



*National Pharmaceutical Control Bureau  
Ministry of Health Malaysia*



*WHO Collaborating Centre  
For Regulatory Control of  
Pharmaceuticals*



*Member of Pharmaceutical  
Inspection Cooperation Scheme*



MS ISO 9001:2000 REG. No. :AR 1171

*MS ISO 9001:2000 Accredited*

# Implementation of Bioequivalence Study for Generic Medicines in Malaysia



**Centre For Product Registration  
National Pharmaceutical Control Bureau (NPCB)  
Ministry of Health Malaysia**

# BE REQUIREMENTS

BE is a requirement enforced by the DCA, MOH for generics, to ensure quality ,safety and efficacy of generics.

## DCA 92ND MEETING (1999)

- review the registration of generic products
- due to ↑ availability of generics + ↑ complaints on efficacy
- decided to include BE studies as a **requirement** for generics (oral Immediate Release solid dosage form)
- ensure that generics are therapeutically equivalent to the innovators → clinically interchangeable.

# Definitions – Generic Medicines



Reference	Definitions
DRGD	A product that is <b>essentially similar to a currently registered product</b> in Malaysia
WHO <i>* Multisource product</i>	a pharmaceutical product, usually <b>intended to be interchangeable with the innovator product</b> , marketed after the expiry of patent or other exclusivity rights
USFDA	a medicine that is <b>identical or bioequivalent to a brand name medicine</b> in dosage form, safety, strength, route of administration, quality, performance, characteristic and intended use
EMA	a medicinal product which has the <b>same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product</b> and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies

# Definitions – Innovator/Comparator Products

## Innovator/comparator/reference products

A pharmaceutical product with which the multi-source product is intended to be interchangeable in clinical practice

- WHO

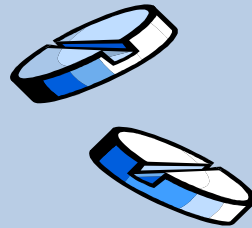


## Examples of innovator & generic medicines

Active ingredients	Innovator	Generic
Ranitidine HCl	Zantac	X'tac
Mefenamic acid	Ponstan	Mefetab
Piroxicam	Feldene	Apo-Piroxicam

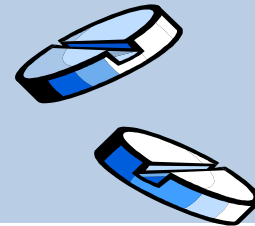
# Generic Medicines

- Active ingredient previously approved
- Product information previously approved
- Route of administration, strength and dosage form equal to those of previously approved product



# Generic Medicines

- Usually intended to be interchangeable with the innovator product
- Manufactured without a licence from innovator company
- Marketed after expiry of patent or other exclusivity rights
- Marketed either under the approved nonproprietary name or under a brand name (proprietary name)



# Implementation of BA/BE Requirements for Generic Medicines



# When equivalence studies are necessary (WHO Criteria)



## (a) Oral immediate-release pharmaceutical products with systemic action :

- critical use medicines;
- narrow therapeutic range
- bioavailability problems or bioinequivalence related to the API or its formulations
- polymorphs of API, the excipients and/or the pharmaceutical processes used in manufacturing could affect bioequivalence.

## (b) Non-oral, non-parenteral pharmaceutical products designed to act systemically

(such as transdermal patches, suppositories, nicotine chewing gum, testosterone gel and skin-inserted contraceptives).

## (c) Modified-release pharmaceutical products designed to act systemically.

(d) Fixed-combination products with systemic action, where at least one of the APIs requires an in vivo study



## When equivalence studies **are not necessary** (WHO Criteria)

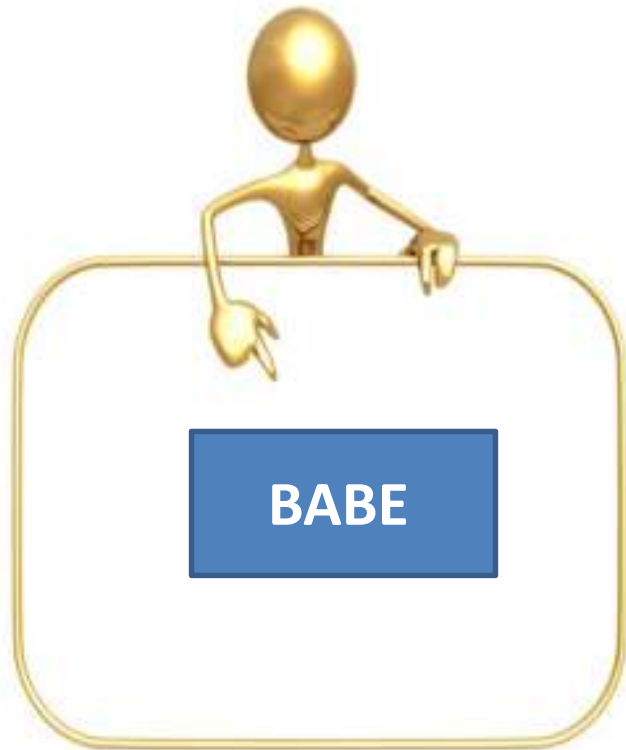
- Products are to be administered parenterally
- Solutions for oral use
- Product is a gas
- Products are powders for reconstitution
- Ophthalmic or otic products as aqueous solutions
- Topical products as aqueous solutions
- Inhalation products or nasal sprays prepared as aqueous solutions.

# BABE?



# BABE

**BA =**  
**Bioavailability**



**BE =**  
**Bioequivalence**

# What is Bioavailability?

Bioavailability means the **rate (how fast)** and **extent (the amount)** to which the active substance is absorbed from a pharmaceutical form and becomes available at the site of action (inside the body).

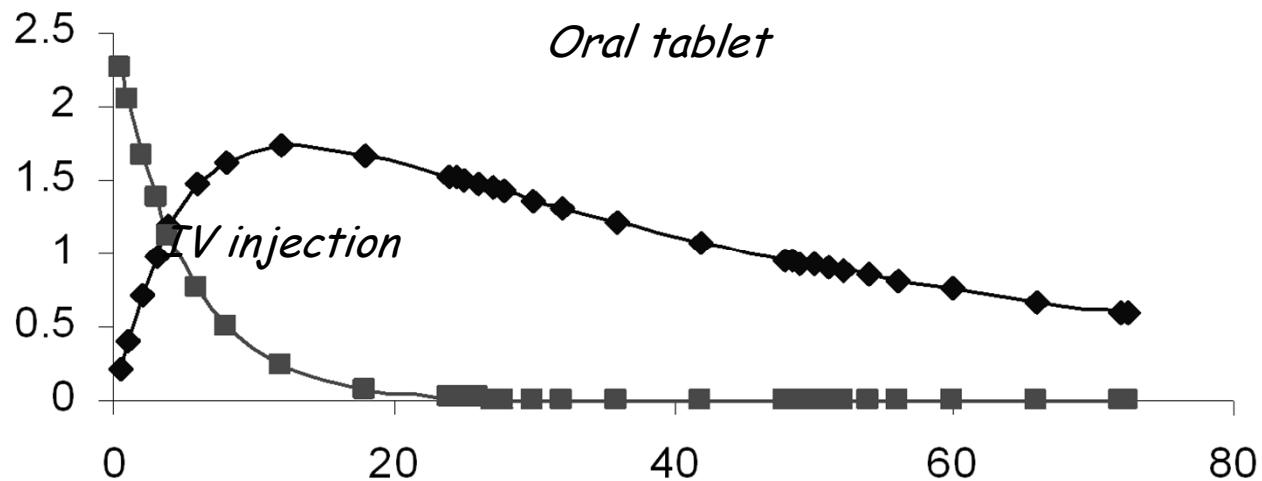


# BA Study

A bioavailability study compares any two formulations in terms of the plasma concentration/time profiles

For example:

Comparison of intravenous injection with oral tablet



# What is Bioequivalence ?

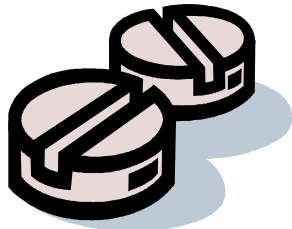
Two medicinal products are bioequivalent if :

- they are pharmaceutically equivalent and
- their bioavailabilities (rate and extent of absorption ) after administration in the same molar dose are similar to such a degree that their effects can be expected to be essentially the same.

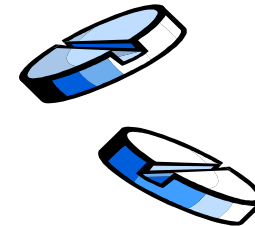
# What is Pharmaceutical Equivalents ?

Medicinal products are pharmaceutical equivalents if they contain the **same amount** of the **same active substance(s)** in the **same dosage forms** that meet the same or comparable standards.

Example: Ketoconazole



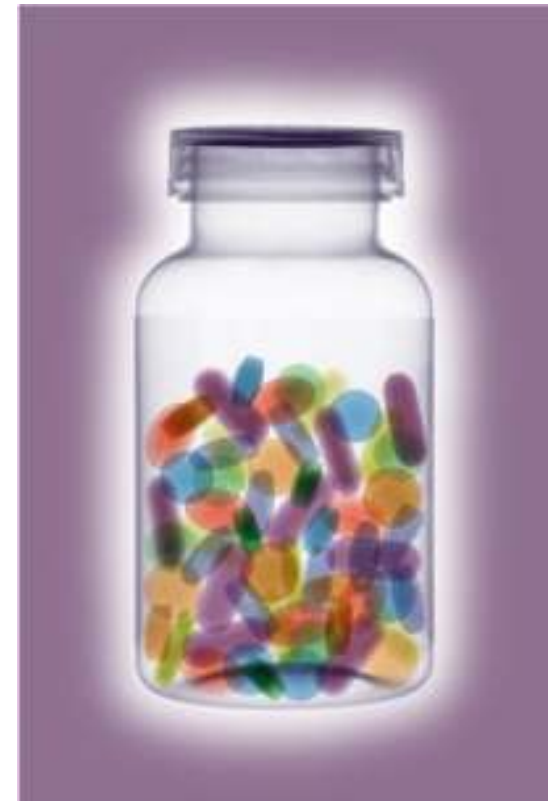
Generic Ketoconazole  
200mg



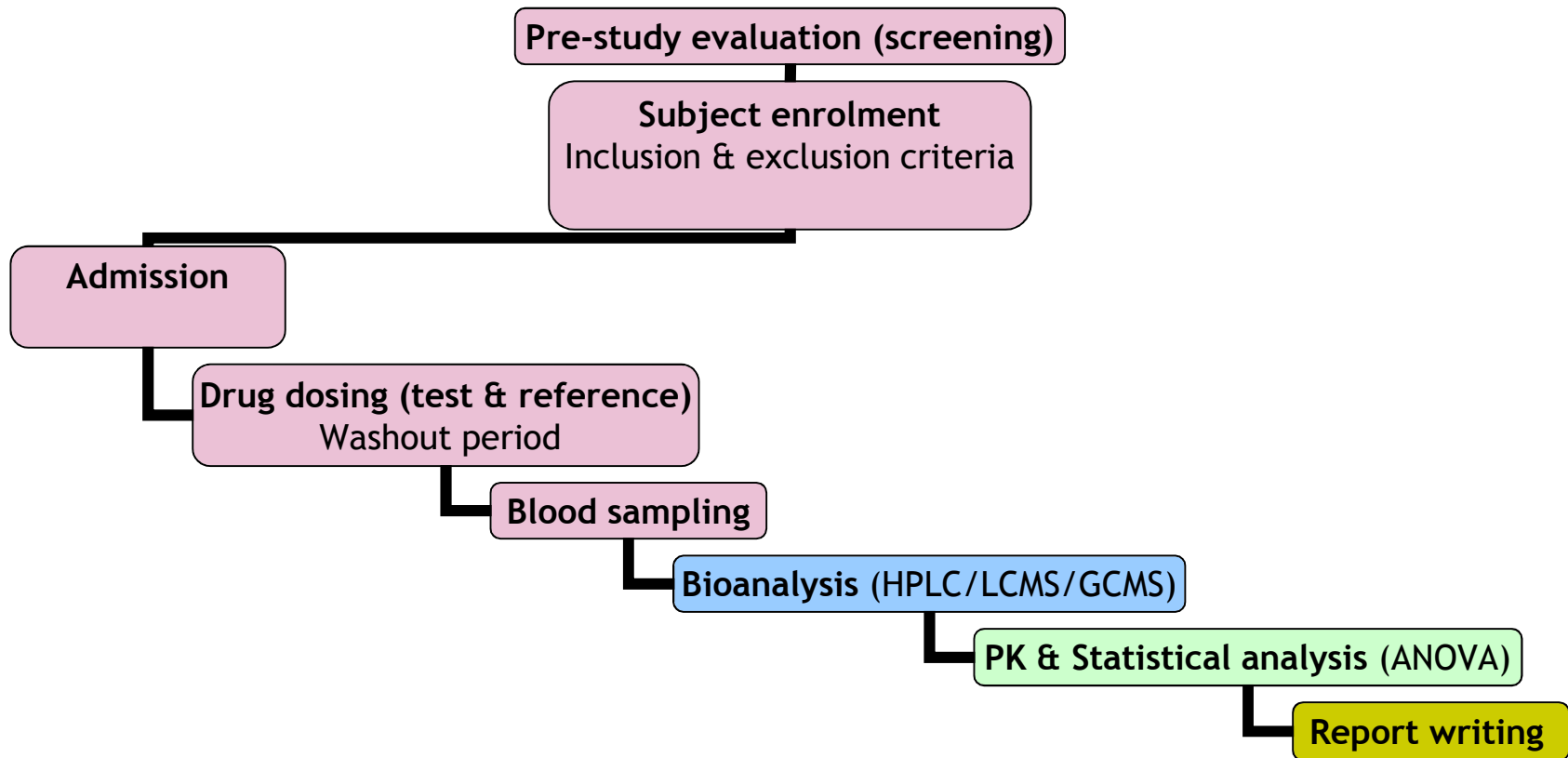
Innovator Ketoconazole  
200mg

## Objective / aim of BE study

To compare the rate & extent of absorption between test & reference product (to show that 2 drugs are bioequivalent to one another)



# Flowchart of a BE study



# Phases of BE Study

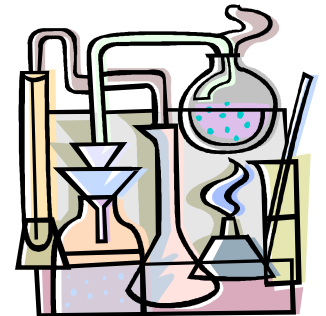
## Clinical

- Subject enrolment
- Drug administration
- Blood sampling



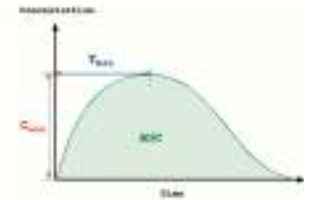
## Analytical

- Measurement of drug levels in blood plasma
- Bioanalytical method of detection eg. LCMS, HPLC

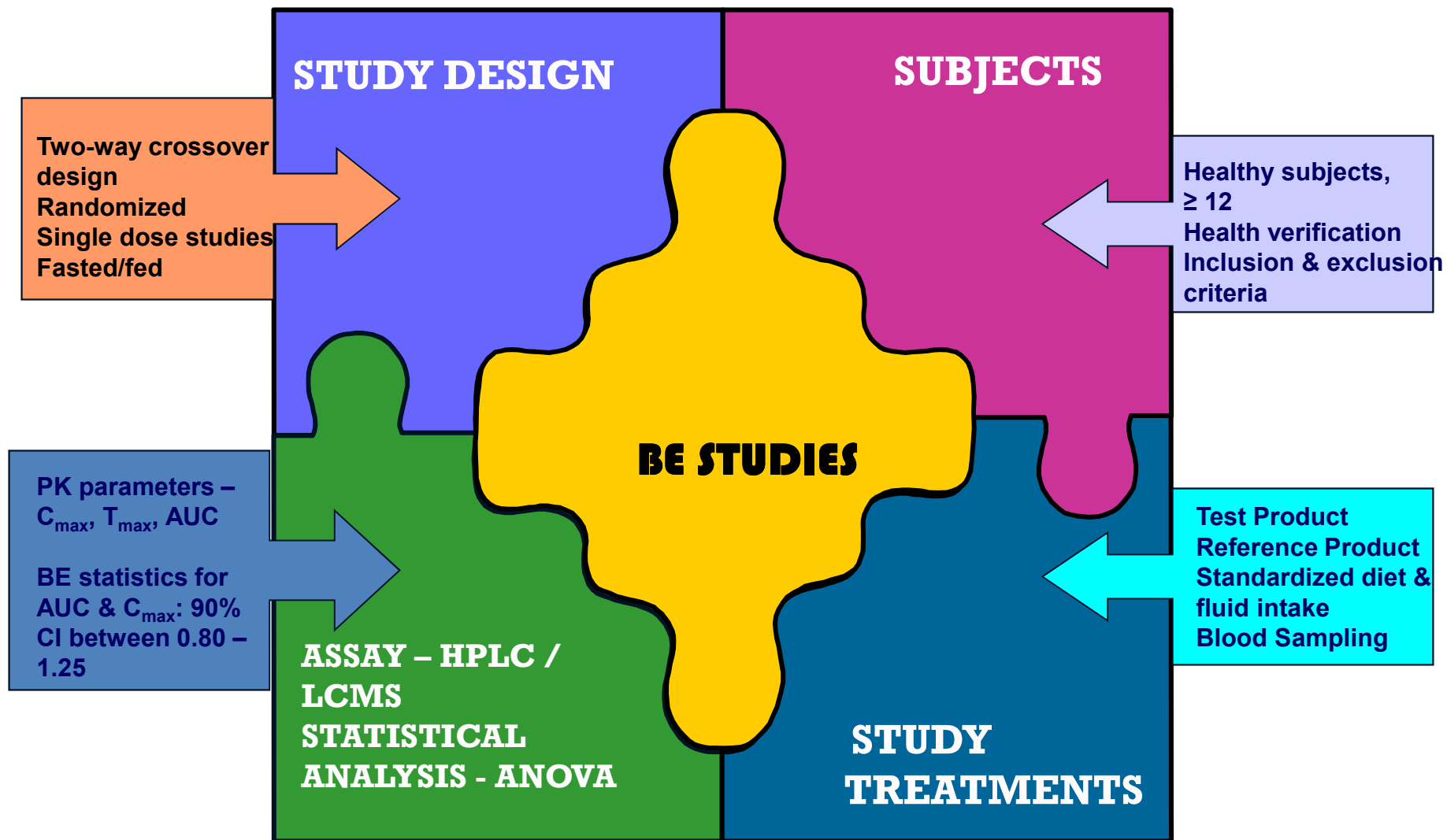


## PK & Statistical

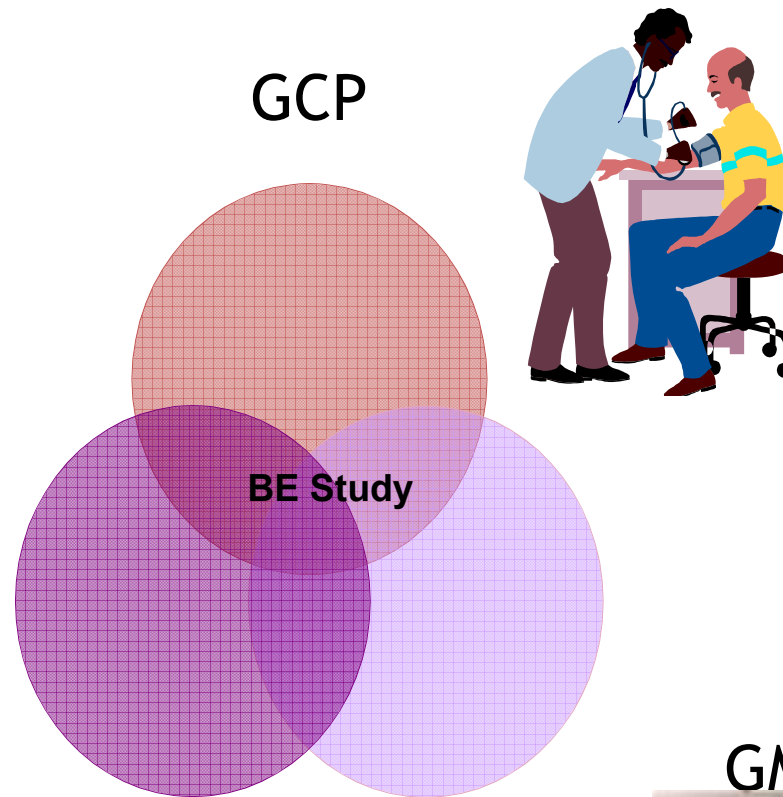
- PK parameters – AUC, C<sub>max</sub> & T<sub>max</sub>
- Statistical analysis - ANOVA



# BE Study



# Standards / elements in BE Study



GLP



GMP



# BE Study Design

**Gold standard study design /  
Design of choice**

**single dose, two-way  
crossover design, fasted**  
(two treatments, two periods, two sequences)

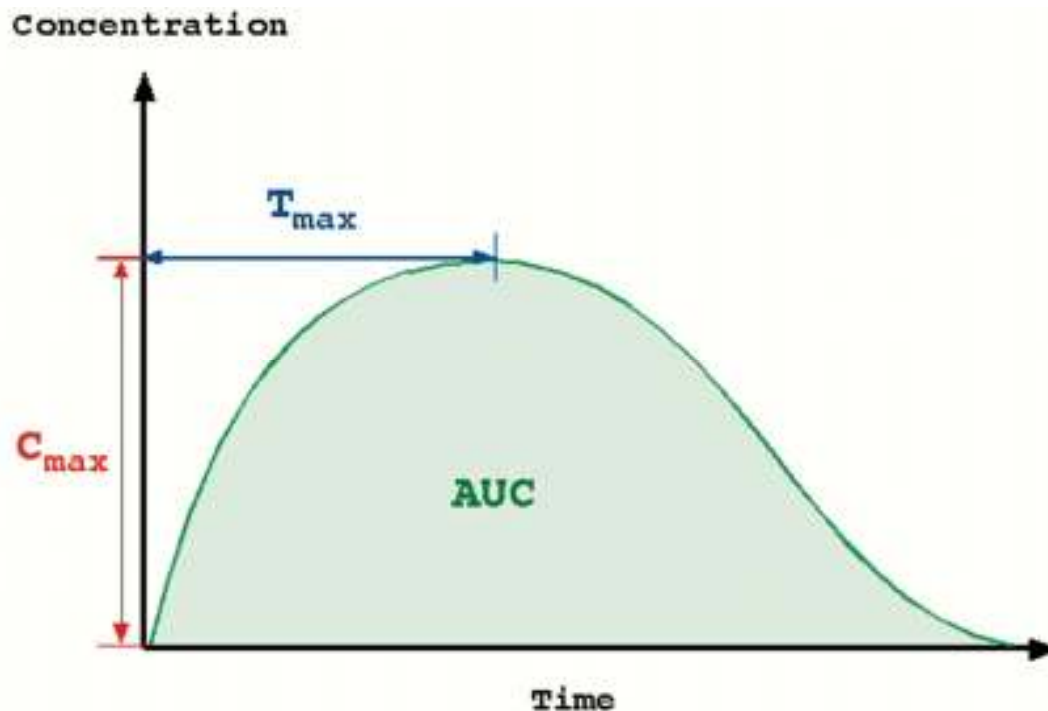
healthy volunteers

Reference (comparator)/  
Test (generic)

<i>Subject No</i>	<i>Period 1</i>	<i>Period 2</i>
1	R	T
2	R	T
3	T	R
4	R	T
5	T	R
6	T	R
7	T	R
8	R	T
9	T	R
10	R	T
11	R	T
12	T	R

# BE Pharmacokinetic (PK) Parameters

- Parameters used to estimate the rate of absorption are the  $C_{max}$  and  $T_{max}$
- Parameter used to estimate extent of absorption is the **AUC** (Area under the curve)



# Definition

## Rate of absorption

$C_{\max}$

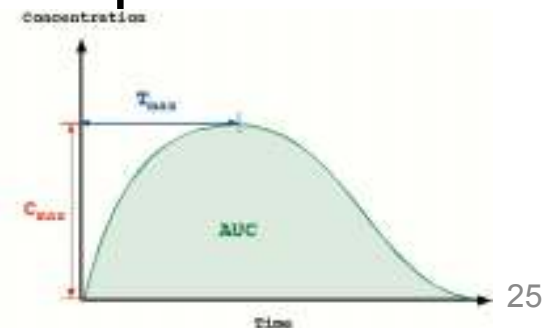
The observed maximum or peak concentration of drug in plasma

$T_{\max}$

Time of maximum or peak concentration of drug in plasma or peak concentration of drug in plasma

## Extent of absorption - **AUC (Area under the curve)**

The area under the drug concentration in plasma versus time curve



# Statistical analysis (ANOVA)

Reference Arm	Test Arm	T/R ratio	log (T/R)	A N O V A
$AUC_R$	$AUC_T$			
$Cmax_R$	$Cmax_T$			



The 2 products are statistically similar if there is no difference in the 2 parameters

Statistically similar → BE

# How do we know whether the generic product is bioequivalent to the comparator?

90% Confidence Interval logAUC ratio & logCmax ratio falling between 80% and 125%

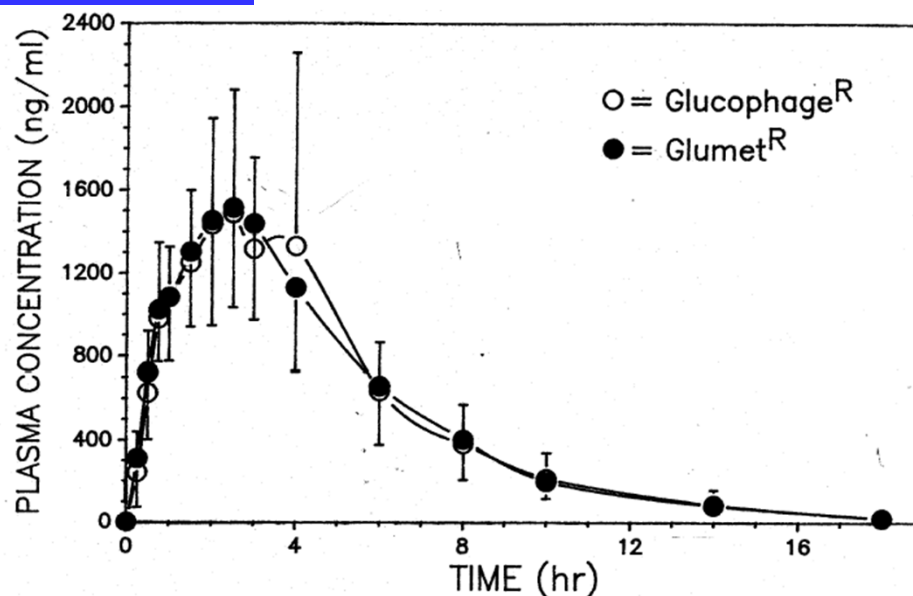


Fig. 1. Mean plasma metformin concentration versus time profiles of Glucophage and Glumet. Mean  $\pm$  SD, N = 12.

BE study **does not** prove that 2 products of the same drug are **exactly identical**  
It shows **2 products are similar enough** to be regarded as equivalent within specified limit that are clinically tolerable

BE study provides a **bridge** to the clinical trial performed by the innovator and consequently to efficacy of original formulation.



Affordable Medicine  
Quality Generic Medicine



# Significance of BE Studies

To assure the interchangeability (switchability) of a patients medication (from innovator brand to a generic medicine) without any significant change in the safety and efficacy of the medication.



# Selection of Test Products for BE Studies in Malaysia

## 1. WHO criteria

Oral immediate-release pharmaceutical products with systemic action and

- Indicated for serious conditions requiring assured therapeutic response
- Narrow therapeutic window / safety margin, steep dose-response curve
- Pharmacokinetics complicated by variable or incomplete absorption or absorption window, non-linear pharmacokinetics, high first-pass metabolism
- Unfavourable physico-chemical properties eg low solubility, instability

## 2. Local situation

- Patient complaint
- High volume usage in hospitals from MOH Drug List.



## Selection of Comparator Products



- **Innovator product in the country**
- **If the innovator product cannot be identified, the choice of comparator in order of preference are:**
  - **Approval in ICH and associated countries (Australia , Canada)**
  - **Pre-qualified by WHO**

Agreed by ASEAN at its ACCSQ-PPWG 13<sup>th</sup> Meeting, July 2007 in Kuala Lumpur

# Roadmap

<b>1999</b>	<b>DCA 92 - review the registration of generic products due to increasing complaints on efficacy Implementation of BE requirement for generics</b>
<b>Sept 1999</b>	<b>The National Working Committee for BE Studies was formed</b>
<b>Dec 1999</b>	<b>BE First List ( 3 active ingredients – nifedipine, cyclosporine, captopril)</b>
<b>Feb 2000</b>	<b>BE Second List (4 active ingredients – enalapril, lisinopril, piroxicam, acyclovir)</b>
<b>Sept 2000</b>	<b>Publication of the ‘Malaysian Guidelines for the Conduct of Bioavailability and Bioequivalence Studies’</b>
<b>May 2001</b>	<b>BE Third List ( 4 active ingredients – theophylline, propranolol, cimetidine, carbamazepine)</b>

# Roadmap

<b>June 2002</b>	<b>BE Fourth List ( 16 active ingredients )</b>
<b>March 04</b>	<b>BE Fifth List ( 16 active ingredients )</b>
<b>July 2004</b>	<b>'ASEAN Guidelines for the Conduct of Bioavailability and Bioequivalence Studies' was adopted</b>
<b>Aug 2006</b>	<b>BE Sixth List (26 active ingredients)</b>
<b>Aug 2008</b>	<b>BE Seventh List ( 26 active ingredients )</b>
<b>Sept 2009</b>	<b>BE Eighth List ( 17 active ingredients )</b>
<b>Jan 2011</b>	<b>BE Ninth List ( 29 active ingredients )</b>
<b>March 2011</b>	<b>BE for all Generics , immediate release, oral solid dosage form containing Scheduled Poison</b>

# BE List (141 active ingredients)

## First List (23/12/1999)

1. NIFEDIPINE
2. CYLOSPORINE
3. CAPTOPRIL

## Second List (14/02/2000)

4. ENALAPRIL
5. LISINOPRIL
6. PIROXICAM
7. ACYCLOVIR

## Third List (08/05/2001)

8. THEOPHYLLINE
9. PROPRANOLOL
10. CIMETIDINE
11. CARBAMAZEPINE

## Fourth List (14/6/2002)

12. CLOMIPRAMINE
13. LITHIUM CARBONATE\*
14. BROMOCRIPTINE MESYLATE
15. RANITIDINE
16. TERBUTALINE SULPHATE
17. DIGOXIN
18. SODIUM VALPROATE
19. AMITRIPTYLINE HCL
20. ATENOLOL
21. METOPROLOL
22. FRUSEMIDE
23. CARBIDOPA/L-DOPA
24. LEVODOPA/BENSERAZIDE
25. PHENYTOIN SODIUM
26. WARFARIN SODIUM
27. DISOPYRAMIDE PHOSPHATE

### **Fifth List (18/03/2004)**

28. Stavudine
29. Nevirapine
30. Ritonavir
31. Ciprofloxacin
32. Ofloxacin
33. Clarithromycin
34. Metformin
35. Glibenclamide
36. Diltiazem
37. Salbutamol
38. Rifampicin
39. Sulpiride
40. Dexamethasone
41. Verapamil
42. Omeprazole
43. Prednisolone

### **Sixth List (15/8/2006)**

44. Gliclazide
45. Glimepiride
46. Cefuroxime Axetil
47. Roxithromycin
48. Azithromycin
49. Metronidazole
50. Doxycycline
51. Ketoconazole
52. Itraconazole
53. Ticlopidine
54. Simvastatin
55. Lovastatin
56. Amlodipine
57. Losartan
58. Carvedilol
59. Tamoxifen
60. Hydroxyzine
61. Lamotrigine
62. Risperidone
63. Buprenorphine
64. Cetirizine
65. Loratadine
66. Meloxicam
67. Ibuprofen
68. Naproxen
69. Ketoprofen

## Seventh List (6/8/2008)

- |                    |                  |
|--------------------|------------------|
| 70. Atorvastatin   | 85. Clopidogrel  |
| 71. Methotrexate   | 86. Valaciclovir |
| 72. Azathioprine   | 87. Fluconazole  |
| 73. Tacrolimus     | 88. Pyrazinamide |
| 74. Sirolimus      | 89. Isoniazid    |
| 75. Mycophenolate  | 90. Topiramate   |
| 76. Etoposide      | 91. Alendronate  |
| 77. Flutamide      | 92. Fluvoxamine  |
| 78. Chlorambucil   | 93. Fluoxetine   |
| 79. Raloxifene Hcl | 94. Sertraline   |
| 80. Valsartan      | 95. Clozapine    |
| 81. Irbesartan     |                  |
| 82. Perindopril    |                  |
| 83. Ramipril       |                  |
| 84. Quinapril      |                  |

## Eighth List (Sept. 2009)

- 96. Amoxicillin
- 97. Ampicillin
- 98. Cephalexin
- 99. Clindamycin
- 100. Cloxacillin
- 101. Erythromycin
- 102. Griseofulvin
- 103. Levofloxacin
- 104. Minocycline
- 105. Nitrofurantoin

- 106. Norfloxacin
- 107. Oseltamivir
- 108. Phenoxymethyl Penicillin
- 109. Terbinafine
- 110. Tetracycline
- 111. Tinidazole
- 112. Trimethoprim

**Ninth List**  
**(Jan 2011)**

**113. Letrozole**  
**114. Anagrelide**  
**115. Chlorpromazine**  
**116. Haloperidol**  
**117. Perphenazine**  
**118. Trifluoperazine**  
**119. Aripiprazole**  
**120. Olanzapine**  
**121. Quetiapine**  
**122. Ziprasidone**  
**123. Escitalopram**  
**124. Citalopram**  
**125. Paroxetine**  
**126. Duloxetine**  
**127. Venlafaxine**  
**128. Mirtazapine**

**129. Imipramine**  
**130. Maprotiline**  
**131. Nortriptyline**  
**132. Pregabalin**  
**133. Diazepam**  
**134. Nitrazepam**  
**135. Zolpidem**  
**136. Chlordiazepoxide**  
**137. Alprazolam**  
**138. Lorazepam**  
**139. Bromazepam**  
**140. Clobazam**  
**141. Zopiclone**

# BE requirements

- Failure to fulfill BE requirements will result in cancellation or suspension of registered product and rejection of application for registration by the DCA.



# BE requirements

- Since Sept 2008
- **> 229** products cancelled/suspended due to failure to fulfill BE requirements
- **> 150** new applications rejected due to failure to submit adequate and satisfactory BE studies

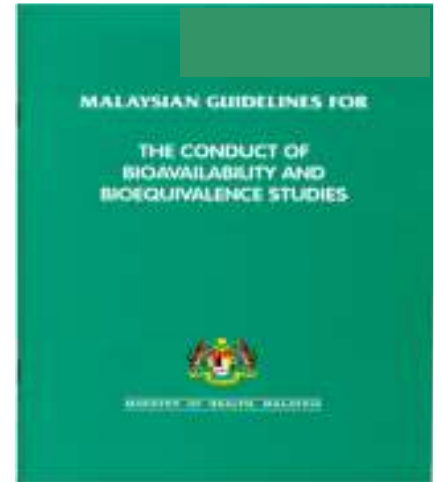


**THE NATIONAL  
WORKING  
COMMITTEE FOR BE  
STUDIES**

# The National Working Committee for BE Studies

- formed in September 1999
- comprising of representatives from
  - UM, UKM,USM(School of Pharmacy, Centre for Drug and Medicines Research, Institute for Research in Molecular Medicine)
  - Pharmaceutical Industries (MOPI ,PhAMA, MAPS)
  - Info Kinetics CRC
  - CRC,Hospital Umum Sarawak
  - Government Institution ( HKL, Drug List Review Panel)
  - NPCB (as secretariat)

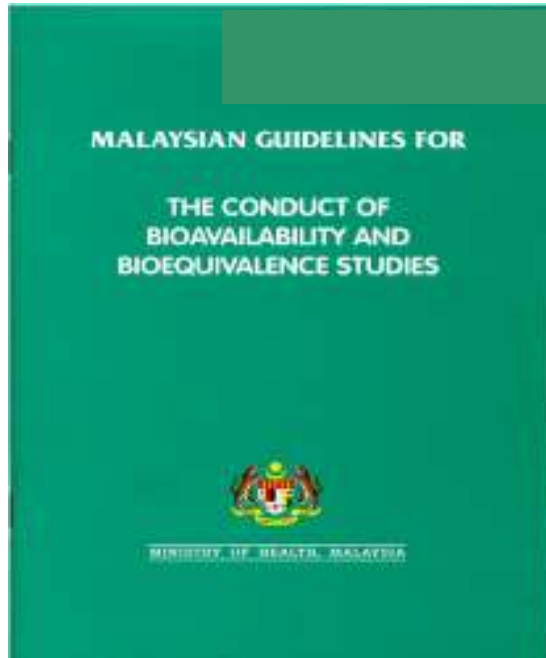
# The National Working Committee for BE Studies



- Objectives: → To assist and facilitate the conduct of BE Studies in Malaysia  
→ To discuss BE related problems and to formulate recommendation and solutions to these problems
- Task : formulating an [action plan for the conduct of BE studies in Malaysia](#) through collaborative efforts.
- Publication of the '[Malaysian Guidelines for the Conduct of Bioavailability and Bioequivalence Studies](#)' marked the first outcome of this committee's objectives.

# BE GUIDELINES

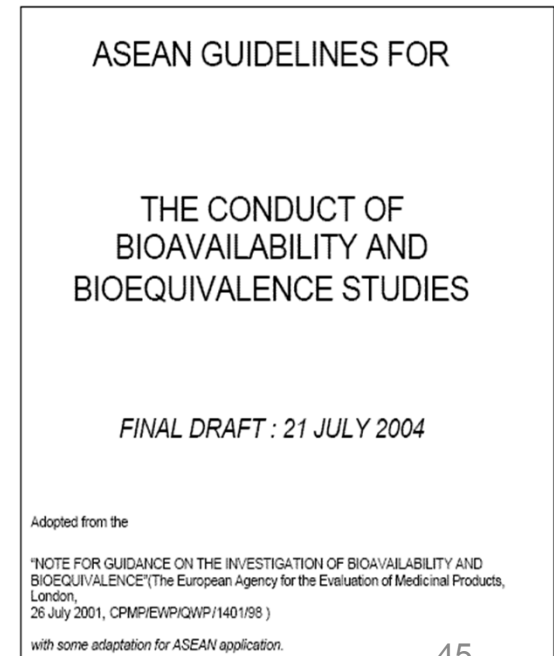
# Guidelines



## Malaysian Guidelines For The Conduct of Bioavailability and Bioequivalence Studies



## ASEAN Guidelines For The Conduct of Bioavailability and Bioequivalence Studies



# MALAYSIAN GUIDELINES FOR

## THE CONDUCT OF BIOAVAILABILITY AND BIOEQUIVALENCE STUDIES



MINISTRY OF HEALTH, MALAYSIA

### Malaysian Guidelines For THE CONDUCT OF BIOAVAILABILITY AND BIOEQUIVALENCE STUDIES

Adapted from the  
NOTE FOR GUIDANCE ON THE INVESTIGATION OF BIOAVAILABILITY AND  
BIOEQUIVALENCE (The European Agency for the Evaluation of Medicinal Products,  
11 December 1995)  
and with adaptation for Malaysian application

Adopted from the 'Note for Guidance on the Investigation of Bioavailability and Bioequivalence', The European Agency for the Evaluation of Medicinal Products, 1998..with some adaptation for Malaysian application



ASEAN GUIDELINES FOR

THE CONDUCT OF  
BIOAVAILABILITY AND  
BIOEQUIVALENCE STUDIES

*FINAL DRAFT : 21 JULY 2004*

Adopted from the

"NOTE FOR GUIDANCE ON THE INVESTIGATION OF BIOAVAILABILITY AND  
BIOEQUIVALENCE"(The European Agency for the Evaluation of Medicinal Products,  
London,  
26 July 2001, CPMP/EWP/QWP/1401/98 )

*with some adaptation for ASEAN application.*

# BE GUIDELINES

1. MALAYSIAN GUIDELINES FOR THE CONDUCT OF BIOAVAILABILITY AND BIOEQUIVALENCE STUDIES-published by MOH in September 2000
2. ASEAN GUIDELINES FOR THE CONDUCT OF BIOAVAILABILITY AND BIOEQUIVALENCE STUDIES-adopted by ASEAN in July 2004 and fully implemented in 2009

# BE GUIDELINES

- Starting from January 2009, ASEAN GL is being fully used
- This guideline should be read in conjunction with other pertinent elements outlined in current and future ASEAN, EU and ICH guidelines and regulations eg. Pharmacokinetic Studies in Man, Modified Release GL, etc.

# BE GUIDELINES

Both GLs provide :

- definitions on the terms such as pharmaceutical equivalence, pharmaceutical alternatives, BA, BE etc.
- guidance in conducting BA/BE studies in accordance to the established international standards
- format of BA/BE study report

The core topic in the GLs is the design and  
conduct of studies

# BE STUDY CENTRES

## **BE Study Centres (local)**

- 1. Centre for Bioequivalence Studies, UM KL**
- 2. School Of Pharmacy, Universiti Sains Malaysia, Penang ( 2 sites)**
- 3. Centre for Drug & Medicines Research, Universiti Sains Malaysia, Penang**
- 4. Institute for Research in Molecular Medicine (INFORMM), Universiti Sains Malaysia, Kubang Kerian, Kelantan**
- 5. Info Kinetics / Clinical Research Centre, Penang**

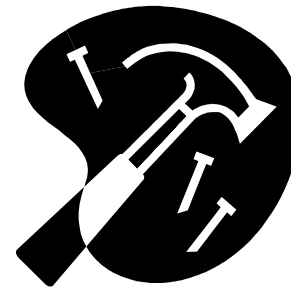
# BE Study Centres (local)

**PROPOSAL BY MOH :**

**CLINICAL RESEARCH CENTRE, HOSPITAL  
UMUM SARAWAK**

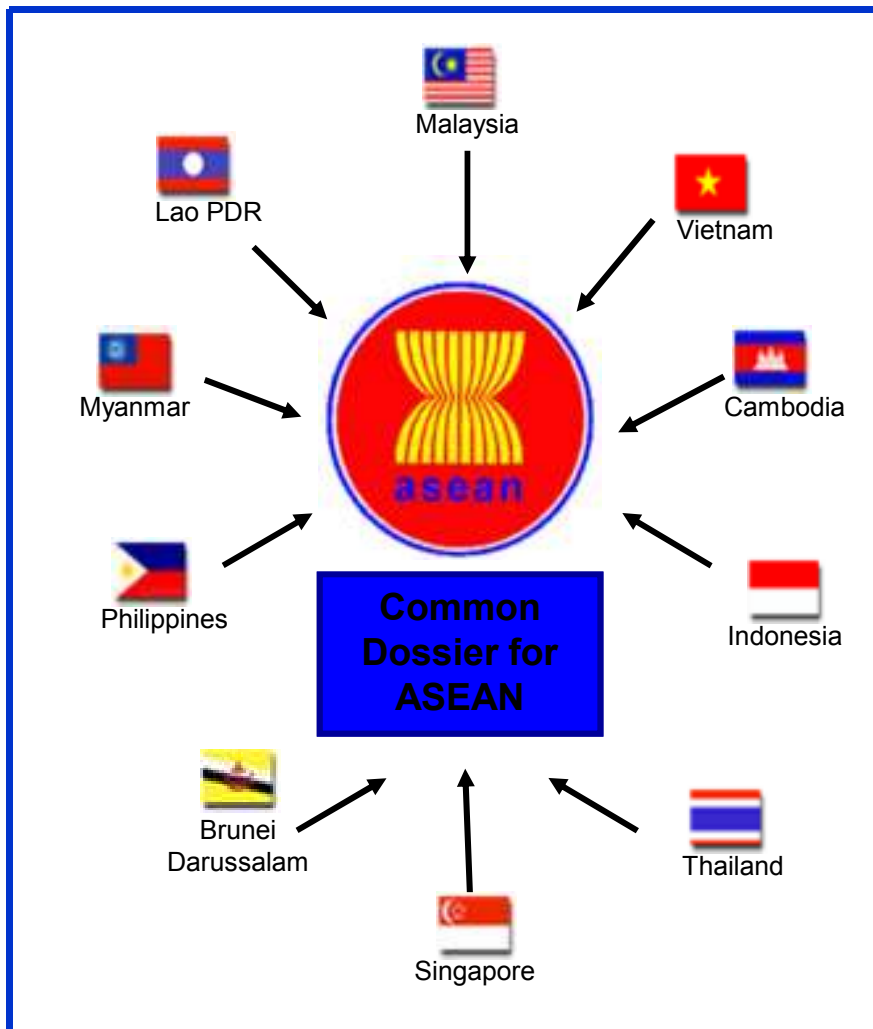
**CURRENT STATUS :**

**DEVELOPMENT OF INFRASTRUCTURE  
AND HUMAN RESOURCES**



# **ASEAN HARMONISATION ON BE REQUIREMENT**

With the advent of globalisation, efforts are currently undertaken towards ASEAN Harmonisation process.



- **Pharmaceutical Product Working Group – ASEAN Consultative Committee for Standards and Quality (PPWG-ACCSQ)**
- **Objective is to develop harmonization schemes of pharmaceutical regulations of the ASEAN member countries to complement and facilitate the objective of AFTA, particularly the elimination of technical barriers to trade posed by regulations, however without compromising product quality, efficacy and safety.**
- **ASEAN Common Technical Dossier/Requirements**
- **ASEAN Technical Documents – Process Validation, Analytical Validation, Stability, BA/BE**

# Status of Implementation of BA/BE Requirements in ASEAN



Malaysia is the lead country for ASEAN BA/BE Guideline

Most ASEAN Member States require BE for generics

The ASEAN Guideline on The Conduct of BA/BE Studies was adopted in July 2004

Harmonisation of BA/BE enables member states to work towards mutual acceptance of BA/BE Study Report on :

- ✓ *Selection of comparator products*
- ✓ *BE Study Reporting Format*
- ✓ *Standards on Good Clinical Practice and Good Laboratory Practice Requirements*



**NEXT**

Standards for audit, inspection, accreditation and certification of BA/BE centres

# FUTURE PLANS



# FUTURE PLANS

**BA/BE REQUIREMENT FOR ALL GENERIC (CONTAINING SCHEDULED POISON), IMMEDIATE RELEASE ORAL SOLID DOSAGE FORM**

**The Drug Control Authority at its 236 Meeting (27 Jan. 2011)**

**has decided on BE implementation for all new submission starting 1.1.2012**

# FUTURE PLANS

- **INSPECTION OF LOCAL BA/BE CENTRES FOR COMPLIANCE ON GCP AND GLP PRINCIPLES;**
  - **Voluntary since 2010**
  - **Proposed Compulsory : 2012**
- **ENFORCEMENT ON THE COMPLIANCE FOR GCP AND GLP PRINCIPLES ON LOCAL AND OVERSEAS BA/BE CENTRES : 2012**  
( involving overseas inspection)