

Overview of vaccine potency, specifications, and stability

New Cells for New Vaccines IV

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Potency

Specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, to effect a given result. -- [21 CFR §600.3 (s)]

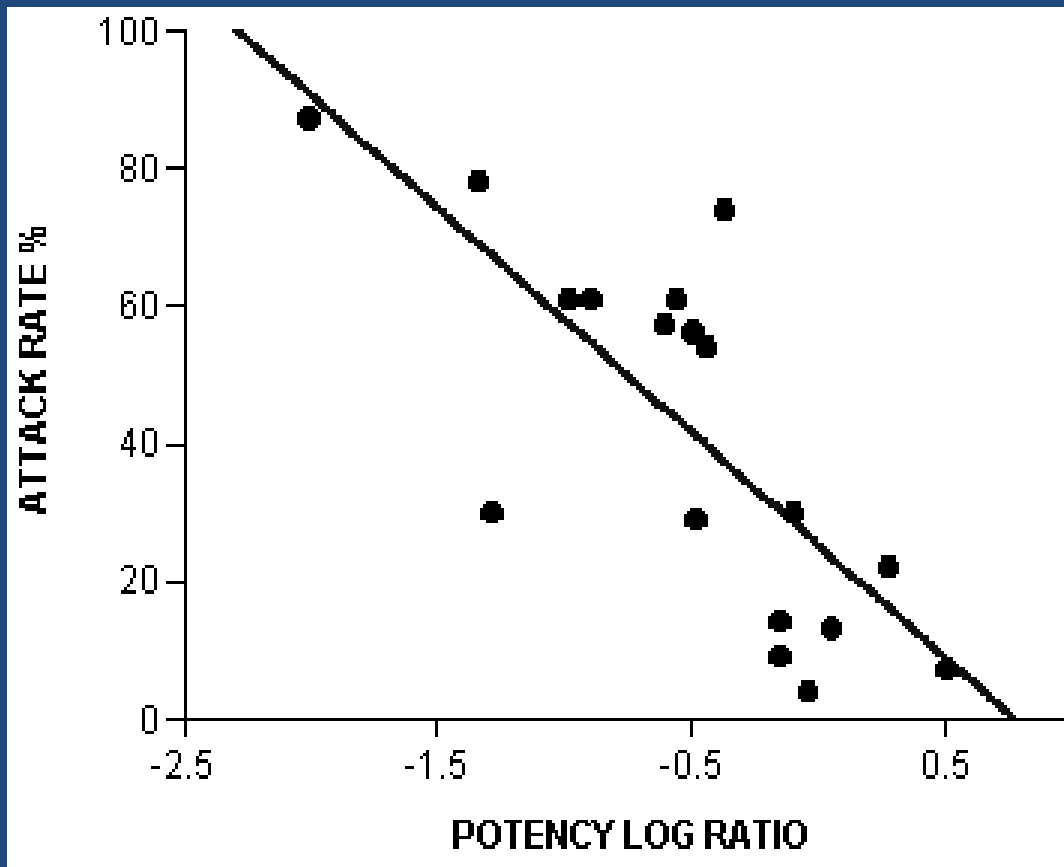
Why do we do a potency assay?

- In development, to:
 - Assure that safe potencies are not exceeded in clinical trials
 - Relate information across different stages of development
 - Obtain information that will support licensure-including correlation of potency with clinical response
- After licensure, to assure that lots behave similarly to those tested in the clinical trials that supported licensure
 - The potency should not be below the lowest potency believed to be efficacious
 - The potency should not exceed the highest potency believed to be safe
- To support post-licensure changes
- The potency assay provides a “bridge” throughout the vaccine life cycle, especially between licensed material and the clinical trials

Necessary attributes for potency assays

- Predictive of ***clinical benefit***
- Possess characteristics that are amenable to ***validation***
- ***Precision*** sufficient to meet goal of potency assays, i.e., provide assurance that vaccine is safe and effective throughout the dating period
 - Includes for use in stability studies
 - Includes for use in the “bridge” between marketed and clinical trial materials
- ***Stability*** indicating

Development of a potency test: whole-cell pertussis vaccine



1950's: UK MRC trials showed a correlation of the MP test with vaccine efficacy
Became the world wide accepted potency test for whole-cell pertussis vaccine

Potency Assays and Vaccines: A Few Examples

- Number of plaque forming units (e.g., mumps, measles, rubella, smallpox)
- Number of colony forming units (e.g., *S. typhi*, TY21a)
- Chemical and Physical chemical characterization (e.g., polysaccharide and polysaccharide-protein conjugate vaccines)
- Serological response in animals (e.g., diphtheria)
- Animal protection against challenge (e.g., rabies, anthrax)

Potency and cell substrates (examples)

- For live products, cell substrates can influence growth and thus provide selective pressure on the product strain
- Cell substrates can influence protein characteristics (*e.g.*, glycosylation) which could influence potency
- Residual cell substrate-related material may influence potency in other ways
- These influences on potency might not be detected in typical potency assays

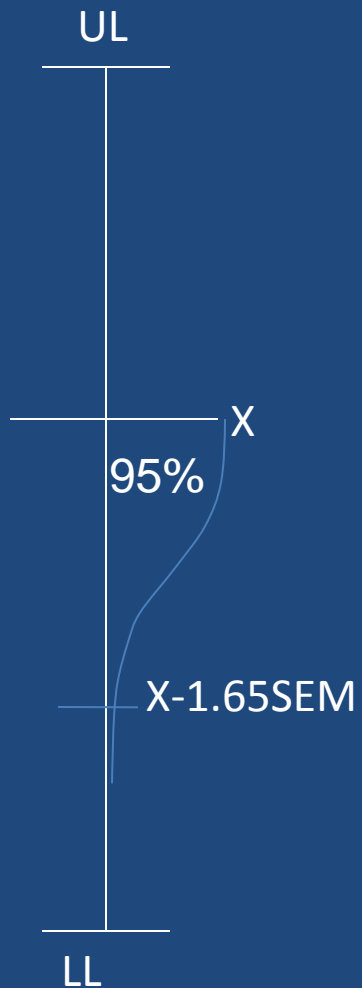
Setting Specifications on Potency Assays: Two Questions

- How much do we need?
- How certain do we need to be of that value?

Clinical information we'd like to have in setting specifications

- Different doses/potencies
 - Tell us how lots of different potencies will behave, which can aid in setting upper and lower clinical limits for the product, or in justifying upper/lower specifications for the product. What is the minimum potency that is believed to be effective (LL)? What is the maximum potency believed to be safe (UL)
- Consistency lots
 - Tell us that a lot of potency X will behave in a certain (predictable) way, even when manufactured in an independent lot

For products with variable assays, we must account for assay variability in setting up specifications



- The minimum release specification implies something about the lots that will be released post-licensure
- Mathematically:
 - A lot released with a mean potency of X has a 95% chance of having an actual potency (at release) greater than $X-1.65*SEM$ (where SEM is the potency assay standard error of the mean)
- A minimum release specification of X is tantamount to saying it's okay for the 95% lower confidence bound on the actual potency to be $X-1.65*SEM$.
- To make this judgment, you should know what that 95% lower bound is, relative to LL (the lowest potency believed to be effective)
- This same argument applies to upper limits

Using stability data and specifications to set shelf life

- Goal: Throughout its shelf life, product must be comparable to batches shown to be safe and effective in clinical studies
- Stability data are used to make predictions that can be extrapolated to future batches of product
- The most accurate predictions are based on mathematical modeling of biologically relevant stability-indicating parameters

21 CFR 600.3

- (l) *Dating period* means the period beyond which the product cannot be expected beyond reasonable doubt to yield its specific results.
- (m) *Expiration date* means the calendar month and year, and where applicable, the day and hour, that the dating period ends.

What can happen to a product over time?

- Loss of potency
- Aggregation
- Formation of potentially toxic degradants
- Alterations of container (including leaching, degradation of stopper material)

What maintains product stability?

- Intrinsic stability of the product
 - Can be cell substrate dependent
- Formulation!
 - Buffers, surfactants, lyophilization
- Container and closure system
- Storage temperatures

What are the opportunities for product degradation?

Drug product

?Excursions

Reconstitution

Storage at manufacturer

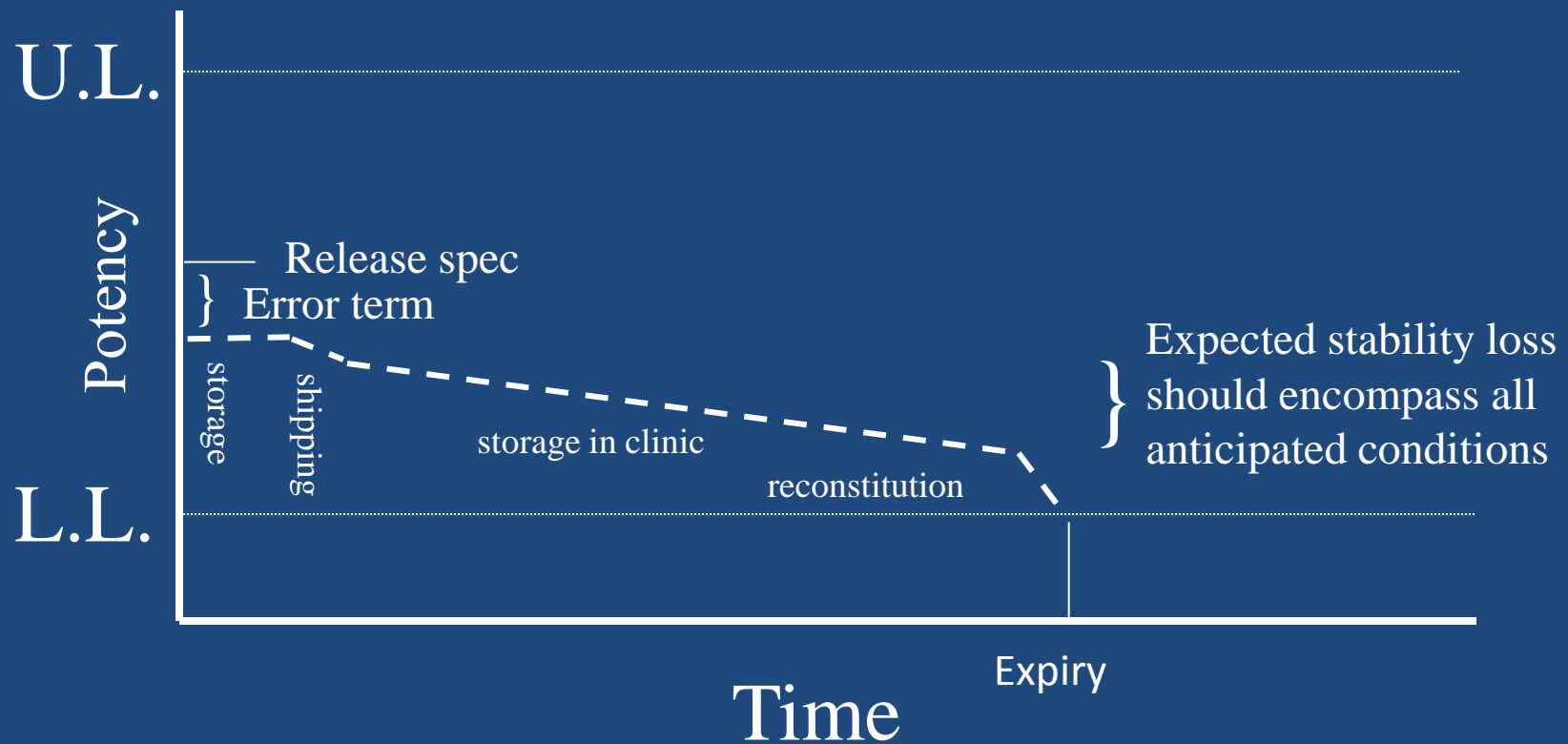
Storage at Clinic

Shipping

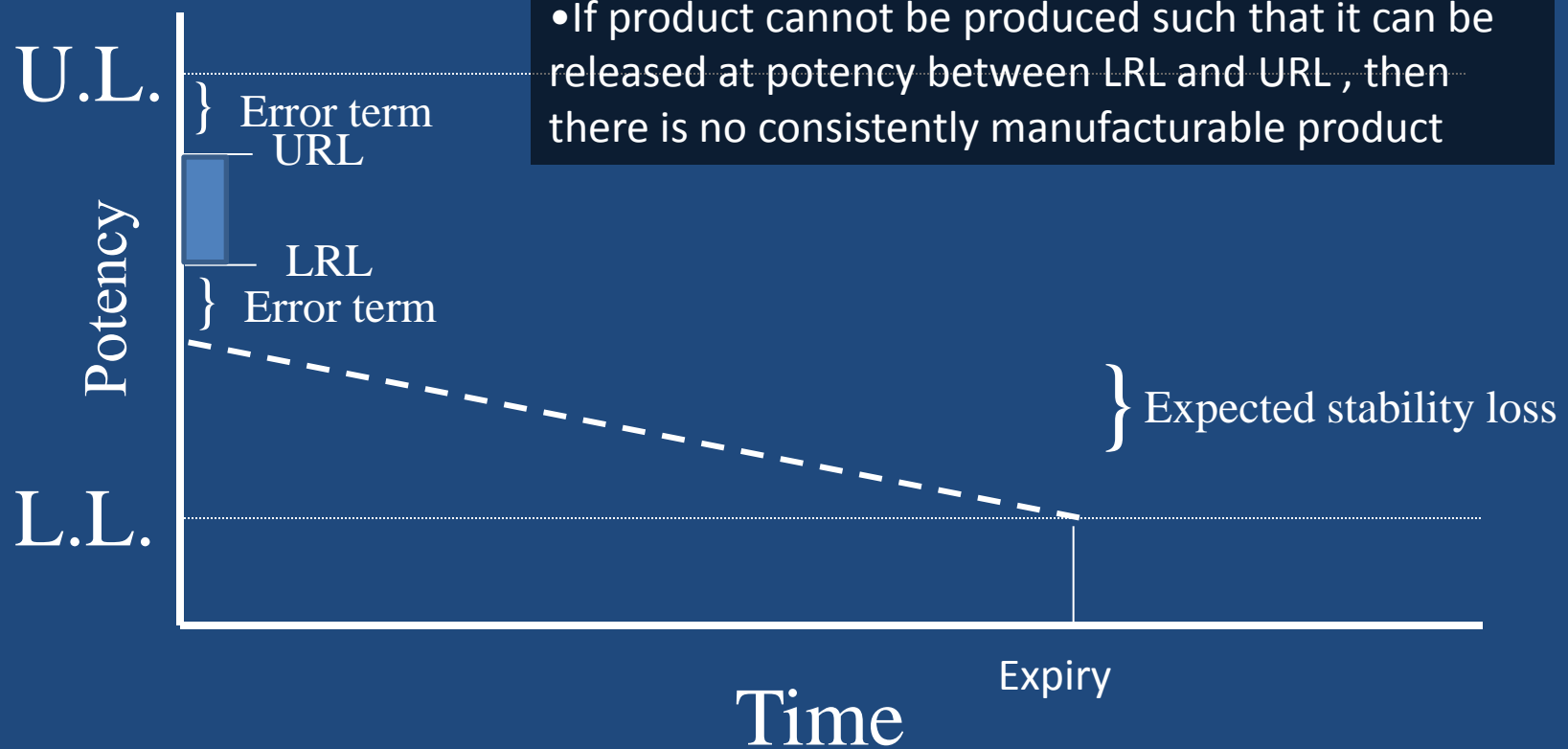
What stability-related quality attributes can we measure over time?

- Direct influencers
 - Potency
 - Toxic degradation products
 - Sterility (container closure)
- Indirect influencers
 - Anything that affects stability relative to a direct influencer
 - E.g., pH, moisture, etc.

Calculation of minimum release potency specification



Release potency window (LRL – URL)



When is this easier?

- Assay precision is high
 - When assay precision is high, it is easier to construct a release model due to improved understanding of release potencies and stability
 - Must be careful that assay is measuring the right thing
- Manufacturing variability is low
 - May depend on cell substrate selection
- Therapeutic index is wide
 - Assumes we understand the therapeutic index (LL and UL)
 - Surrogate markers can help to define the therapeutic index

Stability-indicating assays

- Identify clinically meaningful degradation in product
- Implies that the assay predicts clinical benefit not only at the beginning of the dating period, but also at the end
- Supportive data can often be obtained in accelerated or forced degradation studies

Development-what do we need to know about stability?

- What are the kinetics of decay?
- What are the degradation products?
- Are there stability-influencing factors that should also be controlled?
- Do we have sufficient knowledge of the stability of intermediates?
- Are the assays adequate?
 - Are potency assays stability-indicating?
 - Are potency assays precise enough to support product development?
- Do we have a sufficient understanding of material tested in clinical trials?
- Do we have a sufficient understanding of product performance at potency ranges likely to be encountered post-licensure?
- Can we estimate decay rates over the proposed dating period?
- Do we have a measure of our confidence in our estimates?

Take home messages

- Potency
 - Expected to predict clinical outcomes
 - Provides a critical bridge throughout the vaccine life cycle
 - Key influencers: the product!, assays, cell substrates
- Specifications
 - Assure that product will achieve expected results
 - Key influencers: Clinical data (potency), assays, stability
- Stability
 - Together with potency assays and manufacturing consistency (which may be cell substrate dependent), plays a major role in determining whether product can be manufactured within therapeutic window
 - Key influencers: Assays, storage conditions, formulation, stability study design