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The Development of a Novel Measure for Subject-by-Formulation Interaction

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BACKGROUND

- Subject-by-formulation (SbF) interaction is a bioequivalence (BE) metric presented in FDA guidance intended to demonstrate switchability between two drug formulations.
- Changes in PK variability after switching from one formulation to another can be evaluated by the SbF interaction. Development of a novel measure for SbF could better understand the impact of formulation on the within-subject variability.

OBJECTIVES

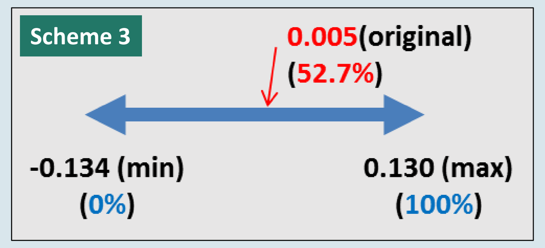
- Demonstrate the importance of within-subject variation in determining SbF interaction.
- Find the minimum and maximum SbF interaction to determine the novel measure of SbF interaction.
- Develop a novel measure to evaluate SbF interaction that could be potentially used for BE assessment.

METHODS

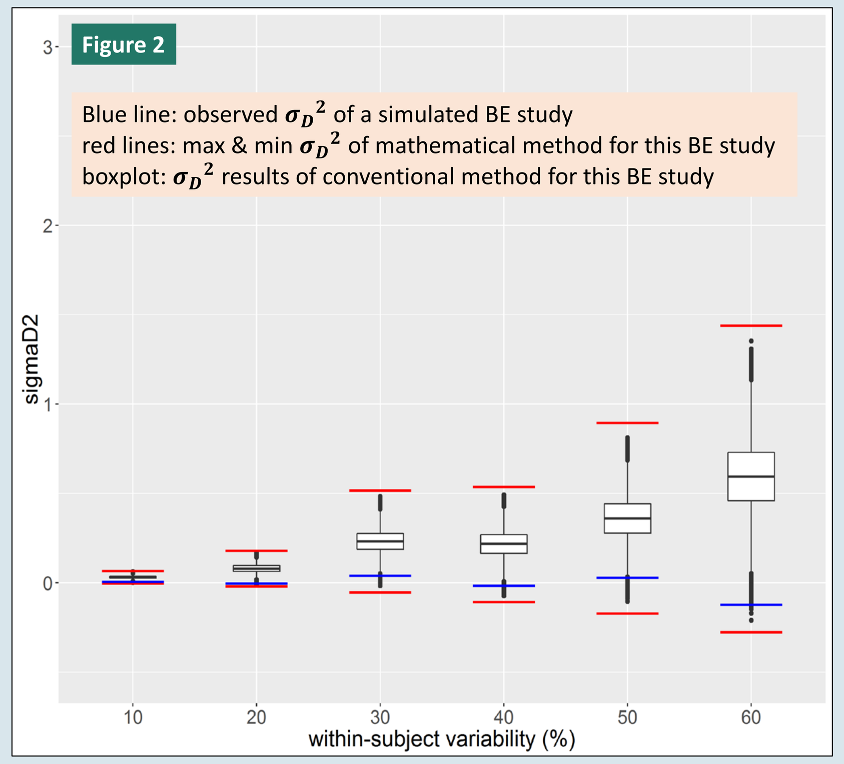
- **Regulatory Standards:**
  - Definition of SbF interaction: (See symbol section for term explanations)
    - $\sigma_D^2 = variance\ of\ (\mu_{Tj} - \mu_{Rj})$
  - Mathematical calculation of SbF interaction in terms of within-subject variances:
    - $\sigma_D^2 = \sigma_I^2 - \frac{1}{2}(\sigma_{WT}^2 + \sigma_{WR}^2)$
- **Finding the minimum / maximum SbF interaction:**
  - Pair each of the individual PK data of the reference product (R) with each of the individual PK data of the test product (T), assuming they are the PK data from the same individual in a crossover PK BE study.
  - Use Mathematical Induction to derive minimum / maximum SbF interaction values in seconds.
- **Simulating BE studies for minimum / maximum SbF methods validation (mathematical *vs.* conventional)**
  - Generating BE studies with $\sigma_D{}^2$ true value as zero by assuming Test and Reference drugs are identical (sample size = 24)
    - $\mu_T = \mu_R,\ \sigma_{BT}^2 = \sigma_{BR}^2,\ \sigma_{WT}^2 = \sigma_{WR}^2$
  - Within-subject Variability: 60 Coefficient of Variations (CV) ranging [0.01, 0.60]
  - Computation environment: R3.3.1 (PC Version)
- **Implementing novel SbF interaction method in observed data:**
  - BE studies in FDA's Abbreviated New Drug Application (ANDA) database were utilized for the novel SbF measure discussion:
    - Drug A & Drug B

RESULTS

- **Minimum/ maximum SbF interaction variance $\sigma_D{}^2$**
  - By mathematical induction, we demonstrated that the min / max value of SbF interaction in an observed data set was related to:
    - Pairing PK data of the individual's test and reference products in the <u>same ascending or descending order</u> led to the <u>minimum</u> SbF interaction.
    - Pairing PK data of the individual's test and reference drugs in the <u>opposite descending and ascending orders</u> respectively led to the <u>maximum</u> SbF interaction.
      - ✓ $\sum_{j=1}^{n_i}\left[\Delta Y_{ijT\cdot}^{a} - \Delta Y_{ijR\cdot}^{a}\right]^2 \le \sum_{j=1}^{n_i}\left[\Delta Y_{ijT\cdot} - \Delta Y_{ijR\cdot}\right]^2 \le \sum_{j=1}^{n_i}\left[\Delta Y_{ijT\cdot}^{a} - \Delta Y_{ijR\cdot}^{d}\right]^2$
  - Validation of the mathematical computation by comparison to 1M times of random (T-R) pairings (conventional method) for a simulated BE study:
    - Table 1 & Figure 2: Comparison of mathematical derivation vs. (conventional) randomized numerical pairing of PK data for min /max SbF.



- **Novel SbF measure (normalized SbF)**
  - Validation of min/max values gives a novel measure of SbF in a normalized way:
    - ***NORM-SbF*** $= \frac{\sigma_{D,original}^2 - \sigma_{D,minimum}^2}{\sigma_{D,maximum}^2 - \sigma_{D,minimum}^2} \times 100\%$
    - Scheme 3: a~~n~~ hypothesized example of measuring SbF in NORM-SbF, starting from original observed σ_D^2 as 0.005 and measured in NORM-SbF as 52.7%.
- **NORM-SbF to describe observed data**
  - Included drugs: Drug A & Drug B
  - Table 4: general information of observed data included for NORM-SbF implementation
  - Figure 5: distribution of observed data implementing NORM-SbF



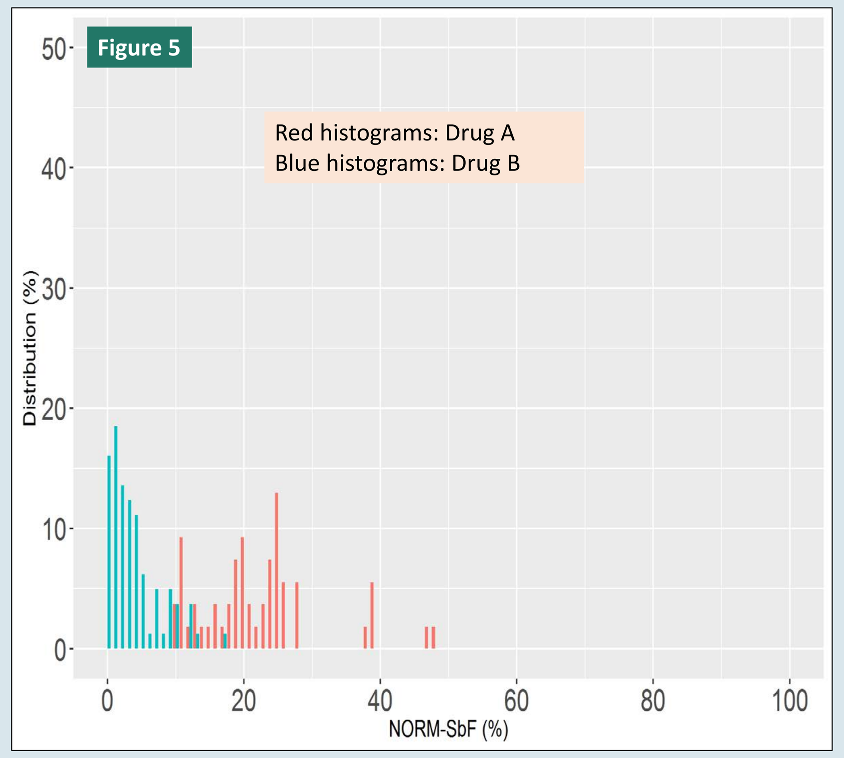
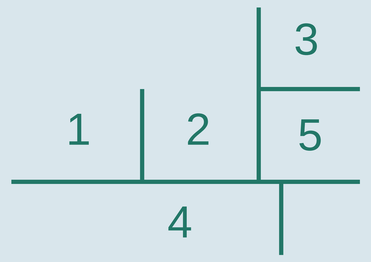


Table 1

Method	Subject No.	Total Wall Time	Mean Max($\sigma_D{}^2$)	Mean Min($\sigma_D{}^2$)
Mathematical	24	0.32 s	100%	0%
Conventional	24	4068 s	93.9%	5.65%

Table 4

Drugs	Total BE Studies	PK Metrics	Average No. of Subjects per Study	σ_{WR}	σ_{BR}	mean σ_D^2
Drug A	54	AUCs & C_{max}	42	0.45 (0.29~0.56)	0.39 (0.28~0.59)	4.45E-3
Drug B	81	AUCs & C_{max}	44	0.14 (0.06~0.32)	0.35 (0.22~0.44)	6.81E-4



CONCLUSIONS

- Mathematical method could obtain minimum and maximum SbF interactions for a given BE study.
- The novel measure of SbF interaction can be determined as follows:

$$NORM\text{-}SbF = \frac{\sigma_{D,original}^2 - \sigma_{D,minimum}^2}{\sigma_{D,maximum}^2 - \sigma_{D,minimum}^2} \times 100\%$$

SYMBOLS

μ_T / μ_R: population average response for measure of T / R formulation;
$\sigma_{BT}^2 / \sigma_{BR}^2$: between-subject variance of the T / R formulation;
$\sigma_{WT}^2 / \sigma_{WR}^2$: within-subject variance of the T / R formulation;
σ_I^2: within-subject T/R ratio variance;
σ_D^2: Subject-by-Formulation interaction variance.

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