Batch-to-batch pharmacokinetic variability of orally inhaled drug products

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Outline

- Batch-to-batch PK difference of orally inhaled drug products
- Quantitative analysis of potential factors contributing to batch-to-batch PK difference
- Recommendation on test batch for PK studies

Orally inhaled drug products

- Complex product as defined in the GDUFA II Commitment Letter
- Take fluticasone propionate; salmeterol xinafoate orally inhaled powder as an example
  - Complex drug – device component
  - Absorption path specific to the delivery route

GDUFA II Commitment Letter, available at: https://www.fda.gov/downloads/forindustry/userfees/genericdruguserfees/ucm525234.pdf

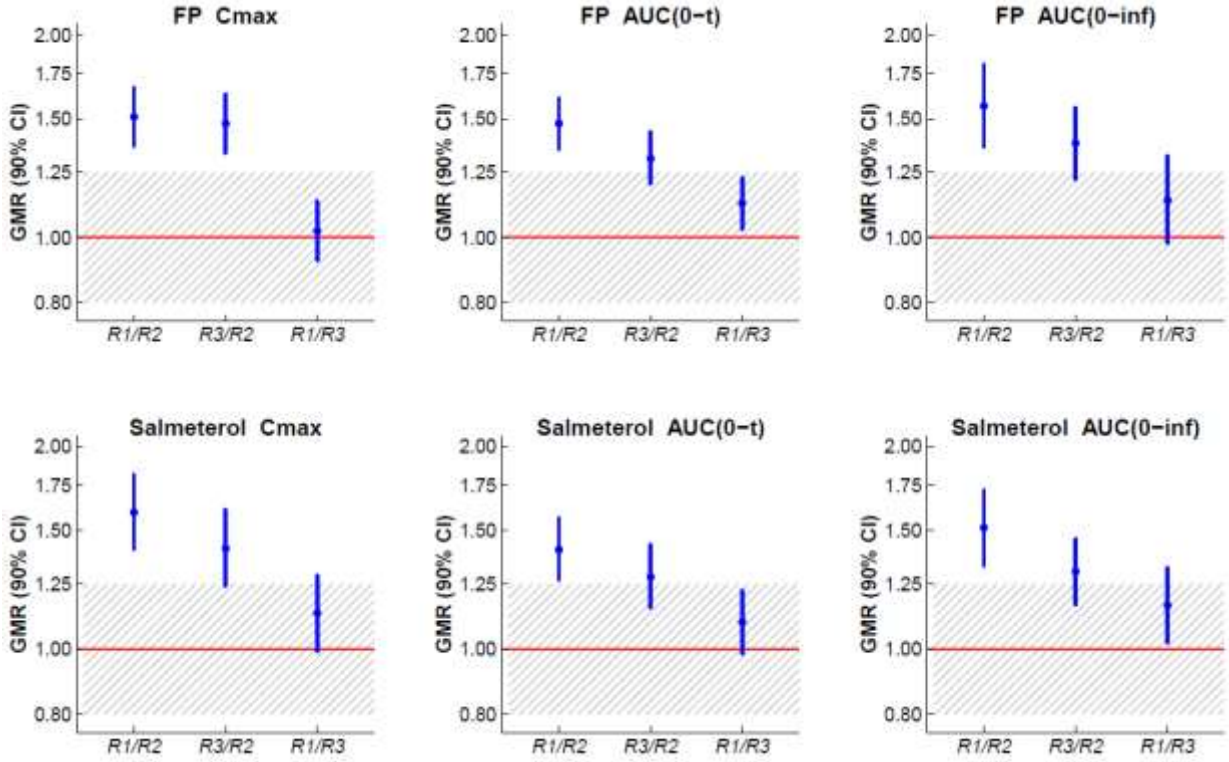
ADVAIR DISKUS®

- Inhaler containing a combination of fluticasone propionate (FP) (100, 250, or 500 mcg) and salmeterol (50 mcg) as a powder formulation for oral inhalation

- Indicated for maintenance treatment of
  - asthma in patients aged 4 years and older
  - airflow obstruction and reducing exacerbations in patients with chronic obstructive pulmonary disease (COPD)

Prescribing information for ADVAIR DISKUS®, available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021077s056s057lbl.pdf

Batch-to-batch PK difference in reference standard?

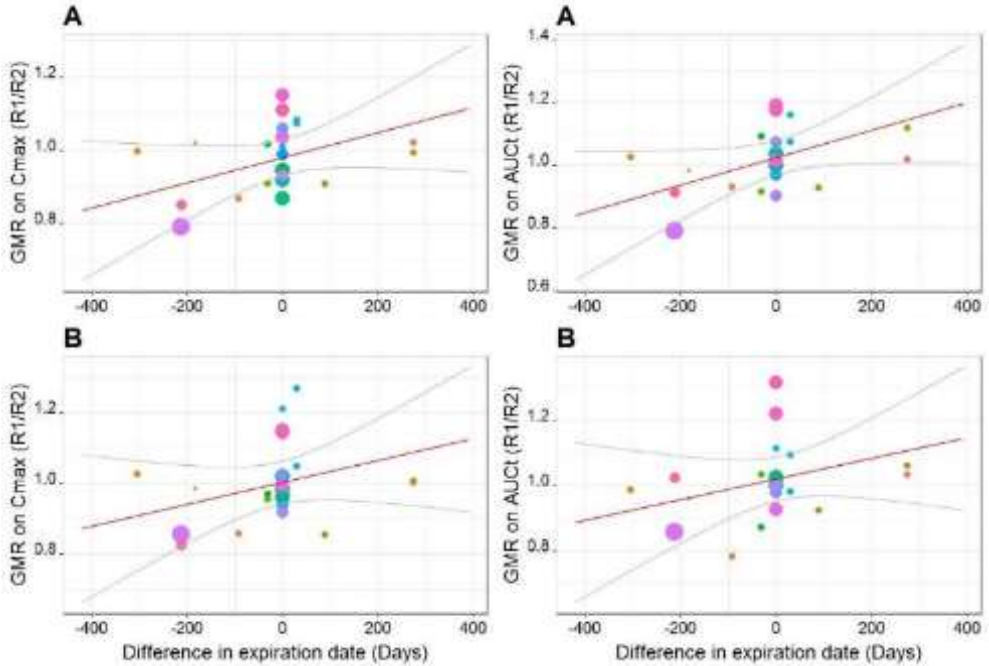


Burmeister Getz E et al. Clin Pharmacol Ther. 2017, 101(3): 331–340

Limited data to understand the root cause of batch-to-batch PK difference

- Possible contributing factors
  - APIs in the products: storage condition and stability
  - Inactive ingredients: source and quality
  - Drug performance: single actuation content (SAC) and aerodynamic particle size distribution (APSD)

Expiry date as a contributing factor to batch-to-batch PK difference



Test of Expiry date as Potential Predictor

Analyte	Parameters	Q	*p*-value
A	C_{max}	2.43	0.119
	AUC_t	3.42	0.064
B	C_{max}	1.56	0.212
	AUC_t	1.29	0.256

Expiry date difference could explain some of the batch-to-batch PK differences.

Demographics and batch-to-batch PK differences

Analyte	Parameter	Variable	Q	*p*-value
A	AUC_t	Age	0.30	0.586
		BMI	0.00	0.989
		Weight	0.53	0.467
	C_{max}	Age	0.99	0.320
		BMI	0.02	0.894
		Weight	0.22	0.641
B	AUC_t	Age	0.71	0.400
		BMI	0.46	0.497
		Weight	1.21	0.272
	C_{max}	Age	0.18	0.668
		BMI	0.00	0.962
		Weight	1.02	0.312

Demographics (e.g., age) may explain some of the batch-to-batch PK differences.

Recommendation on BE approaches

- Conduct in vitro characterization using at least three batches:
  - no fewer than 10 units from each test or reference listed drug batch
  - SAC and APSD

- Contact OGD for guidance (e.g., via controlled correspondence) to discuss alternative approaches before conducting study

Product specific guidance on fluticasone propionate; salmeterol xinafoate inhalation powder, available at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM367643.pdf

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