出國報告(出國類別：開會)

參加 ICH M9 工作組第 5 次會議出國報告

服務機關：衛生福利部食品藥物管理署
姓名職稱：潘香櫻簡任技正
派赴國家：荷蘭
出國期間：108 年 6 月 1 日~108 年 6 月 9 日
報告日期：108 年 8 月

摘要

BE 試驗已廣為各國所採行，用以驗證相同主成分但配方、製程不同的藥品，在安全與療效上的相當。對於某些藥品，進一步以體外溶離率曲線比對替代生體相等性試驗作為驗證安全與療效上相當的工具，正逐漸為全球主要藥政管理機構所接受，但各區域的認定標準仍有差異。國際醫藥法規協和會(International Council for Harmonization of Technical Requirements For Pharmaceuticals for Human Use, 簡稱 ICH) 於 2016 年 6 月成立 M9 工作組，撰寫以生物藥劑學分類系統(Biopharmaceutical Classification System, BCS)為基礎，免除生體相等性試驗的法規指引(Biopharmaceutical Classification System-based Biowaivers guideline, 簡稱 BCS-based biowaivers guideline 或 BCS biowaiver)，協和各區域的法規差異。繼 2016 年 11 月於日本 Osaka、2017 年 5 月於加拿大 Montreal、2017 年 11 月於瑞士 Geneva、2018 年 6 月於日本 Kobe 進行面對面會議，於去年公告 M9 指引草案後，在今年 6 月 3 日到 6 日於荷蘭阿姆斯特丹進行第 5 次面對面會議。

本次工作組會議分別就 M9 指引草案預告期間，各界給予之意見進行討論與修正，美國食品藥物管理局(FDA)報告溶離條件如裝置、轉速、溶媒量和錐形聚集之實驗結果；日本 MHLW/PMDA 報告以水為溶媒的調查結果，因未能舉證增加以水為溶媒即可降低非 BE 結果的風險，所以同意刪除”純水可能在某些區域作為溶離試驗額外要求執行的溶媒；然對於溶離時發生錐形聚集，轉速得以增加至 75rpm 這件事，日方代表持保留態度。

工作組本次會議的重要進度，包括完成 BCS biowaiver 適用範圍、溶解度以單次最高劑量(the highest single dose)計、溶解度測試之穩定性、不同鹽基主成分、固定劑量複方製劑、支持 BCS Ⅲ類藥品配方含量相似之預期限值、溶離相似性的計算方法等議題的討論；並修正 M9 指引草案。

ICH 對於指引制定分為 5 個步驟或階段。M9 工作組於 2019 年 4 月完成第 3 階段－公眾諮詢期。本次會議已議決大部分議題，少數未能獲得解決議題，報告起草人 Jan 打算在 9 月進行電話會議解決，預計 2019 年 11 月完成第 4 階段，並將經由電子方式來完成文件簽署。

全球有越來越多的藥政單位加入 ICH 成為法規成員或觀察員，成員與觀察員的義務有所不同，主要在於參與 ICH 相關會議與指引之制定及落實。食品藥物管理署(以下簡稱食藥署)於 2018 年 6 月成為 ICH 的法規成員後，更積極參與 ICH 相關會議與指引之制定，落實指引之執行。協助我國產業發展國際化，擴展我國參與 ICH 的效益。

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口服固體製劑一般需要經過崩散與溶離等過程，才能經由胃腸道吸收，進入體循環產生藥效。又藥品的組成(配方) 通常除具醫療效能作用的主成分(主要療效成分，或有效成分)外，還包括不具醫療效能作用的賦形劑。相同主成分於不同配方組合時，可藉由生體相等性試驗(bioequivalence, BE)的執行，比較兩種產品之主成分在人體的生體可用率參數，以確認口服藥品在人體吸收的量及快慢是否相當。

故 BE 試驗常在藥品研發過程，作為藥劑相等品(Pharmaceutical Equivalents)或藥劑替代品(Pharmaceutical Alternatives)的評估工具，作為是否具療效相等性(Therapeutic equivalence)的替代(surrogate) 驗證方法，優點是藉此即不需要再次執行大型臨床試驗。

BE 試驗已廣為各國採行，應用範圍廣泛，包括新藥早期研發到最後商品化階段，甚至上市後配方或製程的改變，學名藥上市也同樣是以 BE 試驗與原開發廠藥品比較。然而，BE 試驗畢竟是以人體為試驗對象，同一主成分重複在人體執行生體相等性試驗，衍生浪費資源與輕忽試驗倫理之爭議。如何在嚴謹的科學實證下，減少重複在人體執行不必要的試驗，向來是 ICH 關注的課題。

以體外測試作為體內 BE 試驗的替代評估統稱為生體試驗免除(biowaiver)。而以體外溶離率曲線比對試驗替代生體相等性試驗的應用，主要分為上市後變更(Scale-Up and Post-Approval Changes；SUPAC), 生物藥劑學分類系統(Biopharmaceutical Classification System, BCS)及體外體內關聯性(in vitro/in vivo correlations ;IVIVC)等三方面。其中以藥品的溶解度(Solubility)及穿透性(Permeability)建立的生物藥劑學分類系統免除生體相等性試驗(BCS biowaiver)機制最具發展性，BCS biowaiver 自西元 2000 年為美國 FDA 採納並發布指引以來，被視為新藥開發或產品線擴展(Line extension)的一種可靠的替代評估方式，近 20 年來逐漸被世界各國所採納。

BCS biowaiver 依據主要療效成分的生物藥劑學特性分類，某些類的藥品是可以體外溶離率曲線比對取代生體相等性試驗，做為藥物安全與療效性相當的評估。目前全球主要的藥政機構大多能接受此一理論，多數區域認為 BCS I 類(高溶解度及高穿透性)和 BCS III 類(高溶解度及低穿透性)的藥物可適用於 BCS 生體試驗免除，但各區域的認定標準仍有差異，且適用範圍也因區域有所不同。

所以，ICH 於 2016 年成立 M9 專家工作組，由歐盟代表 Dr. Jan Welink 為報告起草人，美國 FDA 代表 Dr. Paul Seo 任法規機構主席，統籌 BCS 分類如溶解度或穿透性的支持性資料、制定生體相等性試驗的免除條件如配方含量相似的預期限值、解決溶離率曲線比對試驗條件的爭議、協和當前各區域標準，制定一公認之法規指引為主要工作目標，期由體外資料的滿足而免除生體相等性試驗，進而減少在人體執行不必要的試驗。

貳、 過程

一、 行程及會議議程

日期	議程/活動	議題
6 月 3 日	議題討論	➢ 就 FDA 提交溶離試驗條件如裝置、轉速、溶媒量和錐形聚集之實驗結果進行討論。 ➢ PMDA 對以水為溶媒溶離不相似，其結果為生體不相等的調查報告。 ➢ 就下列爭議尋求共識 1.溶解度以最高單位含量或單次最高劑量計 2.溶解度測試的穩定性 3.不同鹽基的主成分可否適用 BCS biowaiver 4.固定劑量複方製劑 5.賦形劑差異的容許範圍 6.溶離試驗轉速問題 7.相似值的計算
6 月 4 日	議題討論與指引草案修正	➢ 就公開諮詢期，被提出的議題進行討論或回應。 ➢ 就生產線擴展，是否僅限口服固體劑型、藥劑替代品能否適用等議題進行討論或回應。
6 月 5 日	議題討論、指引草案修正	➢ 修改案例 1 及 2 的標註。 ➢ BCS III 類藥品之配方差異容許範圍。 ➢ 決策樹及指引草案修改。
6 月 6 日	指引草案修正 大會報告內容指引草案修正 提交大會報告	➢ 盤點指引草案修改達成共識。 ➢ 溶離轉速新文獻。 ➢ 向大會報告工作組會議進度及未來規劃。

二、 會議概況

這次工作組計由 17 個成員或觀察員派出之產官研專家共 29 人與會，名單詳如附錄貳。議程主要就 2018 年 8 月以來於公眾諮詢期蒐集到的意見，進行溝通、討論和議決，大部分議題取得共識，並擬設計 Q&A 以進一步釐清。對於非常棘手之議題曾召開兩次法規機構代表會議(regulatory meeting)，惟仍有 1 議題在本次會議未能獲得解決，報告起草人 Jan 打算在 9 月進行電話會議來解決，最後將經由電子簽署方式來完成第 3 階段與第 4 階段的文件。也就是說，以藥品生物藥劑學分類系統免除生體相等性試驗(BCS Biowaiver)的指引，將在未來幾個月內即可完成，M9 工作組即將解散，下次新加坡的 ICH 會議不再相聚，這使得大家格外珍惜本次聚會。

三、 研習重點摘要

(一) 美國食品藥物管理局(FDA)展示溶離條件和錐形聚集之實驗結果

1. 美國 FDA 以 Fluconazole 50、200 毫克錠劑為樣品，探討溶離條件如裝置、轉速、溶媒量和錐形聚集的影響;以作為槳式裝置(paddle apparatus)於 50rpm 觀察到高變性或錐形聚集時，推薦使用 100rpm 網籃式裝置(basket apparatus)的支持性論據。 另外，研究使用槳式裝置加上沉卡器(sinker)能否克服錐形聚集的問題。
2. 試驗條件如下:
   溶媒量：500ml 及 900 ml。
   溶離裝置：槳式、槳式加沉卡器及網籃式
   轉速：50 轉/分鐘(rpm)、 75 rpm 及 100 rpm
3. 結果：
   轉速 50 rpm 溶離較 75rpm、100rpm 慢，且標準差(percent standard deviation；%SD)較大。
   槳式裝置溶離結果的標準差較網籃式、槳式加沉卡器小。
4. 美國 FDA 以 Pregabalin(BCS I)及 Ranitidine(BCS Ⅲ)為例，研究沉卡器對溶離結果的影響，結果在 Ranitidine(BCS Ⅲ)的 150mg 及 300mg 的實驗中都看到槳式裝置加上沉卡器皆較無沉卡器的溶離結果佳，但對 Pregabalin(BCS I)，槳式裝置有無加上沉卡器則無差別。

(二) 日本 MHLW/PMDA 以水為溶媒的調查報告

1. 前次會議 PMDA / MHLW 基於風險評估，主張溶離曲線比對試驗中的溶媒應包括純水或低緩衝之媒液。經提管委會(MC)會議討論，於草案中加入除了藥典規定的 3 個 pH 溶媒外，純水可能在某些區域作為溶離試驗額外要求執行的溶媒，附加條件是日本必須證明以水為溶媒執行溶離必要性的調查報告。條件設計如下，

(1) 主成分列屬 BCS class Ⅰ或 Ⅲ，

(2) 測試藥品與對照藥品的溶離曲線比對，在 pH1.2, 4.5, 6.8 為溶媒之結果相似，只在純水為溶媒下之溶離結果不相似。

(3) 上述條件下，其體內試驗結果為不 BE 者，即可作為支持證據。

2. 在 MHLW/PMDA 與 JPMA 及 JGA 的合作調查下，主成分列屬 BCS class Ⅰ或Ⅲ，溶離曲線比對只在純水為溶媒下不相似者共有 12 件，但此 12 件的 BE 試驗皆通過。

3. 結論：無法舉證增加以水為溶媒即可降低非 BE 結果的風險，所以 MHLW/PMDA 同意刪除“純水可能在某些區域作為溶離試驗額外要求執行的溶媒”。

(三) 溶解度以單次最高劑量(the highest therapeutic single dose)計

1. 草案預告係以單次最高治療劑量(the highest single dose)在 250 毫升水溶液完全溶解作為判斷依據，並敘明萬一單次最高治療劑量的溶解結果非屬高溶解，但最高單位含量(the highest strength)的溶解結果符合高溶解規定時，需另提供資料以茲判定，例如線性藥動資料證明可涵蓋單次最高治療劑量範圍。

2. 草案預告後，美國方面的廠商反應以“最高單次治療劑量”為溶解度判定標準，與目前如何進行生體相等性試驗的投與劑量原則不一致，且以最高單位含量作為標準，才是對配方改變較靈敏的測試方法，故建議以最高單位含量的溶解度作為標準。

3. 另也有人反應以線性藥動資料確認沒有溶解度限制的假設，是不正確的，並建議以最高單位含量為判斷依據，不過此點於前幾次會議中已充分討論，最後仍以單次最高治療劑量在 250 毫升水溶液完全溶解作為溶解度判斷依據。

(四) 溶解度測試

1. 有人提出對於高度可溶的藥物，僅檢查在 250 毫升水溶液下的溶解度是不夠的，測試平衡下的溶解度是有必要的，然而平衡需要時間，甚至高達 24 小時，時間長會因測試藥物的穩定性、降解和 pH 值變化等問題而增加風險。經討論後，平衡溶液的測試時間，可考慮與臨床相關性予以適當設計。

2. 草案預告後，美國方面的廠商反應不了解在 pKa 進行溶解度測試的必要，特別是在 pKa 處，離子化和非離子化藥物的濃度相等，並不會觀察到最小溶解度。原草案提 pKa 是為了確認溶解度，既然溶解度是在模擬腸胃道 pH 值下進行，經討論最後刪除 pKa 的溶解度測試，直接敘明以 pH1.2-6.8 範圍內的最低溶解度作為該原料藥成分的溶解度屬性判定。

3. 草案敘及在藥物不穩定，且發生高於 10%的以上降解的情況下，因不能充分確定其溶解度評估結果的正確性，故該成分不能進行分類，也就沒

有 BCS biowaiver 的適用。對此各方意見也很多，例如為什麼是 10%，論證後確認維持 10%降解的臨界值。

(五) BCS 生體相等性試驗免除的適用範圍

1. 草案規定測試藥品與對照藥品必須是同成分的藥劑相等品，方可適用 BCS biowaiver；如果屬不同鹽、酯、異構物的主成分即不適用。
2. 本次徵求意見中，有多方表示如果有合理科學資料支持，對於 BCS 1 類藥品應可開放不同鹽基之有效成分亦適用生體相等性試驗免除。尤其歐洲業界代表如 EFPIA, Medicines for Europe，主張新藥研發過程基於某些原因（例如穩定性），而改變鹽基。雖然相對離子(counter ion)的確會影響產物的溶解，但如果不同的鹽基在整個 pH 範圍內以相似的速率溶解，則藥物的吸收將是相同的，且歐盟指引已開放此點。
3. M9 工作組最後同意放寬同屬 BCS class I 主成分的不同鹽基得以適用。主因兩者皆屬速溶的 class I，鹽基改變並不影響其溶解後主成分的吸收。

(六) 固定劑量複方製劑(Fixed dose combinations)的適用範圍

1. 草案規定複方製劑產品中需要<u>所有</u>有效成分皆符合 BCS class I 或 III的標準時，方可適用生體相等性試驗免除。有人認為**如**此規定過於保守，建議修改為“在固定劑量複方製劑，符合指引第 2 節和第 3 節中定義的有效成分即有取得基於 BCS 的生體相等性試驗免除資格。
2. 如果固定劑量複方製劑產品中，只有其中一種有效成分是 BCS I 或 III 類，即使證明有效成分間沒有交互作用，然複方製劑對體內表現的影響可能性也無法得到證實。所以固定劑量複方製劑產品，必須<u>所有</u>有效成分皆符合 BCS I 或 III的標準，才有取得生體相等性試驗免除資格。
3. 歐洲學名藥協會更明白指出如果由屬 BCS class I 或 III成分，與另屬II或IV成分所組成之固定劑量複方製劑，得否就 I 或 III成分執行溶離，就II或IV成分執行 BE 即可，以減少執行 BE 的採血點與人數。
4. 答案是不行，此點係參照美國 FDA 規定，未來將於 Q&A 中敘明。

(七) 除 Caco2 外，能否接受其他細胞株資料證明藥品的高穿透性

草案納入以源自人類結腸腺癌細胞培養的 Caco-2 單層上皮細胞株作為的藥品穿透性測定的工具，以 Caco-2 細胞株的測定結果來支持藥品屬 BCS 的高穿透性，惟此僅限於被動運輸的藥物才得以適用。公開徵詢意見中，多方建議增加其他細胞株作為測試藥品穿透性的工具，慮及目前大部分區域對於以體外方式執行穿透性的審查經驗仍無，僅美國 FDA 有審查經驗，故決定維持原草案僅接受 Caco2 細胞株，在 Q&A 中解釋，視未來有較多案例再擴充發展。

(八) BCS 生體試驗免除能否以藥劑替代品作為對照品

1. 草案中原規定基於 BCS 免除生體試驗的條件，
   (1) 藥品有效成分須符合溶解度和穿透性的標準（BCS I 類和 III 類），
   (2) 具有全身性作用的速放口服劑型之藥品，
   (3) 測試藥品與對照藥品必須為藥劑相等品。
   公開徵求意見中對上述(3)之規定，認為將會顯著降低 M9 指引應用於新藥開發的效用，PhRMA 代表指出新藥研發過程，常先以膠囊劑型作為先導物質進行臨床試驗，直到研發晚期才發展為更合適的劑型(如錠劑)，且劑型轉換對生體效能(bio performance)的影響小，因此要求只要符合上述其他條件，即有資格適用 BCS-生體試驗免除，要求工作組接受以藥劑替代品作為對照品。
2. 為討論此議題，產業界代表被請離場，召開法規機構代表會議 (regulatory meeting)。從賦形劑差異來看，膠囊劑與錠劑要落入容許範圍的機率幾乎很小，另外顆粒劑型(Granules)亦是如此。最終法規代表們仍決定維持須與對照品同劑型(same dosage form) 及同單位含量(strength)，方符合 BCS biowaiver 規定，列入 Q&A 中說明。

(九) 不用配水的口溶產品是否適用 BCS 生體試驗免除

1. 草案中原規定藥品如具有口腔或舌下吸收即不適用 BCS 生體試驗免除申請。並規定口溶產品只有在沒有口腔或舌下吸收，且仿單標示僅用水服用時，才能適用 BCS 生體試驗免除申請。
2. 對此，有人提出許多口溶產品可以在沒有配水的情況下服用，難道就不符合申請條件了嗎？如果測試和對照藥品是以相同方式給藥，沒有理由將不用配水的口溶產品排除在適用 BCS 生體試驗免除之外。
3. 工作組斟酌後，為使文意更明確修改如下，藥品如具有口腔或舌下吸收即不適用 BCS 生體試驗免除申請。口溶產品僅在配水服用時才適用 BCS 生體試驗免除申請。如果產品打算包括以不配水的方式服用時，則應進行不配水的生體相等性試驗。也就是**不用配水服用的口溶產品不適用 BCS** 生體試驗免除，理由將列入 Q&A 中說明。

(十) 支持 BCS III 類藥品配方含量相似之預期限值

1. 含 BCS III 類藥品，測試藥品與對照藥品之賦形劑差異容許範圍，是參照美國上市後變更(SUPAC)規定而制定，僅比較核心含量差異，不包括膜衣或膠囊殼。通常上市後變更係已知變更前配方，如此就不難計算變更前後的差異。但 BCS III 類的學名藥新申請案，是不知原開發廠配方，可能是以逆向工程(reverse engineer)的方法去推估可能配方，部分賦形劑例如香料、矯味劑可能未揭示(disclosure)組成，且有些如滑動劑

(Glidant)甚至必須小於 0.2%，要符合配方差異容許範圍在±10%以內，是有一定難度。公開徵求意見中，一般認為對於 BCS-III 類藥品配方差異容許的要求過於嚴謹。另有人建議比照目前歐洲對這些問題的要求，即可確保 BCS-III 類學名藥與對照藥品的配方相似性，並質疑表 1 的科學合理性。

2. 有關上市後變更(SUPAC)設定值的由來，經洽相關熟悉此一部分人士，表示係以風險最小評估而定，討論後仍維持此表，並修正內文，加註製劑中小量的香料、色素或矯味劑含量差異是可被允許。且提醒申請人應注意，在表 1 應用上是有些限制，例如對照藥品的膜衣層含量，並註明此表係提供申請人作為一目標指引，若偏離表 1 之容許範圍，需有適當的理由或依據，列入 Q&A 中說明。
3. 為避免誤解是表內各賦形劑的正負變更加減總和，取消表 1 各賦形劑含量數值以±標示；並修改表 1 名稱，將原來 BCS Ⅲ類藥品之配方差異容許範圍(Allowable differences in excipients for drug products containing BCS Class Ⅲ drugs)修改為支持 BCS Ⅲ類藥品配方含量相似之預期限值(Expected criteria to demonstrate quantitative similarity for products containing BCS Class Ⅲ drugs.)。
4. 日本 MHLW/PMDA 提議增加 FDC 的賦形劑計算案例，經 M9 工作組討論後將增列於 Q&A 中。

(十一) 溶離試驗的條件

1. 批次及批量選擇，對草案中表述代表性的 1 批，雖有少許質疑意見，但整體上也沒有更好的建議，故仍維持原 1 批具代表性之測試藥品與對照藥品進行溶離比對，批量應至少 1/10 的生產規模或 100,000 個單位。
2. 溶媒體積：900 ml 或更少（建議使用為 QC 溶離測試時所用的體積）。
   溶媒溫度：37±1˚C (藥典溶離訂定的溫度為 37±0.5˚C，這裡雖經 TFDA 與 TGA 及 HELM AG 反映，報告起草人仍決定維持 37±1˚C)。
3. 攪拌速率：槳式裝置→50 轉/分鐘 或網籃式裝置→100 轉/分鐘
   當槳式裝置以 50rpm 觀察到高可變性或錐形聚集時，推薦使用網籃式裝置 100rpm。前述方法仍未能克服錐形聚集，美國 FDA 建議槳式裝置加上使用沉卡器(sinker)來克服諸如錐形聚集之類的問題，日方與歐盟皆接受此點建議，但槳式裝置使用沉卡器或凸底溶離杯(peak vessel)必須檢附資料與理由，列入 Q&A 中說明。
4. 另外，如有好的立論或理由，產界代表建議槳式裝置可增加轉速至 75rpm，此點日本 PMDA 表示不贊同，認為如此辨別相似性有降低之可能，為此召開第 2 次法規機構代表會議，日方表示將攜回此議題詢問專家後回覆，然當晚即寄出一篇 John Golden 等人於 2015 年發表的文獻，佐證攪拌速率不應增加至 75rpm，為未來投下一個變數。

5. 草案載明溶離樣品在收集過程中應過濾，其目的是為去除樣品溶液中未溶解之藥物或賦形劑，減少實驗結果之誤差。但有意見認為應過濾樣品的說法僅與某些測試儀器相關，其他方法亦可達相同效果。所以內文修正當使用溶離試驗光纖（fiber optic）原位偵測系統測量溶解的藥物含量時，不需要過濾樣品。

(十二) 相似性的計算

1. 多方意見表達除了傳統方法計算 f2 值作為溶離相似性評估的結果外，建議有些情況如溶離早期採樣時間點有較高變異性時，可納入其他統計替代方法，例如拔靴法(boot strapping)、雙單尾檢定(Two one-sided tests procedure, TOST)等，作為溶離相似性評估。
2. 草案採用 f2 值評估溶離相似性，原係從區域協和角度而著墨，經本次就風險條件討論後，仍維持採 f2，不納入其他統計替代方法。
3. 對於 f2 值的計算，在某些情況下，因採計不同採樣時間點可能導致不同的 f2 值，即使採樣時間點皆符合指引的規範和條件。 例如，可能 10,20,30min 的時間點給出 f2 <50，而時間點 8,20,30min 給出 f2> 50。這種情況屬於審查議題，將列入 Q&A 中說明。

(十三) 多種單位含量(multiple strength)產品

1. 草案規定具有一種以上單位含量(strength)的產品，須每一單位含量逐一比對適用 BCS 生體相等性試驗免除，即測試和對照藥品須進行每一單位含量之溶離曲線比對。
2. 有多方意見反應此規定過於保守，如產品在多單位含量上具線性 PK 時，建議允許僅最高單位含量進行 BCS 的生體相等性試驗免除比較，即可沿用於其他單位含量(strength)，或者可以接受涵括(bracket)法（測試最高和最低單位含量），無須每一單位含量逐一進行比對。
3. 經討論，工作組認為原 BCS 即以溶離曲線比對替代生體相等性試驗，若再以最高(單位)含量的溶離曲線比對免除其他(單位)含量的溶離曲線比對，形成 waiver 的 waiver，如此過於鬆散，有增加風險之虞，故不同意有此免除，仍維持每一單位含量的測試和對照藥品須逐一進行溶離曲線比對。

參、 心得及建議

一、 明確的議事規則和程序

(一) ICH 對於指引制定有 5 個步驟流程，對於新加入的專家一定請他們先上課熟悉議事規則和流程。M9 工作組的這幾次會議，報告起草人(rapporteur)通常在會議開始前先與專家們確認本次會議擬進行的議題與進度，並於最後一天說明下一步規劃，然後率領工作組專家們向大會報告，取得認可。

(二) M9 工作組自去 (2018) 年 6 月於日本神戶完成第 2 階段草案簽署，事隔一年再召開會議，主要是就第 3 階段期間，各區域收到的意見進行討論和決議。一旦工作組彙整指引草案與諮詢期間收到的意見，完成修訂版，並由 ICH 法規監管機構會員(regulatory member)的議題主導者(topic leader)簽署後即為第 3 階段最終文件。第 4 階段由管委會(MC)下之法規監管機構會員代表簽署，即完成最終指引的制定。現在可經由電子簽署，所以第 3 階段與第 4 階段，不會相距太久的時間。

(三) 接著就會是第 5 階段發佈施行，ICH 指引的採用是根據適用的國家/地方/地區規則實施的，所有 ICH 指引的實施階段也取決於成員或觀察員何時加入 ICH。

二、 英雄所見略同與不同

(一) M9 草案公開徵求意見期間，共收到來自 33 個單位的 592 則意見，其中許多意見雖來自不同單位，但所提內容相同，經報告起草人事先彙整後，屬重複意見者即略過，討論起來比較流暢。其中台灣貢獻了 9 則意見，意見不多但品質高，例如 BCS 免除生體試驗的條件，草案原必須為藥劑相等品，但台灣建議與對照品同劑型(same dosage form) 及同單位含量(strength)即備受讚賞與接受。

(二) 有些跨國公司會由各區域子公司透過當地法規監管機構提出相同意見，這樣糾結起來，就會顯得該議題很多人提，很重要不容忽視。但這樣的操作方式，對於有經驗的報告起草人顯然起不了作用。不過，報告起草人在面對眾多意見時，的確會視提案單位而決定討論深度，有些單位就會在其提案內容上加註緊要的(critical)、重要的(major)等標示，期能引發注意而進行討論。

三、 M9 工作組未來規劃

(一) M9 專家工作組(EWG)在制定指引與回應各界意見的同時，即發現制定 Q&A 的必要性，但依據 ICH 章程，Q&A 是未來另外成立的執行工作組(IWG)的任務之一，而 EWG 和 IWG 兩者的成員未必會相同，PhRMA 代表以 Q11 經驗，說明 IWG 在接手後，花了 2~3 年理解 EWG 的邏輯，過於曠日廢時。所以報告起草人期

待我們可以在完成指引的同時，也完成 Q&A，讓接手的 IWG 比較好入手，而在今(2019)年 7 月底，工作組已開始著手 Q&A。

(二) 對於溶離時發生錐形聚集，槳式裝置攪拌速率增加至 75rpm，日方代表持保留態度，及 John Golden 等人於 2015 年發表的文獻所引發的爭議，預計於 9 月以電話會議討論。

(三) 當 M9 向大會報告將於完成 BCS biowaiver 指引並同時完成 Q&A，果然大會質疑時間的容許性，報告起草人回答會藉由電話會議加強溝通聯繫，且確認 11 月在新加坡的會議，M9 將不進行面對面會議。

四、 台灣學者的貢獻

(一) 含 BCS III 類藥品，必須配方相似方得以適用 BCS biowaiver，配方相似所定測試藥品與對照藥品之賦形劑差異容許範圍，是參照美國上市後變更(SUPAC)規定而來，當有人詢問科學依據時，不免追溯 SUPAC 倡議始末，以作為說明。SUPAC 約是 1990 年左右由馬里蘭大學、FDA 和製藥產業共同合作收集批量放大，配方和其他製造改變對產品品質影響的數據，而研擬出之相關指引，目的係為簡化藥品核准後變更的審查，確保變更前後的安全性和有效性，同時降低產業的監管負擔，其中重要關鍵人物之一即為我國的陳桂恆博士。

(二) 關於以 F2 計算溶離相似性,有兩位出生台灣的學者在會中被提及－周賢忠博士與劉仁沛教授，以前僅知兩位學者在生物統計上有重要貢獻，沒想到在這麼多國家的專家會議中也有代表提到他們的觀點，不禁與有榮焉。

五、 ICH 再擴大與提升台灣產業的參與

(一)國際醫藥法規協和會(ICH) 於 2015 年 10 月 23 日根據瑞士法律改制為非營利性法人後，今年(2019) 6 月 1 日至 6 日在荷蘭阿姆斯特丹舉行的會議，宣稱是 ICH 迄今規模最大一次的會議，聚集來自 ICH 的 16 個成員(國)和 28 個觀察員(國)約 500 名的代表與會。本次大會批准了 4 個新的法規管理機構觀察員(國)，分別是阿根廷 ANMAT、以色列 CPED、約旦 JFDA、和沙特阿拉伯 SFDA，使得 ICH 觀察員(國)總數達到 32 個。這次阿姆斯特丹的會議特別彰顯 ICH 在全球的正向發展。

(二)ICH 係為產業與法規機構的法規制定溝通平台，參與 ICH 會議不僅是法規機構派代表與會，重要的是產業也需有足夠的聲音與貢獻。目前除了 ICH 的創始產業成員，包括 EFPIA、JPMA 及 PhRMA 外，產業成員尚有 BIO、IGBA 及 WSMI 可派代表與會。

(三)在 M9 工作組，日本 JPMA 每次都派了 4~5 名代表出席，本次 IGBA 除歐洲代表 Dr. Susana Almeida 外，並推派日本 Sawai 製藥 Dr. Kazuki Matsui 出席，另外韓國 MSD 公司 Esther Bang 則代表 IFPMA(觀察員)出席，亞洲的產業代表就這 6 位，相對美歐產業，亞洲產業聲音小且代表性

不夠。

(四) 藥品法規要求日趨全球化，須知法規將導引產業的發展方向。台灣原本藥業經濟規模有限，產業界更應深謀遠慮，不僅立足台灣，更需望眼全世界，積極參與國際會議，擴展視野並尋找機會。台灣產業可與國際產業組織合作，如 IGBA 秘書長 Dr. Susana Almeida 即表示台灣產業如有意願，願意協助台灣產業爭取代表國際學名藥及生物相似藥協會(IGBA)出席 ICH 工作組的機會。

六、 字字珠璣、獲益良多

(一) ICH M9 工作組邀請各區域成員派出與此專業相關之代表，集思廣益撰寫指引內容，如何藉由文字將技術要求表達得很精準，是門大學問，更何況英語不是所有參與人的母語。在決定技術層面的要求後，大家分工撰寫內容，彙整後再討論，討論後又再修改，仔細到用字遣詞，字字斟酌。如此往返數回，一方面讓專家們孰悉指引內容，一方面也再次協和不同的聲音。

(二) 如此繁複的過程，是需要很大的耐心與毅力，工作組內有很多資深專家，年紀雖大卻不辭辛勞熱情參與，表明是奉獻自己的專業給予社會，從與他們的交談和知識交換中，學習到很多，再次感謝食藥署給我這個機會，代表 TFDA 參與 ICH M9 工作組，個人獲益良多。

附錄

壹、 工作規劃與期程

Action	**date**	**status**
Adoption of the topic by Approval of ICH Assembly	June 2016	完成
Agreement of Concept Paper and Business Plan by Informal WG	Aug. 2016	完成
Adoption of Concept Paper and Business Plan by MC	Sept. 2016	完成
First EWG meeting (Osaka, Japan)	Nov. 2016	完成
TC; update of progress	Feb. 2017	完成
TC; update of progress and preparation second EWG meeting	March/April 2017	完成
Second EWG meeting (Montreal, Canada)	May 2017	完成.
TC (update progress; aiming to finalise draft guidance during the third EWG meeting)		完成
Third EWG meeting (Switzerland)	Nov. 2017	完成
Adoption of Step 2 a/b Document	1 - 2Q 2018	完成
Adoption of Step 4 Document	Nov. 2019	計畫中

貳、 與會代表清單 (Delegates) 2019 年6月

單位/國家	代表
ANVISA, Brazil	Mr. Eduardo Agostinho Freitas
CFDA, China	Ms. Ning Zhang
EC, Europe	Dr. Jan Welink， Dr. Henrike Potthast
EFPIA	Dr. Horst-Dieter Friedel， Dr. Talia Flanagan
FDA, US	Dr. Paul Seo， Dr. Mehul Mehta， Dr. Ethan Stier
Health Canada, Canada	Dr. Shereeni Veerasingham
IGBA	Dr. Susana Almeida Dr. Kazuki Matsui
JPMA	Mr. Yutaka Takahashi， Dr. Ryuji Kubota， Mr. Kazuhiro Okochi， Dr. Katsuhiko Yamamoto， Mr. Tsuyoshi Kobayashi
MFDS, Republic of Korea	Ms. Juhyun Baek
MHLW/PMDA, Japan	Dr. Hideaki Kuribayashi Dr. Ryosuke Kuribayashi Dr. Hiroyuki Yoshida
PhRMA	Mr. Roger Nosal Mr. Sebastian Haertter
Swissmedic, Switzerland	Dr. Arno Nolting
WSMI	Mr. Bruno Paillard
IFPMA	Ms. Esther Bang
WHO	Dr. John Gordon
HSA, Singapore	Dr. Clare Rodrigues
TFDA, Chinese Taipei	Ms. Shianging (Shirley) Pan

參、　活動照片


YANG WANG
NMPA, CHINA
PAN SOON KIM
MFDS, REPUBLIC OF KOREA
YOUNG-OK KIM
MFDS, REPUBLIC OF KOREA

INTRODUCTION

1.1. Background and Objective

Two drug products containing the same drug substance(s) are considered bioequivalent if their bioavailabilities (rate and extent of drug absorption) after administration in the same molar dose lie within acceptable predefined limits. These limits are set to ensure comparable *in vivo* performance, i.e., similarity in terms of safety and efficacy. In *in vivo* bioequivalence studies, the pivotal pharmacokinetic parameters AUC (the area under the concentration time curve), and C_{max} (the maximum concentration), are generally used to assess the rate and extent of drug absorption.

The BCS (Biopharmaceutics Classification System)-based biowaiver approach is intended to reduce the need for *in vivo* bioequivalence studies i.e., it can provide a surrogate for *in vivo* bioequivalence. *In vivo* bioequivalence studies may be exempted if an assumption of equivalence in *in vivo* performance can be justified by satisfactory *in vitro* data. The BCS is a scientific approach based on the aqueous solubility and intestinal permeability characteristics of the drug substance(s). The BCS categorizes drug substances into one of four BCS classes as follows:

Class I: high solubility, high permeability

Class II: low solubility, high permeability

Class III: high solubility, low permeability

Class IV: low solubility, low permeability

This guidance provides recommendations to support the biopharmaceutics classification of drug substances and the BCS-based biowaiver of bioequivalence studies for drug products. The BCS-based biowaiver principles may be applied for bioequivalence purposes not explicitly specified in the guideline, provided they can be supported by a thorough scientific rationale.

1.2 Scope

BCS-based biowaivers may be used to substantiate *in vivo* bioequivalence. Examples include comparison between products used during clinical development through commercialization, post-approval changes, and applications for generic drug products in accordance with regional regulations.

The BCS-based biowaiver is only applicable to immediate release, solid orally administered dosage forms or suspensions designed to deliver drug to the systemic circulation. Drug products having a narrow therapeutic index are excluded from consideration for a BCS-based biowaiver in this guidance. Fixed-dose combination (FDC) products are eligible for a BCS-based biowaiver when all drug substances contained in the combination drug product meet the criteria as defined in sections 2 and 3 of this guidance.

2. BIOPHARMACEUTICS CLASSIFICATION OF THE DRUG SUBSTANCE

BCS-based biowaivers are applicable to drug products where the drug substance(s) exhibit high solubility and, either high permeability (BCS Class I) or low permeability (BCS Class III).

A biowaiver is applicable when the drug substance(s) in test and reference products are identical. A biowaiver may also be applicable if test and reference contain different salts provided that both belong to BCS Class I (high solubility and high permeability). A biowaiver is not applicable when the test product contains a different ester, ether, isomer, mixture of isomers, complex or derivative of a drug substance from that of the reference product, since these differences may lead to different bioavailabilities not deducible by means of experiments used in the BCS-based biowaiver concept. Pro-drugs may be considered for a BCS-based biowaiver when absorbed as the pro-drug.

2.1. Solubility

A drug substance is classified as highly soluble if the highest single therapeutic dose is completely soluble in 250 ml or less of aqueous media over the pH range of 1.2 – 6.8 at 37 ± 1°C. In cases where the highest single therapeutic dose does not meet this criterion but the highest strength of the reference product is soluble under the aforementioned conditions, additional data should be submitted to justify the BCS-based biowaiver approach.

The applicant is expected to establish experimentally the solubility of the drug substance over the pH range of 1.2 – 6.8 at 37 ± 1ºC. At least three pHs within this range, including buffers at pH 1.2, 4.5 and 6.8, should be evaluated. In addition, solubility at the pH of lowest solubility of the drug substance should be evaluated if it is within the specified pH range. These experiments should demonstrate that solubility is maintained over relevant timeframes to accommodate the expected duration of absorption.

Solubility should be evaluated by a method appropriate to the properties of the drug substance.

Equilibrium solubility experiments may be performed, using a shake-flask technique or an alternative method, if justified. Small volumes of solubility media may be employed if the available experimental apparatus will permit it. The pH for each test solution should be measured after the addition of the drug substance and at the end of the equilibrium solubility study to ensure the solubility measurement is conducted under the specified pH. The pH should be adjusted if necessary. The experiment should be conducted over a suitable timeframe to reach equilibrium.

Alternatively, solubility experiments where the highest therapeutic single dose is examined in a 250 mL volume, or a proportionally smaller amount examined in a proportionally smaller volume of buffer, can be considered.

The lowest measured solubility over the pH range of 1.2 – 6.8 will be used to classify the drug substance.

A minimum of three replicate determinations at each solubility condition/pH is necessary to demonstrate solubility using a suitably validated method, with appropriate compendial media employed.

In addition, adequate stability of the drug substance in the solubility media should be demonstrated In cases where the drug substance is not stable with >10% degradation over the extent of the solubility assessment, solubility cannot be adequately determined and thus the drug substance cannot be classified. In addition to experimental data, literature data may be provided to substantiate and support solubility determinations, keeping in mind that peer reviewed articles may not contain the necessary details of the testing to make a judgement regarding the quality of the studies.

2.2. Permeability

The assessment of permeability should preferentially be based on the extent of absorption derived from human pharmacokinetic studies, e.g., absolute bioavailability or mass balance.

High permeability can be concluded when the absolute bioavailability is ≥ 85%. High permeability can also be concluded if ≥ 85% of the administered dose is recovered in urine as unchanged (parent drug), or as the sum of parent drug, Phase 1 oxidative and Phase 2 conjugative metabolites. Regarding metabolites in feces only oxidative and conjugative metabolites can be considered. Metabolites produced through reduction or hydrolysis should not be included, unless it can be demonstrated that they are not produced prior to absorption, e.g. by microbial action within the gastrointestinal tract. Unchanged drug in feces cannot be

counted toward the extent of absorption, unless appropriate data supports that the amount of parent drug in feces to be accounted for absorbed drug material is from biliary excretion, intestinal secretion or originates from an unstable metabolite, e.g., glucuronide, sulphate, N-oxide that has been converted back to the parent by the action of microbial organisms.

Human *in vivo* data derived from published literature (for example, product knowledge and previously published bioavailability studies) may be acceptable, keeping in mind that peer reviewed articles may not contain the necessary details of the testing to make a judgement regarding the quality of the results.

Permeability can be also assessed by validated and standardized *in vitro* methods using Caco-2 cells (see Annex I). The results from Caco-2 permeability assays should be discussed in the context of available data on human pharmacokinetics. If high permeability is inferred by means of an *in vitro* cell system, permeability independent of active transport should be proven as outlined in Annex I, “Assay Considerations”.

If high permeability is not demonstrated, the drug substance is considered to have low permeability for BCS classification purposes.

Instability in the Gastrointestinal Tract

If mass balance studies are used to demonstrate high permeability, additional data to document the drug’s stability in the gastrointestinal tract should be provided, unless ≥ 85% of the dose is recovered as unchanged drug in urine. Demonstration of stability in the gastrointestinal tract is required if *in vitro* Caco-2 studies are used to support high permeability. Stability in the gastrointestinal tract may be documented using compendial or simulated gastric and intestinal fluids. Other relevant methods may be used with suitable justification. Drug solutions should be incubated at 37ºC for a period that is representative of the in vivo contact of the drug substance with these fluids, i.e., one hour in gastric fluid and three hours in intestinal fluid. Drug concentrations should then be determined using a suitably validated method. Significant degradation (>10 percent) of a drug precludes BCS high permeability classification.

3. SUPPORT OF THE ELIGIBILITY OF A DRUG PRODUCT FOR A BCS-BASED BIOWAIVER

A drug product is eligible for a BCS-based biowaiver provided that the drug substance(s) satisfy the criteria regarding solubility and permeability (BCS Class I and III), the drug product is an immediate-release oral dosage form with systemic action, and the drug product

is the same dosage form and strength as the reference product. In cases where the highest single therapeutic dose does not meet the high solubility criterion but the highest strength of the reference product is soluble under the required conditions, BCS-based biowaivers can be supported based on demonstration of dose proportional pharmacokinetics (i.e. AUC and C_{max}) over a dose range that includes the highest single therapeutic dose.

Drug products with buccal or sublingual absorption are not eligible for a BCS-based biowaiver application. Furthermore, the BCS-based biowaiver approach is applicable only when the mode of administration includes water. If administration without water is also intended (e.g. orodispersible products), a bioequivalence study without water should be conducted.

In order for a drug product to qualify for a BCS-based biowaiver, criteria with respect to the composition (excipients) and *in vitro* dissolution performance of the drug product should be satisfied. The drug product acceptance criteria are described in sections 3.1 and 3.2 below.

3.1. Excipients

Ideally, the composition of the test product should mimic that of the reference product. However, where excipient differences exist, they should be assessed for their potential to affect in vivo absorption. This should include consideration of the drug substance properties as well as excipient effects. To be eligible for a BCS-based biowaiver, the applicant should justify why the proposed excipient differences will not affect the absorption profile of the drug substance under consideration, i.e., rate and extent of absorption, using a mechanistic and risk-based approach. The decision tree for performing such an assessment is outlined in Figures 1 and 2 in Annex II.

The possible effects of excipients on aspects of *in vivo* absorption such as solubility, gastrointestinal motility, transit time and intestinal permeability including transporter mechanisms, should be considered. Excipients that may affect absorption include sugar-alcohols, e.g., mannitol, sorbitol, and surfactants, e.g., sodium lauryl sulfate. The risk that a given excipient will affect the absorption of a drug substance should be assessed mechanistically by considering:

- the amount of excipient used,
- the mechanism by which the excipient may affect absorption,
- absorption properties (rate, extent and mechanism of absorption) of the drug substance.

The amount of excipients that may affect absorption in the test and reference formulations should be addressed during product development, such that excipient changes are kept to a minimum. Small amounts included in the tablet coating, or levels below documented thresholds of effect for the specific drug substance, are of less concern.

By definition, BCS Class I drugs are highly absorbed, and have neither solubility nor permeability limited absorption. Therefore they generally represent a low risk group of compounds in terms of the potential for excipients to affect absorption, compared to other BCS classes. Consideration of excipient effects for BCS Class I drug products should focus on potential changes in the rate or extent of absorption. For example, if it is known that the drug has high permeability due to active uptake, excipients that can inhibit uptake transporters are likely to be of concern. For BCS Class I drugs that exhibit slow absorption, the potential for a given excipient to increase absorption rate should also be considered.

For BCS Class I drugs, qualitative and quantitative differences in excipients are permitted, except for excipients that may affect absorption, which should be qualitatively the same and quantitatively similar, i.e., within ± 10% of the amount of excipient in the reference product. Additionally, the cumulative difference for excipients that may affect absorption should be within ± 10%.

BCS Class III drug substances are considered to be more susceptible to the effects of excipients. These drugs are poorly permeable and may have site-specific absorption, so there are a greater number of mechanisms through which excipients can affect their absorption than for BCS Class I drugs. For BCS Class III drugs, all of the excipients should be qualitatively the same and quantitatively similar (except for film coating or capsule shell excipients). Excipients that may affect absorption should be qualitatively the same and quantitatively similar, i.e., within ± 10% of the amount of excipient in the reference product, and the cumulative difference for excipients that may affect absorption should be within ± 10%. This is defined in Table 1. Examples of acceptable differences in excipients are shown in Annex II. Differences in colourant and flavouring may be permitted when these constitute very small amounts of the formulation.

It is recognised that there are limitations to the application of this table, for example difficulty in determining the film coat weight for the reference product. This is provided as a target to give clarity to applicants. Deviations from this will require appropriate justification, based on the principles described above.

Table 1: Expected criteria to demonstrate quantitative similarity for products containing BCS Class III drugs.

Within the context of quantitative similarity, differences in excipients for drug products containing BCS Class III drugs should not exceed the following targets:	
Excipient class	**Percent of the amount of excipient in the reference**
Excipients which may affect absorption **Per excipient:** **Sum of differences:**	 **10%** **10%**
	Percent difference relative to core weight (w/w)
All excipients:	
Filler	10%
Disintegrant	
Starch	6%
Other	2%
Binder	1%
Lubricant	
Stearates	0.5%
Other	2%
Glidant	
Talc	2%
Other	0.2%
Total % change permitted for all excipients (including excipients which may affect absorption):	**10%**

Note: Core does not include tablet film coat or capsule shell

For FDC formulations containing only BCS Class I drugs, criteria regarding excipients should follow that for a BCS Class I drug. For FDC formulations containing only BCS Class III drugs, or BCS Class I and BCS Class III drugs, criteria regarding excipients should follow that for a BCS Class III drug. This is applicable to FDCs which are the same dosage form and strength.

3.2. *In vitro* Dissolution

When applying the BCS based biowaiver approach, comparative *in vitro* dissolution tests should be conducted using one batch representative of the proposed commercial

manufacturing process for the test product relative to the reference product. The test product should originate from a batch of at least 1/10 of production scale or 100,000 units, whichever is greater, unless otherwise justified. During a (clinical) development phase, smaller batch sizes may be acceptable, if justified. The comparative *in vitro* dissolution experiments should use compendial apparatus and suitably validated analytical method(s).

The following conditions should be employed in the comparative dissolution studies to characterize the dissolution profile of the product:

- Apparatus: paddle or basket
- Volume of dissolution medium: 900 ml or less (it is recommended to use the volume selected for the QC test)
- Temperature of the dissolution medium: 37 ± 1°C
- Agitation: paddle apparatus - 50 rpm
  basket apparatus - 100 rpm
- At least 12 units of reference and test product should be used for each dissolution profile determination.
- Three buffers: pH 1.2, pH 4.5, and pH 6.8. Pharmacopoeial buffers should be employed. Additional investigation may be required at the pH of minimum solubility (if different from the buffers above).
- Organic solvents are not acceptable and no surfactants should be added.
- Samples should be filtered during collection, unless in-situ detection methods are used.
- For gelatin capsules or tablets with gelatin coatings where cross-linking has been demonstrated, the use of enzymes may be acceptable, if appropriately justified.

When high variability or coning is observed in the paddle apparatus at 50 rpm for both reference and test products, the use of the basket apparatus at 100 rpm is recommended. Additionally, use of sinkers or increasing the rotation speed to a maximum of 75 rpm in the paddle apparatus to overcome coning may be considered with justification. All experimental results should be provided.

To qualify for a BCS-based biowaiver for BCS Class I drug substances both the test product and reference product should display either very rapid (≥85% for the mean percent dissolved in ≤15 minutes) *in vitro* dissolution characteristics, or rapid (≥85% for the mean percent dissolved in ≤30 minutes) and similar *in vitro* dissolution characteristics (i.e. f2 comparison), under all of the defined conditions. In cases where one product has rapid dissolution and the other has very rapid dissolution, similarity of the profiles should be demonstrated as below.

For the comparison of dissolution profiles, where applicable, the similarity factor f2 should be

estimated by using the following formula:

$$f2 = 50 \bullet \log \{[1 + (1/n)\Sigma_{t=1}^{n} (R_t - T_t)^2]^{-0.5} \bullet 100\}$$

In this equation f2 is the similarity factor, n is the number of time points, R(t) is the mean percent reference drug dissolved at time t after initiation of the study; T(t) is the mean percent test drug dissolved at time t after initiation of the study.

The evaluation of the similarity factor is based on the following conditions:

- A minimum of three time points (zero excluded)
- The time points should be the same for the two products
- Mean of the individual values for every time point for each product.
- Not more than one mean value of ≥85% dissolved for either of the products.
- To allow the use of mean data, the coefficient of variation should not be more than 20% at early time-points (up to 10 minutes), and should not be more than 10% at other time points.

Two dissolution profiles are considered similar when the f2 value is ≥50. When both test and reference products demonstrate that ≥85% of the label amount of the drug is dissolved in 15 minutes, comparison with an f2 test is unnecessary and the dissolution profiles are considered similar. When the coefficient of variation is too high, f2 calculation is considered inaccurate and a conclusion on similarity in dissolution cannot be made.

To qualify for a BCS-based biowaiver for BCS Class III drug substances both the test product and reference product should display very rapid (≥85 for the mean percent dissolved in ≤15 minutes) *in vitro* dissolution characteristics under the defined conditions.

For FDC formulations, dissolution profiles should meet the criteria for all drug substances in the FDC to be considered. For FDC formulations containing only BCS I drugs, criteria regarding dissolution should follow that for a BCS Class I drug. For FDC formulations containing only BCS Class III drugs, criteria regarding dissolution should follow that for a BCS Class III drug. For FDCs containing both BCS Class I and BCS Class III drugs the dissolution criteria for the applicable BCS class for each component should be applied.

For products with more than one strength the BCS approach should be applied for each strength, i.e., it is expected that test and reference product dissolution profiles are compared at each strength.

4. DOCUMENTATION

The applicant should provide complete information on the critical quality attributes of the test drug substance(s) and drug product and as much information as possible for the reference product, including, but not limited to: polymorphic form and enantiomeric purity; and any information on bioavailability or bioequivalence problems with the drug substance(s) or drug product, including literature surveys and applicant derived studies. All study protocols and reports should be provided. Information on validated test methods should be appropriately detailed according to current regulatory guidances and policies.

The reporting format should include tabular and graphical presentations showing individual and mean results and summary statistics.

The report should include all excipients, their qualitative and, where appropriate, quantitative differences between the test and reference products.

A full description of the analytical methods employed, including validation and qualification of the analytical parameters, should be provided. A detailed description of all test methods and media, including test and reference batch information [unit dose (strength and assay), batch number, manufacturing date and batch size where known, expiry date] should also be provided. The dissolution report should include a thorough description of experimental settings and analytical methods, including information on the dissolution conditions such as apparatus, de-aeration, filtration during sampling, volume, etc.

In addition, complete information with full description of the methods applied should be provided for the Caco-2 cell permeability assay method, if applicable (see Annex I).

5. GLOSSARY

AUC: Area under the concentration versus time curve

BCS: Biopharmaceutics Classification System

C_{max}: Maximum concentration

FDC: Fixed-dose combination

rpm: rotation per minute

ANNEX I: Caco-2 CELL PERMEABILITY ASSAY METHOD CONSIDERATIONS

Permeability assays employing cultured Caco-2 epithelial cell monolayers derived from a human colon adenocarcinoma cell line are widely used to estimate intestinal drug absorption in humans. Caco-2 cells undergo spontaneous morphological and biochemical enterocytic differentiation, and express cell polarity with an apical brush border, tight intercellular junctions, and several active transporters as in the small intestine. Due to a potential for low or absent expression of efflux (e.g., P-gp, BCRP, MRP2) and uptake (e.g., PepT1, OATP2B1, MCT1) transporters, the use of Caco-2 cell assays as the sole data in support of high permeability for BCS classification is limited to passively transported drugs (see Assay Considerations).

Method validation

The suitability of the Caco-2 cell assays for BCS permeability determination should be demonstrated by establishing a rank-order relationship between experimental permeability values and the extent of drug absorption in human subjects using zero, low (<50%), moderate (50 – 84%), and high (≥85%) permeability model drugs. A sufficient number of model drugs are recommended for the validation to characterize high, moderate and low permeability (a minimum 5 for each), plus a zero permeability marker; examples are provided in Table 2. Further, a sufficient number (minimum of 3) of cell assay replicates should be employed to provide a reliable estimate of drug permeability. The established relationship should permit differentiation between low, moderate and high permeability drugs.

Caco-2 cell monolayer integrity should be confirmed by comparing transepithelial electrical resistance (TEER) measures and/or other suitable indicators, prior to and after an experiment.

In addition, cell monolayer integrity should be demonstrated by means of compounds with proven zero permeability (refer to Table 2).

Reporting of the method validation should include a list of the selected model drugs along with data on extent of absorption in humans (mean, standard deviation, coefficient of variation) used to establish suitability of the method, permeability values for each model drug (mean, standard deviation, coefficient of variation), permeability class of each model drug, and a plot of the extent of absorption as a function of permeability (mean ± standard deviation or 95 percent confidence interval) with identification of the high permeability class boundary and selected high permeability model drug used to classify the test drug substance.

In addition, a description of the study method, drug concentrations in the donor fluid, description of the analytical method, equation used to calculate permeability should be provided. Additionally, information on efflux potential, e.g., bidirectional transport data should be provided for a known substrate.

Assay considerations

Passive transport of the test compound should be demonstrated. This may be verified using a suitable assay system that expresses known efflux transporters, e.g., by demonstrating independence of measured *in vitro* permeability on initial drug concentration, e.g., 0.01, 0.1, and 1 times the highest strength dissolved in 250 ml, or on transport direction (efflux ratio, i.e., ratio of apparent permeability (P_{app}) between the basolateral-to-apical and apical-to-basolateral directions <2 for the selected drug concentrations).

$$\text{Efflux ratio} = P_{appBL\rightarrow AP}/P_{appAP\rightarrow BL}.$$

Functional expression of efflux transporters should be verified by using bidirectional transport studies demonstrating asymmetric permeability of selected efflux transporter substrates, e.g., digoxin, vinblastine, rhodamine 123, at non-saturating concentrations.

The test drug substance concentrations used in the permeability studies should be justified. A validated Caco-2 method used for drug permeability determinations should employ conditions established during the validation, and include a moderate and a high permeability model drug as internal standards to demonstrate consistency of the method, i.e., included in the donor fluid along with the test drug. The choice of internal standards should be based on compatibility with the test drug, i.e., they should not exhibit any significant physical, chemical, or permeation interactions. The permeability of the internal standards may be determined following evaluation of the test drug in the same monolayers or monolayers in the same plate, when it is not feasible to include internal standards in the same cell culture well as the test drug permeability evaluation. The permeability values of the internal standards should be consistent between different tests, including those conducted during method validation. Acceptance criteria should be set for the internal standards and model efflux drug. Mean drug and internal standards recovery at the end of the test should be assessed. For recoveries <80%, a mass balance evaluation should be conducted including measurement of the residual amount of drug in the cell monolayer and testing apparatus.

Evaluation of the test drug permeability for BCS classification may be facilitated by selection of a high permeability internal standard with permeability in close proximity to the moderate/high permeability class boundary. The test drug is considered highly permeable when its permeability value is equal to or greater than that of the selected internal standard

with high permeability.

Information to support high permeability of a test drug substance (mean, standard deviation, coefficient of variation) should include permeability data on the test drug substance, the internal standards, *in vitro* gastrointestinal stability information, and data supporting passive transport mechanism.

Table 2. Examples of model drugs for permeability assay method validation

Group	Drug
High Permeability (f_a ≥85 percent)	Antipyrine Caffeine Ketoprofen Naproxen Theophylline Metoprolol Propranolol Carbamazepine Phenytoin Disopyramide Minoxidil
Moderate Permeability (f_a = 50-84 percent)	Chlorpheniramine Creatinine Terbutaline Hydrochlorothiazide Enalapril Furosemide Metformin Amiloride Atenolol Ranitidine
Low Permeability (f_a < 50 percent)	Famotidine Nadolol Sulpiride Lisinopril Acyclovir Foscarnet Mannitol Chlorothiazide

Group	Drug
	Polyethylene glycol 400 Enalaprilat
Zero Permeability	FITC-Dextran Polyethylene glycol 4000 Lucifer yellow Inulin Lactulose
Efflux Substrates	Digoxin Paclitaxel Quinidine Vinblastine

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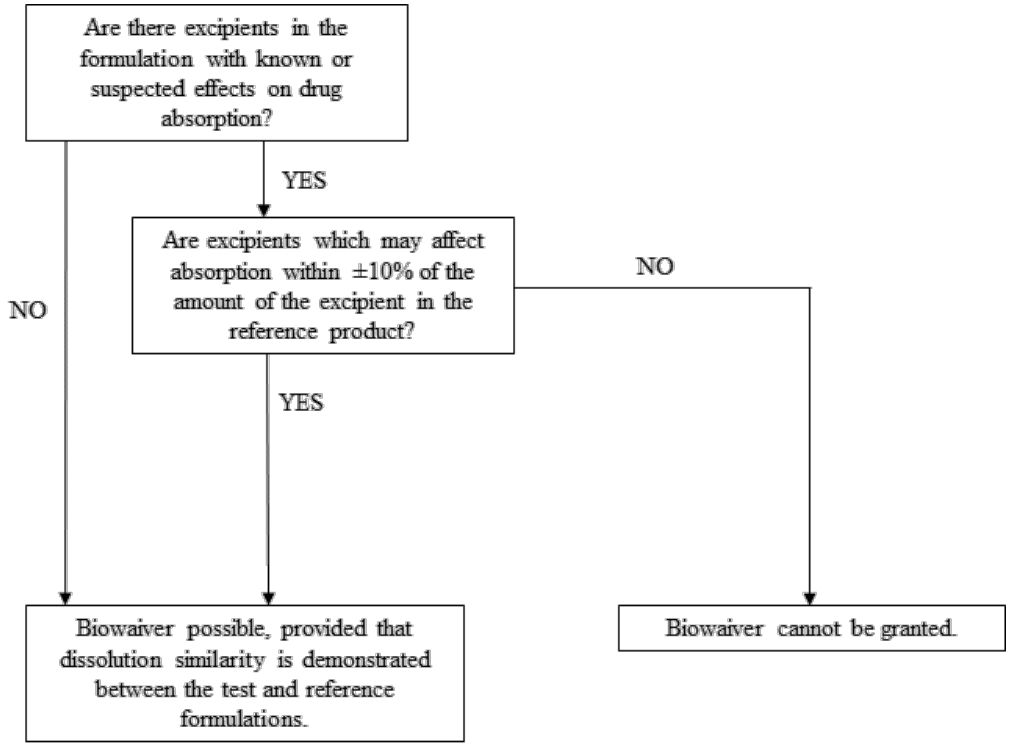
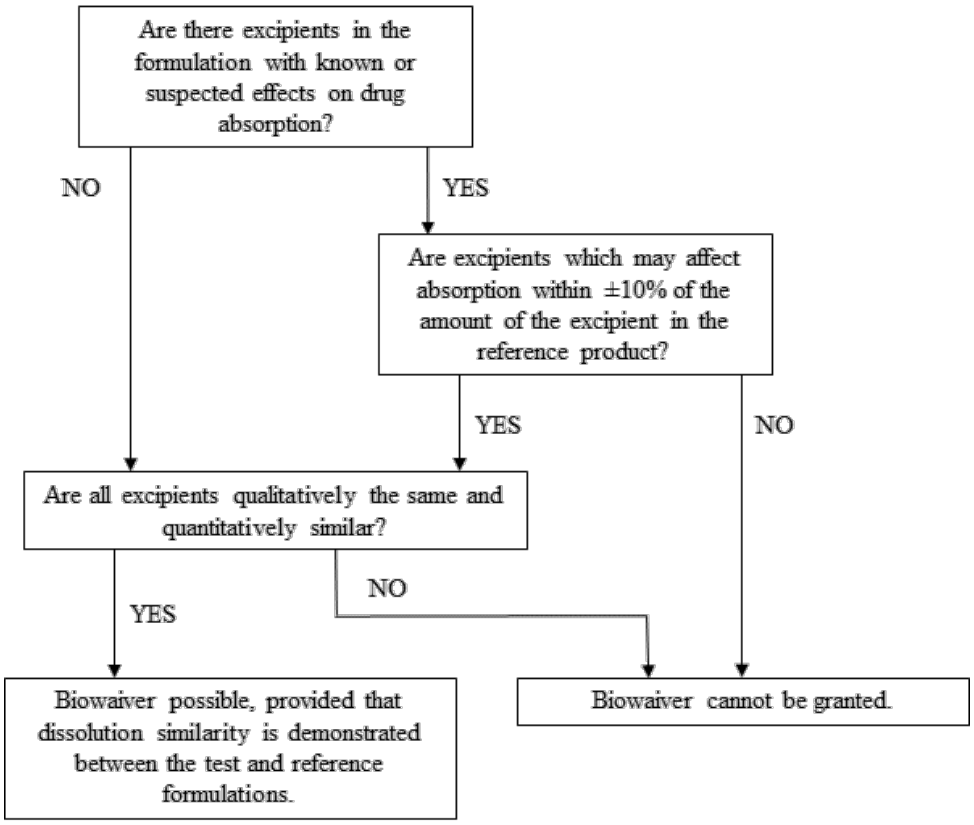
ANNEX II: FURTHER INFORMATION ON THE ASSESSMENT OF EXCIPIENT DIFFERENCES

Figure 1. BCS Class I Drug Substances



new box text Biowaiver will not be granted unless appropriate justification can be provided (refer to Section 3).

Figure 2. BCS Class III Drug Substances



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436 ***new box text*** Biowaiver will not be granted unless appropriate justification can be
437 provided (refer to Section 3).
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439 **EXAMPLES OF ACCEPTABLE DIFFERENCES IN EXCIPIENTS**

440 **Example 1: BCS Class I Biowaiver**
441 The formulation of the test product is qualitatively the same as that of the reference product.
442 Additionally, it contains sorbitol, an excipient with known or suspected effects on drug
443 absorption. The amount of sorbitol in the test formulation is within the permitted range of 45
444 mg to 55 mg based on the amount of sorbitol in the reference formulation (i.e., 50 mg ± 10%).

Component	Amount (mg) reference	Amount (mg) test
Drug substance	100	100
Microcrystalline cellulose (filler)	100	95
Sorbitol (filler)	50	55
HPMC (binder)	10	10

Talc (glidant)	5	5
Total	265	265

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448
449 Example 2: BCS Class III Biowaiver

450 The test formulation is qualitatively the same as the reference formulation. Additionally, it
451 contains sorbitol, an excipient with known or suspected effects on drug absorption. The amount
452 of sorbitol in the test formulation is within the permitted range of 9 mg to 11 mg based on the
453 amount of sorbitol in the reference formulation (i.e., 10 mg ± 10%). For the other excipients the
454 differences were within the criteria provided in Table 1.

Component	Reference Product		Test Product		Absolute percent difference relative to core weights
	Composition (mg)	Proportion relative to core weight (%w/w)	Composition (mg)	Proportion relative to core weight (%w/w)	
Drug substance	100	49.3%	100	46.5%	--
Lactose monohydrate (filler)	85	41.9%	97	45.1%	3.2%
Sorbitol (filler)	10	4.9%	9	4.2%	0.7%
Croscarmellose sodium (disintegrant)	6	3.0%	7	3.3%	0.3%
Magnesium stearate (lubricant)	2	1.0%	2	0.9%	0.1%
Total	203	100%	215	100%	
				Total change:	**4.3%**

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