ICH日本シンポジウム2018
（第38回ICH即時報告会）

ICH M9：BCSに基づくバイオウェーバー

Biopharmaceutics Classification System-based Biowaivers

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本日の内容

- 背景
- M9：概要と経緯
- 神戸会合の成果
- ドラフトガイドラインについて
- 今後の予定

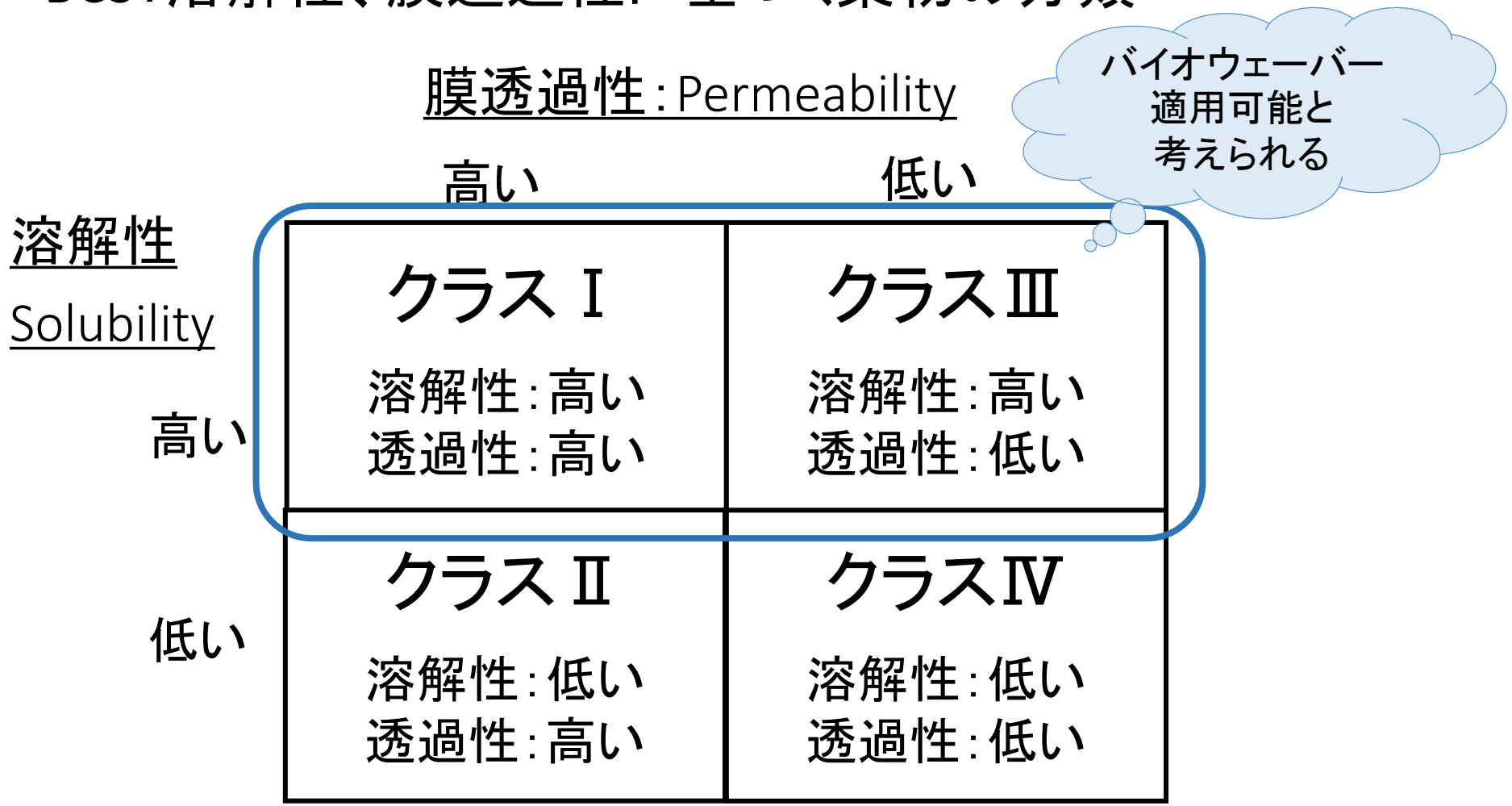
背景

- 製剤の処方変更、後発医薬品の承認
  臨床（*in vivo*）データによる保証が原則
  → ヒトを対象とした生物学的同等性（BE）試験
- BE試験の免除（バイオウェーバー）
  原薬物性，製剤特性を踏まえ
  → *in vitro*データ（溶出試験）による保証も可能

Biopharmaceutics Classification System（BCS）
に基づくバイオウェーバー

Biopharmaceutics Classification System（BCS）

BCS：溶解性、膜透過性に基づく薬物の分類



現状の課題・M9の目的

【現状の課題】

- 各極のガイドラインにおいて、バイオウェーバーに係る基本方針やBCSの分類/BCSに基づくバイオウェーバーの要件が異なる。

【M9の目的】

- BCSに基づくバイオウェーバーに係る基本方針の国際調和
- 基本的な考え方の提示
  - ➢BCSの分類に必要なデータ
  - ➢BCSに基づくバイオウェーバーに必要なデータ

M9：EWG活動経緯

- 2016年　6月　リスボン会合で新規トピックとして採択
- 2016年　9月　Concept paper/Business planの合意
- 2016年 11月　大阪会合（キックオフ会議）
  - バイオウェーバーの適用範囲の合意（クラスI及びIII）
  - BCSの分類・バイオウェーバーに必要なデータの整理
- 2017年　6月　モントリオール会合（2回目対面会議）
- 2017年 11月　ジュネーブ会合（3回目対面会議）
- 2018年 1、3月　電話会議
- 2018年　6月　神戸会合（4回目対面会合）

  step 1 文書完成

  step 2a　→　step 2b 承認

Progress in KOBE meeting 1/2

1. Dissolution

【Discussion point】

Use water as additional dissolution medium

【Outcome】

Water as medium added to the regular media pH 1.2, 4.5 and 6.8

Progress in KOBE meeting 2/2

2. Excipient

【Discussion point】

Criteria for determining acceptable excipient differences for BCS Class I and III biowaivers

【Outcome】

Class I : Excipients that may affect absorption should be qualitatively the same and quantitatively similar

Class III: All of the excipients should be qualitatively the same and quantitatively similar (except for film coating or capsule shell excipients)

Draft Guideline-Contents

1. INTRODUCTION
   - 1.1 Background and Objective
   - 1.2 Scope
2. Biopharmaceutics classification of the drug substance
   - 2.1 Solubility
   - 2.2 Permeability
3. Support of the eligibility of a drug product for a BCS-based biowaiver
   - 3.1 Excipients
   - 3.2 *In vitro* dissolution
4. Documentation
5. Glossary

Draft Guideline -Scope

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.

Draft Guideline -Drug substance

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.

Draft Guideline -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.

Draft Guideline-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.

Permeability can be also assessed by validated and standardized in vitro methods using Caco-2 cells(see Annex I).

Draft Guideline-Excipients

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.

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.

Draft Guideline -Excipients(Cont.)

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%

Draft Guideline –*In vitro* Dissolution

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.

Draft Guideline - *In vitro* Dissolution(Cont.)

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.

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.

今後の予定

- 2018年3～4Q　　パブリックコメントの募集
- 2019年2Q　　Step 4到達（目標）