ANDA Challenges Related to Vasoconstrictor Studies

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Outline

1. Background of Vasoconstrictor Studies
2. Challenges with ED50 Determination and Nonlinear Emax Modeling
3. Impact of Incorrect ED50 Selection on Detector Sample Size
4. Other Challenges and Deficiencies with Vasoconstrictor Studies
5. Challenge Questions and Summary

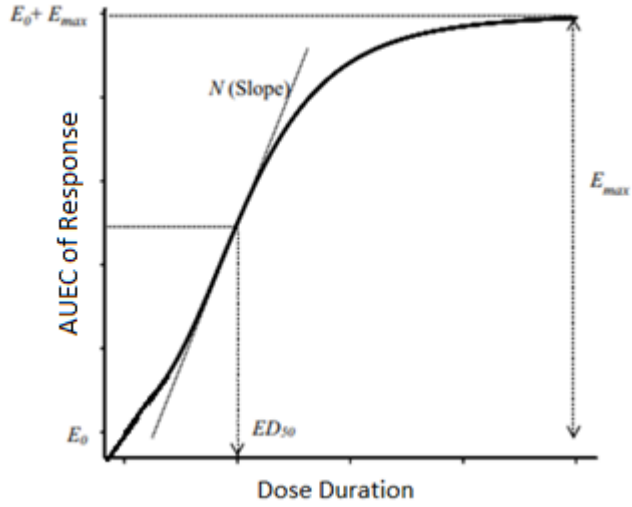
Vasoconstrictor Studies

- FDA draft guidance, Guidance for Industry: Topical Dermatologic Corticosteroids: In Vivo Bioequivalence (2022), recommends conducting a pilot dose duration-response study and a pivotal in vivo vasoconstrictor assay (VCA) bioequivalence (BE) study for topical dermatologic corticosteroids.
- The pilot study establishes the dose duration-response relationship using the Emax model.
- The pivotal study is conducted at three durations based on the ED50 determined in the pilot study to assess BE between test product and reference standard.

ED_{50} Determination via Emax Model

- The Emax model for VCA study describes the measure of effect (*E*) in terms of a baseline effect (E_0=0) at the corresponding dose duration (*D*) in terms of a maximal effect (*Emax*) and a dose duration at which the effect is half-maximal (ED_{50})

$$E = \frac{E_{max} \times D}{ED_{50} + D}$$



- A nonlinear dose response relationship

Response: the pharmacodynamic skin blanching (vasoconstriction) via assessment of baseline skin and skin blanching

AUEC of Response: e.g., $AUEC_{0.5\text{-}24}$ (pre-dose, 0.5, 2, 4, 6, 8, 10, 12, 20, 24 hours)

Dose duration: time periods for staggered application with synchronized removal, e.g., 15, 30, 45 minutes, 1, 2, 3, 4, 6, 8 hours

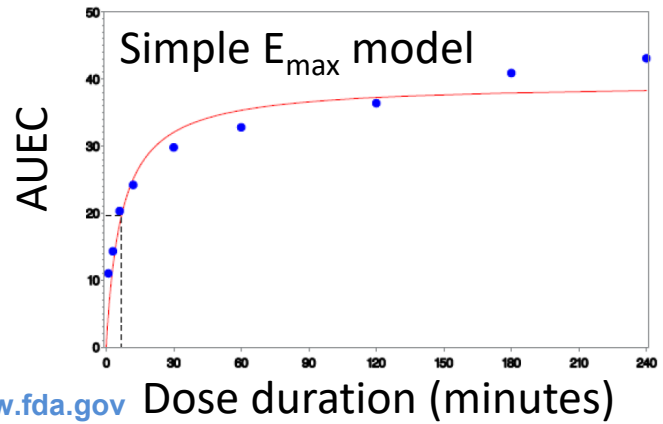
Data: reference standard VCA studies

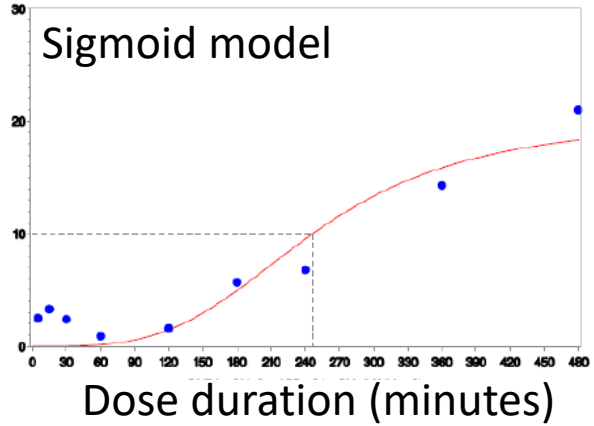
Rationale of ED_{50} Determination

- **Aims**:
  - The responses obtained in the study are situated in the sensitive (steep) region of the dose duration-response curve, allowing for effective discrimination between the test product and reference standard.
  - In the pivotal BE study, detector identification to be included in BE analysis is defined as an AUEC of D2/D1 > 1.25 for the simple Emax model .
- **Methods for Emax model**:

1. Model dependent factor
2. Data dependent factor

- **Results**:
  - Optimal ED_{50} is a crucial parameter for effectively detecting formulation differences.





Why are pilot studies necessary for the known RS products?

ED_{50} Estimation from ANDA Submissions

Multiple submissions for the same drug product, particularly Corticosteroid 4, revealed significant variability in reported ED_{50} values, with differences exceeding 4-fold between the lowest and highest submissions.

Product (Same RLD with different ANDAs)	**ED50 Estimation Range (min) from ANDA Submissions**	**Pivotal study % of detectors**
Corticosteroid 1 (2 ANDAs)	6.11^{1} – 23.00^{2}	57^{1}-73^{2}%
Corticosteroid 2 (2 ANDAs)	400.00^{1} – 831.00^{2}	37^{2}-74^{1}%
Corticosteroid 3	11.00 – 55.81	53-71%
Corticosteroid 4	30.60 – 146.77	30-79%

Multiple reasons: data quality, model estimation. [1, 2]: indicating the same ANDA.

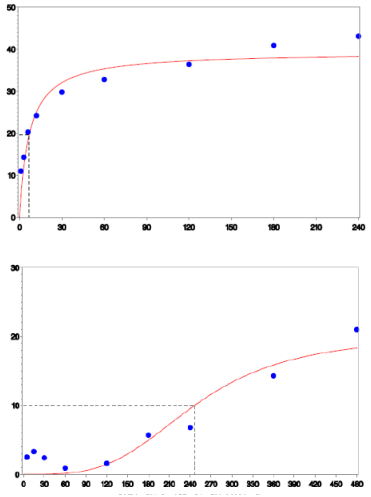
Therefore, conducting a pilot study for accurate ED_{50} determination becomes essential, and employing appropriate modeling practices can lead to the most optimal solution for ED_{50} selection.

Challenges with ED50 Determination and Nonlinear Emax Modeling

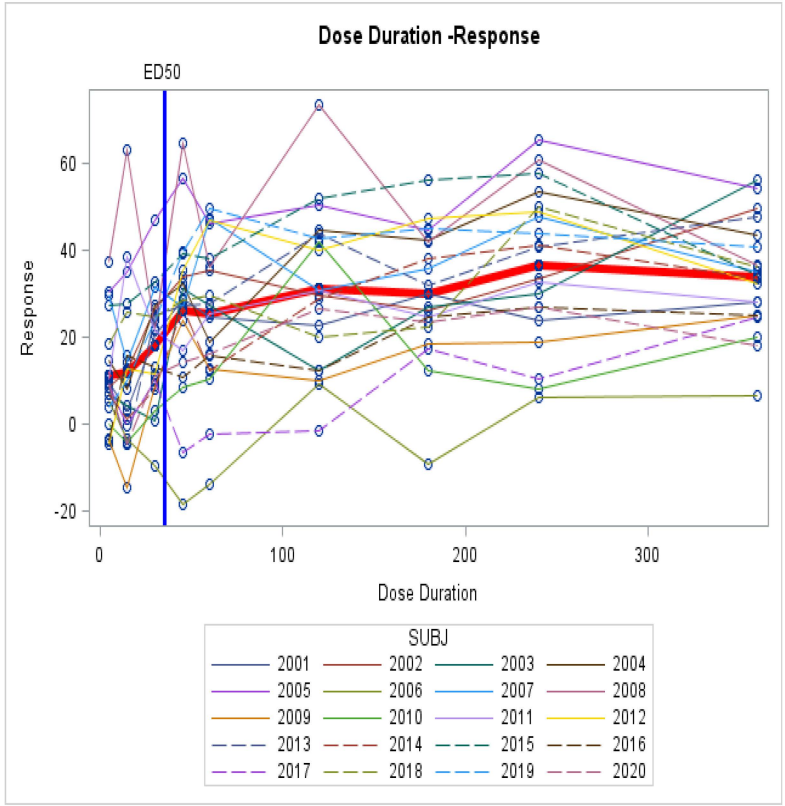
- Different software programs yield varying parameter estimations using different population modeling and analysis methodologies.
- Incorrect estimation of ED50 can result in decreased detector rates in the pivotal study, potentially leading to a smaller sample size for determining bioequivalence.
- To overcome software limitations, it is essential to undertake focused model optimization and establish standardized procedures.

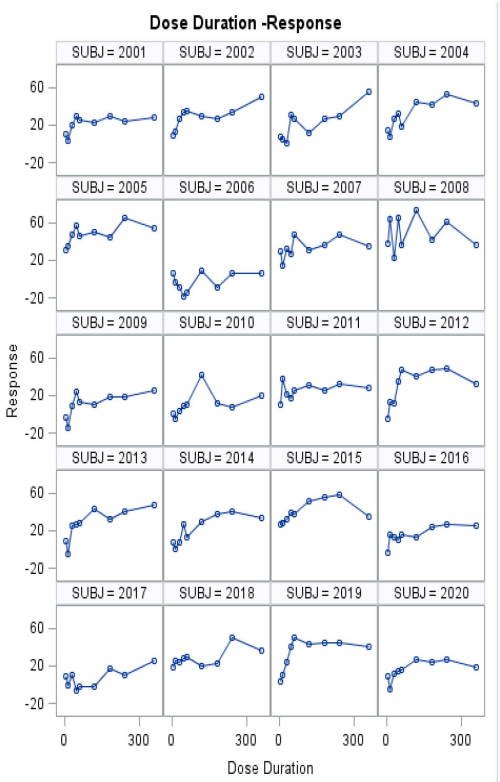
Impact of Incorrect ED_{50} Selection on Detector Subjects

- Importance of Accurate ED_{50}:
  - Avoids ED_{50} being too high or too low, ensuring accurate sensitivity in dose-response relationship.
- Impact of ED_{50} on Highly Potent Corticosteroids:
  - Reduced vasoconstrictor response as strength increases, resulting in a flattened response curve at higher concentrations.
  - High ED_{50} leads to fewer subjects meeting the dose duration-response criterion (AUEC of D2/D1 ratio >= 1.25).
- Impact of ED_{50} on Low Potency Corticosteroids:
  - Challenges in eliciting vasoconstrictor response despite increased dose duration.
  - Low ED_{50} leads to higher uncertainty/variability and requires more subjects for reliable results.



ED_{50} Optimization – Exploratory Data Analysis





Naive pooled method: pooled all the individual data together

NLME method: inter-individual variability, less bias to aberrant observations

Scientific & Regulatory Challenges – Divergent ED_{50} Outcomes Across Software Platforms

- Various implementations of nonlinear mixed effects (NLME) yield divergent outcomes across software platforms including NONMEM®, Phoenix NLME®, SAS®, Monolix, P-PHARM®, and others.
  - *E*

Software	Estimation algorithms	Example dataset #1		Example dataset #2	
		E_{max}	ED_{50} (min)	E_{max}	ED_{50} (min)
P-PHARM®	EM	11.35	89.91	11.16	16.56
SAS®	AGQ	11.16	82.25	18	148
Monolix®	SAEM	11.4	92.4	23.5	276
NONMEM®	FOCE+I	11.42	95.86	23.79	390.2
Phoenix®	FOCE-ELS	11.02	87.26	11.99	98.91

FO- the First Order method; FOCE+I - the First Order Conditional Estimation with Interaction; SAEM- Stochastic Approximation Expectation Maximization; AGQ - adaptive Gaussian quadrature, ELS – Extended least square.

Estimation Model and Algorithms Difference

Modeling Methods		Software	
		NONMEM	SAS
Model Parameter Normality Assumptions on Emax and ED50	Normal	✓	✓
	Log-normal	✓	✓
Residual Error Model	Additive	✓	✓
	Log-normal	✓	
Estimation Algorithms	FO	✓	✓
	FOCE+I	✓	
	SAEM	✓	
	IMP	✓	
	AGQ		✓

FO - the First Order method; FOCE+I- the First Order Conditional Estimation with Interaction; SAEM - Stochastic Approximation Expectation Maximization; IMP- Importance Sampling; AGQ- Adaptive Gauss-Hermite Quadrature

Scientific & Regulatory challenges - ED_{50} Determination

- ED_{50} Results are different even from the same software

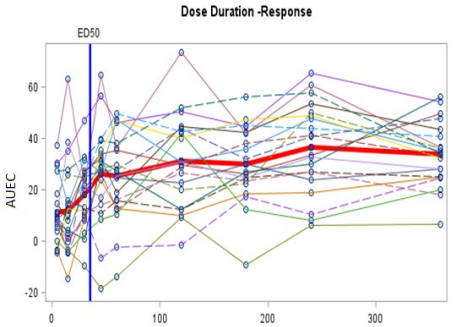
A NONMEM example

Model number	E_{max} random model	ED_{50} Random model	Error model	Estimation Method	AIC/BIC	E_{max}	ED_{50}
1	normal	log	additive	FO	1055	36	18.9
2	normal	log	additive	FOCE+I	1047	71.7	35.9
3	normal	normal	additive	FOCE+I	1159	27.5	9.6
4	log	normal	additive	FOCE+I	1166	33.3	24.7
5	normal	log	log	FOCE+I	1160	27.5	9.05
6	normal	log	additive	FOCE+I	1047	41.7	35.9
7	log	log	additive	SAEM	1046	42.8	35.8

FO - the First Order method; FOCE+I- the First Order Conditional Estimation with Interaction; SAEM - Stochastic Approximation Expectation Maximization; AIC - Akaike information criterion; BIC: Bayesian information criterion

ED_{50} Optimization – Example 1

Study No.	Software	Model No.	Normality Assumption		Error Model	Estimation Algorithms	AIC*	Estimation Results	
			E_{max}	ED_{50} (min)				E_{max}	ED_{50}
Example dataset # 3	NONMEM	1	Normal	Log-normal	Additive	FO	1065	36	18.9
		2	Normal	Log-normal	Additive	FOCE+I	1057	41.7	35.9
		3	Normal	Normal	Additive	FOCE+I	1169	27.5	9.6
		4	Log-normal	Normal	Additive	FOCE+I	1176	33.3	24.7
		5	Normal	Log-normal	Log-normal	FOCE+I	1170	27.5	9.05
		6	Log-normal	Log-normal	Additive	SAEM	1056	42.8	35.8
	SAS	1	Normal	Normal	Additive	FO	1388	36	15
		2	Normal	Log-normal	Additive	FO	1388	36	15
		3	Log-normal	Log-normal	Additive	FO	1388	36	15
		4	Normal	Normal	Additive	AGQ	2355	62	239
		5	Normal	Log-normal	Additive	AGQ	Fail		
		6	Log-normal	Log-normal	Additive	AGQ	1408	37	236



The optimal result is determined by the lowest Akaike information criterion (AIC) value.

The SAS algorithm's performance is subpar as it fails to show changes in the AIC value with different normality assumptions.

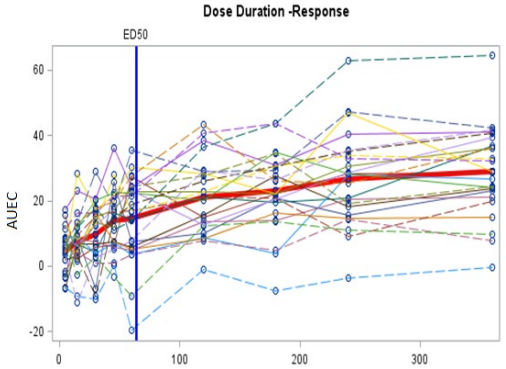
ED_{50} Optimization – Example 2

Study No.	Software	Model No.	Normality Assumption		Error Model	Estimation Algorithms	AIC*	Estimation Results	
			E_{max}	ED_{50} (min)				E_{max}	ED_{50}
Example dataset # 4	NONMEM	1	Normal	Log-normal	Additive	FO	1112	33	60.9
		2	Normal	Log-normal	Additive	FOCE+I	1117	33.8	63.8
		3	Log-normal	Log-normal	Additive	FOCE+I	1169	36.1	89.6
		4	Normal	Log-normal	Log-normal	FOCE+I	Fail		
		5	Normal	Log-normal	Additive	FOCE+I	1117	33.8	63.8
		6	Log-normal	Log-normal	Additive	IMP	1115	35.3	64.8
		7	Normal	Log-normal	Additive	SAEM	1115	35.2	64.5
	SAS	1	Normal	Normal	Additive	FO	1509	33	62
		2	Normal	Log-normal	Additive	FO	1509	33	62
		3	Log-normal	Normal	Additive	FO	1509	33	62
		4	Log-normal	Log-normal	Additive	FO	1509	33	60
		5	Normal	Normal	Additive	AGQ	Failed		
		6	Normal	Log-normal	Additive	AGQ	Failed		
		7	Log-normal	Normal	Additive	AGQ	1515	31	82
		8	Log-normal	Log-normal	Additive	AGQ	1515	42	108

The optimal result is determined by the lowest AIC value.

Both SAS and NONMEM yield similar results, with ED_{50}≈60.

However, the SAS algorithm is not sensitive to parameter normality assumptions.



Recommendation for Model Selection and Building

- When selecting and building models, consider using a software platform that supports the following modeling procedures:
  1. Clearly defined pre-determined model selection process
  2. Emax model selection
  3. Comparison of estimation methods
  4. Selection of model parameters
  5. Choosing error models
  6. Procedure for initial estimates
  7. Appropriate model diagnostics.

Other Challenges and Deficiencies with VCA Studies

- Challenges with Vasoconstrictor Response:
  - Weak vasoconstrictor responses for low potency drugs hinder establishing a dose-response relationship.
  - Truncated vasoconstrictor responses and incomplete plateau levels affect accurate ED_{50} estimation.
- Deficiency in Pilot Study:
  - Agency's ED_{50} estimation (e.g., ~80 minutes) was 5 times greater than the applicant's estimation (~16 minutes).
  - Applicant's selected ED_{50} (e.g., ~16 minutes) falls in an insensitive region (under 20% of Emax).
  - Agency requests reanalysis with good sensitivity (e.g., D1 and D2 responses in 33% to 67% of Emax).
- Deficiency in Pivotal Study:
  - Short dose duration of D1 (e.g., 8 minutes) from estimated ED_{50} shows high variability and low response.
  - Observations suggest unreliable selection of evaluable subjects.

Summary

- Background and Challenges: Vasoconstrictor studies in corticosteroids development face challenges in determining ED_{50} due to varied parameter estimations and biased values.
- Impact of Incorrect ED_{50} Selection: High ED_{50} leads to fewer subjects meeting dose-duration criteria, while low ED_{50} requires more subjects for reliable results.
- Estimation Model and Vasoconstrictor Response Challenges: Differences in model estimation and weak responses in low-potency drugs affect ED_{50} accuracy.
- Deficiencies in Studies: Significant differences in ED_{50} estimations between agency and applicant, requiring reanalysis and addressing unreliable subject selection.

Resources

- FDA's 1995 guidance: Topical Dermatologic Corticosteroids: in Vivo Bioequivalence (June 1995)
- FDA's 2022 Draft revision: Topical Dermatologic Corticosteroids: In Vivo Bioequivalence (October 2022)
- Guidances and references
  - Guidance for Industry: Population Pharmacokinetics Guidance for Industry, February 2022, Clinical Pharmacology (CP)
  - Guidance for Industry: Exposure-Response Relationships – Study Design, Data Analysis, and Regulatory Applications, April 2003, CP
  - Deniz Ozdin, Naveen Sharma, Jorge Lujan-Zilbermann, Philippe Colucci, Isadore Kanfer, Murray P Ducharme, Revisiting FDA's 1995 Guidance on Bioequivalence Establishment of Topical Dermatologic Corticosteroids: New Research Based Recommendations, J Pharm Pharm Sci. 2018;21(1):413-428. doi: 10.18433/jpps30021.
  - R N Upton and D R Mould. Basic Concepts in Population Modeling, Simulation, and Model-Based Drug Development: Part 3—Introduction to Pharmacodynamic Modeling Methods. CPT Pharmacometrics Syst Pharmacol. 2014 Jan; 3(1): e88. Published online 2014 Jan 2. doi: 10.1038/psp.2013.71

Closing Thought

Choose an appropriate software platform, adhere to the population modeling process, and carefully determine ED50 to ensure optimal sensitivity in the dose-response relationship.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