Assessing Bioequivalence of Locally-Acting Generic Products; Statistical Controversies and Arising Issues

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Disclaimer:

1. This presentation reflects the views of the presenter and should not be construed to represent the United States Food and Drug Administration's views or policies.
2. All data sets shown in this presentation have been de-identified

Background/Motivation

- An appropriate statistical methodology is needed to establish bioequivalence by any in vitro or in vivo study approach
- For dermal pharmacokinetic study approaches there are several considerations:
  - Replicate Study Design
  - Key Parameters
  - Variability (and its sources)
  - Bioequivalence Limits
- Developed a statistical approach using results from IVPT studies as a model dermal pharmacokinetic approach

Aim

In recent years, we have realized the need of developing a statistical approach that is well-suited to the special nature of the data, i.e.

- The inherently replicate study design
- The presence of variability

Aim

Such a statistical approach should be able to:

- Treat the dermal-PK data as actual PK data
- Provide the distinct advantage of powering the study

Questions / Concerns

- What should be the optimal choice of the BE limits, such that the test is sensitive?
- What should be the optimal choice of the BE limits, such that the test is not *too* sensitive (such that a product would fail BE relative to itself)?

Study design

The response considered is the log-transformed

- ❑ Total penetration (AUC)
- ❑ Maximum flux rate (Jmax)

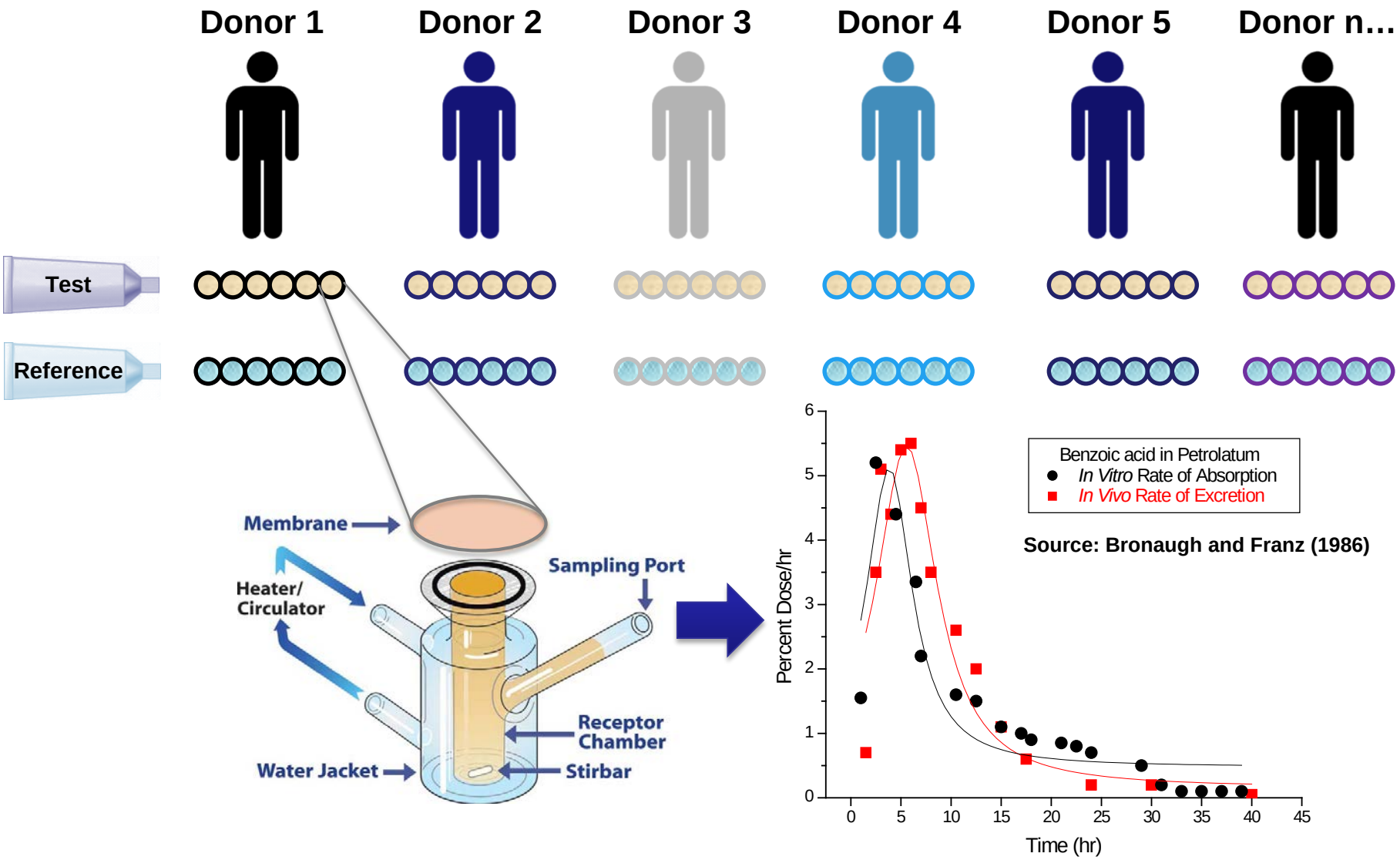
We consider a sample of

***n: donors*,**

r: replicate skin sections from each one of the n donors

2 treatment formulations: test (generic: T) and reference (R)

Study design



Study design

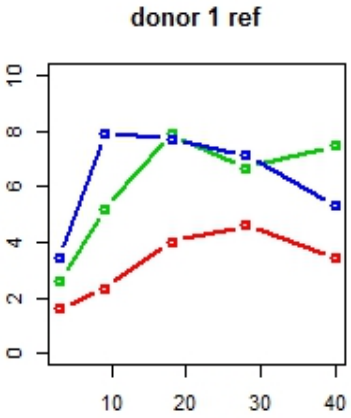
Test:

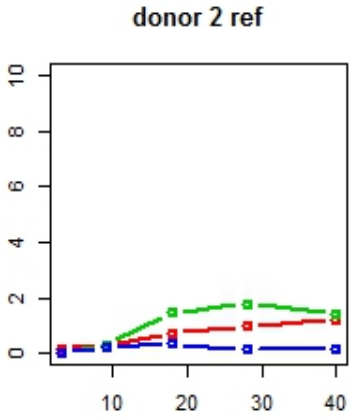
$$T_{11}, T_{12}, \ldots, T_{1r}$$
$$T_{21}, T_{22}, \ldots, T_{2r}$$
$$\vdots$$
$$T_{n1}, T_{n2}, \ldots, T_{nr}$$

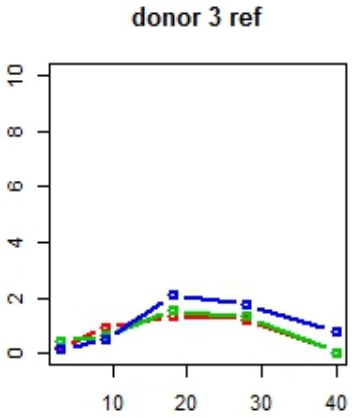
Reference:

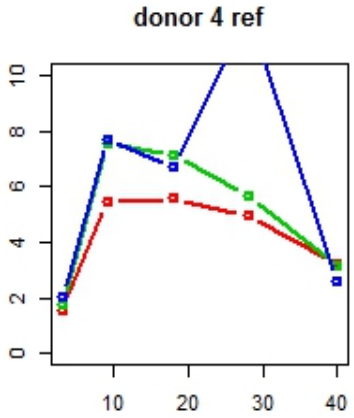
$$R_{11}, R_{12}, \ldots, R_{1r}$$
$$R_{21}, R_{22}, \ldots, R_{2r}$$
$$\vdots$$
$$R_{n1}, R_{n2}, \ldots, R_{nr}$$

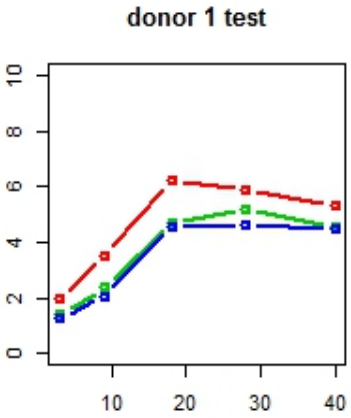
An example of flux curves

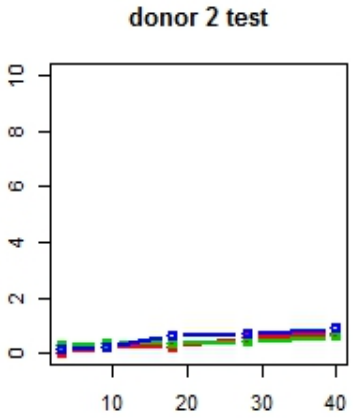


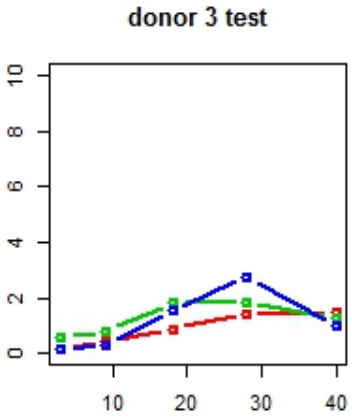


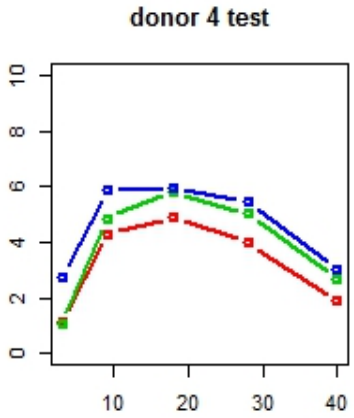












Novel statistical approach

- Based on the mixed scaled criterion used by CDER for Highly Variable Drugs (HVD)
- Has been adapted to dermal PK methods
- Can be adequately powered by 6-36 donors

Statistical analysis

For each donor, we calculate the term

$$I_j = \frac{1}{r}\sum_{i=1}^{r}(T_{ij} - R_{ij})$$

This leads to the derivation of the point estimate:

$$\bar{I}_{\cdot} = \frac{1}{n}\sum_{j=1}^{n} I_j$$

And the estimate of the inter-donor variability:

$$S_I^2 = \frac{1}{(n-1)}\sum_{j=1}^{n}(I_j - \bar{I}_{\cdot})^2$$

Assessing BE

Mixed CDER criterion uses the intra (within) – reference standard deviation (σ_{WR}) as a cutoff point.

For $\sigma_{WR} \leq 0.294$, the test and reference formulations are declared bioequivalent if the (1-α) *100% confidence interval:

$$\bar{I}_{\cdot} \pm t_{(n-1),\alpha/2} * \sqrt{\frac{S_I^2}{n}}$$

is contained within the limits $[\frac{1}{m}, m]$.

Assessing BE

The scaled BE methodology used in the case that $\sigma_{WR} > 0.294$, adopts the FDA/CDER approach for the analysis of highly variable drugs, modified for the particular design. The hypotheses to be tested are:

$$H_0: \frac{(\mu_T - \mu_R)^2}{\sigma_{WR}^2} > \theta$$

$$H_a: \frac{(\mu_T - \mu_R)^2}{\sigma_{WR}^2} \leq \theta$$

Where $\theta = \frac{(\ln(m))^2}{(0.25)^2}$

Assessing BE

- The strategy is to construct a (1-α) *100% confidence interval for the quantity $(\mu_T - \mu_R)^2 - \theta\ \sigma_{WR}^2$ and to observe its upper bound. If this is less than or equal to zero, H_0 will be rejected.
- Rejection of the null hypothesis, H_0, supports BE.
- This criterion is accompanied by a point estimate constraint according to which the geometric mean ratio (point estimate of the log-transformed response has to fall within the pre-specified limits: $[\frac{1}{m}, m]$.

Data sources

- Redacted data from research with commercial topical drug products (creams, ointments, gels) containing a variety of different drugs, including products nominally expected to be BE (i.e. generics vs. RLDs, and multiple lots of the same product)
- Data submitted to FDA in product applications (ANDA), for which there was a clinical and an IVPT study

Data sources

- Redacted data from research was used for model development. This part of the analysis was exploratory in nature and aimed in:
  - Understanding the nature and variability of the PK parameters
  - Determining the range of variability for donors, replicates and products
  - Exploring the model's sensitivity to outliers
- Data from ANDA applications were used in order to evaluate the model's performance

Data sources

The available sources of data:

- Gave us a good range of sources of real-world variability across a variety of drugs and products
- Allowed us to determine the parameters which are important markers for evaluating BE

Performance/Results

Example: Redacted data from research with commercial (nominally expected to be BE) topical drug products

RLD cream vs. Generic cream **(n=4, r=3)**

	Point Estimate GMR	**SWR**	**SABE [0.80, 1.25]**	**SABE [0.75, 1.33]**
Tpen (AUC)	0.9333	0.5358	-0.0368	-0.1433
Jmax (Cmax)	0.8531	0.5085	-0.0008	-0.0014

Performance/Results

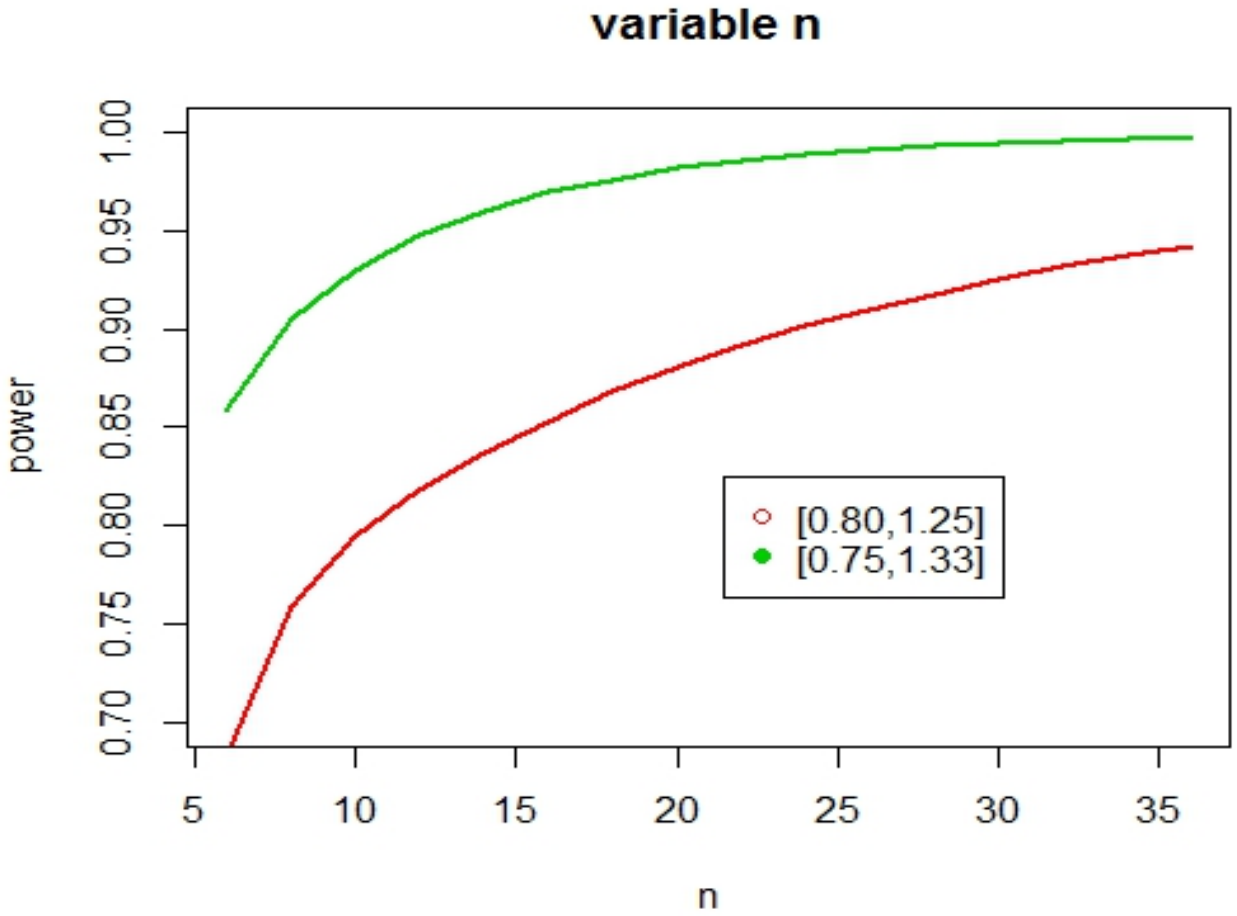
Example: Redacted data from research with commercial (nominally expected to be BE) topical drug products

Pairwise comparisons of 3 batches of RLD cream **(n=4, r=3)**

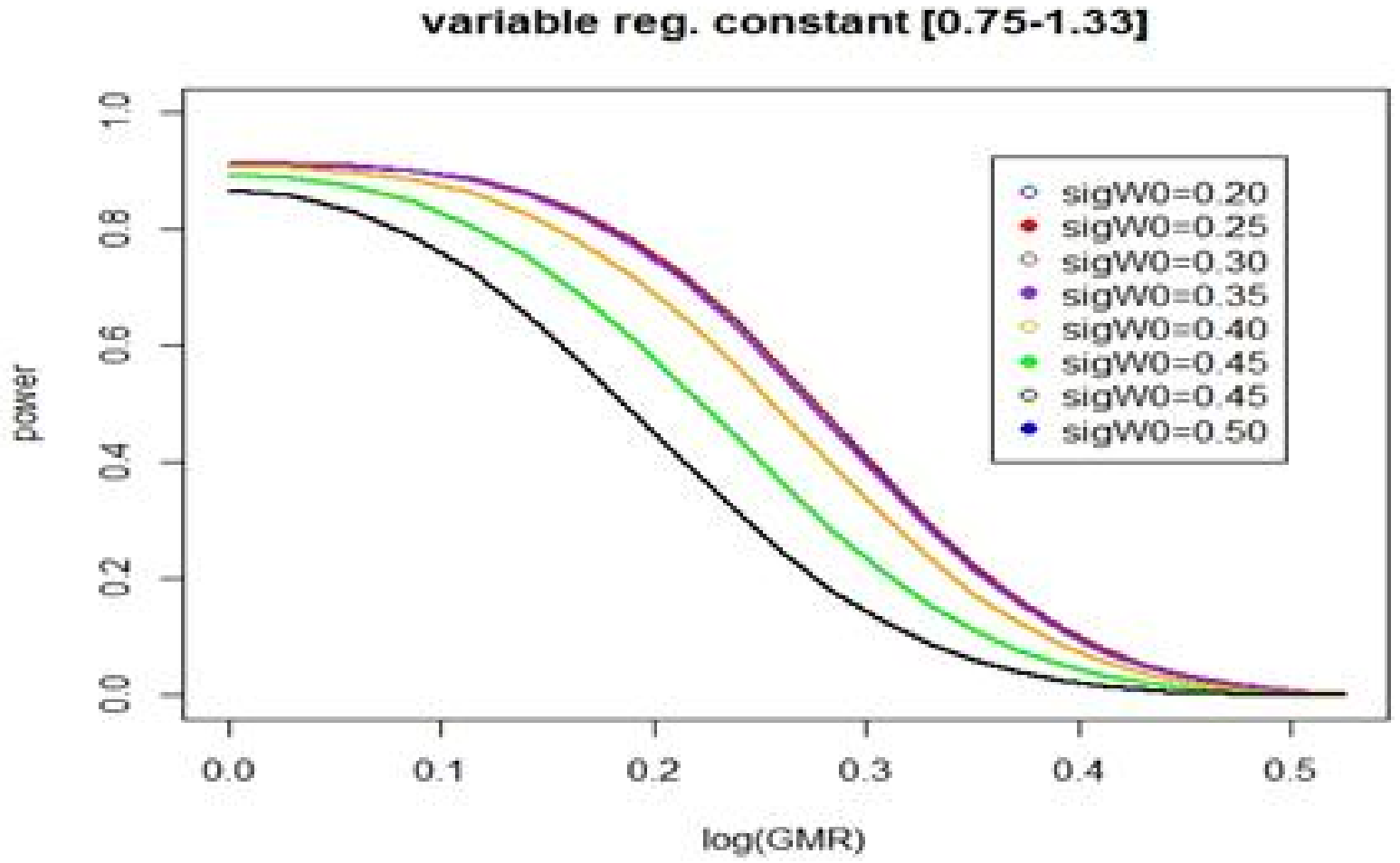
Batch pair		**Point Estimate GMR**	**SWR**	**SABE [0.80, 1.25]**	**SABE [0.75, 1.33]**
2 vs. 1	Tpen (AUC)	0.9822	0.5347	-0.0115	-0.1788
	Jmax (Cmax)	1.0078	0.5082	-0.0409	-0.1362
3 vs. 1	Tpen (AUC)	0.8347	0.5410	0.0065	-0.1003
	Jmax (Cmax)	0.9104	0.5072	0.0959	-0.0134
3 vs. 2	Tpen (AUC)	0.8483	0.3534	0.0607	0.0048
	Jmax (Cmax)	0.9025	0.3901	-0.0141	-0.0672

Power simulations (sample size)

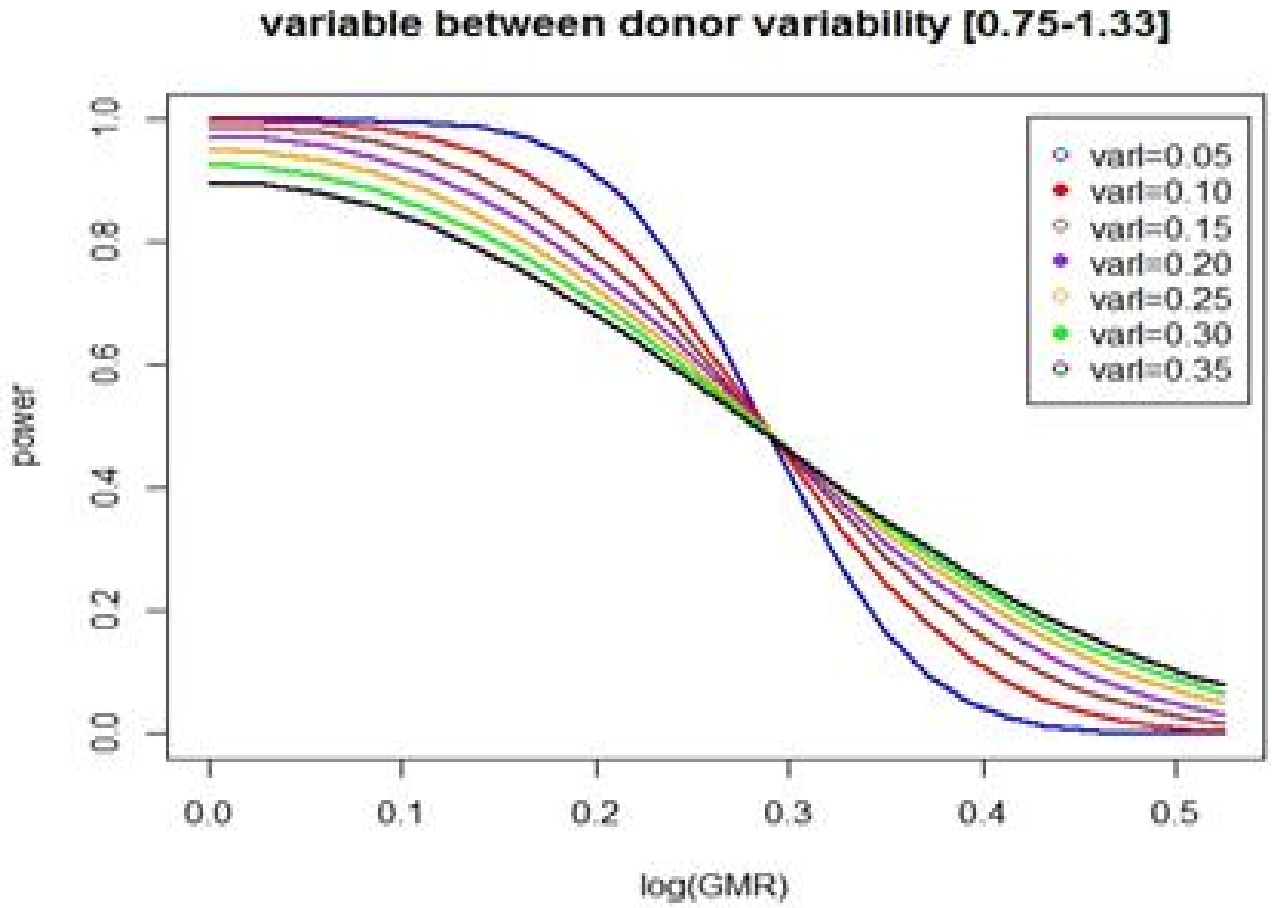
A question that arises once a procedure that fits the study design is developed , is what is a sufficient sample size so that such studies are adequately powered



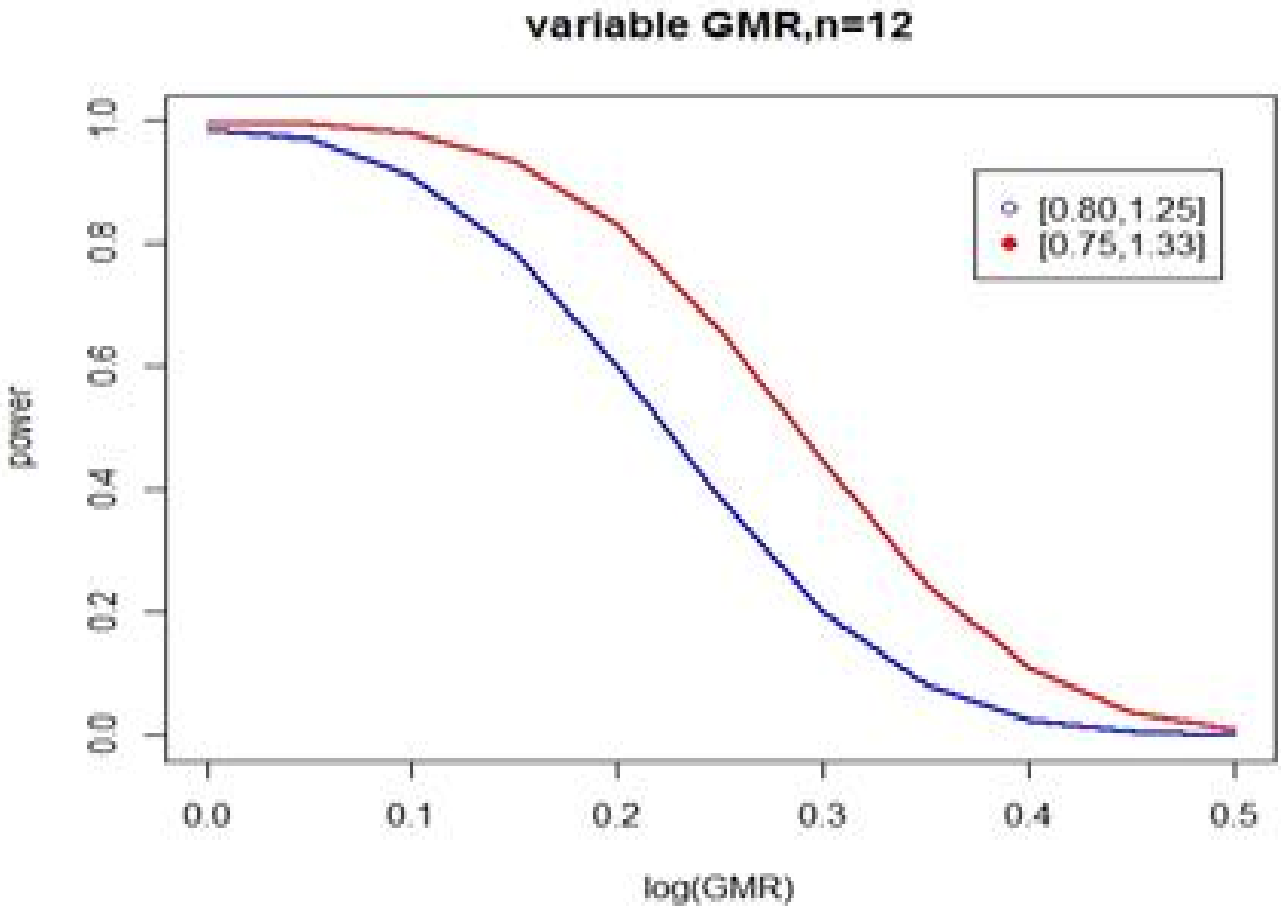
Power simulations



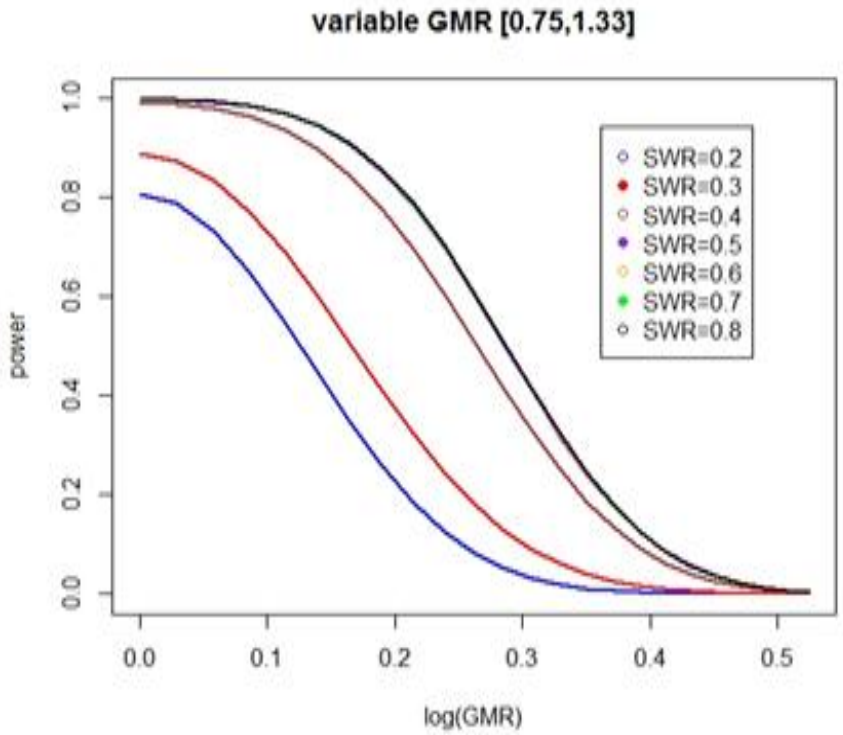
Power simulations

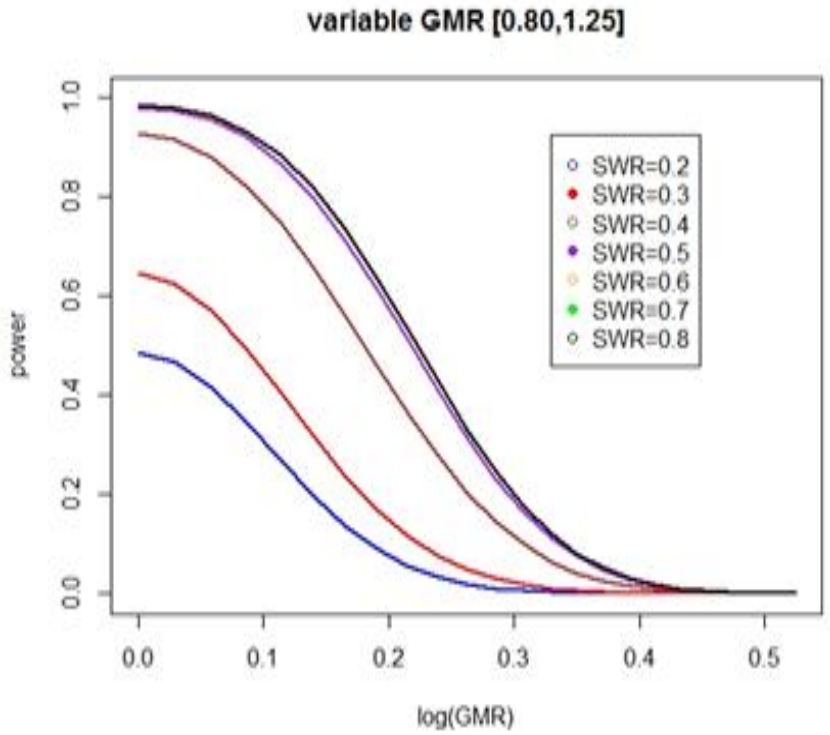


Power simulations



Power simulations





The size of the test

	[0.80, 1.25]	**[0.75, 1.33]**
ABE	0.050034	0.050256
Mixed SABE	0.029904	0.013240

Simulated values of α from 500,000 studies, n=12 donors, σ_{WR}=0.40 and σ_I=0.28.

Performance/Results

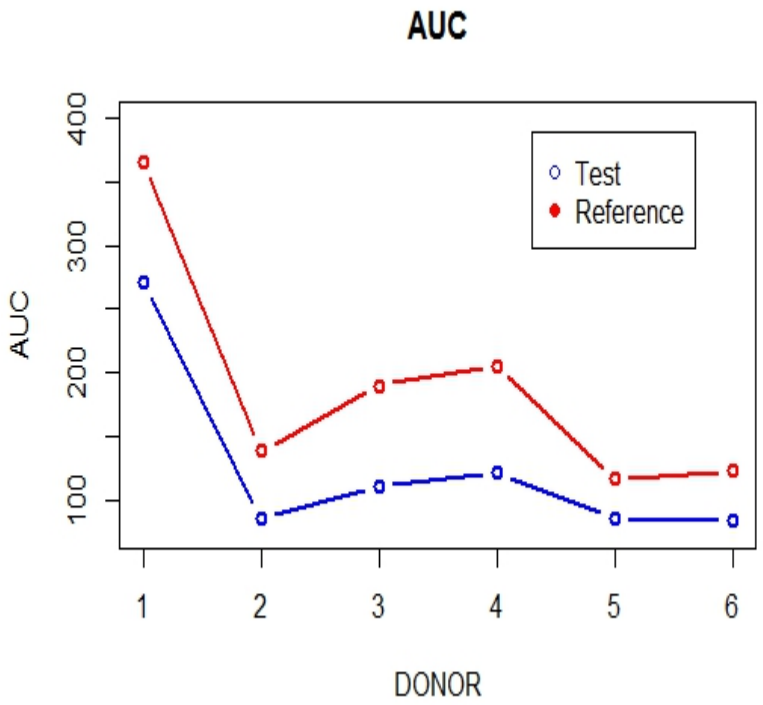
Example: Data from ANDA submissions
T vs. R **(n=6, r=4)**

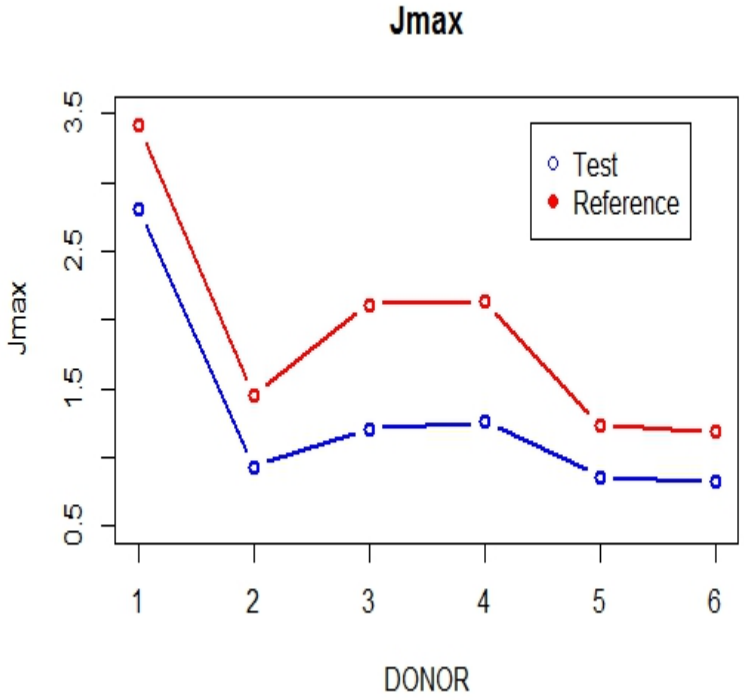
Positive control for BE

	Point Estimate GMR	**SWR**	**SABE [0.80, 1.25]**	**SABE [0.75, 1.33]**
Tpen (AUC)	1.2809	0.9668	-0.2749	-0.6715
Jmax (Cmax)	1.2149	1.1931	-0.6239	-1.1895

Performance/Results

Example: Redacted data from research
T vs. R **(n=6, r=5)**





Performance/Results

Example: Redacted data from research
T vs. R **(n=6, r=5)**

Negative control for BE

	Point Estimate GMR	**SWR**	**SABE [0.80, 1.25]**	**SABE [0.75, 1.33]**
Tpen (AUC)	0.6470	0.2667	0.5952	0.7033
Jmax (Cmax)	0.6537	0.2227	0.5819	0.7346

Conclusions from data analysis

- The results obtained with IVPT and the suggested statistical analysis were in agreement with the original BE assessments for these marketed products. This speaks in favor of the ***validity of this statistical model for assessing BE.***
- The test is sufficiently ***sensitive to discriminate bio-inequivalence***, even under the presence of significant variability
- The test has been used for comparing multiple batches of the same reference product and successfully captured the similarity of these products in terms of BE. The outcomes advocate the ***model's sensitivity to meaningful differences and its resistance to the hazard of rejecting good products***

Concluding remarks

The suggested statistical methodology:

- ❑ Uses traditional PK-parameters
- ❑ Uses the well-accepted methodology of SABE, specifically adapted for the replicate study design
- ❑ Has been developed by looking at a large set of IVPT data

Concluding remarks

In particular, by analyzing a large number of IVPT data sets, we have been able to:

- Confirm that the particular PK-parameters are well-suited to many different products and different flux curves
- Confirm a correct outcome for both BE and non-BE products
- Get an indication of BE limits that may be suitable for this analysis
- Get an idea of the relative size (n), that would be necessary to adequately power such studies

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