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Reference-Scaled Average Bioequivalence (SABE): A Promising Statistical Approach to Analyze Cutaneous Pharmacokinetic Results for Topically Applied Drug Products

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PURPOSE

Dermal open flow microperfusion (dOFM) is a methodology that **characterizes the cutaneous pharmacokinetics** (PK) of topical dermatological drug products and thus has the potential to evaluate bioequivalence (BE) [1]. **Cutaneous PK data can be highly variable** due to substantial intra-individual differences in skin permeability.

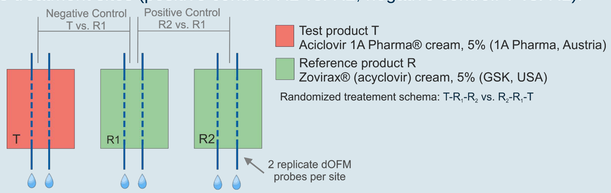
Therefore, a statistical reference-scaled average BE (SABE) analysis can be used when the within-subject variability of the reference product is > 0.294, which might be more appropriate than an average BE (ABE) analysis [2].

OBJECTIVES

The objectives of this work were to **evaluate the within-subject variability of the reference product** for dOFM data, both in-vivo and ex-vivo, to **determine the appropriateness of an analysis using SABE or ABE**, and to evaluate the accuracy, sensitivity and reproducibility of the results when analyzed by SABE compared to ABE.

METHODS

- In-vivo dOFM study: 20 healthy subjects (40 thighs)
- Ex-vivo dOFM study: 40 full-thickness human skin sections (16 donors)
- 3 treatment sites (positive control: R1 vs. R2, negative control: T vs. R1):



- Dermal PK endpoints:
  - Area under the concentration-time curve (AUC_{0-36h})
  - Dermal concentration maximum (C_{max})
- Statistical BE analysis (based on log-transformed data):

Condition for use:

(s_{WR}) ≤ 0.294 -> ABE

(s_{WR}) > 0.294 -> SABE

s_{WR}…Within-subject standard deviation for the reference product

- ABE [3]:
  Criterion for BE: 90% CI of the GMR fall within the BE limits of 0.80–1.25.
- SABE [4]:
  Mixed Criterion for BE: The upper 95% bound of the scaled confidence interval (CI) is less than or equal to zero and the geometric mean ratios (GMR) for AUC_{0-36h} and C_{max} lie within the BE limits of 0.8 – 1.25.

RESULTS

From the measured dermal concentration-time profiles (figure 1) of the in-vivo and ex-vivo dOFM study, the dermal PK endpoints AUC_{0-36h} and C_{max} were computed and BE was evaluated using the ABE and the SABE approach.

ABE (table 1):

- For the in-vivo dOFM study, BE was confirmed for the positive control (R1 vs. R2) for both PK endpoints. The negative control (T vs. R1) failed to demonstrate BE as the calculated 90% CIs do not lie within the BE limits of 0.8 and 1.25.
- For the ex-vivo study, the negative control (T vs. R1) failed to demonstrate BE, as expected, however, due to the high variability in the results, the positive control (R1 vs. R2) also failed to demonstrate BE.

***Table 1**: Results for ABE evaluations for the in-vivo and ex-vivo dOFM study (passed the BE test: ✓, failed the BE test: X)*

		PK endpoint	90% CI	Passed
In-vivo dOFM study	Postive control (R1 vs. R2)	AUC_{0-36h}	0.86-1-18	✓
		C_{max}	0.86-1.21	
	Negative control (T vs.R1)	AUC_{0-36h}	0.69-1.05	X
		C_{max}	0.61-1.02	
Ex-vivo dOFM study	Postive control (R1 vs. R2)	AUC_{0-36h}	0.91-1.54	X
		C_{max}	0.94-1.53	
	Negative control (T vs.R1)	AUC_{0-36h}	0.04-0.12	X
		C_{max}	0.02-0.05	

SABE (table 2):

The within-subject standard deviation for the reference product of both PK endpoints was greater than 0.294 allowing to apply the SABE approach.

- For the in-vivo dOFM study, BE was confirmed for the positive control (R1 vs. R2) as for both PK endpoints the GMR lies within the BE limits of 0.8 and 1.25 and the upper 95% bound of the CI was negative. The negative control (T vs. R1) failed to show BE.
- For the ex-vivo dOFM study, BE was confirmed for the positive control. Furthermore, the negative control failed to demonstrate BE.

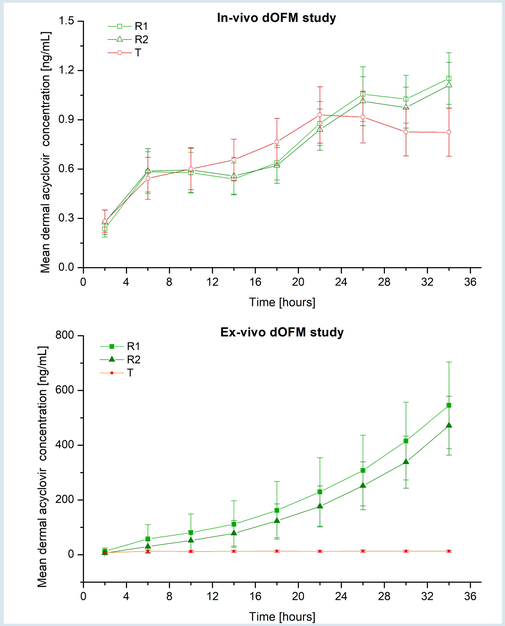


***Figure 1:** Dermal concentration-time profile (±SE) for the in-vivo (upper panel) and ex-vivo (lower panel) studies for the two reference products (R1, R2) and test products (T).*

***Table 2**: Results for SABE evaluations for the in-vivo and ex-vivo dOFM study (passed the BE test: ✓, failed the BE test: X)*

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		PK endpoint	s_{WR}	Upper 95% bound of the scaled CI	GMR	Passed
In-vivo dOFM study	Postive control (R1 vs. R2)	AUC_{0-36h}	0.4	-0.089	0.9991	✓
		C_{max}	0.46	-0.116	0.9881	
	Negative control (T vs.R1)	AUC_{0-36h}	0.4	-0.014	0.8826	X
		C_{max}	0.46	0.069	0.7877	
Ex-vivo dOFM study	Postive control (R1 vs. R2)	AUC_{0-36h}	0.68	-0.159	1.1771	✓
		C_{max}	0.6	-0.094	1.1918	
	Negative control (T vs.R1)	AUC_{0-36h}	0.68	8.989	0.0764	X
		C_{max}	0.6	16.05	0.0293	

CONCLUSIONS

- Using **SABE** to analyze dOFM cutaneous PK data, the **reference product** was accurately and reproducibly found to be **bioequivalent to itself**, both in-vivo and ex-vivo.
- **SABE sensitively discriminated the negative control** (T vs. R1) as not being bioequivalent to the T product, both in-vivo and ex-vivo.
- The **ABE approach failed for the positive control** (R1 vs. R2) of the **ex-vivo** dOFM study due to high variabilities in the data.
- **SABE** statistical analysis is a reliable way to evaluate BE.

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