Developing a Statistical Approach to Facilitate Sameness Assessment of Complex Heterogenous Active Pharmaceutical Ingredients

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Disclaimer

- **This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.**

Outline

- Background
- Method
- Case example (issue and data)
- Results
- Discussion

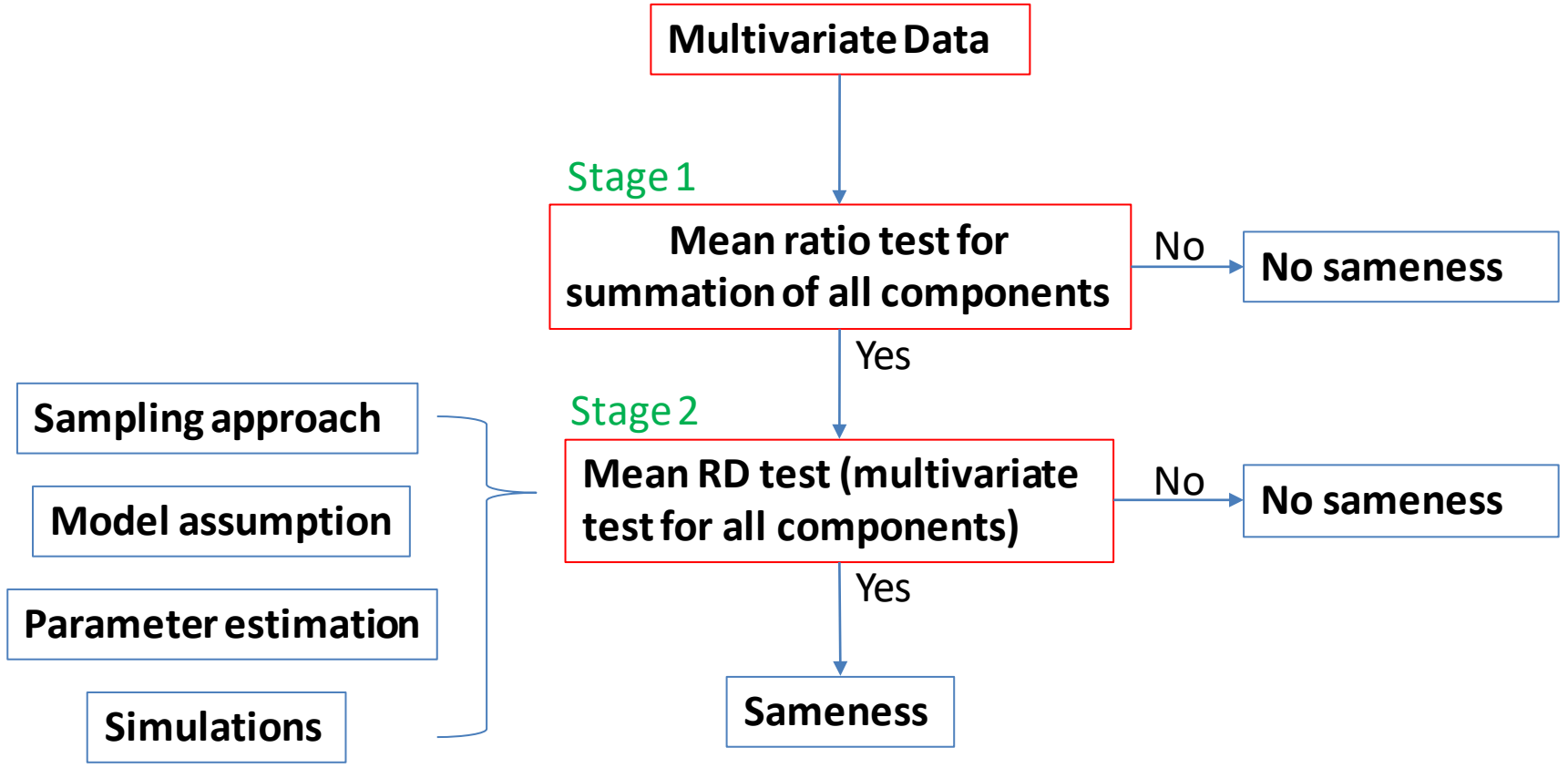
Background

- Sameness of Active Pharmaceutical Ingredient (API) serves as an important component of pharmaceutical equivalence (PE) assessment for generic products.
- API sameness assessment can be challenging, especially for drug products with complex API.
  - API with heterogenous chemical structures and/or heterogenous mixtures
  - Often involves analytical methods that generate multivariate data representing detected multi-component mixture, e.g., by liquid chromatography–mass spectrometry (LC-MS)

Background

- One challenge for demonstrating API sameness, among other things, is the comparison of generated multi-dimensional data (e.g., representing multiple components of interest) from the test and reference products.
- We propose a two-stage framework to address the challenge of sameness assessment due to complex multi-dimensional data.
- A case example is used to demonstrate the potential application of the developed statistical approach for comparing complex heterogenous mixtures.

Proposed Two-stage Approach



*: Adapted from Weber et al., 2015

Stage 1: Mean Ratio Test

- Define μ_T, μ_R as mean sum of area percent of multiple components of interest of two products.

The mean ratio test is defined as:

$$H_0: {}^{\mu_T}/_{\mu_R} \geq 1.1^* \; or \; {}^{\mu_T}/_{\mu_R} \leq 0.9^* \; v.s. \; H_a: 0.9 < {}^{\mu_T}/_{\mu_R} < 1.1$$

**: can be justified from case to case*

- This test is similar to the average bioequivalence test*. The test statistics and corresponding test are provided in the appendix.

**Draft Guidance on Adapalene Benzoyl Peroxide, 2018*

Stage 2: Measure of RD

- Used in FDA's guidance on *Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action* (June 1999)

$$rd = \frac{d_{TRR'}}{d_{RR'}}$$

$$d_{TRR'} = \sum_i \frac{\left[X_{T_i} - \frac{1}{2}\left(X_{R_i} + X_{R'_i}\right)\right]^2}{X_{T_i} + \frac{1}{2}\left(X_{R_i} + X_{R'_i}\right)}$$

$$d_{RR'} = \sum_i \frac{\left(X_{R_i} - X_{R'_i}\right)^2}{\frac{1}{2}\left(X_{R_i} + X_{R'_i}\right)}$$

- We will see smaller components have more impact on Stage 2 in the simulation.

Stage 2: Mean RD Test

- Define RD as the expectation of the distribution of rd.

The mean RD test is defined as:

$$H_0: RD \geq \theta_{BE} \; v.s. \; H_a: RD < \theta_{BE}$$

- To reject H_0, the 95% upper confidence bound for rd, *rd95*, is less than θ_{BE}

Case Example

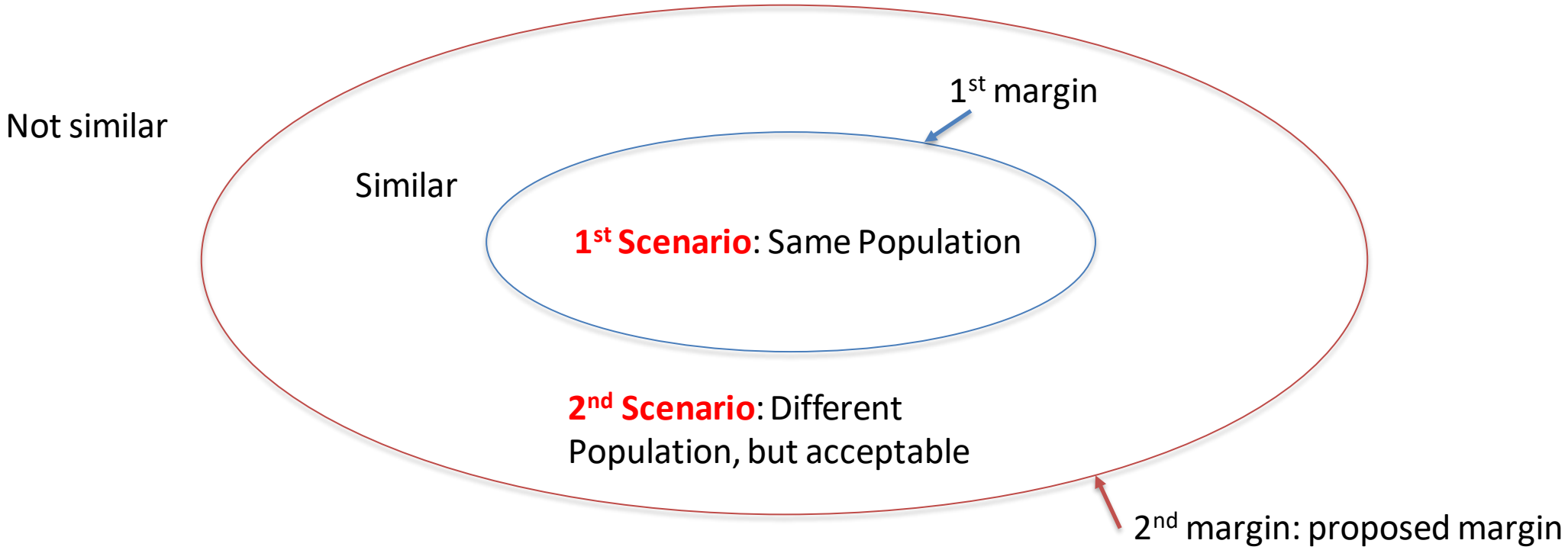
- Case description
  - The drug product with complex API
  - LC-MS was used to characterize components of the API
  - There is a need to demonstrate equivalence of multiple components identified by LC-MS

- Challenge
  - Limited data available
    - Only data from the brand name drug product: How to simulate data from a potential generic (test product)?
  - Multivariate testing
    - How to define a reasonable margin?
    - How to control the type I error rate?

Data of The Case Example

- Data were collected from multiple lots of the reference listed drug (RLD) product (including some repeated lots)
  - 3 samples per lot were tested from the same sample solution.
- Nine components of interest were selected

Simulating Different Scenarios



Simulation (1st scenario)

- Purpose: To find an allowable margin with a high passing probability for samples from the same population (RLD vs. RLD)

Statistical margin ($\hat{\theta}_{BE}$) for Step 2								
Passing rate	# of samples per lot							
	3	4	5	6	7	8	9	10
95th	0.720	0.728	0.679	0.585	0.607	0.691	0.731	0.545
97.5th	0.764	0.762	0.719	0.624	0.644	0.729	0.772	0.571

Note: Use the truncated normal distribution to generate data; n=10

- The margin needs to be larger to have a higher passing rate.
- The margin might be smaller with more samples

Simulation (2nd scenario)

- Purpose: To find an allowable margin with a reasonable false positive rate for samples from different populations
- We tentatively assume the boundary condition for the test product:
  - The test product mean equals to the reference product mean plus/minus one of the following values.
    - 20% reference product mean.
    - $2SD_R$ for each component.
- There are 2^9 = 512 combinations.
- We restrict the ratio between mean sum of area of test product and mean sum of area of reference product to the following equation.

$$0.9 < {}^{\mu_T}/_{\mu_R} < 1.1 \qquad (1)$$

Overlapping Percentage of Distributions from RLD and Simulated Test

Case	Two product overlapping percentage at each component								
	V1	V2	V3	V4	V5	V6	V7	V8	V9
20%_cs	0.747	0.389	0.448	0.679	0.469	0.080	0	0.512	0.400
2sd_cs	0.317	0.317	0.317	0.317	0.317	0.317	0.317	0.317	0.317

20%_cs: 20% of ref mean with compound symmetric covariance matrix
2sd_cs: 2 ref standard deviation with compound symmetric covariance matrix

Test product mean equals to reference product mean plus/minus $2SD_R$ for each component will be considered in the 2nd scenario

Simulation Result (2nd scenario)

Mean Difference	Margin	# of sim in Step i	Type I Error (false positive)			
			5th	50th	95th	max
2sd_cs	1.16	40000	0.26	1.06	3.68	5.31
2sd_cs	1.15	40000	0.35	1.04	2.59	4.47

The proposed margin

Margin from 1st scenario with 3 samples per lot: 0.72 (95th)

Combination restriction criterion: $0.9 < {}^{\mu_T}/_{\mu_R} < 1.1$

The proposed margin can control the type I error rate of all combinations, and it is larger than the margin in the 1st scenario.

Simulation (3rd scenario)

- Purpose: To evaluate type I error rate for test product with one component whose mean difference larger than $2SD_R$, especially for the relatively small component but the ratio between mean sum of area of test product and mean sum of area of reference product satisfies (1).

- We can simulate the test product mean equals to the reference product mean plus $3 \sim 6SD_R$ for each component each time.

Simulation Result (3rd scenario)

Mean Diff	Eval	V1	V2	V3	V4	V5	V6	V7	V8	V9
3sd_cs	*Rd**	0.97	0.74	0.80	0.88	0.87	0.70	0.68	0.87	0.82
	Power	80.40	99.07	97.39	91.74	93.68	99.69	99.82	93.15	96.41
4sd_cs	*Rd**	1.25	0.88	0.96	1.11	1.05	0.79	0.76	1.06	0.98
	Power	34.12	92.05	82.90	57.29	69.42	98.02	98.89	66.93	80.02
5sd_cs	*Rd**	1.57	1.06	1.16	1.39	1.27	0.90	0.85	1.29	1.18
	Power	5.38	65.80	47.32	16.16	30.36	89.51	93.80	27.32	44.50
6sd_cs	*Rd**	1.92	1.27	1.39	1.70	1.51	1.03	0.97	1.54	1.40
	Power	0.32	25.27	13.33	1.67	5.89	60.48	72.61	4.79	12.43

θ_{BE} : 1.155; # of sim in Step i: 40,000; Rd: Simulated expectation of the distribution of rd.*
Rd at 2nd scenario: 1.55; VarTRatio: 1*

Summary

- Only data from the RLD product
  - The simulated test product mean will equal to the RLD product mean plus/minus a certain value.
  - We define a reasonable margin to have a mean difference equal to $2SD_R$ for each component of interest.
- Multivariate testing
  - A two-step procedure is proposed.
  - The simulations show that the type I error rate can control well.

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References

- Cheng B. and Shao J., 2002. Profile analysis for assessing in vitro bioequivalence. Journal of Biopharmaceutical Statistics, V12(3), p323-332.
- Weber B., Lee S.L., Delvadia R., Lionberger R., Li B.V., Tsong Y., Hochhaus G. (2015). Application of the modified chi-square ratio statistic in a stepwise procedure for cascade impactor equivalence testing
- Tsong Y., Zhang J., Wang S.J. (2004). Group Sequential Design and Analysis of Clinical Equivalence Assessment for Generic Nonsystematic Drug Products
- Draft Guidance on Adapalene Benzoyl Peroxide, 2018

Questions or Feedback?

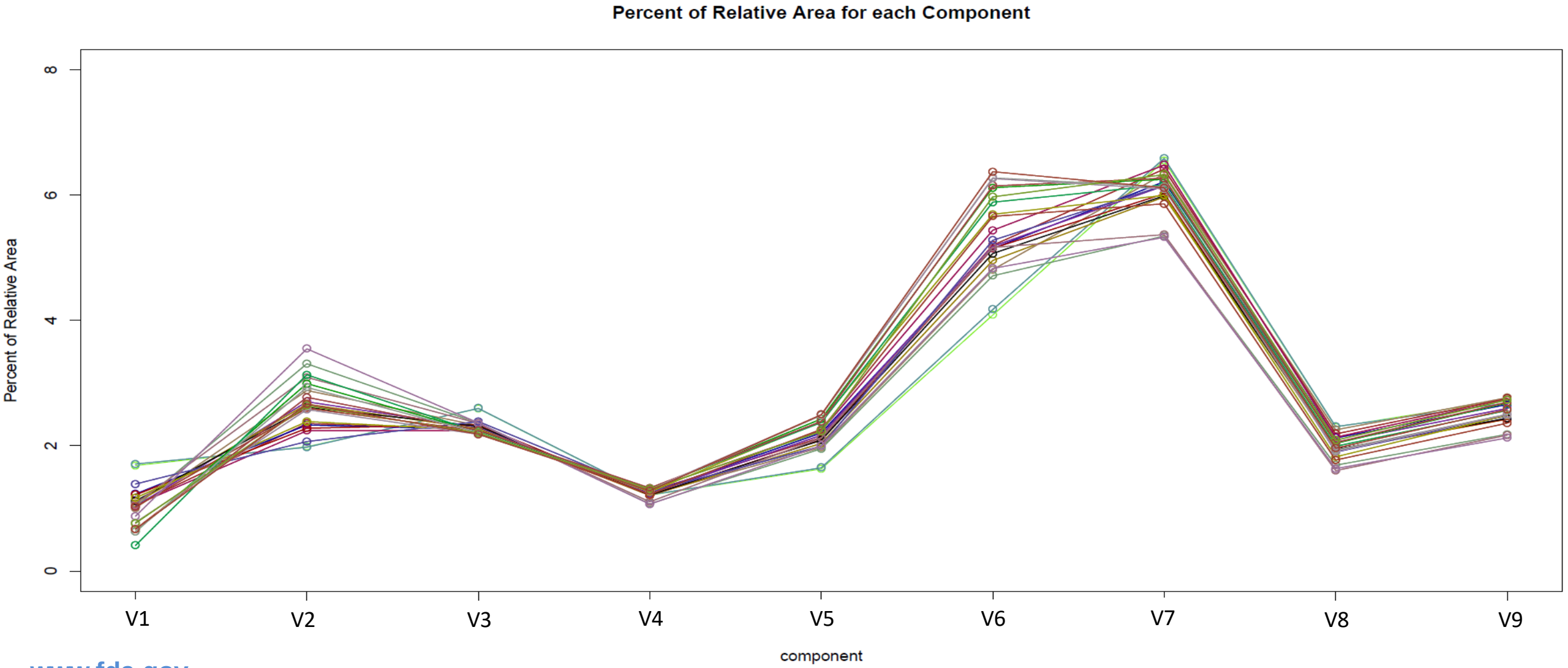
APPENDIX

Data (Cont)

#	Name	mass m/z	RRT	Avg area %
1	Component of Uninterest	349.1115	1	37.06%
2	Component of Uninterest	347.0959	0.937	11.90%
3	**V7**	413.2003	1.28	**6.05%**
4	**V6**	399.2211	2.25	**5.45%**
5	**V2**	351.1272	1.172	**2.62%**
6	Component of Uninterest	351.1272	1.184	2.61%
7	**V9**	415.2162	1.218	**2.51%**
8	**V3**	353.1428	1.341	**2.28%**
9	**V5**	397.2054	2.212	**2.20%**
10	**V8**	415.2162	0.629	**1.94%**
11	Component of Uninterest	345.0802	0.859	1.85%
12	Component of Uninterest	347.0959	0.921	1.29%
13	**V4**	369.1741	1.732	**1.24%**
14	Component of Uninterest	347.0959	0.903	1.21%
15	**V1**	349.1115	0.901	**1.00%**

RRT: Relative retention time

Reference Product



Each line represents one sample within a lot. Different lots will have different colors; three samples from the same lot will have same color.

Estimated Model Parameters

Name	Area (%)	σ_{a^k}
V1	0.9703512	0.30
V2	2.6523336	0.30
V3	2.2816511	0.30
V4	1.2422331	0.30
V5	2.1914588	0.30
V6	5.4412306	0.30
V7	6.0842429	0.30
V8	1.9733662	0.30
V9	2.5323016	0.30

Corr	V1	V2	V3	V4	V5	V6	V7	V8	V9
V2	-0.013								
V3	-0.013	-0.013							
V4	-0.013	-0.013	-0.013						
V5	-0.013	-0.013	-0.013	-0.013					
V6	-0.013	-0.013	-0.013	-0.013	-0.013				
V7	-0.013	-0.013	-0.013	-0.013	-0.013	-0.013			
V8	-0.013	-0.013	-0.013	-0.013	-0.013	-0.013	-0.013		
V9	-0.013	-0.013	-0.013	-0.013	-0.013	-0.013	-0.013	-0.013	
σ_{e^k}	0.0082	0.0679	0.0158	0.0065	0.0360	0.0826	0.0373	0.0160	0.0194

Bootstrap repetitions

Samples	3	4	5	6	7	8	9	10
Repetition	2,400	5,800	11,300	19,400	30,900	46,100	65,600	90,000
Time (hours)	2	4.5	7	13	18	35	52	60

*: *Repetition* ~ $0.2 * C_1^{lot} * C_2^{lot}$ *$Samples^3$, lot = 10*

Bootstrap repetitions

Samples	3	4	5	6	7	8	9	10
Repetition	500	1,200	2,300	3,900	6,200	9,200	13,100	18,000
Time (hours)	<1	1.5	2.5	3	5	8	9	14

*: *Repetition* ~ $0.2 * C_1^{lot} * C_2^{lot}$ *$Samples^3$, lot = 6*

Method

- Proposed two-stage approach
  - Stage 1: Mean ratio test with a well-recognized margin*
  - Stage 2: Mean RD test with a self-defined margin

- Looking for margins
  - Simulations (three scenarios)

**: Tsong Y., Zhang J., Wang S.J. (2004). Group Sequential Design and Analysis of Clinical Equivalence Assessment for Generic Nonsystematic Drug Products*

Stage 1: Test Statistics

$$H_0: {}^{\mu_T}/_{\mu_R} \geq 1.1 \; or \; {}^{\mu_T}/_{\mu_R} \leq 0.9 \; v.s. \; H_a: 0.9 < {}^{\mu_T}/_{\mu_R} < 1.1$$

$$\leftrightarrow H_{0_U}: \mu_T - 1.1 * \mu_R \geq 0 \; v.s. \; H_{a_U}: \mu_T - 1.1 * \mu_R < 0$$

$$and \; H_{0_L}: \mu_T - 0.9 * \mu_R \leq 0 \; v.s. \; H_{a_L}: \mu_T - 0.9 * \mu_R > 0$$

$$\leftrightarrow T_U = \frac{\bar{X}_T - 1.1 * \bar{X}_R}{\sqrt{\frac{S_T^2}{n_T} + \frac{1.1^2 S_R^2}{n_R}}} < -t\big((1-\alpha), v_U\big) \; and \; T_L = \frac{\bar{X}_T - 0.9 * \bar{X}_R}{\sqrt{\frac{S_T^2}{n_T} + \frac{0.9^2 S_R^2}{n_R}}} > t\big((1-\alpha), v_L\big)$$

$$v_U = \frac{\left(\frac{S_T^2}{n_T} + \frac{1.1^2 * S_R^2}{n_R}\right)^2}{\frac{1}{(n_T-1)}\left(\frac{S_T^2}{n_T}\right)^2 + \frac{1}{(n_R-1)}\left(\frac{1.1^2 * S_R^2}{n_R}\right)^2} \; and \; v_L = \frac{\left(\frac{S_T^2}{n_T} + \frac{0.9^2 * S_R^2}{n_R}\right)^2}{\frac{1}{(n_T-1)}\left(\frac{S_T^2}{n_T}\right)^2 + \frac{1}{(n_R-1)}\left(\frac{0.9^2 * S_R^2}{n_R}\right)^2}$$

Looking for Margins

- Data model based on RLD data
- Simulating different scenarios
  - Scenario 1: RLD vs. RLD (Type II error (false negative))
  - Scenario 2: RLD vs. Simulated Test (Type I error (false positive))
  - Scenario 3: Sensitivity Analysis
- Starting from same covariance matrix of area percent of 9 components for both products.

Data Model

$$\overrightarrow{y_{ij}} = \vec{\mu} + \overrightarrow{\alpha_i} + \overrightarrow{\varepsilon_{ij}}, y \geq 0 \; and \; y \leq 100$$

$$\overrightarrow{\alpha_i} \sim N\left(\vec{0}, \sum = \begin{bmatrix} \sigma_a^2 & \dots & \sigma^2 & \dots & \sigma^2 \\ \vdots & \ddots & \vdots & \ddots & \vdots \\ \sigma^2 & \dots & \sigma_a^2 & \dots & \sigma^2 \\ \vdots & \ddots & \vdots & \ddots & \vdots \\ \sigma^2 & \dots & \sigma^2 & \dots & \sigma_a^2 \end{bmatrix}\right)$$

μ: the area average of nine components

$\overrightarrow{\alpha_i}$: effect of lot *i*

$\overrightarrow{\varepsilon_{ij}} \sim N\left(\vec{0}, \sum = diag(\sigma_{e^k}^2)\right)$

$\overrightarrow{\varepsilon_{ij}}$: random error within independent sample j, in lot *i*

Assume $\overrightarrow{\alpha_i}$ is independent of $\overrightarrow{\varepsilon_{ij}}$ and $\overrightarrow{\alpha_{i'}}$, $\overrightarrow{\varepsilon_{ij}}$ is independent of $\overrightarrow{\varepsilon_{ij'}}$

Parameter values: generate from the 23-reference product lots

$$\overrightarrow{y_{ij}} = \begin{pmatrix} y_{ij}^1 \\ \vdots \\ y_{ij}^m \end{pmatrix}, \vec{\mu} = \begin{pmatrix} \mu^1 \\ \vdots \\ \mu^m \end{pmatrix}, \overrightarrow{\alpha_i} = \begin{pmatrix} \alpha_i^1 \\ \vdots \\ \alpha_i^m \end{pmatrix}, \overrightarrow{\varepsilon_{ij}} = \begin{pmatrix} \varepsilon_{ij}^1 \\ \vdots \\ \varepsilon_{ij}^m \end{pmatrix}$$

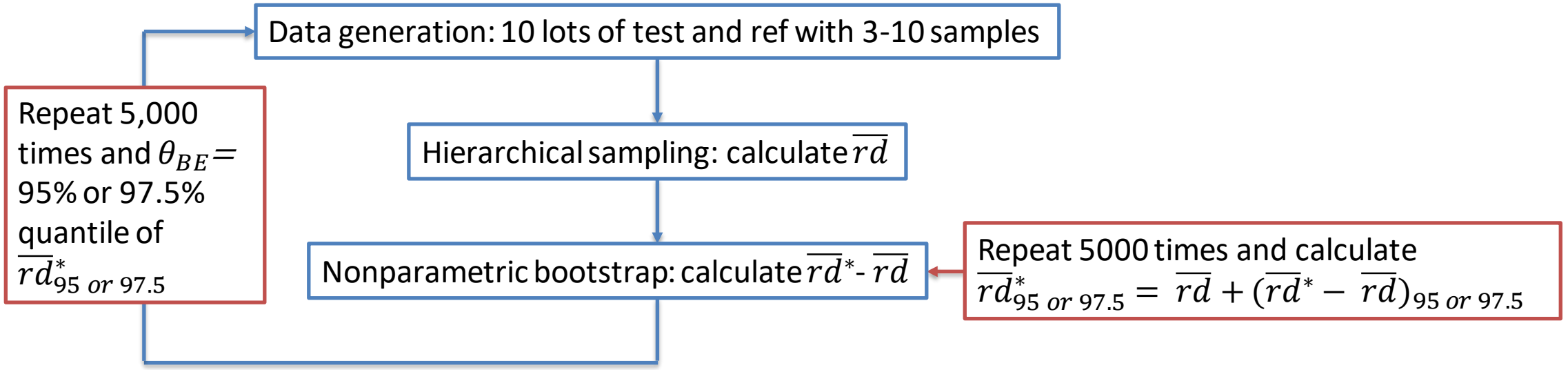
$$cov\left(y_{ij}^k, y_{i'j'}^{k'}\right) = \begin{cases} \sigma_a^2 + \sigma_{e^k}^2, if \; i = i', j = j', k = k' \\ \sigma^2, if \; i = i', j = j', k \neq k' \\ \sigma_a^2, if \; i = i', j \neq j', k = k' \\ \sigma^2, if \; i = i', j \neq j', k \neq k' \\ 0, if \; i \neq i' \end{cases}$$

- All values are listed in the next page

Simulation (1st scenario)

- Purpose: To find an allowable margin with a high passing probability from the same population

- Simulation flowchart:



Simulation (1st scenario)

- Purpose: To find an allowable margin with a high passing probability from the same population

- Simulation steps:
  a. Generate 10 RLD product lots with 3-10 samples and another 10 test product lots with 3-10 samples from the same population (information from the 23 reference product lots). Consider the range of the within-lot variability from the original scale to the scale of the between-lot variability.
  b. Randomly select a lot-triplet (one test product lot and two RLD product lots) with replacement from all possible lot-triplets. With the sampled lot-triplet, randomly select one sample from each lot and calculate the ratio *rd* based on the above measure and repeat *x* times (*x*: 20% of total possibility and increasing by # of samples) to calculate $\overline{rd}$.
  c. Use these *x rd* samples and the statistic $\overline{rd}$ from step b as the base and nonparametrically bootstrap *x* rd^* samples from the base and calculate $\overline{rd}^* - \overline{rd}$
  d. Repeat step c 5,000 times and calculate $\overline{rd}^*_{95\ or\ 97.5} = \overline{rd} + (\overline{rd}^* - \overline{rd})_{95\ or\ 97.5}$
  e. Repeat steps a-d 5,000 times and set θ_{BE} to be the 95% or 97.5% quantile of $\overline{rd}^*_{95\ or\ 97.5}$

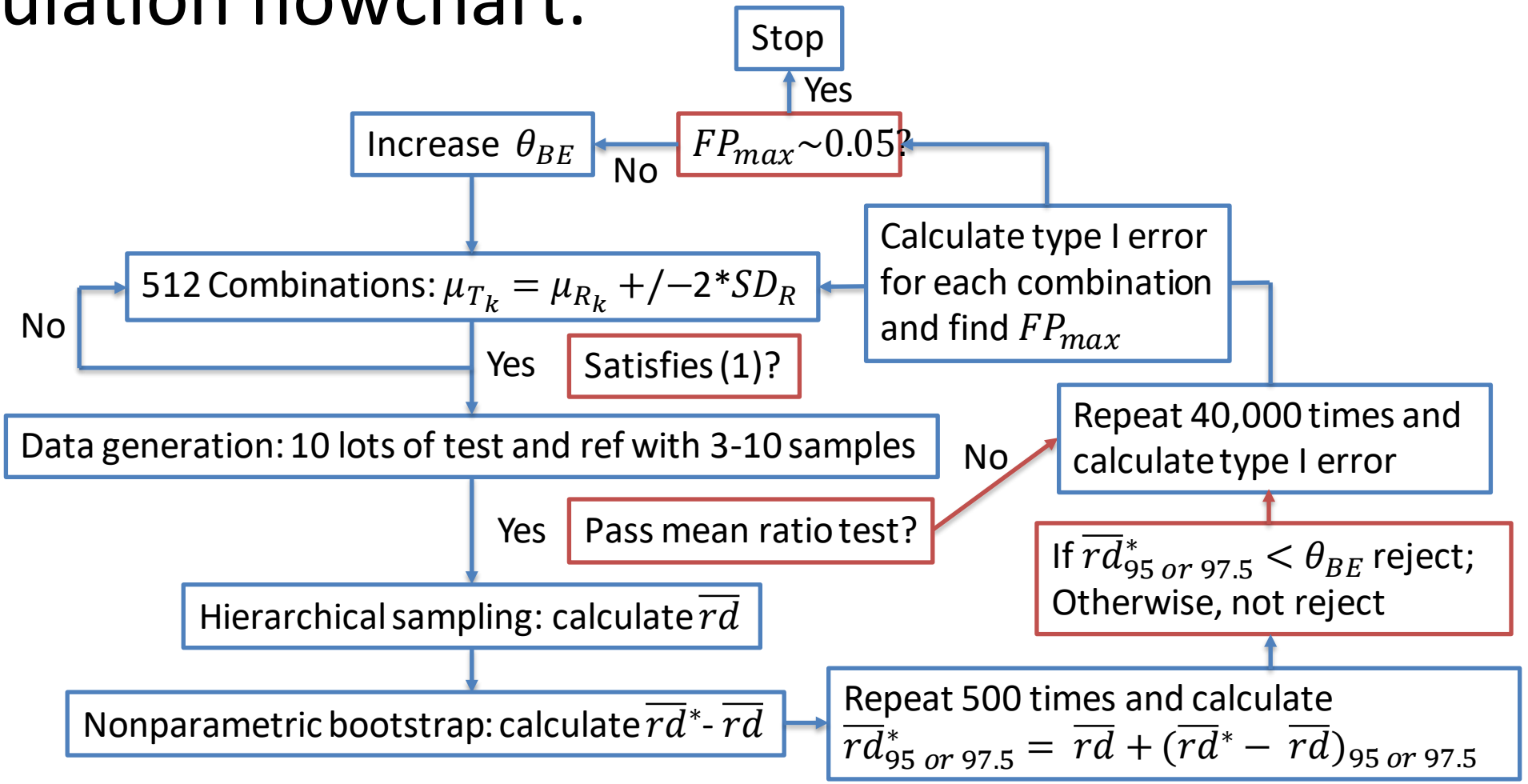
Simulation (2nd scenario) (Cont)

- However, in these 512 combinations, the difference between mean sum of area of test product and mean sum of area of reference product need to be restricted by the mean ratio test, so we can only consider the combinations which satisfy the mean ratio test.
- Although the mean ratio test needs to be conducted, we might be able to simply use the parameter restriction in the alternative hypothesis.
- Then we can restrict the ratio between mean sum of area of test product and mean sum of area of reference product to the following equation.

$$0.9 < {\mu_T}/{\mu_R} < 1.1 \qquad (1)$$

Simulation (2nd scenario) (Cont)

- Simulation flowchart:



FP_{max}: the largest type I error (false positive) rate among 512 combinations

Simulation (2nd scenario)

- Simulation Steps:
  a. Let the margin θ_{BE} be the margin from scenario 1. If the type I error rate of any combination is far away from 0.05, increase the margin a little bit until the largest type I error rate is close to 0.05
  b. For each component, we let $\mu_{T_k} = \mu_{R_k} +/-2*SD_R$ from 512 combinations
  c. If the combination satisfies (1), continue to step d or go back to step b
  d. Generate 10 RLD product lots with 3-10 samples and another 10 test product lots with 3-10 samples from different populations (information from the 23 reference product lots). Consider the range of the within-lot variability from the original scale to the scale of the between-lot variability and the covariance matrix of test and reference products are the same
  e. If the data can pass the mean ratio test, continue to step f or go to step j
  f. Randomly select a lot-triplet (one test product lot and two RLD product lots) with replacement from all possible lot-triplets. With the sampled lot-triplet, randomly select one sample from each lot and calculate the ratio *rd* based on the above measure and repeat *y* times (*y*: 20% of total possibility and increasing by # of samples) to calculate $\overline{rd}$.

Simulation (2nd scenario)

- Simulation Steps:
  g. Use these *y rd* samples and the statistic $\overline{rd}$ from step 6 as the base and nonparametrically bootstrap *y* rd^* samples from the base and calculate $\overline{rd}^*$-$\overline{rd}$
  h. Repeat step g 500 times and calculate $\overline{rd}^*_{95} = \overline{rd} + (\overline{rd}^* - \overline{rd})_{95}$
  i. If $\overline{rd}^*_{95}$ is less than θ_{BE}, we reject the null hypothesis, or we don't reject the null hypothesis
  j. Repeat step d to step i for 4*10^4 times and calculate the type I error rate
  k. Save the type I error rate for this combination and go back to step b

- The proposed margin can control the type I error rate of all combinations and it is larger than the margin in the 1st scenario.

Simulation Result (2nd scenario)

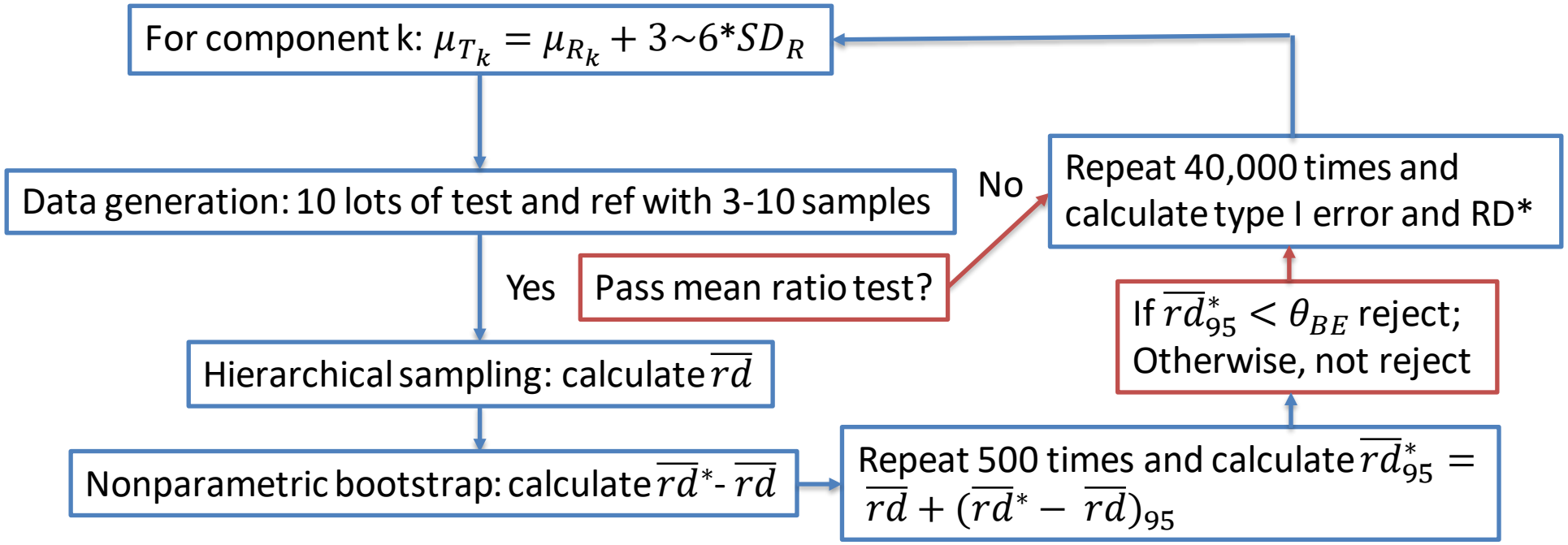
Mean Difference	Margin	# of sim in Step i	5th	50th	95th	max
2sd_cs	1.16	10000	0.29	1.06	3.93	6.32
2sd_cs	1.16	20000	0.20	0.86	4.70	6.69
2sd_cs	1.16	40000	0.26	1.06	3.68	5.31
2sd_cs	1.16	60000	0.25	0.98	3.75	5.52
2sd_cs	1.16	80000	0.29	1.15	3.61	5.20
2sd_cs	1.16	100000	0.27	1.11	3.61	5.41

Margin from 1st scenario: 0.72 (95th); 0.764 (97.5th)

Combination restriction criterion: $0.9 < {}^{\mu_T}/_{\mu_R} < 1.1$

Simulation (3rd scenario) (Cont)

- Simulation flowchart:



Simulation Result (3rd scenario)

Mean Diff	Eval	V1	V2	V3	V4	V5	V6	V7	V8	V9
3sd_cs	*Rd**	0.97	0.74	0.80	0.88	0.87	0.70	0.68	0.87	0.82
	Power	88.6	99.6	99.0	96.0	97.3	99.9	100.0	97.1	98.6
4sd_cs	*Rd**	1.25	0.89	0.97	1.12	1.05	0.79	0.76	1.06	0.99
	Power	52.6	96.6	91.0	71.6	81.8	99.2	99.6	80.0	89.3
5sd_cs	*Rd**	1.57	1.06	1.17	1.39	1.27	0.90	0.85	1.29	1.18
	Power	13.4	78.7	63.2	28.2	45.6	94.1	96.6	42.4	61.1
6sd_cs	*Rd**	1.92	1.27	1.39	1.71	1.51	1.03	0.97	1.54	1.40
	Power	1.2	39.1	24.1	4.4	12.9	70.1	79.7	10.7	22.9

θ_{BE} : 1.25; # of sim in Step i: 10,000; Rd: Simulated expectation of the distribution of rd.*

Simulation Result (3rd scenario)

Mean Diff	Eval	V1	V2	V3	V4	V5	V6	V7	V8	V9
3sd_cs	*Rd**	0.97	0.74	0.80	0.88	0.87	0.70	0.68	0.87	0.82
	Power	36.2	85.3	73.7	54.7	57.5	92.4	94.3	56.3	68.5
4sd_cs	*Rd**	1.25	0.89	0.97	1.12	1.05	0.79	0.76	1.06	0.99
	Power	5.7	52.9	34.0	12.7	18.8	76.7	83.5	17.4	29.8
5sd_cs	*Rd**	1.57	1.06	1.17	1.39	1.27	0.90	0.85	1.29	1.18
	Power	0.1	16.6	6.6	0.9	2.4	48.1	60.5	2.4	6.0
6sd_cs	*Rd**	1.92	1.27	1.39	1.71	1.51	1.03	0.97	1.54	1.40
	Power	0.0	2.1	0.6	0.0	0.1	16.5	28.5	0.1	0.4

θ_{BE} : 0.9; # of sim in Step i: 10,000; Rd: Simulated expectation of the distribution of rd.*

Simulation Result (3rd scenario) (Cont)

Mean Diff	Eval	V1	V2	V3	V4	V5	V6	V7	V8	V9
3sd_cs	*Rd**	1.25	1.06	1.11	1.15	1.20	1.03	1.01	1.19	1.16
	Power	32.40	68.33	56.42	50.95	40.07	73.14	76.46	41.75	47.97
4sd_cs	*Rd**	1.52	1.19	1.27	1.37	1.38	1.12	1.09	1.38	1.32
	Power	6.45	41.37	27.97	16.57	14.63	55.69	61.96	14.95	21.57
5sd_cs	*Rd**	1.83	1.37	1.47	1.65	1.60	1.23	1.18	1.61	1.51
	Power	0.52	15.54	7.90	2.39	2.88	33.10	41.91	2.83	5.61
6sd_cs	*Rd**	2.18	1.57	1.69	1.95	1.85	1.36	1.29	1.86	1.74
	Power	0.02	2.93	1.16	0.11	0.28	11.74	19.17	0.25	0.71

θ_{BE} : 1.155; # of sim in Step i: 40,000; Rd: Simulated expectation of the distribution of rd.*
Rd at 2nd scenario: 1.55; VarTRatio: 2*

When the variance increases, Rd will be larger and the power will be smaller.*

Simulation Result (3rd scenario) (Cont)

Mean Diff	Eval	V1	V2	V3	V4	V5	V6	V7	V8	V9
3sd_cs	*Rd**	0.85	0.76	0.76	0.81	0.82	0.65	0.62	0.77	0.73
	Power	92.72	98.65	98.45	95.74	96.30	99.88	99.96	98.20	99.03
4sd_cs	*Rd**	1.12	0.92	0.93	1.05	1.01	0.74	0.70	0.95	0.89
	Power	56.13	88.53	86.97	68.77	76.77	98.86	99.56	84.89	91.67
5sd_cs	*Rd**	1.43	1.11	1.13	1.32	1.23	0.86	0.79	1.17	1.08
	Power	13.27	56.93	52.96	23.73	37.13	92.16	95.99	47.56	63.33
6sd_cs	*Rd**	1.77	1.33	1.36	1.63	1.47	0.99	0.91	1.41	1.29
	Power	1.08	17.93	15.94	2.97	7.93	64.19	77.10	12.25	23.45

θ_{BE} : 1.155; # of sim in Step i: 40,000; Rd: Simulated expectation of the distribution of rd.*
Rd at 2nd scenario: 1.55; VarTRatio: 0.5*

When the variance decreases, Rd will be smaller and the power will be larger.*

Simulation Result (1st scenario)

Statistical margin ($\hat{\theta}_{BE}$) for Step 2								
Passing rate	# of samples per lot							
	3	4	5	6	7	8	9	10
95th	0.883	0.782	0.547	0.685	0.702	0.666	0.725	0.696
97.5th	0.998	0.854	0.609	0.749	0.779	0.715	0.782	0.768

Note: Use the truncated normal distribution to generate data; n=6

- The margin needs to be larger to have a higher passing rate.
- The margin might be smaller with more samples

Simulation Result (2nd scenario)

Mean Difference	# of Samples	Margin	# of sim in Step i	Type I Error (false positive)			
				5th	50th	95th	max
2sd_cs	3	1.00	40000	0.75	1.86	3.20	4.95
2sd_cs	3	1.01	40000	0.84	2.03	3.45	5.32
2sd_cs	4	1.01	40000	0.58	1.63	3.91	4.88
2sd_cs	4	1.02	40000	0.65	1.78	4.24	5.33

Margin from 1st scenario with 3 samples per lot: 0.88 (95th); Margin from 1st scenario with 4 samples per lot: 0.78 (95th); n=6

Combination restriction criterion: $0.9 < {}^{\mu_T}/_{\mu_R} < 1.1$