Bioequivalence Centre Compliance Programme

National Pharmaceutical Regulatory Agency

Ministry of Health Malaysia

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Bioequivalence & Ethics Committee Compliance Section
Centre for Investigational New Product
National Pharmaceutical Regulatory Agency (NPRA)
31st July 2017-4th August 2017

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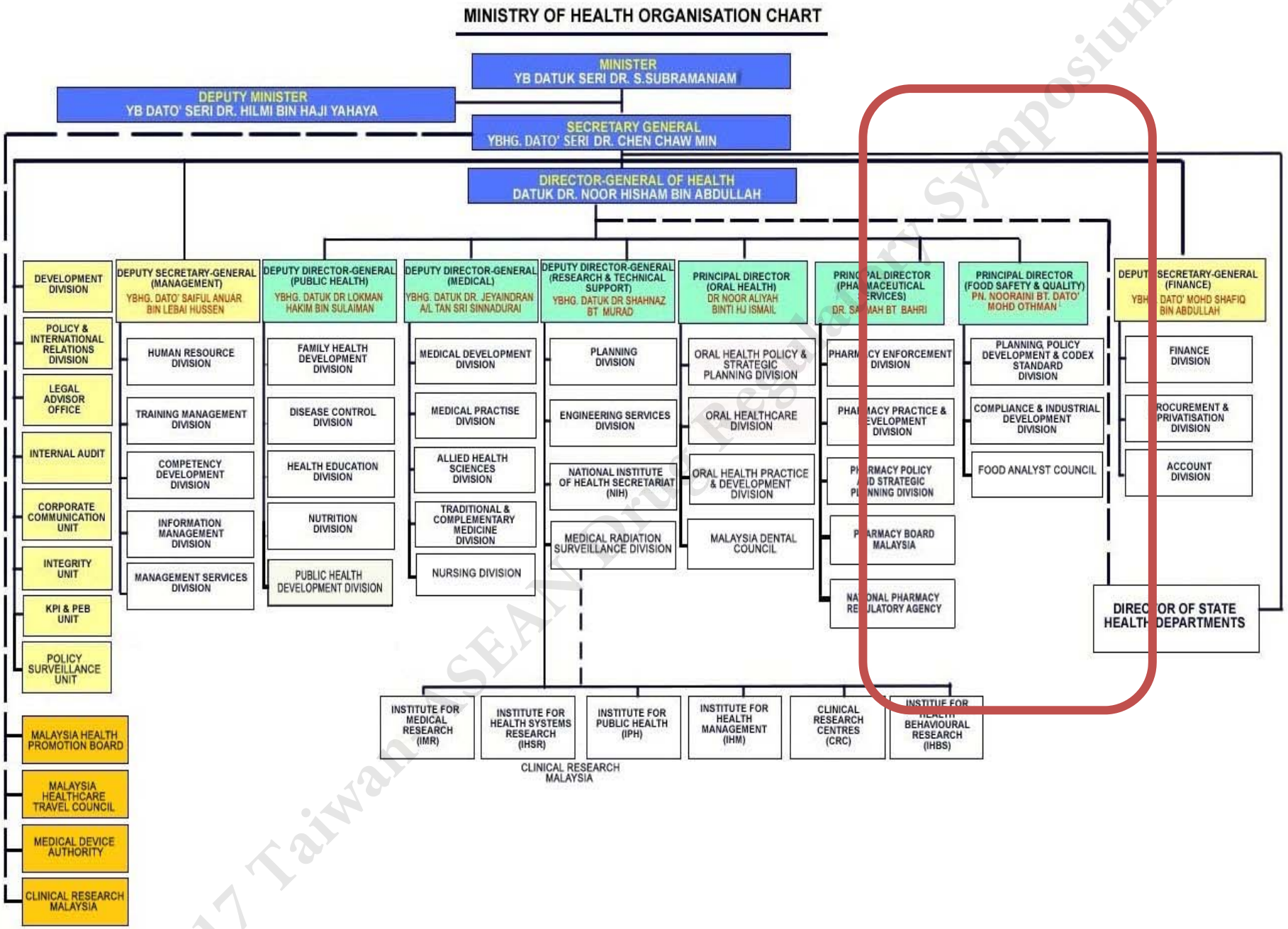
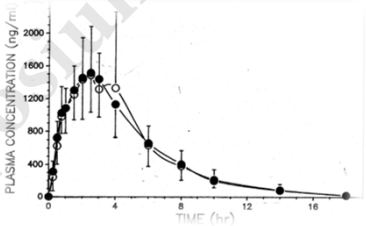


National Pharmaceutical Regulatory Agency
Ministry of Health Malaysia

- Director
  - Centre of Product Registration
  - Centre of Post Product Registration & Cosmetic Control
  - Centre of Compliance & Licensing
  - Centre of Quality Control
  - Centre of Investigational New Product
    - Investigational Product Evaluation
    - Investigational Product Safety Monitoring
    - GCP Compliance
    - GLP Compliance
    - BE Centre & Ethics Committee Compliance
  - Centre of Development & Strategic Planning

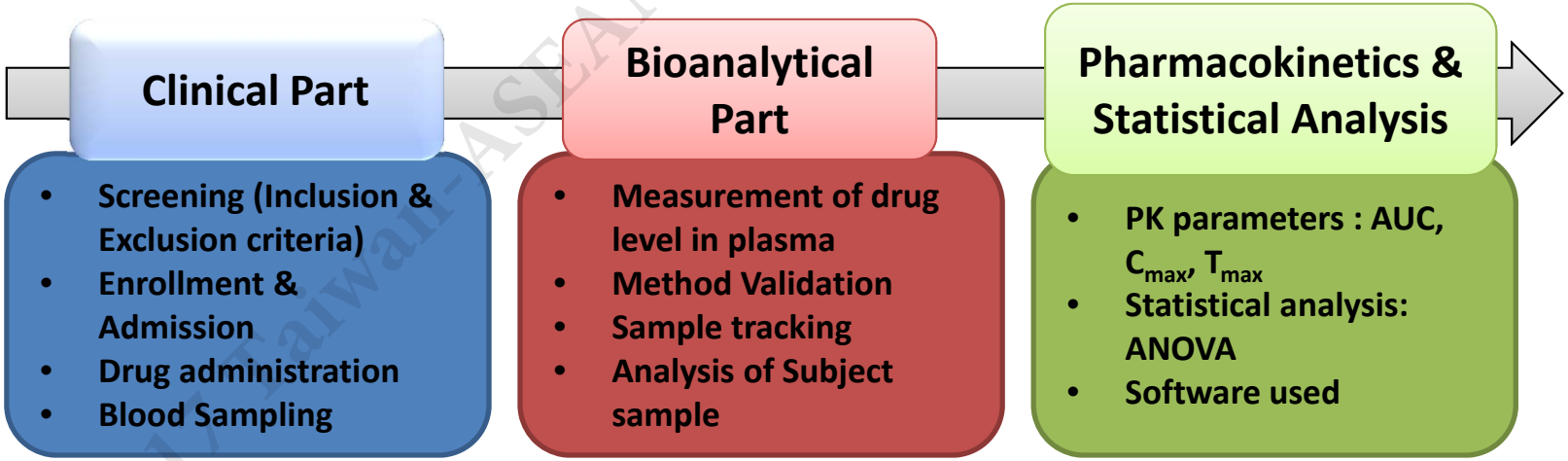
INTRODUCTION



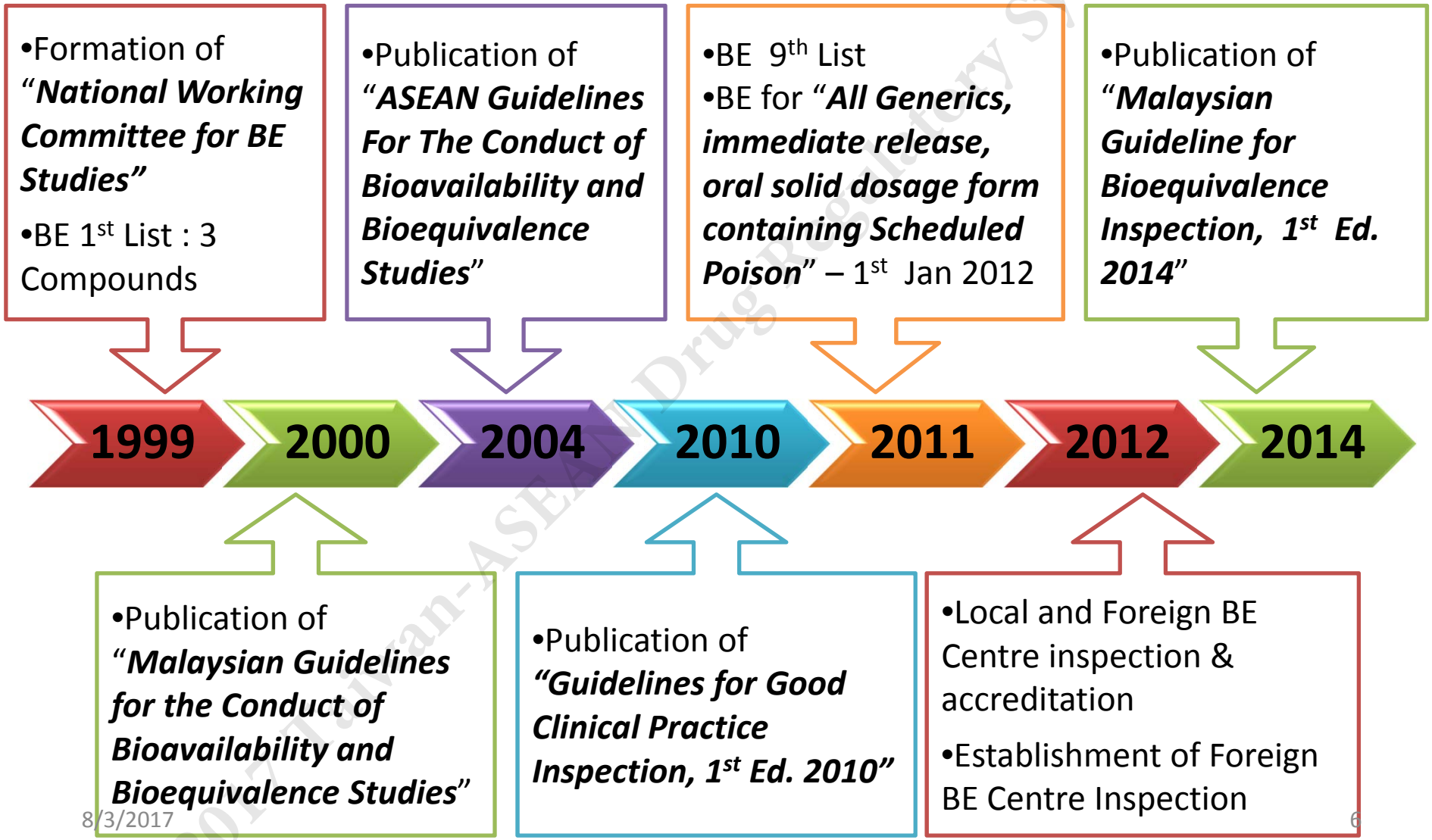
- What is Bioequivalence Study?
  - To compare the rate & extent of absorption between test & reference product
  - Comparison of PK parameters
    - Extend of absorption: AUC
    - Rate of absorption: C_{max}, T_{max}
    - Based on drug concentrations in plasma/serum/blood/urine

Examples

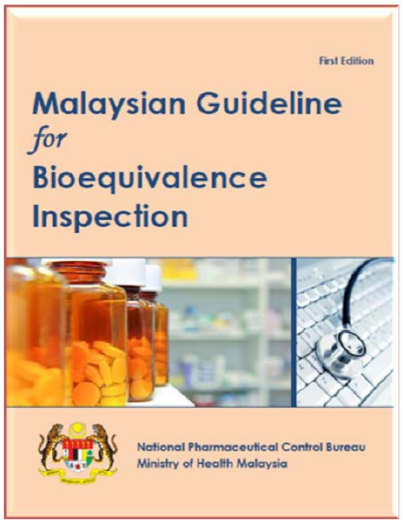
Active ingredients	Innovator	Generic
Ranitidine HCl	Zantac	X'tac
Mefenamic acid	Ponstan	Mefetab
Piroxicam	Feldene	Apo-Piroxicam



ROADMAP

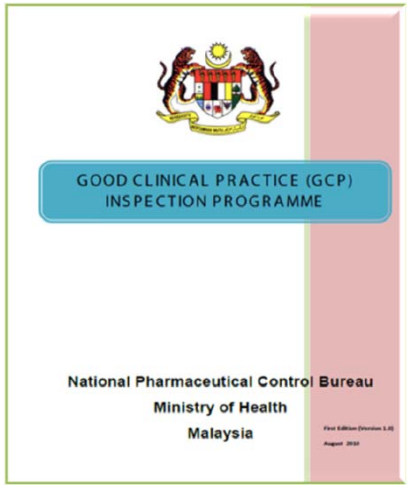


GUIDELINES



Malaysian Guideline for Bioequivalence Inspection, 1st Ed. 2014

Guidelines for Good Clinical Practice Inspection,1st Ed. 2010

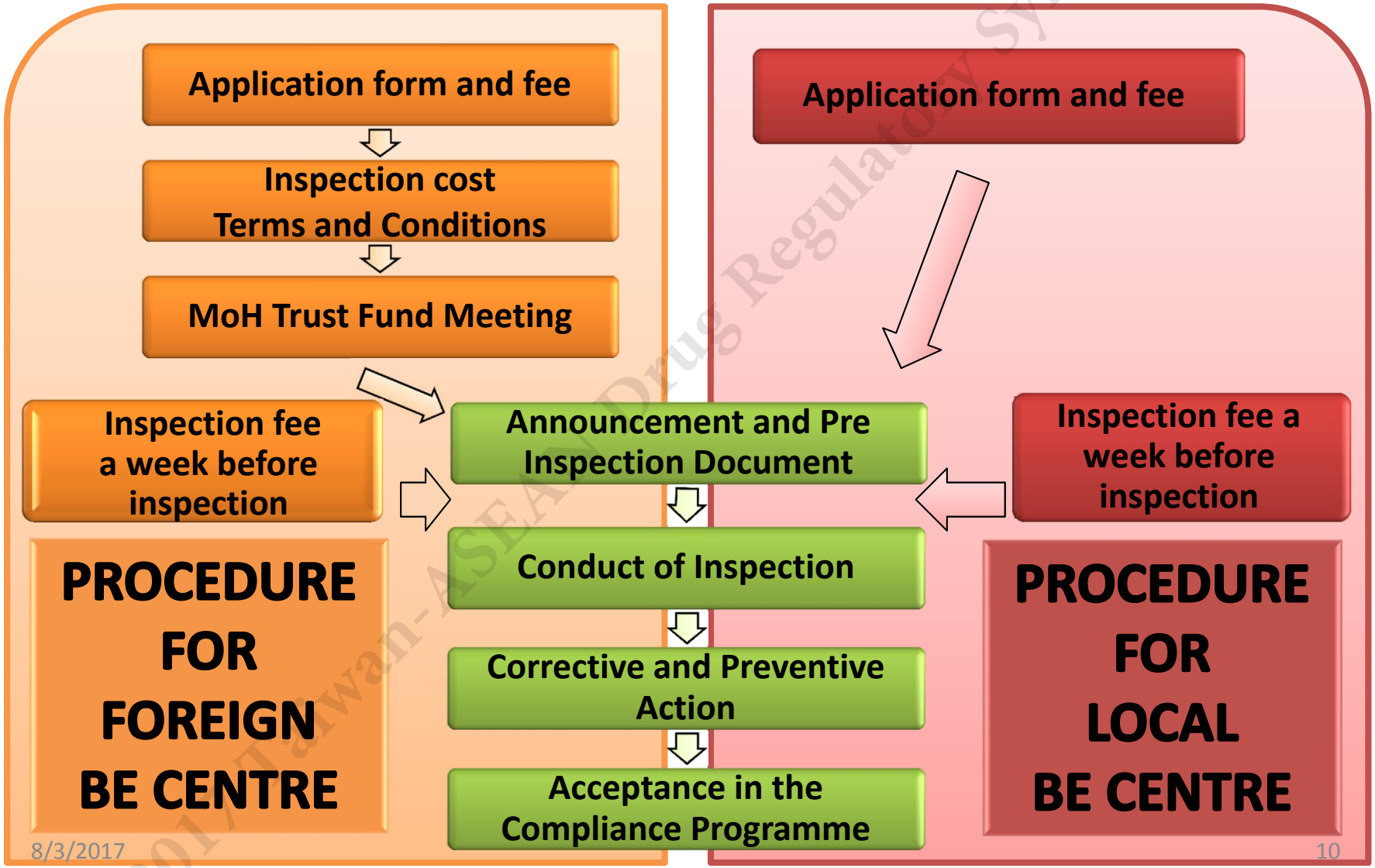


BE Centre Compliance Programme

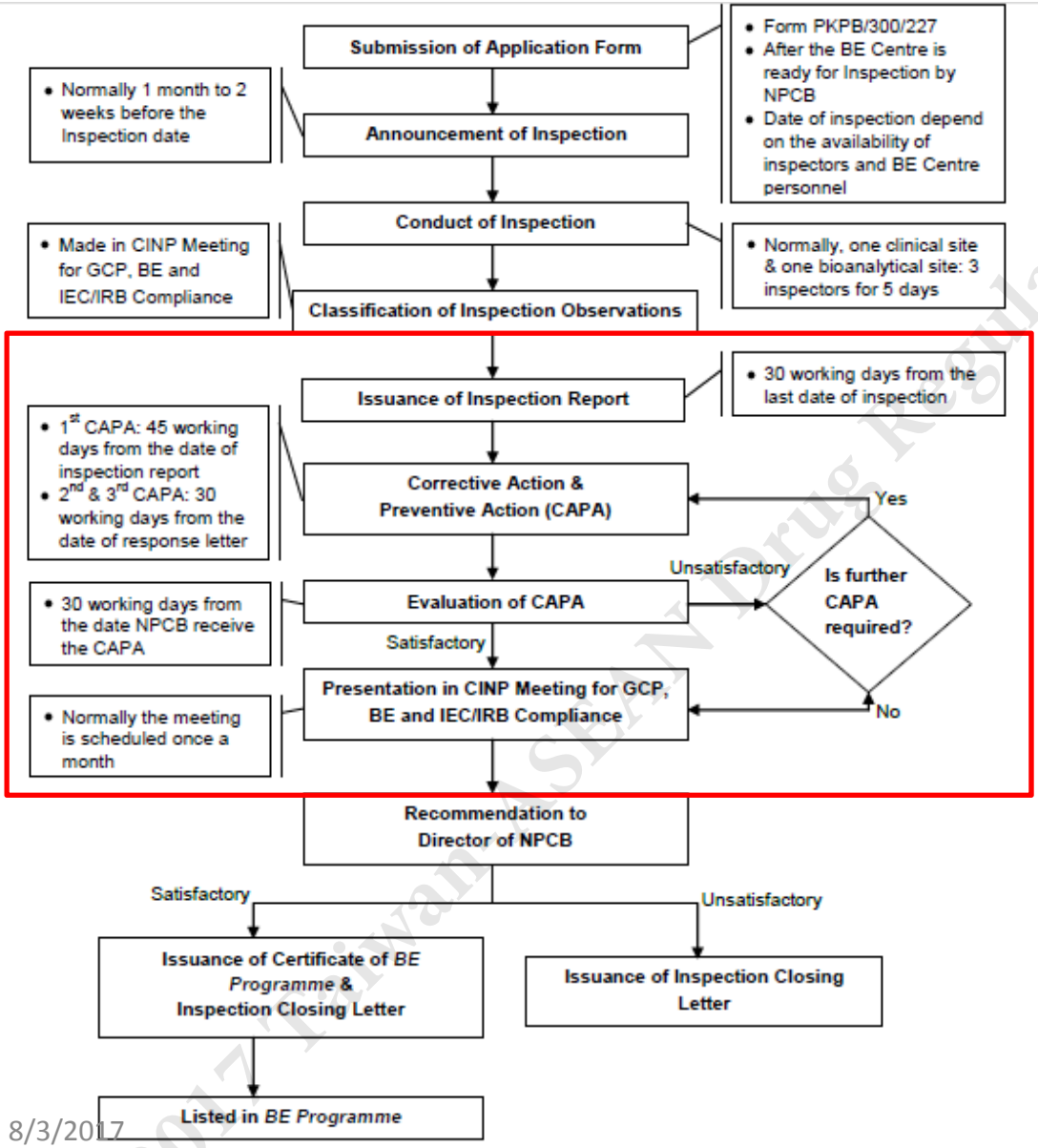
Overview of Compliance Programme

	Local BE Center	Foreign BE Center
Application Form	PKPB/300/521	PKPB/300/531
Application process	RM 1,000	RM 5,000
Inspection Fee	RM 1,000 (Documentation review)	RM 20,000
Inspection Cost	RM 1000/inspector/ working day	Flight ticket, accommodation and other associated expenses (such as ground transport, allowances, visa and etc.)
Duration of Inspection	3 inspectors, 5 working days for 1 Clinical site and 1 Bio-analytical site	
Inspection conducted based on:- Malaysian Guideline for Bioequivalence Inspection, 1st Ed. 2014 Good Clinical Practice (GCP) for the clinical site Good Laboratory Practice (GLP) for the bio-analytical site EMA & US FDA Guidelines – Method Validation		
Certificate of Compliance Programme valid for 3 years from the date of issuance		

Framework of Compliance Programme



Local BE Centre



PUSAT KAJIAN PRODUK BARU
CENTRE FOR INVESTIGATIONAL NEW PRODUCT
AGENSI REGULATORI FARMASI NEGARA
NATIONAL PHARMACEUTICAL REGULATORY AGENCY
KEMENTERIAN KESIHATAN MALAYSIA
MINISTRY OF HEALTH MALAYSIA

PERMOHONAN PEMERIKSAAN UNTUK PROGRAM KOMPLIANS NPRA BAGI PUSAT KAJIAN BIOEKUIVALENS (DALAM NEGARA)

INSPECTION APPLICATION FOR NPRA BIOEQUIVALENCE CENTRE COMPLIANCE PROGRAMME (LOCAL)

SILA BACA ARAHAN BERIKUT SEBELUM MENGISI BORANG.
PLEASE READ THE FOLLOWING INSTRUCTIONS BEFORE COMPLETING THIS FORM.

i. Borang permohonan yang dikemukakan hendaklah dalam salinan asal.
The submitted application form shall be in original copy.

ii. Hanya borang permohonan yang dicetak atas kertas A4 putih (depan dan belakang) sahaja diterima.
Only application form printed on both sides using white A4 size paper will be accepted.

iii. Borang yang telah lengkap hendaklah dihanter kepada Pengarah, Agensi Regulatori Farmasi Negara, Kementerian Kesihatan Malaysia, Lot 36, Jalan Universiti, 46200 Petaling Jaya, Malaysia. (u.p.: Timbalan Pengarah, PUSAT KAJIAN PRODUK BARU).
Please submit the completed form to: Director, National Pharmaceutical Regulatory Agency, Lot 36, Jalan Universiti, 46200 Petaling Jaya, Malaysia (attn.: Deputy Director, CENTRE FOR INVESTIGATIONAL NEW PRODUCT).

iv. Sila rujuk *Malaysian Guideline for Bioequivalence Inspection* edisi pertama untuk maklumat lanjut.
Please refer to Malaysian Guideline for Bioequivalence Inspection first edition for more information.

Payment for:-

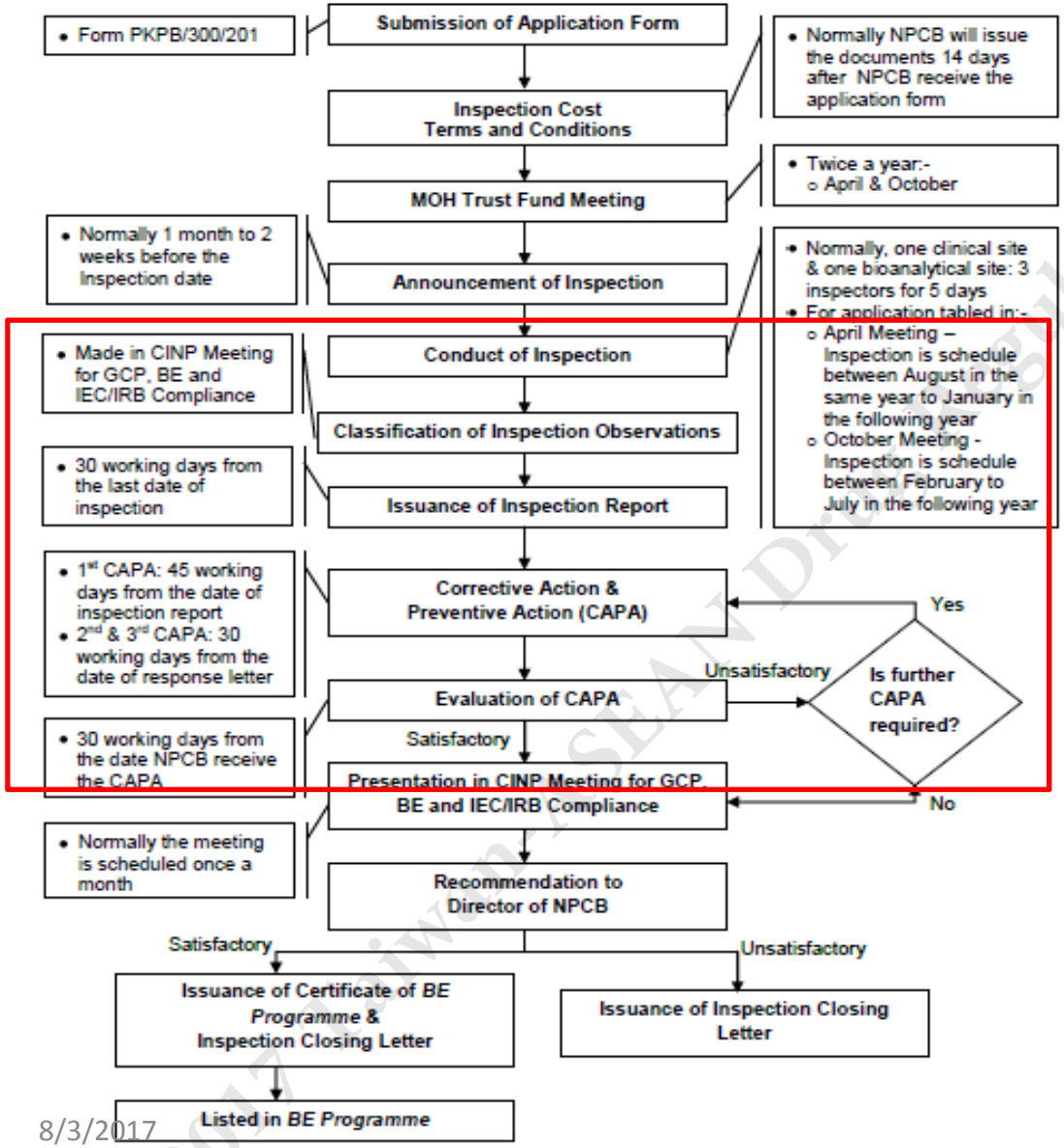
- Application processing fee
- Evaluation of document
- Inspection fee

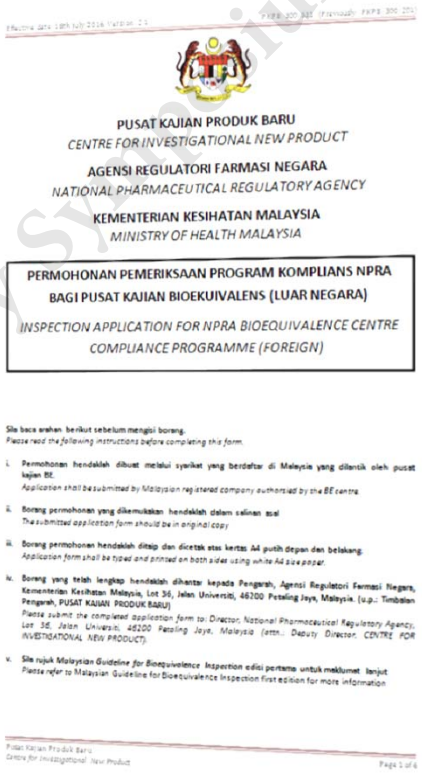
Fee for Local BE Centre Inspection

(Effective from 1st January 2016)

No.	Activity	Fee (RM)
1	Application process	1,000
2	Evaluation of documents (Pre-inspection, corrective and preventive action documents)	1,000
3	Full inspection	1,000/ inspector/ working day
4	Additional site inspection	1,000/ inspector/ working day
5	Verification inspection	1,000/ inspector/ working day
6	Triggered inspection	1,000/ inspector/ working day
*Including application for full inspection, surveillance inspection, additional clinical site inspection & verification inspection.		
Maximum of RM 10,000 per inspection including the application process and documentation review.		
KKM: Free Government Institution (Non KKM): 50% waived		

Foreign BE Centre





PUSAT KAJIAN PRODUK BARU
CENTRE FOR INVESTIGATIONAL NEW PRODUCT
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NATIONAL PHARMACEUTICAL REGULATORY AGENCY
KEMENTERIAN KESIHATAN MALAYSIA
MINISTRY OF HEALTH MALAYSIA

PERMOHONAN PEMERIKSAAN PROGRAM KOMPLIANS NPRA BAGI PUSAT KAJIAN BIOEKUIVALENS (LUAR NEGARA)
INSPECTION APPLICATION FOR NPRA BIOEQUIVALENCE CENTRE COMPLIANCE PROGRAMME (FOREIGN)

Payment for:-

- Application processing fee
- Cost of Inspection: At least 1 month before the Trust Fund meeting.
- Fee of Inspection*: At least 1 week before inspection

Fee for Foreign BE Centre Inspection

(Effective from 1st January 2016)

No.	Activity	Fee (RM)
1	Application process	5,000
2	Inspection fee	20,000
3	Inspection cost	• Flight ticket • Accommodation • Allowances • Ground transport • Visa (If required) • Other associated expenses

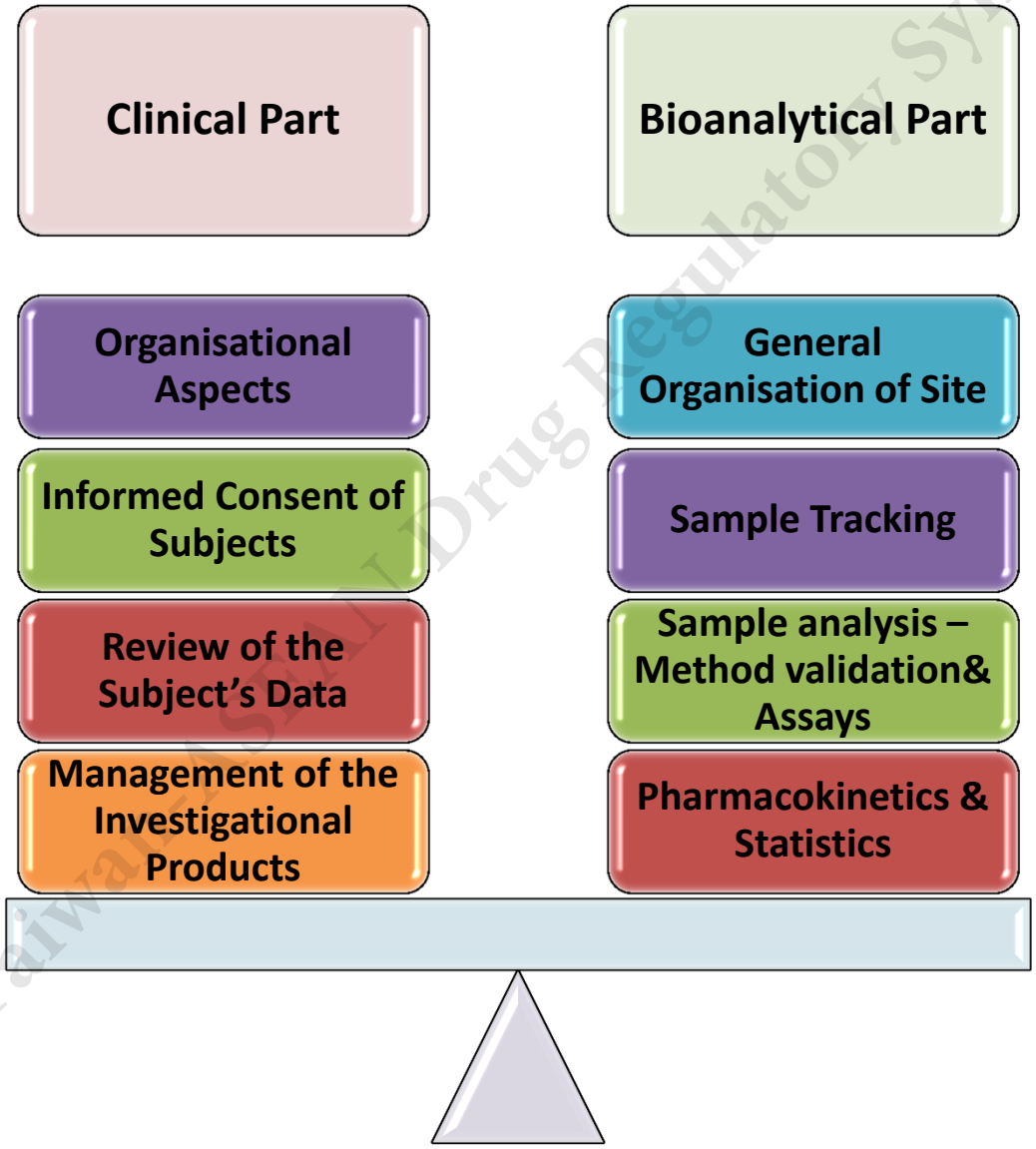
Categories of Inspection

First inspection involves Clinical, Bioanalytical, Pharmacokinetics and Statistical Analysis Part

Subsequent inspections involve covering the Clinical, Bioanalytical, Pharmacokinetics and Statistical Analysis Part

Other inspection:-
Requested by CPR
Study Specific Inspection
Verification inspection
Significant Changes in the BE Centre

Area of Inspection



Clinical Part

Organisational Aspects

- Implementation of the BE Studies at the clinical site
- Facilities and equipment
- Management of biological samples
- Organisation of the documentation
- Monitoring and auditing
- Use of computerised

Clinical Part

Informed Consent of Subjects

- Process of informed consent taken
- The signed and self-dated consent form actually used and approved by the IEC/IRB
- The information sheet used for BE Study
- The centre practice for giving a copy of the informed consent to the patient
- Consent for access to medical records by the authorities

Clinical Part

Review of the Subject's Data

- Characteristics of the subjects included in the BE study
- Subjects' visits calendar
- Efficacy and safety assessment data
- Source document and Case Report Form
- Concomitant therapy and intercurrent illness

Clinical Part

Management of the Investigational Products

- Instructions for handling of IP and study related materials
- Shipping records for IP and study related material. Receipt date(s) of product delivery and quantity.
- Documentation regarding allocation of treatment, randomisation and code breaking
- IP accountability at site

Bioanalytical Part

General Organisation of Site

- Activity
- Personnel
- Quality Assurance System
- Facility and equipment
- Archiving of documentation

Bioanalytical Part

Sample Tracking

- Receipt - Information during receipt of samples
- Storage
  - BE study samples and Method Validation samples (Usage Log)
  - Assessment of the risk of confusion between samples
  - Identification of the freezer(s) used
  - Temperature records of the freezer - Alarms
- Destruction

Bioanalytical Part

Sample analysis – Method validation & Assays

- Bioanalytical method used
  - Method description
  - Equipment
  - Reagents
  - Reference substances
  - Calibration, control samples
  - Development of the method
  - Method validation
- Assays – Subject Sample Analysis

Bioanalytical Part

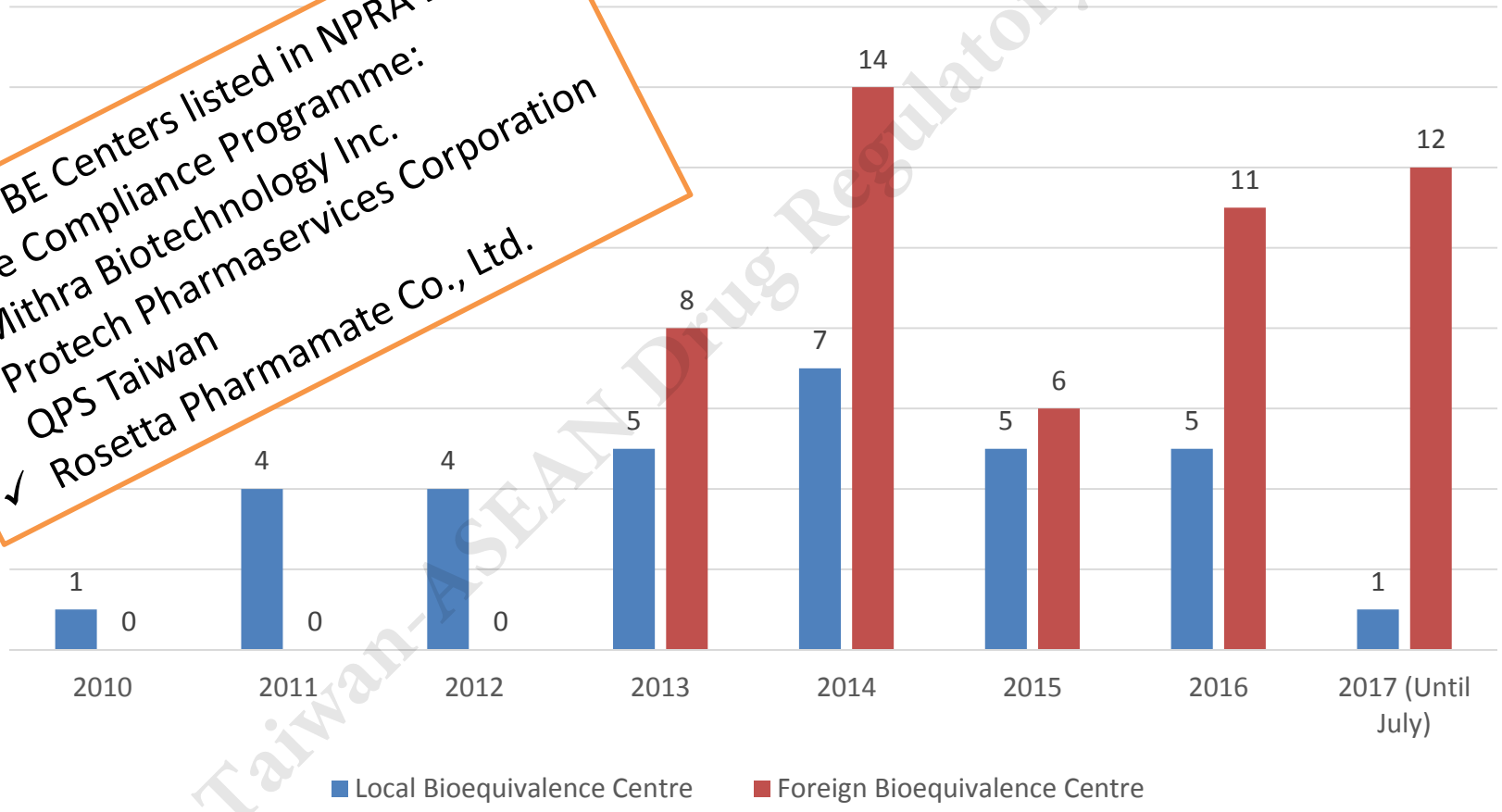
Pharmacokinetics & Statistics

- Quality system in place
- Qualification and job description of the personnel
- Software used and validation
- Practicalities and control of data entry
- Sampling times used
- Method used for calculation of pharmacokinetic parameters
- Consistency of the raw data with the study report

Number of Bioequivalence Inspection for Local & Foreign BE Center (2010-2017)

Taiwan BE Centers listed in NPRA BE Centre Compliance Programme:

- ✓ Mithra Biotechnology Inc.
- ✓ Protech Pharmaservices Corporation
- ✓ QPS Taiwan
- ✓ Rosetta Pharmamate Co., Ltd.



BE Centre Listed in NPRA BE Centre Compliance Programme

Official Portal
NATIONAL PHARMACEUTICAL REGULATORY AGENCY
Formerly known as National Pharmaceutical Control Bureau (BPFK)
BAHAGIAN REGULATORI FARMASI NEGARA | KEMENTERIAN KESIHATAN MALAYSIA

NPRA MALAYSIA

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Bioequivalence (BE)

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BE Centres that are listed in Bioequivalence Centre Compliance Programme, National Pharmaceutical Regulatory Agency, Ministry of Health, Malaysia as of 1 Jun 2017.

MALAYSIA LOCAL BE CENTRES

- Bioxis Sdn Bhd
- Borneo Kinetics Sdn. Bhd.
- Info Kinetics Sdn Bhd.
- Pusat Kajian Bioekuivalens (BE), Pharmacy-Attest Research Sdn Bhd (ARSB) BA/BE Centre, Pusat Pengajian Sains Farmasi, Universiti Sains Malaysia (USM)
- Pusat Pengajian Sains Farmasi, Universiti Sains Malaysia (USM)

FOREIGN BE CENTRES

- Lotus Labs Pvt. Ltd., India
- Accutest Research Laboratories (I) Pvt. Ltd., India

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Website for further reference:-

http://npra.moh.gov.my/index.php/regulatory-information/bioequivalence-be