

We begin by considering the case of a single continuous lifetime variable, T. Specifically, let T be a nonnegative random variable representing the lifetime of individuals in some population. All functions, unless stated otherwise, ate defined over the interval (0, ∞). Let f(t) denote the probability density function (p.d.f.) of T and let the (cumulative) distribution function (c.d.f.) be

$$\mathrm{F}(\mathrm{t}) = \Pr(\mathrm{T} \le \mathrm{t}) = \int_0^{\mathrm{t}} f(x)\,dx. \tag{2.5}$$

The probability of an individual surviving to time t is given by the survivor function

$$S(t) = Pr(T \ge t) = \int_t^{\infty} f(x)dx. \tag{2.6}$$

Note that $S(t)$ is a monotone decreasing continuous function with $S(0) = 1$ and $S(\infty) = lim_{t\to\infty} S(t) = 0.$ A very important concept with lifetime distributions is the hazard function $h(t)$, denoted as

$$\mathrm{h}(\mathrm{t}) = \lim_{\Delta \mathrm{t}\to\infty} \frac{\Pr(\mathrm{t} \le \mathrm{T} < \mathrm{t} + \Delta \mathrm{t} \mid \mathrm{T} \ge \mathrm{t})}{\Delta \mathrm{t}} = \frac{\mathrm{f}(\mathrm{t})}{\mathrm{S}(\mathrm{t})}. \tag{2.7}$$

The hazard function specifies the instantaneous rate of death or failure at time t, given that the individual survives up to t; $h(t)\Delta t$ is the approximate probability of death in

$[t,\ t+\Delta t)$, given survival up to t.

The functions $f(t)$, $F(t)$, $S(t)$ and $h(t)$ give mathematically equivalent specification of the distribution of T. It is easy to derive expressions for $S(t)$ and $f(t)$ in terms of $h(t)$; since $f(t) = -S'(t)$, implies that

$$h(x) = -\frac{d}{dx}\ln S(x). \tag{2.8}$$

Thus

$$\ln S(x)\Big|_0^t = -\int_0^t h(x)\,dx, \tag{2.9}$$

and since $S(0) = 1$, we find that

$$S(t) = \exp\left(-\int_0^t h(x)\,dx\right). \tag{2.10}$$

It is also useful to define the cumulative hazard function

$$H(t) = \int_0^t h(x)\,dx, \tag{2.11}$$

which is related to the survival function by $S(t) = \exp(-H(t))$. If $S(\infty) = 0$, then $H(\infty) = 0$.Finally, it follows immediately that

$$f(t) = h(t)\exp\left(-\int_0^t h(x)\,dx\right). \tag{2.12}$$

In clinical trials, individuals are followed longitudinally over time. The group of cohort of individuals in often, but not necessarily, randomly selected from a population of individuals who are at the time origin $(t = 0)$ for the lifetime variable T. Limitations on the information collected may be imposed by time, cost, and other constraints.

Termination of follow-up before an individual fails causes their lifetime to be right censored. A random censoring process that is often realistic is one in which each individual is assumed to have a life time T and censoring time C, with T and C independent continuous random variables, with survivor functions $S(t)$ and $G(t)$, respectively.

All lifetimes and censoring times are assumed mutually independent, and it is assumed that $G(t)$ does not depend on any of the parameters of $S(t)$. The data from observations on N individuals is assumed to consist of the pairs (y_i, δ_i), $i = 1, \ldots N$, where $y_i = \mathrm{Min}(T_i, C_i), \delta_i = I(T_i \le C_i)$.

The p.d.f. of (y_i, δ_i) is easily obtained: if $f(t)$ and $g(t)$ are the p.d.f.'s for T_i and C_i, then

$$P(y_i = y, \delta_i) = \left[f(y_i) * G(y_i)\right]^{\delta_i} \left[g(y_i) * S(y_i)\right]^{1-\delta_i}. \quad (2.13)$$

And thus the distribution of (y_i, δ_i), $i = 1, \ldots N$ is

$$\prod_{i=1}^{N} \left[f(y_i) * G(y_i)\right]^{\delta_i} \left[g(y_i) * S(y_i)\right]^{1-\delta_i}. \quad (2.14)$$

Since $G(t)$ and $g(t)$ do not involve any of the parameters in $f(t)$, they can be neglected and the likelihood function taken to be

$$L = \prod_{i=1}^{N} \left[f(y_i)\right]^{\delta_i} \left[S(y_i)\right]^{1-\delta_i} \quad (2.15)$$

In this study, we suppose that the lifetimes T_i are independent and follow an

exponential distribution with p.d.f. $f(t)=\lambda_1 \exp(-\lambda_1 t)$ and the censoring times C_i are independent and follow an exponential distribution with p.d.f. $g(c)=\lambda_2 \exp(-\lambda_2 c)$. Let $y_i = \text{Min}(T_i, C_i), \delta_i = I(T_i \le C_i)$. $I(T_i \le C_i)$ is the indicator function. When the data is uncensored, $T_i \le C_i$, $I(T_i \le C_i)=1$. And when the data is uncensored, $T_i > C_i$, $I(T_i \le C_i)=0$. So the p.d.f. of (y_i, δ_i) is

$$(\lambda_1)^{\delta_i}(\lambda_2)^{1-\delta_i} \exp\left(-y_i(\lambda_1+\lambda_2)\right). \tag{2.16}$$

The censored rate is calculated by integrating $P(y_i, \delta_i = 1)$ with respect to y_i, then we have

$$\begin{aligned}\int_0^\infty P(y_i, \delta_i = 1)dy_i &= \int_0^\infty (\lambda_1)^1(\lambda_2)^{1-1}\exp\left(-y_i(\lambda_1+\lambda_2)\right)dy_i \\ &= \frac{\lambda_2}{\lambda_1+\lambda_2} \\ &= \frac{1}{1+\lambda_1/\lambda_2}.\end{aligned} \tag{2.17}$$

Let $\lambda_1/\lambda_2 = k$,the ratio of the two parameters. The censored rate $CR = 1/(1+k)$.

The expected value of lifetime is

$$\begin{aligned}&\int_0^\infty y_i P(y_i, \delta_i = 1)dy_i + \int_0^\infty y_i P(y_i, \delta_i = 0)dy_i \\ &= \int_0^\infty y_i(\lambda_1)^1(\lambda_2)^{1-1}\exp\left(-y_i(\lambda_1+\lambda_2)\right)dy_i + \int_0^\infty y_i(\lambda_1)^0(\lambda_2)^{1-0}\exp\left(-y_i(\lambda_1+\lambda_2)\right)dy \\ &= \lambda_1\left(\frac{1}{\lambda_1+\lambda_2}\right)^2 + \lambda_2\left(\frac{1}{\lambda_1+\lambda_2}\right)^2 \\ &= \frac{1}{\lambda_1+\lambda_2} = \frac{1}{\lambda_1(1+\lambda_2/\lambda_1)} = \frac{1}{\lambda_1(1+1/k)}.\end{aligned} \tag{2.18}$$

.

The hazard rate is reciprocal of the expected value of lifetime. So it is $\lambda_1(1+1/k)$. If

we assumed that censored rate is a fixed constant, then the hazard is affected by the only parameter λ_1.

2.4 Log-hazard Linear Regression Model.

According to Liu and Chow (2010), group means of a well-defined product characteristic can be computed for each dose level for the biosimilar and innovator's product respectively. In this case, the variable of interest is positive and the log transformation is immediately applicable. In other words, the relationship between the log-hazard and the well-defined drug chacteristic can be modeled by a linear regression. Thus the log-hazard linear regression model is given as:

$$\ln(\lambda) = \alpha + \beta x_i. \tag{2.19}$$

where x_i is dose level, α is the intercept and β is the slope .

Now we have the p.d.f. and the survival function for the lifetime of each individual base on α and β:

$$f(y_i) = (\exp(\alpha + \beta x_i))\exp(-y_i \times \exp(\alpha + \beta x_i)). \tag{2.20}$$

$$S(y_i) = \Pr(Y \geq y_i) = \exp(-\lambda y_i) = \exp(-y_i \times \exp(\alpha + \beta x_i)). \tag{2.21}$$

To estimate the parameters, we need to use Method of Maximum Likelihood (MLE).

Let parameters vector $\boldsymbol{\theta} = (\alpha, \beta)^T$. Expressing the probabilities as a log-hazard c function of the covariate and the parameters yields the likelihood function from Eq.(2.15)

$$L(\boldsymbol{\theta}) = \prod_{i=1}^{N} \left\{ \left[\exp[\alpha + \beta x_i - y_i \times \exp(\alpha + \beta x_i)] \right]^{\delta_i} \times \left[\exp[-y_i \times \exp(\alpha + \beta x_i)] \right]^{1-\delta_i} \right\}$$
$$= \prod_{i=1}^{N} \{ (e^{\alpha+\beta x_i})^{\delta_i} \left[e^{-\left(e^{\alpha+\beta x_i}\right) y_i} \right] \}. \tag{2.22}$$

It follows that the log likelihood is

$$\begin{aligned} \ln L(\boldsymbol{\theta}) &= \ln \left\{ \prod_{i=1}^{N} \{ (e^{\alpha+\beta x_i})^{\delta_i} \left[e^{-\left(e^{\alpha+\beta x_i}\right) y_i} \right] \} \right\} \\ &= \alpha \sum_{i=1}^{N} \delta_i + \beta \sum_{i=1}^{N} \delta_i x_i - \sum_{i=1}^{N} y_i \left(e^{\alpha+\beta x_i} \right). \end{aligned} \tag{2.23}$$

The score vector for the parameter is

$$\mathbf{U}(\boldsymbol{\theta}) = [U(\theta)_\alpha, U(\theta)_\beta]^T. \tag{2.24}$$

where the score equation for the intercept is

$$U(\boldsymbol{\theta})_\alpha = \frac{\partial}{\partial \alpha} \ln L(\boldsymbol{\theta}) = \sum_{i=1}^{N} \delta_i - \sum_{i=1}^{N} y_i \left(e^{\alpha+\beta x_i} \right). \tag{2.25}$$

and the score equation for the regression coefficient is

$$U(\boldsymbol{\theta})_\beta = \frac{\partial}{\partial \beta} \ln L(\boldsymbol{\theta}) = \sum_{i=1}^{N} \delta_i x_i - \sum_{i=1}^{N} x_i y_i \left(e^{\alpha+\beta x_i} \right). \tag{2.26}$$

The expected information matrix $\mathbf{I}(\boldsymbol{\theta}) = \begin{bmatrix} \mathbf{I}(\boldsymbol{\theta})_\alpha & \mathbf{I}(\boldsymbol{\theta})_{\alpha\beta} \\ \mathbf{I}(\boldsymbol{\theta})_{\alpha\beta} & \mathbf{I}(\boldsymbol{\theta})_\beta \end{bmatrix}$, where

$$I(\boldsymbol{\theta})_\alpha = -\frac{\partial}{\partial \alpha} U(\boldsymbol{\theta})_\alpha = \sum_{i=1}^{N} y_i \left(e^{\alpha+\beta x_i} \right), \tag{2.27}$$

$$I(\boldsymbol{\theta})_\beta = -\frac{\partial}{\partial \beta} U(\boldsymbol{\theta})_\beta = \sum_{i=1}^{N} x_i^{\,2} y_i \left(e^{\alpha+\beta x_i} \right), \tag{2.28}$$

$$I(\boldsymbol{\theta})_{\alpha\beta} = -\frac{\partial}{\partial \beta} I(\boldsymbol{\theta})_\alpha = \sum_{i=1}^{N} x_i y_i \left(e^{\alpha+\beta x_i} \right). \tag{2.29}$$

Thus we have the expected information matrix

$$I(\boldsymbol{\theta}) = \begin{bmatrix} \sum_{i=1}^{N} y_i \left(e^{\alpha+\beta x_i}\right) & \sum_{i=1}^{N} x_i y_i \left(e^{\alpha+\beta x_i}\right) \\ \sum_{i=1}^{N} x_i y_i \left(e^{\alpha+\beta x_i}\right) & \sum_{i=1}^{N} x_i^{\,2} y_i \left(e^{\alpha+\beta x_i}\right) \end{bmatrix}. \tag{2.30}$$

Note that each score equation involves the complete parameter vector $\boldsymbol{\theta}$ .The MLE is the vector $(\hat{\alpha}, \hat{\beta})^{T}$ that jointly satisfies $U(\boldsymbol{\theta}) = 0$. Since the close-form solution do not exist, the solution must be obtained by an iterative procedure such as the Newton-Raphson algorithm. We review the Newton-Raphson algorithm in the next section.

To solve the MLE of α and β, we let $U(\boldsymbol{\theta})_{\alpha} = 0$, we have

$$\sum_{i=1}^{N} \delta_i = \sum_{i=1}^{N} y_i \times \exp(\hat{\alpha} + \hat{\beta} x_i). \tag{2.31}$$

$$\hat{\alpha} = \ln \frac{\sum_{i=1}^{N} \delta_i}{\sum_{i=1}^{N} y_i e^{\hat{\beta} x_i}}. \tag{2.32}$$

To solve MLE of β, we use Newton–Raphson method, given a function f defined over β:

$$f(\beta) = \frac{\sum_{i=1}^{N} x_i y_i e^{\beta x_i}}{\sum_{i=1}^{N} y_i e^{\beta x_i}} - \frac{\sum_{i=1}^{N} \delta_i x_i}{\sum_{i=1}^{N} \delta_i}, \tag{2.33}$$

and its derivative f'

$$f'(\beta) = \frac{\sum_{i=1}^{N} x_i^{\,2} y_i e^{\beta x_i}}{\sum_{i=1}^{N} y_i e^{\beta x_i}} - \left(\frac{\sum_{i=1}^{N} x_i y_i e^{\beta x_i}}{\sum_{i=1}^{N} y_i e^{\beta x_i}}\right)^2. \tag{2.34}$$

The process is repeated as

$$\beta_{n+1} = \beta_n - \frac{f(\beta)}{f'(\beta)}. \qquad (2.35)$$

The MLE of β is obtained when the solution $f\left(\hat{\beta}_{n+1}\right) = 0$ by definition. The MLE of α is obtained by Eq.(2.32).

The observed information matrix $\mathbf{i}\left(\hat{\boldsymbol{\theta}}\right)$ is obtained by replacing α and β by their MLEs $\hat{\alpha}$ and $\hat{\beta}$, respectively. Using $\mathbf{i}\left(\hat{\boldsymbol{\theta}}\right)$, the vector of parameter estimates can be solved using Newton-Raphson iterative procedure, or another algorithm. Wald tests and large sample confidence limits for the individual parameters, such as β, are readily computed using the large sample variance $\hat{\mathbf{V}}\left(\hat{\beta}\right) = \left[\mathbf{i}\left(\hat{\boldsymbol{\theta}}\right)^{-1}\right]_{\beta}$ obtained as the corresponding diagonal element of the estimated expected information, $\mathbf{i}\left(\hat{\boldsymbol{\theta}}\right)$. The null and fitted likelihoods can also be used as the basis for a likelihood ratio test of the model.

2.5 Newton-Raphson Method

Newton–Raphson method (or Newton's method) is a method for finding successively better approximations to the roots of a real-valued function. Assume that we have an initial guess as to the value of the parameter that is in the neighborhood" of the desired solution $\hat{\theta}$. Taking a Taylor's expansion of the estimating $U\left(\hat{\theta}\right)$ about the starting value $\hat{\theta}^{(0)}$, we have

$$0 = U\left(\hat{\boldsymbol{\theta}}\right) = U\left(\hat{\boldsymbol{\theta}}^{(0)}\right) + \left(\hat{\boldsymbol{\theta}} - \hat{\boldsymbol{\theta}}^{(0)}\right)U'\left(\hat{\boldsymbol{\theta}}^{(0)}\right) + R, \qquad (2.36)$$

which implies that

$$\hat{\boldsymbol{\theta}} \cong \hat{\boldsymbol{\theta}}^{(0)} - \frac{U\left(\hat{\boldsymbol{\theta}}^{(0)}\right)}{U'\left(\hat{\boldsymbol{\theta}}^{(0)}\right)} = \hat{\boldsymbol{\theta}}^{(0)} + \frac{U\left(\hat{\boldsymbol{\theta}}^{(0)}\right)}{i\left(\hat{\boldsymbol{\theta}}^{(0)}\right)}. \tag{2.37}$$

Because Newton's method uses the Hessian at each step, this is equivalent to using the observed information function. This equation is then applied iteratively until $\hat{\boldsymbol{\theta}}$ converges to a constant (the desired solution) using the sequence of equations

$$\hat{\boldsymbol{\theta}}^{(i+1)} = \hat{\boldsymbol{\theta}}^{(i)} - \frac{U\left(\hat{\boldsymbol{\theta}}^{(i)}\right)}{U'\left(\hat{\boldsymbol{\theta}}^{(i)}\right)} = \hat{\boldsymbol{\theta}}^{(i)} + \frac{U\left(\hat{\boldsymbol{\theta}}^{(i)}\right)}{i\left(\hat{\boldsymbol{\theta}}^{(i)}\right)} \tag{2.38}$$

for i = 0, 1, 2,…

For the case where $\boldsymbol{\theta}$ is a vector, the corresponding sequence of equations is characterized as

$$\begin{aligned} \hat{\boldsymbol{\theta}}^{(i+1)} &= \hat{\boldsymbol{\theta}}^{(i)} - \left[\mathbf{U}'\left(\hat{\boldsymbol{\theta}}^{(i)}\right)\right]^{-1} \mathbf{U}\left(\hat{\boldsymbol{\theta}}^{(i)}\right) \\ &= \hat{\boldsymbol{\theta}}^{(i)} + \mathbf{i}\left(\hat{\boldsymbol{\theta}}^{(i)}\right)^{-1} \mathbf{U}\left(\hat{\boldsymbol{\theta}}^{(i)}\right). \end{aligned} \tag{2.39}$$

The MLE is obtained when the solution $\mathbf{U}\left(\hat{\boldsymbol{\theta}}^{(i+1)}\right) = 0$ by definition.

The initial estimate is often the value expected under an appropriate null hypothesis or may be an estimate provided by a simple non-iterative moment estimator when such exists. Then the above expression is equivalent to determining the tangent to the log likelihood contour and projecting it to the abscissa to determine the next iterative estimate. This process continues until the process converges.

The Newton-Raphson iteration is quadratic convergent in the sense that $\mathbf{U}\left(\hat{\boldsymbol{\theta}}\right)$

approaches to 0 and it is a quadratic function of $\hat{\boldsymbol{\theta}}$. However, it is also sensitive to the choice of the initial or starting value. (Lachin, 2000)

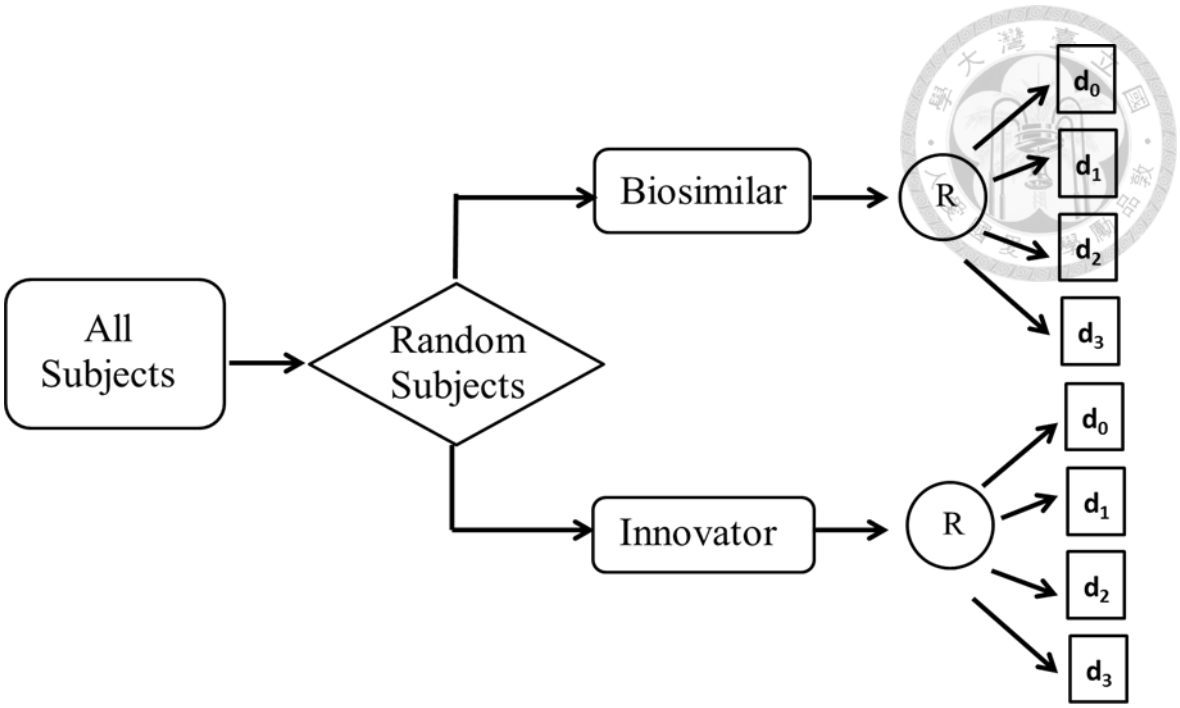


Figure 2.1: Design (a) for evaluation of extrapolation ability

Chapter 3 Proposed Methods

For the indirect assay with censored responses which follows an exponential distribution, we propose to use the log-hazard regressions to evaluation of the similarity of biosimilar products.

3.1 Design

We use the design (a) which proposed by Liu and Chow (2010) and is introduced in section 2.3. If a similar linear relationship via the log-hazard linear regression can be also obtained for the biosimilar product and its corresponding linear regression equation is very close to the one for the innovator's product, then equivalence in efficacy based on the primary efficacy endpoint may be claimed. Because the innovator's product has been approved by the regulatory agencies due to its confirmed efficacy, therefore the objective of Design (a) is not to establish the efficacy of either biological products but to establish the similar patterns of the relationship between the well-defined product characteristics and primary efficacy endpoint for the two products. As a result, the sample size of Design (a) can be reduced significantly.

Similar to the chemical generic drug products, approval for the biosimilar drug products can be treated as the evaluation of post-approval changes. (ICH Q5E, 2005) and this post-approval change is the change of drug manufacturers. Therefore, as indicated by

Liu and Chow (2010), if the biosimilar drug products and the corresponding innovator's biological products appear highly similar, and if in addition, based on the accumulated experience relevant information and data, minute differences observed in the product characteristics are expected to have no clinically meaningful adverse effect of safety and efficacy profiles. Under this circumstance, biosimilar drug products and innovator's products can be considered similar. Therefore, except for the traditional pivotal bioequivalence study, no further data from pivotal phase III trials should be requested. However, the above statement is based on a crucial assumption that at least one of the product characteristics is a validated and reliable predictor of the safety and efficacy profiles of the biological products. This is the reason why Chow and Liu (2010) porposed the Fundamental Biosimilarity Assumption (FBA) given in Section 1.3

For design (a), Liu and Chow (2010) suggest that the standard statistical method for analysis of parallel line assays can be used to construct the $(1-2\alpha)100\%$ confidence interval for the relative potency in the 4 steps, which is provided in Section 2.3. We can use the similar approach to apply in log-hazard linear regression in the following steps when the primary endpoint as a censored random variable:

Step 1: Fit a linear log-hazard regression equation to the censored endpoint with the group mean of the product characteristics at each dose level as the independent variable separately for the biosimilar and innovator's biological products. It is easy to use Method

of Maximum Likelihood (MLE) to estimate the parameters, the intercept and the slope.

Step 2: If the estimate of the slope of any one product is not significant at the pre-defined level, then conclude that no linear relationship based on log-hazard can be established between the product characteristic and the censored endpoint and hence, a full clinical evaluation of the biosimilar product is required. Otherwise, go to Step 3.

Step 3: Test whether the two estimated log-hazard linear regressions are parallel at the predefined significance level. If the two estimated linear log-hazard linear regressions are not parallel, then further clinical evaluation of the biosimilar product is warranted. Otherwise, proceed to Step 4.

Step 4: Compute estimated relative potency and its corresponding $(1-2\alpha)100\%$ confidence interval. If the $(1-2\alpha)100\%$ confidence interval for the relative potency is within the predefined margins (δ_L, δ_U), then equivalence in the product characteristic can be extrapolated to equivalence in the censored endpoint at the α significance level. Otherwise, further clinical investigation of the biosimilar product is needed.

3.2 The Procedure and Methods Based on Relative Potency of Product Characteristics

We can simplify the 4 steps to the follow steps:

Step 1: Fit log-hazard linear models.

Step 2: Test linearity of the two log-hazard regression models. (non-zero slopes)

Step 3: Test for parallelism lines of log-hazard regressions. (equivalence of slopes)

Step 4: Estimate relative potency and its confidence interval.

Step 1 is easy to implement by using Method of Maximum Likelihood (MLE) via the Newton–Raphson method to estimate the parameters, the intercept (α) and the slope (β). In this setting, the innovative biological product is treated as the standard preparation, and the biosimilar product is referred to as the test preparation. Let dependent variable $\mathrm{f_R}(\mathrm{y})(\mathrm{f_T}(\mathrm{y}))$ be the probability of the clinical outcomes such as the death for the biosimilar and innovate products, respectively. Let independent variable (X) be the mean characteristics under different dose levels. Then the log-hazard linear regression models of the innovative product and the biosimilar product are given respectively as

$$\mathrm{f_R}(\mathrm{y}) = \lambda_{\mathrm{R}} \exp(-\lambda_{\mathrm{R}} y), \tag{3.1}$$

$$\mathrm{f_T}(\mathrm{y}) = \lambda_{\mathrm{T}} \exp(-\lambda_{\mathrm{T}} y). \tag{3.2}$$

Therefore we can apply the Wald test to test the linearity of a log-hazard regression model. The hypotheses of the non-zero slope for the innovator's biological products (reference) and the biosimilar (test) are given respectively as

$$\begin{cases} H_0 : \beta_{\mathrm{R}} = 0 \\ v.s. \\ H_a : \beta_{\mathrm{R}} \neq 0 \end{cases}, \tag{3.3}$$

$$\begin{cases} H_0 : \beta_{\mathrm{T}} = 0 \\ v.s. \\ H_a : \beta_{\mathrm{T}} \neq 0 \end{cases}. \tag{3.4}$$

The 100(1-α)% confidence interval for β_R and β_T based on Wald Statistic are given respectively as

$$\hat{\beta}_R \pm Z_{\alpha/2}\sqrt{\hat{V}\left(\hat{\beta}_R\right)}, \tag{3.5}$$

$$\hat{\beta}_T \pm Z_{\alpha/2}\sqrt{\hat{V}\left(\hat{\beta}_T\right)}, \tag{3.6}$$

Where $\hat{\beta}_R\left(\hat{\beta}_T\right)$ are the MLE of $\beta_R\left(\beta_T\right)$ and $\hat{V}\left(\hat{\beta}_R\right)\left(\hat{V}\left(\hat{\beta}_T\right)\right)$ are the corresponding elements of the inverse of the estimated information matrix $i\left(\hat{\theta}\right)$ obtained by the Newton-Raphson method, and $Z_{\alpha/2}$ is the upper $\alpha/2$ percentile of a standard normal value. If the $100(1-\alpha)\%$ confidence interval does not contain 0, the null hypothesis is rejected at the α significance level and the log-hazard regression model is linear. Then we can go to the next step.

3.2.1 Test for Parallelism of Log-hazard Regressions

We want to know whether two linear log-hazard regression lines are parallel to each other. In other words we need to check whether the slopes are equivalent between the two logistic regression lines. The interval hypothesis based on the difference of slopes is given as

$$\begin{cases} H_0 : |\beta_R - \beta_T| \geq C \\ v.s. \\ H_a : |\beta_R - \beta_T| < C \end{cases}, \tag{3.7}$$

where C is some pre-defined limit.

The hypothesis in Eq.(3.7) can be also expressed as

$$\begin{cases} H_0 : \beta_R - \beta_T \le -C \text{ or } \beta_R - \beta_T \ge C \\ v.s. \\ H_a : -C < \beta_R - \beta_T < C \end{cases} . \quad (3.8)$$

Because $\frac{\hat{\beta}_R - \hat{\beta}_T}{\sqrt{\hat{V}\left(\hat{\beta}_R - \hat{\beta}_T\right)}}$ is asymptotical normal as the sample size gets large, we can establish the 100(1-2α)% confidence interval for the difference of slopes as

$$\hat{\beta}_R - \hat{\beta}_T \pm Z_\alpha \sqrt{\hat{V}\left(\hat{\beta}_R - \hat{\beta}_T\right)}. \quad (3.9)$$

Because $\hat{\beta}_R$ and $\hat{\beta}_T$ are independent, $\hat{V}\left(\hat{\beta}_R - \hat{\beta}_T\right) = \hat{V}\left(\hat{\beta}_R\right) + \hat{V}\left(\hat{\beta}_T\right)$.

If the $100(1-2\alpha)\%$ confidence interval for the difference of slopes is within $(-C, C)$, then the null hypothesis is rejected and the slope of biosimilar product is equivalent to that of innovative product at the α significance level. Then we can claim that the slopes are the same and two linear log-hazard regression lines are parallel. The log-hazard regression model of the innovative and the biosimilar product can be reformulated with the same slope as

$$f_R(x) = \ln(\lambda_R) = \alpha_R + \beta_C x, \quad (3.10)$$

$$f_T(x) = \ln(\lambda_T) = \alpha_T + \beta_C x \quad (3.11)$$

where the β_C is the common slope. Then we go to the next step.

To estimate the parameters, the variances and the covariances.

We use Newton-Raphson method to estimate the parameters, the variance and the covariance under the log-hazard common-slope linear models.

The functions of linear log-hazard regression model of the innovative and biosimilar products with common slope are

$$f_i(x) = \ln(\lambda_{ij}) = \alpha_i + \beta_C x_{ij} \tag{3.12}$$

i=1,…,N, j = R, T. Since the ith observation of the jth product is a random variable $\{y_{ij}\}$ which follow an exponential distribution .Let parameters $\boldsymbol{\theta} = (\alpha_T, \alpha_R, \beta_C)^T$. The likelihood is

$$\begin{aligned} L(\boldsymbol{\theta}) &= \prod_{j=R}^{T}\prod_{i=1}^{N}\left[f_j(y_{ij})\right]^{\delta_{ij}}\left[S_j(y_{ij})\right]^{1-\delta_{ij}} \\ &= \prod_{i=1}^{N}\left\{\exp[\alpha_R + \beta_c x_{Ri} - y_{Ri}e^{(\alpha_R+\beta_c x_{Ri})}]\right\}^{\delta_{Ri}}\{\exp\left[-y_{Ri}e^{(\alpha_R+\beta_c x_{Ri})}\right]\}^{1-\delta_{Ri}} \\ &\times\left\{\exp[\alpha_T + \beta_C x_{Ti} - y_{Ti} * e^{(\alpha_T+\beta_C x_{Ti})}]\right\}^{\delta_{Ti}}\{\exp\left[-y_{Ti}e^{(\alpha_T+\beta_C x_{Ti})}\right]\}^{1-\delta_{Ti}} \\ &= \prod_{i=1}^{N}\left[\exp(\alpha_R\delta_{Ri} + \beta_C\delta_{Ri}x_{Ri} + \alpha_T\delta_{Ti} + \beta_C\delta_{Ti}x_{Ti} - y_{Ri} * e^{(\alpha_R+\beta_C x_{Ri})} - y_{Ti} * e^{(\alpha_T+\beta_C x_{Ti})})\right] \end{aligned} \tag{3.13}$$

The log likelihood in corresponding model parameter θ is

$$l(\boldsymbol{\theta}) = \sum_{i=1}^{N}[\alpha_R\delta_{Ri} + \alpha_T\delta_{Ti} + \beta_C(\delta_{Ri}x_{Ri} + \delta_{Ti}x_{Ti}) - y_{Ri} * e^{(\alpha_R+\beta_C x_{Ri})} - y_{Ti} * e^{(\alpha_T+\beta_C x_{Ti})}]. \tag{3.14}$$

The score vector for the parameters is

$$\mathbf{U}(\boldsymbol{\theta}) = [U(\theta)_{\alpha_R}, U(\theta)_{\alpha_T}, U(\theta)_{\beta_C}]^T = \left[\frac{\partial l(\theta)}{\partial \alpha_R}, \frac{\partial l(\theta)}{\partial \alpha_T}, \frac{\partial l(\theta)}{\partial \beta_C}\right]^T, \tag{3.15}$$

where the score equation for intercept of the innovative product is

$$\mathbf{U}(\boldsymbol{\theta})_{\alpha_R} = \frac{\partial l(\boldsymbol{\theta})}{\partial \alpha_R} = \sum_{i=1}^{N}\delta_{Ri} - \sum_{i=1}^{N} y_{Ri} * e^{(\alpha_R+\beta_C x_{Ri})}, \tag{3.16}$$

the score equation for intercept of the biosimilar product is

$$\mathbf{U}(\boldsymbol{\theta})_{\alpha_T} = \frac{\partial l(\boldsymbol{\theta})}{\partial \alpha_T} = \sum_{i=1}^{N} \delta_{Ti} - \sum_{i=1}^{N} y_{Ti} * e^{(\alpha_T + \beta_C x_{Ti})}, \text{ and} \tag{3.17}$$

the score equation for the common regression coefficient is

$$\mathbf{U}(\boldsymbol{\theta})_{\beta_C} = \frac{\partial l(\boldsymbol{\theta})}{\partial \beta_C} = \sum_{i=1}^{N} (\delta_{Ri} x_{Ri} + \delta_{Ti} x_{Ti}) - \sum_{i=1}^{N} x_{Ri} y_{Ri} * e^{(\alpha_R + \beta_C x_{Ri})} - \sum_{i=1}^{N} x_{Ti} y_{Ti} * e^{(\alpha_T + \beta_C x_{Ti})}. \tag{3.18}$$

Then we establish the estimated covariance matrix of coefficients as

$$\begin{bmatrix} \hat{V}(\hat{\alpha}_R) & \hat{cov}(\hat{\alpha}_R, \hat{\alpha}_T) & \hat{cov}(\hat{\alpha}_R, \hat{\beta}_C) \\ \hat{cov}(\hat{\alpha}_T, \hat{\alpha}_R) & \hat{V}(\hat{\alpha}_T) & \hat{cov}(\hat{\alpha}_T, \hat{\beta}_C) \\ \hat{cov}(\hat{\beta}_C, \hat{\alpha}_R) & \hat{cov}(\hat{\beta}_C, \hat{\alpha}_T) & \hat{V}(\hat{\beta}_C) \end{bmatrix} = \begin{bmatrix} -\frac{\partial^2 l(\hat{\boldsymbol{\theta}})}{\partial^2 \alpha_R} & -\frac{\partial^2 l(\hat{\boldsymbol{\theta}})}{\partial \alpha_R \partial \alpha_T} & -\frac{\partial^2 l(\hat{\boldsymbol{\theta}})}{\partial \alpha_R \partial \beta_C} \\ -\frac{\partial^2 l(\hat{\boldsymbol{\theta}})}{\partial \alpha_T \partial \alpha_R} & -\frac{\partial^2 l(\hat{\boldsymbol{\theta}})}{\partial^2 \alpha_T} & -\frac{\partial^2 l(\hat{\boldsymbol{\theta}})}{\partial \alpha_T \partial \beta_C} \\ -\frac{\partial^2 l(\hat{\boldsymbol{\theta}})}{\partial \beta_C \partial \alpha_R} & -\frac{\partial^2 l(\hat{\boldsymbol{\theta}})}{\partial \beta_C \partial \alpha_T} & -\frac{\partial^2 l(\hat{\boldsymbol{\theta}})}{\partial^2 \beta_C} \end{bmatrix}^{-1} \tag{3.19}$$

$$\begin{bmatrix} \sum_{i=1}^{N} y_{Ri} * e^{(\hat{\alpha}_R + \hat{\beta}_C x_{Ri})} & 0 & \sum_{i=1}^{N} x_{Ri} y_{Ri} * e^{(\hat{\alpha}_R + \hat{\beta}_C x_{Ri})} \\ 0 & \sum_{i=1}^{N} y_{Ti} * e^{(\hat{\alpha}_T + \hat{\beta}_C x_{Ti})} & \sum_{i=1}^{N} x_{Ti} y_{Ti} * e^{(\hat{\alpha}_T + \hat{\beta}_C x_{Ti})} \\ \sum_{i=1}^{N} x_{Ri} y_{Ri} * e^{(\hat{\alpha}_R + \hat{\beta}_C x_{Ri})} & \sum_{i=1}^{N} x_{Ti} y_{Ti} * e^{(\hat{\alpha}_T + \hat{\beta}_C x_{Ti})} & \sum_{j=R}^{T} \sum_{i=1}^{N} x_{Ji}^2 y_{Ji} * e^{(\hat{\alpha}_J + \hat{\beta}_C x_{Ji})} \end{bmatrix}^{-1}$$

$$= i\left(\hat{\theta}_{(n)}\right)^{-1} \tag{3.20}$$

Then we apply the Newton-Raphson method to obtain the estimates. The $\theta_0 = [0, 0, 0]^T$ is used as the initial value for iteration. The MLE is obtained when the solution $U\left(\hat{\theta}_{(n+1)}\right) = 0$

3.2.2 Estimate Relative Potency and Its Confidence Interval

Let the dose of the test preparation be x_0. Denote Δ as the horizontal distance between the two linear log-hazard regression lines. Then the response of the biosimilar product at the x_0 dose is the same as that of the innovative product at the $x_0 + \Delta$ dose. Then the relative potency is defined as

$$\Delta = \frac{\alpha_R - \alpha_T}{\beta_C}. \tag{3.21}$$

The MLE of Δ is given as

$$\hat{\Delta} = \frac{\hat{\alpha}_R - \hat{\alpha}_T}{\hat{\beta}_C}, \tag{3.22}$$

where $\hat{\alpha}_R$, $\hat{\alpha}_T$ and $\hat{\beta}_C$ are the MLE of α_R, α_T and β_C respectively.

The confidence interval of Relative Potency

Rewrite Eq.(3.22) as

$$\hat{\alpha}_R - \hat{\alpha}_T - \hat{\beta}_C\hat{\Delta} = 0. \tag{3.23}$$

When the sample size is large enough, it follows that

$$\hat{\alpha}_R - \hat{\alpha}_T - \hat{\beta}_C\hat{\Delta} \sim N\left(0, \mathrm{V}\left(\hat{\alpha}_R - \hat{\alpha}_T - \hat{\beta}_C\hat{\Delta}\right)\right). \tag{3.24}$$

Therefore $\dfrac{\hat{\alpha}_R - \hat{\alpha}_T - \hat{\beta}_C\hat{\Delta}}{\sqrt{\hat{\mathrm{V}}\left(\hat{\alpha}_R - \hat{\alpha}_T - \hat{\beta}_C\hat{\Delta}\right)}}$ follows approximately a standard normal distribution, where $\hat{\mathrm{V}}\left(\hat{\alpha}_R - \hat{\alpha}_T - \hat{\beta}_C\hat{\Delta}\right)$ is the MLE of $\mathrm{V}\left(\hat{\alpha}_R - \hat{\alpha}_T - \hat{\beta}_C\hat{\Delta}\right)$. The probability statement of constructing an 100(1-α)% confidence interval for Δ is given as

$$\mathrm{P}\left[\left(\frac{\hat{\alpha}_R-\hat{\alpha}_T-\hat{\beta}_C\hat{\Delta}}{\sqrt{\hat{\mathrm{V}}\left(\hat{\alpha}_R-\hat{\alpha}_T-\hat{\beta}_C\hat{\Delta}\right)}}\right)^2 \le \mathrm{Z}_\alpha^2\right]=1-2\alpha. \tag{3.25}$$

It turns out that it is a quadratic equation of $\hat{\Delta}$ as expressed in the as follows

$$\left(\hat{\alpha}_R-\hat{\alpha}_T-\hat{\beta}_C\hat{\Delta}\right)^2-\mathrm{Z}_\alpha^2\hat{\mathrm{V}}\left(\hat{\alpha}_R-\hat{\alpha}_T-\hat{\beta}_C\hat{\Delta}\right)\le 0. \tag{3.26}$$

The two roots of the above quadratic equation constitute the lower and upper limits of the 100(1-2α)% confidence interval for Δ is given as

$$\left(\Delta_{\mathrm{U}},\Delta_{\mathrm{L}}\right)=\frac{B\pm\sqrt{B^2-AC}}{A}, \tag{3.27}$$

where

$$A=\hat{\beta}_C{}^2-\mathrm{Z}_\alpha^2\hat{\mathrm{V}}\left(\hat{\beta}_C\right),$$

$$B=\left(\hat{\alpha}_R-\hat{\alpha}_T\right)\hat{\beta}_C-\mathrm{Z}_\alpha^2\left(\hat{\mathrm{cov}}\left(\hat{\alpha}_R,\hat{\beta}_C\right)-\hat{\mathrm{cov}}\left(\hat{\alpha}_T,\hat{\beta}_C\right)\right),$$

$$C=\left(\hat{\alpha}_R-\hat{\alpha}_T\right)^2-\mathrm{Z}_\alpha^2\hat{\mathrm{V}}\left(\hat{\alpha}_R-\hat{\alpha}_T\right),$$

where $\mathrm{cov}\left(X,Y\right)$ denotes the covariance of X and Y, and $\hat{\mathrm{cov}}\left(X,Y\right)$ is the MLE of $\mathrm{cov}\left(X,Y\right)$. The two roots exist when the common slope $\hat{\beta}_C$ is statistically significantly different from zero which implies $A\neq 0$ and $\mathrm{B}^2-AC>0$.

The interval hypothesis based on the relative potency is given as

$$\begin{cases} H_0:\Delta\le\delta_L \ \ or \ \ \Delta\ge\delta_U \\ v.s. \\ H_a:\delta_L\le\Delta\le\delta_U \end{cases}, \tag{3.28}$$

where δ_{L} and δ_{U} are some pre-defined lower and upper margins. If the 100(1-2α)%

confidence interval for Δ given in Eq.(3.27) is within (δ_L, δ_U) then the null hypothesis in Eq.(3.28) is rejected and the biosimilar product is similar to the innovator product at the α significance level.

Chapter 4 A Numerical Example

In this chapter we apply the proposed statistical methods derived in Chapter 3 to a numerical data set. We want to test whether the biosimilar drug product and innovative drug product are similar with respect to the censored endpoint. The proper range of hazard ratio for drug product is between 0.4 and 0.9. Thus we have:

$$0.4 \le \left(1+\frac{1}{k}\right)\lambda \le 0.9 \tag{4.1}$$

devided by $\left(1+\frac{1}{k}\right)$

$$0.4\left(\frac{k}{1+k}\right) \le \exp(\alpha+\beta x) \le 0.9\left(\frac{k}{1+k}\right) \tag{4.2}$$

take natural logarithm

$$\ln\left(0.4\left(\frac{k}{1+k}\right)\right) \le (\alpha+\beta x) \le \ln\left(0.9\left(\frac{k}{1+k}\right)\right) \tag{4.3}$$

minus α

$$\ln\left(0.4\left(\frac{k}{1+k}\right)\right) - \alpha \le \beta x \le \ln\left(0.9\left(\frac{k}{1+k}\right)\right) - \alpha \tag{4.4}$$

devided by β

$$\frac{\ln\left(0.4\left(\frac{k}{1+k}\right)\right)-\alpha}{\beta} \le x \le \frac{\ln\left(0.9\left(\frac{k}{1+k}\right)\right)-\alpha}{\beta} \tag{4.5}$$

Now we have the range of dose level based on the proper hazard. With the

consideration of placebo, we will take 0 as the starting dose level. The remaining dose levels were calculated in order to generate a series of equidistant and increasing hazard rate.

Because we cannot get real data, we use the Fortran to generate the data to evaluate the biosimilar drug and to apply the Newton–Raphson method. In this chapter, Compaq Visual Fortran 6.6 and IMSL's STAT/LIBRARY FORTRAN subroutines RNEXP were used. The purpose of this section is to illustrate the proposed methods with a numerical data set. The steps for generation of data are as below:

Step 1: Assume that 3 doses of drugs with 0 intercept and the slope of -0.5. The hazard is between 0.4 and 0.9. The dose levels (x) are calculated, we have:

{0, [ln(0.9*(0.2)/(1+0.2))-0]/(-0.5), [ln(0.4*(0.2)/(1+0.2))-0]/(-0.5)}

Generate the probability of censored responses (y) based on the log-hazard linear regression models as follow:

$$f_R(y) = \lambda_R \exp(-\lambda_R y)$$

$$f_R(x) = \ln(\lambda_R) = 0.5x,$$

$$f_T(y) = \lambda_T \exp(-\lambda_T y),$$

$$f_T(x) = \ln(\lambda_T) = 0.5x$$

Step 2: Assume that 60 subjects are randomized to each dose of both drug products. The data for each dose level are generated by the exponential distribution. In order to generate

the simulated censored data, we use RNEXP with different parameters to generate a pair of data which include life time and censored time. If lifetime generated from FORTRAN is great than censored time, this data is deemed as censored. Otherwise its lifetime is observed. As Eq.(2.18) in Chapter 2, the censored rate can be determined by the ratio of the two parameters of the two exponential distributions. In this case, we assumed that the censored rate is 0.2, we have $1/(1+\mathrm{k}) = 0.2$, where k is the ratio of the two hazards.

The dose levels and hazard rates for generating the censored data are provided in Table 4.1. Table 4.2 and Table 4.3 provide the generated data for the innovator's and biosimilar products respectively. The Fortran codes given in Appendix 1 were used to generate the data set and to perform all computations and statistical tests for equivalence between the innovator's and biosimilar products.

Fit log-hazard linear regression models.

The IMSL's STAT/LIBRARY CTGLM was employed to obtain the MLEs by the Newton–Raphson method.

The estimated log-hazard regression equations are given as

$$\mathrm{f}_{\mathrm{T}}(x) = 0.124 - 0.5901x$$

$$\mathrm{f}_{\mathrm{R}}(x) = 0.143 - 0.5977x$$

and the estimated standard deviation of the slopes of innovative and biosimilar products are 0.0869 and 0.0874, respectively.

Test linearity of the two log-hazard linear regression models.

The 95% confidence interval for the slopes of the innovative product and biosimilar product by Eq.(3.5) and Eq.(3.6) are given as

$$-0.761 < \beta_T < -0.420$$

$$-0.769 < \beta_R < -0.426$$

Both of 95% confidence intervals do not contain 0, therefore we reject the null hypothesis at the 5% significance level and that the two regression models are linear. Then we can go to the next step.

Test for parallelism of log-hazard linear regressions.

We use Eq.(3.9) to establish 90% confidence interval for the difference of slopes which is given as

$$-0.1952 < \beta_T - \beta_R < 0.2104$$

If the equivalence limits C is set at 0.5, since the 90% confidence interval $(-0.1952, 0.2104)$ is completely contained within $(-0.5, 0.5)$, then the null hypothesis in Eq.(3.7) is rejected and the two loh-hazard linear regressions are parallel to each other at the 5% significance level.

Estimate relative potency and its confidence interval.

We also applied MLE and Newton–Raphson method to estimate the parameters for the log-hazard regressions with the common slope in Eq.(3.12) and to obtain the variances

and the covariances. $\boldsymbol{\theta}^{(0)} = [0,0,0]^{\mathrm{T}}$ was the initial value, and the score function $\mathbf{U}\left(\hat{\boldsymbol{\theta}}^{(0)}\right)$ by Eq.(3.17), Eq.(3.18) and Eq.(3.19) and the $\mathbf{i}\left(\hat{\boldsymbol{\theta}}^{(0)}\right)^{-1}$ by Eq.(3.21)

The convergence condition is set as $\mathbf{U}\left(\hat{\boldsymbol{\theta}}^{(i+1)}\right) < 0.001$.

The estimates of the parameters is $\hat{\boldsymbol{\theta}} = (0.127, 0.139, -0.593)$ with the corresponding estimated covariance matrix : $\hat{\Sigma}_{\hat{\theta}} = \begin{pmatrix} 0.0099 & 0.0034 & -0.0035 \\ 0.0034 & 0.0103 & -0.0037 \\ -0.0035 & -0.0037 & 0.0038 \end{pmatrix}$.

The A, B, and C in Eq.(3.27) are 0.3424, 0.0064, and -0.0549. Then the lower and upper limits of the 90% confidence interval for Δ by Eq.(3.27) is given as $\left(\hat{\Delta}_{\mathrm{L}}, \hat{\Delta}_{\mathrm{U}}\right) = (-0.312,\ 1.055)$. Let $-\delta_L = \delta_U = 2$ Since the 90% confidence interval $(-0.303,\ 0.347)$ is contained within (-2, 2), then the null hypothesis in Eq.(3.28) is rejected and we can conclude that the biosimilar product is equivalent to the innovator product at the 5% significance level.

Table 4.1: The dose levels and the hazard rate of the censored responses of the numerical example

The dose levels	Innovator's product	0.0000	0.66	2.28
	Biosimilar product	0.0000	0.66	2.28
The hazard rate of the censored responses	Innovator's product	1.510338	0.849026	0.368406
	Biosimilar product	1.355327	0.849531	0.3795

Table 4.2: The data of innovator's product of the numerical example

dose level	y	Event	dose level	y	Event	dose level	y	Event
0	0.565676	1	0.66	1.923281	1	2.28	1.694582	1
0	0.02606	1	0.66	1.367449	0	2.28	7.977741	1
0	0.410031	1	0.66	0.138997	1	2.28	1.876833	1
0	0.472187	1	0.66	1.191714	1	2.28	2.364123	1
0	0.736063	0	0.66	1.418966	0	2.28	2.330968	1
0	0.568776	1	0.66	0.286614	1	2.28	1.571399	1
0	0.29147	0	0.66	2.710549	1	2.28	0.080646	1
0	0.545199	0	0.66	1.313776	1	2.28	0.405775	0
0	0.083131	1	0.66	0.857601	1	2.28	0.317192	1
0	1.133658	1	0.66	3.038505	1	2.28	0.749007	1
0	0.924483	1	0.66	1.810163	1	2.28	9.099643	1
0	0.049561	1	0.66	1.806455	1	2.28	0.5124	1
0	1.080554	1	0.66	1.030187	1	2.28	1.297943	0
0	0.858988	1	0.66	0.066627	1	2.28	5.450678	1
0	1.248305	1	0.66	0.348212	1	2.28	0.082459	0
0	0.782595	1	0.66	0.025639	1	2.28	1.906734	1
0	0.776431	1	0.66	0.752121	1	2.28	0.052667	0
0	0.023909	1	0.66	1.650722	1	2.28	4.745401	1
0	0.074743	1	0.66	0.661037	1	2.28	3.717178	1
0	0.531218	1	0.66	2.785606	1	2.28	1.498183	1
0	0.449987	1	0.66	0.317634	1	2.28	0.189629	1
0	0.2753	1	0.66	2.706503	1	2.28	2.465364	1
0	1.221431	1	0.66	1.440482	1	2.28	8.272324	0
0	0.177016	1	0.66	0.325948	0	2.28	0.096546	1
0	1.079794	1	0.66	0.257147	1	2.28	1.16096	1
0	0.128756	0	0.66	1.150389	0	2.28	1.168958	1
0	0.045606	1	0.66	0.098354	1	2.28	4.462077	0
0	0.327799	1	0.66	0.024367	1	2.28	0.909391	1

Table 4.2: The data of innovator's product of the numerical example (continued)

dose level	y	Event	dose level	y	Event	dose level	y	Event
0	0.55645	1	0.66	0.48072	1	2.28	2.634469	1
0	0.797005	1	0.66	0.383678	1	2.28	0.673508	1
0	0.653567	1	0.66	2.218801	1	2.28	2.432333	1
0	0.24007	1	0.66	0.613704	1	2.28	5.356753	1
0	0.076049	1	0.66	2.783111	1	2.28	5.197347	1
0	1.443451	1	0.66	0.205855	1	2.28	1.534791	1
0	0.441252	0	0.66	0.389163	1	2.28	0.894939	1
0	1.000081	1	0.66	0.075427	1	2.28	1.264833	1
0	0.806086	1	0.66	0.720281	1	2.28	1.023505	1
0	0.944224	0	0.66	3.495008	1	2.28	0.217011	1
0	0.770056	1	0.66	2.601237	1	2.28	2.384684	1
0	0.584028	0	0.66	0.179513	1	2.28	0.897016	1
0	0.388369	1	0.66	0.019288	0	2.28	3.971281	1
0	0.134092	1	0.66	1.603333	0	2.28	6.748565	1
0	0.122152	1	0.66	1.259941	1	2.28	3.769679	0
0	0.844321	1	0.66	1.008211	1	2.28	2.487682	1
0	0.731682	0	0.66	0.657773	1	2.28	1.123336	1
0	1.021864	1	0.66	0.494904	1	2.28	7.507009	1
0	1.468538	1	0.66	0.077482	1	2.28	3.969569	1
0	3.15471	0	0.66	1.225173	0	2.28	1.111024	1
0	0.587292	0	0.66	0.897588	1	2.28	1.756796	0
0	0.200894	0	0.66	0.194839	1	2.28	5.764542	1
0	0.001502	1	0.66	2.62858	1	2.28	0.501156	1
0	0.251845	1	0.66	0.140639	0	2.28	1.196662	1
0	1.295347	0	0.66	0.134844	1	2.28	4.322077	0
0	1.196807	1	0.66	0.05955	1	2.28	0.714241	1
0	1.014896	1	0.66	0.677278	1	2.28	15.08122	0
0	0.627956	1	0.66	0.427583	1	2.28	3.131157	1
0	0.528782	1	0.66	1.103551	1	2.28	0.773972	1
0	0.301193	1	0.66	3.297792	1	2.28	0.473469	0
0	2.486148	1	0.66	2.127027	1	2.28	5.54246	1
0	0.166783	1	0.66	6.982264	1	2.28	1.949759	1

Event: Censored:0, Dead:1

Table 4.3: The data of biosimilar product of the numerical example

dose level	y	Event	dose level	y	Event	dose level	y	Event
0	1.721094	1	0.66	0.510484	1	2.28	4.991991	1
0	1.294801	1	0.66	0.569712	1	2.28	0.056591	1
0	1.144222	1	0.66	0.269048	1	2.28	3.047076	1
0	0.594078	1	0.66	2.496932	1	2.28	8.603676	1
0	0.298683	0	0.66	1.574189	1	2.28	7.607112	0
0	0.956284	1	0.66	0.484248	1	2.28	1.21665	1
0	0.819084	0	0.66	0.722476	1	2.28	0.182194	1
0	0.357555	0	0.66	1.744877	1	2.28	1.675487	0
0	0.72876	0	0.66	0.015427	1	2.28	5.154934	0
0	0.08172	1	0.66	1.476822	1	2.28	1.479413	1
0	1.890951	1	0.66	0.642912	1	2.28	1.443568	1
0	0.431873	1	0.66	1.692001	1	2.28	1.359838	0
0	0.433627	1	0.66	0.557561	1	2.28	2.376215	1
0	0.638916	1	0.66	0.27989	1	2.28	6.51016	0
0	0.199472	1	0.66	0.970529	1	2.28	0.141446	0
0	0.384602	1	0.66	1.709343	1	2.28	0.371591	1
0	0.11718	1	0.66	0.010818	1	2.28	0.935804	1
0	0.575555	1	0.66	0.706653	1	2.28	1.157323	1
0	2.020102	1	0.66	0.405729	1	2.28	5.248139	1
0	1.162981	1	0.66	1.379279	1	2.28	4.286729	1
0	2.559277	1	0.66	0.178001	1	2.28	3.827849	1
0	1.608851	1	0.66	0.094762	0	2.28	1.486865	1
0	0.984141	1	0.66	1.580914	0	2.28	1.127366	1
0	0.237841	1	0.66	0.356701	1	2.28	0.086622	1
0	0.852416	1	0.66	1.767197	1	2.28	2.025157	1
0	0.575711	0	0.66	0.476606	1	2.28	6.001138	1
0	0.718332	1	0.66	4.93984	1	2.28	0.330683	0
0	0.6823	1	0.66	0.80909	1	2.28	6.440555	1
0	1.889656	1	0.66	1.689126	1	2.28	1.392898	0
0	0.065221	1	0.66	0.042969	1	2.28	1.267012	1
0	0.215603	1	0.66	0.013299	1	2.28	0.306707	1

Table 4.3: The data of biosimilar product of the numerical example (continued)

dose level	y	Event	dose level	y	Event	dose level	y	Event
0	1.004243	1	0.66	0.244039	1	2.28	0.629441	1
0	0.261976	1	0.66	0.366161	1	2.28	0.449935	1
0	0.724079	1	0.66	4.642448	0	2.28	3.998625	1
0	0.612284	1	0.66	0.086116	1	2.28	11.06248	1
0	1.327974	1	0.66	0.819024	1	2.28	1.446124	1
0	0.411204	0	0.66	0.576629	0	2.28	0.919951	1
0	0.513032	1	0.66	4.200744	1	2.28	5.764718	0
0	0.020909	1	0.66	0.990621	1	2.28	4.00696	1
0	1.455456	1	0.66	0.898939	0	2.28	1.719995	1
0	0.027104	1	0.66	0.133478	1	2.28	0.218392	1
0	0.536978	1	0.66	0.042831	1	2.28	1.922051	1
0	0.115581	1	0.66	0.675738	1	2.28	9.982935	1
0	0.728335	1	0.66	2.296272	1	2.28	0.538326	1
0	0.062005	1	0.66	3.2429	1	2.28	2.553875	0
0	0.636433	1	0.66	1.788975	1	2.28	1.105582	1
0	0.134311	1	0.66	1.10186	1	2.28	0.212008	1
0	0.407422	1	0.66	1.481999	1	2.28	1.45022	0
0	0.278559	1	0.66	3.501577	0	2.28	0.158631	1
0	0.252044	1	0.66	0.637491	1	2.28	6.231051	1
0	0.552686	1	0.66	0.56429	1	2.28	2.753375	1
0	0.248078	1	0.66	1.131293	1	2.28	0.97435	1
0	0.622436	0	0.66	0.101492	1	2.28	0.080649	1
0	0.404154	1	0.66	0.612287	1	2.28	0.696167	1
0	0.897294	0	0.66	0.381466	0	2.28	0.983322	0
0	0.436052	1	0.66	1.732586	1	2.28	2.60156	1
0	1.963485	1	0.66	0.896109	1	2.28	2.969105	1
0	1.765326	1	0.66	1.903747	1	2.28	4.753149	1
0	1.61982	1	0.66	0.31775	1	2.28	4.118247	0
0	0.009605	0	0.66	5.090944	1	2.28	1.662898	1

Event: Censored:0, Dead:1

Chapter 5 Simulation Studies

In this chapter, Compaq Visual Fortran 6.6 and IMSL's STAT/LIBRARY FORTRAN subroutines RNEXP were used in the simulation study to generate the data to do the simulation to compare the coverage probability, size and power with different sample sizes, slopes and number of doses. Because it can fail sometimes to get the MLE by Newton–Raphson when the $\mathbf{U}\left(\hat{\boldsymbol{\theta}}\right)$ may be larger than 0.001, we first get the appropriate dose levels by the small-scale simulation, and then we use the resulting dose levels to perform the simulation.

5.1 Selection of Dose Levels

A flow chart for selection of dose process is given in Figure 5.1. The dose level is determined when the maximum and minimum hazard, the number of doses, the censored rate, the slope and the intercept are given. The recommend hazard ratio range for a drug is between 0.4 and 0.9 by 0.1. We choose all combinations of 0.4, 0.5, 0.6, 0.7, 0.8 and 0.9 as the ranges of hazard ratio. For example (0.6, 0.9) is one of ranges for the hazard ratio. With the consideration of placebo, we take 0 as the starting dose level. The remaining dose levels are calculated in order to generate a series of equidistant and increasing hazard rate. Then the probabilities were calculated by following log-hazard regression equations at each dose,

$$f_R(x) = \ln(\lambda_R) = \alpha_R + \beta_R x$$

$$f_T(x) = \ln(\lambda_T) = \alpha_T + \beta_T x$$

where $\beta_R = \beta_T$ is -0.1 to -0.9 by -0.2. The simple size is for 100 each dose level, the censored rates are 0.2 and 0.3. We use the exponential distribution to generate the probabilities of censored responses. In order to generate the simulated censored data, we use RNEXP with different combinations of parameters to generate a pair of data which include life time and censored time. If lifetime generated from FORTRAN is great than censored time, this data is deemed as censored. Otherwise its lifetime is observed. As Eq.(2.18) in Chapter 2, the censored rate can be determined by the ratio of the two parameters of the two exponential distributions.

Then we use the statistical method mentioned in Chapter 3 to determine the 90% confidence interval, and repeat for 10000 times to determine the empirical power. The equivalence limits are set to be ±2 for the method based on the relative potency of the product characteristics. The empirical power is calculated as the proportion of 10000 random samples in which the confidence intervals fall entirely within (-2, 2) when $\Delta = 0$.

The results are given in Table 5.1 to Table 5.3. We choose the dose levels whose empirical power is the highest among all combinations of slopes, the number of doses, and two levels of censored rate.

5.2 Simulation Processes

Simulation process is similar to selection of dose levels. A flow chart of the simulation process is given in Figure 5.2. The simulation used the dose levels chosen in the previous section. The probabilities were calculated by the similar log-hazard linear regression equations at each dose as follow:

$$f_R(y) = \lambda_R \exp(-\lambda_R y),$$

$$f_T(y) = \lambda_T \exp(-\lambda_T y)$$

where $\beta_R = \beta_T = \beta_C$ is -0.1 to -0.9 by -0.2. The censored rate is 0.2 and 0.3. We give the simple size is from 20 to 100 by 20 each dose level, and we used the exponential distribution to generate the censored endpoints. Then we repeat for 10000 times to determine the coverage probability, empirical size, and empirical power. The equivalence limits are set to be ±2 for the method based on the relative potency of the product characteristic.

The coverage probability is computed as the proportion of 10000 confidence intervals containing the specified true parameters of Δ. The empirical size is estimated as the proportion of 10000 random samples for which the confidence intervals are totally contained within (-2, 2) when $\Delta = \pm 2$ .The empirical power is calculated as the proportion of 10000 random samples in which the confidence interval falls entirely within (-2, 2), where $\Delta = -1, 0 \text{ and } 1$.

At the 5% nominal significance level, a simulation study with 10000 samples that 95% of the empirical sizes will be small than 0.0536 if the method can adequately control the type one error rate at the 5% nominal level. Similarly, empirical coverage probability for the 90% confidence interval will be between 0.8941 and 0.9059 if the method can provide adequate coverage probability at the 90% level.

5.3 Simulation Results

The simulation results of coverage probability for the relative potency are given from Table 5.4 to Table 5.6. Table 5.7 presents summary results about the number of coverage probabilities that are within (0.8941, 0.9059). From Table 5.7, 94.9% (356/375) for censored rate=0.2 and 92.5% (347/375) of empirical coverage probabilities are within (0.8941, 0.9059). These results indicate that the confidence intervals by the proposed procedure can provide sufficient coverage probability.

The simulation results of empirical size and empirical power for the relative potency are given from Table 5.8 to Table 5.11. From Table 5.8 to Table 5.10, the empirical size at $\Delta = -2$ is approximately the same as at $\Delta = 2$. This may indicate that the power curve may be symmetric about 0. Table 5.11 provides summary results about the numbers of empirical sizes are smaller than 0.0536. In general, the empirical size decreases as the number of the doses increases. 98% (147/150) for censored rate=0.2 and 94.6% (142/150)

for censored rate=0.3 of empirical sizes are smaller than 0.0536 as shown in Table 5.11. Although the higher censored rate slightly reduces the size and power, the simulation results show that the proposed procedure can provide an excellent control of type I error rate at the nominal significance under the exponential distribution with a right and random censoring mechanism.

The results given from Table 5.8 to Table 5.10 show that the empirical power increases as the sample size increases on the true relative potency Δ approaches to 0. In addition, the empirical power for censored rate of 0.2 is greater than that of 0.3. On the other hand, the empirical power increases as the number of doses increases. The magnitude of the slopes seems also has an impact on the empirical power. For example, the empirical power with slope between -0.3 and -0.7 are larger than those with slope -0.1 or -0.9. However, the impact of the magnitude of the slopes on power is less than that of the sample size. Furthermore, sufficient power can be provided even the sample size is small. For example when there are 3 doses, slope is -0.5, a sample size of 40 per group for a total sample size 120 can provided a power almost 90% when the true relative potency is 0.

The empirical power for the proposed method increases as Δ increases from -2 to 0. It reaches the maximum at $\Delta = 0$. As Δ increases from 0 to 2, it is a decreasing function of Δ. Figure 5.3 presents a power curve when the slope = -0.3, number of doses is three,

and the sample per group is 40. It shows that the power curve is symmetric about 0.

In summary, our proposed procedure not only can provide sufficient coverage probability but also can adequately control the type I error rate at the nominal significance level. Moreover, the proposed method can provide sufficient power even when the sample size is relatively small for some combinations of the number of doses, magnitude of slopes, and the true relative potency.

Table 5.1: The results of empirical power for selection of doses based on relative potency for n=100, 3 doses

Slope	-0.1		-0.3		-0.5		-0.7		-0.9	
Hazard	Censored rate		Censored rate		Censored rate		Censored rate		Censored rate	
range	0.2	0.3	0.2	0.3	0.2	0.3	0.2	0.3	0.2	0.3
0.4~0.5	0.3824	0.2818	1.0000	0.9997	0.9998	0.9999	0.9726	0.9842	0.8333	0.8669
0.4~0.6	0.3868	0.2912	0.9999	0.9997	0.9995	0.9998	0.9584	0.9725	0.7752	0.8234
0.4~0.7	0.3895	0.2840	0.9999	0.9998	0.9996	0.9998	0.9549	0.9715	0.7645	0.8097
0.4~0.8	0.3813	0.2871	0.9999	0.9999	0.9999	0.9999	0.9560	0.9716	0.7772	0.8104
0.4~0.9	0.3791	0.2889	0.9999	1.0000	0.9997	0.9999	0.9637	0.9717	0.7929	0.8218
0.5~0.6	0.3783	0.2807	0.9997	0.9994	0.9924	0.9970	0.8508	0.9083	0.5512	0.6595
0.5~0.7	0.3659	0.2832	0.9992	0.9985	0.9890	0.9953	0.8063	0.8756	0.4801	0.6026
0.5~0.8	0.3609	0.2758	0.9994	0.9993	0.9839	0.9946	0.8007	0.8612	0.4736	0.5681
0.5~0.9	0.3677	0.2806	0.9996	0.999	0.9868	0.9936	0.8145	0.8640	0.4896	0.5686
0.6~0.7	0.3555	0.2627	0.9949	0.9977	0.9270	0.9744	0.5946	0.7443	0.2121	0.3758
0.6~0.8	0.3502	0.2678	0.9906	0.9972	0.8986	0.9580	0.5204	0.6837	0.1500	0.3116
0.6~0.9	0.3390	0.2700	0.9912	0.9956	0.8928	0.9493	0.5167	0.6589	0.1467	0.2872
0.7~0.8	0.321	0.2592	0.9340	0.9819	0.6944	0.8637	0.2252	0.4711	0.0000	0.0894
0.7~0.9	0.3193	0.2572	0.9074	0.9712	0.641	0.8244	0.1633	0.3825	0.0000	0.0298
0.8~0.9	0.2692	0.2494	0.6754	0.8902	0.2782	0.6067	0.0249	0.1433	0.0000	0.0000

Table 5.2: The results of empirical power for selection of doses based on relative potency for n=100 and 5 doses.

Slope	-0.1		-0.3		-0.5		-0.7		-0.9	
Hazard	Censored rate		Censored rate		Censored rate		Censored rate		Censored rate	
range	0.2	0.3	0.2	0.3	0.2	0.3	0.2	0.3	0.2	0.3
0.4~0.5	0.7292	0.6511	1.0000	1.0000	0.9999	1.0000	0.9882	0.9925	0.8952	0.9238
0.4~0.6	0.7215	0.6495	1.0000	1.0000	0.9999	1.0000	0.9800	0.9896	0.8514	0.9021
0.4~0.7	0.7235	0.6524	1.0000	1.0000	0.9999	0.9999	0.9740	0.9846	0.8321	0.8760
0.4~0.8	0.7241	0.6489	1.0000	1.0000	0.9999	0.9999	0.9745	0.9835	0.8340	0.8666
0.4~0.9	0.7292	0.6487	1.0000	1.0000	0.9999	1.0000	0.9743	0.9858	0.8399	0.8641
0.5~0.6	0.7074	0.6392	1.0000	1.0000	0.9973	0.9995	0.9182	0.9570	0.6726	0.7714
0.5~0.7	0.7020	0.6321	1.0000	1.0000	0.9946	0.9989	0.8858	0.9274	0.6022	0.7088
0.5~0.8	0.6959	0.6388	0.9999	1.0000	0.9918	0.9977	0.8636	0.9136	0.5622	0.6605
0.5~0.9	0.6995	0.6333	1.0000	1.0000	0.9929	0.9972	0.8601	0.9072	0.5790	0.6601
0.6~0.7	0.6790	0.6140	0.9989	0.9999	0.9642	0.9900	0.7130	0.8339	0.3443	0.5248
0.6~0.8	0.6693	0.6151	0.9972	0.9997	0.9456	0.9772	0.6398	0.7728	0.2656	0.4369
0.6~0.9	0.6772	0.6106	0.9961	0.9991	0.9419	0.9739	0.6123	0.7434	0.2426	0.4031
0.7~0.8	0.6328	0.5892	0.9739	0.9956	0.8079	0.9310	0.3527	0.5927	0.0084	0.2192
0.7~0.9	0.6177	0.5844	0.9526	0.9916	0.7462	0.8997	0.2820	0.5143	0.0000	0.1375
0.8~0.9	0.5250	0.5401	0.7837	0.9494	0.4295	0.7423	0.0009	0.2669	0.0000	0.0000

Table 5.3: The results of empirical power for selection of doses based on relative potency for n=100 and 7 doses.

Slope	-0.1		-0.3		-0.5		-0.7		-0.9	
Hazard	Censored rate		Censored rate		Censored rate		Censored rate		Censored rate	
range	0.2	0.3	0.2	0.3	0.2	0.3	0.2	0.3	0.2	0.3
0.4~0.5	0.8880	0.8381	1.0000	1.0000	1.0000	1.0000	0.9922	0.9959	0.9222	0.9456
0.4~0.6	0.8865	0.8384	1.0000	1.0000	0.9999	1.0000	0.9882	0.9932	0.8885	0.9228
0.4~0.7	0.8807	0.8296	1.0000	1.0000	1.0000	1.0000	0.9873	0.9904	0.8759	0.9111
0.4~0.8	0.8828	0.8275	1.0000	1.0000	1.0000	1.0000	0.9850	0.9896	0.8793	0.9030
0.4~0.9	0.8890	0.8307	1.0000	1.0000	1.0000	1.0000	0.9889	0.9911	0.8914	0.9108
0.5~0.6	0.8700	0.8299	1.0000	1.0000	0.9987	0.9999	0.9366	0.9673	0.7208	0.8051
0.5~0.7	0.8711	0.8240	1.0000	1.0000	0.9980	0.9993	0.9143	0.9496	0.6591	0.7598
0.5~0.8	0.8712	0.8252	1.0000	1.0000	0.9971	0.9989	0.9048	0.9389	0.6410	0.7293
0.5~0.9	0.8672	0.8247	1.0000	1.0000	0.9963	0.9985	0.9090	0.9427	0.6608	0.7328
0.6~0.7	0.8534	0.8061	0.9998	1.0000	0.9779	0.9925	0.7455	0.8577	0.4070	0.5638
0.6~0.8	0.8407	0.8043	0.9991	1.0000	0.9594	0.9888	0.6910	0.8168	0.3278	0.5013
0.6~0.9	0.8413	0.8001	0.9989	0.9998	0.9611	0.9868	0.6891	0.7966	0.3282	0.4709
0.7~0.8	0.8065	0.7808	0.9810	0.9969	0.8487	0.9466	0.4136	0.6382	0.0523	0.2694
0.7~0.9	0.7786	0.7716	0.9777	0.9933	0.8007	0.9252	0.3493	0.5790	0.0052	0.2053
0.8~0.9	0.6699	0.7259	0.8233	0.9620	0.4821	0.7812	0.0249	0.3278	0.0000	0.0019

Table 5.4: The coverage probability based on relative potency for 3 doses

3 Doses											
		censored rate=0.2					censored rate=0.3				
		Δ					Δ				
Beta	N	-2	-1	0	1	2	-2	-1	0	1	2
-0.1	40	0.9004	0.8954	0.9020	0.8989	0.9020	0.8978	0.8960	0.8975	0.9004	0.8921
	80	0.9015	0.9005	0.8960	0.8963	0.8977	0.9071	0.9009	0.8963	0.9009	0.8967
	120	0.9037	0.9004	0.8985	0.8985	0.8979	0.8957	0.8987	0.8992	0.8997	0.9030
	160	0.8976	0.8953	0.9003	0.8957	0.8983	0.9008	0.8975	0.9049	0.8978	0.9056
	200	0.8999	0.8956	0.9026	0.9037	0.9054	0.8955	0.9047	0.9040	0.9002	0.9028
-0.3	40	0.8973	0.8933	0.8977	0.8988	0.8957	0.8939	0.9003	0.8987	0.8983	0.8960
	80	0.8958	0.9016	0.8981	0.8963	0.9007	0.9001	0.9001	0.9018	0.9007	0.9052
	120	0.8936	0.8998	0.8987	0.8967	0.8946	0.9036	0.9049	0.8973	0.8968	0.9010
	160	0.9035	0.8974	0.9007	0.8975	0.8983	0.9010	0.9043	0.8953	0.8949	0.8942
	200	0.9019	0.9005	0.9022	0.9009	0.8960	0.8978	0.8982	0.9002	0.9001	0.8983
-0.5	40	0.9052	0.9022	0.8920	0.8990	0.9033	0.8911	0.9023	0.8998	0.8963	0.9005
	80	0.9011	0.9005	0.8982	0.8984	0.9004	0.9000	0.8959	0.9019	0.9038	0.8933
	120	0.8956	0.9023	0.8932	0.9006	0.9037	0.8952	0.9000	0.8960	0.9041	0.8981
	160	0.8982	0.9033	0.8973	0.8946	0.8989	0.8980	0.9035	0.9012	0.9037	0.9000
	200	0.9020	0.8945	0.9042	0.8979	0.9047	0.9045	0.8982	0.8997	0.8962	0.8970
-0.7	40	0.8995	0.8941	0.9061	0.8959	0.9055	0.8994	0.9015	0.9007	0.8970	0.9087
	80	0.9006	0.8981	0.8970	0.8965	0.8990	0.8984	0.8996	0.8930	0.8995	0.8994
	120	0.8962	0.8978	0.8958	0.9006	0.9001	0.8983	0.8987	0.8989	0.8989	0.8978
	160	0.9009	0.8996	0.8974	0.8974	0.8946	0.9011	0.9018	0.8978	0.8996	0.9052
	200	0.9012	0.9008	0.8979	0.8995	0.8962	0.8981	0.9019	0.9028	0.8995	0.9050
-0.9	40	0.8944	0.9006	0.8827	0.9084	0.8931	0.9007	0.8888	0.9094	0.8965	0.8898
	80	0.8973	0.8962	0.8977	0.8956	0.8996	0.9037	0.9032	0.8987	0.9044	0.8932
	120	0.8969	0.9000	0.9014	0.8987	0.9027	0.8965	0.8969	0.8960	0.8992	0.8977
	160	0.8978	0.8978	0.8979	0.9000	0.9006	0.8997	0.9002	0.8953	0.8946	0.9005
	200	0.9017	0.9004	0.8988	0.8989	0.8991	0.9004	0.9045	0.8947	0.8981	0.8967

The shaded blocks indicate that the coverage probability is between 0.8941 and 0.9059.

Table 5.5: The coverage probability based on relative potency for 5 doses

5 Doses											
		censored rate=0.2					censored rate=0.3				
		Δ					Δ				
Beta	N	-2	-1	0	1	2	-2	-1	0	1	2
-0.1	40	0.9045	0.8983	0.8934	0.9019	0.8958	0.8965	0.8964	0.8962	0.8941	0.8999
	80	0.8979	0.8980	0.9019	0.8993	0.8998	0.9043	0.8992	0.8989	0.9034	0.8985
	120	0.9015	0.9006	0.9025	0.8961	0.9031	0.9028	0.9008	0.8972	0.9007	0.8955
	160	0.8972	0.8937	0.9017	0.9010	0.9012	0.8967	0.8992	0.8983	0.8964	0.8978
	200	0.9005	0.8975	0.9023	0.9026	0.8983	0.9015	0.9028	0.9002	0.8987	0.9030
-0.3	40	0.8944	0.8991	0.8963	0.9005	0.9010	0.9002	0.8987	0.9014	0.9022	0.8967
	80	0.8965	0.8993	0.8967	0.9017	0.8998	0.9037	0.8946	0.9006	0.9013	0.9013
	120	0.9013	0.8949	0.8992	0.9007	0.8986	0.9017	0.8947	0.8946	0.8981	0.9005
	160	0.8944	0.9028	0.8979	0.8960	0.8965	0.9017	0.9008	0.8936	0.9015	0.8989
	200	0.9007	0.8983	0.9037	0.9055	0.9008	0.9027	0.8971	0.9048	0.8957	0.9000
-0.5	40	0.8966	0.9015	0.8974	0.9040	0.8962	0.8951	0.8996	0.8966	0.8970	0.8964
	80	0.9004	0.8969	0.8929	0.8986	0.9012	0.8988	0.9012	0.8975	0.8949	0.8985
	120	0.9005	0.8989	0.9035	0.8985	0.9022	0.8983	0.9007	0.8962	0.8982	0.8983
	160	0.8989	0.9007	0.8957	0.8992	0.8965	0.9040	0.8998	0.8950	0.9004	0.9006
	200	0.8981	0.8993	0.9006	0.8988	0.9050	0.9073	0.9014	0.8952	0.9014	0.8939
-0.7	40	0.8902	0.8981	0.8973	0.8938	0.9018	0.9017	0.9038	0.9001	0.9043	0.9086
	80	0.8965	0.8984	0.8986	0.9056	0.8968	0.8997	0.9041	0.9044	0.8966	0.8935
	120	0.9045	0.9041	0.9018	0.8959	0.8988	0.8985	0.8946	0.8981	0.8997	0.8939
	160	0.9019	0.8984	0.9015	0.8961	0.9010	0.8981	0.8981	0.9005	0.8950	0.9021
	200	0.9032	0.9014	0.8988	0.8979	0.9007	0.9005	0.9011	0.8961	0.9002	0.8986
-0.9	40	0.9120	0.8962	0.9003	0.8812	0.8953	0.9028	0.8948	0.9054	0.9072	0.8995
	80	0.9039	0.9002	0.8947	0.8951	0.9025	0.9005	0.9002	0.8996	0.8979	0.9035
	120	0.9012	0.8958	0.9017	0.9021	0.9045	0.9023	0.8970	0.8999	0.9026	0.8961
	160	0.8978	0.8963	0.8948	0.8991	0.9007	0.8983	0.9018	0.8984	0.8985	0.8976
	200	0.8994	0.9045	0.8989	0.8993	0.9032	0.9031	0.8961	0.8961	0.8959	0.9008

The shaded blocks indicate that the coverage probability is between 0.8941 and 0.9059.

Table 5.6: The coverage probability based on relative potency for 7 doses

7 Doses											
		censored rate=0.2					censored rate=0.3				
		Δ					Δ				
Beta	N	-2	-1	0	1	2	-2	-1	0	1	2
-0.1	40	0.8985	0.8982	0.9008	0.9017	0.9047	0.8967	0.8967	0.9018	0.8971	0.8980
	80	0.9017	0.8953	0.8979	0.8960	0.9038	0.8986	0.8983	0.8929	0.9025	0.8992
	120	0.9005	0.9030	0.8992	0.9055	0.8987	0.8975	0.8997	0.8930	0.8950	0.9019
	160	0.8992	0.9016	0.9004	0.8992	0.8988	0.9020	0.8982	0.9043	0.9025	0.9009
	200	0.9033	0.9038	0.9006	0.9037	0.8963	0.9002	0.8955	0.8998	0.8954	0.9013
-0.3	40	0.8998	0.9006	0.8949	0.9002	0.9009	0.9024	0.9021	0.9031	0.9017	0.8970
	80	0.8959	0.8968	0.8910	0.8974	0.9018	0.9014	0.8998	0.8973	0.8963	0.8957
	120	0.9001	0.9010	0.9007	0.8970	0.9016	0.9035	0.9054	0.9072	0.9053	0.8982
	160	0.8965	0.8972	0.9001	0.8991	0.8986	0.8929	0.8996	0.9048	0.9014	0.8998
	200	0.9016	0.9000	0.9005	0.8982	0.8948	0.8987	0.9015	0.9002	0.9011	0.8998
-0.5	40	0.9032	0.9016	0.8977	0.8970	0.9027	0.8947	0.9022	0.8977	0.9021	0.8984
	80	0.9016	0.9037	0.8976	0.8982	0.9004	0.8985	0.8996	0.9052	0.8968	0.8978
	120	0.9020	0.8954	0.8997	0.8955	0.9060	0.8991	0.9020	0.8979	0.8958	0.8990
	160	0.8980	0.9046	0.8970	0.9012	0.8980	0.8962	0.8979	0.9023	0.9018	0.8958
	200	0.9002	0.9019	0.8982	0.9050	0.9003	0.9000	0.9001	0.8990	0.9036	0.8992
-0.7	40	0.9038	0.8996	0.8997	0.8986	0.9005	0.9001	0.9039	0.8990	0.8990	0.9062
	80	0.9036	0.9033	0.8983	0.8969	0.8958	0.9000	0.9039	0.8920	0.8980	0.8951
	120	0.8980	0.8933	0.8986	0.9010	0.9000	0.9060	0.9005	0.8994	0.8938	0.8995
	160	0.9005	0.9003	0.9056	0.8958	0.9030	0.8983	0.8969	0.9044	0.8969	0.8981
	200	0.8973	0.8965	0.8979	0.8986	0.8980	0.8940	0.9033	0.9023	0.8935	0.8980
-0.9	40	0.9057	0.8979	0.8960	0.8989	0.9040	0.8977	0.8984	0.9028	0.9047	0.9045
	80	0.8983	0.8972	0.9044	0.9005	0.9005	0.8978	0.8980	0.8991	0.9019	0.8987
	120	0.8973	0.8993	0.8990	0.8974	0.9009	0.8986	0.8966	0.8990	0.8990	0.9005
	160	0.8980	0.8988	0.8950	0.8983	0.8971	0.8980	0.8975	0.8965	0.8951	0.8953
	200	0.9010	0.8985	0.8984	0.8912	0.8997	0.8991	0.8982	0.9011	0.8986	0.8997

The shaded blocks indicate that the coverage probability is between 0.8941 and 0.9059.

Table 5.7: A summary of coverage probabilities

Censored rate=0.2						
dose	beta					total
	-0.1	-0.3	-0.5	-0.7	-0.9	
3	25	23	23	24	22	117
5	23	25	24	23	23	118
7	25	24	24	24	24	121
total	73	72	71	71	69	356
proportion	0.973	0.96	0.946	0.946	0.92	0.949
Censored rate=0.3						
Dose	beta					total
	-0.1	-0.3	-0.5	-0.7	-0.9	
3	23	24	23	23	21	114
5	25	24	23	22	24	118
7	23	23	25	19	25	115
Total	71	71	71	64	70	347
proportion	0.946	0.946	0.946	0.853	0.933	0.925

The entries are the numbers of coverage probability that are between 0.8941 and 0.9059.

Table 5.8: The empirical size and empirical power based on relative potency for 3 doses

3 Doses											
		censored rate=0.2					censored rate=0.3				
		Δ					Δ				
Beta	N	-2	-1	0	1	2	-2	-1	0	1	2
-0.1	40	0.0026	0.0044	0.0067	0.0052	0.0023	0.0009	0.0006	0.0013	0.0012	0.0006
	80	0.0358	0.1386	0.2164	0.1421	0.0375	0.0241	0.0923	0.1403	0.0955	0.0303
	120	0.0489	0.2907	0.5265	0.2918	0.0487	0.0505	0.2426	0.4283	0.2451	0.0440
	160	0.0532	0.3718	0.7196	0.3792	0.0504	0.0486	0.3355	0.6327	0.3390	0.0479
	200	0.0503	0.4488	0.8376	0.4486	0.0489	0.0525	0.4097	0.7745	0.3999	0.0479
-0.3	40	0.0503	0.5368	0.9314	0.5439	0.0515	0.0529	0.5134	0.9101	0.5107	0.0476
	80	0.0527	0.7965	0.9988	0.7974	0.0477	0.0491	0.7667	0.9976	0.7637	0.0479
	120	0.0526	0.9181	1.0000	0.9199	0.0526	0.0454	0.8991	0.9999	0.8957	0.0479
	160	0.0456	0.9683	1.0000	0.9688	0.0515	0.0500	0.9573	1.0000	0.9589	0.0530
	200	0.0528	0.9909	1.0000	0.9897	0.0525	0.0526	0.9827	1.0000	0.9835	0.0486
-0.5	40	0.0397	0.6932	0.8971	0.6917	0.0412	0.0452	0.6937	0.9095	0.7012	0.0451
	80	0.0452	0.9523	0.9980	0.9571	0.0478	0.0507	0.9519	0.9992	0.9500	0.0517
	120	0.0521	0.9945	1.0000	0.9946	0.0476	0.0495	0.9923	1.0000	0.9926	0.0516
	160	0.0526	0.9993	1.0000	0.9992	0.0490	0.0516	0.9987	1.0000	0.9991	0.0490
	200	0.0496	1.0000	1.0000	0.9999	0.0455	0.0461	0.9999	1.0000	0.9998	0.0509
-0.7	40	0.0251	0.4454	0.5247	0.4424	0.0229	0.0264	0.4781	0.5663	0.4796	0.0277
	80	0.0418	0.9007	0.9146	0.8933	0.0453	0.0459	0.9113	0.9269	0.9082	0.0449
	120	0.0478	0.9849	0.9862	0.9850	0.0493	0.0501	0.9885	0.9887	0.9888	0.0481
	160	0.0482	0.9977	0.9979	0.9978	0.0505	0.0499	0.9987	0.9989	0.9980	0.0486
	200	0.0452	0.9995	1.0000	0.9998	0.0523	0.0513	0.9997	0.9999	0.9998	0.0451
-0.9	40	0.0067	0.1310	0.1507	0.1307	0.0057	0.0078	0.1681	0.1927	0.1762	0.0095
	80	0.0327	0.6541	0.6654	0.6551	0.0329	0.0326	0.6876	0.6920	0.6858	0.0364
	120	0.0464	0.8839	0.8758	0.8783	0.0458	0.0439	0.8945	0.8911	0.9004	0.0408
	160	0.0442	0.9634	0.9575	0.9572	0.0457	0.0513	0.9700	0.9675	0.9648	0.0465
	200	0.0481	0.9856	0.9843	0.9850	0.0497	0.0479	0.9909	0.9907	0.9893	0.0520

Table 5.9: The empirical size and empirical power based on relative potency for 5 doses

5 Doses											
		censored rate=0.2					censored rate=0.3				
		Δ					Δ				
Beta	N	-2	-1	0	1	2	-2	-1	0	1	2
-0.1	40	0.0246	0.0839	0.1212	0.0814	0.0275	0.0172	0.0454	0.0674	0.0498	0.0205
	80	0.0484	0.3185	0.5788	0.3177	0.0493	0.0452	0.2747	0.4929	0.2807	0.0490
	120	0.0487	0.4434	0.8267	0.4471	0.0500	0.0495	0.4066	0.7630	0.4053	0.0503
	160	0.0516	0.5398	0.9310	0.5326	0.0480	0.0510	0.4962	0.8921	0.5012	0.0538
	200	0.0485	0.6131	0.9738	0.6144	0.0512	0.0490	0.5741	0.9540	0.5718	0.0472
-0.3	40	0.0507	0.6774	0.9860	0.6836	0.0481	0.0493	0.6460	0.9848	0.6602	0.0504
	80	0.0495	0.9088	0.9999	0.9143	0.0489	0.0486	0.8972	1.0000	0.8969	0.0484
	120	0.0459	0.9779	1.0000	0.9773	0.0498	0.0499	0.9734	1.0000	0.9708	0.0501
	160	0.0544	0.9954	1.0000	0.9945	0.0508	0.0508	0.9937	1.0000	0.9937	0.0523
	200	0.0485	0.9994	1.0000	0.9993	0.0514	0.0543	0.9982	1.0000	0.9990	0.0491
-0.5	40	0.0509	0.7985	0.9306	0.8046	0.0484	0.0507	0.8136	0.9425	0.8102	0.0458
	80	0.0500	0.9848	0.9988	0.9853	0.0499	0.0494	0.9849	0.9991	0.9871	0.0531
	120	0.0506	0.9993	1.0000	0.9988	0.0493	0.0538	0.9990	1.0000	0.9990	0.0532
	160	0.0502	1.0000	1.0000	0.9999	0.0529	0.0476	1.0000	1.0000	1.0000	0.0516
	200	0.0538	1.0000	1.0000	1.0000	0.0499	0.0499	1.0000	1.0000	1.0000	0.0523
-0.7	40	0.0294	0.5455	0.5916	0.5385	0.0298	0.0336	0.5877	0.6312	0.5858	0.0295
	80	0.0464	0.9296	0.9377	0.9302	0.0506	0.0477	0.9445	0.9503	0.9469	0.0492
	120	0.0457	0.9923	0.9916	0.9922	0.0515	0.0495	0.9936	0.9953	0.9945	0.0546
	160	0.0485	0.9989	0.9988	0.9990	0.0490	0.0509	0.9996	0.9995	0.9990	0.0461
	200	0.0491	0.9999	0.9997	1.0000	0.0492	0.0499	1.0000	1.0000	0.9997	0.0480
-0.9	40	0.0106	0.2091	0.2204	0.2112	0.0115	0.0134	0.2506	0.2659	0.2596	0.0152
	80	0.0359	0.7146	0.7195	0.7163	0.0365	0.0390	0.7537	0.7546	0.7457	0.0384
	120	0.0457	0.9139	0.9061	0.9183	0.0446	0.0451	0.9265	0.9324	0.9294	0.0477
	160	0.0510	0.9746	0.9704	0.9708	0.0473	0.0501	0.9788	0.9807	0.9797	0.0488
	200	0.0515	0.9916	0.9930	0.9923	0.0477	0.0480	0.9950	0.9955	0.9952	0.0499

Table 5.10: The empirical size and empirical power based on relative potency for 7 doses

7 Doses											
		censored rate=0.2					censored rate=0.3				
		Δ					Δ				
Beta	N	-2	-1	0	1	2	-2	-1	0	1	2
-0.1	40	0.0435	0.1866	0.3122	0.1838	0.0402	0.0369	0.1500	0.2327	0.1463	0.0372
	80	0.0488	0.4176	0.7863	0.4074	0.0484	0.0532	0.3814	0.7071	0.3704	0.0516
	120	0.0517	0.5458	0.9362	0.5468	0.0510	0.0528	0.5086	0.8971	0.5111	0.0523
	160	0.0485	0.6525	0.9839	0.6517	0.0503	0.0483	0.6055	0.9751	0.6099	0.0505
	200	0.0491	0.7420	0.9959	0.7290	0.0512	0.0467	0.6872	0.9923	0.6865	0.0463
-0.3	40	0.0463	0.7728	0.9967	0.7853	0.0504	0.0499	0.7545	0.9969	0.7525	0.0515
	80	0.0504	0.9631	1.0000	0.9626	0.0503	0.0482	0.9485	1.0000	0.9495	0.0585
	120	0.0500	0.9944	1.0000	0.9949	0.0482	0.0489	0.9924	1.0000	0.9922	0.0533
	160	0.0524	0.9992	1.0000	0.9989	0.0487	0.0537	0.9992	1.0000	0.9990	0.0510
	200	0.0514	1.0000	1.0000	0.9999	0.0561	0.0523	0.9999	1.0000	1.0000	0.0497
-0.5	40	0.0475	0.8824	0.9614	0.8829	0.0469	0.0527	0.8847	0.9670	0.8831	0.0533
	80	0.0522	0.9954	0.9998	0.9950	0.0483	0.0530	0.9944	0.9999	0.9956	0.0534
	120	0.0489	0.9999	1.0000	0.9998	0.0467	0.0512	0.9997	1.0000	0.9998	0.0503
	160	0.0513	1.0000	1.0000	1.0000	0.0535	0.0550	1.0000	1.0000	1.0000	0.0518
	200	0.0485	1.0000	1.0000	1.0000	0.0499	0.0488	1.0000	1.0000	1.0000	0.0507
-0.7	40	0.0316	0.6488	0.6884	0.6531	0.0363	0.0372	0.6820	0.7106	0.6815	0.0360
	80	0.0477	0.9647	0.9649	0.9646	0.0505	0.0502	0.9699	0.9749	0.9688	0.0520
	120	0.0495	0.9969	0.9964	0.9969	0.0511	0.0465	0.9983	0.9977	0.9973	0.0518
	160	0.0518	0.9995	1.0000	0.9997	0.0503	0.0525	0.9999	0.9996	1.0000	0.0505
	200	0.0519	1.0000	1.0000	1.0000	0.0523	0.0546	1.0000	1.0000	1.0000	0.0522
-0.9	40	0.0154	0.3094	0.3182	0.3101	0.0163	0.0206	0.3510	0.3586	0.3410	0.0178
	80	0.0393	0.7907	0.7988	0.7972	0.0375	0.0403	0.8165	0.8254	0.8180	0.0422
	120	0.0448	0.9463	0.9455	0.9504	0.0435	0.0485	0.9553	0.9563	0.9555	0.0479
	160	0.0524	0.9877	0.9844	0.9878	0.0519	0.0481	0.9906	0.9882	0.9893	0.0494
	200	0.0503	0.9961	0.9974	0.9968	0.0510	0.0514	0.9981	0.9980	0.9987	0.0504

Table 5.11: A summary of empirical sizes.

Censored rate=0.2						
dose	beta					total
	0.1	0.3	0.5	0.7	0.9	
3	10	10	10	10	10	50
5	10	9	9	10	10	48
7	10	9	10	10	10	49
total	30	28	29	30	30	147
probability	1	0.93	0.967	1	1	0.98
Censored rate=0.3						
dose	beta					total
	0.1	0.3	0.5	0.7	0.9	
3	10	10	10	10	10	50
5	9	9	9	9	10	46
7	10	8	9	9	10	46
total	29	27	28	28	30	142
probability	0.967	0.9	0.93	0.93	1	0.946

The entries are number of sizes that are small than 0.0536

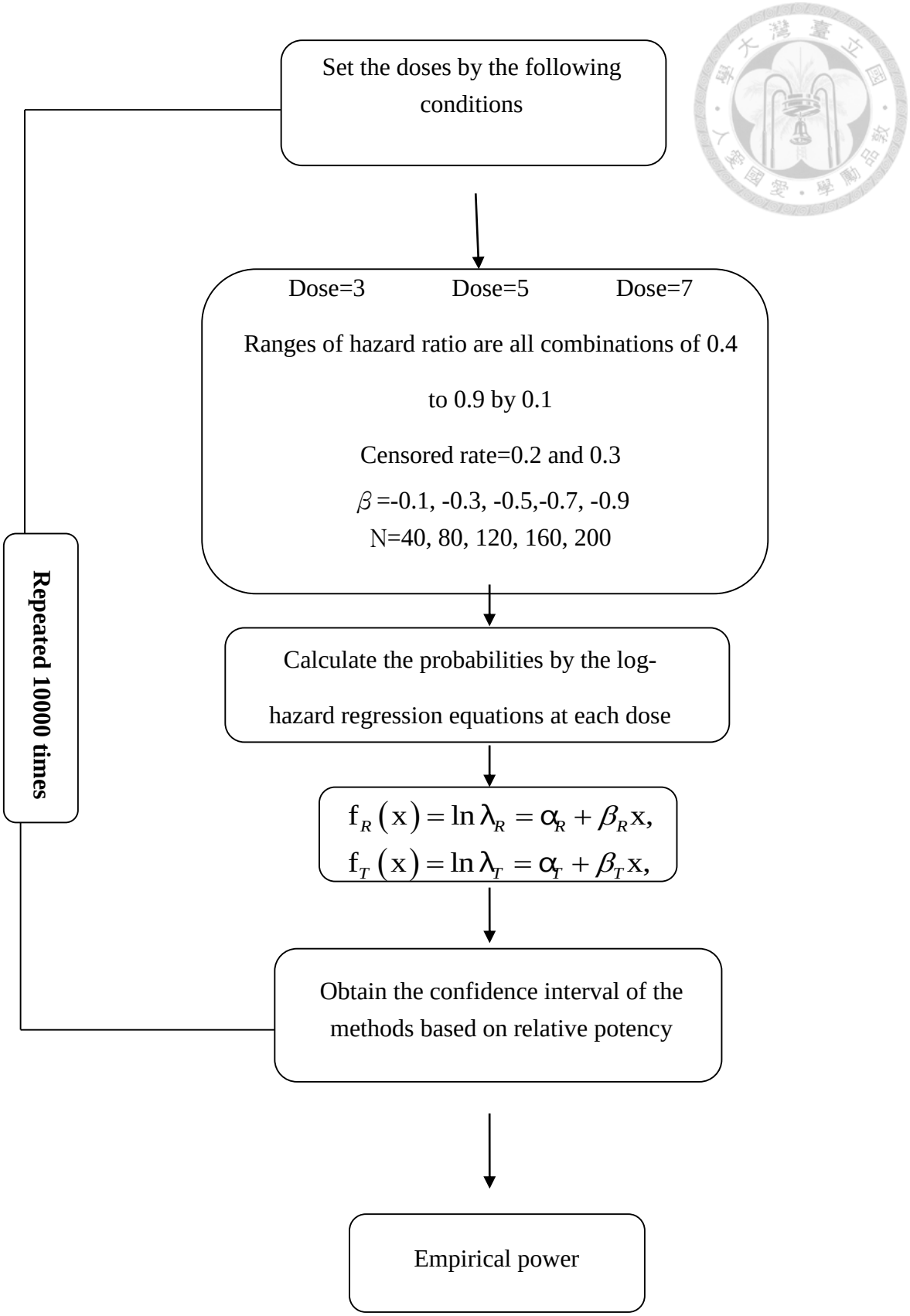


Figure 5.1: Flow chart of selection of dose levels

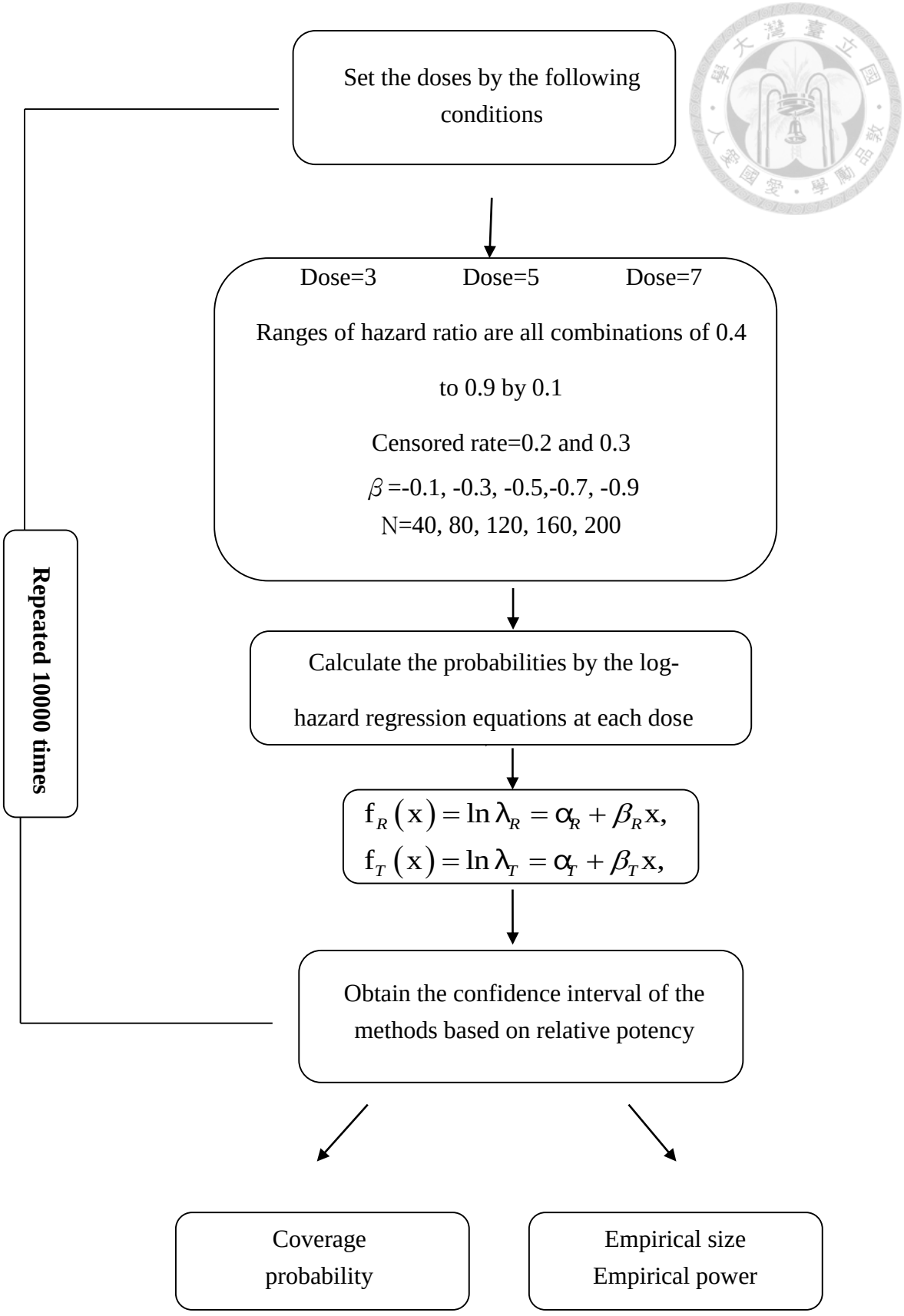


Figure 5.2: Flow chart of simulation process

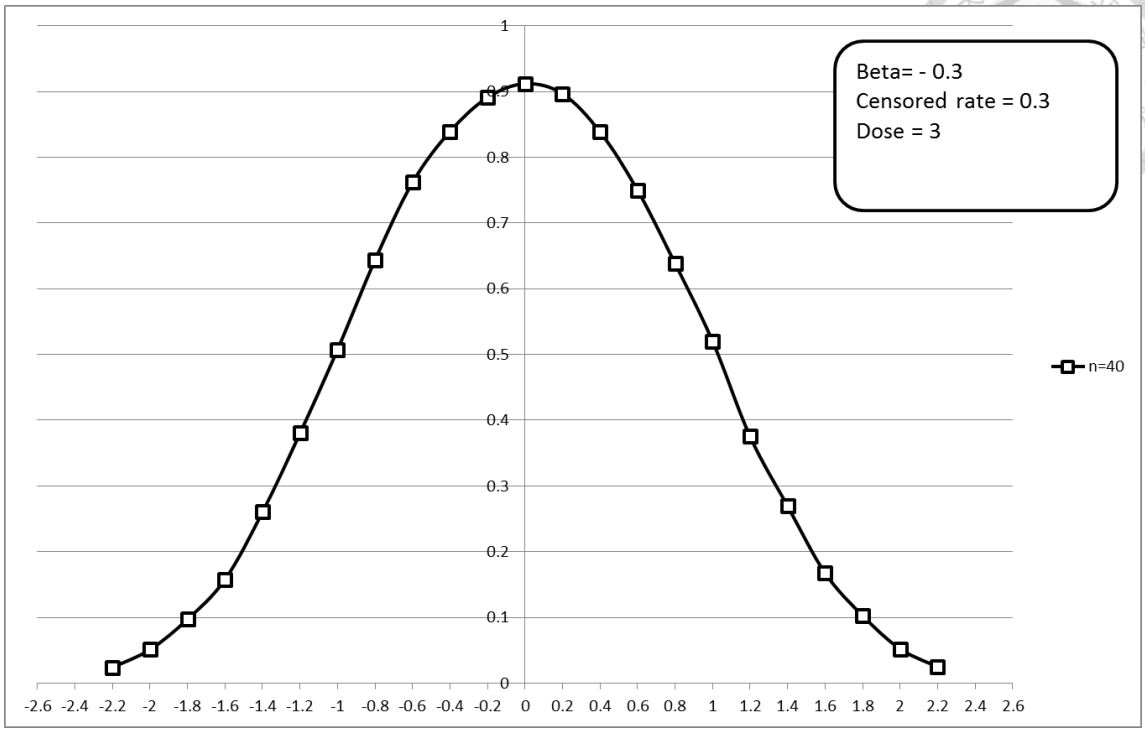


Figure 5.3: The empirical power curve of relative potency from -2.2 to 2.2 by 0.2 when the slope =-0.3, doses = 3 ,censored rate = 0.3 and n = 40.

Chapter 6 Discussions and Conclusions

Most of the biologicals drug products are for the treatment of Cancer such as lung cancer, breast cancer or colorectal cancer. The efficacy endpoints for evaluation of the biological drug products in cancer trials are censored endpoints such as overall survival or progression-free survival. As a result, we extended the design and concept of parallel-line assay to assessment of equivalence between the biosimilar drug product and its corresponding innovative biologic drug based on the censored data. We derived the proposed procedure under the assumptions that the censored endpoint follow a single-parametric exponential distribution and the log-hazard can be modelled as a linear regression with the well-defined drug characteristic as the independent variable.

The empirical investigation by simulation studies demonstrates that the confidence intervals constructed by the proposed method provide sufficient converge probability. On the other hand, under the assumptions of the exponential distribution and the log-hazard linear regression, the proposed procedure can also adequately control the size at the nominal significance level. Furthermore, sufficient power can be provided if the sample size is moderate. For example, for the slope being -0.3 or -0.5, $\Delta=0$, power exceed 0.9 even when sample size is 40 per group.

In this thesis we only consider the exponential parametric model which satisfies the

proportional hazard assumption. In addition, we also assume that the relationship between the log-hazard and the well-defined drug characteristic is linear with a right and random censoring mechanism. More research is required to examine the impact of violating the assumptions on performance of the proposed procedure. On the other hand, extension of the proposed method to other parametric distributions such as Weibull or log-logistic distributions also requires more research. The cox proportion hazard is a semi-parametric method which does not assume a particular form of the mortality distribution for the censored data. It follows that the Cox proportional hazard model is more flexible and has widespread applications. However, the inference procedure for application of the parallel-line assay to evaluation of equivalence between the biosimilar drug products and the innovative product based on the proportional hazard requires further research.

References

中文文獻：

沈明來(2000)，生物檢定統計法 第一版，九州圖書文物有限公司　台北市 台灣

行政院衛生署 食品藥物管理局(2009) 藥品生體可用率及生體相等性試驗準則

林亞靚（2010）平行檢定法於生物製劑學名藥對等性評估之應用 台灣大學

張志熙（2011）羅吉斯回歸於生物相似性藥品對等性評估之應用 台灣大學

林治華、李元鳳、王蓉君(2011) 生物相似性藥品 Biosimilar 財團法人醫藥品查驗中心 當代醫藥法規 RegMed Vol.3

生物仿製藥市場及發展概況
http://cdnet.stpi.narl.org.tw/techroom/market/bio/2009/bio_09_005.htm Accessed on 2013/05/03.

英文文獻：

Biosimilar and Biologic (2011), Wikipedia http://en.wikipedia.org/wiki/ "Biosimilar" and "Biologic" Accessed on 2013/05/03

Chow, S. C. and Liu, J. P. (2010). *Design and Analysis of Bioavailability and Bioequivalence Studies.* 3rd ed. Marcel Dekker, Inc. New York, USA

Chow, S. C. and Liu, J. P. (2010). Statistical Assessment of Biosimilar Products. *Journal of Biopharmaceutical Statistics*, 20:10-30

(EMEA) 2001. *Note for Guidance on the Investigation of Bioavailability and Bioequivalence*, London, UK.

EMEA (2006a). Annex guideline on similar biological medicinal products containing biotechnology-derived proteins as drug substance – Non clinical and clinical issues – Guidance on similar medicinal products containing recombinant erythropoietins. The European Medicines Agency Evaluation of Medicines for Human Use.

EMEA/CHMP/94526/05: London, United Kingdom.
EMEA (2006b). Annex guideline on similar biological medicinal products containing biotechnology-derived proteins as drug substance – Non clinical and clinical issues – Guidance on similar medicinal products containing recombinant granulocyte-colony stimulating factor. The European Medicines Agency Evaluation of Medicines for Human Use. EMEA/CHMP/31329/05: London, United Kingdom.

EMEA (2006c). Annex guideline on similar biological medicinal products containing biotechnology-derived proteins as drug substance – Non-clinical and clinical issues – Guidance on similar medicinal products containing somatropin. The European Medicines Agency Evaluation of Medicines for Human Use. EMEA/CHMP/94528/05: London, United Kingdom.

EMEA (2006d). Annex guideline on similar biological medicinal products containing biotechnology-derived proteins as drug substance – Non clinical and clinical issues – Guidance on similar medicinal products containing recombinant human insulin. The European Medicines Agency Evaluation of Medicines for Human Use. EMEA/CHMP/32775/05: London, United Kingdom.

FDA (2001). *Guidance on Statistical Approaches to Establishing Bioequivalence*, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Rockville, MD.

FDA (2003). *Guidance on Food-Effect Bioavailability and Fed Bio equivalence Studies*, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Rockville, MD.

FDA (2011a). Draft Guidance on Questions and Answers Regarding Implementation of Biologic Price Competition and Innovation Act of 2009. U.S. Food and Drug Administration, Rockville, MD, U.S.A.

FDA (2011b). Draft Guidance on Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. U.S. Food and Drug Administration, Rockville, MD, U.S.A.

FDA(2011c). Draft Guidance on Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product. U.S. Food and Drug Administration, Rockville, MD, U.S.A.

ICH (2005). Q5E *Guideline on Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process.* Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, the US Food and Drug Administration, Rockville, Maryland, USA

Kleinbaum, D.G. (1998), Survival Analysis, a Self-Learning Text. *Biometrical Journal* , 40: 107–108.

Lin J.R., Chow S.C., Chang C.H., Lin T.C. and Liu J.P. (2013) Application of the parallel line assay to assessment of biosimilar products based on binary endpoints. *Statistics in Medicine*, 32 449-461.

Lawless, J. F. (2011). *Statistical models and methods for lifetime data.* Wiley-Interscience.

Schellekens, H. (2004). How similar do 'biosimilar' need to be? Nat Biotechnol, 22, 1357-1359.

Schuirmann, D. J. (1987). A Comparison of the Two One-Sided Tests Procedure and the Power Approach for Assessing the Equivalence of Average Bioavailability. *Journal of Pharmacokinetics and Biopharmaceutics*, Vol. 15, No. 6, 1987

Thomson Database of Pharmaceutical Invention (2007)

Webber K.O. (2007). Biosimilars: Are we there yet? Presented at Biosimilars 2007, George Washington University, Washington DC, USA.

Appendix 1, Fortran Codes for Numerical Example

```
program main
USE msimsl
IMPLICIT NONE
integer :: I,J,K,L,M,N,O,P,Q,R,S,T,U,NOUT,ISEEDT,ISEEDR
real*8 :: Z0025,Z0050,C,Delta,II,TTSS,X,Xinc,Xstart,
RatioT,CensRateT,BetaT0,AlphaT0,LamdaTL,LamdaTC,ThetaTL,ThetaTC,
RatioR,CensRateR,BetaR0,AlphaR0,LamdaRL,LamdaRC,ThetaRL,ThetaRC,
NumCensT,NumLifeT,NumCensR,NumLifeR,
AlphaTh,BetaTh,ErrorAT0,ErrorBT0,VarAlphahT,VarBetahT,CovABhT,StdAlphahT,
StdBetahT,
AlphaRh,BetaRh,ErrorAR0,ErrorBR0,VarAlphahR,VarBetahR,CovABhR,StdAlphahR,
StdBetahR, BetaCh,ErrorAR,ErrorAT,ErrorBC,
VarAlphaCRh,VarAlphaCTh,VarBetaCh,CovARBC,CovATBC,CovATAR,DeltaL,Delt
aU,AA,BB,CC, VarBetaRT,StdBetaRT, Haza,Hazb
integer :: Size,Doses,TTS,SimuN,Burn,NCensT,NLifeT,NCensR,NLifeR
real*8 , allocatable :: Xs(:)
real*8 , allocatable :: LifeR(:),CensR(:),LifeT(:),CensT(:)
real*8 , allocatable ::
Datas(:,:),RTLCDatas(:,:),caR(:,:),caT(:,:),scaR(:),scaT(:),Tests(:,:),caC(:,:),scaC(:)
real*8 :: SDL(5,5,5),IND
parameter(SimuN=1,Burn=1000,C=0.5d0,Delta=2.0d0)
Forall(i=1:5,j=1:5,k=1:5) SDL(i,j,k)=0
IND=0
Z0025=ANORIN(0.975)
Z0050=ANORIN(0.95)
CensRateT=0.2d0
CensRateR=0.2d0
RatioT=CensRateT/(1-CensRateT)
RatioR=CensRateR/(1-CensRateR)
open(unit=15, file='Power_function.txt')
```

```
DO U=1,1
Doses=3.0d0+(DFLOAT(U)-1.0d0)*2.0d0
DO T=3,3
BetaT0=-0.1d0-0.2d0*(DFLOAT(T)-1.0d0)
BetaR0=-0.1d0-0.2d0*(DFLOAT(T)-1.0d0)
write(*,"(A,F4.1)") "The slope is ",BetaT0
write(15,"(A,F4.1)") "The slope is ",BetaT0
DO R=1,1
!AlphaT0=BetaT0*(-2.2+0.2*(DFLOAT(R)-1))
AlphaT0=0.0d0
AlphaR0=0.0d0
DO O=1,1
size=60
TTS=Doses*Size
DO P=4,4    !跑 cp,power
DO Q=9,9
Haza=0.1d0*DFLOAT(P)*(1-CensRateT)
Hazb=0.1d0*DFLOAT(Q)*(1-CensRateT)
allocate(LifeT(size),CensT(size),LifeR(size),CensR(size))
allocate(DATAS(TTS,10))
allocate(caT(TTS,7),caR(TTS,7),scaT(7),scaR(7),caC(TTS,7),scaC(7))
allocate(Tests(SimuN,9))
Forall(i=1:SimuN,j=1:9) Tests(i,j)=0
allocate(Xs(Doses-1))
DO I=1,Doses-1
II=dfloat(I)
Xs(I)=DLOG(Hazb-(II-1.0d0)*(Hazb-Haza)/(Doses-2.0d0))/BetaR0
END DO
DO N=1,SimuN
!ISEEDT=1
!=======Biosimilar====T
        DO I=1,Doses
        IF (I==1) THEN
        X=0.0d0
        ELSE
        !II=dfloat(I)
        X=Xs(I-1)
        !X=Xstart+Xinc*(II-2)
```

```
            ENDIF
            LamdaTL=DEXP(AlphaT0+X*BetaT0)
            LamdaTC=LamdaTL*RatioT
            ThetaTL=(LamdaTL)**(-1)
            ThetaTC=(LamdaTC)**(-1)
        !ISEEDT=ISEEDT+1
            !CALL RNSET(ISEEDT)
            CALL DRNEXP(SIZE,LifeT)
            CALL DSCAL(SIZE,ThetaTL,LifeT,1)
            CALL DRNEXP(SIZE,CensT)
            CALL DSCAL(SIZE,ThetaTC,CensT,1)
                    DO L=1,Size
                K=L+(I-1)*Size
                DATAS(K,5)=X
                    IF (LifeT(L)>CensT(L)) THEN                    !
LT,CT,Yt,DLT,Xt,LR,CR,Yr,DLR,Xr
                    DATAS(K,1)=LifeT(L)
                DATAS(K,2)=CensT(L)
                    DATAS(K,3)=CensT(L)
                    DATAS(K,4)=0.0d0
                    ELSEIF (LifeT(L)<=CensT(L)) THEN
                    DATAS(K,1)=LifeT(L)
                DATAS(K,2)=CensT(L)
                    DATAS(K,3)=LifeT(L)
                    DATAS(K,4)=1.0d0
                    END IF
                    END DO
            END DO
TTSS=DFLOAT(TTS)
NlifeT=SUM(DATAS(:,4))
NumLifeT=DFLOAT(NlifeT)
BetaTh=0.0d0
ErrorBT0=1.0d0
DO WHILE
(ErrorBT0>0.000000001d0)                                                !D
ATAS(1 ,2 ,3 ,4    ,5 ,6 ,7 ,8 ,9    ,10)
```

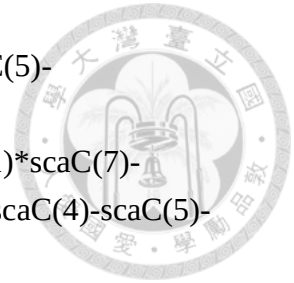
```
        DO
J=1,Size*Doses                                                    !
LT,CT,Yt,DLT,Xt,LR,CR,Yr,DLR,Xr
        caT(J,1)=DATAS(J,3)*DEXP(BetaTh*DATAS(J,5))
        caT(J,2)=DATAS(J,3)*DATAS(J,5)*DEXP(BetaTh*DATAS(J,5))
        caT(J,3)=DATAS(J,4)*DATAS(J,5)
        caT(J,4)=((DATAS(J,5))**2)*DATAS(J,3)*DEXP(BetaTh*DATAS(J,5))
        END DO
scaT(1)=SUM(caT(:,1))
scaT(2)=SUM(caT(:,2))
scaT(3)=SUM(caT(:,3))
scaT(4)=SUM(caT(:,4))
BetaTh=BetaTh-(scaT(2)/scaT(1)-scaT(3)/NumlifeT)/(scaT(4)/scaT(1)-
(scaT(2)/scaT(1))**2)
ErrorBT0=ABS(-(scaT(2)/scaT(1)-scaT(3)/NumlifeT)/(scaT(4)/scaT(1)-
(scaT(2)/scaT(1))**2))
IF (ErrorBT0<0.000000001d0) EXIT
END DO

DO J1,Size*Doses
caT(J,1)=DATAS(J,3)*DEXP(BetaTh*DATAS(J,5))
caT(J,2)=DATAS(J,3)*DATAS(J,5)*DEXP(BetaTh*DATAS(J,5))
caT(J,3)=DATAS(J,4)*DATAS(J,5)
caT(J,4)=((DATAS(J,5))**2)*DATAS(J,3)*DEXP(BetaTh*DATAS(J,5))
END DO
scaT(1)=SUM(caT(:,1))
scaT(2)=SUM(caT(:,2))
scaT(3)=SUM(caT(:,3))
scaT(4)=SUM(caT(:,4))
BetaTh=BetaTh-(scaT(2)/scaT(1)-scaT(3)/NumlifeT)/(scaT(4)/scaT(1)-
(scaT(2)/scaT(1))**2)
        DO J=1,Size*Doses
        caT(J,1)=DATAS(J,3)*DEXP(BetaTh*DATAS(J,5))
        END DO
scaT(1)=SUM(caT(:,1))
AlphaTh=log(numlifeT/scaT(1))

        DO J=1,Size*Doses
```

```
caT(J,5)=DATAS(J,3)*DEXP(AlphaTh+BetaTh*DATAS(J,5))
caT(J,6)=DATAS(J,3)*DATAS(J,5)*DEXP(AlphaTh+BetaTh*DATAS(J,5))
caT(J,7)=((DATAS(J,5))**2)*DATAS(J,3)*DEXP(AlphaTh+BetaTh*DATAS(J,5))
            END DO
scaT(5)=SUM(caT(:,5))
scaT(6)=SUM(caT(:,6))
scaT(7)=SUM(caT(:,7))
VarAlphahT=scaT(7)/(scaT(5)*scaT(7)-scaT(6)**2)
VarBetahT=scaT(5)/(scaT(5)*scaT(7)-scaT(6)**2)
CovABhT=-scaT(6)/(scaT(5)*scaT(7)-scaT(6)**2)
StdAlphahT=DSQRT(VarAlphahT)
StdBetahT=DSQRT(VarBetahT)
IF (0.0d0<=BetaTh-Z0025*StdBetahT .OR. BetaTh+Z0025*StdBetahT<=0.0d0 )
THEN
Tests(N,1)=1
END IF
!write(*,*) BetaTh-Z0025*StdBetahT,BetaTh+Z0025*StdBetahT,StdBetahT
!=======Innovator====R
            DO I=1,Doses
            IF (I==1) THEN
            X=0.0d0
            ELSE
            !II=dfloat(I)
            X=Xs(I-1)
            !X=Xstart+Xinc*(II-2)
            ENDIF
            LamdaRL=DEXP(AlphaR0+X*BetaR0)
            LamdaRC=LamdaRL*RatioR
            ThetaRL=(LamdaRL)**(-1)
            ThetaRC=(LamdaRC)**(-1)
      !ISEEDR=ISEEDR+1
            !CALL RNSET(ISEEDR)
            CALL DRNEXP(SIZE,LifeR)
            CALL DSCAL(SIZE,ThetaRL,LifeR,1)
            CALL DRNEXP(SIZE,CensR)
            CALL DSCAL(SIZE,ThetaRC,CensR,1)
                  DO L=1,Size
                K=L+(I-1)*Size
```

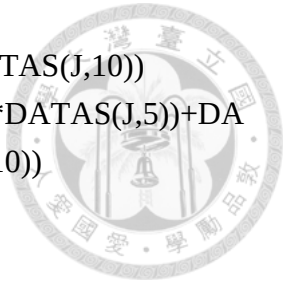
```
                DATAS(K,10)=X
                    IF (LifeR(L)>CensR(L)) THEN
                    DATAS(K,6)=LifeR(L)
                DATAS(K,7)=CensR(L)
                    DATAS(K,8)=CensR(L)
                    DATAS(K,9)=0.0d0
                    ELSEIF (LifeR(L)<=CensR(L)) THEN
                    DATAS(K,6)=LifeR(L)
                DATAS(K,7)=CensR(L)
                    DATAS(K,8)=LifeR(L)
                    DATAS(K,9)=1.0d0
                    END IF
                    END DO
            END DO
TTSS=DFLOAT(TTS)
NLifeR=SUM(DATAS(:,9))
NumLifeR=DFLOAT(NlifeR)
BetaRh=0.0d0
ErrorBR0=1.0d0
DO WHILE (ErrorBR0>0.000000001d0)
            DO J=1,TTS
            caR(J,1)=DATAS(J,8)*DEXP(BetaRh*DATAS(J,10))
            caR(J,2)=DATAS(J,8)*DATAS(J,10)*DEXP(BetaRh*DATAS(J,10))
            caR(J,3)=DATAS(J,9)*DATAS(J,10)
            caR(J,4)=((DATAS(J,10))**2)*DATAS(J,8)*DEXP(BetaRh*DATAS(J,10))
            END DO
scaR(1)=SUM(caR(:,1))
scaR(2)=SUM(caR(:,2))
scaR(3)=SUM(caR(:,3))
scaR(4)=SUM(caR(:,4))
BetaRh=BetaRh-(scaR(2)/scaR(1)-scaR(3)/NumlifeR)/(scaR(4)/scaR(1)-
(scaR(2)/scaR(1))**2)
ErrorBR0=ABS(-(scaR(2)/scaR(1)-scaR(3)/NumlifeR)/(scaR(4)/scaR(1)-
(scaR(2)/scaR(1))**2))
IF (ErrorBR0<0.000000001d0) EXIT
END DO
            DO J=1,TTS
caR(J,1)=DATAS(J,8)*DEXP(BetaRh*DATAS(J,10))
```

```
caR(J,2)=DATAS(J,8)*DATAS(J,10)*DEXP(BetaRh*DATAS(J,10))
caR(J,3)=DATAS(J,9)*DATAS(J,10)
caR(J,4)=((DATAS(J,10))**2)*DATAS(J,8)*DEXP(BetaRh*DATAS(J,10))
END DO
scaR(1)=SUM(caR(:,1))
scaR(2)=SUM(caR(:,2))
scaR(3)=SUM(caR(:,3))
scaR(4)=SUM(caR(:,4))
BetaRh=BetaRh-(scaR(2)/scaR(1)-scaR(3)/NumlifeR)/(scaR(4)/scaR(1)-
(scaR(2)/scaR(1))**2)
        DO J=1,TTS
        caR(J,1)=DATAS(J,8)*DEXP(BetaRh*DATAS(J,10))
        END DO
scaR(1)=SUM(caR(:,1))
AlphaRh=log(numlifeR/scaR(1))
        DO J=1,TTS
caR(J,5)=DATAS(J,8)*DEXP(AlphaRh+BetaRh*DATAS(J,10))
caR(J,6)=DATAS(J,8)*DATAS(J,10)*DEXP(AlphaRh+BetaRh*DATAS(J,10))
caR(J,7)=((DATAS(J,10))**2)*DATAS(J,8)*DEXP(AlphaRh+BetaRh*DATAS(J,10))
END DO
scaR(5)=SUM(caR(:,5))
scaR(6)=SUM(caR(:,6))
scaR(7)=SUM(caR(:,7))
VarAlphahR=scaR(7)/(scaR(5)*scaR(7)-scaR(6)**2.0d0)
VarBetahR=scaR(5)/(scaR(5)*scaR(7)-scaR(6)**2.0d0)
CovABhR=-scaR(6)/(scaR(5)*scaR(7)-scaR(6)**2.0d0)
StdAlphahR=VarAlphahR**(0.5d0)
StdBetahR=VarBetahR**(0.5d0)
!write(*,*) BetaRh-Z0025*StdBetahR,BetaRh+Z0025*StdBetahR,StdBetahR
IF (0.0d0<=BetaRh-Z0025*StdBetahR .OR. BetaRh+Z0025*StdBetahR<=0.0d0 )
THEN
Tests(N,2)=1
END IF
!write(*,"(4(2XF13.10))") AlphaTh,BetaTh,AlphaRh,BetaRh
!=======Common Slope Testing======
IF (Tests(N,1)==1 .AND. Tests(N,2)==1) THEN
VarBetaRT=VarBetahR+VarBetahT
StdBetaRT=VarBetaRT**(0.5d0)
```

```
IF (-C<=BetaTh-BetaRh-Z0050*StdBetaRT .AND. BetaTh-
BetaRh+Z0050*StdBetaRT<=C ) THEN
Tests(N,3)=1
END IF
END IF
!write(*,*) BetaTh-BetaRh-Z0050*StdBetaRT,BetaTh-BetaRh+Z0050*StdBetaRT
!======Common Slope Model Newton-Raphson====
IF (Tests(N,3)==1) THEN
AlphaRh=0.0d0
AlphaTh=0.0d0
BetaCh=0.0d0
ErrorAR=1.0d0
ErrorAT=1.0d0
ErrorBC=1.0d0
DO S=1,Burn
!write(*,*) AlphaRh,AlphaTh,BetaCh
        DO
J=1,TTS
 ! LT,CT,Yt,DLT,Xt,LR,CR,Yr,DLR,Xr
caC(J,1)=DATAS(J,3)*DEXP(AlphaTh+BetaCh*DATAS(J,5))    !YtExp(At+BC*Xt)
caC(J,2)=DATAS(J,8)*DEXP(AlphaRh+BetaCh*DATAS(J,10)) !YrExp(Ar+BC*Xr)
caC(J,3)=DATAS(J,4)*DATAS(J,5)
caC(J,4)=DATAS(J,9)*DATAS(J,10)
caC(J,5)=DATAS(J,3)*DATAS(J,5)*DEXP(AlphaTh+BetaCh*DATAS(J,5))
caC(J,6)=DATAS(J,8)*DATAS(J,10)*DEXP(AlphaRh+BetaCh*DATAS(J,10))
caC(J,7)=DATAS(J,3)*(DATAS(J,5)**2)*DEXP(AlphaTh+BetaCh*DATAS(J,5))+DA
TAS(J,8)*(DATAS(J,10)**2)*DEXP(AlphaRh+BetaCh*DATAS(J,10))
        END DO
        scaC(1)=SUM(caC(:,1))
        scaC(2)=SUM(caC(:,2))
        scaC(3)=SUM(caC(:,3))
        scaC(4)=SUM(caC(:,4))
        scaC(5)=SUM(caC(:,5))
        scaC(6)=SUM(caC(:,6))
        scaC(7)=SUM(caC(:,7))
AlphaTh=AlphaTh+((scaC(2)*scaC(7)-scaC(6)*scaC(6))*(NumlifeT-
scaC(1))+scaC(5)*scaC(6)*(NumlifeR-scaC(2))-scaC(2)*scaC(5)*(scaC(3)+scaC(4)-
```



```
scaC(5)-scaC(6)))/(scaC(1)*scaC(2)*scaC(7)-scaC(2)*scaC(5)*scaC(5)-
scaC(1)*scaC(6)*scaC(6))
AlphaRh=AlphaRh+(scaC(5)*scaC(6)*(NumlifeT-scaC(1))+(scaC(1)*scaC(7)-
scaC(5)*scaC(5))*(NumlifeR-scaC(2))-scaC(1)*scaC(6)*(scaC(3)+scaC(4)-scaC(5)-
scaC(6)))/(scaC(1)*scaC(2)*scaC(7)-scaC(2)*scaC(5)*scaC(5)-
scaC(1)*scaC(6)*scaC(6))
BetaCh=BetaCh+(-scaC(2)*scaC(5)*(NumlifeT-scaC(1))-scaC(1)*scaC(6)*(NumlifeR-
scaC(2))+scaC(1)*scaC(2)*(scaC(3)+scaC(4)-scaC(5)-
scaC(6)))/(scaC(1)*scaC(2)*scaC(7)-scaC(2)*scaC(5)*scaC(5)-
scaC(1)*scaC(6)*scaC(6))
!write(*,*) AlphaRh,AlphaTh,BetaCh
ErrorAT=ABS(NumlifeT-scaC(1))
ErrorAR=ABS(NumlifeR-scaC(2))
ErrorBC=ABS(scaC(3)+scaC(4)-scaC(5)-scaC(6))
!write(*,*) ErrorAT,ErrorAR,ErrorBC
!ErrorAT=ABS(((scaC(2)*scaC(7)-scaC(6)*scaC(6))*(NumlifeT-
scaC(1))+scaC(5)*scaC(6)*(NumlifeR-scaC(2))-scaC(2)*scaC(5)*(scaC(3)+scaC(4)-
scaC(5)-scaC(6)))/(scaC(1)*scaC(2)*scaC(7)-scaC(2)*scaC(5)*scaC(5)-
scaC(1)*scaC(6)*scaC(6)))
!ErrorAR=ABS((scaC(5)*scaC(6)*(NumlifeT-scaC(1))+(scaC(1)*scaC(7)-
scaC(5)*scaC(5))*(NumlifeR-scaC(2))-scaC(1)*scaC(6)*(scaC(3)+scaC(4)-scaC(5)-
scaC(6)))/(scaC(1)*scaC(2)*scaC(7)-scaC(2)*scaC(5)*scaC(5)-
scaC(1)*scaC(6)*scaC(6)))
!ErrorBC=ABS((-scaC(2)*scaC(5)*(NumlifeT-scaC(1))-scaC(1)*scaC(6)*(NumlifeR-
scaC(2))+scaC(1)*scaC(2)*(scaC(3)+scaC(4)-scaC(5)-
scaC(6)))/(scaC(1)*scaC(2)*scaC(7)-scaC(2)*scaC(5)*scaC(5)-
scaC(1)*scaC(6)*scaC(6)))
IF (ErrorAR<0.000000001d0 .AND. ErrorAT<0.000000001d0 .AND.
ErrorBC<0.000000001d0) EXIT
END DO
!write(*,"(3(2XF13.10))") AlphaTh,AlphaRh,BetaCh
!======Relative Potency======
          DO
J=1,TTS
             ! LT,CT,Yt,DLT,Xt,LR,CR,Yr,DLR,Xr
caC(J,1)=DATAS(J,3)*DEXP(AlphaTh+BetaCh*DATAS(J,5))
caC(J,2)=DATAS(J,8)*DEXP(AlphaRh+BetaCh*DATAS(J,10))
caC(J,5)=DATAS(J,3)*DATAS(J,5)*DEXP(AlphaTh+BetaCh*DATAS(J,5))
```



```
caC(J,6)=DATAS(J,8)*DATAS(J,10)*DEXP(AlphaRh+BetaCh*DATAS(J,10))
caC(J,7)=DATAS(J,3)*(DATAS(J,5)**2)*DEXP(AlphaTh+BetaCh*DATAS(J,5))+DA
TAS(J,8)*(DATAS(J,10)**2)*DEXP(AlphaRh+BetaCh*DATAS(J,10))
END DO
scaC(1)=SUM(caC(:,1))
scaC(2)=SUM(caC(:,2))
scaC(5)=SUM(caC(:,5))
scaC(6)=SUM(caC(:,6))
scaC(7)=SUM(caC(:,7))
VarAlphaCTh=(scaC(2)*scaC(7)-scaC(6)*scaC(6))/(scaC(1)*scaC(2)*scaC(7)-
scaC(2)*scaC(5)*scaC(5)-scaC(1)*scaC(6)*scaC(6))
VarAlphaCRh=(scaC(1)*scaC(7)-scaC(5)*scaC(5))/(scaC(1)*scaC(2)*scaC(7)-
scaC(2)*scaC(5)*scaC(5)-scaC(1)*scaC(6)*scaC(6))
VarBetaCh=scaC(1)*scaC(2)/(scaC(1)*scaC(2)*scaC(7)-scaC(2)*scaC(5)*scaC(5)-
scaC(1)*scaC(6)*scaC(6))
CovATBC=-scaC(2)*scaC(5)/(scaC(1)*scaC(2)*scaC(7)-scaC(2)*scaC(5)*scaC(5)-
scaC(1)*scaC(6)*scaC(6))
CovARBC=-scaC(1)*scaC(6)/(scaC(1)*scaC(2)*scaC(7)-scaC(2)*scaC(5)*scaC(5)-
scaC(1)*scaC(6)*scaC(6))
CovATAR=scaC(5)*scaR(6)/(scaC(1)*scaC(2)*scaC(7)-scaC(2)*scaC(5)*scaC(5)-
scaC(1)*scaC(6)*scaC(6))
!write(*,*) VarAlphaCTh,VarAlphaCRh,VarBetaCh,CovATBC,CovARBC,CovATAR
AA=BetaCh**2.0d0-(Z0050**2.0d0)*VarBetaCh
BB=2.0d0*(AlphaRh-AlphaTh)*BetaCh-2.0d0*(Z0050**2.0d0)*(CovATBC-
CovARBC)
CC=(AlphaTh-AlphaRh)**2-(Z0050**2.0d0)*(VarAlphaCTh+VarAlphaCRh-
2.0d0*CovATAR)
!write(*,*) AA,BB,CC
IF (BB**2.0d0-AA*CC<0) THEN
IND=1
EXIT
ELSE
DeltaL=(-BB-DSQRT(BB**2.0d0-4.0d0*AA*CC))/(2.0d0*AA)
DeltaU=(-BB+DSQRT(BB**2.0d0-4.0d0*AA*CC))/(2.0d0*AA)
!DeltaL=((AlphaTh-AlphaRh)*BetaCh-Z0050**2*(CovATBC-CovARBC)-
(((AlphaTh-AlphaRh)*BetaCh-Z0050**2*(CovATBC-CovARBC))**2-(BetaCh**2-
Z0050**2*VarBetaCh)*((AlphaTh-AlphaRh)**2-
```

```
Z0050**2*(VarAlphaCTh+VarAlphaCRh-2*CovATAR)))**(0.5))/(BetaCh**2-
Z0050**2*VarBetaCh)
!DeltaU=((AlphaTh-AlphaRh)*BetaCh-Z0050**2*(CovATBC-
CovARBC)+(((AlphaTh-AlphaRh)*BetaCh-Z0050**2*(CovATBC-CovARBC))**2-
(BetaCh**2-Z0050**2*VarBetaCh)*((AlphaTh-AlphaRh)**2-
Z0050**2*(VarAlphaCTh+VarAlphaCRh-2*CovATAR)))**(0.5))/(BetaCh**2-
Z0050**2*VarBetaCh)
!write(*,*) DeltaL,DeltaU
!write(15,*) DeltaL,DeltaU
!write(*,*) ' '
END IF
IF (-Delta<DeltaL .AND. DeltaU<Delta) THEN
Tests(N,4)=1
END IF
END IF

WRIT(*,"((1XF4.1),A,(1XF6.4))")    AlphaT0/BetaT0,' ',SUM(Tests(:,4))/SimuN
WRITE(15,"((1XF4.1),A,(1XF6.4))") AlphaT0/BetaT0,' ',SUM(Tests(:,4))/SimuN

deallocate(LifeT,CensT,LifeR,CensR)
deallocate(DATAS)
deallocate(caT,caR,scaT,scaR,caC,scaC)
deallocate(Tests)
deallocate(Xs)
END DO !Q
END DO !P
END DO !O
END DO !R
END DO !T
END DO !U
end program
```

Appendix 2, Fortran Codes for Selection of Dose

Levels Program

```
program main
USE msimsl
IMPLICIT NONE
integer :: I,J,K,L,M,N,O,P,Q,R,S,T,U,NOUT,ISEEDT,ISEEDR
real*8 :: Z0025,Z0050,C,Delta,II,TTSS,X,Xinc,Xstart,
RatioT,CensRateT,BetaT0,AlphaT0,LamdaTL,LamdaTC,ThetaTL,ThetaTC,
RatioR,CensRateR,BetaR0,AlphaR0,LamdaRL,LamdaRC,ThetaRL,ThetaRC,
NumCensT,NumLifeT,NumCensR,NumLifeR,
AlphaTh,BetaTh,ErrorAT0,ErrorBT0,VarAlphahT,VarBetahT,CovABhT,StdAlphahT,
StdBetahT,
AlphaRh,BetaRh,ErrorAR0,ErrorBR0,VarAlphahR,VarBetahR,CovABhR,StdAlphahR,
StdBetahR, BetaCh,ErrorAR,ErrorAT,ErrorBC,
VarAlphaCRh,VarAlphaCTh,VarBetaCh,CovARBC,CovATBC,CovATAR,DeltaL,Delt
aU,AA,BB,CC, VarBetaRT,StdBetaRT, Haza,Hazb
integer :: Size,Doses,TTS,SimuN,Burn,NCensT,NLifeT,NCensR,NLifeR
real*8 , allocatable :: Xs(:)
real*8 , allocatable :: LifeR(:),CensR(:),LifeT(:),CensT(:)
real*8 , allocatable ::
Datas(:,:),RTLCDatas(:,:),caR(:,:),caT(:,:),scaR(:),scaT(:),Tests(:,:),caC(:,:),scaC(:)
real*8 :: SDL(5,5,5),IND
parameter(SimuN=10000,Burn=1000,C=0.5d0,Delta=2.0d0)
Forall(i=1:5,j=1:5,k=1:5) SDL(i,j,k)=0
IND=0
Z0025=ANORIN(0.975)
Z0050=ANORIN(0.95)
write(*,*) "Input the censored rate, assuming the two censored rates are equil: "
read(*,*) CensRateT
CensRateR=CensRateT
!CensRateT=0.2d0
!CensRateR=0.2d0
RatioT=CensRateT/(1-CensRateT)
RatioR=CensRateR/(1-CensRateR)
open(unit=15, file='Power_function.txt')
```

```
DO U=1,3
Doses=3.0d0+(DFLOAT(U)-1.0d0)*2.0d0
DO T=1,5
BetaT0=-0.1d0-0.2d0*(DFLOAT(T)-1.0d0)
BetaR0=-0.1d0-0.2d0*(DFLOAT(T)-1.0d0)
write(*,"(A,F4.1)") "The slope is ",BetaT0
write(15,"(A,F4.1)") "The slope is ",BetaT0
DO R=3,3
!AlphaT0=BetaT0*(-2.2+0.2*(DFLOAT(R)-1))
!AlphaR0=0.0d0
AlphaT0=0.0d0
AlphaR0=0.0d0
!write(*,*) R-3
DO O=1,1
TTS=Doses*Size
DO P=4,8     !從起始值決定  we use this
DO Q=P+1,9
Haza=0.1d0*DFLOAT(P)*(1-CensRateT)
Hazb=0.1d0*DFLOAT(Q)*(1-CensRateT)
!write(*,"(A,F3.1,A,F3.1,A)") "The minimun hazard is ",Haza,". The maximun hazard
is ",Hazb,"."
!write(15,"(A,F3.1,A,F3.1,A)") "The minimun hazard is ",Haza,". The maximun hazard
is ",Hazb,"."
allocate(LifeT(size),CensT(size),LifeR(size),CensR(size))
allocate(DATAS(TTS,10))
allocate(caT(TTS,7),caR(TTS,7),scaT(7),scaR(7),caC(TTS,7),scaC(7))
allocate(Tests(SimuN,9))
Forall(i=1:SimuN,j=1:9) Tests(i,j)=0
allocate(Xs(Doses-1))
DO I=1,Doses-1
II=dfloat(I)
Xs(I)=DLOG(Hazb-(II-1.0d0)*(Hazb-Haza)/(Doses-2.0d0))/BetaR0
END DO
!open(unit=10, file='exp_data_T.txt')
DO N=1,SimuN
              !ISEEDT=1
!=======Biosimilar====T
            DO I=1,Doses
```

```
            IF (I==1) THEN
            X=0.0d0
            ELSE
            !II=dfloat(I)
            X=Xs(I-1)
            !X=Xstart+Xinc*(II-2)
            ENDIF
            LamdaTL=DEXP(AlphaT0+X*BetaT0)
            LamdaTC=LamdaTL*RatioT
            ThetaTL=(LamdaTL)**(-1)
            ThetaTC=(LamdaTC)**(-1)
        !ISEEDT=ISEEDT+1
            !CALL RNSET(ISEEDT)
            CALL DRNEXP(SIZE,LifeT)
            CALL DSCAL(SIZE,ThetaTL,LifeT,1)
            CALL DRNEXP(SIZE,CensT)
            CALL DSCAL(SIZE,ThetaTC,CensT,1)
                    DO L=1,Size
                K=L+(I-1)*Size
                DATAS(K,5)=X
            IF (LifeT(L)>CensT(L)) THEN
            DATAS(K,1)=LifeT(L)
                DATAS(K,2)=CensT(L)
                    DATAS(K,3)=CensT(L)
                    DATAS(K,4)=0.0d0
                    ELSEIF (LifeT(L)<=CensT(L)) THEN
                    DATAS(K,1)=LifeT(L)
                DATAS(K,2)=CensT(L)
                    DATAS(K,3)=LifeT(L)
                    DATAS(K,4)=1.0d0
                    END IF
                    END DO
            END DO
!           DO I=1,TTS
!       write(10,'(f11.8,2Xf11.8,2Xf11.8,2XF2.0,2XF11.8)') DATAS(I,1:5)
!           END DO
TTSS=DFLOAT(TTS)
NlifeT=SUM(DATAS(:,4))
```

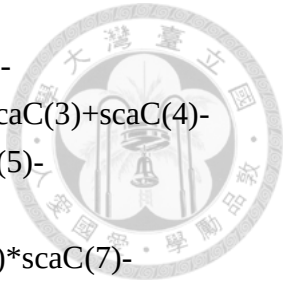
```
NumLifeT=DFLOAT(NlifeT)
BetaTh=0.0d0
ErrorBT0=1.0d0
DO WHILE (ErrorBT0>0.000000001d0)
DO J=1,Size*Doses
caT(J,1)=DATAS(J,3)*DEXP(BetaTh*DATAS(J,5))
caT(J,2)=DATAS(J,3)*DATAS(J,5)*DEXP(BetaTh*DATAS(J,5))
caT(J,3)=DATAS(J,4)*DATAS(J,5)
caT(J,4)=((DATAS(J,5))**2)*DATAS(J,3)*DEXP(BetaTh*DATAS(J,5))
END DO
scaT(1)=SUM(caT(:,1))
scaT(2)=SUM(caT(:,2))
scaT(3)=SUM(caT(:,3))
scaT(4)=SUM(caT(:,4))
BetaTh=BetaTh-(scaT(2)/scaT(1)-scaT(3)/NumlifeT)/(scaT(4)/scaT(1)-
(scaT(2)/scaT(1))**2)
ErrorBT0=ABS(-(scaT(2)/scaT(1)-scaT(3)/NumlifeT)/(scaT(4)/scaT(1)-
(scaT(2)/scaT(1))**2))

IF (ErrorBT0<0.000000001d0) EXIT
END DO
DO J=1,Size*Doses
caT(J,1)=DATAS(J,3)*DEXP(BetaTh*DATAS(J,5))
caT(J,2)=DATAS(J,3)*DATAS(J,5)*DEXP(BetaTh*DATAS(J,5))
caT(J,3)=DATAS(J,4)*DATAS(J,5)
caT(J,4)=((DATAS(J,5))**2)*DATAS(J,3)*DEXP(BetaTh*DATAS(J,5))
END DO
scaT(1)=SUM(caT(:,1))
scaT(2)=SUM(caT(:,2))
scaT(3)=SUM(caT(:,3))
scaT(4)=SUM(caT(:,4))
BetaTh=BetaTh-(scaT(2)/scaT(1)-scaT(3)/NumlifeT)/(scaT(4)/scaT(1)-
(scaT(2)/scaT(1))**2)
        DO J=1,Size*Doses
        caT(J,1)=DATAS(J,3)*DEXP(BetaTh*DATAS(J,5))
        END DO
scaT(1)=SUM(caT(:,1))
AlphaTh=log(numlifeT/scaT(1))
```

```
        DO J=1,Size*Doses
caT(J,5)=DATAS(J,3)*DEXP(AlphaTh+BetaTh*DATAS(J,5))
caT(J,6)=DATAS(J,3)*DATAS(J,5)*DEXP(AlphaTh+BetaTh*DATAS(J,5))
caT(J,7)=((DATAS(J,5))**2)*DATAS(J,3)*DEXP(AlphaTh+BetaTh*DATAS(J,5))
END DO
scaT(5)=SUM(caT(:,5))
scaT(6)=SUM(caT(:,6))
scaT(7)=SUM(caT(:,7))
VarAlphahT=scaT(7)/(scaT(5)*scaT(7)-scaT(6)**2)
VarBetahT=scaT(5)/(scaT(5)*scaT(7)-scaT(6)**2)
CovABhT=-scaT(6)/(scaT(5)*scaT(7)-scaT(6)**2)
StdAlphahT=DSQRT(VarAlphahT)
StdBetahT=DSQRT(VarBetahT)
IF (0.0d0<=BetaTh-Z0025*StdBetahT .OR. BetaTh+Z0025*StdBetahT<=0.0d0 )
THEN
Tests(N,1)=1
END IF
!write(*,*) BetaTh-Z0025*StdBetahT,BetaTh+Z0025*StdBetahT,StdBetahT

!=======Innovator====R
        DO I=1,Doses
        IF (I==1) THEN
        X=0.0d0
        ELSE
        !II=dfloat(I)
        X=Xs(I-1)
        !X=Xstart+Xinc*(II-2)
        ENDIF
        LamdaRL=DEXP(AlphaR0+X*BetaR0)
        LamdaRC=LamdaRL*RatioR
        ThetaRL=(LamdaRL)**(-1)
        ThetaRC=(LamdaRC)**(-1)
    !ISEEDR=ISEEDR+1
        !CALL RNSET(ISEEDR)
        CALL DRNEXP(SIZE,LifeR)
        CALL DSCAL(SIZE,ThetaRL,LifeR,1)
        CALL DRNEXP(SIZE,CensR)
        CALL DSCAL(SIZE,ThetaRC,CensR,1)
```

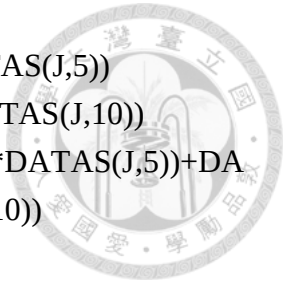
```
                DO L=1,Size
            K=L+(I-1)*Size
            DATAS(K,10)=X
                IF (LifeR(L)>CensR(L)) THEN
                DATAS(K,6)=LifeR(L)
            DATAS(K,7)=CensR(L)
                DATAS(K,8)=CensR(L)
                DATAS(K,9)=0.0d0
                ELSEIF (LifeR(L)<=CensR(L)) THEN
                DATAS(K,6)=LifeR(L)
            DATAS(K,7)=CensR(L)
                DATAS(K,8)=LifeR(L)
                DATAS(K,9)=1.0d0
                END IF
                END DO
        END DO
TTSS=DFLOAT(TTS)
NLifeR=SUM(DATAS(:,9))
NumLifeR=DFLOAT(NlifeR)

BetaRh=0.0d0
ErrorBR0=1.0d0
DO WHILE (ErrorBR0>0.000000001d0)
        DO J=1,TTS
        caR(J,1)=DATAS(J,8)*DEXP(BetaRh*DATAS(J,10))
        caR(J,2)=DATAS(J,8)*DATAS(J,10)*DEXP(BetaRh*DATAS(J,10))
        caR(J,3)=DATAS(J,9)*DATAS(J,10)
        caR(J,4)=((DATAS(J,10))**2)*DATAS(J,8)*DEXP(BetaRh*DATAS(J,10))
        END DO
scaR(1)=SUM(caR(:,1))
scaR(2)=SUM(caR(:,2))
scaR(3)=SUM(caR(:,3))
scaR(4)=SUM(caR(:,4))
BetaRh=BetaRh-(scaR(2)/scaR(1)-scaR(3)/NumlifeR)/(scaR(4)/scaR(1)-
(scaR(2)/scaR(1))**2)
ErrorBR0=ABS(-(scaR(2)/scaR(1)-scaR(3)/NumlifeR)/(scaR(4)/scaR(1)-
(scaR(2)/scaR(1))**2))
IF (ErrorBR0<0.000000001d0) EXIT
```

```
END DO
DO J=1,TTS
caR(J,1)=DATAS(J,8)*DEXP(BetaRh*DATAS(J,10))
caR(J,2)=DATAS(J,8)*DATAS(J,10)*DEXP(BetaRh*DATAS(J,10))
caR(J,3)=DATAS(J,9)*DATAS(J,10)
caR(J,4)=((DATAS(J,10))**2)*DATAS(J,8)*DEXP(BetaRh*DATAS(J,10))
END DO
scaR(1)=SUM(caR(:,1))
scaR(2)=SUM(caR(:,2))
scaR(3)=SUM(caR(:,3))
scaR(4)=SUM(caR(:,4))
BetaRh=BetaRh-(scaR(2)/scaR(1)-scaR(3)/NumlifeR)/(scaR(4)/scaR(1)-
(scaR(2)/scaR(1))**2)
DO J=1,TTS
caR(J,1)=DATAS(J,8)*DEXP(BetaRh*DATAS(J,10))
END DO
scaR(1)=SUM(caR(:,1))
AlphaRh=log(numlifeR/scaR(1))

DO J=1,TTS
caR(J,5)=DATAS(J,8)*DEXP(AlphaRh+BetaRh*DATAS(J,10))
caR(J,6)=DATAS(J,8)*DATAS(J,10)*DEXP(AlphaRh+BetaRh*DATAS(J,10))
caR(J,7)=((DATAS(J,10))**2)*DATAS(J,8)*DEXP(AlphaRh+BetaRh*DATAS(J,10))
END DO
scaR(5)=SUM(caR(:,5))
scaR(6)=SUM(caR(:,6))
scaR(7)=SUM(caR(:,7))
VarAlphahR=scaR(7)/(scaR(5)*scaR(7)-scaR(6)**2.0d0)
VarBetahR=scaR(5)/(scaR(5)*scaR(7)-scaR(6)**2.0d0)
CovABhR=-scaR(6)/(scaR(5)*scaR(7)-scaR(6)**2.0d0)
StdAlphahR=VarAlphahR**(0.5d0)
StdBetahR=VarBetahR**(0.5d0)
!write(*,*) BetaRh-Z0025*StdBetahR,BetaRh+Z0025*StdBetahR,StdBetahR
IF (0.0d0<=BetaRh-Z0025*StdBetahR .OR. BetaRh+Z0025*StdBetahR<=0.0d0 )
THEN
Tests(N,2)=1
END IF
!write(*,"(4(2XF13.10))") AlphaTh,BetaTh,AlphaRh,BetaRh
```

```
!=======Common Slope Testing======
IF (Tests(N,1)==1 .AND. Tests(N,2)==1) THEN
VarBetaRT=VarBetahR+VarBetahT
StdBetaRT=VarBetaRT**(0.5d0)
IF (-C<=BetaTh-BetaRh-Z0050*StdBetaRT .AND. BetaTh-
BetaRh+Z0050*StdBetaRT<=C ) THEN
Tests(N,3)=1
END IF
END IF
!write(*,*) BetaTh-BetaRh-Z0050*StdBetaRT,BetaTh-BetaRh+Z0050*StdBetaRT
!======Common Slope Model Newton-Raphson====
IF (Tests(N,3)==1) THEN
AlphaRh=0.0d0
AlphaTh=0.0d0
BetaCh=0.0d0
ErrorAR=1.0d0
ErrorAT=1.0d0
ErrorBC=1.0d0
DO S=1,Burn
!write(*,*) AlphaRh,AlphaTh,BetaCh
DO
J=1,TTS
caC(J,1)=DATAS(J,3)*DEXP(AlphaTh+BetaCh*DATAS(J,5))    !YtExp(At+BC*Xt)
caC(J,2)=DATAS(J,8)*DEXP(AlphaRh+BetaCh*DATAS(J,10)) !YrExp(Ar+BC*Xr)
caC(J,3)=DATAS(J,4)*DATAS(J,5)
caC(J,4)=DATAS(J,9)*DATAS(J,10)
caC(J,5)=DATAS(J,3)*DATAS(J,5)*DEXP(AlphaTh+BetaCh*DATAS(J,5))
caC(J,6)=DATAS(J,8)*DATAS(J,10)*DEXP(AlphaRh+BetaCh*DATAS(J,10))
caC(J,7)=DATAS(J,3)*(DATAS(J,5)**2)*DEXP(AlphaTh+BetaCh*DATAS(J,5))+DA
TAS(J,8)*(DATAS(J,10)**2)*DEXP(AlphaRh+BetaCh*DATAS(J,10))
END DO
scaC(1)=SUM(caC(:,1))
scaC(2)=SUM(caC(:,2))
scaC(3)=SUM(caC(:,3))
scaC(4)=SUM(caC(:,4))
scaC(5)=SUM(caC(:,5))
scaC(6)=SUM(caC(:,6))
scaC(7)=SUM(caC(:,7))
```



```
AlphaTh=AlphaTh+((scaC(2)*scaC(7)-scaC(6)*scaC(6))*(NumlifeT-
scaC(1))+scaC(5)*scaC(6)*(NumlifeR-scaC(2))-scaC(2)*scaC(5)*(scaC(3)+scaC(4)-
scaC(5)-scaC(6)))/(scaC(1)*scaC(2)*scaC(7)-scaC(2)*scaC(5)*scaC(5)-
scaC(1)*scaC(6)*scaC(6))
AlphaRh=AlphaRh+(scaC(5)*scaC(6)*(NumlifeT-scaC(1))+(scaC(1)*scaC(7)-
scaC(5)*scaC(5))*(NumlifeR-scaC(2))-scaC(1)*scaC(6)*(scaC(3)+scaC(4)-scaC(5)-
scaC(6)))/(scaC(1)*scaC(2)*scaC(7)-scaC(2)*scaC(5)*scaC(5)-
scaC(1)*scaC(6)*scaC(6))
BetaCh=BetaCh+(-scaC(2)*scaC(5)*(NumlifeT-scaC(1))-scaC(1)*scaC(6)*(NumlifeR-
scaC(2))+scaC(1)*scaC(2)*(scaC(3)+scaC(4)-scaC(5)-
scaC(6)))/(scaC(1)*scaC(2)*scaC(7)-scaC(2)*scaC(5)*scaC(5)-
scaC(1)*scaC(6)*scaC(6))
!write(*,*) AlphaRh,AlphaTh,BetaCh
ErrorAT=ABS(NumlifeT-scaC(1))
ErrorAR=ABS(NumlifeR-scaC(2))
ErrorBC=ABS(scaC(3)+scaC(4)-scaC(5)-scaC(6))
!write(*,*) ErrorAT,ErrorAR,ErrorBC
!ErrorAT=ABS(((scaC(2)*scaC(7)-scaC(6)*scaC(6))*(NumlifeT-
scaC(1))+scaC(5)*scaC(6)*(NumlifeR-scaC(2))-scaC(2)*scaC(5)*(scaC(3)+scaC(4)-
scaC(5)-scaC(6)))/(scaC(1)*scaC(2)*scaC(7)-scaC(2)*scaC(5)*scaC(5)-
scaC(1)*scaC(6)*scaC(6)))
!ErrorAR=ABS((scaC(5)*scaC(6)*(NumlifeT-scaC(1))+(scaC(1)*scaC(7)-
scaC(5)*scaC(5))*(NumlifeR-scaC(2))-scaC(1)*scaC(6)*(scaC(3)+scaC(4)-scaC(5)-
scaC(6)))/(scaC(1)*scaC(2)*scaC(7)-scaC(2)*scaC(5)*scaC(5)-
scaC(1)*scaC(6)*scaC(6)))
!ErrorBC=ABS((-scaC(2)*scaC(5)*(NumlifeT-scaC(1))-scaC(1)*scaC(6)*(NumlifeR-
scaC(2))+scaC(1)*scaC(2)*(scaC(3)+scaC(4)-scaC(5)-
scaC(6)))/(scaC(1)*scaC(2)*scaC(7)-scaC(2)*scaC(5)*scaC(5)-
scaC(1)*scaC(6)*scaC(6)))
IF (ErrorAR<0.000000001d0 .AND. ErrorAT<0.000000001d0 .AND.
ErrorBC<0.000000001d0) EXIT
END DO
!write(*,"(3(2XF13.10))") AlphaTh,AlphaRh,BetaCh

!======Relative Potency======
DO J=1,TTS
caC(J,1)=DATAS(J,3)*DEXP(AlphaTh+BetaCh*DATAS(J,5))
caC(J,2)=DATAS(J,8)*DEXP(AlphaRh+BetaCh*DATAS(J,10))
```



```
caC(J,5)=DATAS(J,3)*DATAS(J,5)*DEXP(AlphaTh+BetaCh*DATAS(J,5))
caC(J,6)=DATAS(J,8)*DATAS(J,10)*DEXP(AlphaRh+BetaCh*DATAS(J,10))
caC(J,7)=DATAS(J,3)*(DATAS(J,5)**2)*DEXP(AlphaTh+BetaCh*DATAS(J,5))+DA
TAS(J,8)*(DATAS(J,10)**2)*DEXP(AlphaRh+BetaCh*DATAS(J,10))
END DO
scaC(1)=SUM(caC(:,1))
scaC(2)=SUM(caC(:,2))
scaC(5)=SUM(caC(:,5))
scaC(6)=SUM(caC(:,6))
scaC(7)=SUM(caC(:,7))
VarAlphaCTh=(scaC(2)*scaC(7)-scaC(6)*scaC(6))/(scaC(1)*scaC(2)*scaC(7)-
scaC(2)*scaC(5)*scaC(5)-scaC(1)*scaC(6)*scaC(6))
VarAlphaCRh=(scaC(1)*scaC(7)-scaC(5)*scaC(5))/(scaC(1)*scaC(2)*scaC(7)-
scaC(2)*scaC(5)*scaC(5)-scaC(1)*scaC(6)*scaC(6))
VarBetaCh=scaC(1)*scaC(2)/(scaC(1)*scaC(2)*scaC(7)-scaC(2)*scaC(5)*scaC(5)-
scaC(1)*scaC(6)*scaC(6))
CovATBC=-scaC(2)*scaC(5)/(scaC(1)*scaC(2)*scaC(7)-scaC(2)*scaC(5)*scaC(5)-
scaC(1)*scaC(6)*scaC(6))
CovARBC=-scaC(1)*scaC(6)/(scaC(1)*scaC(2)*scaC(7)-scaC(2)*scaC(5)*scaC(5)-
scaC(1)*scaC(6)*scaC(6))
CovATAR=scaC(5)*scaR(6)/(scaC(1)*scaC(2)*scaC(7)-scaC(2)*scaC(5)*scaC(5)-
scaC(1)*scaC(6)*scaC(6))
!write(*,*) VarAlphaCTh,VarAlphaCRh,VarBetaCh,CovATBC,CovARBC,CovATAR
AA=BetaCh**2.0d0-(Z0050**2.0d0)*VarBetaCh
BB=2.0d0*(AlphaRh-AlphaTh)*BetaCh-2.0d0*(Z0050**2.0d0)*(CovATBC-
CovARBC)
CC=(AlphaTh-AlphaRh)**2-(Z0050**2.0d0)*(VarAlphaCTh+VarAlphaCRh-
2.0d0*CovATAR)
!write(*,*) AA,BB,CC
IF (BB**2.0d0-AA*CC<0) THEN
IND=1
EXIT
ELSE
DeltaL=(-BB-DSQRT(BB**2.0d0-4.0d0*AA*CC))/(2.0d0*AA)
DeltaU=(-BB+DSQRT(BB**2.0d0-4.0d0*AA*CC))/(2.0d0*AA)
!DeltaL=((AlphaTh-AlphaRh)*BetaCh-Z0050**2*(CovATBC-CovARBC)-
(((AlphaTh-AlphaRh)*BetaCh-Z0050**2*(CovATBC-CovARBC))**2-(BetaCh**2-
Z0050**2*VarBetaCh)*((AlphaTh-AlphaRh)**2-
```

```
Z0050**2*(VarAlphaCTh+VarAlphaCRh-2*CovATAR)))**(0.5))/(BetaCh**2-
Z0050**2*VarBetaCh)
!DeltaU=((AlphaTh-AlphaRh)*BetaCh-Z0050**2*(CovATBC-
CovARBC)+(((AlphaTh-AlphaRh)*BetaCh-Z0050**2*(CovATBC-CovARBC))**2-
(BetaCh**2-Z0050**2*VarBetaCh)*((AlphaTh-AlphaRh)**2-
Z0050**2*(VarAlphaCTh+VarAlphaCRh-2*CovATAR)))**(0.5))/(BetaCh**2-
Z0050**2*VarBetaCh)
!write(*,*) DeltaL,DeltaU
!write(15,*) DeltaL,DeltaU
!write(*,*) ' '
END IF
IF (-Delta<DeltaL .AND. DeltaU<Delta) THEN
Tests(N,4)=1
END IF
END IF
WRITE(*,"((1XF4.1),A,(1XF6.4))")    AlphaT0/BetaT0,' ',SUM(Tests(:,4))/SimuN
WRITE(15,"((1XF4.1),A,(1XF6.4))") AlphaT0/BetaT0,' ',SUM(Tests(:,4))/SimuN
deallocate(LifeT,CensT,LifeR,CensR)
deallocate(DATAS)
deallocate(caT,caR,scaT,scaR,caC,scaC)
deallocate(Tests)
deallocate(Xs)
END DO !Q
END DO !P
END DO !O
END DO !R
END DO !T
END DO !U
end program
```

Appendix 3, Fortran Code for Simulation

Program

```
program main
USE msimsl
IMPLICIT NONE
integer :: I,J,K,L,M,N,O,P,Q,R,S,T,U,NOUT,ISEEDT,ISEEDR
real*8 :: Z0025,Z0050,C,Delta,II,TTSS,X,Xinc,Xstart,
RatioT,CensRateT,BetaT0,AlphaT0,LamdaTL,LamdaTC,ThetaTL,ThetaTC,
RatioR,CensRateR,BetaR0,AlphaR0,LamdaRL,LamdaRC,ThetaRL,ThetaRC,
NumCensT,NumLifeT,NumCensR,NumLifeR,
AlphaTh,BetaTh,ErrorAT0,ErrorBT0,VarAlphahT,VarBetahT,CovABhT,StdAlphahT,
StdBetahT,
AlphaRh,BetaRh,ErrorAR0,ErrorBR0,VarAlphahR,VarBetahR,CovABhR,StdAlphahR,
StdBetahR, BetaCh,ErrorAR,ErrorAT,ErrorBC,
VarAlphaCRh,VarAlphaCTh,VarBetaCh,CovARBC,CovATBC,CovATAR,DeltaL,Delt
aU,AA,BB,CC, VarBetaRT,StdBetaRT, Haza,Hazb
integer :: Size,Doses,TTS,SimuN,Burn,NCensT,NLifeT,NCensR,NLifeR
real*8 , allocatable :: Xs(:)
real*8 , allocatable :: LifeR(:),CensR(:),LifeT(:),CensT(:)
real*8 , allocatable ::
Datas(:,:),RTLCDatas(:,:),caR(:,:),caT(:,:),scaR(:),scaT(:),Tests(:,:),caC(:,:),scaC(:)
real*8 :: SDL(5,5,5),IND
parameter(SimuN=10000,Burn=1000,C=0.5d0,Delta=2.0d0)
Forall(i=1:5,j=1:5,k=1:5) SDL(i,j,k)=0
IND=0
Z0025=ANORIN(0.975)
Z0050=ANORIN(0.95)
write(*,*) "Input the censored rate, assuming the two censored rates are equil: "
read(*,*) CensRateT
CensRateR=CensRateT
!CensRateT=0.2d0
!CensRateR=0.2d0
RatioT=CensRateT/(1-CensRateT)
RatioR=CensRateR/(1-CensRateR)
open(unit=15, file='Power_function.txt')
DO U=1,3
Doses=3.0d0+(DFLOAT(U)-1.0d0)*2.0d0
DO T=1,5
BetaT0=-0.1d0-0.2d0*(DFLOAT(T)-1.0d0)
BetaR0=-0.1d0-0.2d0*(DFLOAT(T)-1.0d0)
```

```
write(*,"(A,F4.1)") "The slope is ",BetaT0
write(15,"(A,F4.1)") "The slope is ",BetaT0
DO R=1,5
!AlphaT0=BetaT0*(-2.2+0.2*(DFLOAT(R)-1))
!AlphaR0=0.0d0
AlphaT0=0.0d0
AlphaR0=0.0d0
!write(*,*) R-3
DO O=1,5
size=40*DFLOAT(O)
TTS=Doses*Size
DO P=4,4    !跑 cp,power
DO Q=9,9
Haza=0.1d0*DFLOAT(P)*(1-CensRateT)
Hazb=0.1d0*DFLOAT(Q)*(1-CensRateT)
!write(*,"(A,F3.1,A,F3.1,A)") "The minimun hazard is ",Haza,". The maximun hazard
is ",Hazb,"."
!write(15,"(A,F3.1,A,F3.1,A)") "The minimun hazard is ",Haza,". The maximun hazard
is ",Hazb,"."
allocate(LifeT(size),CensT(size),LifeR(size),CensR(size))
allocate(DATAS(TTS,10))
allocate(caT(TTS,7),caR(TTS,7),scaT(7),scaR(7),caC(TTS,7),scaC(7))
allocate(Tests(SimuN,9))
Forall(i=1:SimuN,j=1:9) Tests(i,j)=0
allocate(Xs(Doses-1))
DO I=1,Doses-1
II=dfloat(I)
Xs(I)=DLOG(Hazb-(II-1.0d0)*(Hazb-Haza)/(Doses-2.0d0))/BetaR0
END DO
!open(unit=10, file='exp_data_T.txt')
DO N=1,SimuN
              !ISEEDT=1
!=======Biosimilar====T
            DO I=1,Doses
            IF (I==1) THEN
            X=0.0d0
            ELSE
            !II=dfloat(I)
```

```
            X=Xs(I-1)
            !X=Xstart+Xinc*(II-2)
            ENDIF
            LamdaTL=DEXP(AlphaT0+X*BetaT0)
            LamdaTC=LamdaTL*RatioT
            ThetaTL=(LamdaTL)**(-1)
            ThetaTC=(LamdaTC)**(-1)
        !ISEEDT=ISEEDT+1
            !CALL RNSET(ISEEDT)
            CALL DRNEXP(SIZE,LifeT)
            CALL DSCAL(SIZE,ThetaTL,LifeT,1)
            CALL DRNEXP(SIZE,CensT)
            CALL DSCAL(SIZE,ThetaTC,CensT,1)
                    DO L=1,Size
                K=L+(I-1)*Size
                DATAS(K,5)=X
            IF (LifeT(L)>CensT(L)) THEN
            DATAS(K,1)=LifeT(L)
                DATAS(K,2)=CensT(L)
                    DATAS(K,3)=CensT(L)
                    DATAS(K,4)=0.0d0
                    ELSEIF (LifeT(L)<=CensT(L)) THEN
                    DATAS(K,1)=LifeT(L)
                DATAS(K,2)=CensT(L)
                    DATAS(K,3)=LifeT(L)
                    DATAS(K,4)=1.0d0
                    END IF
                    END DO
            END DO
!           DO I=1,TTS
!       write(10,'(f11.8,2Xf11.8,2Xf11.8,2XF2.0,2XF11.8)') DATAS(I,1:5)
!           END DO
TTSS=DFLOAT(TTS)
NlifeT=SUM(DATAS(:,4))
NumLifeT=DFLOAT(NlifeT)
BetaTh=0.0d0
ErrorBT0=1.0d0
DO WHILE (ErrorBT0>0.000000001d0)
```

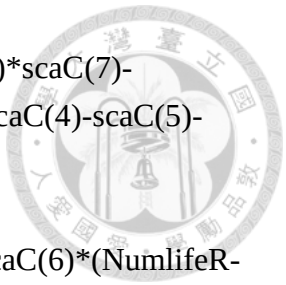
```
DO J=1,Size*Doses
caT(J,1)=DATAS(J,3)*DEXP(BetaTh*DATAS(J,5))
caT(J,2)=DATAS(J,3)*DATAS(J,5)*DEXP(BetaTh*DATAS(J,5))
caT(J,3)=DATAS(J,4)*DATAS(J,5)
caT(J,4)=((DATAS(J,5))**2)*DATAS(J,3)*DEXP(BetaTh*DATAS(J,5))
END DO
scaT(1)=SUM(caT(:,1))
scaT(2)=SUM(caT(:,2))
scaT(3)=SUM(caT(:,3))
scaT(4)=SUM(caT(:,4))
BetaTh=BetaTh-(scaT(2)/scaT(1)-scaT(3)/NumlifeT)/(scaT(4)/scaT(1)-
(scaT(2)/scaT(1))**2)
ErrorBT0=ABS(-(scaT(2)/scaT(1)-scaT(3)/NumlifeT)/(scaT(4)/scaT(1)-
(scaT(2)/scaT(1))**2))

IF (ErrorBT0<0.000000001d0) EXIT
END DO
DO J=1,Size*Doses
caT(J,1)=DATAS(J,3)*DEXP(BetaTh*DATAS(J,5))
caT(J,2)=DATAS(J,3)*DATAS(J,5)*DEXP(BetaTh*DATAS(J,5))
caT(J,3)=DATAS(J,4)*DATAS(J,5)
caT(J,4)=((DATAS(J,5))**2)*DATAS(J,3)*DEXP(BetaTh*DATAS(J,5))
END DO
scaT(1)=SUM(caT(:,1))
scaT(2)=SUM(caT(:,2))
scaT(3)=SUM(caT(:,3))
scaT(4)=SUM(caT(:,4))
BetaTh=BetaTh-(scaT(2)/scaT(1)-scaT(3)/NumlifeT)/(scaT(4)/scaT(1)-
(scaT(2)/scaT(1))**2)
        DO J=1,Size*Doses
        caT(J,1)=DATAS(J,3)*DEXP(BetaTh*DATAS(J,5))
        END DO
scaT(1)=SUM(caT(:,1))
AlphaTh=log(numlifeT/scaT(1))
        DO J=1,Size*Doses
caT(J,5)=DATAS(J,3)*DEXP(AlphaTh+BetaTh*DATAS(J,5))
caT(J,6)=DATAS(J,3)*DATAS(J,5)*DEXP(AlphaTh+BetaTh*DATAS(J,5))
caT(J,7)=((DATAS(J,5))**2)*DATAS(J,3)*DEXP(AlphaTh+BetaTh*DATAS(J,5))
```

```
END DO
scaT(5)=SUM(caT(:,5))
scaT(6)=SUM(caT(:,6))
scaT(7)=SUM(caT(:,7))
VarAlphahT=scaT(7)/(scaT(5)*scaT(7)-scaT(6)**2)
VarBetahT=scaT(5)/(scaT(5)*scaT(7)-scaT(6)**2)
CovABhT=-scaT(6)/(scaT(5)*scaT(7)-scaT(6)**2)
StdAlphahT=DSQRT(VarAlphahT)
StdBetahT=DSQRT(VarBetahT)
IF (0.0d0<=BetaTh-Z0025*StdBetahT .OR. BetaTh+Z0025*StdBetahT<=0.0d0 )
THEN
Tests(N,1)=1
END IF
!write(*,*) BetaTh-Z0025*StdBetahT,BetaTh+Z0025*StdBetahT,StdBetahT

!=======Innovator====R
            DO I=1,Doses
            IF (I==1) THEN
            X=0.0d0
            ELSE
            !II=dfloat(I)
            X=Xs(I-1)
            !X=Xstart+Xinc*(II-2)
            ENDIF
            LamdaRL=DEXP(AlphaR0+X*BetaR0)
            LamdaRC=LamdaRL*RatioR
            ThetaRL=(LamdaRL)**(-1)
            ThetaRC=(LamdaRC)**(-1)
      !ISEEDR=ISEEDR+1
            !CALL RNSET(ISEEDR)
            CALL DRNEXP(SIZE,LifeR)
            CALL DSCAL(SIZE,ThetaRL,LifeR,1)
            CALL DRNEXP(SIZE,CensR)
            CALL DSCAL(SIZE,ThetaRC,CensR,1)
                  DO L=1,Size
                K=L+(I-1)*Size
                DATAS(K,10)=X
                  IF (LifeR(L)>CensR(L)) THEN
```

```
                DATAS(K,6)=LifeR(L)
            DATAS(K,7)=CensR(L)
                DATAS(K,8)=CensR(L)
                DATAS(K,9)=0.0d0
                ELSEIF (LifeR(L)<=CensR(L)) THEN
                DATAS(K,6)=LifeR(L)
            DATAS(K,7)=CensR(L)
                DATAS(K,8)=LifeR(L)
                DATAS(K,9)=1.0d0
                END IF
                END DO
        END DO
TTSS=DFLOAT(TTS)
NLifeR=SUM(DATAS(:,9))
NumLifeR=DFLOAT(NlifeR)

BetaRh=0.0d0
ErrorBR0=1.0d0
DO WHILE (ErrorBR0>0.000000001d0)
        DO J=1,TTS
        caR(J,1)=DATAS(J,8)*DEXP(BetaRh*DATAS(J,10))
        caR(J,2)=DATAS(J,8)*DATAS(J,10)*DEXP(BetaRh*DATAS(J,10))
        caR(J,3)=DATAS(J,9)*DATAS(J,10)
        caR(J,4)=((DATAS(J,10))**2)*DATAS(J,8)*DEXP(BetaRh*DATAS(J,10))
        END DO
scaR(1)=SUM(caR(:,1))
scaR(2)=SUM(caR(:,2))
scaR(3)=SUM(caR(:,3))
scaR(4)=SUM(caR(:,4))
BetaRh=BetaRh-(scaR(2)/scaR(1)-scaR(3)/NumlifeR)/(scaR(4)/scaR(1)-
(scaR(2)/scaR(1))**2)
ErrorBR0=ABS(-(scaR(2)/scaR(1)-scaR(3)/NumlifeR)/(scaR(4)/scaR(1)-
(scaR(2)/scaR(1))**2))
IF (ErrorBR0<0.000000001d0) EXIT
END DO
DO J=1,TTS
caR(J,1)=DATAS(J,8)*DEXP(BetaRh*DATAS(J,10))
caR(J,2)=DATAS(J,8)*DATAS(J,10)*DEXP(BetaRh*DATAS(J,10))
```

```
caR(J,3)=DATAS(J,9)*DATAS(J,10)
caR(J,4)=((DATAS(J,10))**2)*DATAS(J,8)*DEXP(BetaRh*DATAS(J,10))
END DO
scaR(1)=SUM(caR(:,1))
scaR(2)=SUM(caR(:,2))
scaR(3)=SUM(caR(:,3))
scaR(4)=SUM(caR(:,4))
BetaRh=BetaRh-(scaR(2)/scaR(1)-scaR(3)/NumlifeR)/(scaR(4)/scaR(1)-
(scaR(2)/scaR(1))**2)
DO J=1,TTS
caR(J,1)=DATAS(J,8)*DEXP(BetaRh*DATAS(J,10))
END DO
scaR(1)=SUM(caR(:,1))
AlphaRh=log(numlifeR/scaR(1))

DO J=1,TTS
caR(J,5)=DATAS(J,8)*DEXP(AlphaRh+BetaRh*DATAS(J,10))
caR(J,6)=DATAS(J,8)*DATAS(J,10)*DEXP(AlphaRh+BetaRh*DATAS(J,10))
caR(J,7)=((DATAS(J,10))**2)*DATAS(J,8)*DEXP(AlphaRh+BetaRh*DATAS(J,10))
END DO
scaR(5)=SUM(caR(:,5))
scaR(6)=SUM(caR(:,6))
scaR(7)=SUM(caR(:,7))
VarAlphahR=scaR(7)/(scaR(5)*scaR(7)-scaR(6)**2.0d0)
VarBetahR=scaR(5)/(scaR(5)*scaR(7)-scaR(6)**2.0d0)
CovABhR=-scaR(6)/(scaR(5)*scaR(7)-scaR(6)**2.0d0)
StdAlphahR=VarAlphahR**(0.5d0)
StdBetahR=VarBetahR**(0.5d0)
!write(*,*) BetaRh-Z0025*StdBetahR,BetaRh+Z0025*StdBetahR,StdBetahR
IF (0.0d0<=BetaRh-Z0025*StdBetahR .OR. BetaRh+Z0025*StdBetahR<=0.0d0 )
THEN
Tests(N,2)=1
END IF
!write(*,"(4(2XF13.10))") AlphaTh,BetaTh,AlphaRh,BetaRh
!=======Common Slope Testing======
IF (Tests(N,1)==1 .AND. Tests(N,2)==1) THEN
VarBetaRT=VarBetahR+VarBetahT
StdBetaRT=VarBetaRT**(0.5d0)
```

```
IF (-C<=BetaTh-BetaRh-Z0050*StdBetaRT .AND. BetaTh-
BetaRh+Z0050*StdBetaRT<=C ) THEN
Tests(N,3)=1
END IF
END IF
!write(*,*) BetaTh-BetaRh-Z0050*StdBetaRT,BetaTh-BetaRh+Z0050*StdBetaRT
!======Common Slope Model Newton-Raphson====
IF (Tests(N,3)==1) THEN
AlphaRh=0.0d0
AlphaTh=0.0d0
BetaCh=0.0d0
ErrorAR=1.0d0
ErrorAT=1.0d0
ErrorBC=1.0d0
DO S=1,Burn
!write(*,*) AlphaRh,AlphaTh,BetaCh
DO
J=1,TTS
caC(J,1)=DATAS(J,3)*DEXP(AlphaTh+BetaCh*DATAS(J,5))    !YtExp(At+BC*Xt)
caC(J,2)=DATAS(J,8)*DEXP(AlphaRh+BetaCh*DATAS(J,10)) !YrExp(Ar+BC*Xr)
caC(J,3)=DATAS(J,4)*DATAS(J,5)
caC(J,4)=DATAS(J,9)*DATAS(J,10)
caC(J,5)=DATAS(J,3)*DATAS(J,5)*DEXP(AlphaTh+BetaCh*DATAS(J,5))
caC(J,6)=DATAS(J,8)*DATAS(J,10)*DEXP(AlphaRh+BetaCh*DATAS(J,10))
caC(J,7)=DATAS(J,3)*(DATAS(J,5)**2)*DEXP(AlphaTh+BetaCh*DATAS(J,5))+DA
TAS(J,8)*(DATAS(J,10)**2)*DEXP(AlphaRh+BetaCh*DATAS(J,10))
END DO
scaC(1)=SUM(caC(:,1))
scaC(2)=SUM(caC(:,2))
scaC(3)=SUM(caC(:,3))
scaC(4)=SUM(caC(:,4))
scaC(5)=SUM(caC(:,5))
scaC(6)=SUM(caC(:,6))
scaC(7)=SUM(caC(:,7))
AlphaTh=AlphaTh+((scaC(2)*scaC(7)-scaC(6)*scaC(6))*(NumlifeT-
scaC(1))+scaC(5)*scaC(6)*(NumlifeR-scaC(2))-scaC(2)*scaC(5)*(scaC(3)+scaC(4)-
scaC(5)-scaC(6)))/(scaC(1)*scaC(2)*scaC(7)-scaC(2)*scaC(5)*scaC(5)-
scaC(1)*scaC(6)*scaC(6))
```



```
AlphaRh=AlphaRh+(scaC(5)*scaC(6)*(NumlifeT-scaC(1))+(scaC(1)*scaC(7)-
scaC(5)*scaC(5))*(NumlifeR-scaC(2))-scaC(1)*scaC(6)*(scaC(3)+scaC(4)-scaC(5)-
scaC(6)))/(scaC(1)*scaC(2)*scaC(7)-scaC(2)*scaC(5)*scaC(5)-
scaC(1)*scaC(6)*scaC(6))
BetaCh=BetaCh+(-scaC(2)*scaC(5)*(NumlifeT-scaC(1))-scaC(1)*scaC(6)*(NumlifeR-
scaC(2))+scaC(1)*scaC(2)*(scaC(3)+scaC(4)-scaC(5)-
scaC(6)))/(scaC(1)*scaC(2)*scaC(7)-scaC(2)*scaC(5)*scaC(5)-
scaC(1)*scaC(6)*scaC(6))
!write(*,*) AlphaRh,AlphaTh,BetaCh
ErrorAT=ABS(NumlifeT-scaC(1))
ErrorAR=ABS(NumlifeR-scaC(2))
ErrorBC=ABS(scaC(3)+scaC(4)-scaC(5)-scaC(6))
!write(*,*) ErrorAT,ErrorAR,ErrorBC
!ErrorAT=ABS(((scaC(2)*scaC(7)-scaC(6)*scaC(6))*(NumlifeT-
scaC(1))+scaC(5)*scaC(6)*(NumlifeR-scaC(2))-scaC(2)*scaC(5)*(scaC(3)+scaC(4)-
scaC(5)-scaC(6)))/(scaC(1)*scaC(2)*scaC(7)-scaC(2)*scaC(5)*scaC(5)-
scaC(1)*scaC(6)*scaC(6)))
!ErrorAR=ABS((scaC(5)*scaC(6)*(NumlifeT-scaC(1))+(scaC(1)*scaC(7)-
scaC(5)*scaC(5))*(NumlifeR-scaC(2))-scaC(1)*scaC(6)*(scaC(3)+scaC(4)-scaC(5)-
scaC(6)))/(scaC(1)*scaC(2)*scaC(7)-scaC(2)*scaC(5)*scaC(5)-
scaC(1)*scaC(6)*scaC(6)))
!ErrorBC=ABS((-scaC(2)*scaC(5)*(NumlifeT-scaC(1))-scaC(1)*scaC(6)*(NumlifeR-
scaC(2))+scaC(1)*scaC(2)*(scaC(3)+scaC(4)-scaC(5)-
scaC(6)))/(scaC(1)*scaC(2)*scaC(7)-scaC(2)*scaC(5)*scaC(5)-
scaC(1)*scaC(6)*scaC(6)))
IF (ErrorAR<0.000000001d0 .AND. ErrorAT<0.000000001d0 .AND.
ErrorBC<0.000000001d0) EXIT
END DO
!write(*,"(3(2XF13.10))") AlphaTh,AlphaRh,BetaCh

!======Relative Potency======
DO J=1,TTS
caC(J,1)=DATAS(J,3)*DEXP(AlphaTh+BetaCh*DATAS(J,5))
caC(J,2)=DATAS(J,8)*DEXP(AlphaRh+BetaCh*DATAS(J,10))
caC(J,5)=DATAS(J,3)*DATAS(J,5)*DEXP(AlphaTh+BetaCh*DATAS(J,5))
caC(J,6)=DATAS(J,8)*DATAS(J,10)*DEXP(AlphaRh+BetaCh*DATAS(J,10))
caC(J,7)=DATAS(J,3)*(DATAS(J,5)**2)*DEXP(AlphaTh+BetaCh*DATAS(J,5))+DA
TAS(J,8)*(DATAS(J,10)**2)*DEXP(AlphaRh+BetaCh*DATAS(J,10))
```

```
END DO
scaC(1)=SUM(caC(:,1))
scaC(2)=SUM(caC(:,2))
scaC(5)=SUM(caC(:,5))
scaC(6)=SUM(caC(:,6))
scaC(7)=SUM(caC(:,7))
VarAlphaCTh=(scaC(2)*scaC(7)-scaC(6)*scaC(6))/(scaC(1)*scaC(2)*scaC(7)-
scaC(2)*scaC(5)*scaC(5)-scaC(1)*scaC(6)*scaC(6))
VarAlphaCRh=(scaC(1)*scaC(7)-scaC(5)*scaC(5))/(scaC(1)*scaC(2)*scaC(7)-
scaC(2)*scaC(5)*scaC(5)-scaC(1)*scaC(6)*scaC(6))
VarBetaCh=scaC(1)*scaC(2)/(scaC(1)*scaC(2)*scaC(7)-scaC(2)*scaC(5)*scaC(5)-
scaC(1)*scaC(6)*scaC(6))
CovATBC=-scaC(2)*scaC(5)/(scaC(1)*scaC(2)*scaC(7)-scaC(2)*scaC(5)*scaC(5)-
scaC(1)*scaC(6)*scaC(6))
CovARBC=-scaC(1)*scaC(6)/(scaC(1)*scaC(2)*scaC(7)-scaC(2)*scaC(5)*scaC(5)-
scaC(1)*scaC(6)*scaC(6))
CovATAR=scaC(5)*scaR(6)/(scaC(1)*scaC(2)*scaC(7)-scaC(2)*scaC(5)*scaC(5)-
scaC(1)*scaC(6)*scaC(6))
!write(*,*) VarAlphaCTh,VarAlphaCRh,VarBetaCh,CovATBC,CovARBC,CovATAR
AA=BetaCh**2.0d0-(Z0050**2.0d0)*VarBetaCh
BB=2.0d0*(AlphaRh-AlphaTh)*BetaCh-2.0d0*(Z0050**2.0d0)*(CovATBC-
CovARBC)
CC=(AlphaTh-AlphaRh)**2-(Z0050**2.0d0)*(VarAlphaCTh+VarAlphaCRh-
2.0d0*CovATAR)
!write(*,*) AA,BB,CC
IF (BB**2.0d0-AA*CC<0) THEN
IND=1
EXIT
ELSE
DeltaL=(-BB-DSQRT(BB**2.0d0-4.0d0*AA*CC))/(2.0d0*AA)
DeltaU=(-BB+DSQRT(BB**2.0d0-4.0d0*AA*CC))/(2.0d0*AA)
!DeltaL=((AlphaTh-AlphaRh)*BetaCh-Z0050**2*(CovATBC-CovARBC)-
(((AlphaTh-AlphaRh)*BetaCh-Z0050**2*(CovATBC-CovARBC))**2-(BetaCh**2-
Z0050**2*VarBetaCh)*((AlphaTh-AlphaRh)**2-
Z0050**2*(VarAlphaCTh+VarAlphaCRh-2*CovATAR)))**(0.5))/(BetaCh**2-
Z0050**2*VarBetaCh)
!DeltaU=((AlphaTh-AlphaRh)*BetaCh-Z0050**2*(CovATBC-
CovARBC)+(((AlphaTh-AlphaRh)*BetaCh-Z0050**2*(CovATBC-CovARBC))**2-
```

```
(BetaCh**2-Z0050**2*VarBetaCh)*((AlphaTh-AlphaRh)**2-
Z0050**2*(VarAlphaCTh+VarAlphaCRh-2*CovATAR)))**(0.5))/(BetaCh**2-
Z0050**2*VarBetaCh)
!write(*,*) DeltaL,DeltaU
!write(15,*) DeltaL,DeltaU
!write(*,*) ' '
END IF
IF (-Delta<DeltaL .AND. DeltaU<Delta) THEN
Tests(N,4)=1
END IF
END IF
probility=',SUM(Tests(:,I+4))/SimuN,'                    Power is ',
SUM(Tests(:,4))/SimuN
!WRITE(15,"((1XF6.4),A,(1XF6.4))") SUM(Tests(:,I+4))/SimuN,'
Power is ', SUM(Tests(:,4))/SimuN
!ELSE
!WRITE(*,"(A,(1XF6.4),A,(1XF6.4))") 'Coverage
probility=',SUM(Tests(:,I+4))/SimuN,'                    Size is ',
SUM(Tests(:,4))/SimuN
!WRITE(15,"((1XF6.4),A,(1XF6.4))") SUM(Tests(:,I+4))/SimuN,'
Size is ', SUM(Tests(:,4))/SimuN
!ENDIF
!ENDIF
!END DO
!write(15,"(F)") SUM(Tests(:,4))/SimuN
WRITE(*,"((1XF4.1),A,(1XF6.4))")    AlphaT0/BetaT0,' ',SUM(Tests(:,4))/SimuN
WRITE(15,"((1XF4.1),A,(1XF6.4))") AlphaT0/BetaT0,' ',SUM(Tests(:,4))/SimuN
deallocate(LifeT,CensT,LifeR,CensR)
deallocate(DATAS)
deallocate(caT,caR,scaT,scaR,caC,scaC)
deallocate(Tests)
deallocate(Xs)
END DO !Q
END DO !P
END DO !O
END DO !R
END DO !T
END DO !U
```

```
end program
```