ICHアムステルダム会合　第40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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Agenda

- **Background**
- **M9 : Overview and Activity contents**
- **Progress in Amsterdam meeting**
- **Updated draft guideline**
- **Work Plan**

Background

- 先発医薬品の処方変更や、後発医薬品の承認等には、臨床試験（***in vivo***）のデータによる保証が原則である。

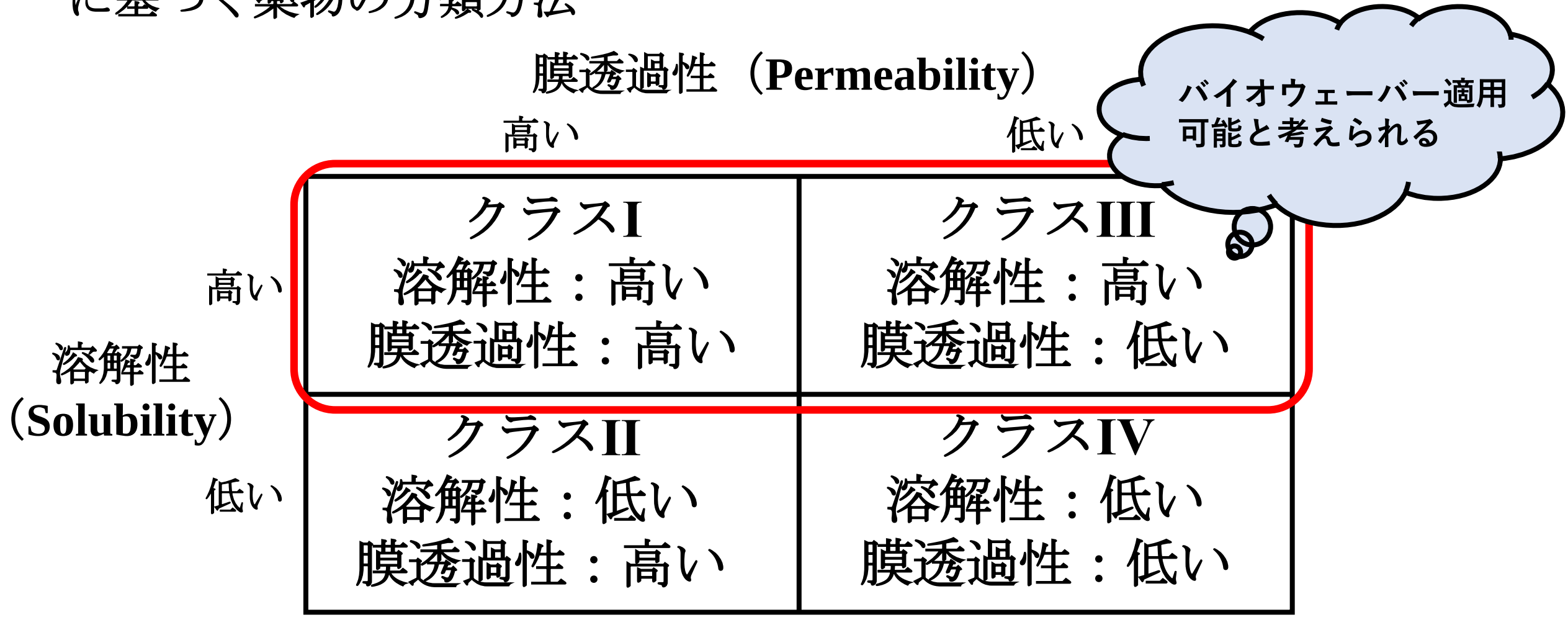
→ヒトを対象とした**BE**試験の実施が要求される。

- 一方、**BE**試験の免除（バイオウェーバー）の方法論の一つとして、原薬の物性（溶解性、膜透過性）及び製剤特性（添加剤）を踏まえた***in vitro***データ（溶出試験）による製剤間の**BE**の保証も可能と判断。

「Biopharmaceutics Classification System（BCS）に基づくバイオウェーバー」として、ICH M9ガイドラインの作成を開始。

Biopharmaceutics Classification System（BCS）

- 原薬の溶解性（Solubility）及び膜透過性（Permeability）に基づく薬物の分類方法



Problem and Purpose in M9 Guideline

【Problem】

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

【Purpose in M9】

- BCSに基づくバイオウェーバーにかかる基本方針の国際調和を目指す。

M9 : Activity Contents

- **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）
- **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　6月**　神戸会合（4回目対面会合）**Step 2到達**
- **2018年 11月～2019年1月**　パブリックコメント
- **2019年　6月**　アムステルダム会合（5回目対面会合）

  各局のパブリックコメントを踏まえ、ガイドライン案の修正を実施

Progress in Amsterdam meeting

Most important topics:

1. **Different salt**（塩違いの薬物のバイオウェーバー）
2. **Solubility testing**（溶解性評価試験）
3. **Excipients, including examples of expected differences**
   （許容される添加剤の変更の程度）
4. **Water as dissolution media**（精製水の要否）
5. **Rotation speed in dissolution testing**（回転数の規定）

1. Different salt

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.

1. Different salt

- **Some agencies do not agree this concept.**

- **Although some agencies agree to contain the concept in M9 guideline, not accepting the application of different salt biowaivers even if the related data are submitted.**

2. Solubility testing

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.

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.

3. Excipients, including examples of expected differences

For BCS Class I drugs, qualitative and quantitative differences in excipients are permitted, …….. Additionally, the cumulative difference for excipients that may affect absorption should be within ± 10%.

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.

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

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%

4. Water as dissolution media

The following conditions should be employed…….

- 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.~~

In cooperation with JPMA and JGA, we tried find the cases that met the following conditions,

- Drug substance(s) is classified as BCS class I or III
- Dissolution profiles between test and reference products are different only in condition of purified water.
- In human BE study using the above products, they are not bioequivalent.

4. Water as dissolution media

【Result】

- At present, the evidence for requiring the dissolution test with purified water cannot be found from the survey.

【Conclusion】

- The phrase is to be deleted on the condition that the drug product contains a highly soluble drug substance and shows rapid or very rapid dissolution profiles.

5. Rotation speed in dissolution testing

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.

This proposed text should be reconciled.

5. Rotation speed in dissolution testing

- **The possibility of false positive is shown about increasing the rotation speed to a maximum of 75 rpm to overcome coning in literature.**

- **EWG members cannot completely ignore the findings, so this phrase is still under discussion.**

Work Plan

- **Final draft guideline will be reviewed by each region.**
- **The EWG would like to prepare an Appendix document to be issued concurrently with the guideline.**
- **It would be ideal to achieve Step 4 for both the Guideline and the Appendix document simultaneously (before November 2019).**

Work Plan

Expected Completion date	Deliverable
November 2019	・Guideline at Step 4
November 2019	・Appendix document for training and implementation