出國報告(出國類別：國際會議)

參加 ICH M9-工作組第 4 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：日本
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報告日期：107 年 8 月

摘要

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之法規指引(Biopharmaceutical Classification System-based Biowaivers guideline, 簡稱 BCS-based biowaivers guideline 或 BCS biowaiver)係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 專家工作組(Expert Working Group; EWG)的主要工作目標， M9 專家工作組繼 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 進行面對面會議後，接續在今年 3 月及 5 月初進行電話會議討論，並於今年 6 月 4 日到 7 日於日本 Kobe 進行 M9 專家工作組的第 4 次面對面會議。

本次工作組會議分別就 FDA 進行的配方組成相似所進行逆向工程、溶離試驗的溶媒體積和錐體效應、Caco2 細胞株資料等議題之實驗數據進行討論；並就配方組成相似之計算與相關問題尋求共識；另溶離比對試驗之溶媒除了藥典規定之三種外，是否將純水列入要求之一，因日本有不同看法而提管理委員會(Management Committee; 以下簡稱管委會或 MC)討論；並協和溶離相似性的計算方法；完成 M9 指引草案等，是本次工作組會議的重要進展。

ICH 對於指引制定流程中有五個公開透明的步驟。於 2018 年 6 月 7 日 M9 專家工作組成員完成步驟 1 之簽署，接著由大會會員及藥政法規單位會員認可，完成步驟 2a/b，現在(2018 年 8 月)已進入步驟 3－公眾諮詢期。ICH M9 指引草案已可以在 ICH 網頁下載。

法規管理的協和與匯流，在程度上有所不同，ICH 自 1990 年成立以來，致力於各種指引制定，旨在協和現行各區域法規標準不一致之處，縮小差距。ICH 於 2015 年 10 月 23 日根據瑞士法律改制為非營利性法人，在改革後擁有明確的管理架構和作業模式，會員也持續增加中。而會員必須參與 ICH 相關會議與指引之制定，且落實指引之執行。

食品藥物管理署(以下簡稱食藥署)於本次會議成為 ICH 的藥政法規單位會員，對長期致力於生技發展及醫藥法規國際化的台灣是很大的鼓舞，但如何在人力與資源有限的情況下，持續積極參與 ICH 相關活動、建構符合 ICH 標準之法規環境，並輔導我國產業落實相關規範是重要的課題。

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壹、 目的

藉由生體相等性試驗(bioequivalence, BE)驗證兩個同主成分不同配方的藥品在安全與療效性上的相當，是目前各國普遍採行的方法。然而，生體相等性試驗畢竟是人體試驗的一種，同一主成分不同廠牌的學名藥重複與原廠藥在人體執行生體相等性試驗，除造成資源浪費外，也衍生醫學倫理之爭議。如何在嚴謹的科學實證下，減少重複在健康人身上執行生體相等性試驗，是 ICH 會員的共識。

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(Biopharmaceutical Classification System, BCS)為基礎，免除生體相等性試驗之審查機制，即被視為是一種可作為相同主成分不同配方的藥品在安全與療效性上相當的替代評估方式。期由體外資料的滿足而免除生體相等性試驗，進而減少對生體相等性試驗的需求。

此議題係於 2016 年 10 月得到 ICH 管委會的認可，主要是為了以生物藥劑學分類系統為基礎的生體相等性試驗免除(BCS-based biowaivers)能有一致性的技術要求與審查標準。多數區域認為 BCS I 類和 BCS III 類的藥物可適用於 BCS 的生體相等性試驗免除，但各區域的認定標準仍有差異，也就是說藥品公司會因不同地區，需要遵循不同的技術資料要求。

為此，ICH 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 為藥政法規單位主席，各區域專家代表共 30 人，以解決支持 BCS 分類的資料如溶解度或穿透性資料上的爭議，及支持生體相等性試驗免除的資料如配方相似性或藥品溶離率曲線比對試驗上的爭議，並協和當前各區域的標準，制定一公認之法規指引。

BCS-based biowaivers 應用範圍廣泛，包括早期臨床研發到最後商品化階段，從原開發廠到學名藥及各類需要執行 BE 變更的情況皆可適用。M9 BCS-based biowaivers 指引，協和現行各區域法規不一致之處，將可作為申請人檢附資料之依循，並利全球性藥物研發的整合。

貳、 過程

一、 行程及會議議程

日期	議程/活動	議題
6 月 4 日	議題討論	➢ 就 FDA 提交關於配方相似性所進行逆向工程之實驗數據（仍在進行的實驗）進行討論。 ➢ 就有爭議的問題尋求共識。
6 月 5 日	議題討論與指引草案撰寫	➢ 就 FDA 提交關於溶離試驗之溶媒體積和錐體效應之實驗數據（仍在進行的實驗）進行討論。 ➢ 就專家/成員有疑慮的議題進行協商或回應以達成共識。 ➢ 就組成相似性，溶媒，Caco2 細胞株資料等議題進行討論並作成結論。
6 月 6 日	議題討論、指引草案撰寫與大會報告內容準備	➢ 完成討論。 ➢ 指引草案撰寫
6 月 7 日	向大會報告本次會議進度及指引最終草案	➢ 就指引最終版本達成共識。 ➢ 完成步驟 1 專家簽署表。 ➢ 提交大會請求批准。

二、 會議概況

本次會議由日本 MHLW/PMDA 主辦，來自美國、歐盟、日本、南美、亞洲之官方及產研界專家共 28 人與會，就 BCS Biowaiver 指引草案尚有爭議的部分進一步討論及協和，完成第 8 版指引草案，由專家代表簽名後完成步驟 1 。ICH M9 依生物藥劑學分類系統為基礎之免除生體相等性試驗指引於 2018 年 6 月進入 ICH 指引制定流程的步驟 2a/b，現在(2018 年 8 月)進入步驟 3－公眾諮詢期；該指引草案建議支持藥品生物藥劑學分類系統與免除生體相等性試驗的資料。 這將引導現行各區域準則或指引趨於一致，進而加快全球藥物的開發，ICH M9 指引草案已可以在 ICH 網頁下載。

三、 會議重點摘要

(一) 美國食品藥物管理局(FDA)的配方逆向研究進度說明

美國 FDA 以屬 BCS Class 3 之 Atenolol 25 毫克 速放型（IR）錠劑作為逆向工程研究的例子；示範測試產品(test product)如何取得與對照藥品(RLD)相同的 Q1 和 Q2，而被認可的。賦形劑的定性描述通常在藥品的標仿單可找到，透過各種分析方法作定性確認是較容易進行的，但定量組成在原就不知含量範圍，且同一基質中的其他賦形劑也可能產生干擾的情況下，而具有挑戰性。盡管如此，有些商業分析套組可以協助，最後採用了一系列性分析技術進行實驗後，Atenolol 錠劑的定量組成即被解碼成功。

(二) 澳洲醫藥品管理局(TGA)-海外對照藥品的比對

澳州允許採用本國未上市產品作為生體相等性試驗的對照品，但有幾個條件限制，詳細資訊可在以下網址取得。

https://www.tga.gov.au/guidance-15-biopharmaceutic-studies 此一海外對照品必須是在與澳洲藥政管理系統類似的國家或區域購買，由原廠藥之同一跨國公司（或該公司許可的第二家公司）在兩國銷售。且有效成分不得屬於有特定的藥動性質者，例如療效濃度範圍狹窄(NTI)，藥動具高變異性，首次代謝率(first pass)大於 40%等。採用海外對照品時，必須檢附溶離率曲線比對結果及檢驗成績書；證明海外對照品與澳洲核准之對照品具相同的外觀，相同的定性及定量配方，並有一些確效過的物理化學方法進行分析佐證。海外和澳洲對照品兩者賦形劑的含量差通常須小於 0.5%w / w。

(三) 世界藥學會-生體相等性試驗免除基準(Biowaiver Monographs)

世界藥學會(FIP)得到世界衛生組織（WHO）的支持，參考美國食品藥品管理局和歐洲藥品管理局(EMA)的相關指引以及該領域的科學發展與文獻，自 2004 年起陸續發表適用 BCS biowaiver 的品項與基準，所收集的訊息經過嚴格審查，並作為 FIP 藥物科學委員會官方期刊“藥學雜誌”的專著出版， 到目前為止已發表了近 50 個品項。

(四) 賦形劑在測試與對照藥品中的範圍和 BE 結果的關聯性

歐洲製藥公會(EFPIA)代表就日本製藥公會(JPMA)所提供 21 個品項，進一步分析賦形劑如 HPMC, Magnesium Stearate, Mannitol, PEG 400 及 Sodium Lauryl Sulfate 之 含量範圍(以製劑的%w / w 表示)，加上有關原料藥(API)的藥動(PK)特性，以便了解特定賦形劑影響吸收的風險， 並進一步與加拿大衛生部所蒐集的數據進行比較。另由加拿大衛生部(HC)提供分類屬 BCS 3 的 15 個有效成份，就已通過生體相等性試驗之製劑，分析其賦形劑含量對吸收的影響。

(五) 美國食品藥物管理局更新 Caco2 資料(指引草案的附件 I)

以源自人結腸腺癌細胞株培養的 Caco-2 上皮細胞，其單層的滲透性測定被廣泛用於評估藥物在人體的腸道吸收。 Caco-2 細胞經歷自發的形態學和生物化學的細胞分化，並且表現出細胞極性，具有頂端刷狀緣，緊密的細胞間連接，並具有如小腸中的幾種活性轉運蛋白。 由於排出（例如，P-gp，BCRP，MRP2）和攝取（例如，PepT1，OATP2B1，MCT1）轉運蛋白的低表現或不表現的可能，使用 Caco-2 細胞株測定來支持 BCS 的高滲透性分類僅限於被動運輸的藥物。Caco-2 細胞對 BCS 通透性測定的適用性應透過建立實驗滲透率值與人類受試者藥物吸收程度之間的等級關係來證明，使用零，低（<50%），中度（50 - 84%）和高（≥85%）滲透性模型藥物進行方法驗證。

(六) 溶離試驗的條件

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

攪拌：槳式設備→50 轉/分鐘 或網籃式設備→100 轉/分鐘

當槳式設備中以 50rpm 觀察到高可變性或錐形效應時，建議使用網籃式設備 100rpm。 另外，槳式設備中使用沉降片來克服諸如錐形效應之類的問題是可被接受的。

(七) 使用水作為溶媒的討論

PMDA / MHLW 說明基於風險評估，主張溶離曲線比對試驗中的溶媒應包括純水或低緩衝量之媒液。他們擔心藥典規定之三種媒液(pH1.2,pH4.5,及 pH 6.8)可能無法在生理條件下適當地檢測到有效成分屬 BCS Ⅰ 或 BCSⅢ之較低或不同的溶離度，結果非 BE 的風險可能較低但仍不可忽略，因此堅持將低緩衝量的媒液納入溶離率比對試驗之溶媒要求。但多數專家代表不贊同如此說法，認為 BE 或溶離率比對試驗的目的皆是要獲知配方差異所造成的影響。由於意見不同，報告起草人(Rapporteur)裁示提管委會(MC)會議討論。

(八) 在範圍內使用“地區性法規”

雖然 M9 在報告起草人與法規主席向 MC 反映日本 MHLW/PMDA 所提以純水為溶媒與大多數專家代表看法不同，然 MC 最後仍決定接受日方提議，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。原文如下:

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). Purified water may be used as an additional dissolution medium in some regions.

參、 心得及建議

一、 學會 convergence 與 harmonization 的不同

(一) 法規管理協和 (Regulatory Harmonization):依據世界衛生組織(WHO）定義，技術指引的解釋或應用可以一致或相互兼容。即藥品法規的技術要求，包括法律、規範，程序等皆統一，而法規管理的匯流(Regulatory Convergence)，依據 APEC 指的是逐步採用國際公認的技術指導文件和標準，各經濟體的管理要求隨著時間的推移變得更加相似或一致的過程，並不要求法律或規範的協調，技術要求的一致性和更大的法規管理合作不是必要。兩者主要不同在於 convergence 為 harmonization 前整合不同藥政法規單位意見的過程。

(二) ICH 主要目標是促進公共衛生，目的是促進新藥及時引入，提供患者使用。例如，透過大幅度地減少動物試驗和防止不必要的人體臨床試驗重複，在同時不影響安全性和有效性下，有效率地增進安全且高品質的藥物開發、註冊和製造 。ICH 藉由藥政法規單位和產業界的專家代表經由科學共識的過程，製定統一的指引來實現此一目標。而 ICH 成功的關鍵，在於藥政法規單位成員對實施 ICH 所制定指引的承諾。

(三) 日本代表說在過去 20 年的 ICH，為什麼 PMDA 不是 FDA 核准後的橡皮圖章？主因是 CONVERGENCE，產品經某一國家核准上市，在相同或相似的法規標準下，其他審查機構的決定應是相同的。

二、 君子重承諾

由於日本對溶離比對試驗之溶媒除了藥典規定之三種外，將純水也列入要求之一的堅持，而提 Management Committee(以下簡稱管委會或 MC)討論，在第 3 次面對面會議向大會報告時，管委會副主席 Dr. Toshiyoshi Tominaga 曾叮嚀由於日本尚無 BCS biowaiver 制度，所以請報告起草人及工作組要有耐性引導日本 PMDA/MHLW 專家代表，不要給他們壓力。這次因溶離曲線比對試驗的溶媒看法不一致，提 MC 會議討論時，Tominaga 先生即以此反問報告起草人，是否記得此一承諾？大家頓然了解到先前的客套話原來也是一種承諾，氣勢馬上低了下來。可見承諾(promise)對維持國際社會運作的重要性。

三、 爭端解決機制

(一) 在特殊情況下，專家工作組無法就技術文件的各方面及問題達成共識時，報告起草人在法規主席的支持下，可向管委會(MC)提交一份報告，說明會員間存在差異的地方。工作組的專家代表將對 MC 解釋他們的立場，並提出一個

可能的解決方案，或由少數意見一方的專家提出的不同替代方案。

(二) 但是縱然提了管委會(MC)，仍需要一個答案。MC 的決定可能允許工作組延長原預定時間表，有更多的時間尋求共識，或建議大會暫停或放棄此一議題的協和並解散工作組。ICH 是一個重承諾的組織，其作業程序相當明確，在無法獲得多數人支持時，可依循一定程序提出訴求。

四、 完成草案

ICH 對於指引制定流程中有五個公開的步驟。有關是否以純水為溶離試驗額外要求執行的溶媒之爭議提管委會討論，最後決定接受日方建議，並賦予工作組進一步的工作，蒐集以水為溶媒之溶離比對呈不相似且結果不 BE 的資料進行分析。然後工作組繼續進行第 1 步專家簽收。於 2018 年 6 月 7 日 M9 專家工作組成員完成步驟 1 之簽署，接著由大會會員及藥政藥政法規單位會員認可，完成步驟 2a/b，現在(2018 年 8 月)已進入步驟 3－公眾諮詢期。ICH M9 指引草案已可以在 ICH 網頁下載。目前歐盟意見蒐集截止日期為 2019 年 2 月 6 日，加拿大意見蒐集截止日期為 2018 年 11 月 4 日

五、 台灣 TFDA 成為會員。

國際醫藥法規協和會(ICH)自 1990 年成立以來，致力於各種指引制定，旨在協和現行各區域法規標準不一致之處，縮小差距。於 2015 年 10 月 23 日根據瑞士法律改制為非營利性法人。於 2018 年 6 月 2 日至 7 日在日本神戶舉行會議，繼續執行 2015 年改革未完成步驟之一，大會選出了其他成員加入管委會。管委會除了現行創始會員和常任理事會員，有五個 ICH 會員加入管委會，藥政藥政法規單位包括中國 CFDA，新加坡 HAS 及韓國和 MFDS，產業代表包括 BIO 和 IGBA。並同意台灣 TFDA，成為新的藥政藥政法規單位會員，另同意摩爾多瓦 MMDA，馬來西亞 NPRA，亞美尼亞 SCDMTE 和土耳其 TİTCK 為新的觀察員。現在有 16 個 ICH 會員和 27 個觀察員，在 ICH 改革後擁有明確的治理和全球有越來越多的會員加入。

六、 下一步工作規劃

會員除參與 ICH 相關會議與指引之制定外，且必須落實指引之執行。有關 BCS biowaiver 我們目前已有兩項公告，然實際申請案仍非常有限，規劃舉辦相關訓練協助國內藥品產業瞭解 BCS biowaiver 規範及推動我國 BCS 免除生體相等性試驗，提升國內藥品品質管理，是後續工作目標。

TFDA 成為 ICH 會員對長期致力於生技發展及醫藥法規國際化的台灣是很大的鼓舞，但如何在人力與資源有限的情況下，持續積極參與 ICH 相關活動、建構符合 ICH 標準之法規環境，並輔導我國產業落實相關規範是重要的課題。

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	2Q 2019	計畫中

貳、 與會代表清單 (Delegates) 2018 年8月

單位/國家	代表
ANVISA, Brazil	Mr. Gustavo Mendes Lima Santos
CFDA, China	Mr. Jinbo Yang， 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， Mr. Paul A. Wielowieyski
IGBA	Dr. Susana Almeida
JPMA	Mr. Yutaka Takahashi， Dr. Ryuji Kubota， Mr. Kazuhiro Okochi， Dr. Katsuhiko Yamamoto， Mr. Tsuyoshi Kobayashi
MFDS, Republic of Korea	Ms. Juhyun Baek Dr. Raeseok Jung
MHLW/PMDA, Japan	Dr. Yukiko Komori Dr. Ryosuke Kuribayashi Dr. Hiroyuki Yoshida
PhRMA	Mr. Roger Nosal Sebastian Haertter
Swissmedic, Switzerland	Dr. Arno Nolting
WSMI	Mr. Bruno Paillard
WHO	Dr. John Gordon
HSA, Singapore	Dr. Clare Rodrigues
TFDA, Chinese Taipei	Ms. Shianging (Shirley) Pan

參、　活動照片


ICH 2018
Kairaku
Waraku 1
Waraku 2
Kikusui
Kitano
Ikuta
Nunobiki

肆、 指引草案

ICH M09: Biopharmaceutics Classification System-based Biowaivers
Technical Document DRAFT version 8.0
(date June 6, 2018)

Contents:

INTRODUCTION

1.1. Background and Objective

Two drug products containing the same active substance 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. 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 will provide recommendations to support the biopharmaceutics classification of drug substances and the BCS-based biowaiver of bioequivalence studies for drug products.

1.2 Scope

BCS-based biowaivers may be used to demonstrate bioequivalence for example between products used in early clinical development through commercialization, for line extensions of the same pharmaceutical form of innovator products, in applications for generic drug products, and post-approval changes that would otherwise require *in vivo* bioequivalence evaluation, 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 exhibits high solubility and, either high permeability (BCS Class I) or low permeability (BCS Class III).

A biowaiver is only applicable when the drug substance(s) in test and reference products are identical. For example, a biowaiver is not applicable when the drug substance in the test product is a different salt, ester, isomer, or mixture of isomers from that in the reference product. 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 equilibrium saturated solubility of the drug substance over the pH range of 1.2 – 6.8 at 37 ± 1ºC using a shake-flask technique or an alternative method, if justified. At least three buffers within this range, including buffers at pH 1.2, 4.5 and 6.8, should be evaluated. In addition, solubility at the pKa of the drug substance should be evaluated if it is within the specified pH range. 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 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 validated stability-indicating method, with appropriate compendial references for the 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 this case a BCS-based biowaiver cannot be applied. 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 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. *In vitro* cell permeability assays (Caco-2) used in support of high permeability should be appropriately validated and standardized as outlined in Annex 1. 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 (e.g. BCS class III).

Instability in the Gastrointestinal Tract

If mass balance studies or *in vitro* Caco-2 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. Stability in the gastrointestinal tract may be documented using compendial and simulated gastric and intestinal fluids or, with suitable justification, other relevant methods. 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 validated stability indicating assay method. Significant degradation (>10 percent) of a drug in this study could suggest potential instability.

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 a dosage form that is pharmaceutically equivalent to 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 additional data. An example of such additional data is demonstration of dose proportional pharmacokinetics (i.e. AUC and C_{max}) over a dose range that includes the highest therapeutic dose.

Drug products with buccal or sublingual absorption are not eligible for a BCS-based biowaiver application. As such, an orodispersible product is eligible for a biowaiver application only if there is no buccal or sublingual absorption and the product is labelled to be taken with water only.

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

Excipient differences between the proposed test and the reference products 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 ClassI 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 fora 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 ± 10.0% of the amount of excipient in the reference product.

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). This is defined in Table 1. Examples of acceptable differences in excipients are shown in Annex II.

Table 1: Allowable differences in excipients for drug products containing BCS Class III drugs.

Excipient class	Percent of the amount of excipient in the reference	Percent difference relative to core weight (w/w)
Excipients which may affect absorption:	**± 10.0%**	
All excipients:		
Filler		± 10.0%
Disintegrant		
Starch		± 6.0%
Other		± 2.0%
Binder		± 1.0%
Lubricant		
Ca or Mg stearate		± 0.5%
Other		± 2.0%
Glidant		
Talc		± 2.0%
Other		± 0.2%
	Total % change permitted:	**10.0%**

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 pharmaceutically equivalent.

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 one batch of 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 apparatuses and validated analytical methods.

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). Purified water may be used as an additional dissolution medium in some regions.
- Organic solvents are not acceptable and no surfactants should be added.
- Samples should be filtered during collection
- 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, the use of the basket apparatus at 100 rpm is recommended. Additionally, use of sinkers in the paddle apparatus to overcome issues such as coning may be considered with justification.

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) or rapid (≥85 for the mean percent dissolved in ≤30 minutes) and similar *in vitro* dissolution characteristics under all of the defined conditions. In cases where one product has rapid dissolution and the other has very rapid dissolution, statistical 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 twelve individual values for every time point for each product.
- Not more than one mean value of ≥85% dissolved for any 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. In case the coefficient of variation is too high, f2 calculation is considered not accurate and reliable 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 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 or drug product, including literature surveys and applicant derived studies. All study protocols including standards, quality assurance and testing methods should be appropriately detailed and validated according to current regulatory guidance's and policies.

The reporting format should include tabular and graphical presentations showing individual and mean results and summary statistics. The tabular presentation should include standard deviation and coefficient of variation.

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

A full description of the analytical methods employed, including validation, e.g. method linearity, accuracy and precision, should be provided. A detailed description of all test methods andmedia, including test and reference batch information [unit dose (milligram and %), batch number, manufacturing date and batch size where known, expiry date, and any comments] 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

Pharmaceutically equivalent: Medicinal products containing the same amount of the same

active substance(s) in the same dosage forms.

pKa: Acid dissociation constant at logarithmic scale

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 in support of high permeability for BCS classification is limited to passively transported drugs (for definition 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 the full permeability range (a minimum 5 for each permeability category, high, moderate and low is recommended; examples are provided in Table 1). 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.

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 internal standard 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, and where appropriate, information on efflux potential, e.g., bidirectional transport data should be provided for a known substrate.

Assay considerations

As noted above, the use of Caco-2 cell assays in support of BCS permeability determination is limited to passively transported drugs. A passive transport mechanism can be inferred when the pharmacokinetics of the drug (assessed as AUC and C_{max} parameters) are dose proportional over the relevant clinical dose range. Alternatively, the absence of an active transport mechanism 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 membrane.

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

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

ANNEX II: FURTHER INFORMATION ON THE ASSESSMENT OF EXCIPIENT DIFFERENCES

Figure 1. BCS Class I Drug Substances

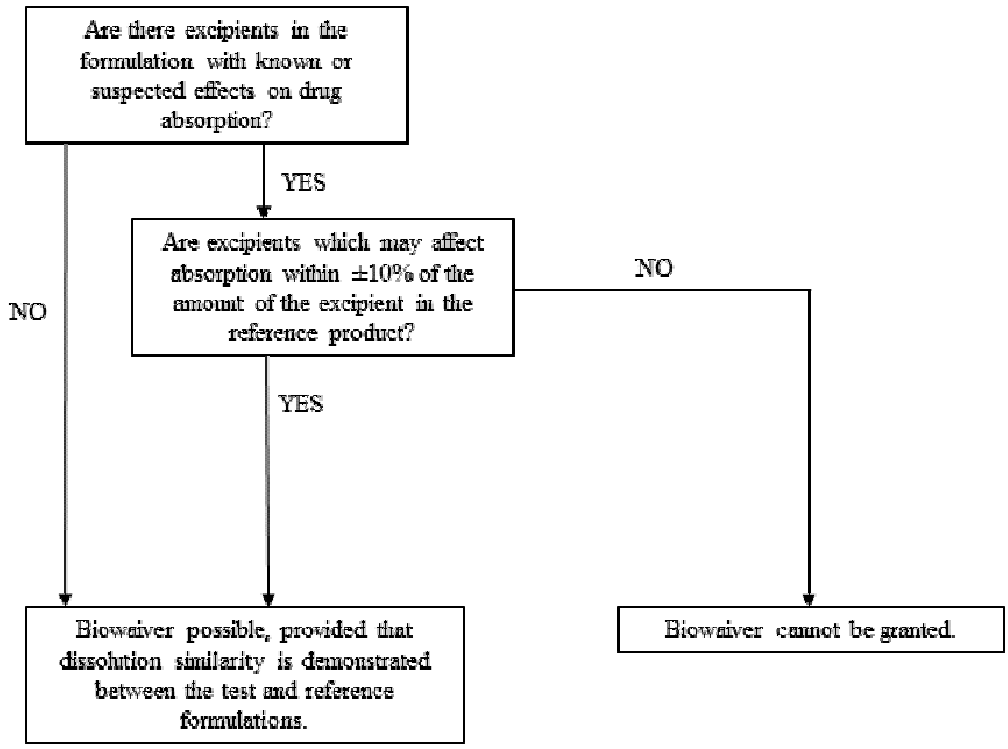
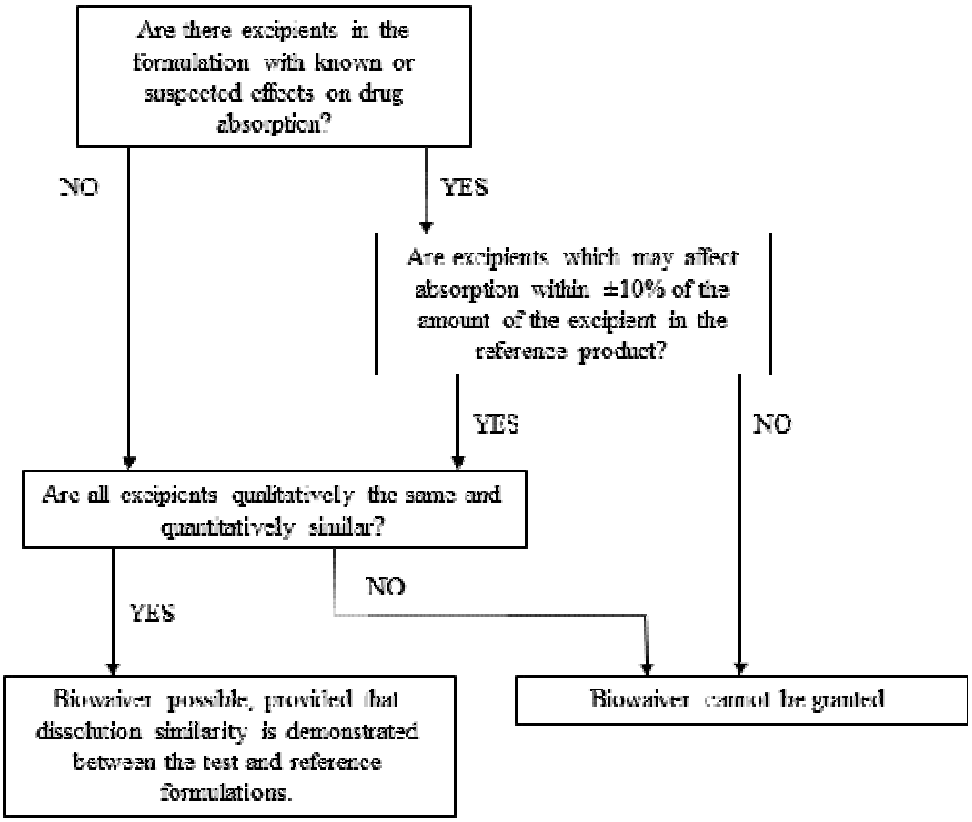


Figure 2. BCS Class III Drug Substances



EXAMPLES OF ACCEPTABLE DIFFERENCES IN EXCIPIENTS

Example 1: BCS Class I Biowaiver

The amount of sorbitol (an excipient that affects absorption) in the test formulation is different from the reference formulation. The permitted range is 45 mg to 55 mg of sorbitol based on the amount in the reference formulation (50 mg ± 10.0%).

Component	Amount (mg) reference	Amount (mg) test
Drug substance	100	100
Microcrystalline cellulose (filler)	100	95
HPMC (binder)	10	10
Talc	5	5
Sorbitol (filler)	50	55
Total	265	265

Example 2: BCS Class III Biowaiver

The test formulation is qualitatively the same as the reference formulation. The amount of sorbitol (an excipient that affects absorption) in the test formulation is different from the reference formulation. The permitted range is 9 mg to 11 mg of sorbitol based on the amount in the reference formulation (10 mg ± 10.0%). For the other excipients the 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%
Croscarmellose sodium (disintegrant)	6	3.0%	7	3.3%	0.3%
Magnesium stearate	2	1.0%	2	0.9%	0.1%
Sorbitol (filler)	10	4.9%	9	4.2%	0.7%
Total	203	100%	215	100%	
				Total change:	**4.3%**