

**STATISTICS,
OR HOW TO MEET FDA
REQUIREMENTS**

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Introduction

- In 1994, the Food and Drug Administration (FDA) released the Tentative Final Monograph (TFM) requiring the product's **average** reductions to meet the \log_{10} reduction requirements. Later, they changed this to the lower bounds of the 95% confidence intervals. Then they added the 70% responder rates.
- Both test and control products must meet 70% responder rates.
- This created a major obstacle. Now, the common control products cannot meet requirements. The industry has pushed back through the American Cleaning Institute.
- As a result, the FDA has presented more reasonable requirements:
 - Test Product is non-inferior to Control Product
 - Test Product is superior to Vehicle Product
- How can firms in the industry successfully meet FDA requirements?

Background

- The purpose of the original 1994 FDA TFM for healthcare antiseptic drug products was to provide instructions for testing products to determine if test and positive control products were different and whether they achieved the required mean reduction level(s).
- The FDA provides a formula for determining sample size for meeting the power but not for tightening the confidence intervals for meeting the reductions or the 70% responder rate.

- The FDA uses a medical or biostatistical approach, meaning both types of errors (alpha $\{\alpha\}$ and beta $\{\beta\}$) are important in the analysis.

H_0 : *Product A = Product B*

H_A : *Product A \neq Product B* ← This is what we are attempting to prove.

Condition	Accept H_0	Reject H_0
H_0 true	Correct	Type I Error $\alpha = 0.05$
H_0 false	Type II Error $\beta = 0.20$	Correct

If $\alpha = 0.05$ and $\beta = 0.20$

$Power = 1 - 0.20 = 0.80$ or 80%

$Confidence Level = 1 - 0.05 = 0.95$ or 95%

The Sample Size Formula

The sample size formula is:

$$n \geq \frac{x s^2 (z_{\alpha/2} + z_{\beta})^2}{d^2}$$

where:

$n \geq$ sample size needed per product arm of the study

x = the number of different products in the study

s^2 = largest variance of the products used

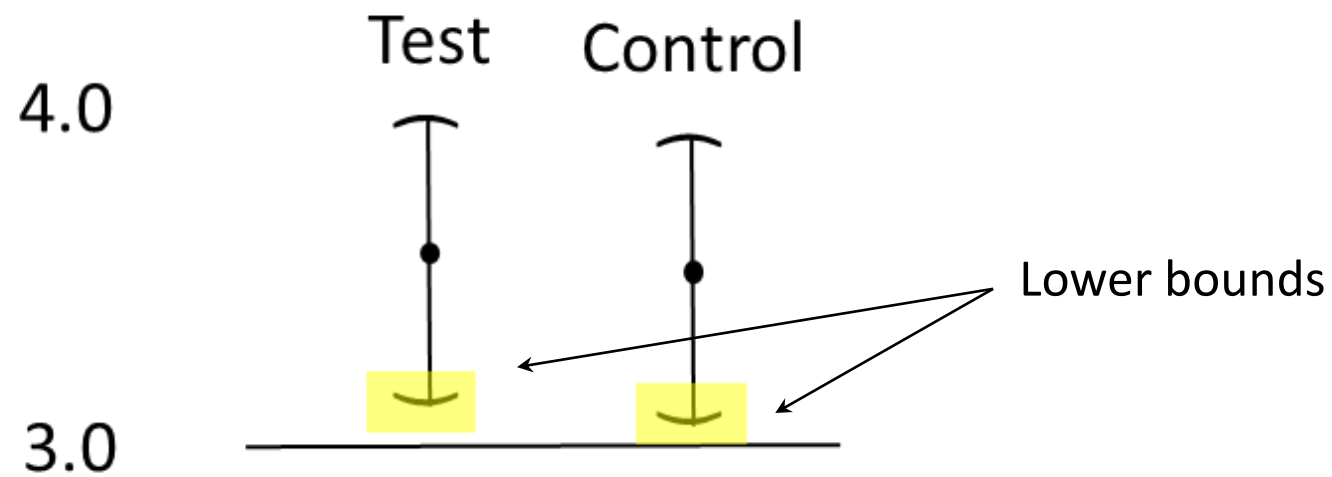
$z_{\alpha/2} = 1.96$ in the z table = Type I error (α)

$z_{\beta} = 0.842$ in the z table = Type II error (β)

d = detectable difference = $0.5 \log_{10}$

- This sample size formula is only for making sure that the beta error is 0.20.
- It does not indicate what number of subjects are necessary in a study to achieve the lower bounds of the 95% confidence interval, nor does it indicate the number of subjects necessary to pass the 70% responder rate.

- Let us step back and look at an example – the inguinal (groin) site in a pre-operative skin preparation study.
- What the FDA means is that the lower bounds of the 95% confidence interval must be greater than or equal to 3.0 \log_{10} reductions for both the test and positive control products at the immediate time point.



As n (sample size) gets larger, the 95% confidence interval gets smaller. If $s = 2.2$, and $\bar{x} = 3.5$. How it works is shown on A and B, using 18 and 95 subjects.

$$\bar{x} \pm 1.96 \frac{s}{\sqrt{n}}$$

A $\frac{2.2}{\sqrt{18}} = 0.5185$

$n=18$

$$\mu = 3.5 \pm 1.96 \frac{2.2}{\sqrt{18}}$$

$$2.48 \leq \mu \leq 4.52$$

This is wider. It will not pass the $3.0 \log_{10}$ reduction

B $\frac{2.2}{\sqrt{95}} = 0.2257$

$n=95$

$$\mu = 3.5 \pm 1.96 \frac{2.2}{\sqrt{95}}$$

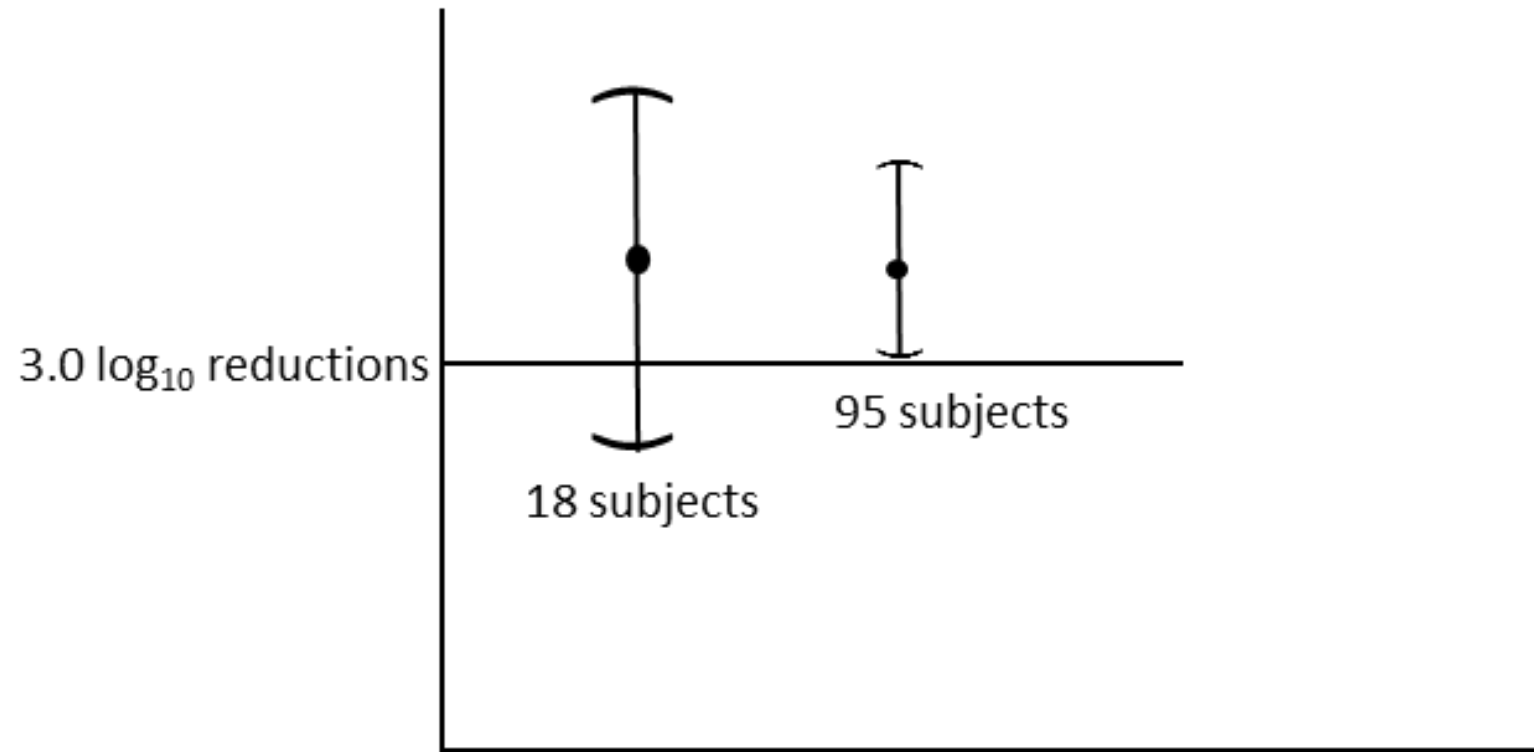
$$3.04 \leq \mu \leq 3.96$$

This is tighter. It will pass the $3.0 \log_{10}$ reduction.

Note: 1.96 is the value for $z_{\alpha/2} \rightarrow z_{0.05/2} \rightarrow z_{0.025}$. Look this up in the z table.

For example,

Confidence Intervals



95% confidence interval = $\mu = \bar{x} \pm 1.96 \frac{s}{\sqrt{n}}$ = standard error of the mean

The study with 18 subjects fails. The study with 95 subjects passes.

- However, the FDA included an additional requirement:
 - 70% responder rate with the 95% confidence intervals
- Neither the 1994 TFM nor the 2015 supplemental version even discusses this component from a statistical perspective.
- The sample size formula does not calculate the number of subjects required for the 95% confidence intervals' lower bounds to be above the 2.0 or 3.0 \log_{10} reductions in the abdomen or groin.

$$n \geq \frac{x s^2 (1.96 + 0.842)^2}{d^2}$$

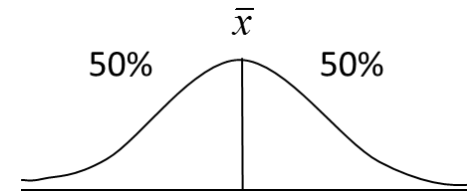
- Again, the original sample size calculation formula in the TFM does not address these last two requirements. It can only inform the statistician if enough subjects are used to meet or the power of 0.80.
- What can one do to pass the evaluation, especially the 70% responder rate?

70% Responder Rates

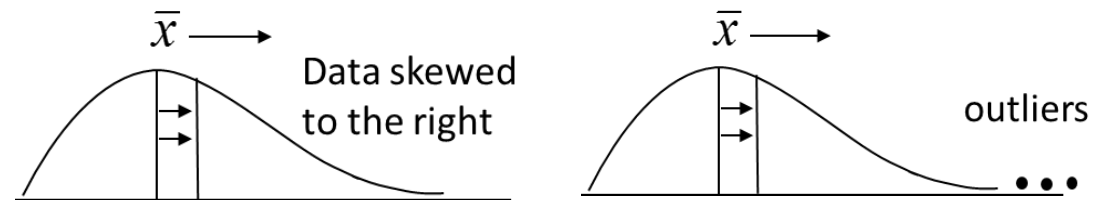
Originally, the FDA wanted to determine if the distribution was normal without skewed data or outliers to the right.

1. If skewed data were present in the data, they would shift the mean to the right, giving “false” higher reductions.

2. Instead of looking like a normal distribution

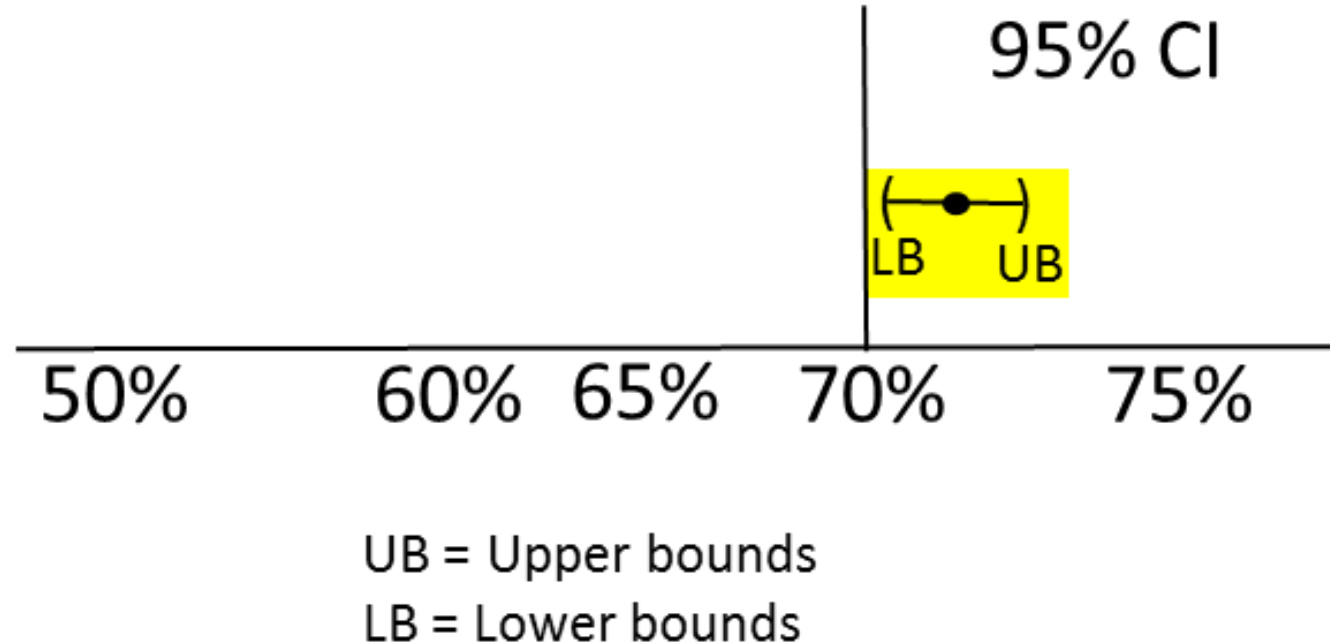


Skewed data tend to pull the mean to the right (higher values) A distribution that contains outliers looks like this:



3. This could be better done with exploratory data analysis (EDA), using stem-and-leaf displays, Letter-Values displays, and Boxplots.

In addition, the FDA states the 70% responder rate must have the lower bounds of the 95% confidence interval greater than or equal to 70% for both the test and positive control products at the first sample time. This is the most difficult hurdle to meet.



70% Responder Rate with 95% Confidence Interval

The original formula for this computation was:

$$\pi = p \pm z_{\alpha/2} \sqrt{\frac{p(1-p)}{n}} \pm \frac{1}{2n}$$

where:

π = 95% confidence interval of responder rate success

p = proportion of success of $\frac{\text{number of successes}}{\text{number of total observations}}$ *

n = sample size of this portion of the study (one product and one sample time)

$z_{\alpha/2}$ = 95% confidence interval = $\frac{0.05}{2} = 0.025$. $z = 1.96$ for a two-tail confidence interval.

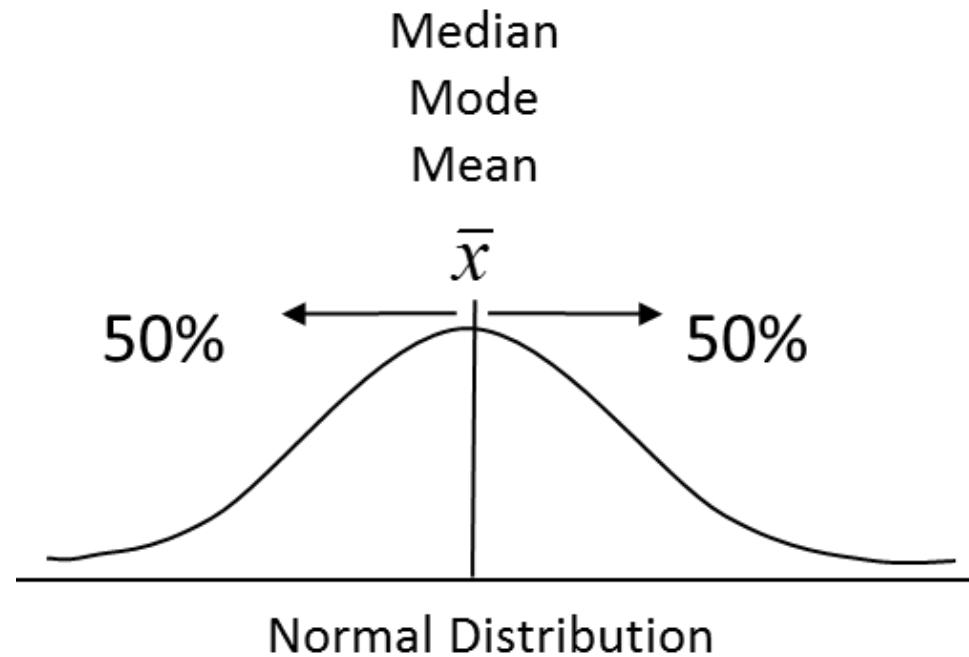
The Yates correction factor was also used, which is $\frac{1}{2n}$ or $\frac{0.5}{n}$.

“0” = lower than the 3.0 (for the inguinal) \log_{10} reductions; “1” = equal to or higher than the 3.0 (for the inguinal) \log_{10} reductions. The values that received the “1s” are successes, and the “0s” are failures.

- However, the Yates correction factor is no longer necessary, according to the FDA's comments on the latest studies. So, the formula now is $\pi = p \pm z_{\alpha/2} \sqrt{\frac{p(1-p)}{n}}$
- This makes the 95% confidence interval a little more narrow. To pass the 70% responder rate with the lower bounds of the 95% confidence interval equal to or greater than 70% is difficult.
- In order to pass, the lower bounds of the 95% confidence interval of the \log_{10} reductions must be equal to or greater than 3.0 for the inguinal sites.
- But for the 70% responder rate without the 95% confidence interval must be much greater. For example, if the \log_{10} reduction level is 3.0 \log_{10} , the value would have to be 3.5 \log_{10} for the 70% responder rate to be passed.

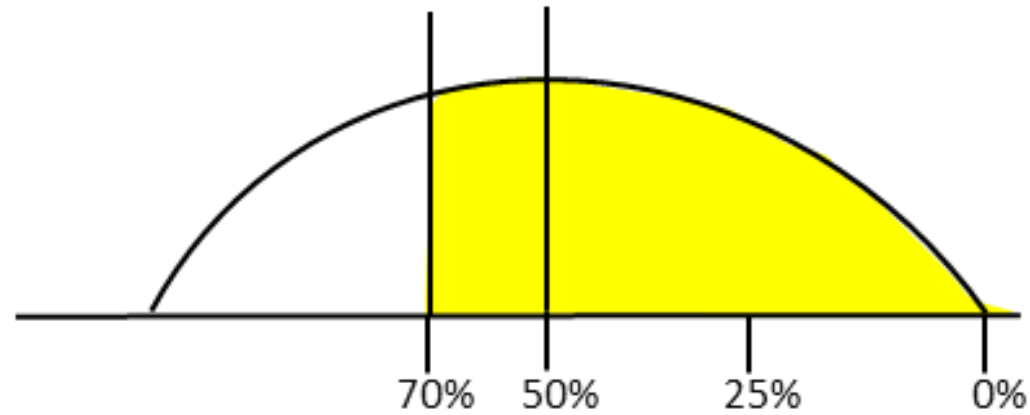
- Looking at this situation in greater detail, for a normal Gaussian distribution, the median, mode, and the mean have equal percentages of 50% data below and 50% data above the mean (Figure 2).

Figure 2. Normal Distribution

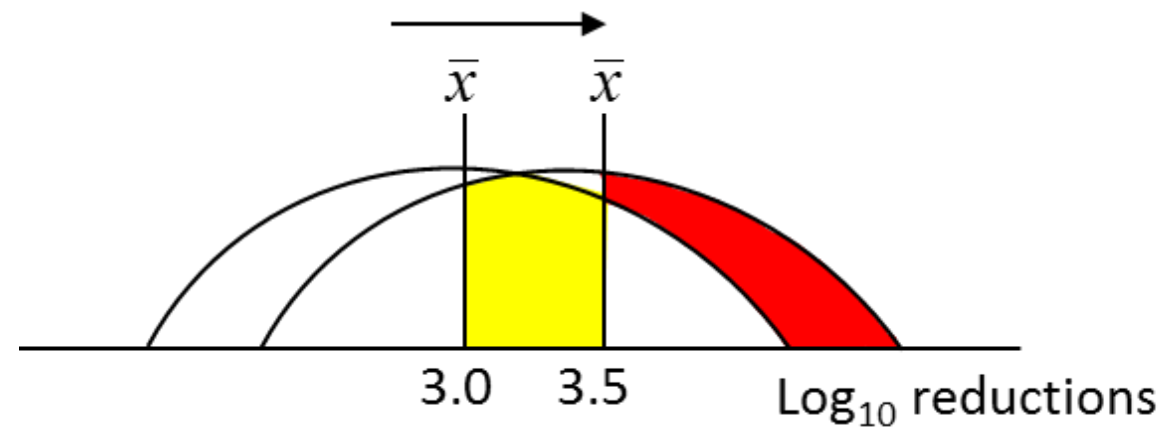


- If a product achieved a $3.0 \log_{10}$ reduction, according to Figure 2, this would result in a responder rate of 50%.

But the FDA wants 70%.



The left-hand portion is not 50% but 70%. We have to move the 70% to the 50% line (\bar{x}).



- That is not all. The lower bounds of the 95% confidence interval must be 70% or better.
 - 1. The responder rate should be 75%.
 - 2. This requires many more subjects.
- Increasing the number of subjects will tighten up the 95% confidence interval of the responder rate.
- However, these rules are not absolute. If, for example, a product achieves a responder rate of 74%, this will be alright but will require more subjects than if it was at 75%.

- But with these new requirements, the positive control products do not pass.
- Abbreviated New Drug Applications (ANDAs) and New Drug Applications (NDAs) are a way to avoid these problems, but they require a lot of money.
- Last year, many companies began collaborating through the American Cleaning Institute to demonstrate that control products will not pass these regulations.
- The FDA was sued by a firm who then got their product to pass without meeting the requirements.
- Now the FDA has a new method, which seems more appropriate.

New Testing Requirements of the FDA

- There are three products involved in these evaluations:
 1. Test Product
 2. Control Product
 3. Vehicle

- There are two tests involved in these evaluations:
 1. Test vs. Positive Control
 2. Test vs. Vehicle

1. Test vs. Positive Control

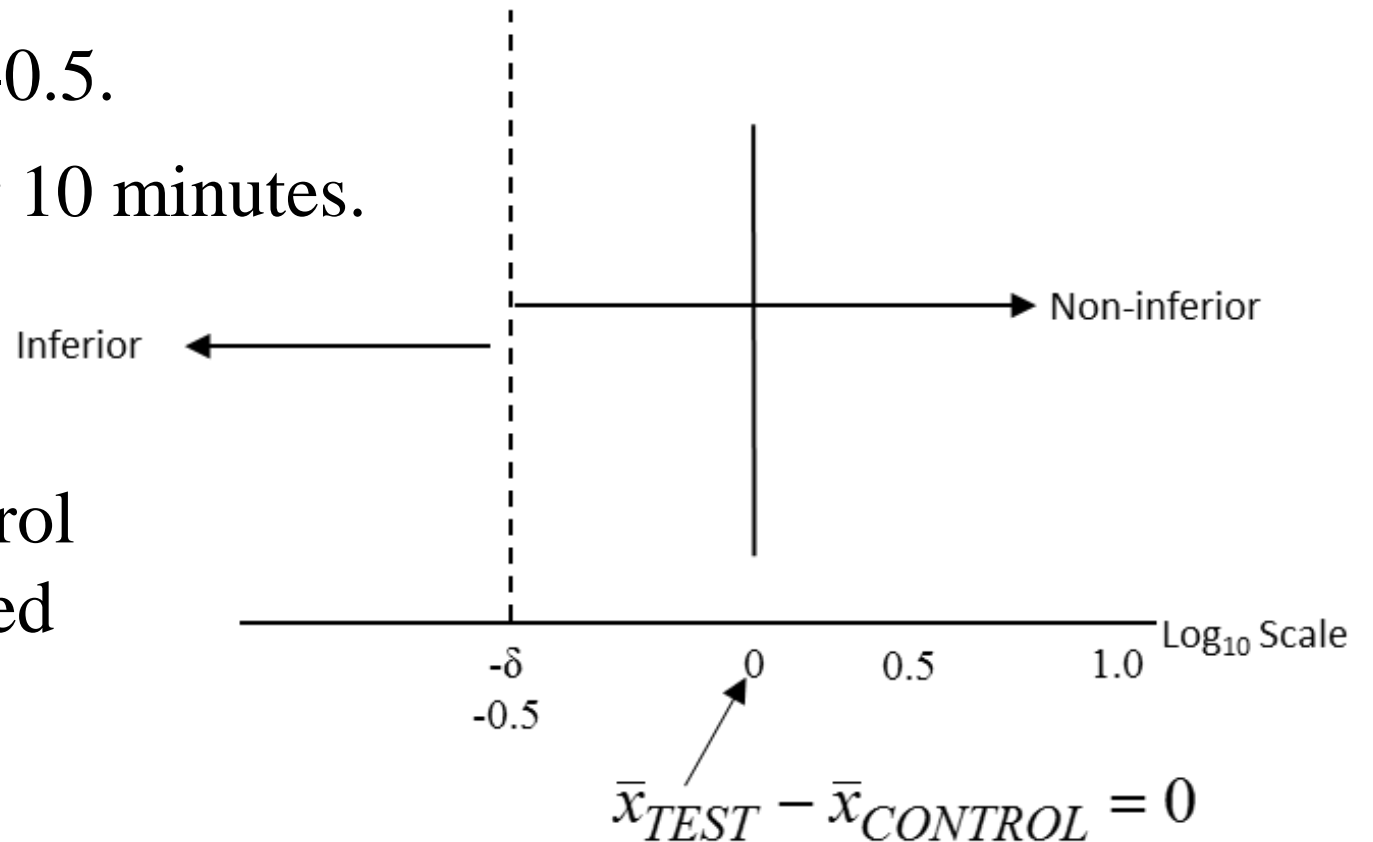
$H_0: A \geq B$ Non-inferior

$H_A: A < B$ Inferior

This is what has to be concluded.

- where A = Test Product, and B = Control Product
- The equivalence margin is $\delta = -0.5$.
- Sample times are 30 seconds or 10 minutes.

The Test Product minus the Control Product must be ≥ -0.5 to be called non-inferior.

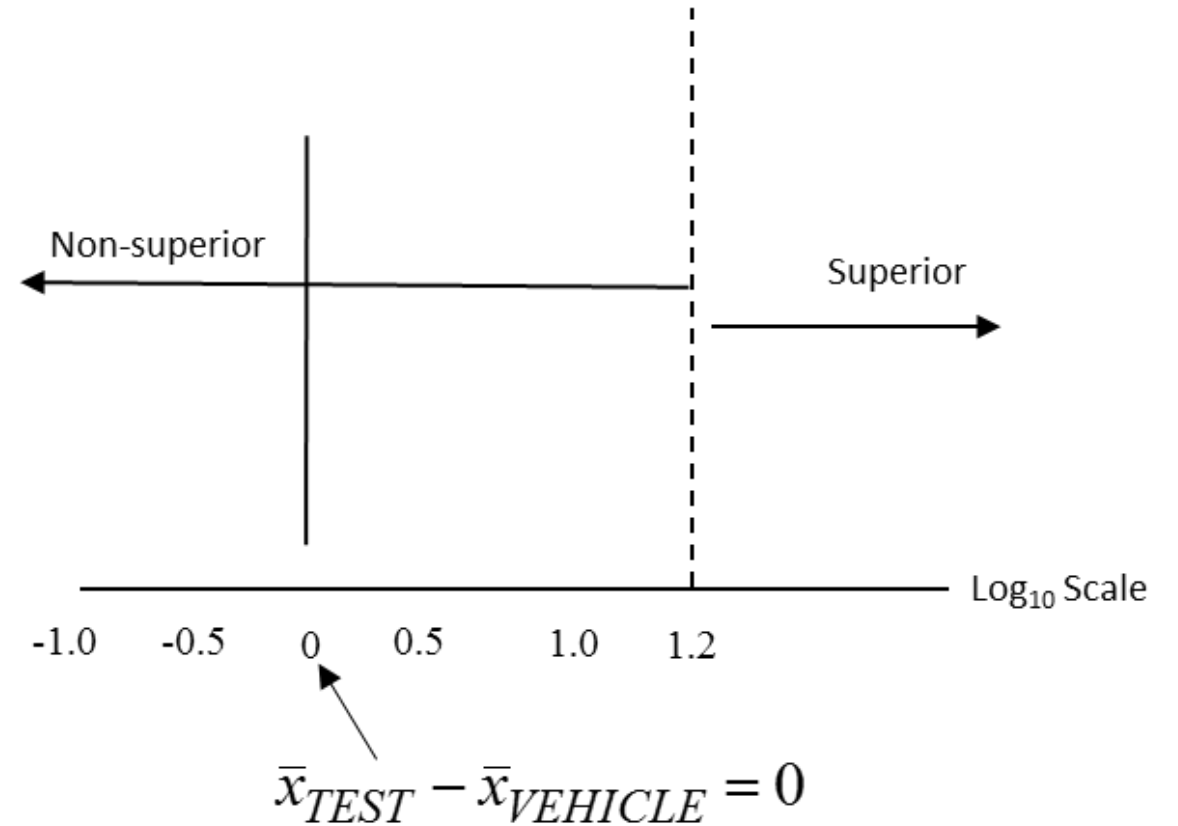


2. Test vs. Vehicle Control:

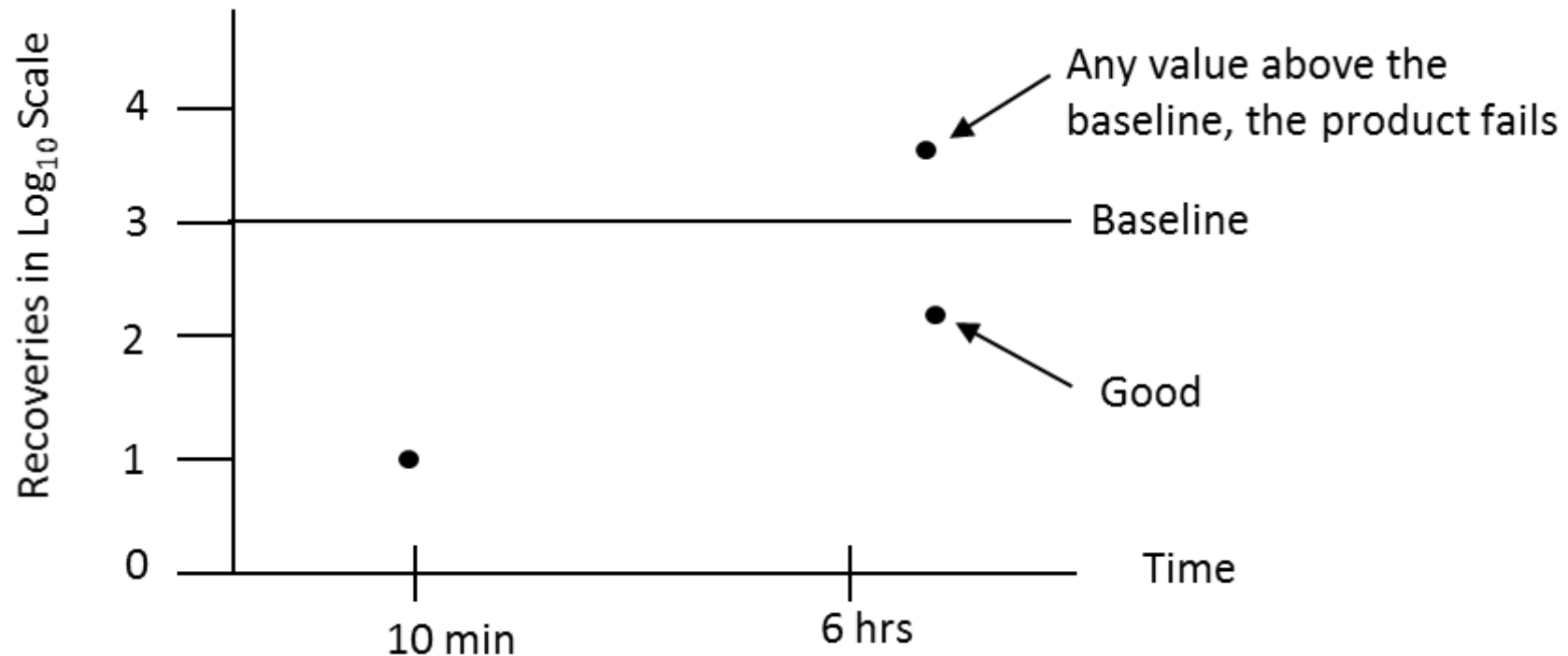
H_0 : *Test Product* \leq *Vehicle Product* (Non-superior)

H_A : *Test Product* $>$ *Vehicle Product* (Superior)

The Test Product has to be much better than the Vehicle Product by at least $1.2 \log_{10}$ to be termed superior.



- Additionally, all the reduction values at the 6-hour sample time must be equal to or less than the baseline sample for all the subjects used.
- A minimum of 100 subjects per product must be tested.
- This will not be 300 subjects. The minimum number of subjects will be $3(100)/2 = 150$.



How to Successfully Meet FDA Requirements

- In the protocol, include two possible statistical analyses to be performed.
 - Use the standard statistical method to determine the \log_{10} reduction and the 70% responder rate.
 - If the product fails, then perform the non-inferior and superior tests on the data.

- Keys to passing the FDA requirements with the non-inferior and superior claims:
 - Is the Test Product non-inferior to the Control Product?
 - Control Product – which one will the FDA require?
 - Is the Test Product superior to the Vehicle by $1.2 \log_{10}$?
 - How is the Test Product applied – sponge applicator, cloth?

Conclusion

- The FDA, over time, has made it harder to pass these evaluations.
- A firm now has two choices:
 - 95% confidence interval and 70% responder rate
- OR
- Test Product – Control ≥ -0.5 (non-inferior)
- Test Product – Vehicle ≥ 1.2 (superior)
- I recommend both statistical analyses be included in the protocol.