FEV1 Based Bioequivalence Study for Inhaled Corticosteroids

AAPS/EUFEPS GLOBAL BIOEQUIVALENCE HARMONIZATION INITIATIVE (GBHI):
4TH INTERNATIONAL WORKSHOP

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Outline

- **FDA's Current Recommendations of Comparative Clinical Endpoint Bioequivalence (BE) Studies for Developing Generic Orally Inhaled Drug Products (OIDPs)**
  - Published Product-Specific Guidances (PSGs)
  - Justification for currently recommended endpoints

- **Variability and Dose-Response Relationship Using FEV_1 As a BE Metric in Comparative Clinical Endpoint BE Studies of OIDPs**
  - Observed Variability
  - Study Sample Sizes
  - Dose-Response Relationship

- **Summary and Future Outlooks**

Challenges in OIDP Generic Drug Development

- The forced expiratory volume in 1 second (FEV_1) is generally considered as a pharmacodynamic (PD) or clinical endpoint for most OIDPs
- High between-subject variations in FEV_1 have been reported
- High between-subject variabilities in FEV_1 leads to the requirement of large sample sizes for BE studies

Published PSGs & Active Ingredients

Published PSGs

Category	# PSGs	*# without PSGSs*
Inhalation Solution - Aerosol metered (pMDI) - Local Action	4	2
Inhalation Suspension - Aerosol Metered (pMDI)- Local Action	9	2
Inhalation Powder (DPI) - Local Action	15	8
Inhalation - Total – PSGs	**28**	**12**

As of November 21, 2019

Active Ingredients

Aclidinium Bromide
Albuterol Sulfate
Beclomethasone Dipropionate
Budesonide
Budesonide Formoterol; Fumarate Dihydrate
Ciclesonide
Fluticasone Furoate
Fluticasone furoate; Vilanterol Trifenatate
Fluticasone Propionate
Fluticasone Propionate; Salmeterol Xinafoate
Salmeterol Xinafoate
Formoterol Fumarate
Mometasone Furoate
Glycopyrrolate
Indacaterol Maleate
Ipratropium Bromide
Levalbuterol
Mometasone Furoate
Tiotropium Bromide
Umeclidinium Bromide
Epinephrine
Flunisolide
Umeclidinium; Vilanterol

Recommendations in PSGs

Drug Products	Formulation	Primary Endpoint(s)[a]	Study Design	Treatment Duration	Study Population
Fluticasone Furoate; Vilanterol Fluticasone Proprionate; Salmeterol Xinafoate	DPI DPI, MDI	FEV_1 AUC_{0-12} (first day) Trough FEV_1 (last day)	Parallel	4 weeks	Asthma
Budesonide; Formoterol Fumarate Dihydrate	MDI		Parallel	6 weeks	Asthma
Salmeterol Xinafoate Glycopyrrolate Formoterol Fumarate	DPI DPI	FEV_1 AUC_{0-12}	Parallel / Crossover[b]	Single-dose	Asthma COPD Asthma
Indacaterol Maleate Tiotropium Bromide Umeclidinium Bromide	DPI DPI DPI	FEV_1 AUC_{0-24}	Parallel / Crossover[b]	Single-dose	COPD
Aclidinium Bromide Ipratropium Bromide	DPI MDI	FEV_1 AUC_{0-6}	Parallel / Crossover[b]	Single-dose	COPD
Beclomethasone Dipropionate Budesonide Fluticasone Furoate Fluticasone Propionate Mometasone Furoate	MDI DPI DPI DPI, MDI DPI, MDI	Trough FEV_1 (last day)	Parallel	4 weeks	Asthma
Ciclesonide	MDI		Parallel	8 weeks	Asthma
Albuterol Sulfate Levalbuterol	MDI, DPI MDI	PC_{20} (PD_{20})	Crossover	>4 visits (wash-out ≥ 24 hours)	Asthma

Abbreviations: MDI, metered dose inhaler; DPI, dry powder inhaler; AUC, including area under the serial FEV_1-time curve; COPD, chronic obstructive pulmonary disease; PC_{20} or PD_{20}, provocation concentration or dose producing a 20% fall in FEV_1.

[a] The above FEV1 based endpoints are baseline-adjusted. Equivalence is evaluated based on T/R ratio for the primary endpoint. The 90% confidence intervals for the T/R ratios for the BE study endpoint should fall within 80.0-125.0%, except PC_{20}, which is 67.0-150.0% [b] PSG recommends that the study should include appropriate justification for the design chosen.

Source: https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm

A General Design for the Comparative Clinical Endpoint BE Study of Inhaled Corticosteroids (1)

Fluticasone Propionate DPI

Recommendation in PSG

Type of study: Comparative clinical endpoint BE study

Design: A randomized, multiple-dose, placebo-controlled, parallel-group design, consisting of a 2-week placebo run-in period followed by a 4-week treatment period of the placebo, T, or R drug product

Dose: 0.044 mg/INH, two inhalations twice daily

Study Design

A minimum of 3 visits to the clinic should be scheduled:

a. At start of the run-in period (Visit 1); b. At the start of the randomized treatment, after the 2-week run-in period (Visit 2); and c. At week 4 of treatment (Visit 3)

Run-in Period	Treatment Period	
Visit 1 (Day -14)	**Visit 2 (Day 1)**	**Visit 3 (Day 28)**
Placebo given BID via the T drug product	Fluticasone propionate given BID via the R drug product OR Fluticasone propionate given BID via the T drug product OR Placebo given BID via the T drug product	

A General Design for the Comparative Clinical Endpoint BE Study of Inhaled Corticosteroids (2)

Fluticasone Propionate DPI

BE study endpoints

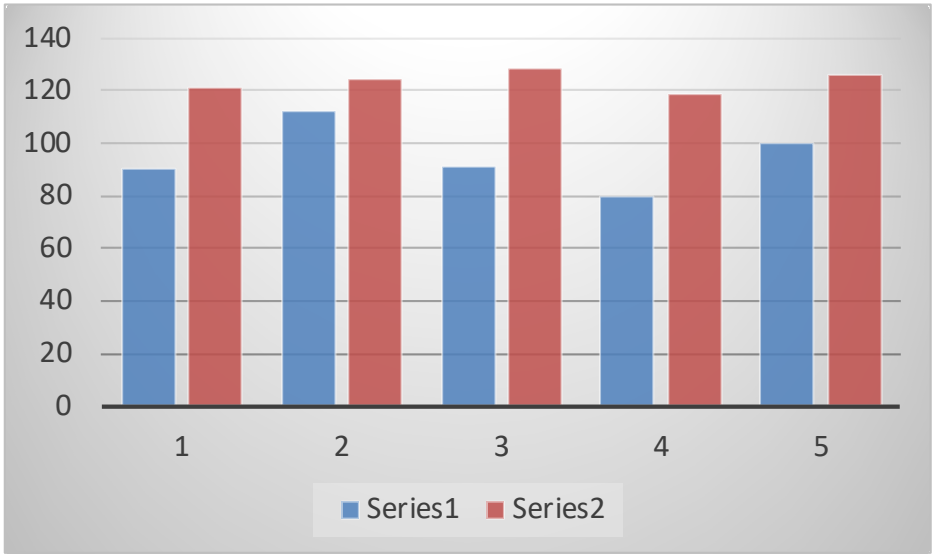
- FEV_1 measured in the morning prior to the dosing of inhaled medications on the last day of the 4-week treatment
- The above primary endpoint should be baseline adjusted (change from baseline)
- An FEV1 baseline is defined as the average of pre-dose FEV1 values of at least two time points measured in the morning of the first day of a 4-week treatment period
- Sampling is recommended to correspond to the same time of day as used on the last day of a 4-week treatment

Equivalence based on:

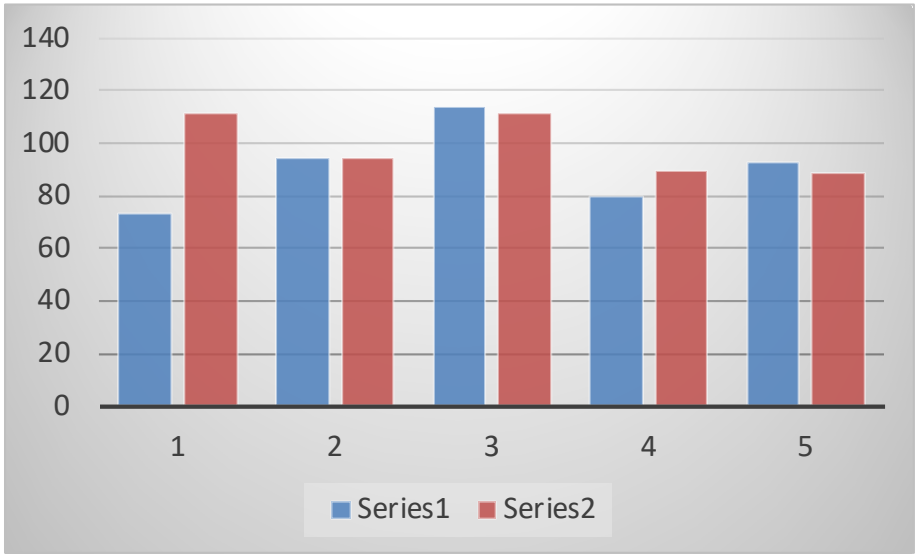
- T/R ratio for the primary endpoint
- The 90% confidence intervals for the T/R ratio for the primary endpoint should fall within the limits of 80.00 - 125.00%

Assumed vs. Observed Variability

Assumed vs. Observed CV (%) of Trough FEV_1



Assumed vs. Observed CV (%) of FEV_1 AUC

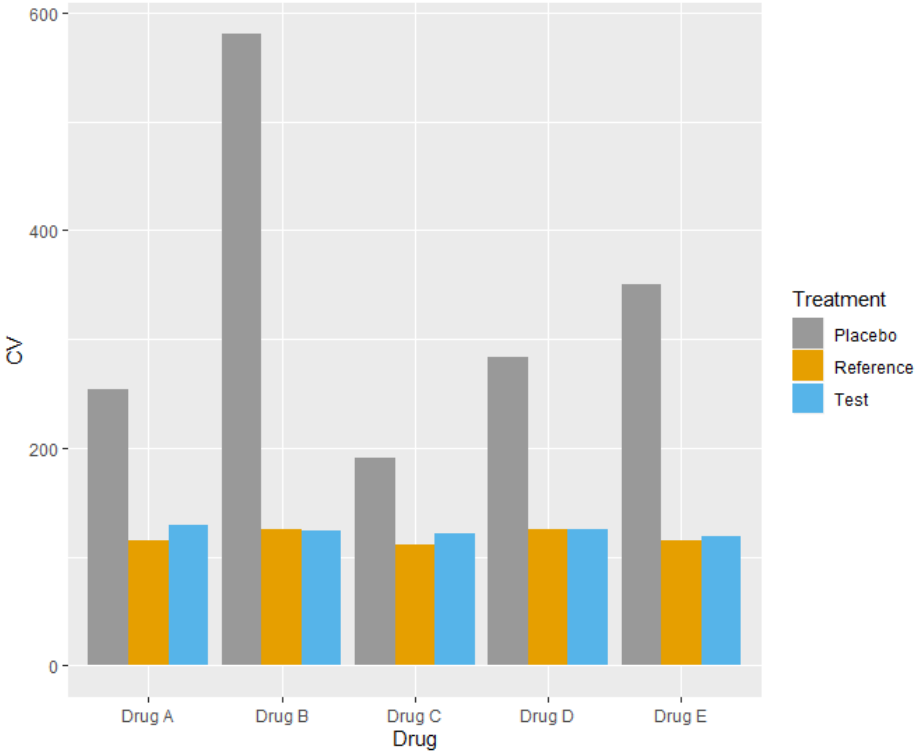


Data source: 5 ANDA submissions which have available spirometry data

Sample size in the clinical studies ranged from 800 to 1500.

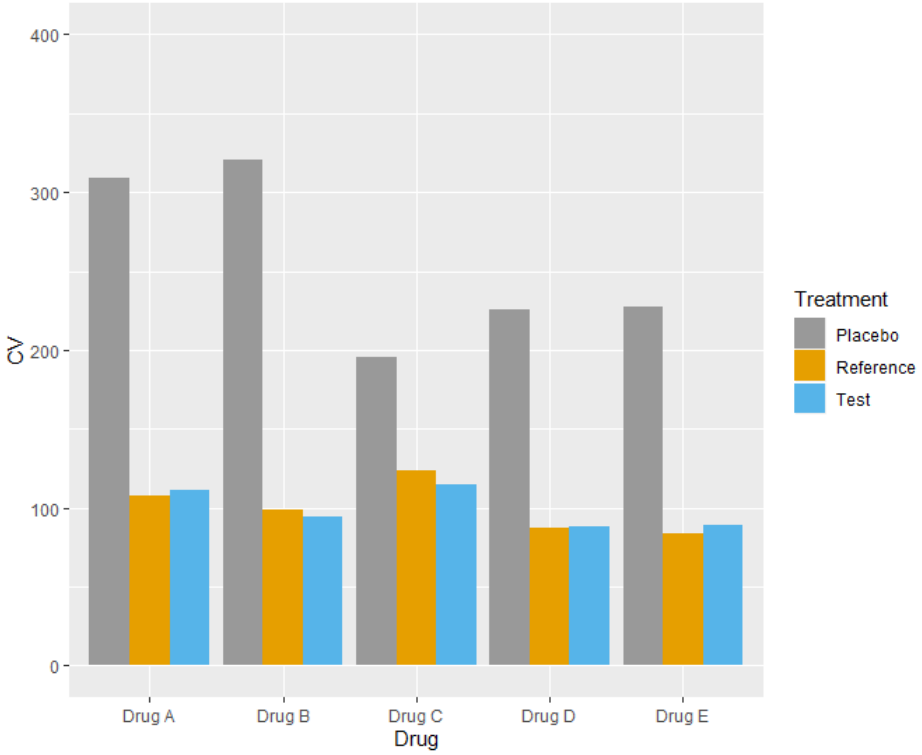
Observed Variability

CV (%) of baseline corrected trough FEV_1



Median [Min-Max] of CV(%):
Placebo: 267.8% [186.6-547.3]
Reference: 126.7% [113.4-128.0]
Test: 122.9% [115.8-125.8]

CV (%) of baseline corrected AUC of FEV_1



Median [Min-Max] of CV(%):
Placebo: 228.6% [189.8-319.1]
Reference: 98.5% [83.5-125.4]
Test: 94.5% [88.3-111.2]

*CV, coefficient of variation; AUC_{0-12} and AUC_{0-24} were used per PSG recommendations.

Data Analysis on FEV1-based Metrics

- **ANCOVA models**: For 4 out of 5 ANDA submissions, the ANCOVA models were fitted for each primary endpoint and least square (LS) means were derived for each treatment for the primary endpoints.
  - The LS means from the ANCOVA models for each endpoints were used to generate ratios (LS mean of treatment group/LS mean of reference group).
  - Two-sided CIs was generated for the ratios for each endpoint.
  - If the two-sided 90% CIs for the ratios were wholly contained within the interval 80.00% to 125.00% then the bioequivalence of test drugs was concluded.
- **Fixed effects**: treatment, study center and region
- **Covariates**: Demographic factors (e.g., age, height), and baseline FEV_1

Simulation Inferred Sample Size Estimations

- **Sample size to achieve 80% power to pass bioequivalence, based on the observed CV%s and a true T/R ratio of 105%**
  - **N=1,584-1,862***
- **With a fixed sample size (n=1,000), what are the maximum difference in FEV_1 metrics which pass BE with 80% power?**
  - **3.87%**

The sample size calculated are dauntingly large to demonstrate BE based on currently observed variabilities using FEV_1-based metrics.

Note: *Considering placebo group (4:4:1) and discontinuation rate (10%), the require sample size is 1,917-2,149.

Performance of FEV1-Based Metrics for BE Assessment

- Costly due to large sample size trials
  - High variabilities
- Sensitivity to detect difference in product performance is in large dependent on the location of approved doses on the dose-response curves
  - Difficult to differentiate random effect from effect of drug bioavailability at the site of action in clinical performance if approved doses locate in the plateau portion of the dose-response curves

Summary on Dose-Response Relationships

Product Name	Clinical ;Endpoint	Approved dose range (mcg)	Dose-Response relationship
Fluticasone Propionate	Trough FEV_1	100 – 500	Not significant
Tiotropium Bromide	Trough FEV_1	18	The approved dose lies on or near the upper flat portion of the dose-response curve.
Fluticasone Furoate; Vilanterol	FEV_1 AUC_{0-12} Trough FEV_1,	100 – 200; 25	There were no reports documenting the dose-response.
Fluticasone Propionate; Salmeterol Xinafoate	FEV_1 AUC_{0-12} Trough FEV_1	50	Not significant (As the fold change in response between doses ranged from 1.06 – 1.35)
Beclomethasone Dipropionate	Trough FEV_1	40 – 80	Lack of established D-R relationship
Mometasone Fuorate	Trough FEV_1	50 – 100	Both of the higher doses in this trial appear to be on the plateau of a dose-response curve across the three MDI doses
Aclidinium Bromide DPI	FEV_1 AUC_{0-6h}	400	Shallow D-R relationships of both the PD endpoints for all approved doses
Budesonide; Formoterol	FEV_1 AUC_{0-12} Trough FEV_1	80 – 160; 4.5	• Budesonide: lack of established D-R relationship • Formoterol: clear D-R relationship

The dose-response relationship was being analyzed by fitting the data into the E_{max} model.

ED_{50}: 10 times lower than lowest dose

E_{max} model

ED_{50}: ~8 times lower than lowest dose

*based on MG/INH, not MG BASE/INH ; NA, not applicable; NS, not significant

Summary

- FEV_1-based endpoints are one of the recommended metrics for BE assessment
- High variabilities of FEV_1-based metrics have been observed for inhaled corticosteroid (ICS) OIDPs, leading to the requirement of a large sample size for BE establishment
- The approved ICS dose(s) appears to be at the plateau part of the dose-response relationships, or with ED_{50} lower than the lowest dosing strengths

Alternatives

- FDA's current PSG recommendations are intended to infer equivalence in regional lung deposition of OIDPs
- FDA's pathway for alternative approaches is via the pre-ANDA meeting process
  - Generic applicants should propose alternative approaches that are more sensitive and efficient than the current recommendations
- Scientific justification should be responsive to the goal of inferring equivalence in regional lung deposition
  - Additional in vitro testing + PK?
  - Additional in vitro testing + PK + Modeling & Simulation?
  - Other PD endpoints?

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BACK-UP SLIDES

Sample Size Calculation

ANDA	CV (%)	Power (%)	T/R true ratio	Type 1 error (2-sided)	Total N
Drug A	90	90	0.95	5%	800
Drug B	112	>81	1	5%	1100
Drug C	107-121	80	0.95	5%	1440
Drug D	80	90	0.95	5%	1130
Drug E	100	87.1	0.95	5%	1470*

*Sample size for superiority test was also calculated.

Alternative markers/FEV1 metrics which have been evaluated drug PSG development

Product Name	Alternative Endpoints	Review Conclusion
Fluticasone furoate; Vilanterol Fluticasone Propionate Fluticasone Propionate; Salmeterol Xinafoate	FeNO, allergen challenge, asthma stability model, sputum eosinophilia	Lack of D-R relationship
Aclidinium Bromide	FEV_1 AUC_{0-6h} (multiple dose) FEV_1 AUC_{0-12h} (multiple dose) PC_{35}	Required sample size (>5000) → not suitable for BE determination
Salmeterol	PD_{20}, Mean % increase in FEV1 Bronchodilatation/Bronchopro vocation studies	Lack of D-R relationship
Glycopyrrolate	E_{max} FEV1 change (Day 1)	Lack of D-R relationship
Beclomethasone Dipropionate	FeNO, PC_{20}	Lack of D-R relationship
Budnoside; Formoterol	FeNO	No D-R relationship
Ciclesonide	FeNO, PC_{20}	No D-R relationship

Questions

- **Q1. What is a sample size to achieve 80% power to pass bioequivalence (B), assuming CV as 100%, T/R true ratio as 5%?**

- **Q2. With a fixed sample size (n=1,000), what are maximum differences in FEV_1 metrics which pass BE with 80% power?**

- **Q3-1. With a 20% difference in FEV_1 metrics, what is a sample size to fail BE test with 80% chance?**

- **Q3-2. BE Passing Rate (%) vs. sample size based on ANDA datasets**
  - Fluticasone Propionate and Salmeterol DPI, (A208891, approved)

Methods

Data

Reference ANDA

- Spirometry data from a reference study
- Per-protocol population
- Calculation of observed variability for the endpoints.

Primary Endpoints: ΔAUEC, ΔtFEV1

Simulation

To address question 3;

- Select a random subset, (various sample size N= 10, 20, 100, 200, 400, 600, 800, 1000, 2000, 2500)

To address questions 1-2;

- A package 'PowerTost' was used to estimate sample size using observed CVs (R ver 3.6.0)
- Sample size was calculated for reference and treatment group.

BE test

- 1000 replicates for calculation of BE passing rate (%)
- BE evaluation for ΔAUEC and tFEV1 in each scenario
- Calculation of BE passing rate
  - Passing rate (%) = (Npass/1000)*100

Simulation Results (3)

Q3. With a 10% difference in FEV_1 metric, what is the sample size to pass BE test with 80% power?

- **Sample size under 2,476**

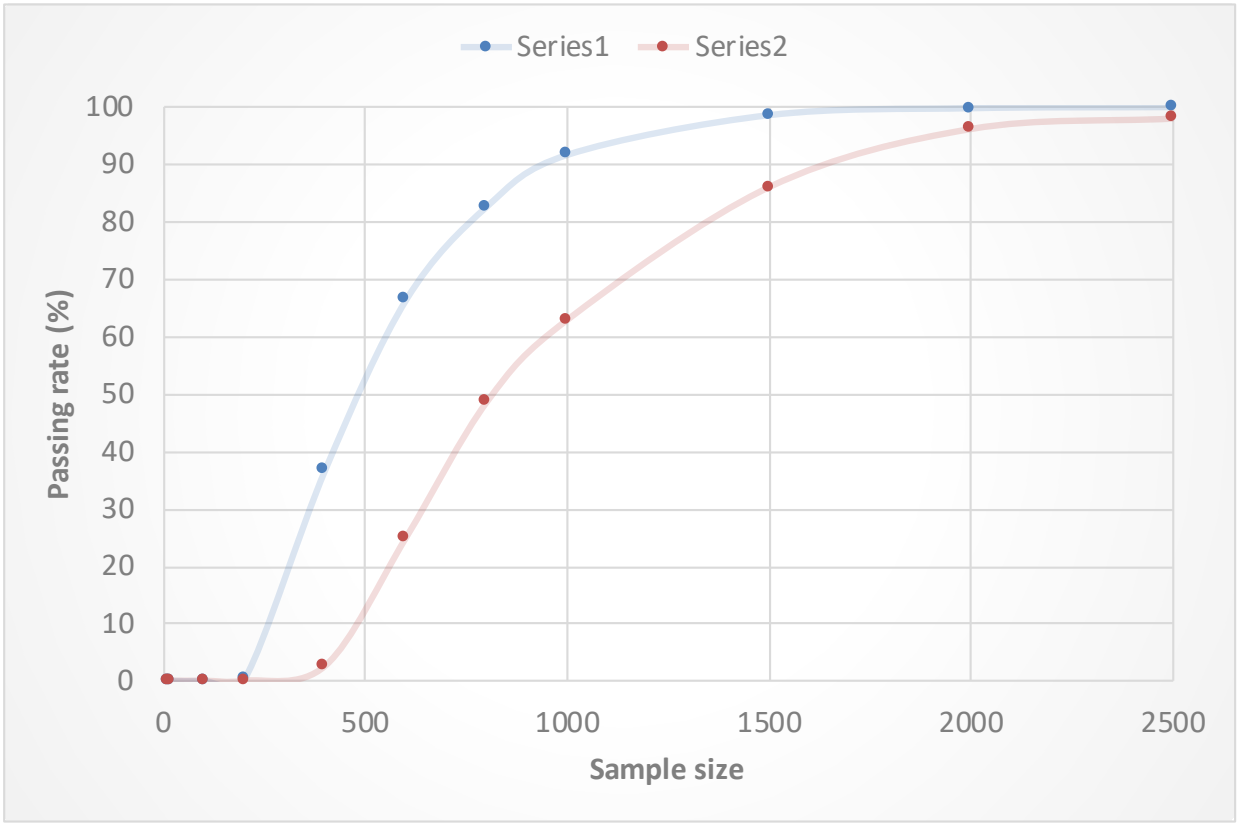
T/R true ratio	Required sample size (reference + treatment)
1	858
0.95	1120
0.9	2476
0.85	9894
0.825	39570

Note: Simulation was being conducted assuming a fixed 80% power (not 80% chance). To address '80% chances', the BE Passing Rate (%) vs. sample size based on ANDA datasets was simulated using actual datasets, which had 5-12% differences in FEV_1 metrics. (results are being summarized in page 6).

Simulation Results

BE Passing Rate (%) using Actual datasets (Fluticasone, N208891)

Simulation (replicates 1000 times)



N*	Passing rate (%) based on AUEC	Passing rate (%) based on $tFEV_1$
10	0	0
20	0	0
100	0	0
200	0.5	0
400	37.0	2.7
600	66.5	25.1
800	82.7	48.7
1000	91.7	63.0
1500	98.6	86.1
2000	99.8	96.2
2500	100.0	98.0

$$Passing\ rate\ (\%) = \frac{Npassing}{Nrep\ (1000)} * 100$$

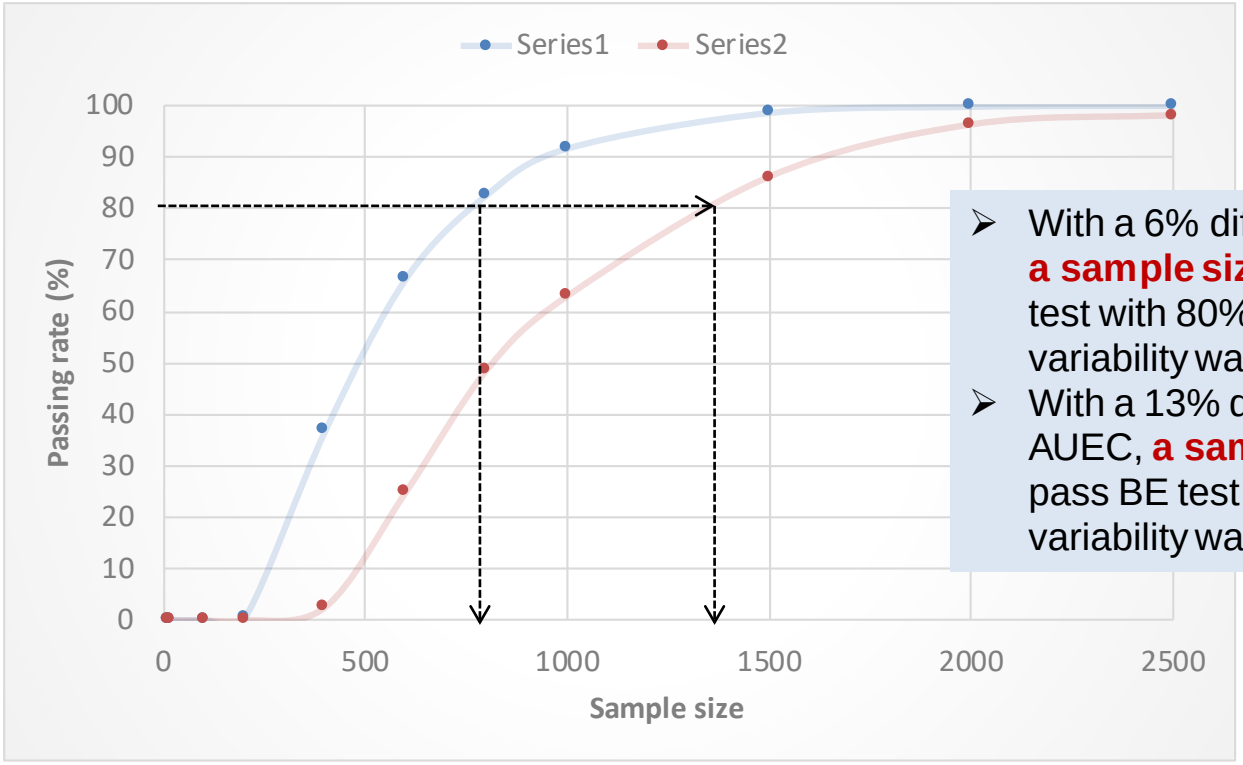
N, total sample size of reference group and treatment group

Simulation Results

BE Passing Rate (%) using Actual datasets (Fluticasone, N208891)

Simulation (replicates 1000 times)

Q3-2. With a observed T/R difference in $tFEV_1$, what is the sample size to pass BE test with 80% chance?



- With a 6% difference (observed T/R) in $tFEV_1$, **a sample size (~1400)*** is required to pass BE test with 80% chance. (Ref: observed variability was 124.1%)
- With a 13% difference (observed T/RI in AUEC, **a sample size (~750)*** was required to pass BE test with 80% chance. (Ref: observed variability was 94.5%)

$$Passing\ rate\ (\%) = \frac{Npassing}{Nrep\ (1000)} * 100$$

* Placebo group/discontinuation rate was not being considered.