



# REGULATORY ASSESSMENT OF CRITICAL DOSE DRUGS / NARROW THERAPEUTIC RANGE DRUGS IN HONG KONG

CLIVE CHAN  
DRUG OFFICE  
DEPARTMENT OF HEALTH

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## MAIN DRUG LEGISLATION

- Pharmacy and Poisons Ordinance (Chapter 138, Laws of Hong Kong)
  - To consolidate and amend the law relating to pharmacy, pharmaceutical products and poisons.
- Pharmacy and Poisons Board (the Board)
  - A statutory body established under section 3 of the Pharmacy and Poisons Ordinance to carry out functions in accordance with the provisions of the said ordinance and its subsidiary legislation.

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## EXECUTIVE COMMITTEES OF THE BOARD

- Examination Committee
- Pharmacy and Poisons (Listed Sellers of Poisons) Committee
- Pharmacy and Poisons (Manufacturers Licensing) Committee
- Pharmacy and Poisons (Registration of Pharmaceutical Products and Substances: Certification of Clinical Trial/Medicinal Test) Committee\*
- Pharmacy and Poisons (Wholesale Licenses) Committee
- Pharmacy Internship Training Committee
- Poisons Committee

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## DUTIES OF EXECUTIVE COMMITTEE (1)

- Pharmacy and Poisons (Registration of Pharmaceutical Products and Substances: Certification of Clinical Trial/Medicinal Test) Committee\* (the Registration Committee)
  - Consider new or renewal applications for registration of pharmaceutical products or substances, and issue registration certificates subject to any conditions it thinks fit to impose;

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## DUTIES OF EXECUTIVE COMMITTEE (2)



- The Registration Committee (continue):
  - Deregister a pharmaceutical product or substance, suspend the registration of a pharmaceutical product or substance for a specified period, issue warning letter(s) to the holder of a registration certificate or vary a condition of the registration of a pharmaceutical product or substance;
  - Consider applications for approval to change any of the registrable particulars of a pharmaceutical product or substance;

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## DUTIES OF EXECUTIVE COMMITTEE (3)



- The Registration Committee (continue):
  - Consider applications for conducting a clinical trial on human beings or a medicinal test on animals, and issue a clinical trial certificate or medicinal test certificate, subject to any conditions it thinks fit to impose; and
  - Cancel a clinical trial certificate or medicinal test certificate, suspend a clinical trial certificate or medicinal test certificate for a specified period, issue warning letter(s) to the holder of the certificate or vary a condition of the certificate.

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## REQUIREMENT OF BIOAVAILABILITY AND BIOEQUIVALENCE STUDIES IN HONG KONG



- 2009
  - Review Committee on Regulation of Pharmaceutical Products in Hong Kong:
    - Bioavailability and bioequivalence (BABE) studies as registration requirement for pharmaceutical products to enhance the quality of generic drugs
  - Implementation by phases

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## REQUIREMENT OF BIOAVAILABILITY AND BIOEQUIVALENCE STUDIES IN HONG KONG



- 2009
  - Review Committee on Regulation of Pharmaceutical Products in Hong Kong (continue):
    - Phase 1 on antiepileptic drugs where a comparatively small difference in the absorption of the drug by the human body may lead to undesirable consequences

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## REQUIREMENT OF BIOAVAILABILITY AND BIOEQUIVALENCE STUDIES IN HONG KONG



- 2009
  - The Registration Committee:
    - Endorse the decision to implement the Phase 1 requirement for BABE studies covering 29 antiepileptic drugs
  - Implementation date on 1 April 2010

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## REQUIREMENT OF BIOAVAILABILITY AND BIOEQUIVALENCE STUDIES IN HONG KONG



- 2010

- Phase 1 requirement for BABE studies covering 29 antiepileptic drugs:

Carbamazepine	Clobazam	Clonazepam	Clorazepate	Divalproex
Ethosuximide	Ethotoin	Felbamate	Fosphenytoin	Gabapentin
Lamotrigine	Lacosamide	Levetiracetam	Mephenytoin	Mesuximide
Oxcarbazepine	Pheneturide	Phensuximide	Phenytoin	Pregabalin
Primidone	Rufinamide	Sultiame	Tiagabine	Topiramate
Trimethadione	Vigabatrin	Valproates	Zonisamide	

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## REQUIREMENT OF BIOAVAILABILITY AND BIOEQUIVALENCE STUDIES IN HONG KONG



- 2013
  - The Board endorsed the decision to establish the Expert Advisory Group on BABE studies (the BABE Expert Group) to facilitate the implementation of the registration requirement for BABE studies
  - The BABE Expert Group is chaired by the Assistant Director (Drug), and includes 11 local members from the academia\*, pharmaceutical trade, Hospital Authority, Department of Health, pharmacy and medical professions, and 2 overseas co-opted members\*\*

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## REQUIREMENT OF BIOAVAILABILITY AND BIOEQUIVALENCE STUDIES IN HONG KONG




- Special compliments to
  - Academia\*
    - Professor Vincent Lee, CUHK
    - Professor Vivian Lee, CUHK
    - Professor Ian Wong
    - Professor Lam Ching Wan
  - Overseas co-opted members\*\*
    - Professor Atholl Johnston, UK
    - Professor Leslie Benet, US

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## BABE EXPERT GROUP:


### Terms of Reference:

- Provide professional advice to the Registration Committee on the implementation plan of the registration requirement for BABE studies
  - Provide professional support to the Registration Committee on issues related to BABE studies
  - Provide expert opinions on the methodology, protocol and data of BABE studies as provided by the applicants of pharmaceutical product registration
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## ENDORSEMENT BY THE BABE EXPERT GROUP

- The BABE studies should be conducted in accordance with the World Health Organization guidance on the “Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability”
    - 2006, WHO Technical Report Series, No. 937 (Annex 7)
    - 2015, WHO Technical Report Series, No. 992 (Annex 7)
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## The WHO guidance on the “Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability

- Generic pharmaceutical products need to conform to the same appropriate standards of safety, quality and efficacy of the originator’s or comparator’s product
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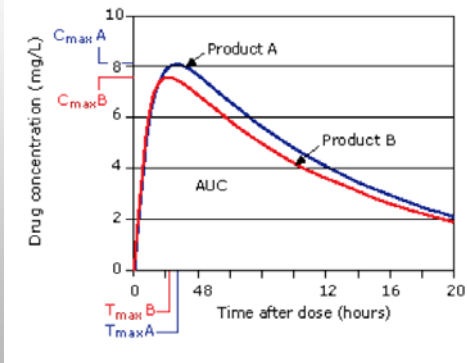
## The WHO guidance on the “Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability

- Documentations
    - Comparative *in-vivo* pharmacokinetic studies (BE studies)
    - Comparative *in-vivo* pharmacodynamic studies
    - Comparative clinical trials
    - Comparative *in-vitro* tests
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## COMPARATIVE *IN-VIVO* PHARMACOKINETIC STUDIES (BE STUDIES)



### Study Design:

- Two-period, two-sequence, single-dose, cross-over, randomized study

### Minimum Subjects:

- 12

### Acceptance Limits:

- 90% confidence interval
- 0.80 - 1.25 AUC-ratio & C<sub>max</sub>-ratio

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## ENDORSEMENT BY THE BABE EXPERT GROUP

- Adopts the WHO requirements for the BABE acceptance range:

- 90% confidence interval
- 0.80 – 1.25 AUC-ratio and C<sub>max</sub>-ratio

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## ENDORSEMENT BY THE BABE EXPERT GROUP



- Other BABE studies can be accepted if official evidence of registration approval of the generic drugs in the following countries or regions can be provided:

- Australia,
- Canada,
- the European Union,
- Japan and
- the United States

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## ENDORSEMENT BY THE BABE EXPERT GROUP



- Phase 2 requirement for BABE studies covering 38 Critical Dose Drugs / Narrow Therapeutic Range Drugs:

Acetohexamide	Aminophylline	Aprindine	Chloramphenicol	Choline theophylline
Clindamycin	Clonidine	Cyclosporine	Digitoxin	Digoxin
Diprophylline	Disopyramide	Ethinyl Estradiol	Flecainide	Glibenclamide
Gliclazide	Glybuzole	Glycopyramide	Guanethidine	Isoetharine
Isoprenaline	Levodopa and Carbidopa	Levothyroxine	Lithium	Metaproterenol
Methotrexate	Minoxidil	Phenobarbital	Prazosin	Procainamide
Proxyphylline	Quinidine	Sirolimus	Tacrolimus	Theophylline
Tolazamide	Tolbutamide	Warfarin		

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## ENDORSEMENT BY THE BABE EXPERT GROUP

Implementation plan of the Phase 2 requirement for BABE studies

- proposed timeline of one year after formal announcement
- consultation with the stakeholders on the proposed Phase 2 requirement and timeline

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## PHASE 1 REQUIREMENT: EXPERIENCE

- Commencement of the Phase 1 requirement for BABE studies in 2010:
  - 155 antiepileptic drugs
- After 5 years, i.e. one cycle of renewal of registration, in 2015:
  - 61 antiepileptic drugs were renewed without BABE study reports
    - e.g. innovator or injection products
  - 45 antiepileptic drugs were renewed with BABE study reports
  - 49 antiepileptic drugs were not renewed

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## PHASE 1 REQUIREMENT: EXPERIENCE

- New registered antiepileptic drugs between 2010 - 2015
  - 71 new registered antiepileptic drugs

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## PHASE 2 REQUIREMENT: PREPARATION

- Consultation with the stakeholders on the proposed Phase 2 requirement and timeline

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## CONSULTATION


- In August 2015, two consultation sessions with the following stakeholders:
    - the Hong Kong Association of the Pharmaceutical Industry
    - the Hong Kong Pharmaceutical Manufacturers Association
    - the Pharmaceutical Distributors Association of Hong Kong
  - Attended by a total of about 180 people from 100 companies
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## CONSULTATION


### Feedback:

- in general, the stakeholders supported the proposed Phase 2 requirement and timeline
  - but two major concerns were raised by the stakeholders
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## MAJOR CONCERNS

- Capacities of the two local clinical trial centers to conduct BABE studies
    - the University of Hong Kong
    - the Chinese University of Hong Kong
  - Lack of comparators
    - some grandfather products which are manufactured and used in Hong Kong for a long time.
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## CLINICAL TRIAL CENTERS

- Reassurance to reserve sufficient resources to conduct BABE studies
    - CUHK engaging in BABE studies for years
    - HKU planning to engage in BABE studies in 2016
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## CRITICAL DOSE DRUGS / NARROW THERAPEUTIC RANGE DRUGS IN HONG KONG

In 2015, about 323 registered pharmaceutical products belonged to Critical Dose Drugs / Narrow Therapeutic Range Drugs, including:

- 269 imported products and
- 54 local manufactured products

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## CRITICAL DOSE DRUGS / NARROW THERAPEUTIC RANGE DRUGS IN HONG KONG

For the 54 local manufactured products:

- 31 single-ingredient products
- 23 multiple-ingredient products
  - 13 multiple-ingredient products (non-active; registration withdrawn)
  - 10 multiple-ingredient products (active)
    - some shared common formulations and common manufacturers

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## GRANDFATHER PRODUCTS

- When comparator products cannot be available:
  - conduct pharmacokinetic studies,
  - the BABE Expert Group will consider the study results, and
  - the Registration Committee will further consider the study results endorsed by the BABE Expert group before the approval of the applications for registration will be decided

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## PHASE 2 REQUIREMENT: POST CONSULTATION

- In March/April 2016, the findings and follow-up actions of the consultation were reported to the BABE Expert Group;
- The proposed implementation plan and timeline of the Phase 2 requirement for BABE studies covering 38 Critical Dose Drugs / Narrow Therapeutic Range Drugs were subsequently endorsed by the BABE Expert Group

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- Phase 2 requirement for BABE studies covering 38 Critical Dose Drugs / Narrow Therapeutic Range Drugs:

Acetohexamide	Aminophylline	Aprindine	Chloramphenicol	Choline theophylline
Clindamycin	Clonidine	Cyclosporine	Digitoxin	Digoxin
Diprophylline	Disopyramide	Ethinyl Estradiol	Flecainide	Glibenclamide
Gliclazide	Glybuzole	Glycopyramide	Guanethidine	Isoetharine
Isoprenaline	Levodopa and Carbidopa	Levothyroxine	Lithium	Metaproterenol
Methotrexate	Minoxidil	Phenobarbital	Prazosin	Procainamide
Proxyphylline	Quinidine	Sirolimus	Tacrolimus	Theophylline
Tolazamide	Tolbutamide	Warfarin		

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## PHASE 2 REQUIREMENT: POST CONSULTATION

- In June 2016, the Registration Committee decided to implement the Phase 2 requirement for BABE studies covering 38 Critical Dose Drugs / Narrow Therapeutic Range Drugs endorsed by the BABE Expert Group according to the following timeline:

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## PHASE 2 REQUIREMENT: IMPLEMENTATION

### Implementation Timeline

- New applications received before 1 August 2016
  - For the new applications received before 1 August 2016 but have not been completed for registration before 1 August 2017, the applicants must satisfy the Phase 2 requirement for BABE studies before the applications will be approved for registration

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## PHASE 2 REQUIREMENT: IMPLEMENTATION

### Implementation Timeline

- New applications received on or after 1 August 2016
  - With effect from 1 August 2016, all new applications must include evidence to satisfy the Phase 2 requirement for BABE studies. Otherwise, the applications will not be accepted for evaluation.

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## PHASE 2 REQUIREMENT: IMPLEMENTATION

### Implementation Timeline

- Renewal applications
  - With effect from 1 August 2017, all renewal applications must include evidence to satisfy the Phase 2 requirement for BABE studies. Otherwise, the registration will not be renewed

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## PHASE 2 REQUIREMENT: FORMAL ANNOUNCEMENT

In July 2016, the Department of Health (DH) Drug Office has issued the following formal announcements on the Phase 2 requirement for BABE studies:

- Letters to the stakeholders
- Announcement on the DH Drug Office website
- Updated the Guidance Notes on Registration of Pharmaceutical Products/Substances

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THANK YOU

Q & A

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