Statistical Inputs in Deciding Go/No Go for Generics and Biosimilars in Early Development

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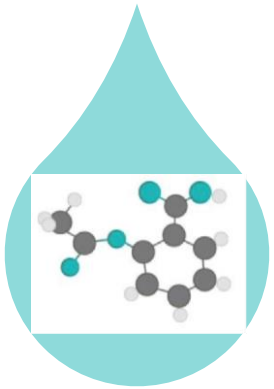
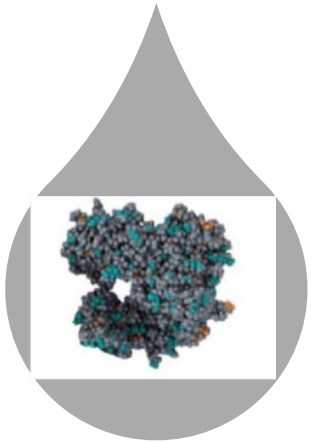
Motivation

	Small Molecule	Generics	Biologics	Biosimilars
Dev Cost (USD)	1 Billion	2 to 10 Million	1 Billion	50-300 Million
Time to Market (Yrs)	8-10	2-3	8-10	7-8
Clinical Studies	Phase I-III studies	Bioequivalence In HV	Phase I-III studies	At least PK and immuno study
Prob of Success	10%	90%	10%	78%
Savings	80% to 90%		20% to 30%	

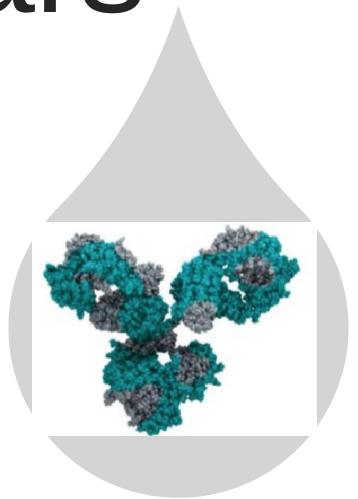
Generics and Biosimilars



Small Molecule
Low molecular weight.
Chemically synthesized.
Well-defined structure.



Biological Molecule
High molecular weight.
Derived from living organisms.
Large and complex structure



Monoclonal Antibody
High molecular weight.
Derived from living organisms.
More complex structure

Generics and Biosimilars

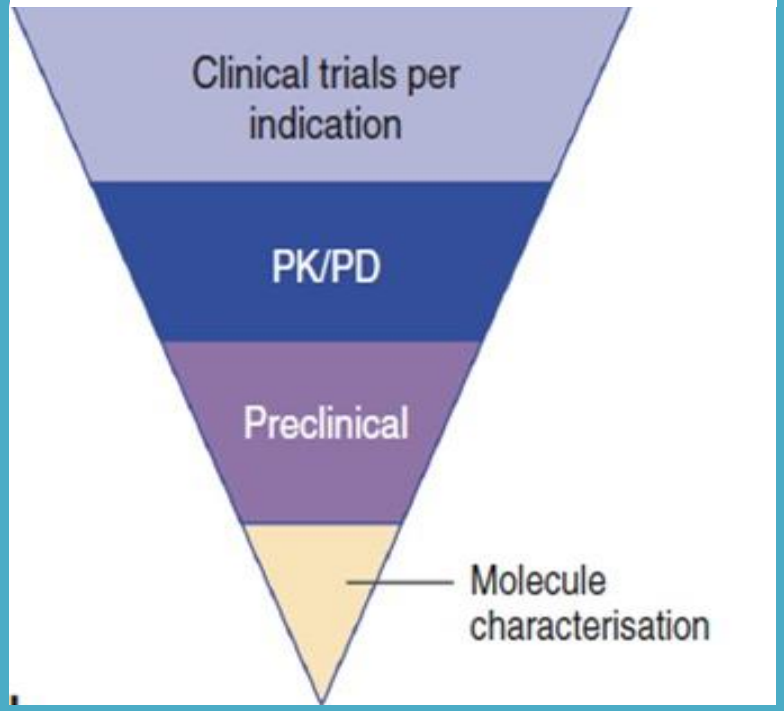
Generic Drug

same in dosage form, safety, strength, route of administration, quality, performance characteristics, and intended use.

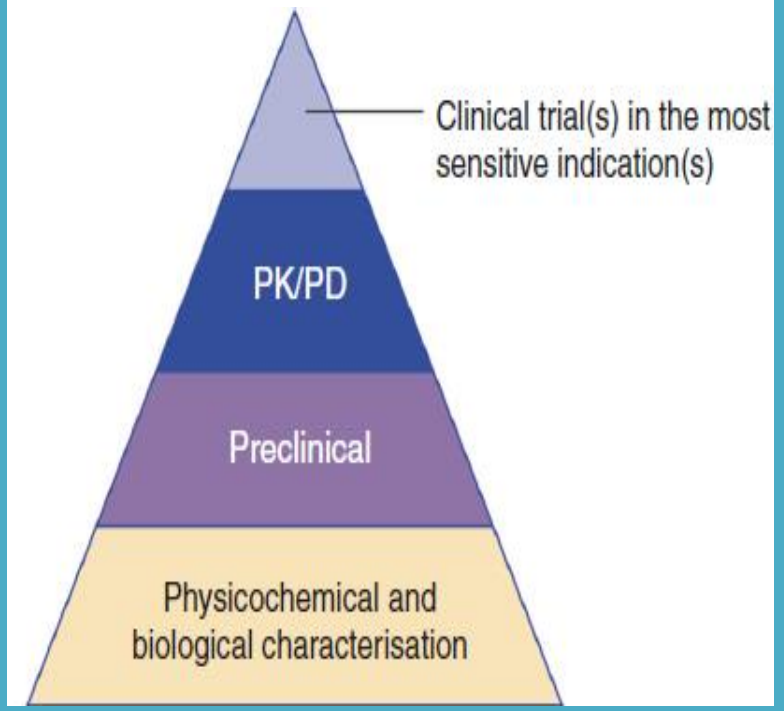
Biosimilar

biological product that is highly similar to and has no clinically meaningful differences from an existing approved reference product.

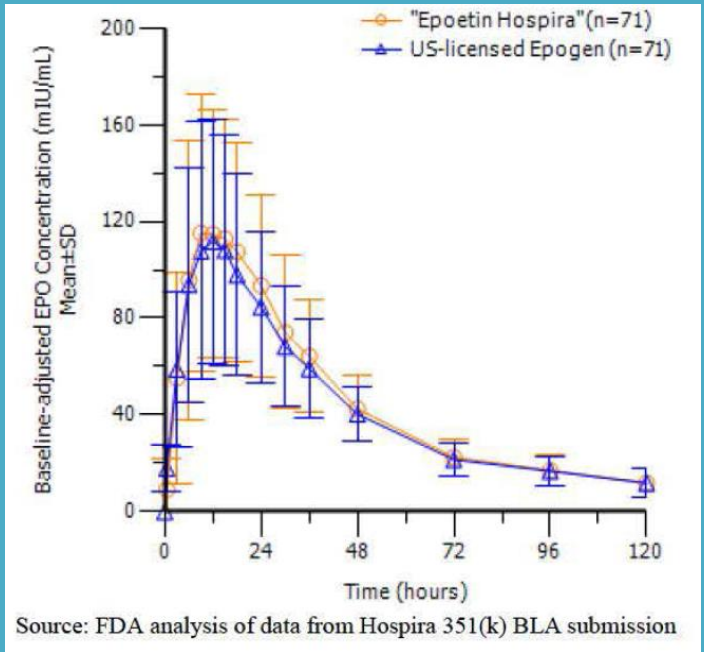
New Drug Development



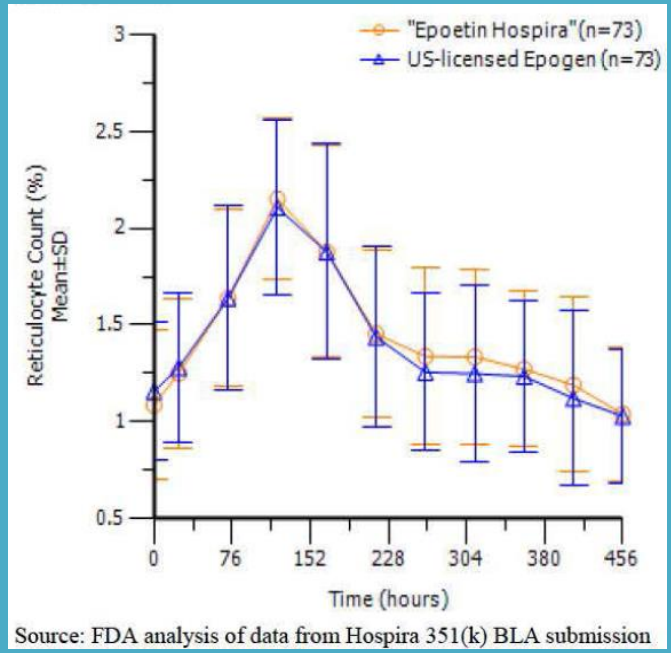
Generics/Biosimilars



Bioavailability and Bioequivalence



Source: FDA analysis of data from Hospira 351(k) BLA submission



Source: FDA analysis of data from Hospira 351(k) BLA submission

Pharmacokinetics (PK)

- ✓Movement of drugs in the body

Pharmacodynamics (PD)

- ✓Body's biological response to the drug

Bioavailability (BA)

- ✓Rate (CMAX) and Extent (AUC)

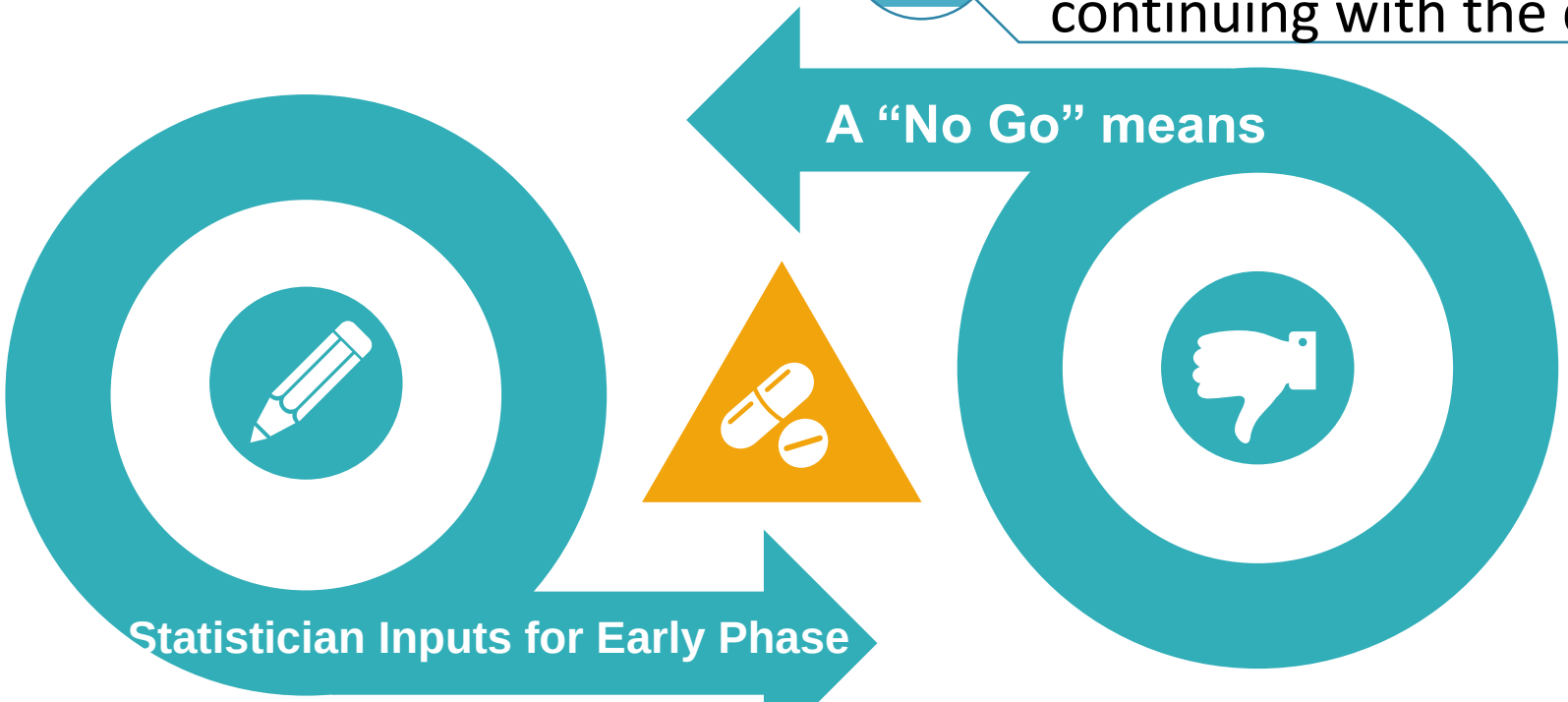
Bioequivalence (BE)

- ✓Absence of a significant difference in the bioavailability
- ✓Rely on a criterion (ex: CMAX, AUC), confidence interval (usually 90% CI) and a predetermined limit (80% - 125%)

Go / No Go Decision

there is a good chance that the drug may not work

the risk-benefit ratio for subjects/patients does not justify continuing with the development



Study Design

Sample Size

Challenges

No regulatory guidance and limited references on the originator drug

Designing for multiple markets/ countries

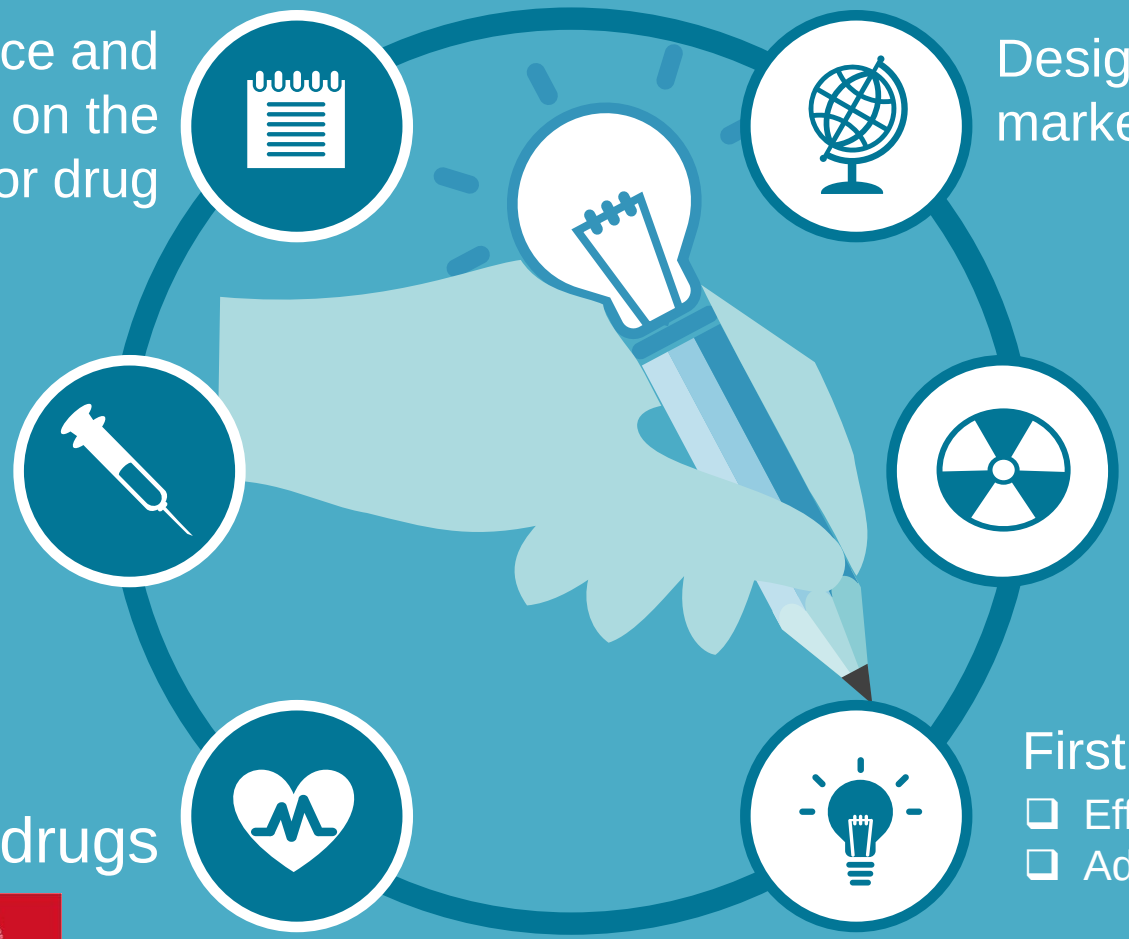
Drugs with long half-life

Drug toxicity

Highly variable drugs

First in Market Biosimilar

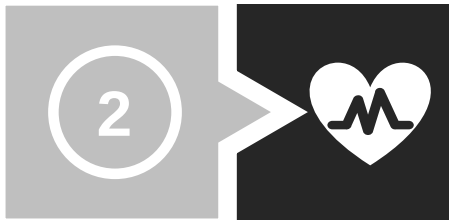
- ❑ Efficacy and safety studies
- ❑ Advisory committee



Statistical Tools and Techniques

Study Design

- BA/Pilot/Sequential Design
- Replicate Design (Full/Partial)



Highly Variable Drugs

- ABEL/SABE/Parameter specific limit
- Sample Size Inputs (Design, GMR, Variability)

Pooled Var and Upper Conf. Limit

- 80%-90% Power
- Pooling weighted Variance
- 75% upper CL of the CV

Prob of Success

- Prior Distribution to Hypothesis Parameter
- Get expected power based on the prior distribution

Example 1

Highly Variable Drug/Pooled Variability/Upper Confidence Limit

	PK Parameter	MSE	CVintra	N
Country 1	AUC0-t	3.07	35.0%	6
	Cmax	2.89	25.0%	6
Country 2	AUC0-t	3.03	33.0%	6
	Cmax	2.84	21.0%	6

Example 1

Highly Variable Drug/Pooled Variability/Upper Confidence Limit

Design	2-treatment, 3-Sequence, 3-period (RRT-RTR-TRR)
Power	≥ 90%
Alpha	5%
$CV_{Intra\text{-}subject}$	35%
Study treatment duration	1 Day
Geometric Mean Ratio (GMR), T/R	Within 10% of 1
Number of evaluable subjects	50
Drop-out rate	5%
Total Sample Size	57 (19 per sequence)

Example 2

Different Formulations

Official Title ICMJE	A Phase 1 Study Assessing The Pharmacodynamic And Pharmacokinetic Equivalence Of [redacted] With US-approved [redacted] (Registered) And EU-approved [redacted] (Registered) Administered As A Single Subcutaneous Dose To Healthy Volunteers
Brief Summary	This study is for healthy participants. This study tests single dose of the research drug [redacted] against two existing approved drugs United States - approved [redacted] and European Union-approved [redacted]
Detailed Description	There will be 25 healthy participants in each of the six sequence groups. A total of 150 participants will be studied in one site in Australia. In addition to the 150 participants included, alternate subjects will be asked to come to the site on the day prior to when dosing is scheduled to begin. There will be 3 treatment options with 3 study dosing periods (1, 2 and 3) and at least 56 days between each treatment. The subject once asked to take part in the study will be assigned by chance (randomized) to one of the sequence groups as mentioned above (1, 2, 3, 4, 5, or 6).
Study Type ICMJE	Interventional
Study Phase ICMJE	Phase 1
Study Design ICMJE	Allocation: Randomized Intervention Model: Crossover Assignment Masking: None (Open Label)
Condition ICMJE	Neutropenia
Intervention ICMJE	• Drug: [redacted] Other Name: [redacted] • Drug: US-approved [redacted] Other Name: [redacted] • Drug: EU-approved [redacted] Other Name: [redacted]

Example 3

Expected Power for NTID

Design	A single-dose, randomized, two-treatment, two-period crossover design
Endpoints	Bioequivalence of 4 Analytes
Results	1 Analyte did not meet Bioequivalence
Problem	New regulatory guidance with new design (a single-dose, four-way, fully replicated crossover design) with only 1 of the analytes needed
Statistics	Determine probability of Success using results from previous study

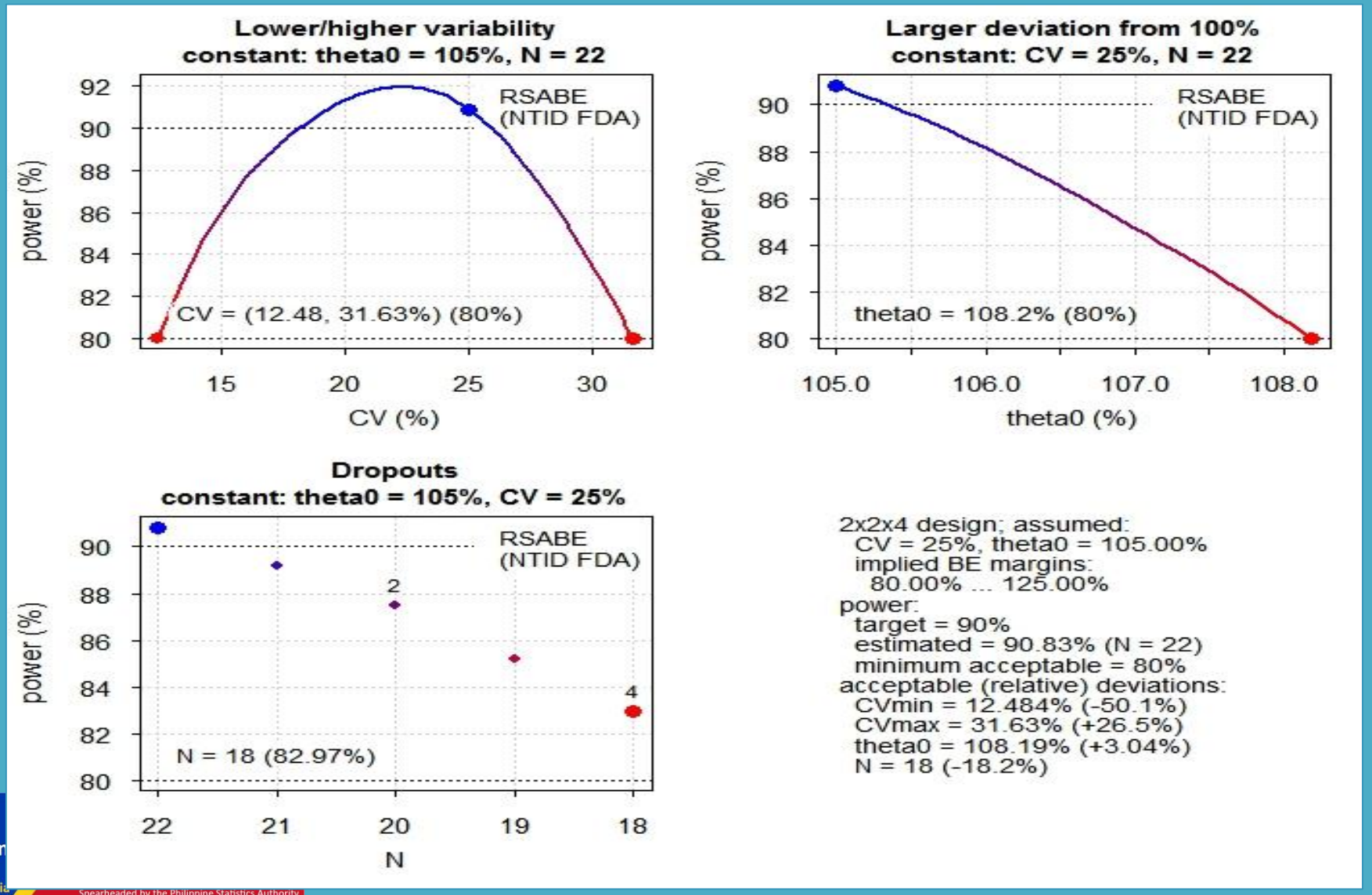
Example 3

Expected Power for NTID

N	GMR	CV	Power
22	92 to 108%	13 to 32%	≥ 80%
28	92 to 108%	10 to 36%	≥ 80%
36	92 to 108%	9 to 42%	≥ 80%

Example 3

Expected Power for NTID



Summary

Cost and Time to Market
High-level clinical plans to determine cost and time to market

01

Too conservative clinical plan
Higher cost; longer study length; higher risk

02

Too optimistic plan
Underpowered and potential study failure; increase cost; delay

03

04

Stats Input
Study Design; Sample Size

05

Drug Characteristics
Consider drug characteristics

06

Uncertainties
Adjust for uncertainties in the estimates


Thank you