ATIM Session 2

Chairman

Dr. Ryosuke Kuribayashi

Pharmaceuticals and Medical Devices Agency(PMDA)

Japan

Panelist

Dr. L. Rizka Andalucia

National Agency of Drug and Food Control (BPOM)

Indonesia

Panelist

Mr. Chien-Liang Lin

Taiwan Food and Drug Administration(TFDA)

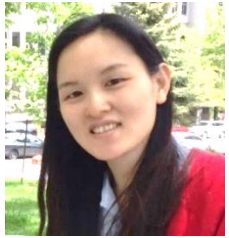
Taiwan

Panelist

Ms. Ya-Wen Chang

Center for Drug Evaluation(CDE)

Taiwan



Speaker

Mr. Tomonori Nakagawa

Japan Pharmaceutical Manufacturers Association(JPMA)

Japan

ATIM Session 2

Post approval change

Position paper on efficient CMC/GMP for Access To Innovative Medicine (proposed revision)

GOAL and ACHIVEMENT

APAC 2021 proposes the following recommendations for the efficient post approval change activities while keeping regulatory science justification:

- Introduce science and risk base approach to secure product stability during/after post approval change
- **Implement mutual understanding and commitment approach by increasing regulatory reliance and convergence among Health Authorities and streamline of communication from the industry**. This could be applied for the change management using the tools such as Post-Approval Change Management Protocol (PACMP) and Biopharmaceutics Classification System (BCS)
- Increase opportunities for dialogue and collaboration between industry and regulators to discuss integrated science and risk based approaches **to have regulatory flexibility for the Product Lifecycle Management and to support the stability of the product**.

Position paper on efficient CMC/GMP from ATIM

About GMP Qualification

- Asia Training Center
- SMF Template

Pharmaceutical Quality System

- Promote ICH Q10

CMC Registration

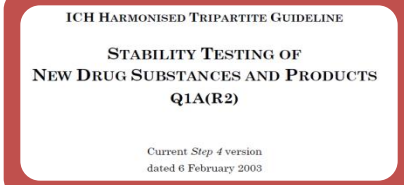
- Science-base and Risk-base approach
- Established Condition

Change Mgmt (CM)

- PACMP / BCS
- Use of Existing Data (ie Stability data)

Tools for Convergence of Post-approval Change Control Stability Study

Introduce **science-base and risk-base approach** for change review process for efficient use of resources such in WHO guideline

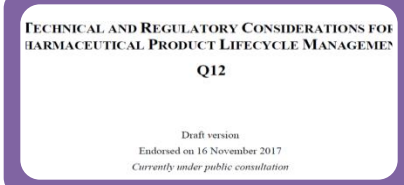

ICH HARMONISED TRIPARTITE GUIDELINE

STABILITY TESTING OF NEW DRUG SUBSTANCES AND PRODUCTS Q1A(R2)

Current *Step 4* version dated 6 February 2003

ICH Q1 series

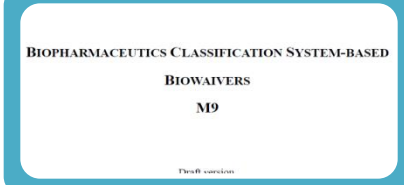
- Stability study program for new DS/DP
- Matrixing and Bracketing for Stability study


TECHNICAL AND REGULATORY CONSIDERATIONS FOR PHARMACEUTICAL PRODUCT LIFECYCLE MANAGEMENT Q12

Draft version
Endorsed on 16 November 2017
Currently under public consultation

ICH Q12 (Now Step 4 document!)

- Product Lifecycle Management – Established Condition, PACMP
- Stability Data Approaches to Support the Evaluation of CMC Change


BIOPHARMACEUTICS CLASSIFICATION SYSTEM-BASED BIOWAIVERS M9

Draft version

ICH M9 (Now Step 5 document in Japan!)

- Recommendations biopharmaceutics classification of medicinal products
- Support the waiver of bioequivalence studies

APAC

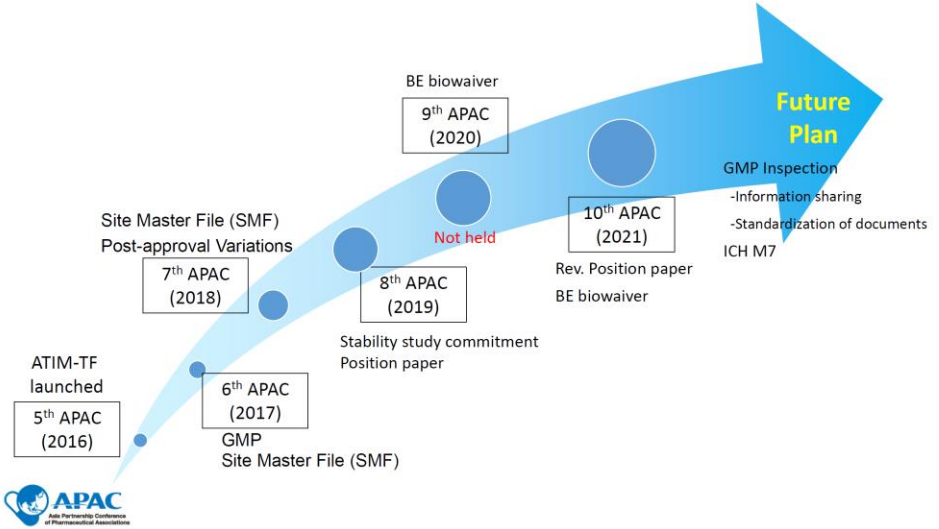
ATIM-TF history report

History Report of ATIM-TF activity was prepared as a memorial material at 10th anniversary APAC.

8th APAC ATIM session summary

The post-approval change procedure by stability study commitment

- JPMA proposed the 'position paper' to accomplish APAC mission, including the post-approval change procedure.
- The position paper recommends the procedure for change application to employ stability commitment, instead of the submission of newly collected stability data throughout the shelf life at the time of change application. Discussion was made on this point with the participants in ASEAN.
- All the authorities participated in a panel discussion (Malaysia, Thailand and Indonesia) agreed to consider this commitment procedure based on the science and risk based approach, by keeping regulatory science justification for the commitment.
- PMDA introduced PACMP (Post-Approval Change Management Protocol) pilot program, starting from April 2018 in Japan.



Position Paper and History Report were uploaded on the APAC website.

Background for Discussing Biopharmaceutics Classification System in Asia

- Introduction of harmonized BE biowaiver will **reduce unnecessary clinical study** and may proceed efficient change control procedure based on in vitro
- **Rapid solid dosage drug is better way to bring the drug product to the patient** who need drugs but difficult to visit hospitals periodically
- Implement and promote biowaiver based on science base
- Although ASEAN GL for the Conduct of BA and BE Studies (Final: Mar. 2015) exist to present BE/BA test, however, there is no clear BE Biowaiver ASEAN GL in Asia and survey for current state of BE studies was conducted by questionnaire to each association.
- Introduce BCS (Biopharmaceutics Classification System-based Biowaiver (ICH M9)) and promote within Asia?

Brand Drug Bioequivalency

Pharmaceutical life cycle management:

Excipient Change
Manufacturing Changes
(API, Drug product)

Growth and emerging market expansion:

Procurement
New API source, scale up

Comparison of BCS biowaver criteria in Guidelines

Authority	Classification	Highest strength or max dose	pH range	Difference salt	Highly permeability in vivo	In vitro permeability	Dissolution temp.	3pH value
ICH	Class I & III	Dose	1.2-6.8	No	>85%	Yes	37±1	1.2, 4.5, 6.8
EMA	Class I & III	Dose	1-6.8	Yes	>85%	No(supportive)	37±1	1.2, 4.5, 6.8
WHO	Class I & III	Dose	1.2-6.8	No	>85%	No(supportive)	37±1	1.2, 4.5, 6.8
ASEAN	Class I & III	Dose	1-6.8	Yes	>85%	No(supportive)	37±1	1.2, 4.5, 6.8
Taiwan	Class I & III	Strength	1-6.8	No	>85%	No(supportive)	37±1	1.2, 4.5, 6.8
Korea	Class I	Strength	1-.7.5	No	>90%	Yes	37±0.5	1.2, 4.0, 6.8
Singapore	Class I & III	Dose	1-6.8	Yes	>85%	No(supportive)	37±1	1.2, 4.5, 6.8
Malaysia	Class I	Dose	1-6.8	Yes	>85%	No(supportive)	37±1	1.2, 4.5, 6.8
USA	Class I & III	Strength	1-6.8	No	>85%	Yes	37±0.5	1.2, 4.5, 6.8
Australia	Class I & III	Dose	1-6.8	Yes	>85%	No(supportive)	37±1	1.2, 4.5, 6.8
Brazil	Class I	Dose	1.2-6.8	No	>85%	No(supportive)	37±1	1.2, 4.5, 6.8
Canada	Class I & III	Dose	1.2-6.8	No	>85%	No(supportive)	37±1	1.2, 4.5, 6.8

J. van Oudtshoon et al., J Pharm. Pharm. Sci., 21, 27-37(2018), and Katharina Holl, Deutsche gesellschaft fur regulatory affairs report(2019) (partially modified)

Different Biowaiver Guidelines

《EU》Guideline on the investigation of bioequivalence (2010)

《USA》Waiver of in vivo bioavailability and bioequivalence studies for immediate- release solid oral dosage forms based on a biopharmaceutics classification system guidance for industry (2017)

《JAPAN》Guideline for bioequivalence studies of generic products (2020 as Japanese only)

《ASEAN》Guideline for the conduct of bioequivalence studies (2015)

《WHO》WHO Technical Report Series 992. WHO Expert Committee on specifications for pharmaceutical preparations, 49th report, Annex 7(2015)

Issues

- It is necessary to converge the principals for Biowaiver (Biopharmaceutics Classification and standard for administration change)
- It is necessary to converge the data required fro BCS classification and evaluation method

Impact of the US FDA "Biopharmaceutics Classification System" (BCS) Guidance on Global Drug Development

- In 2017, US-FDA published an article to review the progress and application results of using BCS guideline to share the FDA's current thinking on areas of improvement of this guidance
- During the period between 2004 and 2017, >160 applications were approved, or tentatively approved, based on the BCS approach across multiple therapeutic areas;
- At least 50% of these approvals were in the central nervous system (CNS) area (2nd : anti-infectives and oncology)
- These findings indicate a robust utilization of the BCS approach toward reducing unnecessary in vivo BE studies and speeding up availability of high quality pharmaceutical products.

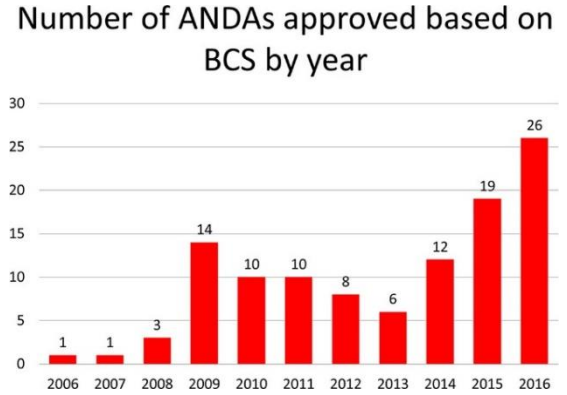


Table 1. BCS Class 1 Applications Received and Approved for New and Generic Drugs from 2004 to March 2017

type of application	new drug		generic drug
# applications	48		25
# approved (% of total)	28 (58%)		23 (92%)
	IND stage	NDA stage	
# applications	18	30	
# approved (% of total)	12 (67%)	16 (53%)	

Published in: Mehul U. Mehta; Ramana S. Uppoor; Dale P Conner; Paul Seo; Jayabharathi Vaidyanathan; Donna A. Volpe; Ethan Stier; Dakshina Chilukuri; Angelica Dorantes; Tapash Ghosh; Haritha Mandula; Kimberly Raines; Pariban Dhanormchitphong; Janet Woodcock; Lawrence X Yu; *Mol. Pharmaceutics* **2017,** 14, 4334-4338.

Impact of the US FDA "Biopharmaceutics Classification System" (BCS) Guidance on Global Drug Development

The success of BCS guidance is indicated in several ways:

A) On cost, the guidance has saved the industry in excess of $100 million. This estimate is arrived at using the methodutilized by Cook et al. 6 and using the number of approvals summarized in this article;

B) Several other agencies across the globe have issued their version of the BCS guidance. EMA formalized its position on BCS in 2010, ANVISA (Brazil) in 2011, and Health Canada has come out with their final position in 2014. Perhaps the greatest impact has been seen by the utilization of this approach by the WHO which has created its Essential Medicines list and several of these products are approved based on the BCS principles across many parts of the world where there is limited regulation; and

C) A very large number of human subjects have been spared from being subjected to unnecessary BE trials.

Development and Outline of ICH M9

- Simplified Approval of Formulation Change in Drug Product
  - Use of clinical data (*in vivo*) to assure the product reliability
  - Waiver of bioequivalence (BE) by human
- Waiver of BE test（Biowaiver）
  - Use physical property data of API and quality attribute of the drug product→Potential acceptance of the used of *in vitro data* to assure the change
  - Could be applied for Class I and Class III

Scope

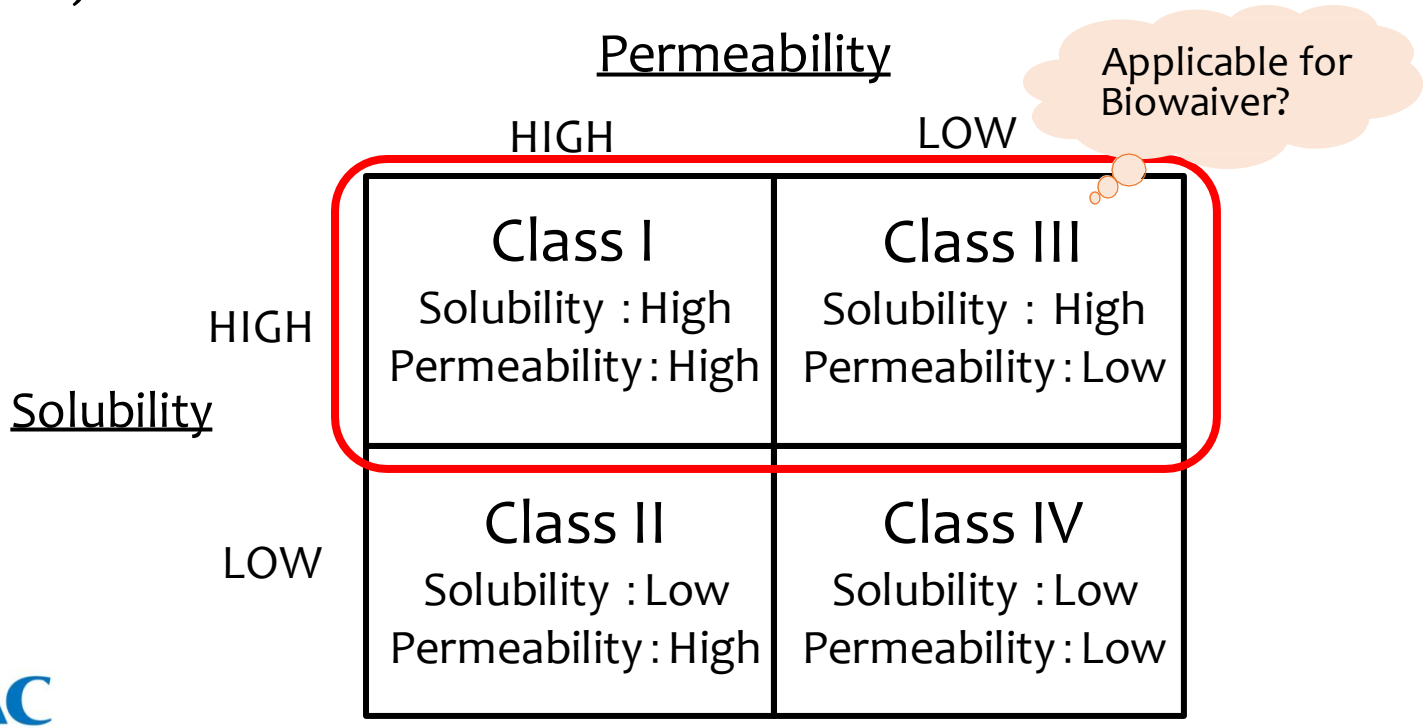
- Biopharmaceutics Classification System-based Biowaivers

Purpose

- A guideline related to BE test and its biowaiver
- Harmonization of global guideline
- Submission of basic information
  - Necessary data for BCS classification
  - Necessary data for biowaiver based on BCS

Biopharmaceutics Classification System(BCS)

- BCS : Classification of compound based on solubility and permeability (membrane)



Questionnaire about Bioequivalence Studies

- A questionnaire was conducted to APAC participating organization to seek current BE requirement for various changes propose
- In general, no BE change is required for minor proposed changes, but may require BE is the change impacts BA of the drug

Questionnaire about Bioequivalence Studies

Change item	Country A	Country B	Country C	Country D	Country E	Country F
Q1 *Dosage form*	Yes/in vivo ·need clinical study(MA) to change dosage form ·Not appricable to biowaiver	Yes/in vivo ·need BE study to change dosage form ·Class I, not narrow therapeutic drug, and dissolution rate is >85% within 15min	Yes/other ·need clinical study to change from fine granule to tablet, narrow therapy index, modified-release ·No change to the percentage and rapid of API in to system circulation	Yes/in vivo or vitro ·need BE study to change modified-release ·refer to SUPAC/ASEAN varidation guideline ·BCS Class I		Yes/in vivo or vitro ·need BE study(MA) to depend on BCS Class of API ·need BE study to modified-release ·BCS Class I & III
Q2 *Strength*	Yes/in vivo or vitro ·basically, need BE study to change strength ·change composition is low	Yes/in vitro ·basically, need in vitro study to change strength ·narrow therapeutic index or class IV need to BE study ·lower strength	Yes/other ·need clinical study to higher strength, narrow therapy index, controlled release ·in vitro study: lower strength, same site and same formulation ratio ·N/A	Yes/in vivo or vitro ·depend on dose proportionate ·BCS Class I		Yes/in vivo or vitro ·need BE study(MA)to depend on BCS Class of API ·need to BE study to the highest strength ·need BE study to modified-release ·BCS Class I & III
Q3 *Formulation change*	Yes/in vivo ·need clinical study to formulation change ·Not appricable to biowaiver	Yes/in vivo ·need BE study to major formulation change ·in vitro study need to minor formulation change	Yes/other ·in vitro study: change excipient component, narrow therapy index, ClassIV, coating weight ·No criteria of justification on BE waiver	Yes/in vivo or vitro? ·refer to SUPAC/ASEAN varidation guideline ·BCS Class I	Yes/in vivo or vitro ·need BE study(MA) to major change	Yes/in vivo or vitro ·need BE study(MA) to new excipient change ·need to in vitro study to same function excipient change(SUPAC GL) ·need BE study to modified-release ·BCS Class I & III
Q4 *API change*	Yes/in vitro ·need in vitro study .	Yes/in vivo or vitro ·need BE study to narrow therapeutic drug ·Normally, need in vitro study	Yes/other ·need BE study to mfg. site change ·in vitro study: process change ·No criteria of justification on BE waiver	Yes/in vivo or vitro? ·refer to SUPAC/ASEAN varidation guideline	Yes/in vitro ·need in vitro study to mfg. site/process of API	Yes/in vivo or vitro ·refer to ASEAN varidation guideline ·need BE study(MA) to API form change depend on BCS Class ·form change of BCS Class I & III API

Questionnaire about Bioequivalence Studies

Change item	Country A	Country B	Country C	Country D	Country E	Country F
Q5 *Excipient change*	Yes/in vivo or vitro ·need BE study or in vitro study according to change level .	Yes/in vivo or vitro ·need BE study or in vitro study according to change level .	Yes/other ·in vitro study: change excipient component, narrow therapy index, ClassIV, coating weight ·No criteria of justification on BE waiver	Yes/in vivo or vitro? ·refer to SUPAC/ASEAN varidation guideline		Yes/in vivo or vitro ·refer to SUPAC/ASEAN varidation guideline ·BCS Class I & III
Q6 *Mfg. site*	Yes/in vitro or No ·need in vitro study or batch analysis according to change level .	Yes/in vivo or vitro ·need BE study or in vitro study according to change level .	Yes/other ·need BE study ·No criteria of justification on BE waiver	Yes/in vitro ·refer to SUPAC/ASEAN varidation guideline	Yes/in vitro ·need in vitro study	Yes/in vivo or vitro ·need in vitro study to same formulation and mfg. equipment/process ·BCS Class I & III
Q7 *Batch size*	Yes/in vitro or No ·in vitro study: more than 10 times ·batch analysis: less than 10 times .	Yes/in vitro or No ·in vitro study: more than 10 times ·batch analysis: less than 10 times .	Yes/in vitro ·in vitro study: more than 10 times ·batch analysis: less than 10 times ·No criteria of justification on BE waiver	Yes/in vitro ·refer to SUPAC/ASEAN varidation guideline	Yes/in vitro ·need in vitro study	Yes/in vitro ·need in vitro study
Q8 *Mfg. equipment*	Yes/in vitro or No ·in vitro study: influence on product quality ·batch analysis: no influence on quality .	Yes/in vitro or No ·in vitro study: influence on product quality ·batch analysis: no influence on quality .	No	Yes/in vitro ·refer to SUPAC/ASEAN varidation guideline	Yes/in vitro ·need in vitro study	Yes/in vitro or No ·need in vitro study to mfg. principle change or major process change ·Normally no need
Q9 *Mfg. process*	Yes/in vivo or vitro or No ·need BE study or in vitro study or batch analysis according to change level .	Yes/in vivo or vitro ·need BE study or in vitro study according to change level .	Yes/other ·in vitro study ·No criteria of justification on BE waiver	Yes/in vitro? ·refer to SUPAC/ASEAN varidation guideline	Yes/in vivo or vitro ·need BE study(MA) to major change	Yes/in vivo or vitro ·refer to SUPAC/ASEAN varidation guideline ·BCS Class I & III

Significance for Expanding Biopharmaceutics Classification System in Asia

- BE biowaiver based on BCS can contribute the faster development, avoid unnecessary exposure of healthy patient during BE, and efficient review of formulation change in pre- and post- submission
- Rapid oral dosage formulation is an easy distribution of the drug products to the patients
- With development ICH guideline, how can we adopt new BCS and its method, to harmonize the procedure to adopt BCS approvals?
  - Including the criteria of BE for the approval changes

Thank you for your attention

10th APAC ATIM Session2

Consensus summary

- Expedite BE biowaiver for post approval change using in vitro evaluation by science and risk based approach.
- International guidelines of BE studies (such as ASEAN GL for the Conduct of BA and BE Studies (2015)) and domestic GL in Asian economies have been released. However, there are slight differences among them.
- Expect to provide innovative medicines to Asian patients faster by implementation of BCS-based biowaver (ICH M9) with obtained knowledges during development stage.