• 計畫中文名稱	銜接性試驗之相關性研究---共變數共線性關係對不同參數分佈模式之人群模式參數評估的影響性		
• 計畫英文名稱	Relative Research on Bridging Studies---The Influence of Collinearity of Covariates on Parameter Estimates in Population Models with Different Distribution for Parameters		
• 系統編號	PG9101-0252	• 研究性質	基礎研究
• 計畫編號	DOH91-TD-1103	• 研究方式	委託研究
• 主管機關	行政院衛生署	• 研究期間	9101 ~ 9112
• 執行機構	台北醫學大學		
• 年度	91 年	• 研究經費	650 千元
• 研究領域	藥學		
• 研究人員	葉健全		
• 中文關鍵字	銜接性試驗；共線性；藥動學參數；藥效學參數；分佈型態；；；		
• 英文關鍵字	bridging study；collinearity；pharmacokinetic parameter；pharmacodynamic parameter；distribution；；；		
• 中文摘要	本研究計劃之目的在於探討共變數之共線性對於不同模式評估時，於不同藥動學或藥效學參數分佈模式下，對其人群模式參數評估的影響。由於市場全球化的趨勢，以及避免於不同地區或人種重複不必要的臨床試驗，免除銜接性試驗已成爲全球性藥廠於新藥開發時期所必須考量的一個重要課題。能免除銜接性試驗的主要前提是必須確認影響藥物之藥效與安全性的變數與其相關性在不同族群並無統計上明顯之差異，而不同族群對於藥動學或藥效學參數的影響因子會藉由對參數之影響而影響藥物的臨床有效性與安全性，此些因子稱之爲共變數，因此臨床試驗的設計與模式評估就必須能導致正確的確認能預估藥動學或藥效學參數之共變數模式。但是共變數的共線性程度將影響參數評估，而參數分佈模式的不同也使得參數的評估結果以及模式篩選更趨複雜，因此正是目前人群藥動學或藥效學模式評估過程，最值得研究探討的相關課題，以提供做爲審查相關案件時準確判定人種因素之影響性的參考。所以本計畫將利用實際數據的共變數模式爲基礎，假設參數的分佈模式爲連續性的對數常態分佈或非連續性的多組態模式分佈，並加入共線性關係矩陣，以電腦模擬建立近似臨床試驗的數據，再以非線性混合效果模式法 (nonlinear mixed-effect model，NONMEM)、非參數式預期值極大值模式法 (nonparametric EM，NPEM)、及相關性分析法 (Canonical correlation analysis，CCA) 分別比較對於不同參數分佈模式所能建立的人群模式 (population model) 與模擬模式之差異，以瞭解如何建構一個藥物合適的人群模式，並由其中準確的篩選人種差異的影響因子，以作爲免除銜接性試驗之審查基準，而其相關模式的影響因子可以做爲銜接性試驗的試驗設計之參考依據。本計劃預期能模擬建立與實際臨床狀況或人群模式更接近的臨床數據，而比較人群模式的篩選模式將建立更合適的模式預估能力，並確認影響人群藥動學或藥效學模式的關鍵性因子，		

	以作爲銜接性試驗之審查依據。
• 英文摘要	The purpose of this study is to explore the influence of collinearity of covariates on the evaluation of population parameters based on different frequency distribution of pharmacokinetic or pharmacodynamic parameters when examining with various screening methods. Prerequisite to be qualified for exempting from conducting bridging studies is to prove that there exists no significant difference in the extent of influence of variables on drug efficacy and safety among different ethnic populations. However, those influencing factors on pharmacokinetic or pharmacodynamic parameters among different ethnic populations could be various and different correspondingly resulting in various extent of influence on clinical efficacy and safety of drugs. Those influencing factors are called covariates. As a result, the design of clinical trial and screening methods selected must have ability to accurately identify a covariate model for pharmacokinetic or pharmacodynamic parameters with a higher predictivity. Nevertheless, the extent of collinearity among the covariates will affect the precision of the regression parameters in linear regression. Various frequency distributions of parameters further complicate its effect on the screening process selected and the estimation of parameters. Since that, knowledge about the collinearity among covariates becomes an issue worthy of exploration in developing population models of pharmacokinetic or pharmacodynamic parameters. The results will be critical reference for regulatory personnel in the evaluation of the influence of ethnic factors. This proposal will use simulated plasma data randomly generated by computer based on real data of covariate model incorporated with a matrix of collinearity relationship with the assumption of continuous distribution or multiple-mode distribution for parameters. Several screening methods, including nonlinear mixed-effect model (NONMEM), nonparametric EM (NPEM), and canonical correlation analysis (CCA), will be applied to compare the difference between the obtained and the expected population model. Optimally, an appropriate approach to construct the population model for a drug will be proposed and the influence of ethnic factors can be accurately evaluated. This can provide a reference for authority to evaluate the exemption of conducting a bridging study.