Topical Corticosteroid Bioequivalence
An Evaluation of the FDA Guidance

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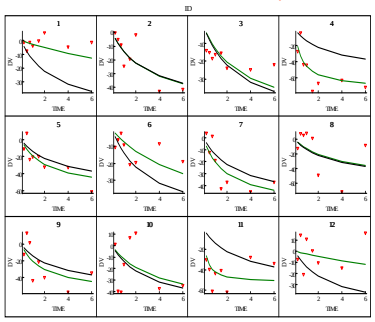
Analysis of FDA Example AUEC Data

NONMEM Emax No E0, FOCE



Topical Objective: The US FDA has issued a guidance describing a methodology for the conduct and analysis of clinical studies aiming to establish bioequivalence of topical corticosteroids (1). The guidance and a subsequent report from FDA authors (2) recommend that bioequivalence is based on skin blanching observations obtained with an application duration ("ED50") estimated to produce 50% of the maximum area under the blanching effect curve (AUEC) after removal of the formulation. A population analysis of data provided in the guidance was used to evaluate the robustness of the "ED50" estimate to the estimation method and model assumptions. A simulation study was undertaken to explore the rationale for the choice of the "ED50" as the optimal design point for detecting differences in rate and extent of absorption.

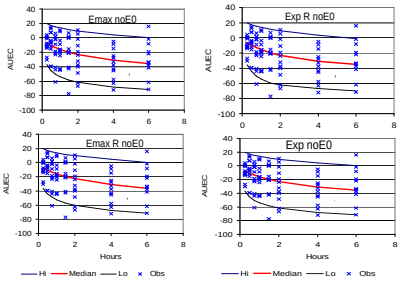
Methods: NONMEM was used to estimate the "ED50" using different models and estimation methods. The uncertainty of the "ED50" estimate was evaluated by bootstrapping the data.
A semi-physiological compartmental model was constructed to simulate the rate and extent of absorption from the epidermis to skin vasculature. Corticosteroid loss from the skin vasculature was assumed to be determined by blood flow so that vasoconstriction induced by a corticosteroid would affect the time course of skin blanching. An Emax model was used to describe the relationship between corticosteroid concentration at the vasculature and changes in blood flow. Skin blanching was assumed to be proportional to the effect of the corticosteroid on blood flow.
Results: The estimate of "ED50" reported in the FDA guidance is 1.89 h. NONMEM estimates ranged from 0.7 to 3.73 h depending on the model and estimation method. Using a model similar to that proposed in the guidance and the FOCE method the median "ED50" was 2.54 with 90% confidence interval of 0.88 to 8.06 h.
The simulation study showed that AUEC reflected differences in extent of bioavailability (0.8 - 1.25 x reference) and potency (0.5 – 2 x reference) but was insensitive to the choice of the duration of application. With a 60 min reference absorption half-life differences in test absorption half-life (30 – 120 min) were detected with increasing sensitivity to AUEC as duration of application increased. AUEC was insensitive to application duration with rapid absorption half-life (10 min reference).
Conclusion: The method proposed in the FDA guidance for estimation of "ED50" is not robust. Differences in rate and extent of absorption of topical corticosteroids are largely insensitive to the timing of the AUEC design point unless absorption is slow. There is no mechanistic support for choosing the "ED50" as the optimal design point for assessment of bioequivalence.
Reference: 1. FDA Guidance for Industry. Topical dermatological corticosteroids:*in vivo* bioequivalence.
http://www.fda.gov/cder/guidance/old098fn.pdf 1995:1-36.
2. Singh GJ, Adams WP, Lesko LJ, Shah VP, Molzon JA, Williams RL, et al. Development of in vivo bioequivalence methodology for dermatologic corticosteroids based on pharmacodynamic modeling. Clin Pharmacol Ther 1999;66(4):346-57.

NONMEM Estimates
POP T50 is "ED_{50}"

Model	POP E0	POP EMAX	POP T50	PPV E0	PPV EMAX	PPV T50	RUV SD	R12
exp_E0	-3.18	-45.1	2.74	0.00015	0.20	1.44	14.6	.
exp_R_noE0	.	-42.4	1.90	.	0.23	1.19	14.6	-0.392
exp_noE0	.	-46.3	2.17	.	0.20	1.32	14.6	.
emax_E0	-2.62	-54.3	3.73	2.7E-05	0.21	1.52	14.8	.
emax_R_noE0	.	-61.2	3.52	.	0.21	1.57	14.8	0.409
emax_noE0	.	-55.3	2.99	.	0.20	1.42	14.9	.
exp_E0_FO	-0.104	-31.7	0.703	1.57	0.54	0.85	14.6	.
exp_noE0_FO	.	-31.8	0.702	.	0.54	0.85	14.6	.
emax_E0_FO	-0.018	-39.7	1.13	2.98	0.50	1.02	15.0	.
emax_noE0_FO	.	-39.7	1.13	.	0.50	1.02	15.0	.

PPharm (Emax noE0) "ED50" is 1.89 h

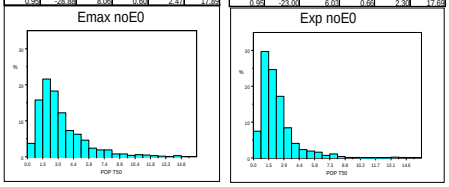
Visual Predictive Check



T50 Imprecision
1000 Bootstraps

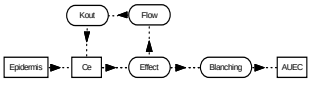
	POP_EMAX	POP_T50	PPV_EMAX	PPV_T50	RUV_SD
median	-52.00	2.54	0.19	1.31	14.66
average	-53.37	7.80	0.18	1.40	14.64
stdev	14.21	101.88	0.22	1.13	1.99
0.05	-79.90	0.88	0.00	0.0002	11.40
0.95	-28.88	8.06	0.60	2.47	17.88

	POP_EMAX	POP_T50	PPV_EMAX	PPV_T50	RUV_SD
median	-43.80	1.73	0.18	1.21	14.42
average	4.64E+09	7.47E+13	22400.23	46001.36	14.43
stdev	1.47E+07	2.36E+15	7.08E+05	1.45E+06	2.10
0.05	-65.43	0.66	0.00	0.0004	11.14
0.95	-23.00	6.03	0.60	2.30	17.69



Simulation Evaluation of AUEC

Steroid Blanching Model



Skin application assumed to give constant rate input to epidermis
Ce decreases flow which affects clearance from effect site via Emax model
Blanching is proportional to effect

Steroid Blanching Equations

$$\frac{dEpidermis}{dt} = Extent \cdot Rate - \frac{\ln(2)}{Tabs} \cdot Epidermis$$

$$\frac{dCe}{dt} = \frac{\ln(2)}{Tabs} \cdot Epidermis \cdot \frac{Flow \cdot Effect}{Ve} \cdot Ce$$

$$Effect = 1 - \frac{Emax \cdot Ce}{Ce + EC50}$$

$$Blanching = E0 \cdot Effect$$

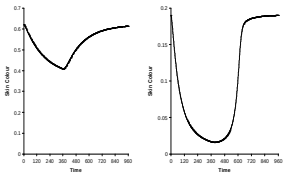
$$\frac{dAUEC_{Tapp-t}}{dt} = \text{if } t > Tapp \text{ then } Blanching - E0$$

Steroid Blanching Parameters

Parameter	Low Effect 33% Emax	High Effect 90% Emax
Extent	1	1
Tabs	120	60
Rate	0.2	0.65
$Flow_0$	1	1
Ve	10	10
Emax	1	1
EC50	5	5
E0*	0.62	0.19

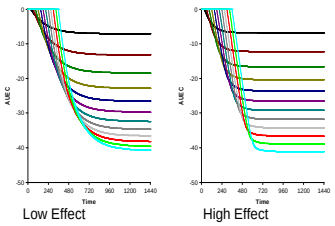
* = scaled to produce identical $AUEC_{Tapp-1440}$ with Tapp=360

Blanching Effect



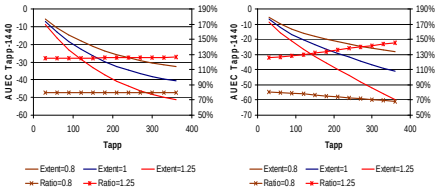
Low Effect High Effect

AUEC Time Course



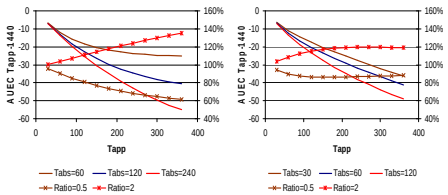
Low Effect High Effect

Extent of Absorption



Low Effect High Effect

Rate of Absorption



Low Effect High Effect

Conclusions

AUEC maximum ("Emax") is most sensitive to differences in
- Extent of absorption
- Rate of absorption

- "ED_{50}" is poorly estimated and the point estimate is dependent on the estimation procedure
- A simulation investigation using plausible pharmacological models for steroid blanching provides no support for the "ED_{50}" design point for the pivotal study bioequivalence analysis
- The FDA Topical Steroid guidance should be revised