Dose-Response Study for Bridging Data Generation

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Dose-Response Relationships

- Basic information on drug
- Dose selection
  - Reasonable starting dose
  - Dose adjustment
- Population (average) vs. individual dose-response relationships
- Size of (unexplainable) interindividual variability
  - Uncertainty in prescription
Dose-Response Relationships

(Sigmoid) Emax Model

- **Effect** = \[ E_0 + \frac{E_{\text{max}} \cdot \text{Dose}^\gamma}{\text{Dose}_{50}^\gamma + \text{Dose}^\gamma} \]

- **Parameters**
  - Emax, ED_{50} (or EC_{50})
  - Hill coefficient, (Baseline Effect)
Linear or Log-Linear Relationships

- Effect = \textit{Slope} \times \textit{Dose} + \textit{E0}
- Effect = \textit{Slope} \times \log(\textit{Dose}) + \textit{E0}
- Parameters
  - \textit{Slope}, Baseline Effect
Use of Bridging Data

• Use of foreign clinical data package by Extrapolation

• Decision based on bridging data
  – **Acceptability**
    • Whether the drug is approvable in a new region
      – The dosage approved in foreign country will be effective in a new region?
      – Adverse drug reaction will be tolerable in a new region
  
  – **Dose adjustment**
    • Comparison of dose-effect or dose-adverse drug reaction relationship with foreign country
Classes of Bridging Study

• Pharmacokinetic study (Phase 1 study)
  - Dose → Concentration → Response

• Phase III study
  – Confirmatory in nature
  – Whether the drug is effective or not?

• Dose-Response study (Phase II study)
  – Dose-response relationships
    • Evidence of drug effect
      – Dose-control
    • Comparison between original and new region => dose modification
    • Dose-rising study => tolerability data in new region
Issues in dose-response studies as bridging studies

• How can we evaluate the similarity of the dose-response relationships between original and new region?

• **Sample size**
  – Objective of bridging study is to minimize the duplication of clinical data in the new region
  – Evidence of effect / Similarity
  – Usually require large number of subjects
Comparison of Dose-Response Relationships

![Graph showing dose-response relationships with various curves and labeled axes for dose and effect.]
Evaluation of Similarity

• “Similarity” or “no substantial difference” (ICH E5)
  – Equivalence
    • Two one-sided test or average bioequivalence
    • Sample size
      – Test for difference ($N_d$)
        » Ho: $\mu_1 - \mu_2 = 0$ vs. Ha: $\mu_1 - \mu_2 \neq 0$
        » Number required to achieve (1-$\beta$) power of detecting the treatment difference at two-sided $\alpha$ level test
      – Test for similarity ($N_s$)
        » Difference of treatment effects ($\theta$) between two regions is within clinically acceptable limit ($\delta$)
        » Ho: $\theta \leq -\delta$ or $\theta \geq \delta$ vs. Ha: $-\delta < \theta < \delta$
        » Require much large sample size than $N_d$

(Biometrical journal 44:88, 969-981)
Some Bridging Studies in Japan

- Fexofenadine: Randomized placebo-controlled double blind dose-finding study (allergic rhinitis n=310)
- Oseltamivir: Randomized placebo-controlled double blind phase III study (n=316)
- Anastrozole: Randomized phase II study (n=31)
- Sumatriptan: Randomized placebo-controlled double blind dose-finding study (n=274)
- Zolmitriptan: randomized placebo-controlled double blind dose-finding study (n=289)
- Palivizumab: single arm open trial (n=31)
- Oseltamivir dry-syrup: single arm open trial (n=71)

Fujiwara F. 3rd Kitasato-Harvard Sympo 2002.10
Study Design

• Signal versus Noise

• Clear dose-response
  – Signal enhancing design
    • Factorial design
  – Noise reducing design
    • Blocking design
Parallel Group Design

- Simple and easy to implement
- Less complicated analysis and interpretation
- Universally accepted
- Applicable to acute conditions (irreversible effect)
- Relative large variability
  - Inter-patient + Intra-patient
- Naïve pooled Analysis
  - No consideration of interindividual variation
Cross-over Design

• More than one treatment to each subject
  – Within subject characterization of dose-response

• Good precision for comparing treatments
  – All sources of variability between subjects are excluded from the experimental error
  – Reduce sample size

  – Cannot be feasible: Effect should be reversible / Chronic disease
  – Carryover effect: biased result

Subjects → Randomization

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Dose-Titration Design

- Individual dose response relationships
- Size of (unexplained) interindividual variability
- Forced or Optional titration design
  - Ethical issue
  - Data analysis
    - Modeling analysis

![Graph showing dose-titration design with blood pressure versus dose, illustrating non-responders and responders with desired effect levels.](image-url)
Dose-Response relationship considering inter-individual difference

Subjects for each dose group: 6(a)+2(p); 9+3; 8+2
Modeling Approach

• Comparison of Parameter estimates
  – E.g. Emax, ED50
  – 90% Confidence interval
    • The smaller in sample size, the wider
    • More chance of Equivalence in smaller sample size
  – Equivalence test
    • Two-one sided test for the difference of parameter estimates

• (Unexplained) Interindividual variation (?)
Typical parameter estimates and Variance of individual parameter estimates

![Graph showing parameter estimates and variance.](image-url)
Population Analysis

- Mixed Effect Modeling
  - NONMEM®

- Sparse, rich, unbalanced, unstructured data
  - Small number of measurement per subject
  - Freedom of study design
  - Ethically favorable
  - Heterogeneous subjects
    - More representative data
Recent Experience in Korea

- Ivabradine (Procoralan)
  - Stable angina pectoris
  - Acts by reducing the heart rate
- Ivabradine PK/PD study for bridging data generation in Korea

**Modeling Approach**

![Study periods diagram](image)
Overall Strategy

- PK/PD data from Caucasian
- Approval

Discrepancies in dosages used in PK/PD studies

-Korean PK/PD data from the study for bridging data

Direct comparison not feasible

Is the model valid for the simulation?
- Reliability of the simulated data
- Simulated data vs. real PKPD data

Simulation of PK/PD
- Under the same study design with the Korean study
- Using PK/PD model from Caucasian data

Comparison of PKPD
### Methods

**PK comparison**
- Simulation of time course of plasma concentrations of S16257 and S18982 for the same design with the Korean study using Caucasian population PK/PD model (1,000 replicates)
- Noncompartmental PK analysis (NCA) of the Korean study to obtain (AUC, Cmax, Tmax)
- Compare the 90% prediction intervals of time course of the concentrations obtained from the simulation and real observed data from Koreans
- Compare the 90% prediction intervals of time course of the simulated data (AUC, Cmax, Tmax)

**PD comparison**
- Apply the Caucasian PK/PD model to the Korean individual concentration data to obtain the individual time course of Heart Rates (HR) in Caucasians in the concentration ranges observed in Koreans
- Simulation of the time course of HR using Caucasian population PK/PD model (1,000 replicates)
- Compare the PK results (AUC, Cmax, Tmax)
- Compare the 90% prediction intervals of time course of HR obtained from the simulation and real observed data from Koreans
Comparison between Korean and Caucasian Pharmacokinetics

Figure (4.3.1) 2 – S 16257 plasma concentration-time profiles in Korean healthy volunteers (observed median data) and Caucasian control groups (simulated P5-P95 interval)

- P5-P95 predictions in Caucasians
- Observations in Korean

Pharmacodynamics

Figure (4.3.2) 1 – HR-time profiles in Korean healthy volunteers (observed median) compared with Caucasian control groups (simulated median and P5-P95 interval) in Period 1 (single dose administration) and Period 2 (repeated dose administration)

- Korean observed medians
- P5-P95 of Caucasian
- Median of Caucasian
Predictability of PK/PD model for Ivabradine

- Passed External Validation
- Models were built using data from various studies
  - Administration of both ivabradine and S18982, orally and intravenously; ivabradine with metabolic inhibitors, such as ketoconazole, josamycine or verapamil etc.
  - Interpolation vs. Extrapolation
- Semi-physiologic model
- Others
  - Estimation of covariances among interindividual variabilities
Pharmacogenomic Approach

• Quantitative information for intrinsic ethnic factor
  – Interpretation of the bridging data

• Genetic polymorphisms significantly affecting drug response are not similar between the two regions
  – More clear dose-response relationships
  – Optimal dose selection
  – Sample size may be reduced
Dose-Response study using mechanism based biomarker

• PET imaging
  – Vast potential for use as biomarkers
    • Measuring treatment efficacy
  – Early proof of mechanism / Proof of concept
    • E.g. Receptor occupancy study
Thank for your attention