To encourage scientific and risk based approach to Bioequivalence (BE) Studies for post approval change (PAC) in "your Country/ Region" in the present status,

Question 1: ***Have you ever applied "BCS-based Biowaiver approach" * for the PAC (ex. formulation change or manufacturing site change) of branded (new) drugs?***

**** "BCS-based Biowaiver approach " means in vivo bioequivalence studies is not required by this approach.***

Please click "YES" or "NO",

YES

APAC

If Yes,

please provide examples that BCS-based biowaiver approach were applied.

1	The Bioequivalence (BE) Studies for post approval change (PAC) can apply BCS based biowaiver in Taiwan. If the dosage form of the medicinal products can fit the biopharmaceutics classification of ICH M9 definition and the degree of change meet the criteria of 「Solid Oral Dosage Forms: Post-Approval Changes」 which announced by TFDA on 23 July, 2020. In this case , it could apply BCS based biowaiver.

Could you please show your local guideline based on BCS-based Biowaiver approach?

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表一、速放製劑：

項目 \ 改變程度		不屬主次要改變	次要改變	主要改變
應檢附資料		-	溶離率曲線比對	生體相等性試驗
•成分及組成變更*1				
填充劑(Filler)		≦5%	>5%且≦10%	>10%
崩散劑(Disintegrant)	Starch	≦3%	>3%且≦6%	>6%
	Other	≦1%	>1%且≦2%	>2%
結合劑(Binder)		≦0.5%	>0.5%且≦1%	>1%
潤滑劑(Lubricant)	Ca or Mg Stearate	≦0.25%	>0.25%且≦0.5%	>0.5%
	Other	≦1%	>1%且≦2%	>2%
滑動劑(Glidant)	Talc	≦1%	>1%且≦2%	>2%
	Other	≦0.1%	>0.1%且≦0.2%	>0.2%
膜衣(Film Coat)		≦1%	>1%且≦2%	>2%
變更百分率總和		≦5%	>5%且≦10%	>10%
賦形劑		只去除或減少某一色素或矯味劑	改變技術等級或規格	新增或刪除
•批量(Batch Size)變更*2		≦10	>10 倍*3	-
•製程機器(Manufacturing Equipment)變更		1.由非自動或非機械改用自動或機械 2.改用相同設計及相同原理之設備	改用不同設計及不同原理之設備	-

•製程(Manufacturing Process)變更	製程改變未超過確效範圍	1.已執行確效者，其製程改變超過確效範圍。 2. 其餘，視個案而定。	製程步驟改變 如:由濕式造粒法改由乾粉直接壓製
•製造場所(Manufacturing Site)變更	同一廠房同一生產區(生產線)或同一廠房不同生產區(生產線搬遷或變更)、廠房搬移等	新增/變更製造廠*3	-

項目 \ 改變程度		不屬主次要改變	次要改變	主要改變
主成分	特殊考量	療效範圍狹窄之藥品	-	生體相等性試驗	生體相等性試驗
		列屬 BCS Class IV			
		列屬 BCS Class I及 Class III 並提供主成分具高溶解度證明，且非為療效濃度範圍狹窄者	-	溶離率曲線比對(同成品檢驗規格之溶離條件)	生體相等性試驗

*1. 變更百分率(%)係指該成分變更前後差之絕對值於變更前處方總量的百分率，變更前處方係指原查驗登記之處方。

*2. 批量變更係指相較於執行 pivotal bio-study 批次之批量的改變程度。

*3. 未涉及配方、製程(含原料來源、規格及製造設備)之改變者，執行溶離率曲線比對試驗時得採用同成品檢驗規格之溶離條件。

表二、控釋製劑：

項目 ＼ 改變程度		不屬主次要改變	次要改變	主要改變
應檢附資料		-	溶離率曲線比對*6	生體相等性試驗
•不影響釋放之賦形劑(Non-release controlling excipient)變更 *1				
填充劑(Filler)		≦5%	>5%且≦10%	>10%
崩散劑 (Disintegrant)	Starch	≦3%	>3%且≦6%	>6%
	Other	≦1%	>1%且≦2%	>2%
結合劑(Binder)		≦0.5%	>0.5%且≦1%	>1%
潤滑劑 (Lubricant)	Ca or Mg Stearate	≦0.25%	>0.25%且≦0.5%	>0.5%
	Other	≦1%	>1%且≦2%	>2%
滑動劑 (Glidant)	Talc	≦1%	>1%且≦2%	>2%
	Other	≦0.1%	>0.1%且≦0.2%	>0.2%
膜衣(Film Coat)		≦1%	>1%且≦2%	>2%
變更百分率總和		≦5%	>5%且≦10%	>10%
賦形劑		只去除或減少某一色素或矯味劑	改變技術等級或規格	新增或刪除
•影響釋放之賦形劑(Release controlling excipient)變更 *2				
變更百分率總和		≦5%	>5%且≦10%*3	>10%
賦形劑		-	改變技術等級*3或規格	新增或刪除
•批量(Batch Size)變更 *4		≦10	>10 倍	-
•製程機器(Manufacturing Equipment)變更		1.由非自動或非機械改用自動或機械 2.改用相同設計及相同原理之設備	改用不同設計及不同原理之設備	-

•製程(Manufacturing Process)變更	製程改變未超過確效範圍	1.已執行確效者，其製程改變超過確效範圍。 2. 其餘，視個案而定。	製程步驟改變 如：由濕式造粒法改由乾粉直接壓製
•製造場所(Manufacturing Site)變更	同一廠房同一生產區(生產線)	同一廠房不同生產區(生產線搬遷或變更)、廠房搬移等	新增/變更製造廠 *5

*1.不影響釋放之賦形劑(Non-release controlling excipient)變更百分率(%)，係指該成分變更前後差之絕對值於變更前處方總量的百分率，變更前處方係指原查驗登記之處方。

*2.影響釋放之賦形劑(Release controlling excipient)變更百分率(%)，係指該成分變更前後差之絕對值於變更前處方之影響釋放賦形劑總量的百分率，變更前處方係指原查驗登記之處方。

*3. 若主成分屬療效範圍狹窄之藥品，則屬主要改變。

*4. 批量變更係指相較於執行 pivotal bio-study 批次之批量的改變程度。

*5. 惟經中央衛生主管機關判定其改變不影響產品製造及品質時，得以溶離率曲線比對報告取代生體相等性試驗報告。

*6. 控釋製劑次要改變之溶離率曲線比對要求如下：

A. 延釋劑型(Extended release)-模擬胃腸道 pH 值或至少包含 3 種媒液(例如:水、0.1N HCl、pH 4.5 及 6.8 緩衝液)中之多點溶離率曲線比對試驗。

B. 遲釋劑型(Delayed release)-按檢驗規格溶離率條件，在酸性段(0.1N HCl)及緩衝液段(pH 4.5~7.5)分段執行之多點溶離率曲線比對試驗，並另增 2 個轉速(共 3 種轉速)進行測試。有關 3 種轉速之設定，若成品檢驗規格之溶離試驗裝置為網籃裝置(Basket Method)，可設定為每分鐘 50、100 與 150 轉速；若為攪拌槳裝置(Paddle Method)，可設定為每分鐘 50、75 與 100 轉速。

ICH-M9 guideline (BCS Biowaiver) was agreed among major regulatory agencies at the Singapore meeting in Nov.2019.

Question 2: ***Does your country has a plan to expand the application of "BCS based biowaiver approach" following to the ICH recommendation in the future?***

Please click "YES" or "NO",

YES

APAC

If Yes,

Please provide your opinion what your country can expand “BCS based biowaiver approach” based on the ICH-M9 guideline.

1	In Taiwan, the BCS-based biowaiver can refer to「Guideline for Generic drugs on Biopharmaceutical Classification System (BCS) -Based Biowaiver Application」which announced by TFDA in 9 Aug, 2016. Although there is a partial difference of the applicable criteria compared to ICH M9, it does not become a major issue. ICH-M9 guideline (BCS Biowaiver) will plan to be announced in the 2021 to comply with international standards.

Any other comments regarding the <u>future</u> requirements for (if any)

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