# National Regulatory Conference 2015

# Updates on Bioavailability/Bioequivalence Study Requirements Focusing on Biowaiver

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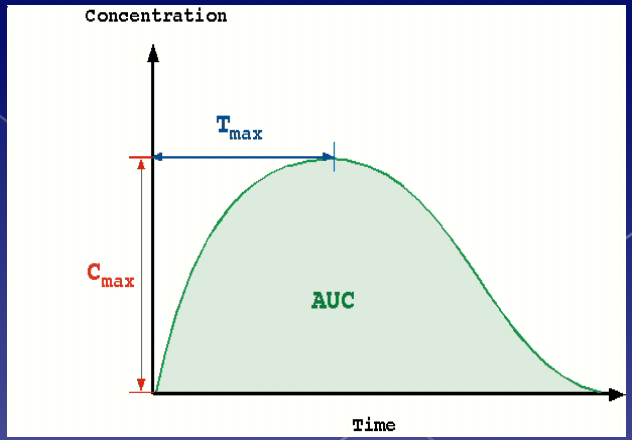
# PRESENTATION OUTLINE

- Definitions
- Road Map
- BA/BE Study Reports
- Biowaiver
- Conclusion



# DEFINITIONS

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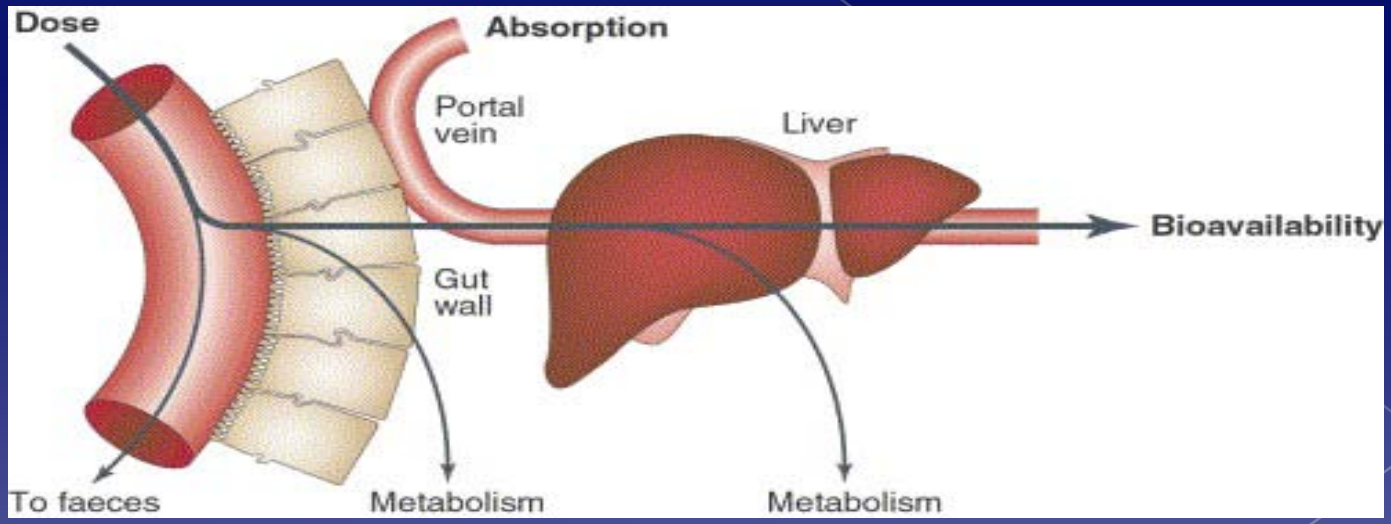
- **<u>Bioavailability</u> –** rate and extent at which a drug substance becomes available in the general system



# DEFINITIONS

- **Bioequivalence** – equivalent bioavailability within pre-set acceptance ranges between generic and innovator/comparator

# DEFINITIONS

- The main aim in conducting a bioequivalence (BE) study is to demonstrate that the active substance in a generic product is absorbed into the body at the same rate and amount as in the innovator/comparator product

  → To ensure that the generic product delivers the same therapeutic effect as the innovator/comparator product and is interchangeable

# ROAD MAPS

# ROAD MAP

| | |
|---|---|
| 1999 | DCA 92 - review the registration of generic medicines due to increasing complaints on efficacy : Implementation of BE requirement for generic medicines ( oral, immediate release, solid dosage form) – in phases |
| Sept 1999 | The National Working Committee for BE Studies was formed |
| Dec 1999 | BE 1$^{ST}$ List ( 3 active ingredients – nifedipine, cyclosporine, captopril) |
| Feb 2000 | BE 2$^{nd}$ List (4 active ingredients – enalapril, lisinopril, piroxicam, acyclovir) |
| Sept 2000 | Publication of the 'Malaysian Guidelines for the Conduct of Bioavailability and Bioequivalence Studies' |

# ROAD MAP

| | |
|---|---|
| May 2001 | BE 3rd List ( 4 active ingredients – theophylline, propranolol, cimetidine, carbamazepine) |
| June 2002 | BE 4th List ( 16 active ingredients ) |
| April 2003 | Implementation of BE for ARVs |
| March 04 | BE 5th List ( 16 active ingredients ) |
| July 2004 | 'ASEAN Guidelines for the Conduct of Bioavailability and Bioequivalence Studies' was adopted |
| Aug 2006 | BE 6th List (26 active ingredients) |

# ROAD MAP

| | |
|---|---|
| Aug 2008 | BE 7th List ( 27 active ingredients ) |
| Sept 2009 | BE 8th List ( 16 active ingredients ) |
| Jan 2011 | BE 9th List ( 29 acitive ingredients ) |
| Jan 2012 | BE for all generic medicines ( oral, immediate release, solid dosage form) |
| Jan 2012 | Accreditation of BE Centres ( local and oversea) |
| Jan 2013 | Guidance on Biopharmaceutics Classification System(BCS) - Based Biowaiver |
| March 2015 | ASEAN Guideline For The Conduct of Bioequivalence Studies (Revision 1,March 2015 ) |

# ROAD MAP

| | |
|---|---|
| 1st July 2016 | Implementation Of Bioequivalence Requirements For Generic Products In Dosage Forms Of Oral Effervescent, Dispersible, Orodispersible, Sublingual, Buccal And Chewable Tablets/Capsules- for new application |
| 1st July 2017 | Implementation Of Bioequivalence Requirements For Generic Products In Dosage Forms Of Oral Effervescent, Dispersible, Orodispersible, Sublingual, Buccal And Chewable Tablets/Capsules – for registered products where the registration expiring from 1st. July 2017 |

# BA/BE STUDY REPORTS

# Submission of BE Study Reports- for new application

- Upon submission of application for registration through online
- ACTD,P9 (Product Interchangeability, Equivalence evidence)
- Softcopies ( CDs) may be submitted in situation where the size of data has exceeded the size allowed through online
- Report should be compiled according to ASEAN BE Reporting Format

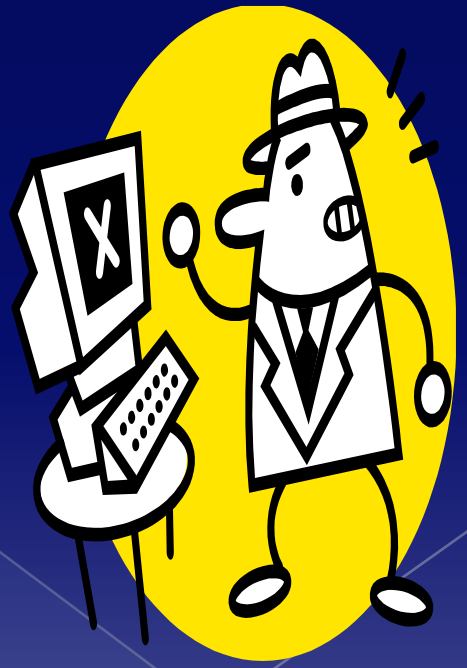
# Submission of BE Study Reports- for registered products

- Upon renewal of registration( at least 6 months before the expiry date of registration)
- Hardcopies
- Report should be compiled according to ASEAN BE Reporting Format
- Evaluation through manual system
- Upon completion of evaluation and satisfactory, uploading of complete and approved reports together with approval letter from NPCB onto online system through application for variation

# BE Study Reports

Failure to fulfill BE requirements:

- rejection of new application
- suspension of regisration
- cancellation of registration

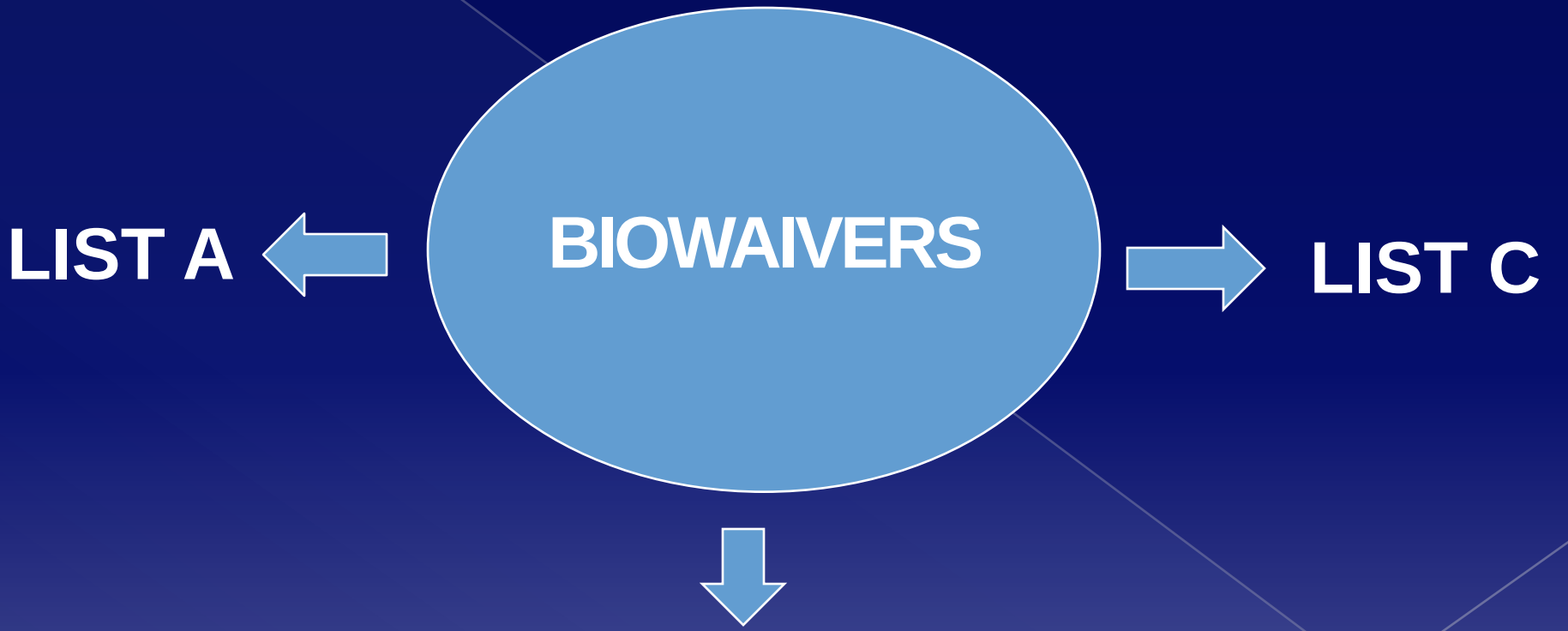


# BIOWAIVER

# Biowaiver

- Although the implementation on BE study is compulsory for generic products, in certain circumstances, waivers of BE study (biowaiver) can be considered
- The term biowaiver is applied to a regulatory approval process when the application(dossier) is approved on the basis of evidence of equivalence other than an *in vivo* bioequivalence test

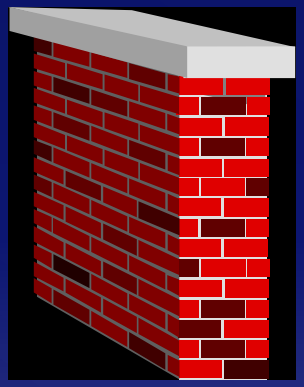
# BIOWAIVER



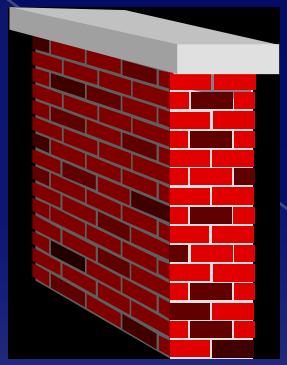
# BIOWAIVER (LIST A )

## BCS-based biowaiver

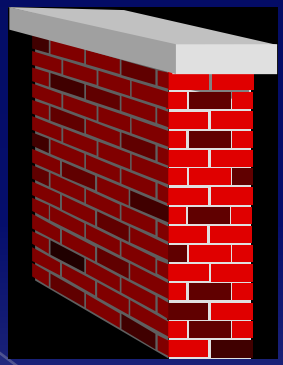
*Pillars of the BCS*



Solubility



Permeability (Absorption)



Dissolution

# What does BCS stands for?

Biopharmaceutics Classification System

| | |
|---|---|
| **Class I**<br>High solubilty<br>High permeability | **Class II**<br>Low solubility<br>High permeability |
| **Class III**<br>High solubility<br>Low permeability | **Class IV**<br>Low solublity<br>Low permeability |

# BIOWAIVER (LIST A)

BCS - Based Biowaiver :

Applicable if :

- the drug substance has been proven to exhibit high solubility and complete absorption/permeability (BCS Class 1)
- Either very rapid (>85% within 15min) or rapid (85% within 30min ) *in vitro* dissolution characteristics of the test and reference product has been demonstrated

# BCS-based biowaiver

**Evaluation of drug substance**

***and*** **drug product**

Requiring data supporting :

- High solubility of 
- High permeability of 

- Rapid and similar dissolution of 

# BIOWAIVER (LIST A)

- Data to support a request for biowaiver :

1. High solubility profile of the drug substance :

- the highest single ***dose*** is completely soluble in 250 ml or less of aqueous solution at pH 1 - 6.8 (37 °C)
- requires the investigation in at least three buffers within this range (preferably at pH 1.2,4.5 and 6.8)

# BIOWAIVER (LIST A)

2. Demonstration of complete drug absorption of drug substance in humans → high permeability

   - demonstration of complete absorption ie. ≥ 85% and normally the complete absorption in human is preferred based on results of pharmacokinetic studies (absolute bioavailability or mass-balance studies)

   Peer-reviewed literature may be acceptable from known/established references to describe the drug substance characteristics

# BIOWAIVER (LIST A)

3. Demonstration of similar dissolution profiles between generic and reference products ie. comparative dissolution profiles within the range of pH 1-6.8 ( at least pH 1.2,4.5 and 6.8) .

Determination of dissolution profile similarity between test and reference product : similarity factor ($f_2$).

Usage of surfactant in dissolution medium is not allowed.

# BIOWAIVER (LIST A)

- Current : Involving 9 drug substances
- The list is not exhaustive and will be reviewed from time to time by the National Committee for BE Study

# Guidance on BCS-Based Biowaiver

**GUIDANCE ON BIOPHARMACEUTICS CLASSIFICATION SYSTEM (BCS)-BASED BIOWAIVER**

National Pharmaceutical Control Bureau,
Ministry Of Health Malaysia.
January 2013

Adopted and adapted mainly from the following:

1. Guideline On The Investigation Of Bioequivalence (European Medicines Agency, London, 20 January 2010, CPMP/EWP/QWP/1401/98 Rev. 1/Corr)

2. Annex 7: Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability (World Health Organization (WHO), Technical Report Series, No 937, 2006)

3. Annex 8: Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms (World Health Organization (WHO), Technical Report Series, No 937, 2006)

*to suit local requirements.*

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# BIOWAIVER (LIST B)

- Biowaivers granted based on unavailability of innovator/comparator product for old molecules/drug substance

  ( innovators registered before the implementation of BE requirements in Malaysia  ie. before 1999 )

# BIOWAIVER (LIST B)

- Issues on the unavailability of comparators have been dealt as case to case basis
- Current : Involving 36 active ingredients

# BIOWAIVER (LIST B)

- Data required in lieu of bioequivalence study report:
  1. Process Validation Report (PV) for 3 consecutive batches of product
  2. Comparative Dissolution Profile (CDP) for 3 consecutive batches of product

  → **To prove consistency between batches**
- List is not exhaustive and will be reviewed from time to time if and when there are issues on comparator/innovator product

# BIOWAIVER (LIST C)

- Based on other considerations such as :

1. Product exhibit local effect with no significant systemic absorption
2. Product exhibit different dissolution profile or release specification between innovator ( in-house specs.) and generics ( pharmacopoeia specs.)

- Current : Involving 6 drug substances

# BIOWAIVER (LIST C)

- Other requirements may applied such as special labeling requirements, related *in- vitro* studies ( eg. *in-vitro* binding study), CDP , PV
- List C is not exhaustive and will be reviewed from time to time if and when there are issues

# BIOWAIVERS

- Biowaiver should be considered only when there is an acceptable benefit-risk balance in terms of public health and risk to the individual patient (country specific)
- The drug substance allowed for biowaiver should not belong to the group of narrow therapeutic index
- The drug substance allowed for biowaiver should not belong to the group of medicines used to treat critical illness

# BIOWAIVERS

- Biowaivers will NOT be granted automatically to generic products containing the listed drug substances. It will be subjected to the completeness and fulfillment of the requirements and supporting data

# BIOWAIVERS

- National Pharmaceutical Control Bureau (NPCB) reserves the rights to request for additional information/data not specifically described in guidance to support biowaiver in order to ensure safety, efficacy and quality of generic products

# CONCLUSION

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All progress and changes made on the bioequivalence requirements for generic products in Malaysia are in tandem with global practice and international standards with some adaptations to suit national requirements, usage and risks

# CONCLUSION

All matters related to BE requirements has been discussed and agreed upon in Technical Working Group and National Committee for BE Study attended by all stakeholders including the industries before they become policies

# WEBSITE FOR FURTHER REFERENCE

**www.bpfk.gov.my**

- Guidelines
- List of comparators
- BE Study Centres
- Circulars
- Biowaiver


# THANK YOU

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