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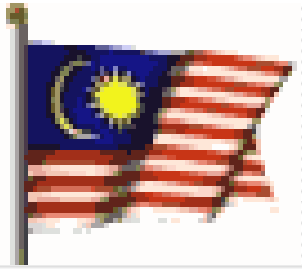
IMPLEMENTATION OF BIOEQUIVALENCE STUDY FOR GENERIC MEDICINES IN MALAYSIA



National Regulatory Conference 2013
7-9 May, Istana Hotel, Kuala Lumpur

Mazuwin Zainal Abidin
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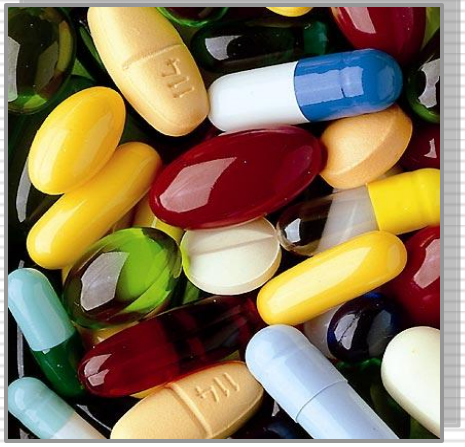
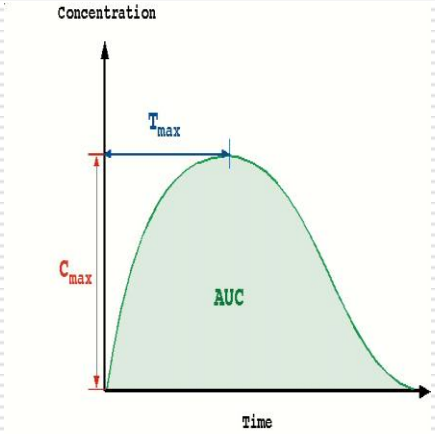
PRESENTATION OUTLINE

- Bioequivalence Study
- The National Working Committee for Bioequivalence Study
- Bioequivalence Guidelines and Circulars/Directives
- Bioequivalence Study Centres
- ASEAN Harmonisation on Bioequivalence Requirements
- Conclusion





BIOEQUIVALENCE STUDY

BABE?

BABE

BA = Bioavailability

BE = Bioequivalence

What is Bioavailability?

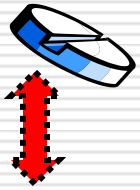
Bioavailability means the **rate (how fast)** and **extent (the amount)** to which the active substance is absorbed from a pharmaceutical form and becomes available at the site of action (inside the body).

BIOEQUIVALENCE STUDY

- A bioequivalence study is a clinical study to show that there is the same quantity of the active substance in the human body whenever the same dose of the reference/innovator or generic medicine is taken over a defined period of time
- Bioequivalent means that the active substance in a generic medicine is absorbed into the body at the **same rate and amount** as in the innovator product

This ensures that the generic medicine delivers the same therapeutic effect as the innovator product and can be **interchangeable without any significant change in the efficacy of the medication**

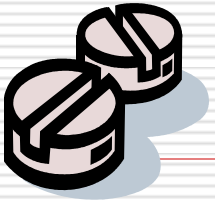
PRODUCT FORMULATION ⟷ BIOEQUIVALENCE STUDY



A generic medicine contains same active ingredient in the same amount as in innovator/reference product , however may differ in excipients eg . diluents, binders, disintegrating agents, coatings

Different formulation /excipients may affect /influence the absorption of active ingredient in the blood circulation/site of action

Therefore , the effect of formulation on absorption in the blood circulation/site of action between generic medicine and innovator product need to be studied



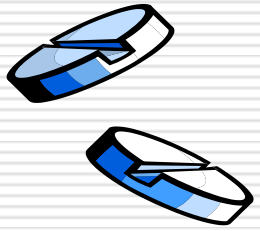
Demonstration of Bioequivalence is generally the most appropriate method and internationally accepted by regulatory bodies to prove the therapeutic equivalence between innovator and generic medicine

BIOEQUIVALENCE STUDY

The objective / aim of BE study is

to compare the BA between test & reference product ie. to show that 2 products are bioequivalent to one another

Generic



Innovator

When equivalence studies are necessary (WHO Criteria)

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

- critical use medicines
- narrow therapeutic range of products
- 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

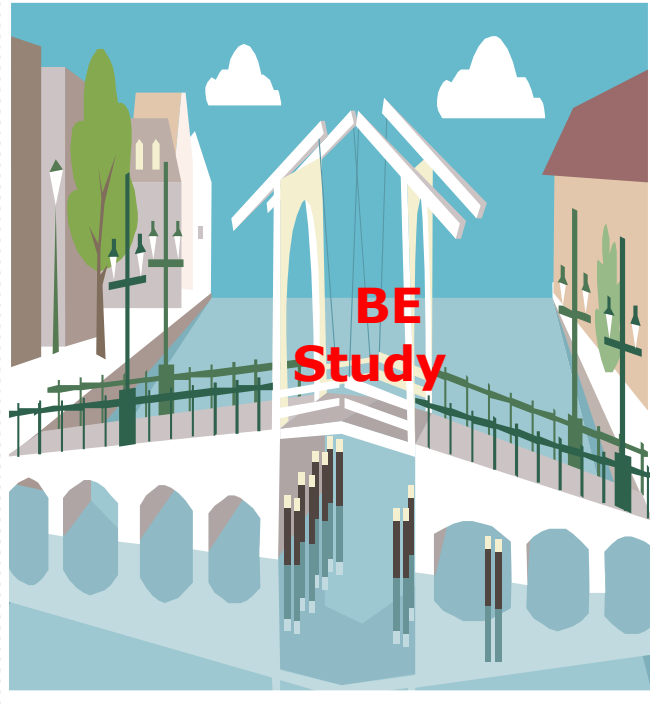
(d) Fixed- dosed combination products

BIOEQUIVALENCE STUDY

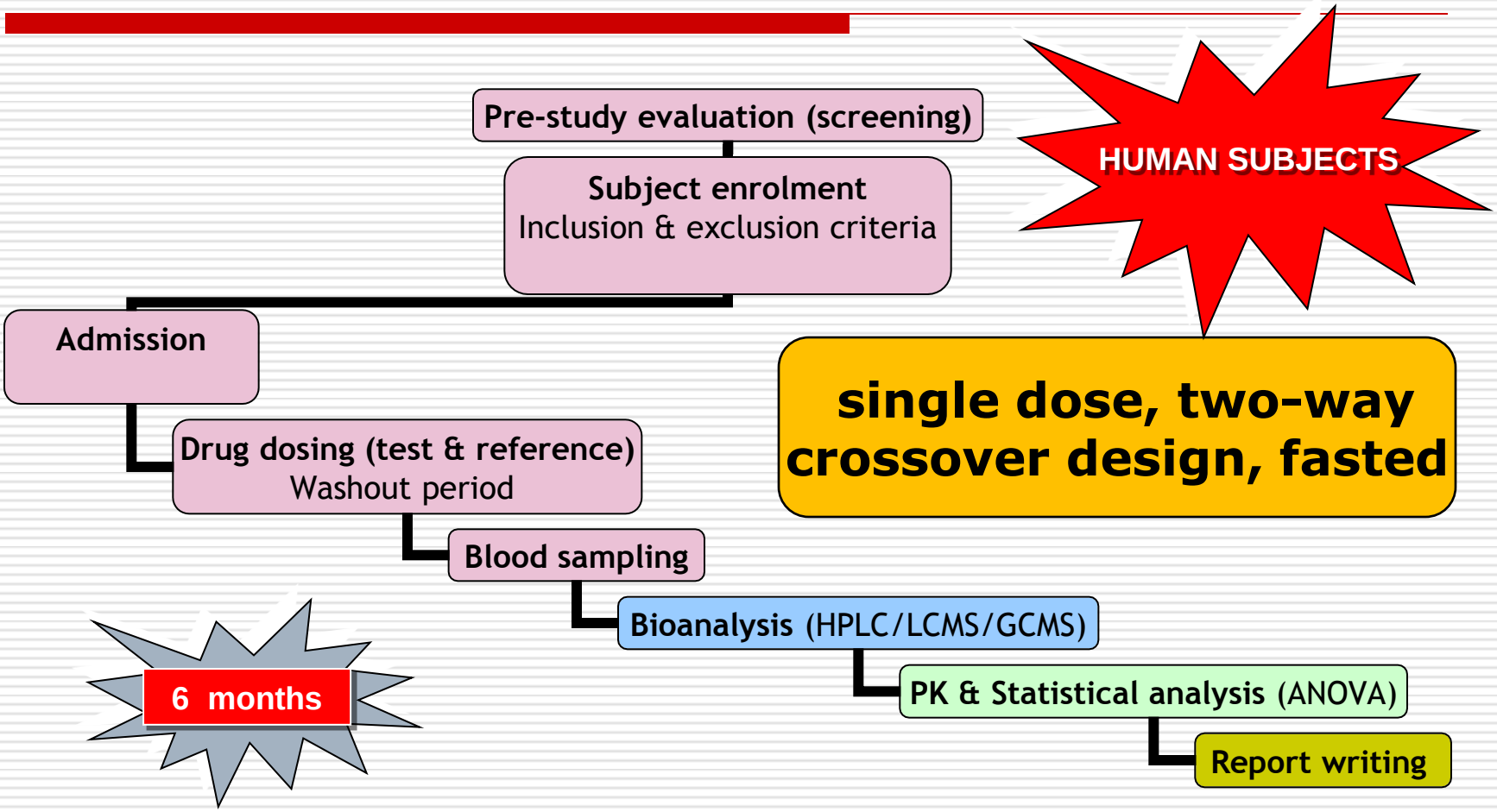
- Bioequivalence (BE)study is a requirement enforced by the Drug Control Authority (DCA), MOH since 1999 (DCA 92nd. Meeting) to ensure quality , safety and efficacy of generic medicines
- As generic medicines contain well documented active ingredients, it is the global practice to accept bioequivalence study in lieu of clinical trials for generic medicines

BIOEQUIVALENCE STUDY

The purpose of establishing bioequivalence study is to demonstrate equivalence between generic medicine and an innovator product in order to allow bridging of clinical trial performed by the innovator and consequently to efficacy of innovator formulation



Flowchart of a BE Study



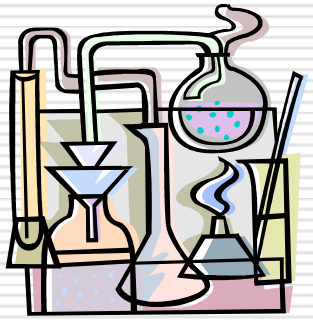
Phases of BE Study

Clinical

- Subject enrolment
- Drug administration
- Blood sampling

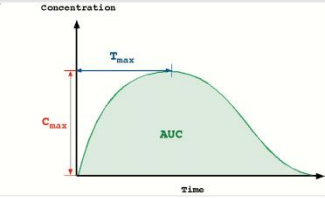
Bioanalytical

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



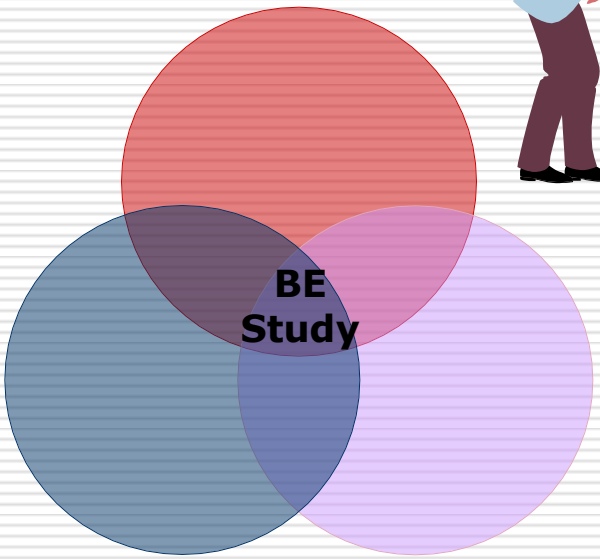
Statistical

- PK parameters – AUC, Cmax & Tmax
- Statistical analysis - ANOVA



Standards in BE Study

GCP



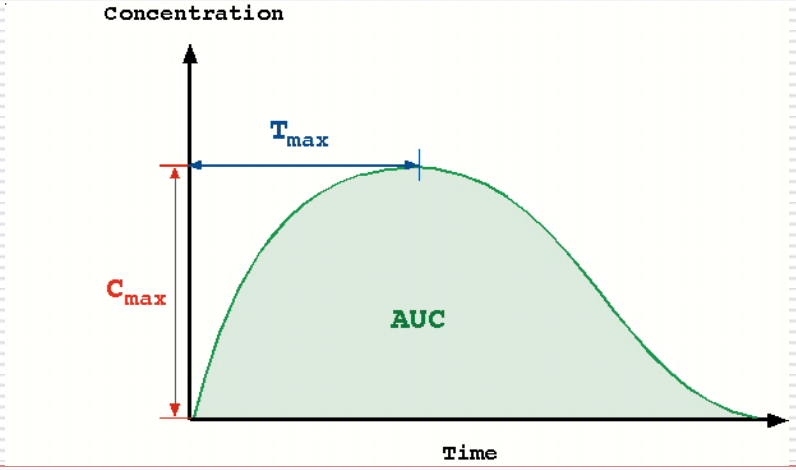
GLP

GMP

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)



How do we know whether the generic medicine is bioequivalent to the comparator/innovator?

90% Confidence Interval logAUC (amount of absorption) ratio & logCmax (rate of absorption) ratio lie within acceptable limits ie. between 80% and 125%

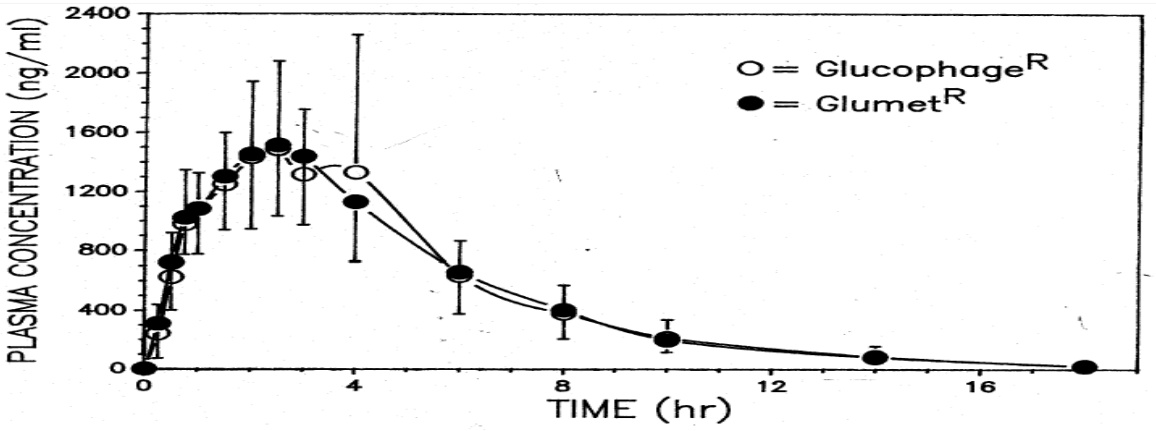


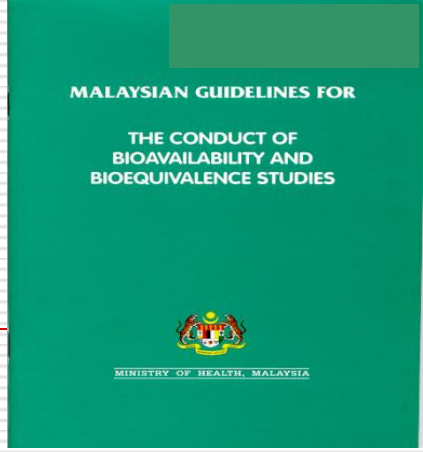
Fig. 1. Mean plasma metformin concentration versus time profiles of Glucophage and Glumet. Mean ± SD, N = 12.

THE NATIONAL WORKING COMMITTEE FOR BIOEQUIVALENCE STUDY

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, MAPS & PhAMA)
  - 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**

BIOEQUIVALENCE GUIDELINES AND CIRCULARS/ DIRECTIVES

BIOEQUIVALENCE 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

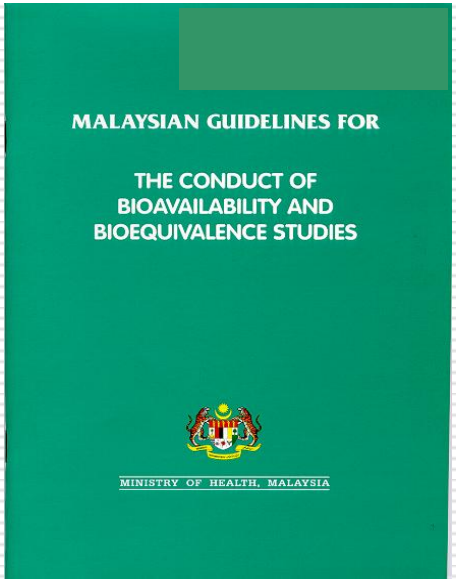
BIOEQUIVALENCE GUIDELINES

Both GLs provide :

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

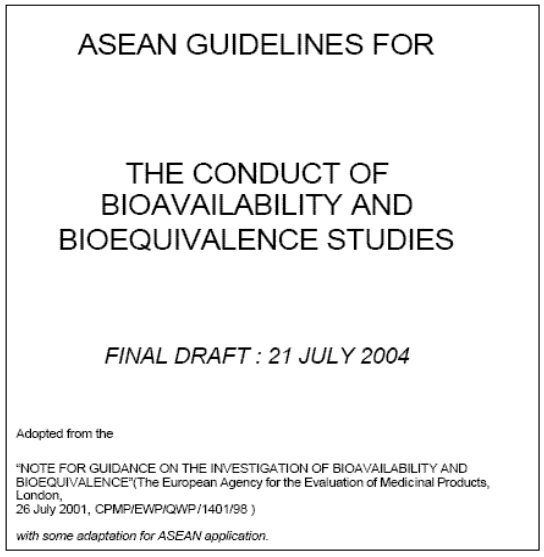
The core topic in the GLs is the design and conduct of studies

BIOEQUIVALENCE GUIDELINES



Malaysian Guidelines For The Conduct of Bioavailability and Bioequivalence Studies

ASEAN Guidelines For The Conduct of Bioavailability and Bioequivalence Studies


ASEAN GUIDELINES FOR

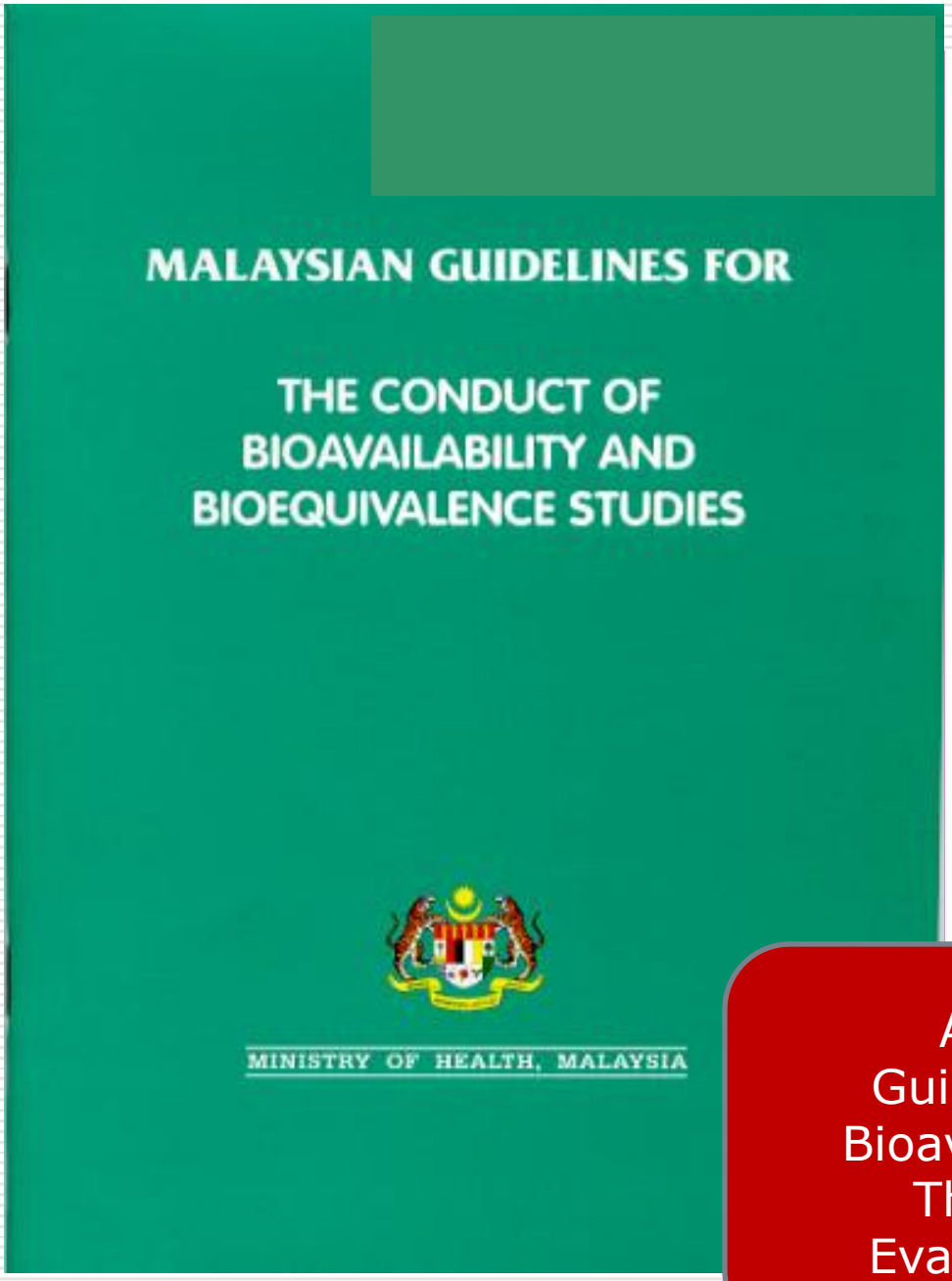
THE CONDUCT OF
BIOAVAILABILITY AND
BIOEQUIVALENCE STUDIES

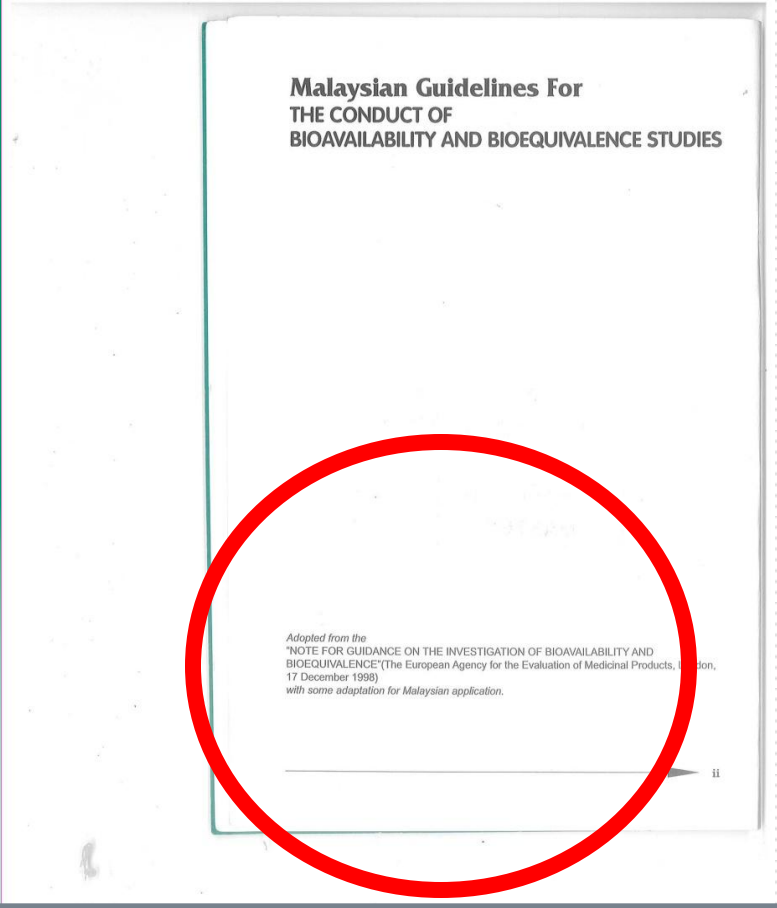
FINAL DRAFT : 21 JULY 2004

Adopted from the

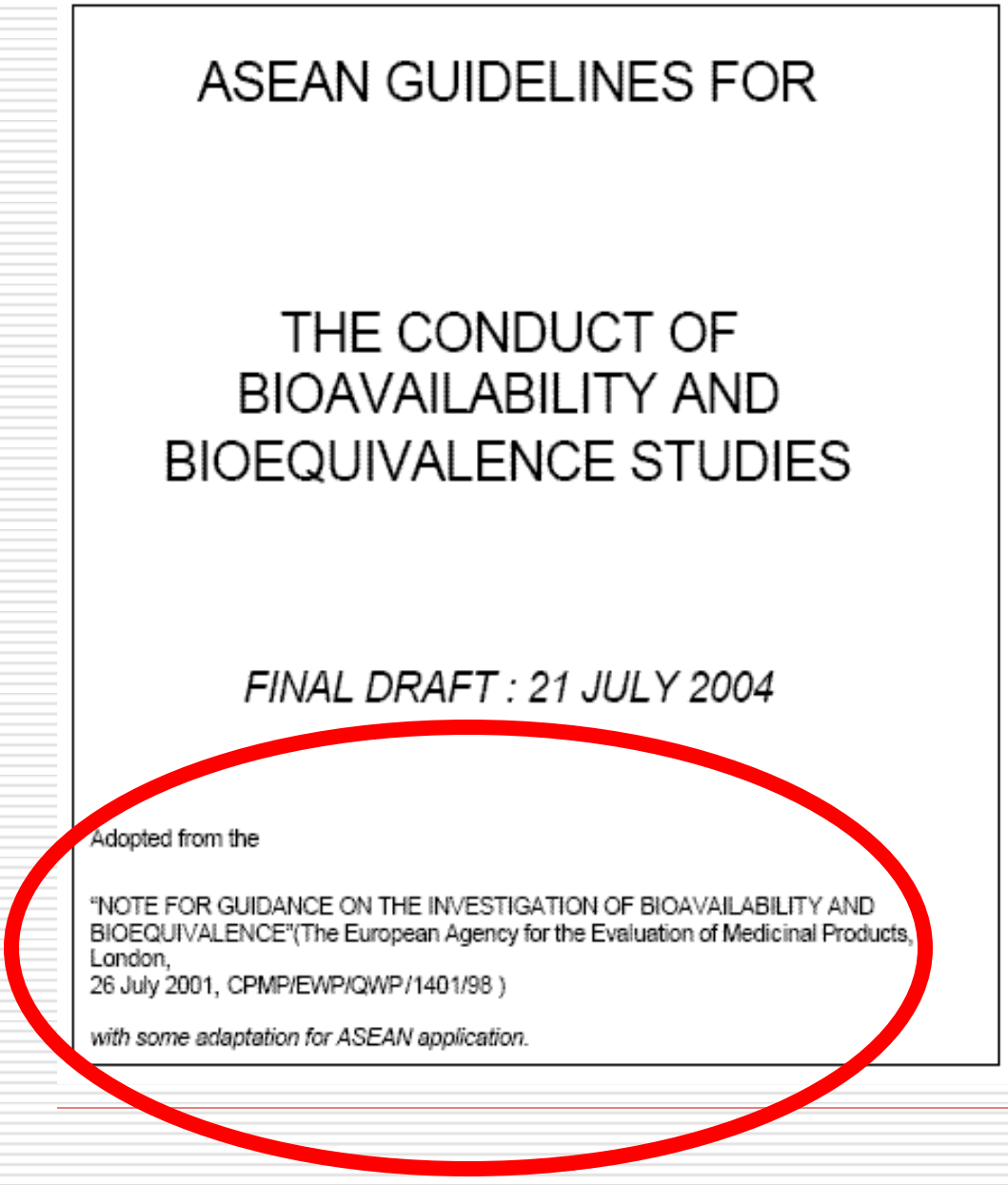
"NOTE FOR GUIDANCE ON THE INVESTIGATION OF BIOAVAILABILITY AND BIOEQUIVALENCE"(The European Agency for the Evaluation of Medicinal Products, London,
26 July 2001, CPMP/EWP/QWP/1401/98)

with some adaptation for ASEAN application.





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*



In the process of revision to be in line with latest European Medicines Agency(EMA) Guideline on the Investigation of Bioequivalence (CPMP/EWP/1401/98Rev.1/Corr**,20 January 2010

BIOEQUIVALENCE GUIDELINES

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.

TABLE OF CONTENTS

Circulars/Directives

- 1st. List (1999) : Bil(50)dlm.BPFK/007/3.7
- 2nd. List (2000) : Bil(85)dlm.BPFK/007/3.7
- 3rd. List (2001) : Bil(50)dlm.BPFK/007/3.8
- 4th. List (2002) : Bil(85)dlm.BPFK/007/3.8
- Bioequivalence on ARVs:Newsletter of the DCA, Vol. 20,April, 2003
- 5th. List (2004): Bil(85)dlm.BPFK/007/3.8
- Kajian Semula Keperluan dan Tarikh Kuatkuasa (2005) : Bil(51)dlm.BPFK/02/5/1.3

Circulars/Directives

- 6th. List (2006) : Bil(63)dlm.BPFK/02/5/1.3
- Exemption of BE for FEO products (2008) : Bil(5)dlm.BPFK/PPP/01/03
- 7th. List (2008) : Bil(38)dlm.BPFK/PPP/07/1
- Amendments on 7th. List (2009) : Bil(25)dlm.BPFK/PPP/01/03
- BE for products undergo Change of Site(2009) : Bil(31)dlm.BPFK/PPP/01/03
- 8th. List (2009) : Bil(46)dlm.BPFK/PPP/01/03

Circulars/Directives

- 9th. List (2011): Bil(8)dlm.BPFK/PPP/01/03 Jld. 1
- BE for all Generics (Solid, Oral Immediate Release Dosage Form(2011): Direktif Arahan di Bawah Peraturan 29, Peraturan-peraturan Kawalan Dadah dan Kosmetik 1984,Bil. 1 Tahun 2011,Bil(10)dlm.BPFK/PPP/01/03 Jld. 1
- Accreditation of BE Centres (2011): as above
- BE for Second Source Product (2011) : Bil(10)dlm.BPFK/PPP/07/18 Jld. 1

Circulars/Directives

- Guidance on BCS-Based Biowaiver (2013): Direktif Arahan di Bawah Peraturan 29, Peraturan-peraturan Kawalan Dadah dan Kosmetik 1984,Bil. 1 Tahun 2013,Bil(101)dlm.BPFK/PPP/01/03 Jilid 2

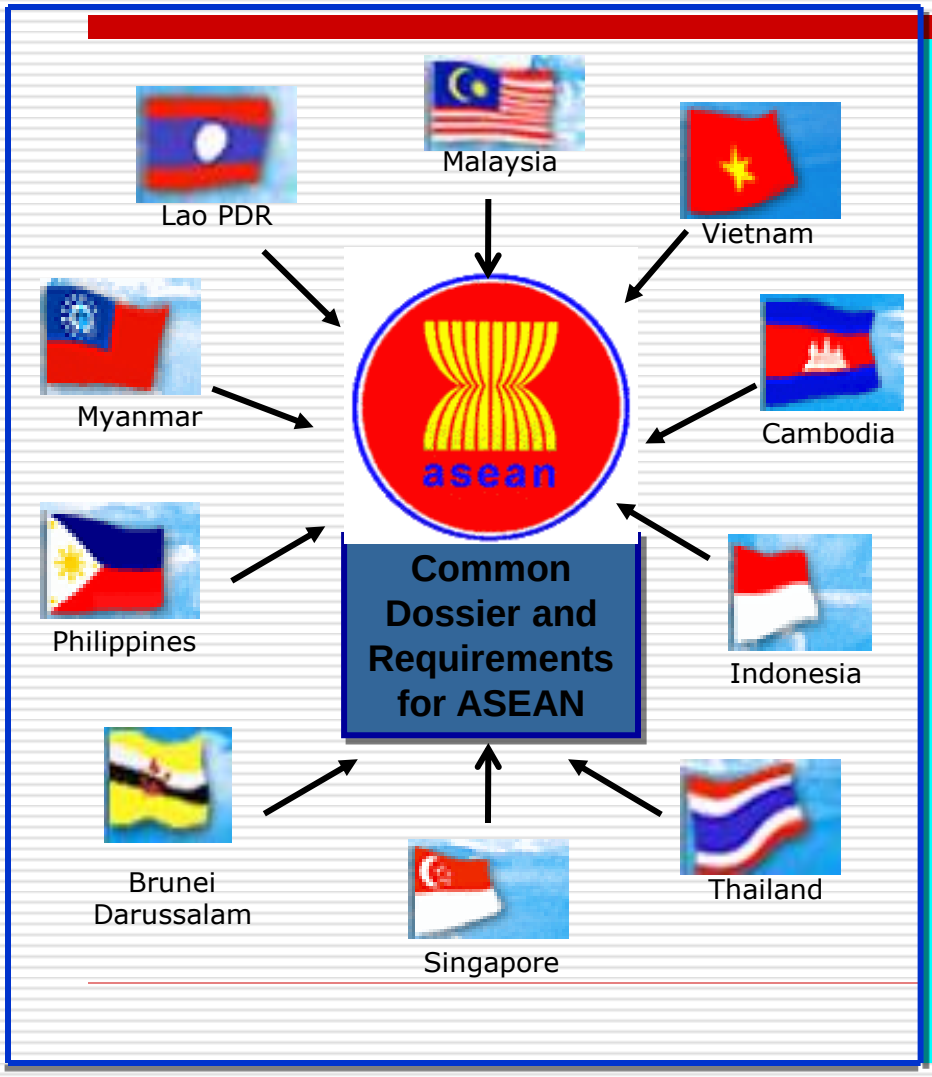
BIOEQUIVALENCE STUDY CENTRES

BE Study Centres (Local)

1. INFO KINETICS SDN. BHD.
2. PUSAT PENGAJIAN SAINS FARMASI,UNIVERSITI SAINS MALAYSIA(USM)
3. UNIVERSITY OF MALAYA BIOEQUIVALENCE AND TESTING CENTRE (UBAT)

ASEAN HARMONISATION

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 harmonisation 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 (ACTD/ACTR)
- ASEAN Technical Requirements – Process Validation, Analytical Validation, Stability, BA/BE, Variation

Status of Implementation of BA/BE Requirements in ASEAN

- ✓ *The ASEAN Guideline on The Conduct of BA/BE Studies*
- ✓ *Selection criteria of comparator products*
- ✓ *BE Study Reporting Format*
- ✓ *Standards on Good Clinical Practice*
- ✓ *Standards on Good Laboratory Practice*

NEXT

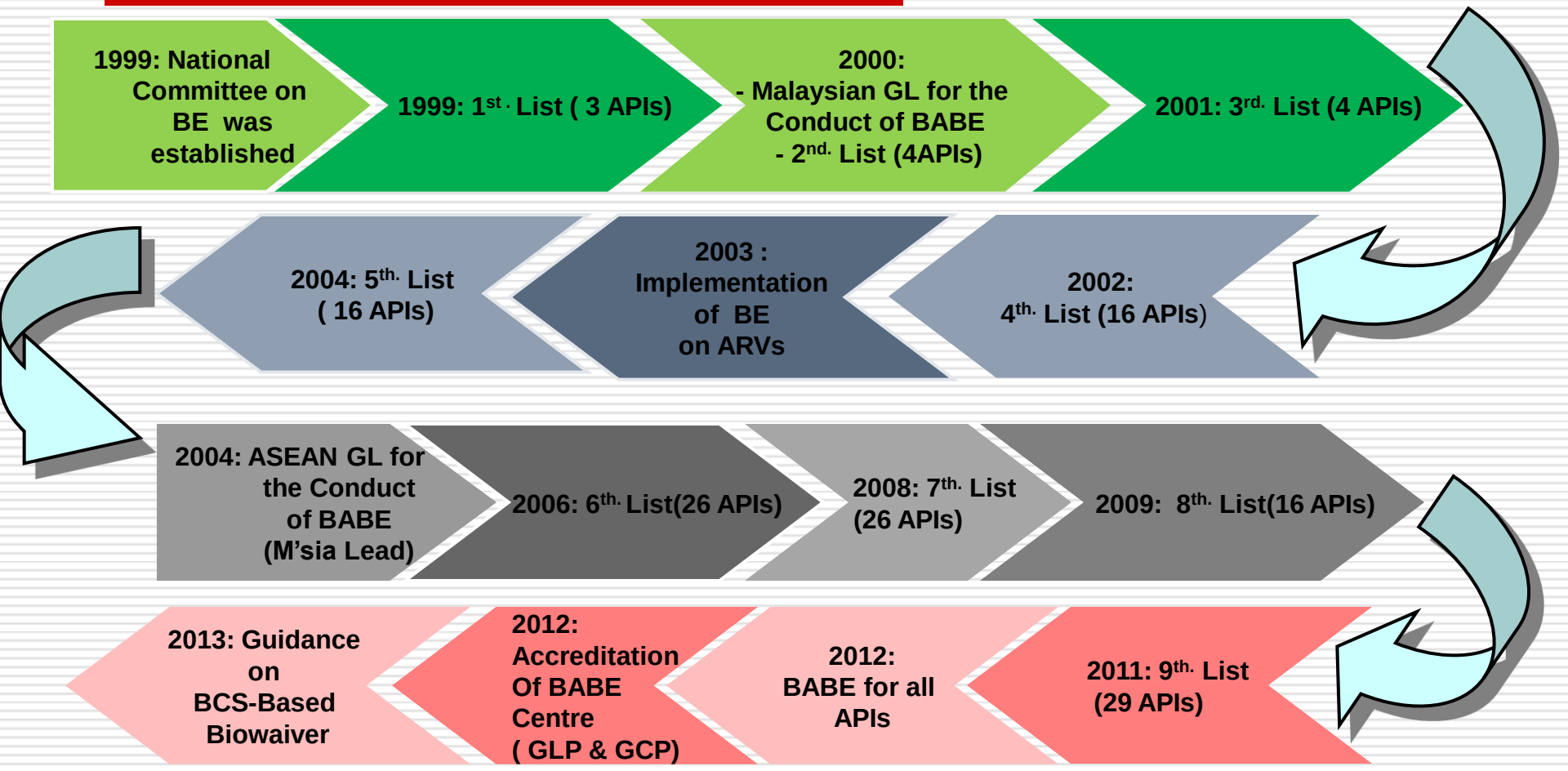
Standards for audit, inspection, accreditation and certification of BA/BE centres

NEXT

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

CONCLUSION

IMPLEMENTATION OF BIOEQUIVALENCE IN MALAYSIA



CONCLUSION

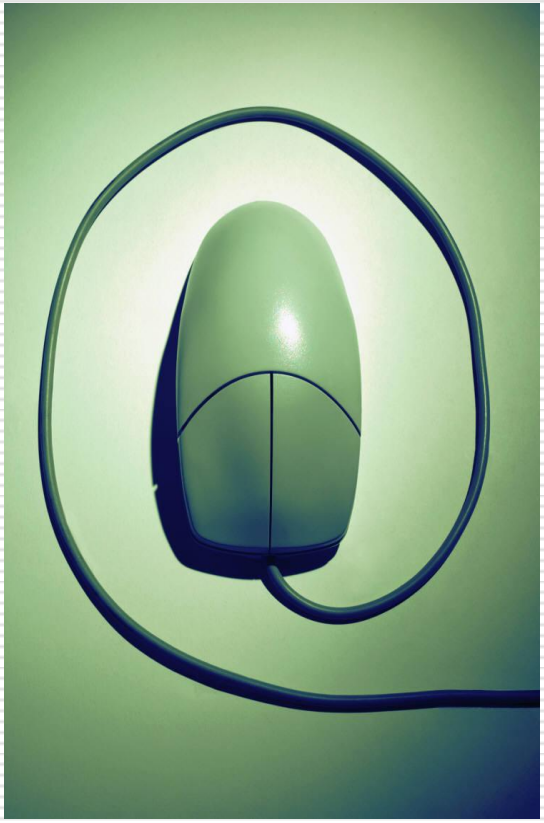
The implementation of BE studies as part of the requirement for registration of generic medicines provides an added value and benefits for the government, pharmaceutical industries, healthcare sectors and also the consumers/patients:

- BE Studies provide assurance of interchangeability between innovators and generic medicines as well as between brands of generic medicines
- reducing the healthcare costs by increasing the use of generic medicines which are much cheaper

CONCLUSION

- enhance the affordability and availability of medicines, in line with the WHO recommendations
- boost the local pharmaceutical industries to produce higher quality products and to penetrate international export markets
- encourage local BE centres to intensify their abilities to comply to international standards
- the consumers and patients can rest assured that generic medicines registered by the DCA are safe, efficacious and of good quality with the implementation of BE studies

WEBSITE FOR FURTHER REFERENCE



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- **Guidelines**
- **List of comparators**
- **BA/BE Study Centres**
- **Circulars**

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Thank you for your kind attention

Terima kasih