INFO KINETICS SDN BHD /CLINICAL RESEARCH CENTRE

Design Updates and Requirements in Bioequivalence Study

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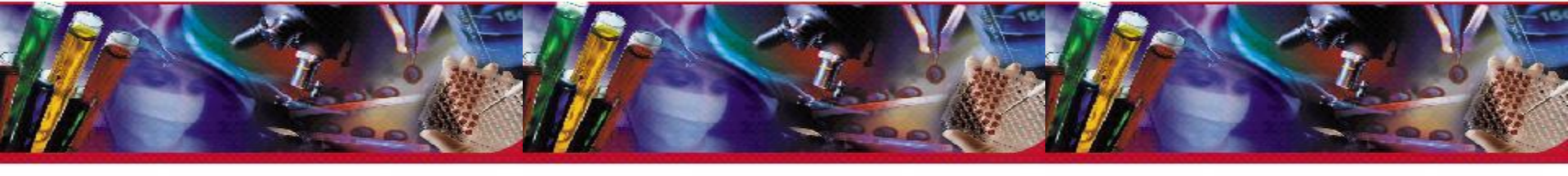
Outline

1. New Guide Structure
2. Design
3. PK and evaluation
4. Design example
5. Strength



The new Guideline on the investigation of Bioequivalence:

- 4.1.1 Study design
- 4.1.2 Reference and test product
- 4.1.3 Subjects
- 4.1.4 Study conduct
- 4.1.5 Characteristics to be investigated
- 4.1.6 Strength to be investigated
- 4.1.7 Bioanalytical methodology
- 4.1.8 Evaluation
- 4.1.9 Narrow therapeutic index drugs
- 4.1.10Highly variable drugs or drug products

The new Guideline Concept

- Clarity on the study conduct to reduce individual interpretation
- To utalise all data if possible
- Protecting healthy volunteer form exposure to unnecessary clinical intervention

Standard Design, Cross Over

- 2-way crossover
  - 2-product , 2-sequence, 2 period
- Test/Reference
- Randomised equally at each period
- Washout interval, at least 5 t1/2, below LOQ, <5% or 1% Cmax
- Doses are administered under close supervision
- Enrollment process / GCP/ Monitoring
- Critical issue is to decide when and how many blood samples are to be collected.

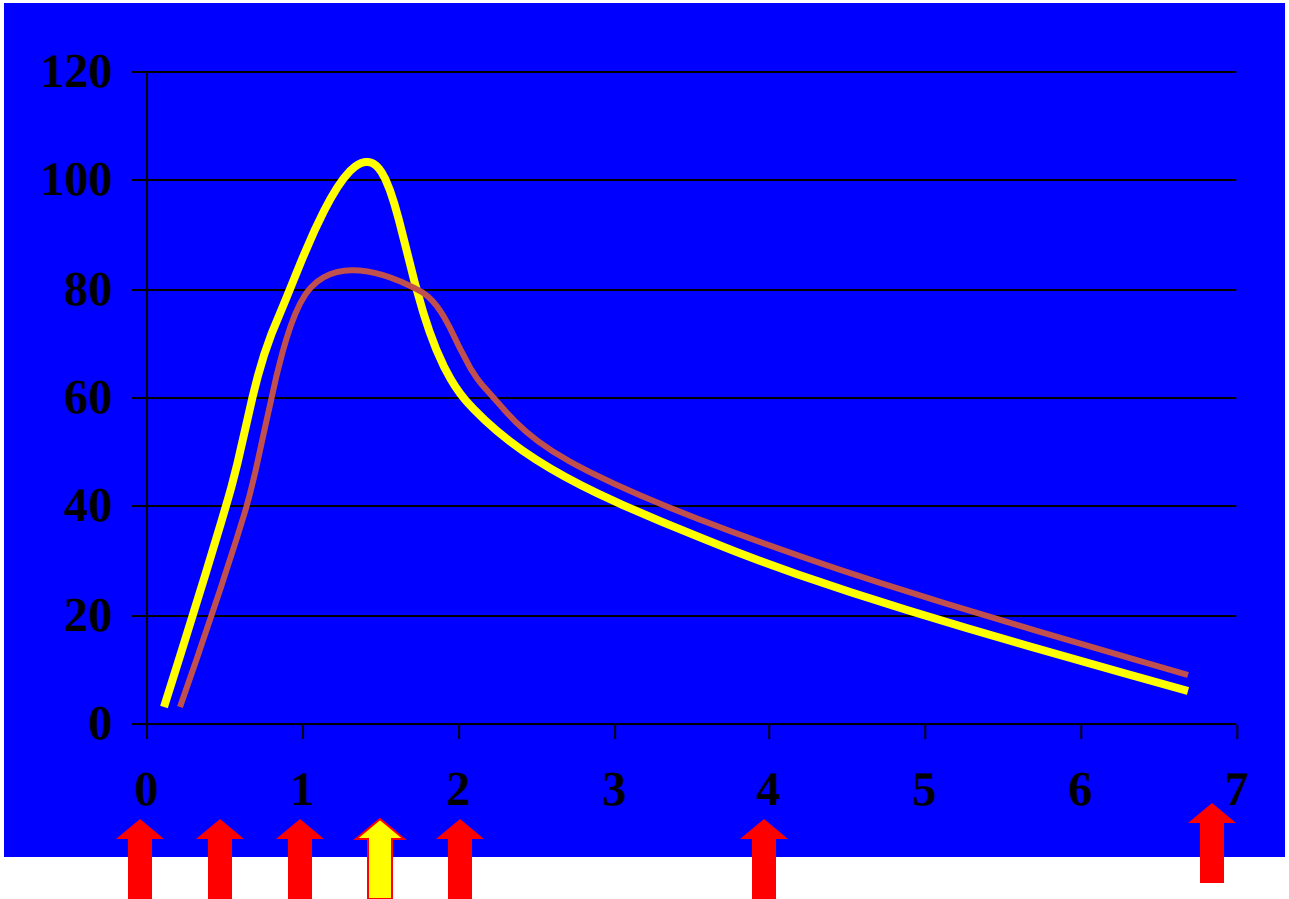
Alternative Designs

- multiple dose study
  - option if have assay sensitivity challenges
- multiple dosing study
  - option for special pharmacokinetics properties, eg auto induction, less variable at ss
  - Easier to study at patients population
- parallel group (long half-life)
- replicate design (high variability)
- two stage
- two cohort

Sampling Point

- Very Important to ensure an adequate characterization of the blood-time profile
- Cmax and AUCt (80% of AUCinf)
- AUC72h !!

Sampling Point



Study Conduct

- at least 12 (criteria set by regulator), so best to enrol 14.

- in case combined with other product, BE may be proven alone or combined

Fasting or Fed

- Should be at fasting conditions
- Unless the SPC recommends intake of the originator product only in the fed state
- Fed state: meal according to SPC, otherwise high fat high caloric meal, vs normocaloric
- For products with enhanced release characteristics performed under both fasted and fed conditions are required.
  - two separate 2-way crossover studies or
  - a 4 -way crossover study

4.1.5 Characters to be investigated: Pharmacokinetic parameters

- AUCt, AUCinf, Cmax, AUC0-72h, tmax, (kel, T1/2)

- Not written, common agreement is after Cmax and with several kel point, best after distribution phase

4.1.8 Parameters to be analysed and acceptance limits

- AUCt, Cmax, or AUC0-72h
- Limit is 80.00% to 125.00%

- Tmax
  - clinical efficacy on onset or related to safety

Statistical Analysis

- Using ANOVA and logarithmic transformed

- The model should take into account sources of variation
  - Sequence (RT, TR), subject within sequence, period, formulation;
  - cohort, stage
  - Software?

Example of Cross Over Studies

- two periods
  two formulation
  two type of diet

- three periods
  three formulation

- four periods
  two cohort
  two formulation + two type of diet
  replicate study for highly variable products

Two Cohort

- This is acceptable if the facility capacity are limited
- Pre-plan and analysis at the end of 2 cohort
- Simple 2 cohort, 60 subjects, each cohort of 30 subjects
- 4 periods, compared cohort 1 vs cohort 2 (ANOVA) not stat diff and included in the model.

- 3 cohort is possible, but ANOVA is slightly complicated.

Two Stage

- Very similar to 2 cohort. But we have interim analysis after 1st cohort
- 2nd cohort sample size is adjusted after we have the ISCV. Only needed if not BE and not enough power.
- Final analysis has adjusted sig level with CI of 94.12%, with stage at the ANOVA model.
- You are stretching if you are using cohort + stage.

HVD

- ISCV >30%
- From 2005 till 2008 FDA drug submission, 31% (57/180) are HDV

- Replicate study design [TRTR] [RTRT]; [TRT] [RTR] 1 to 1 (12 to 12) vs [TRR|RTR|RRT] 1 to 2 (8 to 16) randomisation
- Reference Scaled Average Bioequivalence
- Minimum sample size 24 subjects
- GMR restricted to [0.80,1.25]
- CI scale with ISCV for Cmax up to 69.84% to 143.19%

- *Highly Variable Drugs: Observations from Bioequivalence Data Submitted to the FDA for New Generic Drug Applications*
- The AAPS Journal 10/1, 148–56 (2008)

HVD

- 4-period replicate designs:
  - sample size = ~½ of 2×2 study's sample size.

- 3-period replicate designs:
  - sample size = ~¾ of 2×2 study's sample size.

2 to 4 way study

Randomisation scheme

- Full replicate (TRTR | RTRT), (TRT | RTR)
- Partial replicate (TRR | RTR | RRT) or (TRT | RTR)
- Standard 2×2 cross-over (RT | RT)
- Parallel (R | T)

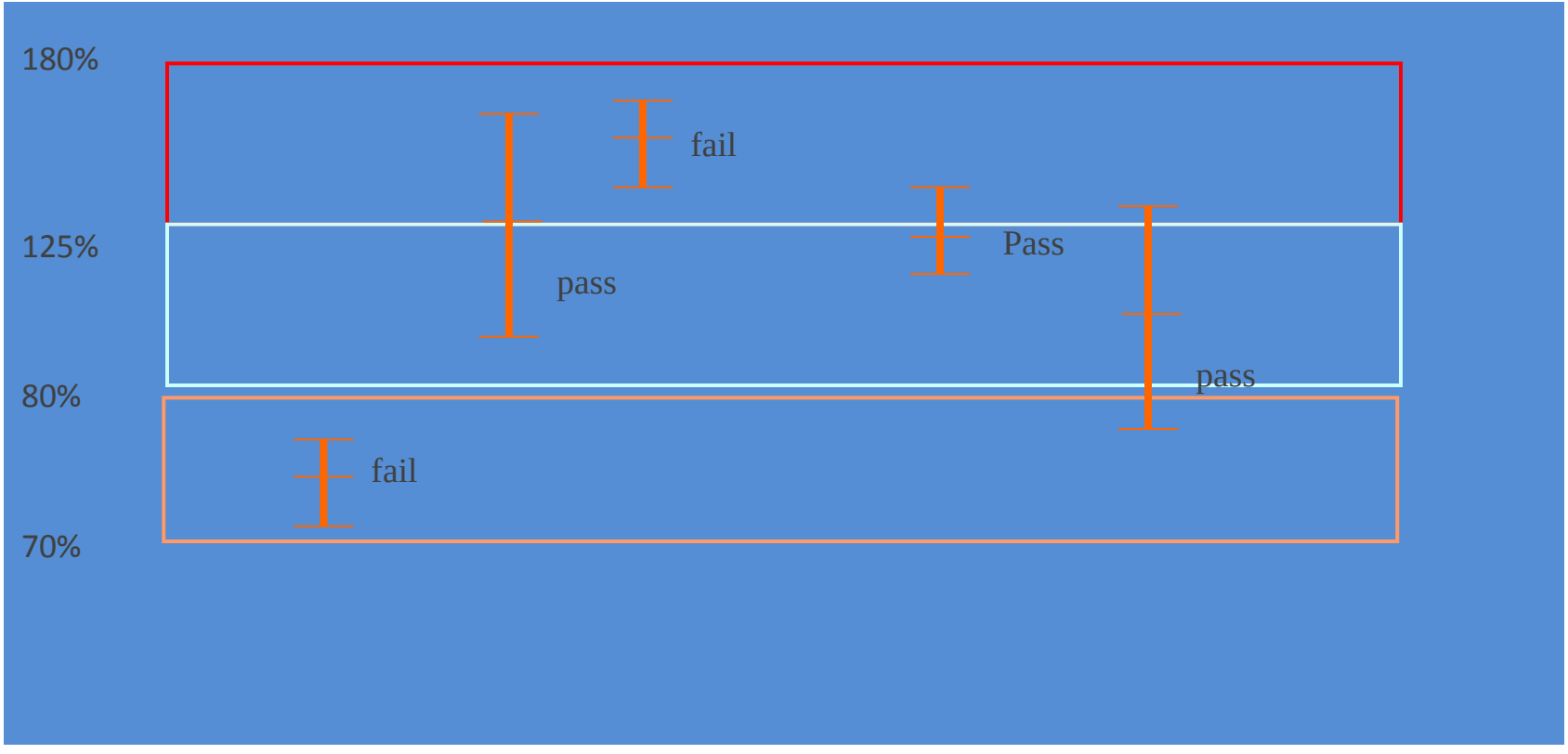
Statistical Analysis

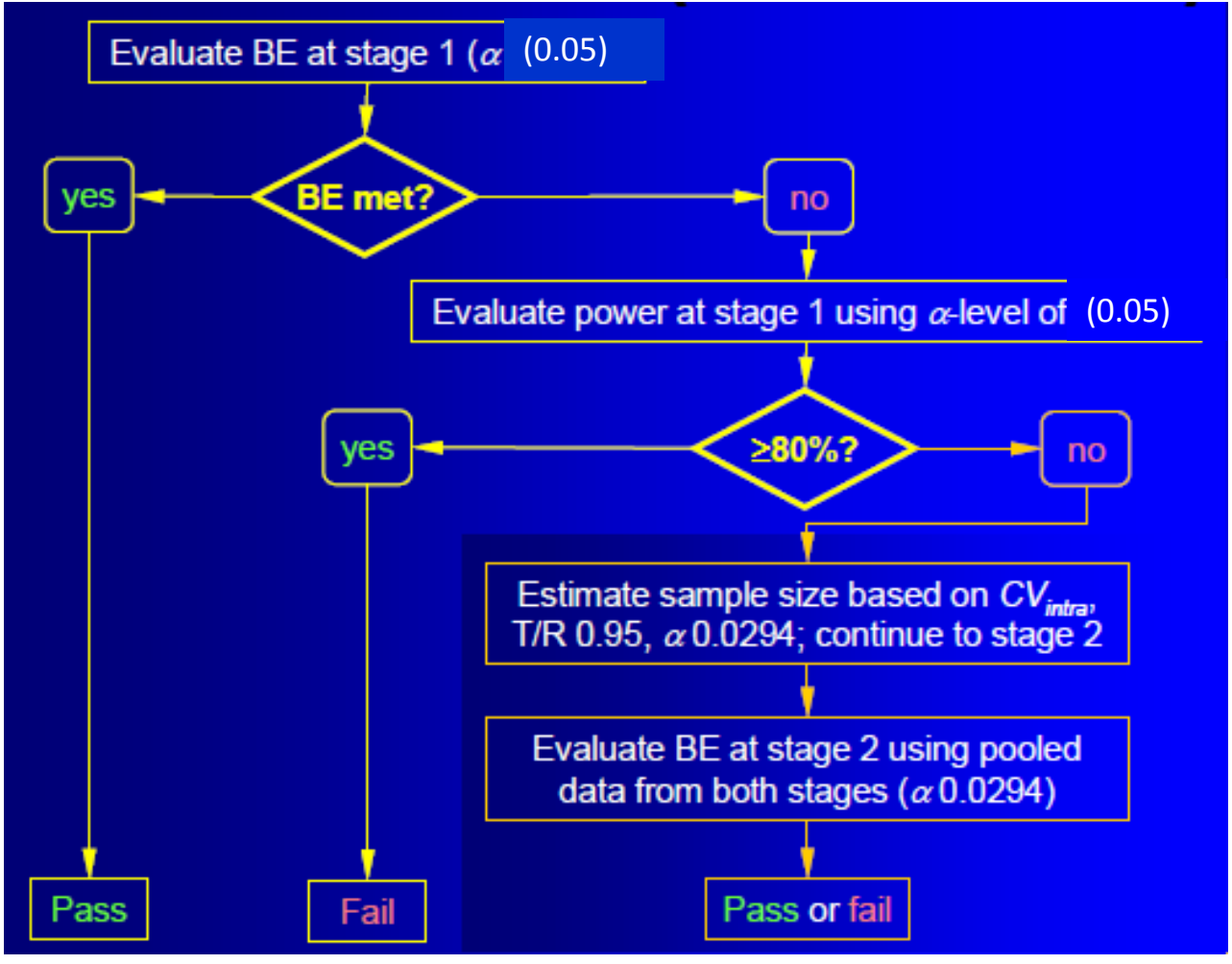
- Power
  - 80%
  - >90% force BE?

Desired Power	
α	
intra-subject CV (ISV)	
Expected μ_T/μ_R Ratio	
Lower Equivalence Limit	
Upper Equivalence Limit	

- Base on ISCV
  - Log vs Ln
  - Azithromycin 15% vs 33%; 20 vs 38 subjects

Is 2 stage useful for *Post Hoc* addition?




Evaluate BE at stage 1 (α (0.05)
BE met?
yes
no
Evaluate power at stage 1 using α-level of (0.05)
≥80%?
yes
no
Estimate sample size based on CV_{intra}, T/R 0.95, α 0.0294; continue to stage 2
Evaluate BE at stage 2 using pooled data from both stages (α 0.0294)
Pass
Fail
Pass or fail

FDC

- What design with different ISCV, Drug A>30%, Drug B <10%?
- Drug A, n= 36
- Drug B, n=14
- Norm is n =36
- What about n=24, with Drug A replicate design? 3-way. 1 to 1 (12 to 12) vs 1 to 2 (8 to 16) randomisation

Parent or Metabolite

- Parent!!
- pro-drugs: parent recommended
- metabolite data instead of active parent:
  - unreliable measurement parent
  - metabolite exposure reflects parent drug
  - and metabolite formation not saturated

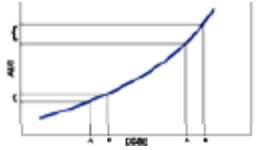
4.1.6 Strength

- linearity PK active substance
  - dose adjusted mean AUCs <25%
- high solubility (BCS Class I, III)
- Proportionality composition/ product related issues
  - same manufacturing process
  - similar qualitative composition/ ratio
  - quantitative proportional, active substance <5% core, amounts core excipients same
  - appropriate in vitro dissolution data

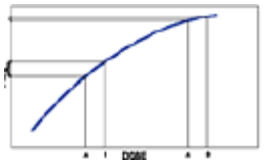
4.1.6 Strength (Cont)

- General highest strength
- Class I, lowest strength is acceptable
- lower strength for safety/tolerability reasons
- higher dose, in case of analytical sensitivity

- Non-linear PK:



  - Highest strength



  - Lowest and highest strength

4.1.6 Strength (Cont)

- Assessment at more than 2 strengths as deviation from proportional composition
- Choose represent the most 2 extreme

Active Substance	30	60	90	120
Dose Ratio	1	2	3	4
Microcryst Cellulose	150	300	450	600
Croscarmellose	12	24	36	48
Lactose	50	50	50	50
Mg Stearate	1.25	2.5	3.75	5
Total Wt	244.25	438.5	632.75	827
Wt Ratio	1.0	1.8	2.6	3.4

Achievement in Phase 1 Studies

SUCCESSFUL Clinical TRIALS Begin HERE

- 200 completed BA/BE & Phase 1 studies, with over 3,900 healthy subjects enrolled

- Include First-In-Patient and First-In-Man

Hospital Based Phase 1 Unit


UMMC, KL

Hospital Pantai Penang

Gleneagles Penang


Sarawak Heart Centre


LohGuanLye , Penang

Phase 1 Malaysia

BE® the same

Track Records

Fulfilled their needs....

…. the world's leading generic pharma can't be wrong

Track records

Fulfilled their Phase 1 solutions

SPHERIX A World of Solutions
TRANSTECH PHARMA
CYNAPSUS
Norwich Pharma
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ProtoPharma
PanGenetics
KYOWA KIRIN
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Site for Phase II-III Studies from…

Pfizer
Bristol-Myers Squibb
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DANONE RESEARCH
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sanofi aventis Because health matters
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Roche
Abbott A Promise for Life

A partnership, a journey…

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