出國報告(出國類別：國際會議)

參加 ICH M9 工作小組會議出國報告

服務機關：衛生福利部食品藥物管理署
姓名職稱：潘香櫻科長
派赴國家：加拿大
出國期間：106 年 5 月 27 日~106 年 6 月 2 日
報告日期：106 年 7 月

摘要

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 工作小組，撰寫依藥品溶解度及穿透性分類免除生體相等性試驗指導原則(Biopharmaceutical Classification System-based Biowaivers guideline, 簡稱 BCS-based biowaivers guideline)，協和現行各區域間所定原則不一致之處，以作為申請人檢附資料之依循，以利全球性藥物研發的整合。M9 工作小組於去年(2016 年)11 月於日本 Osaka 進行第一次面對面會議後，接續在今年 2 月及 5 月初進行電話會議討論，並於今年(2017 年)5 月 29 日到 6 月 1 日進行 M9 工作小組的第 2 次面對面會議。

本次工作小組會議分別從溶解度、穿透性與吸收、溶離比對試驗及配方條件等方面進行理論探討、法規研析及案例分享。內容包括以最高單一治療劑量(highest single therapeutic dose)或最高單位含量(highest dose strength) 來界定溶解度高低，美國與歐盟存有不同看法，在各自論述後，擬以加註方式取得平衡點為大家接受。又在大部分區域都沒有 Caco2 cell line 體外資料審查經驗下，美國 FDA 說服與會人員增列 Caco2 cell line 體外資料可作為高穿透性的主要支持性資料。另外溶離比對試驗在各區域施行多年，但區域間計算相似性的條件不同，如何協和大家的計算方法等都是本次工作小組會議的重要議題。

為達 ICH 國際法規協和的目標，法規單位代表、國際公協會代表及區域專家從蒐集資料及論述主張，是職參加本次工作小組會議的寶貴學習。本次從美國 FDA 的經驗分享學到開放角度的管理 BCS-based biowaivers，從歐盟代表的論述學到以嚴謹態度對待生體相等性試驗的免除，從日本 MHLW/PMDA 的資料整理學到法規協和的技巧。

台灣要發展生技，醫藥法規國際化是不可或缺的一環，如何在人力與資源有限的情況下，精進藥品技術文件要求，是重要的課題。有關 BCS biowaiver 我們目前已有兩項公告，然實際 BCS biowaiver 申請案卻非常有限，更遑論審查經驗的累績。參加本次 M9 工作小組有助於我國了解國際間 BCS 免除生體相等性試驗的要求，以利規劃及推動我國 BCS 免除生體相等性試驗，提升國內藥品品質管理。

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壹、 目的

兩個含相同主成分的藥劑相等品或藥劑替代品，以相同條件、相同莫耳劑量(molar dose)投與人體，比較兩者生體可用率，如比值落在規定範圍，即認為兩者具生體相等性(bioequivalence, BE)。藉由生體相等性試驗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 會員國家的共識。

以藥品的溶解度(Solubility)及穿透性(Permeability)分類原則(Biopharmaceutical Classification System, BCS)為基礎，建立免除生體相等性試驗之審查機制(BCS biowaiver)，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。藉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。

BCS-based biowaivers 應用範圍廣闊，於從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。ICH 特別成立 M9 工作小組，撰寫 BCS-based biowaivers 指引，作為申請人檢附資料之依循，並協和現行各區域間所定原則不一致之處，以利全球性藥物研發的整合。

貳、 過程

一、 行程及會議議程

日期	活動	講者/主持人
5 月 27~28 日	啟程、抵達加拿大蒙特婁	
5 月 29 日	報到	Jan Welink.
	歡迎致辭 Welcome of members /experts Adoption of the draft Agenda	
	溶解度(Solubility) Use highest strength or highest dose. Solubility testing.	Mehul Mehta, Henrike Potthast
		Roger Nosal
	穿透性(Permeablity) Use of in vitro Caco2 cells data Evaluation of extent of absorption (ADME)	Mehul Mehta, Ethan Stier
		Sebastian Haertter
5 月 30 日	溶離試驗 Rotation speed and dynamics Rotation speed/coning Use of water as dissolution media Use of enzymes in dissolution media Additional dissolution testing around pKa	Roger Nosal, Horst-Dieter Friedel
		MHLW/PDMA
		MHLW/PDMA
		MHLW/PDMA
	溶離試驗 F2 testing: additional cut-off values F2 calculation Buffer media High potency drugs	MHLW/PDMA
		Mehul Mehta, Ethan Stier, Henrike Potthast
		Roger Nosal, Talia Flanagan

5 月 31 日	配方 API: different salts Pro-drugs Critical excipients	Ethan Stier
		Mehul Mehta, Ethan Stier
		Talia Flanagan
	指引修訂 Update guideline Preparation outcomes for the Committee	Jan Welink.

二、 會議概況

本次工作小組會議主要來自美國、歐盟、日本、南美、亞洲之官方及產研界專家共 26 人，就藥品水溶解度及腸道吸收特性所建立的科學方法(BCS classification)，進行理論探討、法規研析及案件審查經驗分享。

三、 研習重點摘要

(一) BCS 遇到的問題

BCS biowaiver 主要用於 BCS Class I(高溶解度/高穿透性) 及 III(高溶解度/低穿透性)的藥品，但是這兩類藥品的定義範圍並非全世界有相同的認定。目前雖有歐盟、美國、加拿大及世界衛生組織等出版之基準或草案，但對申請資料的要求並不一致，甚至分類也有差異。導致藥品公司在不同區域申請時，需要準備不同的資料。

(二) 待解決的問題

1. 支持性資料包括 BCS 分類及免除試驗，

(1) BCS 分類的支持性資料，例如溶解度(Solubility)高低，是以最高治療劑量(highest therapeutic dose)或最高單位含量(highest dose strength) 來界定。穿透性(Permeablity) 評估是以體外或體內或兩者的方法，界限如何設定。文獻資料可否做為依據等議題都是本次會議討論的重點。

(2) 免除試驗的支持性資料：

高溶解度藥品分屬 BCS Class I 及Ⅲ，溶離比對試驗界限值(Cut-off)的設定。測試品與對照品的配方比對，重要賦形劑(critical excipients)的影響評估，配方賦形劑含量的比對標準，確認非屬重要性賦形劑的資料型態。

(3) 其他

溶離比對試驗條件的設定，例如溶離儀器轉速的設定與調整。對照品如有多種單位含量時，BCS biowaiver 的比對方式， 是要逐一比對或以一應多。

（三） 本次會議重點

議題	進展	結論	備註
溶解度(Solubility)			
Use highest strength or highest dose.	美國 FDA 主張以 highest strength 作為溶解度高低的判定。歐盟及修訂後的 WHO 指引則以 highest dose 能否於 250 毫升水溶液完全溶解為判定基準。	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℃. 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 demonstrate that the pharmacokinetics, i.e., AUC and Cmax parameters, are dose proportional over a dose range that includes the highest therapeutic dose.	美國 FDA 對結論表示遺憾。 我方與韓國表示支持美國。
穿透性(Permeability)			
Use of in vitro CaCO2 cells data.	美國 FDA 可接受單以 Caco2 體外資料作為高穿透性的支持性資料，但 EMA 和加拿大仍以人類體內試驗為主，體外資料為輔。	The assessment of permeability can be based on the extent of absorption derived from human pharmacokinetic studies (e.g., absolute bioavailability or mass balance) and/or from in vitro testing using Caco-2 cell lines. Caco-2 cell permeability assays used in support of high	日方支持 EMA 和加拿大說法。 我方無 Caco-2 cell lines 之審查經驗。

		permeability are limited to passively transported drugs and should be appropriately validated and standardized.	
Evaluation of extent of absorption (ADME).	常用評估方法與準確性 Abs BA ADME-urine only ADME-urine and faecal metabolites	High permeability can be concluded when the absolute bioavailability is ≥ 85 %. High permeability can also be concluded if ≥ 85% of drug is recovered unchanged in urine. If mass balance studies are used to demonstrate high permeability, additional data to document the drug's stability in the gastro-intestinal tract is required. Data from mass balance studies may also support high permeability if the sum of urinary and fecal recovery of total drug material is ≥ 85 %.	
What is BCS?	BCS 分類 Ⅰ高溶解度高穿透性 Ⅱ低溶解度高穿透性 Ⅲ高溶解度低穿透性 Ⅳ低溶解度低穿透性	A drug product is eligible for a BCS-based biowaiver providing that the drug substance(s) satisfy the criteria regarding solubility and permeability (BCS Class I and III), the drug product is an immediate-release solid oral dosage form, and the drug product is a dosage form that is the same as the reference product.	口腔或舌下吸收不適用 biowaiver 申請
溶離比對試驗(Dissolution)			
Rotation speed and dynamics.	Obtain examples on rotation speed and dynamics in case rpm increases from 50 to 75 rpm (paddle).	Agitation: paddle apparatus - 50 rpm basket apparatus - 100 rpm	我國範圍較寬 網籃(basket) 50-100rpm 攪拌槳(paddle) 50-75rpm

Rotation speed/coning.	MHLW/PDMA: use of paddle 50 rpm. In case of coning, as alternative the basket method 100 rpm should be used. Share experience and supporting data.	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.	日本不接受攪拌槳(paddle) 75rpm 轉速
Dissolution media water.	MHLW/PDMA: use of water as additional dissolution media. Share experience and supporting data that water may be not a good media.	Three buffers: pH 1.2, pH 4.5, and pH 6.8. Pharmacopoeia buffers should be applied. Additional investigation may be required using purified water.	日本建議以註解標記可能額外要求以純水為溶媒進行溶離，不管 Pharma 及 EfPIA 的質疑。
Use of enzymes in dissolution media.	Gather data on pro's and con's. 日本認為溶媒加酵素(enzyme)是不當的	In the case of gelatin capsules or tablets with gelatin coatings, the use of enzymes may be acceptable, if appropriately justified.	日本建議以註解標記特殊情況下接受溶媒加入 enzyme
Additional dissolution testing around pKa	MHLW/PMDA: request of additional data. 日本的基準，溶媒的選擇係依對照品的溶離情況而定，而非原料藥的特性。日本建議註解標記除採用 pH4.5 溶媒外，特定 pH dependent 產品將被要求其他 pH 例如 Pka 溶媒進行溶離。		日本的建議不為工作小組所接受
F2 calculation.	Use reference and Test or Reference or Test for 85% cut-of point.	Not more than one mean value of ≥ 85% dissolved for any of the formulations.	歐盟、美國及 WHO 計算方式不同
Buffer media	Comparison of regional buffer media	The compendia do <u>not</u> describe specific methods on how to measure solubility. The compendia describe how to prepare buffers to represent various pH values.	Differences in buffer preparation are <u>not</u> significant
High potency drug.	Additional data/testing needed. Acceptance?	Options for low-content forms /non- standard	未做決定

配方(Formulations)			
API: different salts.	May the BCS biowaiver applicable in case of different salts. Experience/supporting data.	Ethan Stier 藥劑相等品(相同鹽類)	EU 相對嚴格但可接受
Pro-drugs.	BCS biowaiver applicable only when pro-drug is completely absorbed. FDA examples of opposite.	Mehul Mehta, Ethan Stier	
Critical drugs.	Experience with critical drugs.	For BCS Class I drugs, some differences between the test and reference formulation are permitted except in excipients which could affect absorption. BCS Class III drug substances often exhibit gastrointestinal region specific absorption.	少數賦形劑例如 Mannitol、Sorbitol、Sodium acid pyrophosphate、Oleic acid、PEG 400 等可能影響腸道穿透
Similarity in excipients.	What is similar? Experience with SUPAC.	BCS Class III products, excipients in the proposed (test) formulation should be qualitatively the same and quantitatively similar to that of the reference product.	未有深入討論
指導原則草案(Draft guidance)			
Draft guidance.	Prepare draft version.	Rapporteur/Jan Welink.	完成草案第二版

參、 心得及建議

一、 本次會議主要進展如下

(一) 完成 BCS biowaivers 指導原則草案(draft guidance)。

(二) 溶解度：究竟以最高單一治療劑量(highest single therapeutic dose)或最高單位含量(highest dose strength) 來界定溶解度高低，仍存有不同看法，大部分時候兩者是相等的，可能以額外註解的方式解決，法規單位需要攜回與各區域專家確認。

(三) 穿透性與吸收：主要爭議點在於 Caco2 cell line 體外資料能否如同人體資料作為高穿透性的主要支持性資料，美國 FDA 似乎已有足夠證據顯示 Caco2 可作為人體內吸收的指標，但大部分區域仍缺乏以此為主要資料的審查經驗，工作小組未達共識，現行方案是將 Caco2 cell line 列入指導原則中，載明試驗條件，與各區域專家確認。

(四) 溶離比對試驗：溶離裝置與轉速設定為攪拌槳(paddle) 50rpm、網籃(basket) 100rpm，溶媒為 pH1.2, 4.5 及 6.8，藥典要求之溶離條件。此外因不同法規單位要求，如下建議

1. 日本 MHLW/PMDA 建議在攪拌槳(paddle)發生 coning 時，僅可以網籃裝置作為替代而非增加轉速。
2. 日本 MHLW/PMDA 要求增列水為溶媒，以加註方式記載於指導原則，但不限制其他會員也須接受。
3. 日本 MHLW/PMDA 除了 85%，增加以 60%作為容離相似的判定已獲解決，因速放劑型不需做此考量。
4. 加拿大建議 high potency 藥物以量產批次的產品進行溶離比對試驗，雖不放入指導原則，可能放在 Q&A。
5. 日本 MHLW/PMDA 不允許 gelatin capsules 溶媒加入酵素，其建議的字句獲得同意放入指導原則中。
6. 日本 MHLW/PMDA 要求額外 pH 進行溶離比對試驗，被認為與 biowaiver 不相干，PMDA 同意將此議題攜回與他們的專家討論。
7. 以 F2 計算作為溶離比對相似的判定。
8. 不同單位含量間的免除試驗如何進行，將進一步討論。

(五) 配方

1. 申請免除 BE 試驗(biowaiver)限於 IR、藥劑相等品(相同鹽類)，EU 相對嚴格但可接受。
2. 原型藥(prodrug)能否用於免除 BE 試驗，FDA 部分同意。
3. 重要賦形劑經廣泛研析後，僅有少數賦形劑可能會影響，可能不是重要的問題了，但仍未能確定。

4. 非屬重要賦形劑的影響仍待進一步評估。

二、 美國 FDA 、歐盟 EMA 及日本 MHLW/PMDA 在本次會議的表現

(一) 不可諱言，在本次研討會歐、美、日三方主管機關的投入，仍屬美國 FDA 最多，而展現出審查經驗、案例分享及法規邏輯也較完整。

(二) 歐盟則由荷蘭及德國代表參加，其中荷蘭 Dr. Jan Welink 並擔任本工作小組召集人，負責主持會議。德國 Dr. Henrike Potthast 對 BCS based biowaiver 相對嚴謹，其主張相較美國 FDA 保守，故兩大法規主體意見常相左。當意見不一致時，主席 Dr. Jan Welink 常藉著詢問其他法規單位的意見以求達到共識，其中 WHO 代表 Dr. John Gordon 是加拿大人，為主席 Dr. Jan Welink 多年好友，會幫忙打圓場，另外拉著加拿大健康部(Health Canada, 簡稱 HC)代表表示意見， 然本次國際產業協會代表多來自歐洲，所以美國 FDA 的主張被孤援，例如美國 FDA 的主張以 highest strength 作為溶解度高低的判定時，與會者大部分支持歐盟主張，當我方與韓國表示支持美方主張時，美方代表竟來表示感謝，讓我深刻體會到關鍵少數的重要。台灣雖然小，如何發揮關鍵少數的力量，立足於國際社會也是未來可思考的方向。

(三) 日本 MHLW/PMDA 及產業 JPMA 代表共 6 人，會議期間都在一起，鮮與其他區域代表交換意見。但極力爭取在指導原則加入他們原有基準的主張，即使備註方式也行。

三、 本次會議的學習

為達 ICH 國際法規協和的目標，法規單位代表、國際公協會代表及區域專家從蒐集資料及論述主張，是參加本次工作小組會議的寶貴學習。本次從美國 FDA 的經驗分享學到開放角度的管理 BCS-based biowaivers，從歐盟代表的論述學到以嚴謹態度對待生體相等性試驗的免除，從日本 MHLW/PMDA 的資料整理學到法規協和的技巧。從歐洲藥業協會(European Federation of Pharmaceutical Industries and Associations, 簡稱 EFPIA)熱情的參與，並直接表達希望指導原則擬定清楚，以利業界資料的準備，學習到明確的規範反而是產業所期待的。

四、 醫藥法規國際化是必走的路

台灣要發展生技，醫藥法規國際化是不可或缺的一環，如何在人力與資源有限的情況下，精進藥品技術文件要求，是重要的課題。有關 BCS

biowaiver 我們目前已有兩項公告，然實際 BCS biowaiver 申請案卻非常有限，更遑論審查經驗的累績。參加本次 M9 工作小組有助於我國了解國際間 BCS 免除生體相等性試驗的要求，以利規劃及推動我國 BCS 免除生體相等性試驗，提升國內藥品品質管理。

五、 感恩、論述有據與包容

這是我第一次參加 ICH 工作小組面對面會議，出發前有許多不了解及憂心，當抵達會場時，工作人員的友善立時解除我的焦慮，例如很快幫我建立帳號，讓我可進入 ICH 群組網頁下載所需資料。還有參加工作小組會議前，先進行 ICH 簡介，了解程序及工作小組運作模式，如何經由 ICH 平台達到國際醫藥法規的協和。這樣的平台如何有效率執行法規協和及相關人員的素養培育，皆是我國可效法的地方。

因為過去美國在東亞的影響力，我國與韓國在醫藥法規上較偏向美規，而學習到的思維也較傾向美國 FDA 的規定，參加本次會議讓我感受到醫藥品的技術法規，除了科學依據外，其實具有相當的協和空間，論述相對變得重要。

為提升我國藥品產業的國際競爭力，對於不同區域的醫藥法規需採更包容的態度，以利邁向國際化的路徑。

附錄

壹、 工作規劃與期程

Action	**date**	**status**
Adoption of the topic by Approval of ICH Assembly	June 2016	Adopted/Finalised.
Agreement of Concept Paper and Business Plan by Informal WG	Aug. 2016	Agreement/Finalised.
Adoption of Concept Paper and Business Plan by MC	Sept. 2016	Adopted/Finalised.
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	Planned 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) 將經由電話會議持續更新指導原則草案，對本次會議共識蒐集更多資料。	Planned; date to be decided.	預計 2017 年 7 月或 8 月進行電話會議
Third EWG meeting (Switzerland)	Nov. 2017	計畫中
Adoption of Step 2 a/b Document	1 - 2Q 2018	計畫中
Adoption of Step 4 Document	2Q 2019	計畫中

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參、　活動照片

指導原則草案

ICH M09: Biopharmaceutics Classification System-based Biowaivers
Technical Document DRAFT version 2

(date June 05, 2017)

1. INTRODUCTION

1.1. Background and Objective

Two drug products containing the same active substance are considered bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and their bioavailabilities (rate and extent) 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 pharmacokinetic parameters AUC (the area under the plasma concentration time curve), Cmax (the maximum plasma concentration), and tmax (time to maximum plasma concentration) are generally used to assess the rate and extent of drug absorption. Bioequivalence can be determined when the pharmacokinetic results for the tested products are within the established acceptance limits.

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 absorption 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 guideline 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 between products used in early clinical development through commercialization, for line extensions of innovator

products, in applications for generic drug products, and variations that require bioequivalence testing.

The BCS-based biowaiver is only applicable to immediate release, solid, orally administered dosage forms demonstrating systemic action. Drug products having a narrow therapeutic index are excluded from consideration for a BCS-based biowaiver in this guidance. Fixed-dose combination (FDC) products may be eligible for a 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. Support of the biopharmaceutics classification of medicinal products

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, ether, 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℃. 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 demonstrate that the pharmacokinetics, i.e., AUC and Cmax parameters, are dose proportional over a dose range that includes the highest therapeutic dose.

The applicant is expected to establish experimentally the equilibrium solubility of the drug substance over the pH range of 1.2 – 6.8 at 37℃ ± 1℃ using shake-flask technique or a similar method, if justified. At least three buffers within this range i.e., at pH 1.2, 4.5 and 6.8, should be evaluated. In addition solubility at the pKa must be evaluated if it is within

the specified pH range. The pH for each test solution has to be confirmed before and after the addition of the drug substance in order to ensure pH stability of the buffered medium. 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 (3) determinations at each solubility condition/pH is necessary to demonstrate solubility using a validated method (with appropriate compendial references). Adequate stability of the drug substance in the solubility media should be demonstrated. In case the drug substance is not stable over the pH range it implies that solubility cannot be 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.

2.2. Permeability

The assessment of permeability can be based on the extent of absorption derived from human pharmacokinetic studies (e.g., absolute bioavailability or mass balance) and/or from in vitro testing using Caco-2 cell lines.

High permeability can be concluded when the absolute bioavailability is ≥ 85 %. High permeability can also be concluded if ≥ 85% of drug is recovered unchanged in urine. If mass balance studies are used to demonstrate high permeability, additional data to document the drug's stability in the gastro-intestinal tract is required. Data from mass balance studies may also support high permeability if the sum of urinary and fecal recovery of total drug material is ≥ 85 %. Only oxidative and conjugative metabolites can be considered. Metabolites produced through reduction or hydrolysis should not be included. Unchanged drug in feces cannot be counted toward the extent of absorption. These data can be derived from published literature or product information/review reports from regulatory agencies.

Caco-2 cell permeability assays used in support of high permeability are limited to passively transported drugs and should be appropriately validated and standardized. The definition of passive transport and methodology conditions are described in Annex 1. The results from Caco-2 permeability assays should be discussed in light of available published literature data on human absorption.

If high permeability is not demonstrated, the drug is considered to have low permeability (e.g. BCS class III).

3. Support of the eligibility of a drug product for a BCS-based biowaiver

A drug product is eligible for a BCS-based biowaiver providing that the drug substance(s) satisfy the criteria regarding solubility and permeability (BCS Class I and III), the drug product is an immediate-release solid oral dosage form, and the drug product is a dosage form that is the same as the reference product.

Drug products subject to buccal or sublingual absorption are not eligible for a 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 consumed with water.

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

3.1. Excipients

Excipient differences between the proposed test product and the reference should be assessed in terms of their potential to affect the absorption process. This should include consideration of the drug substance properties as well as excipient effects.

For BCS Class I drugs, some differences between the test and reference formulation are permitted except in excipients which could affect absorption. The possible effects of these excipients, e.g. based upon e.g. based on literature data, on aspects of the absorption process such as solubility, gastrointestinal motility, transit time, and intestinal permeability should be considered. Examples of excipients that may affect absorption are alcohol-sugars (e.g. mannitol, sorbitol), or surfactants (e.g. sodium lauryl sulfate). The amount of these excipients included in the formulation should be considered carefully, for example, small amounts included in the coating or levels below documented thresholds of effect may be of less concern. Ideally, these issues should be addressed during product development.

BCS Class III drug substances often exhibit gastrointestinal region specific absorption. Therefore, BCS Class III products are considered to be more susceptible to the effects of

excipients. Hence, unless otherwise justified, excipients in the proposed (test) formulation should be qualitatively the same and quantitatively similar to that of the reference product. In line with BCS Class I drugs, special consideration should be given to excipients that may affect absorption in the amounts present in the formulation.

3.2. In vitro dissolution

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. The comparative in vitro dissolution experiments should use compendial apparatuses and follow the compendial procedures.

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
- Temperature of the dissolution medium: 37±0.5℃
- Agitation: paddle apparatus - 50 rpm
  basket apparatus - 100 rpm
- Sampling schedule: e.g. 5, 10, 15, 20, 30 and 45 min
- 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. Pharmacopoeia buffers should be applied. Additional investigation may be required using purified water.
- Organic solvents are not acceptable and no surfactants should be added.
- In the case of gelatin capsules or tablets with gelatin coatings, 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.

To qualify for a biowaiver, for BCS Class I drug substances, both the test product and reference product should display either very rapid (>85% dissolved in ≤15 minutes) or comparable rapid (>85% dissolved in ≤30 minutes) in vitro dissolution characteristics under the defined conditions.

To qualify for a biowaiver, for BCS Class III drug substances, both the test product and reference product should display very rapid in vitro dissolution (>85% dissolved in ≤15 minutes) characteristics under the defined conditions.

For the comparison of dissolution, where applicable, the similarity factor f2 should be estimated, i.e. by using the following formula:

$$f2 = 50 \cdot \log \{[1 + (1/n)\Sigma t=1n (Rt - Tt)2]-0.5 \cdot 100\}$$

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.

Mean dissolution values can be used to estimate f2. 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 formulations
- Twelve individual values for every time point for each formulation
- Not more than one mean value of ≥ 85% dissolved for any of the formulations.
- To allow the use of mean data, the coefficient of variation should not be more than 20 percent at the first time point (e.g., 5 minutes), and should not be more than 10 percent at other time points.

Two dissolution profiles are considered similar when the f2 value is ≥50. When both test and reference products dissolve 85% or more of the label amount of the drug in 15 minutes in one of the three dissolution media recommended above, the dissolution profile comparison with an f2 test for this media is unnecessary.

For FDCs, the similarity of the dissolution profiles has to meet the criteria for all active pharmaceutical ingredients in the FDC.

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 sponsor shall provide complete information on the critical quality attributes of the drug substance and finished product for both the test and reference product including, but not limited to: polymorphic form and enantiomeric purity; and any information on bioavailability or bioequivalence problems with the substance or drug product, including literature surveys and sponsor 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 an identification of all excipients, and qualitative and quantitative differences between the test and reference products.

A full description of the analytical methods employed, including validation, should be provided. A detailed description of all test methods and solutions, including test and reference batch information [unit dose (milligram and %), batch number, manufacturing date and batch size where known, expiry date, and any comments] examined is required. 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 process during sampling, volume, etcetera.

5. Glossary

AUC: Area under the concentration time curve

BCS: Biopharmaceutics Classification System

Cmax: Maximum concentration

e.g.: Exempli gratia (for example)

FDC: Fixed-dose combination

ml: Milliliter

Pharmaceutically equivalent: Medicinal products containing the same amount of the same active substance(s) in the same dosage forms that meet the same or comparable standards.

Pharmaceutical alternatives: Medicinal products with different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active moiety, or which differ in dosage form or strength.

pKa: Acid dissociation constant at logarithmic scale

tmax: time to maximum plasma concentration