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# Targeted Potency

David Siev
Statistics Section Leader
Center for Veterinary Biologics

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"Public Service is a Public Trust"
5CFR §2635.101

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# Core

- ***Data-driven*** ***Criteria***
- ***Consistent*** ***Principles***
- ***Coherent*** ***System***

# Targeted Potency

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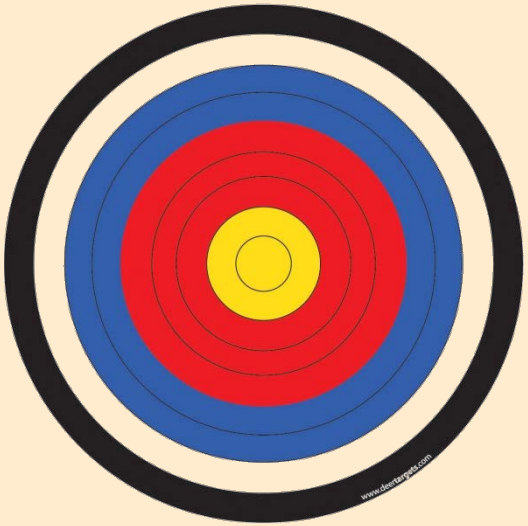

Release

Throughout-Dating

Dating Period

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# Terminology

"Minimum Protective Dose" (MPD)

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# Terminology

## “Minimum Protective Dose” (MPD)

‘Dose’ has at least four different usages:

- Concentration (e.g. 8mg/dL dose)
- Volume (e.g. 1mL dose)
- Treatment (e.g. 2-dose vaccine)
- Potency (as implied by MPD)

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# Terminology

"Minimum Protective Dose" (MPD)

Not designed for minimum

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# Terminology

"Minimum Protective Dose" (MPD)

Often not protective but reductive

Non-dichotomous outcome

Term not meaningful

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# Terminology

"Minimum Protective Dose" (MPD)

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# Terminology

"Minimum Protective Dose" (MPD)

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# Terminology

"Antigen Overage"

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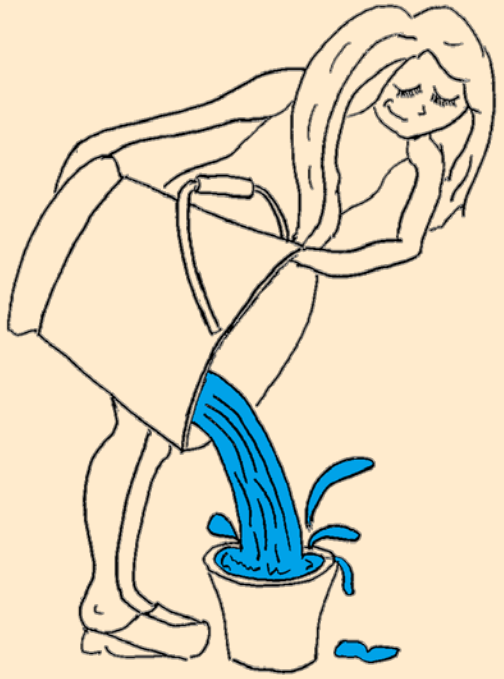
# Terminology

"Antigen Overage"

OMG



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# Terminology

"Antigen Overage"

Antigen ≠ Potency

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# Terminology

Overage?

Outdated 9CFR term

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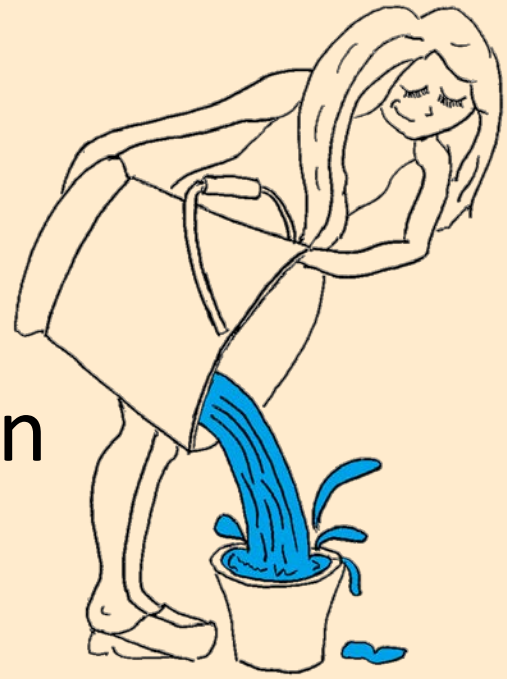
# Terminology

Overage?

Outdated 9CFR term

Intent is **not** adding excess antigen



# Terminology

Increment ~~Overage?~~

Measurement Uncertainty

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# Measurement Uncertainty

Guide to the Expression of Uncertainty in Measurement.

ISO/IEC Guide 98-3 (“The GUM”). *International Organization for Standardization*, 2008.

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# Measurement Uncertainty

- ISO/IEC Guide 98-3, Guide to the Expression of Uncertainty in Measurement. *International Organization for Standardization*, 2008. ("GUM")
- NIST Technical Note 1297, Guidelines for Evaluating and Expressing the Uncertainty of NIST Measurement Results. *National Institute of Standards and Technology*, United States Department of Commerce, 1994.
- G104 – Guide for Estimation of Measurement Uncertainty in Testing. *American Association of Laboratory Accreditation*, 2014.
- G108 – Guidelines for Estimating Uncertainty for Microbiological Counting Methods. *American Association of Laboratory Accreditation*, 2014.
- UKAS Publication ref: Lab 12. The Expression of Uncertainty in Testing. *United Kingdom Accreditation Service*, 2000.

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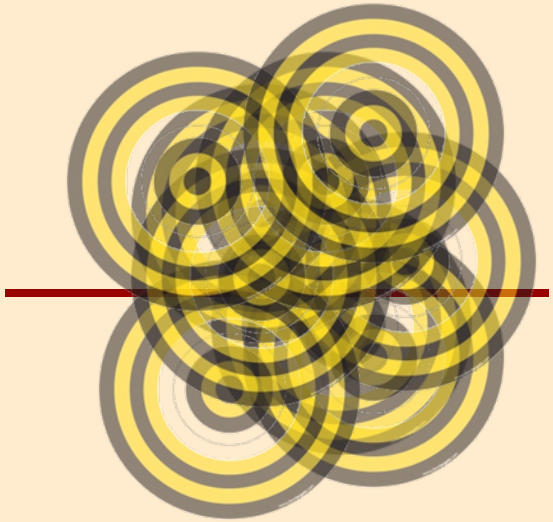
# Targeted Potency



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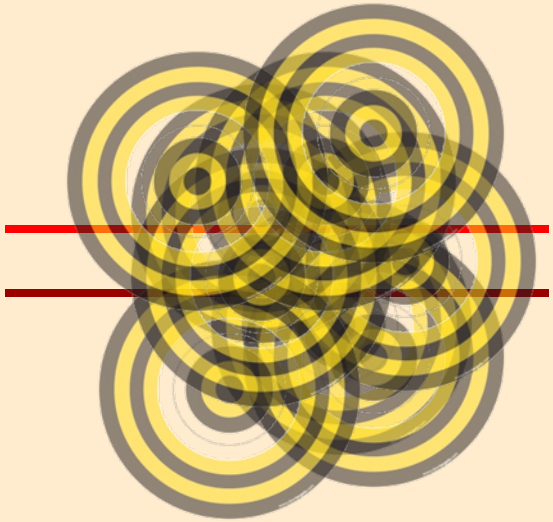
# Targeted Potency



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# Targeted Potency

Observed in pivotal efficacy study (PES)

+

Increment due to measurement uncertainty

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# The Impact of Terminology

Target = PES Observed + Uncertainty

Expiry = Minimum Protective + Overage

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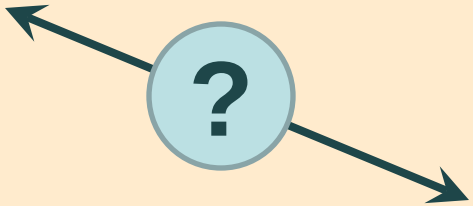
# The Impact of Terminology

Target = PES Observed + Uncertainty




Expiry = Minimum Protective + Overage

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# The Impact of Terminology

Target = PES Observed + Uncertainty

Determine target by estimating an **unknown** quantity

Expiry = Minimum Protective + Overage

Add extra to a **known** target just to be extra sure

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# The Impact of Terminology

Contemporary

Target = PES Observed + Uncertainty

Determine target by estimating an **unknown** quantity

Outdated

Expiry = Minimum Protective + Overage

Add extra to a **known** target just to be extra sure

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# PES Efficacy Uncertainty

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# PES Efficacy Uncertainty

- ***Subjects*** not necessarily representative of target population

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- ***Vaccine lot*** may not match production serial

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- ***Challenge*** method does not usually emulate natural exposure

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- Experimental ***outcome*** often differs from clinical outcome

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# PES Efficacy Uncertainty

- ***Subjects*** not necessarily representative of target population
- ***Vaccine lot*** may not match production serial
- ***Challenge*** method does not usually emulate natural exposure
- Experimental ***outcome*** often differs from clinical outcome
- ***Clinical course*** of the disease not well matched by observation period, etc., etc.

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# PES Efficacy Uncertainty

- ***Licensure may be based on a single study, and there is no limit on number of tries***

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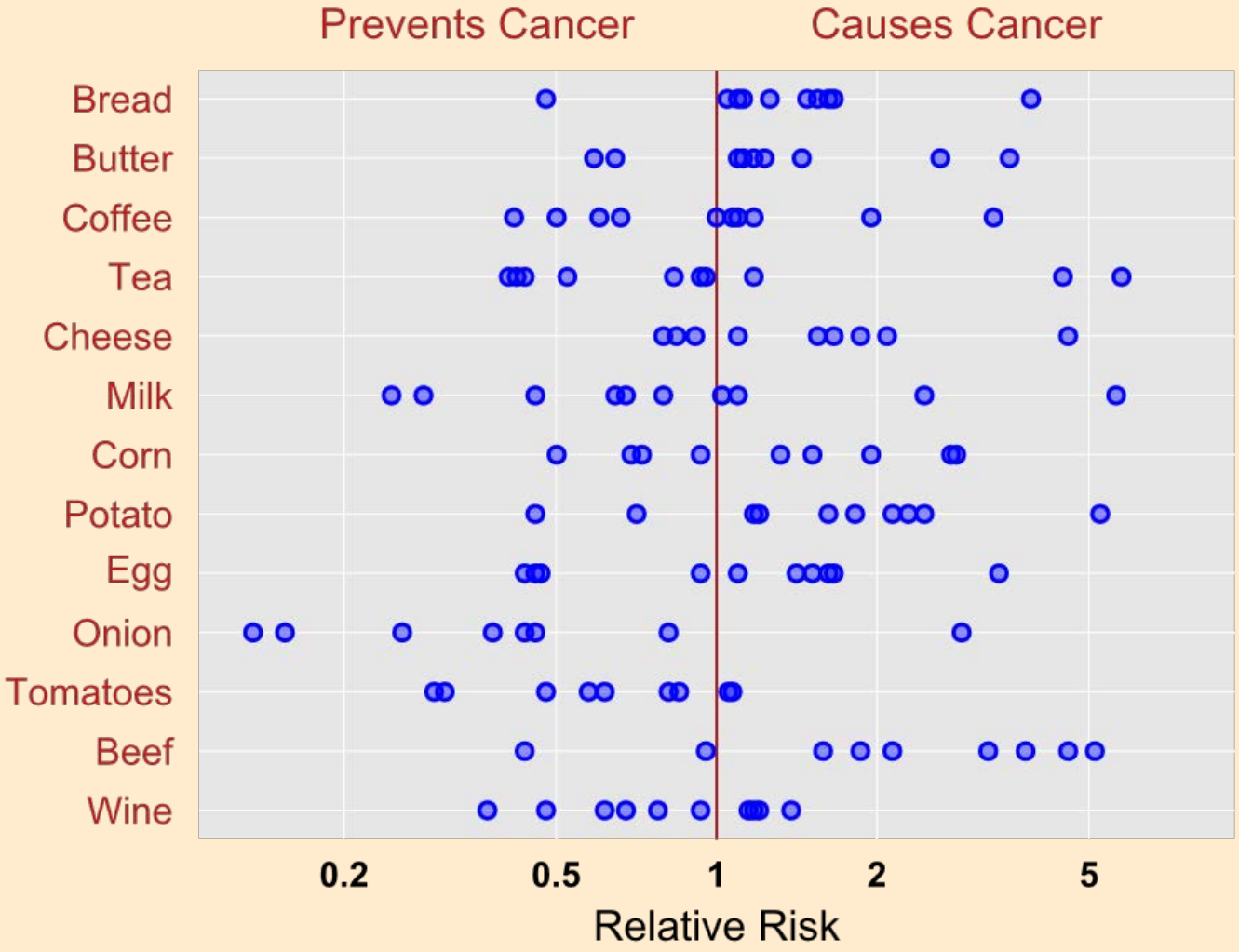
# Do common foods prevent or cause cancer?




Schoenfeld JD, Ioannidis JPA, 2012. Is everything we eat associated with cancer? *American Journal of Clinical Nutrition*, 97: 127-134

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# PES Efficacy Uncertainty

| | DHHS-FDA | USDA-CVB |
|---|---|---|
| *Target Population* | Design | Not required |
| *Trial Location* | Clinical | Manufacturer |
| *Trials Inspected* | Usually | Rarely |
| *Serious Problems* | 2%* | ? |

*Saife C, 2015. Research misconduct identified by the US Food and Drug Administration. *JAMA Intern Med*, online 2015.02.09

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# PES Observed Efficacy

- Random variable
  - Not a constant

# PES Observed Efficacy

- Random variable
  - Not a constant
- Measured with uncertainty
  - Not omniscience

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# PES Observed Efficacy

- Random variable
  - Not a constant
- Measured with uncertainty
  - Not omniscience
  - Measured only once

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# Some Other Sources of Uncertainty

**Uncertainty in Potency Assay**

- Assay probably not validated
- Potency may be function of more than one element
- Assay imprecision

**Uncertainty in PES Vaccine Potency**

- Potency-efficacy relationship not established
- Assay may not be the same as release assay

**Uncertainty in the Lot Release Test**

- Serial release testing may be done on a single vial
- Biased retesting may be done
- Manufacturing consistency

**Uncertainty in Stability Profile**

- No stability-indicating assay
- Stability study may have only included pre-licensing serials
- No stability requirements for bulk vaccine preparations

**And many others …**

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# Can we quantify the uncertainty?

# Can we quantify the uncertainty?

## Error = Systematic + Random

(BTW statistical error is only a part of uncertainty)

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# Can we quantify the uncertainty?

$$\text{Error} = \text{Systematic} + \text{Random}$$

$$\text{Bias}^2 \qquad \text{Variance}$$

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# Quantify variance and bias?

Can only quantify variance and bias by assuming a distribution for X

$$X \sim f(x)$$

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# Quantify variance and bias?

But many of the uncertainties here are about the *distributional form* of X

$$X \overset{?}{\sim} f(x)$$

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# Quantify variance and bias?

But many of the uncertainties here are about the *distributional form* of X

# Uncertainty about the nature of the uncertainty

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# Quantify variance and bias?

And …

There are ***many*** random variables

…, W, X, Y, …

not just one

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# Industry Proposal

Eliminate increment over PES altogether

Observed in pivotal efficacy study (PES)

+

~~Increment due to measurement uncertainty~~

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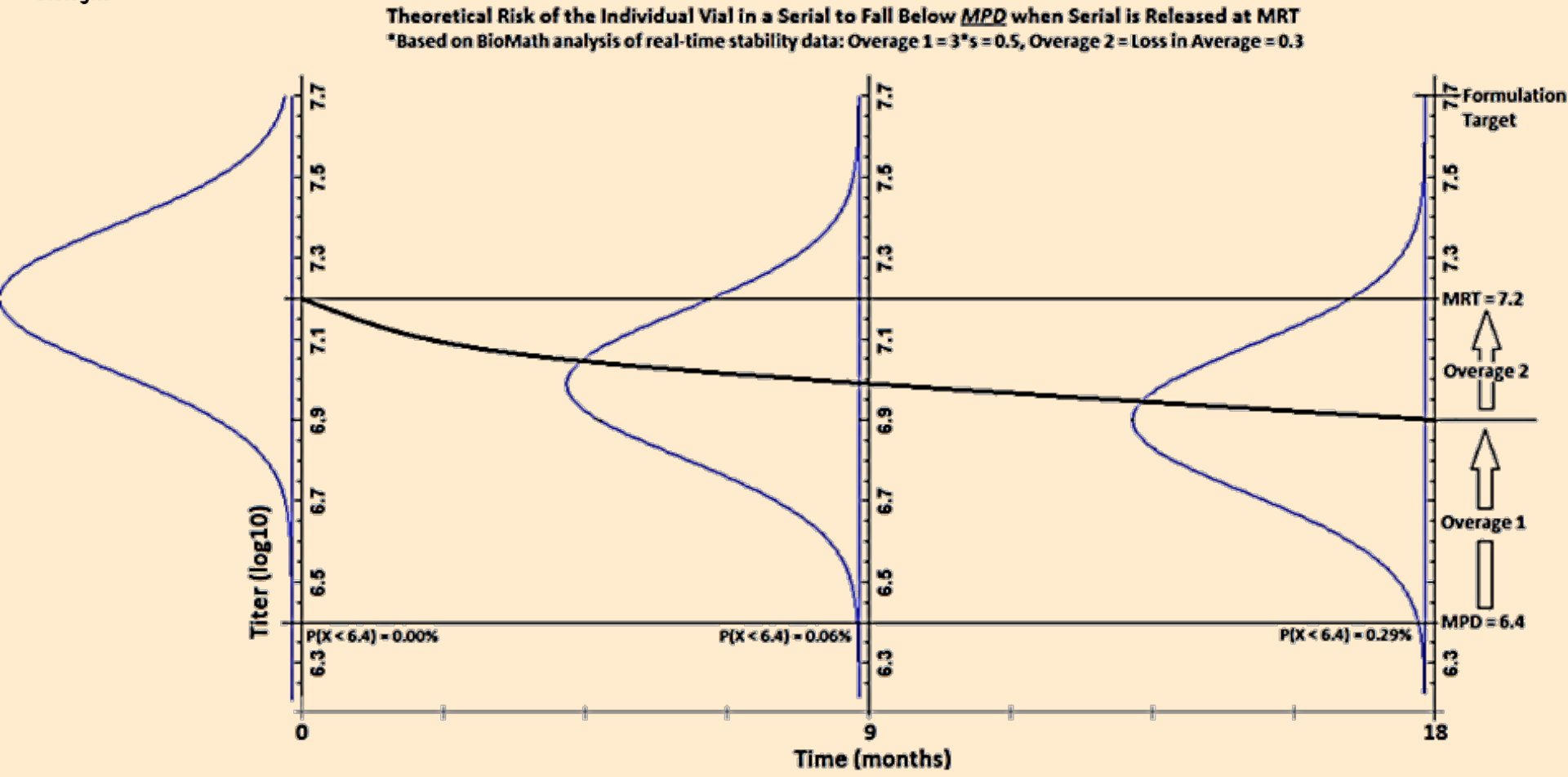
# Proposal to Eliminate Increment



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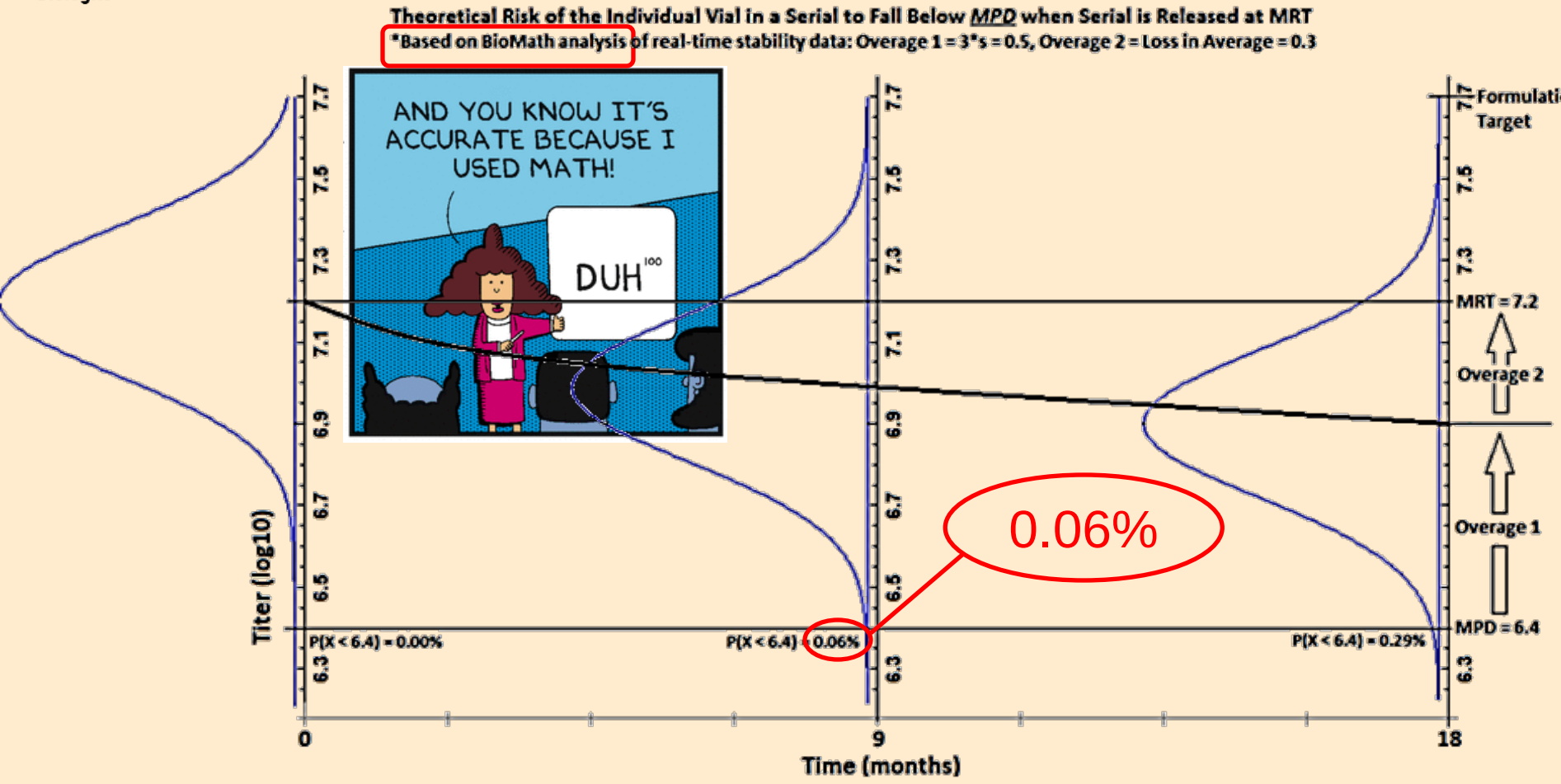
# Proposal to Eliminate Increment



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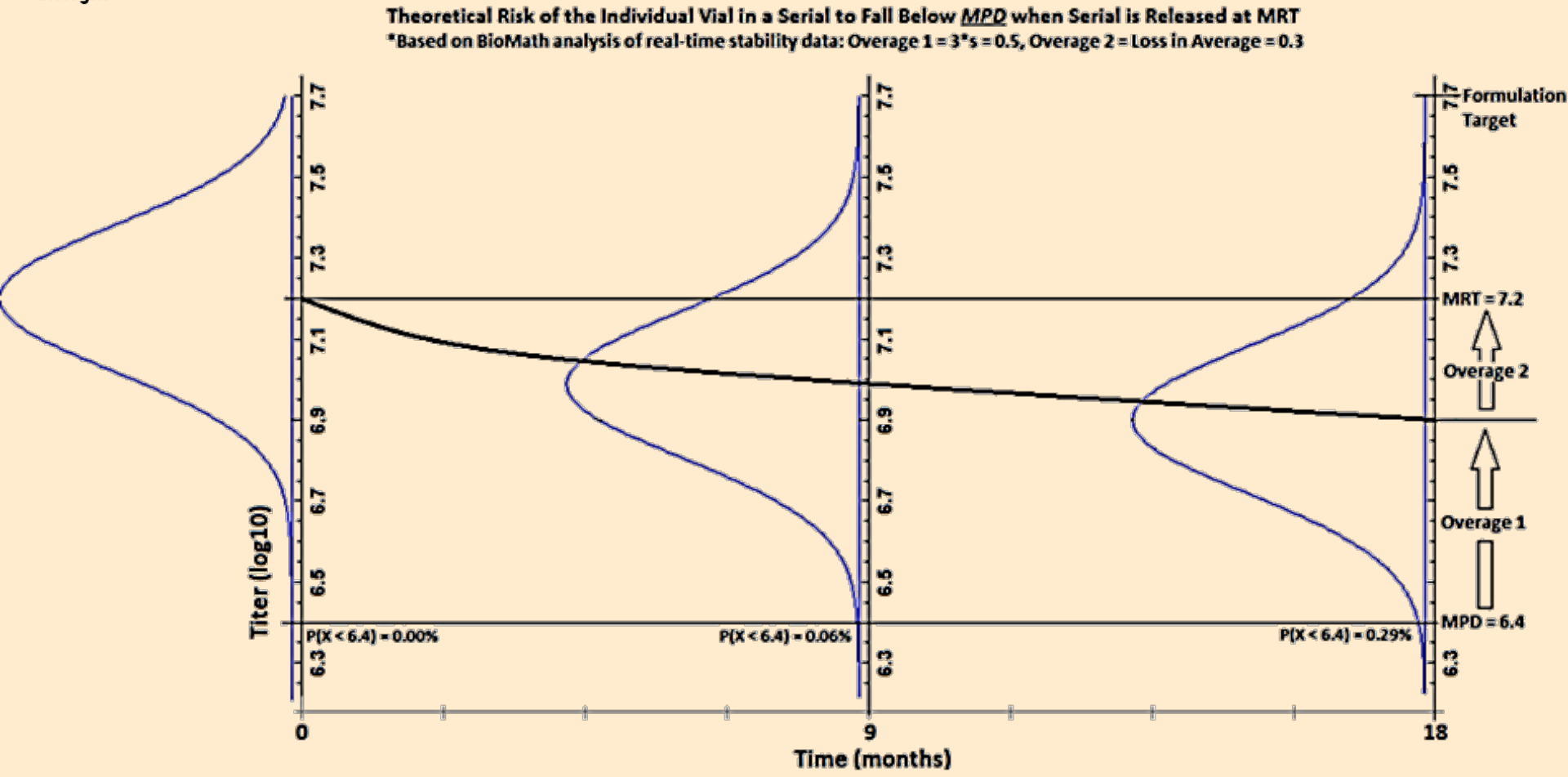
# You don't see this



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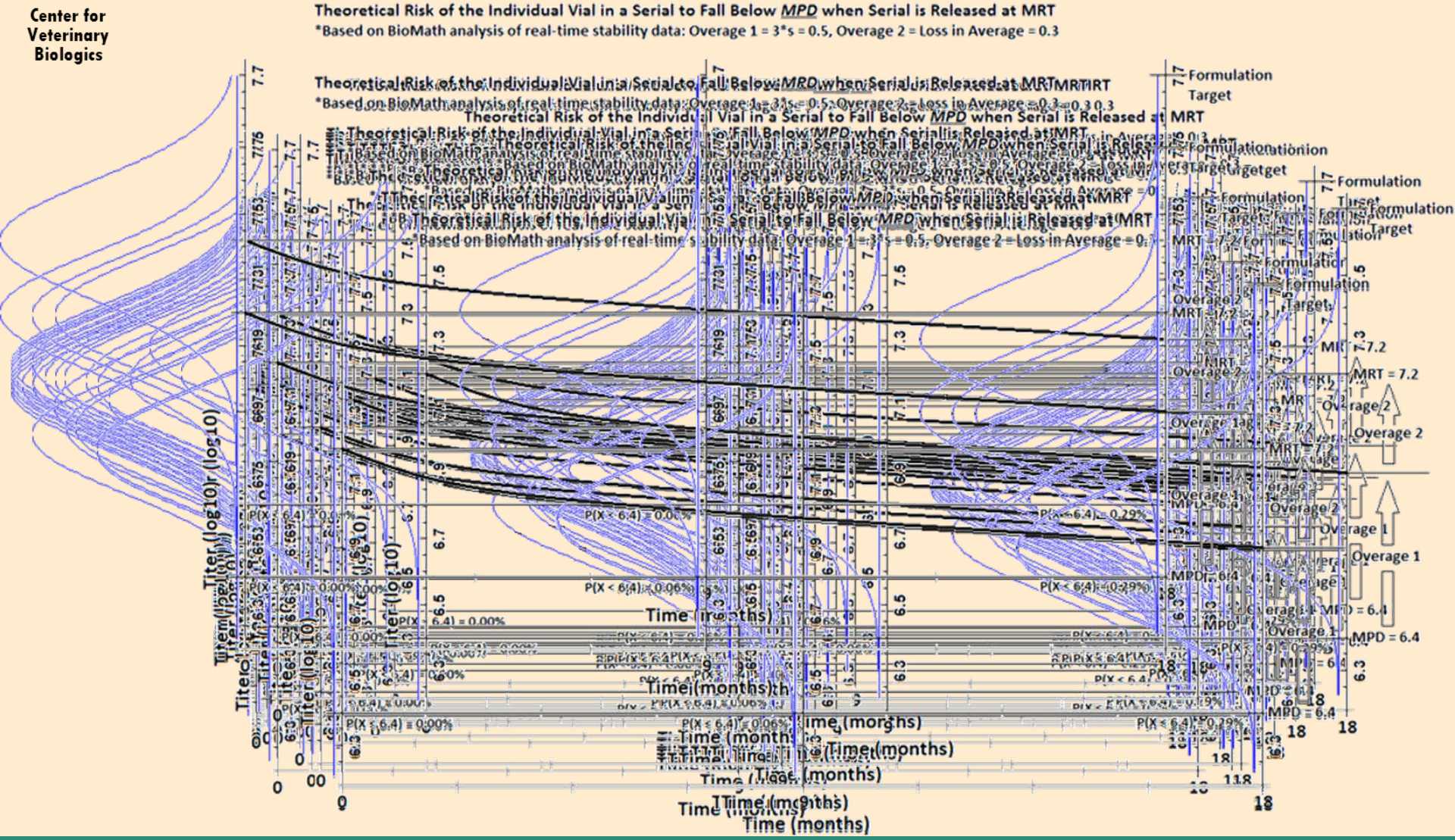
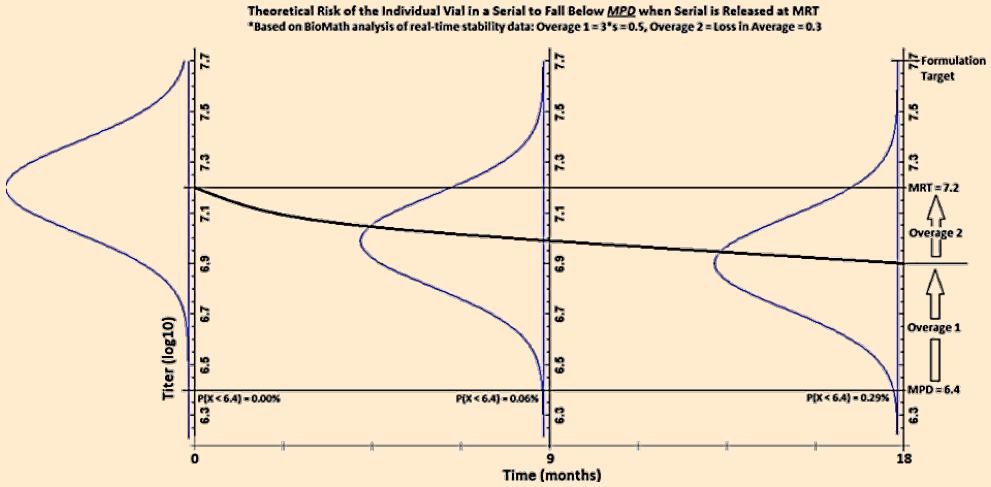


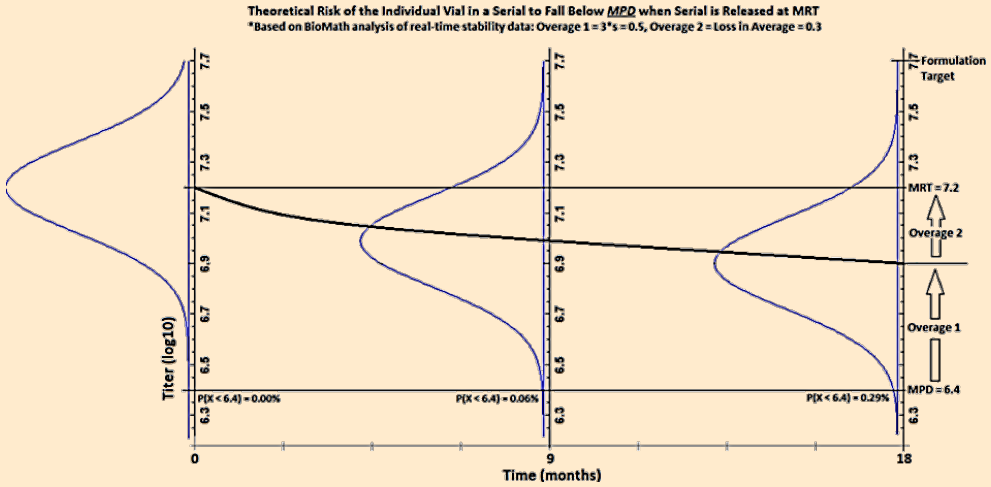
# Targeted Potency

Poor relationship to reality



# Targeted Potency

Poor relationship to reality




No probabilities without sampling

# Targeted Potency

- Lot Release – Draft 440 does **not** use the concept of *confidence* or refer to *confidence intervals*

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# Interval Estimation?

- Lot Release – Draft 440 does **not** use the concept of *confidence* or refer to *confidence intervals*

- Stability
  Draft 155 – *prediction intervals*
  PQRI – *tolerance intervals*

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# Targeted Potency

## PES Observed + Uncertainty Increment

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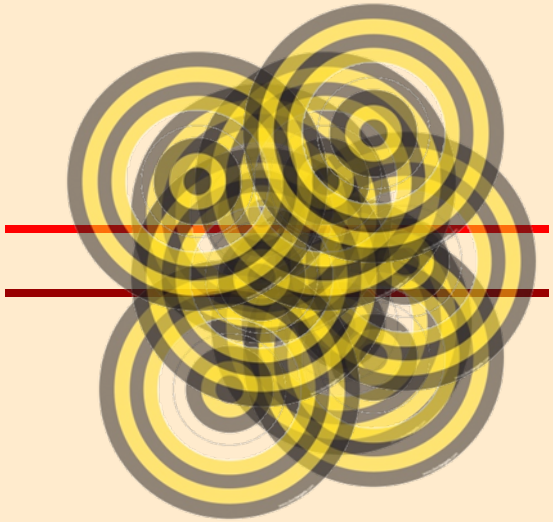
# Targeted Potency



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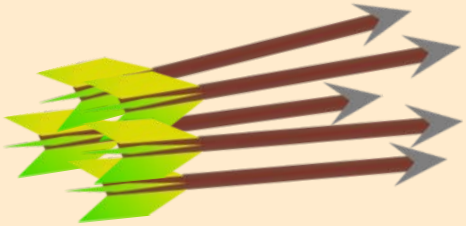
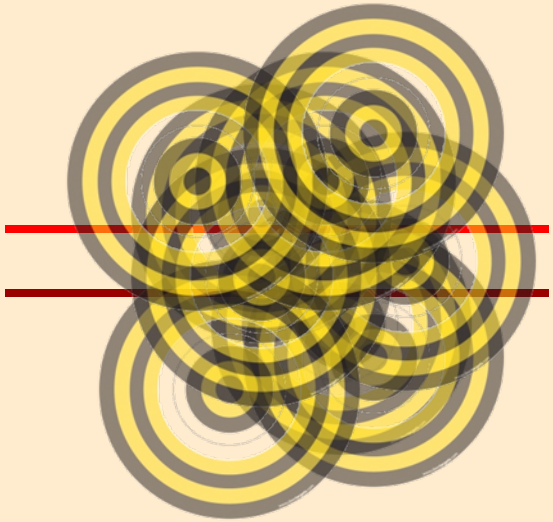
# Aiming at the Target

## Release





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# Trajectory

Where is there uncertainty?

Target (throughout-dating spec)

Aim (release spec)

Trajectory (shelf life stability)

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# Target Potency

Where is uncertainty considered?

**Target (throughout-dating spec)**

Aim (release spec)

Trajectory (shelf life stability)

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# RP ELISA

In the past, target required no increment

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# RP ELISA

In the past, target required no increment

New reference qualified in host species vaccination-challenge study every 2-3 years

# RP ELISA

Extended reference dating instituted in 2011 (VSM 800.211)

“To facilitate the development of well-designed and rigorously validated assays”

# RP ELISA

Extended reference dating instituted in 2011 (VSM 800.211)

"To facilitate the development of well-designed and rigorously validated assays"

15 years –
legacy assays with minimal monitoring

Indefinite dating –
assays with rigorous monitoring

# RP ELISA

Extended reference dating instituted in 2011 (VSM 800.211)

Sound assay design –

Eliminates old burdensome requirement

Through modern validation methods

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# Potency too high?

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# Potency too high?

- May be an important consideration

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# Potency too high?

- May be an important consideration
- Lower limit can't control for uncertainty at the upper limit

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# Summary

- Terminology
  - Targeted Potency
  - Increment
- Measurement Uncertainty
  - Target (the only place where it is considered)
  - Release
  - Stability Profile
- Data based target
  - All assay types
  - including RP ELISAs
- Let's stay real
  - Please don't use unwarranted jargon

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# Core

- ***Data-driven*** ***Criteria***
- ***Consistent*** ***Principles***
- ***Coherent*** ***System***

# Targeted Potency

"Public Service is a Public Trust"
5CFR §2635.101