Considerations for FEV_1-based Comparative Clinical Endpoint or Pharmacodynamic Bioequivalence Studies for Orally Inhaled Drug Products

FDA-CRCG Workshop

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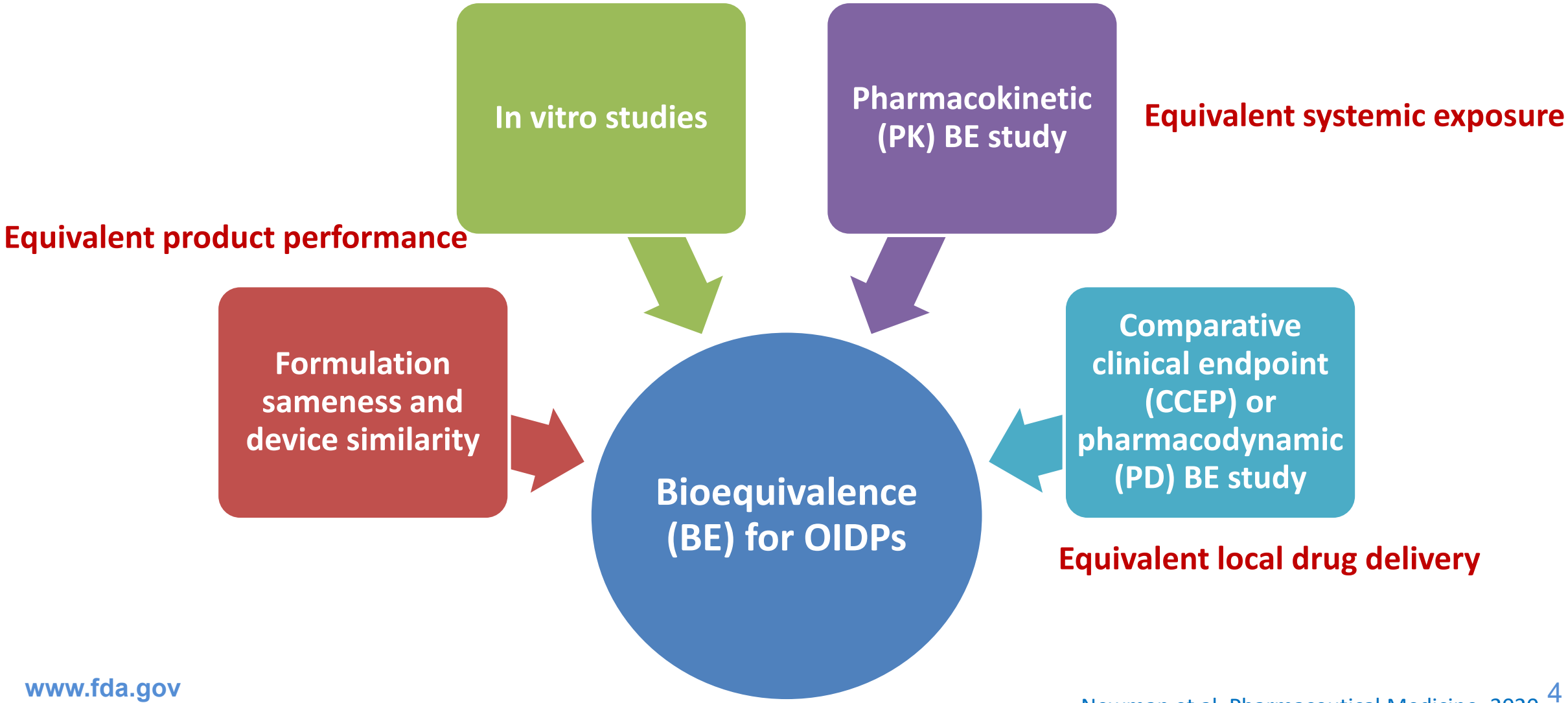
Disclaimer

- This presentation represents the views and perspectives of the speaker and does not necessarily reflect the views of the U.S. FDA.

Outline

- Challenges for FEV_1-based comparative clinical endpoint (CCEP) or pharmacodynamic (PD) bioequivalence (BE) studies for orally inhaled drug products (OIDPs)
  - High variability
  - Flat dose-response relationship
- Potential opportunities and strategies to address the challenges
  - Covariate adjustment
  - Alternative BE studies
- Summary
- References

Weight of Evidence Approach for Orally Inhaled Drug Products (OIDPs)



Newman et al. Pharmaceutical Medicine. 2020

CCEP or PD Studies Recommended in Product-Specific Guidance (PSGs)

- Baseline-adjusted mean FEV_1 AUEC (e.g., $AUEC_{0\text{-}12h}$, $AUEC_{0\text{-}24h}$) and/or trough FEV_1 are recommended in CCEP BE studies for >25 OIDPs
  - Inhaled corticosteroids (ICS): e.g., fluticasone propionate MDI/DPI, beclomethasone dipropionate MDI; long-acting β2 adrenergic receptor agonist (LABA): e.g., salmeterol xinafoate DPI; long-acting muscarinic antagonist (LAMA): e.g., tiotropium bromide DPI
  - Commonly as parallel design (e.g., study duration 4-6 weeks)
- PD BE studies with dose-scale analysis are recommended for short-acting β2 -agonist (albuterol, levalbuterol)
  - Bronchoprovocation study (methacholine challenge test): post-dose PC_{20} or PD_{20}
  - Adequate dose–response relationship

FEV_1- Forced expiratory volume in 1 second; AUEC- area under the effect-time curve; MDI- metered dose inhaler; DPI- dry powder inhaler

Challenges in CCEP or PD BE Studies for OIDPs

CCEP or PD BE studies often need to be conducted in asthma/chronic obstructive pulmonary disease (COPD) patients

FEV_1 can be influenced by many intrinsic and extrinsic factors, including age, sex, height, ethnicity, genetic variations, and smoking status

High day-to-day variations in FEV_1 have been reported in patients with asthma, COPD, and cystic fibrosis

High variabilities in FEV_1 lead to the requirement of large sample sizes for BE studies

High Variabilities Observed in CCEP BE Studies

Observed variabilities (CV%) of FEV_1 endpoints in CCEP BE studies submitted to FDA

Primary Endpoints	Test (%) Mean [Min–Max]	RLD (%) Mean [Min–Max]	Placebo (%) Mean [Min–Max]
FEV_1 AUEC (first day)	102.8 [87.1–111.1]	103.2 [84.2–125.3]	259.7 [189.8–320.2]
Trough FEV_1 (last day)	122.6 [103.0–128.6]	113.2 [105.9–125.0]	244.3 [190.9–580.0]

- The mean variabilities (CV%) of FEV_1 AUEC and trough FEV_1 were > 100% for both the test products and the reference listed drugs (RLDs)
- The variabilities were >200% in the placebo groups

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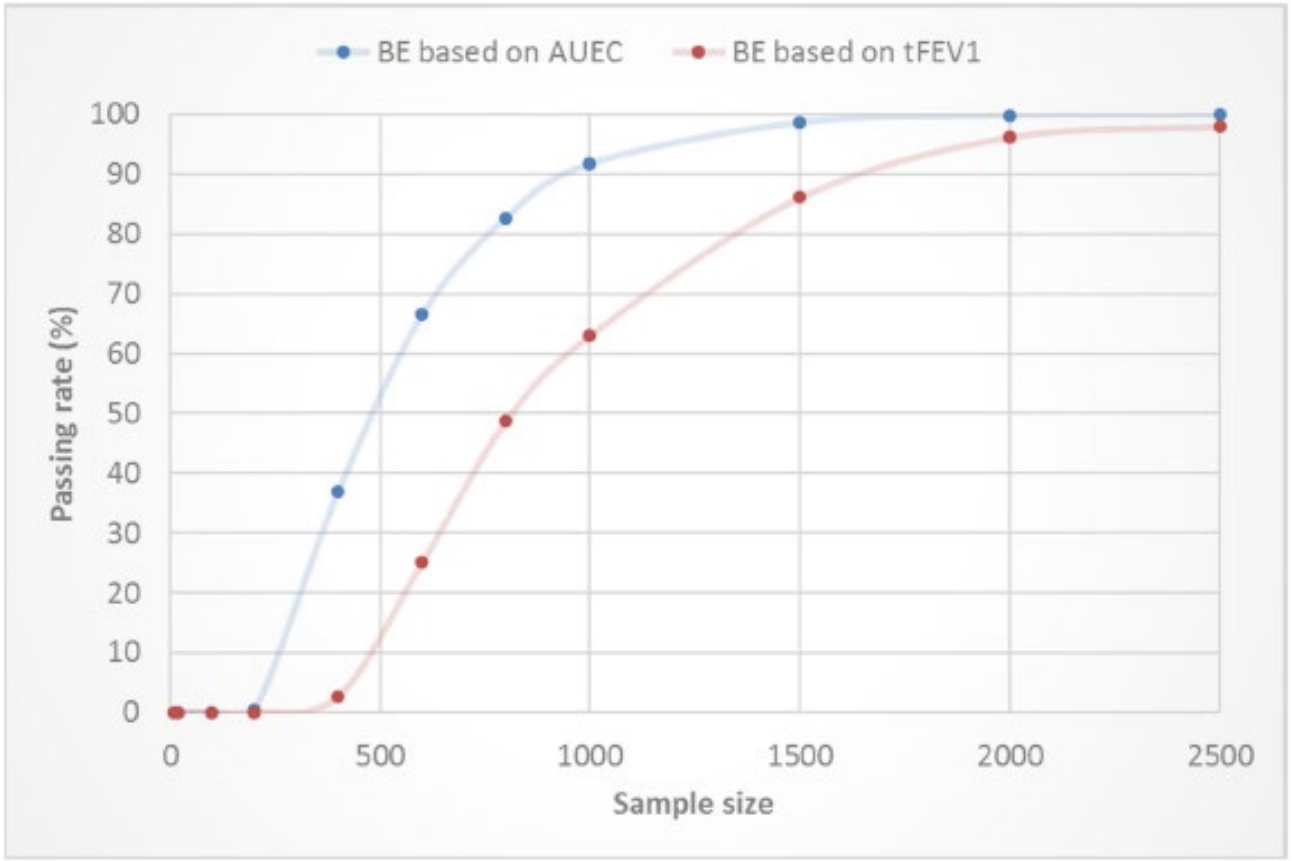
Predicted Sample Size to Achieve 80% Study Power



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

- Sample size of ~750 (for both test and RLD groups) is needed to achieve 80% study power for BE based on FEV_1 AUEC
- Sample size of ~ 1,400 is needed to achieve 80% study power for BE based on trough FEV_1

Simulations were conducted based on observed T/R ratio and variabilities of an approved ANDA. 1000 simulations were conducted for each sample size. N = total sample size of test and RLD groups.

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Dose-Response (D-R) Relationship

Drug Products	Classifications	Dose-Response (D-R) Relationship
Formoterol Fumarate (DPI)	LABA	No significant D-R relationship for FEV_1 $AUEC_{0\text{-}12h}$; Appeared to exhibit D-R relationship in PC_{20} in bronchoprovocation study, however, no sufficient evidence to ensure a PD BE study is feasible.
Beclomethasone Dipropionate (MDI) Budesonide (DPI) Fluticasone Furoate (DPI) Fluticasone Propionate (DPI, MDI) Mometasone Furoate (DPI, MDI) Ciclesonide* (MDI)	ICS	No significant D-R relationship OR the approved doses appeared to be near the plateau of the D-R curve.
Salmeterol Xinafoate (DPI) Vilanterol Trifenatate (DPI) Indacaterol Maleate (DPI)	LABA	
Glycopyrrolate (DPI) Tiotropium Bromide (DPI) Aclidinium Bromide (DPI) Umeclidinium Bromide (DPI)	LAMA	
Ipratropium Bromide (MDI)	SABA	
Epinephrine (MDI)	Bronchodilator	

- Lack of D-R relationships for FEV1-based metrics were found → low sensitivity to detect formulation-related differences in drug exposure between the test and the RLD at the site of action
- The current investigation did not find a strong evidence to recommend PD BE studies in lieu of CCEP studies for these OIDPs

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Potential Opportunities to Address the Challenges

Covariate Adjustment

- FDA guidance on Statistical Approaches to Establishing Bioequivalence (December 2022): the applicant may consider prespecifying inclusion of important demographic and baseline prognostic covariates in the statistical model for parallel studies.
- Covariate analysis (ANCOVA) can be used to adjust baseline variables in estimating treatment effects for CCEP studies
  - Baseline covariates include: demographic factors (age, sex, ethnicity, weight, height, and race), disease characteristics, or other related information

Covariate Adjustment – Case Example

- A generalized linear model with ANCOVA analysis was used for an example CCEP study
  - Demographic variables: age, sex, weight, height
  - Study information: study region
  - Spirometry data: baseline FEV_1, baseline FVC, and FEV_1/FVC (FVC: forced vital capacity)
- Covariate selection was conducted using a stepwise regression approach to minimize the Akaike information criteria (AIC)

- For the example dataset, the selected ANCOVA models explained 80.1% of the variation in baseline FEV1, but only a limited portion of the variation (8.0 – 21.3%) for the primary BE endpoints (i.e., trough FEV_1 and FEV1 $AUEC_{0\text{-}12}$).
- The use of ANCOVA with selected covariates reduced the number of subjects by approximately 10%.
- Prospective applicants should pre-specify the ANCOVA analysis in the statistical analysis plan before conducting the CCEP BE study.

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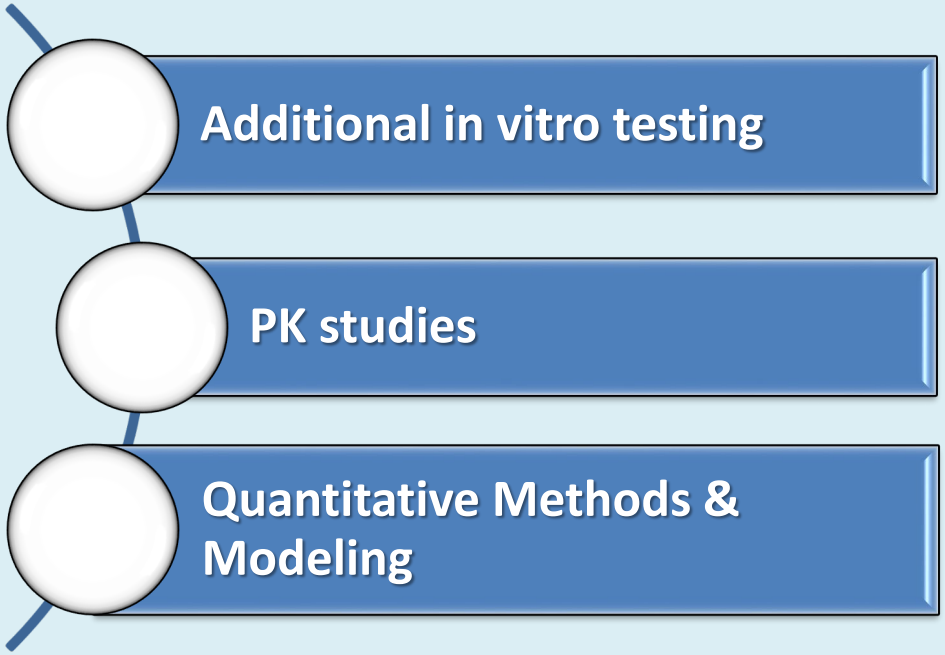
Alternative PD Models or Endpoints

- Alternative PD models or endpoints were available in literatures
  - In the case of ICS, several alternative PD models are available including induced allergen challenge, asthma stability model, sputum eosinophilia, and exhaled nitric oxide. However, many of these PD models are challenging to be used for BE assessment due to the highly variable D-R relationship.
- FDA encourages the exploration of novel approaches or BE metrics that may offer improved study sensitivity in establishing BE for OIDPs

Alternative Approaches to the CCEP or PD BE Study

PSGs of beclomethasone dipropionate MDI suggested alternative approach may include but is not limited to following studies:



1) more predictive APSD testing, 2) characterization of emitted aerosol sprays, 3) dissolution, and 4) morphology imaging comparisons

Alternative in vivo PK BE studies

Modeling & simulation (e.g., computational fluid dynamic studies and physiologically-based PK modeling)

- **Scientific justifications are needed to help ensure the equivalence of the test product and the RLD at the local sites of action in the lungs**

FDA Draft Guidance on Beclomethasone Dipropionate (Recommended Jan 2016; Revised Mar 2020)

Early Communication with FDA

- FDA strongly encourages prospective applicants to discuss their development program for an alternative approach to BE with the FDA via the pre-ANDA meeting pathway.
- Early communication with the FDA can help clarify expectations in product development, and assist applicants to submit an ANDA as complete as possible.

FDA Guidance for Industry: Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA (October 2022)

Summary

- FEV1-based metrics are the most recommended CCEP for locally acting OIDPs.
- High variabilities of FEV1-based metrics were observed, resulting in a need for a large sample size (> 1,000) to achieve sufficient power to establish BE for generic OIDPs.
- The flat dose-response relationships lead to low sensitivity to detect clinically meaningful differences and, consequently, formulation-related differences in drug exposure between the test and the RLD at the site of action.
- Adapting covariate analysis for BE evaluation reduced the sample size, but to a limited extent.
- FDA continues to explore and evaluate new approaches for BE assessment that may help mitigate the high cost and time investments associated with development of locally acting generic OIDPs.
- Prospective applicants and academia are encouraged to participate in this effort by submitting new approaches in product development pre-ANDA meeting requests and advancing research in collaborative grants and contracts with the FDA.

Reference

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- Guidance for Industry: Statistical Approaches to Establishing Bioequivalence (December 2022): https://www.fda.gov/media/163638/download
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Questions?

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