Use and interpretation of accelerated stability studies

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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)]

Key attributes of potency assays

- Predictive of *"**ability of the product . . . to effect a given result**"* (21 CFR 600.3(s))
- 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

Stability-indicating assays

- Identify degradation that is related to vaccine effect
- Implies that the assay is relevant to vaccine effect 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

What can happen to a vaccine over time?

- Loss of potency
  - May occur through various chemical mechanisms, even in the same product
- Aggregation
  - May cause loss of potency, interfere with assay, or both
- Formation of potentially toxic degradants
- Alterations of container (including leaching, degradation of stopper material)

Working definition of accelerated stability studies

- Stability studies under conditions of increased stress, where decay is expected to be faster than under normal storage conditions

The role of statistical models in stability analysis

- Provide an indication of the level of confidence in reported results
- Assessing whether this level of confidence is sufficient is an important regulatory function
- Where feasible, appropriate statistical models should be used to analyze data supporting regulatory decisions

Modeling accelerated stability studies

- If decay is linear (normally after log-transformation), key parameters are the slope and intercept
- The intercept estimates the starting potency, while the slope describes the rate of decay
- Thus, the slope is the most important parameter of decay in typical accelerated stability studies

Relevance of Arrhenius equation to stability modeling

$$k = Ae^{-Ea/RT}$$

- If we know slope at different temperatures, we can calculate the other parameters
- This allows us to predict slope at temperatures where we don't already know it
- Arrhenius modeling is potentially more reliable when interpolating vs. extrapolating stability from existing information
- Arrhenius modeling does not work across phase changes

How to analyze decay slopes?

- Evaluation of accelerated stability studies depends on our ability to assess slopes, and our confidence in those slopes
- Evaluation of accelerated stability studies may also depend on our ability to compare slopes, e.g.
  - Does Lot A have different decay vs. Lot B?
  - Do different lots have similar enough slopes to pool them?
  - Does Process A lead to different decay vs. Process B?

Factors influencing confidence in decay slopes

- Number of replicates
  - Number of lots tested
  - Number of samples tested
- Timing of samples
- Assay variability
  - May be affected by how samples are grouped in assay runs

Demonstrating similarity of decay slopes

- Failure to show that slopes are statistically different is not the same as showing that they are similar
- Confidence in similarity of slopes is increased if studies are designed with the power to detect potentially important differences
  - This depends on assay variability, study design

Formulation and accelerated stability

- Selecting a formulation that assures adequate stability is a critical function in product development
- It is normally not practical to use real-time studies to do all formulation development
- Stability associated with different formulations can be compared using accelerated studies
- Stability of final formulation can then be evaluated in real-time
- How certain do we need to be that two formulations are similar or different?

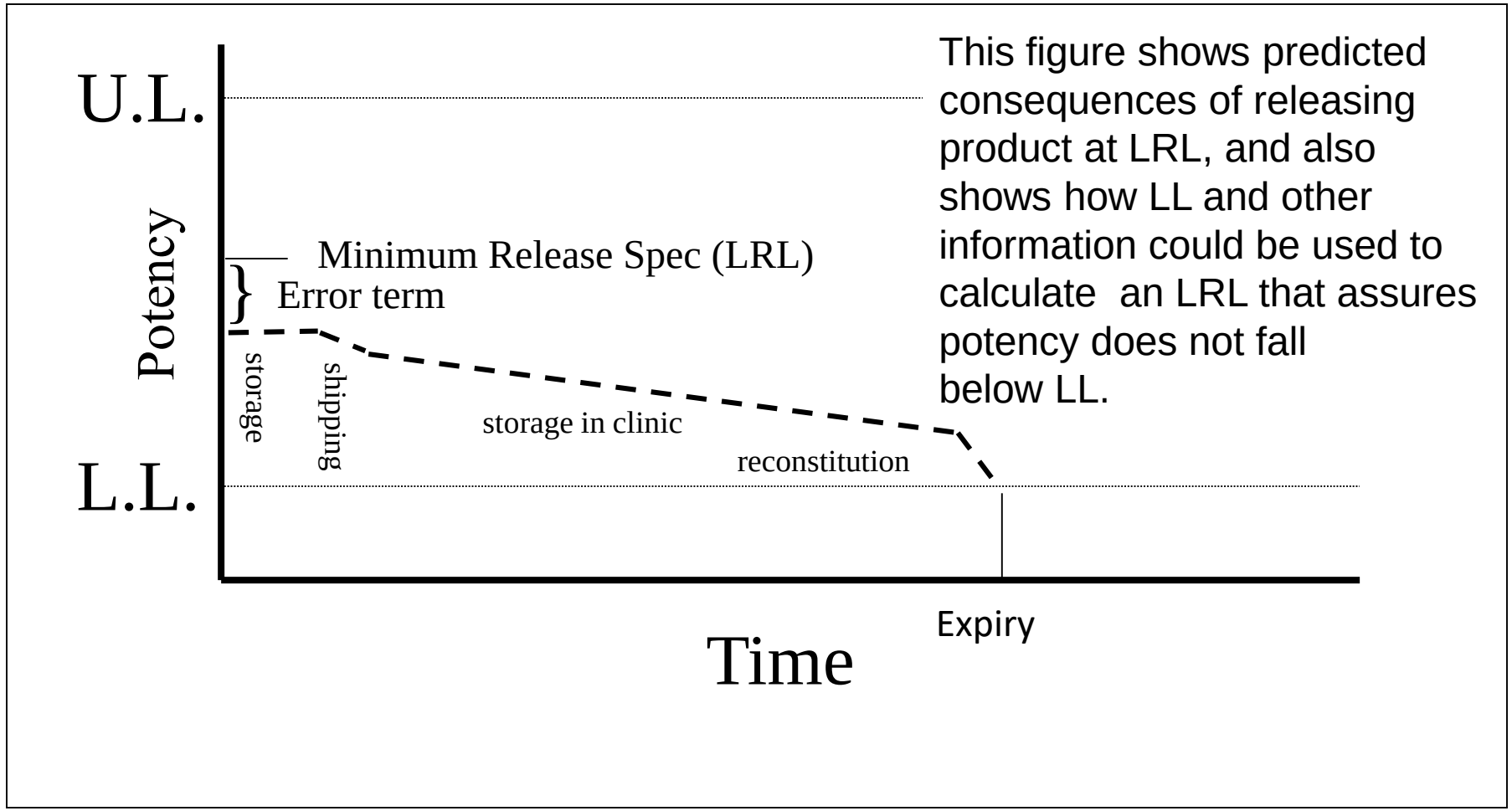
Comparability and accelerated stability

- Manufacturing changes frequently lead to a need to assure that product has not changed after vs. before manufacturing change
- CQAs are normally tested in this context
- Assuring no change in stability can add to confidence that post-change product is similar to the pre-change product
- In this setting, accelerated stability studies likely predict real-time stability (i.e., no change in accelerated stability means real time stability is also unlikely to be different)

Using stability data and specifications to set shelf life

- The *dating period* means the period beyond which the product cannot be expected beyond reasonable doubt to yield its specific results [21 CFR 600.3(l)].
- 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 reliable predictions to support the dating period are based on mathematical modeling of biologically relevant stability-indicating parameters

Relationship between release potency (specification) and end-expiry potency



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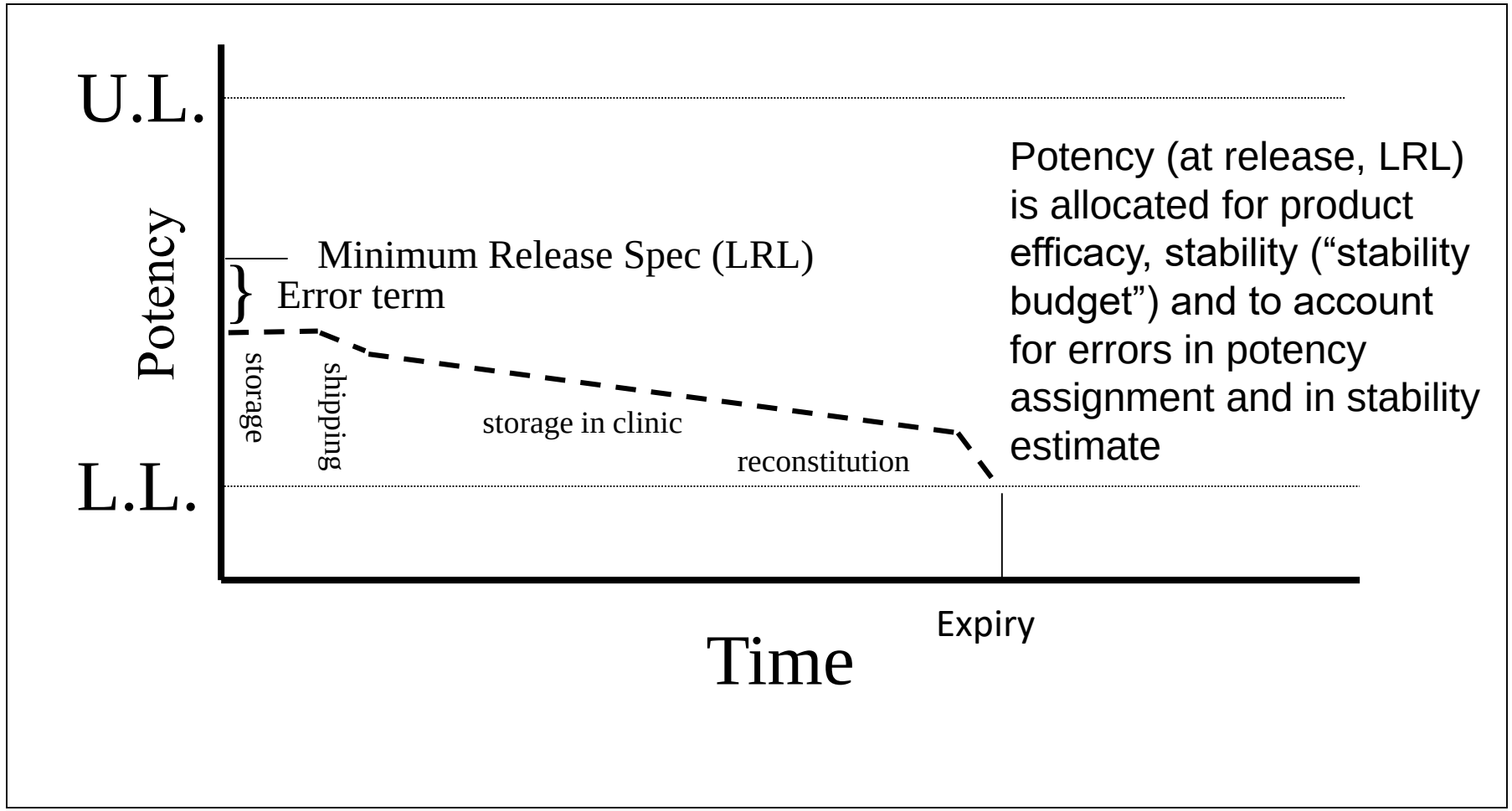
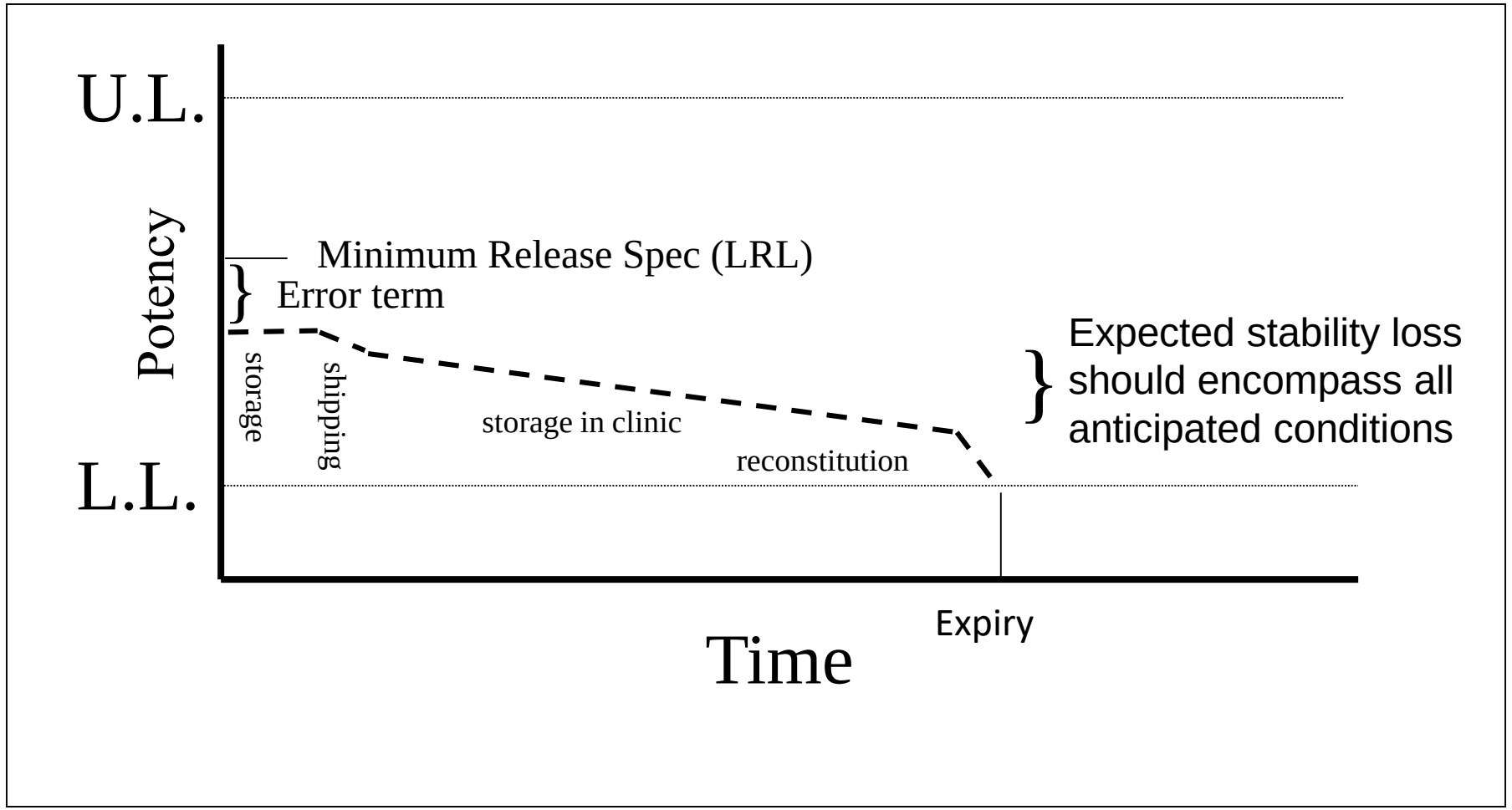


Calculation of minimum acceptable potency at release



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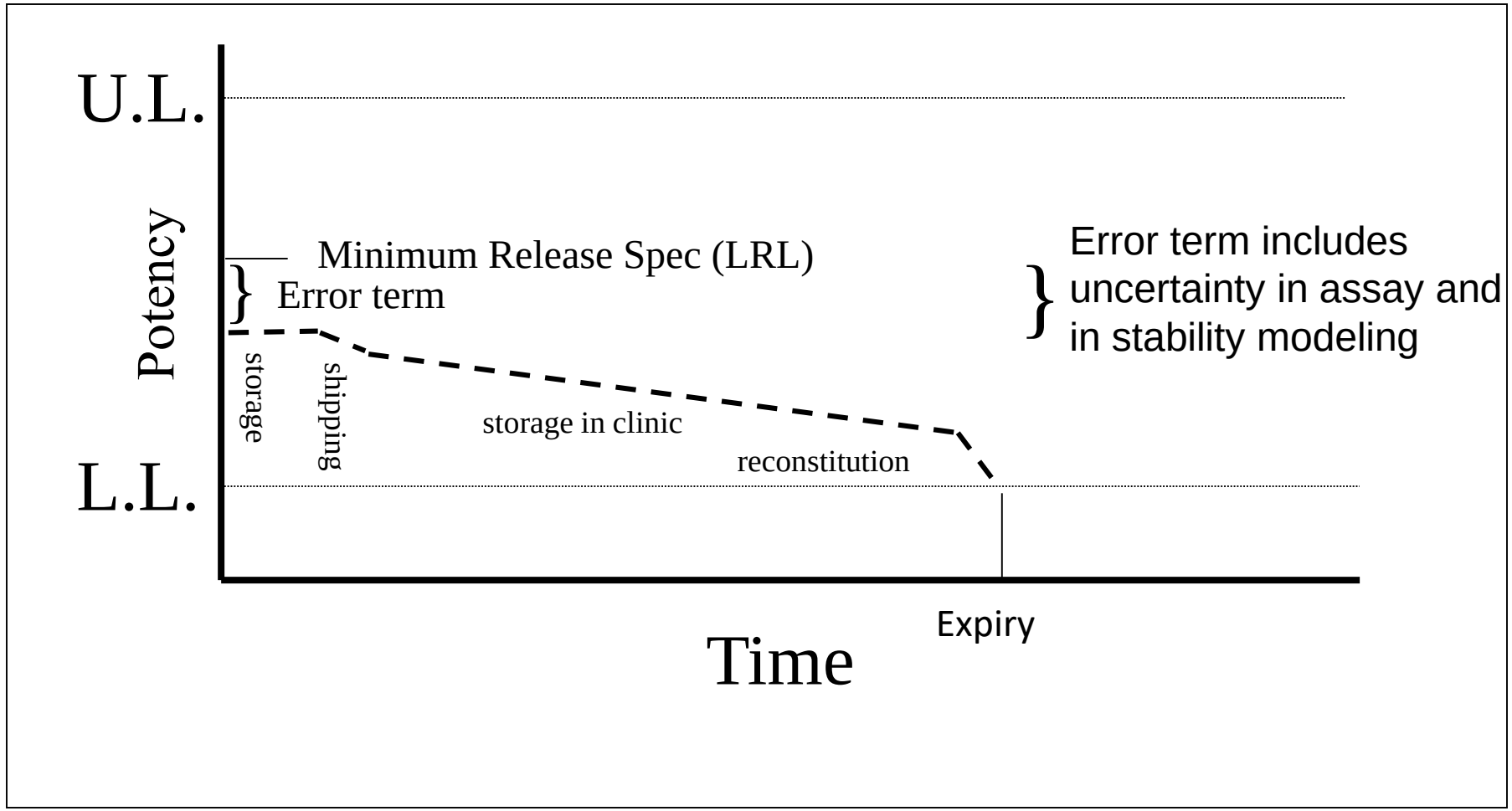
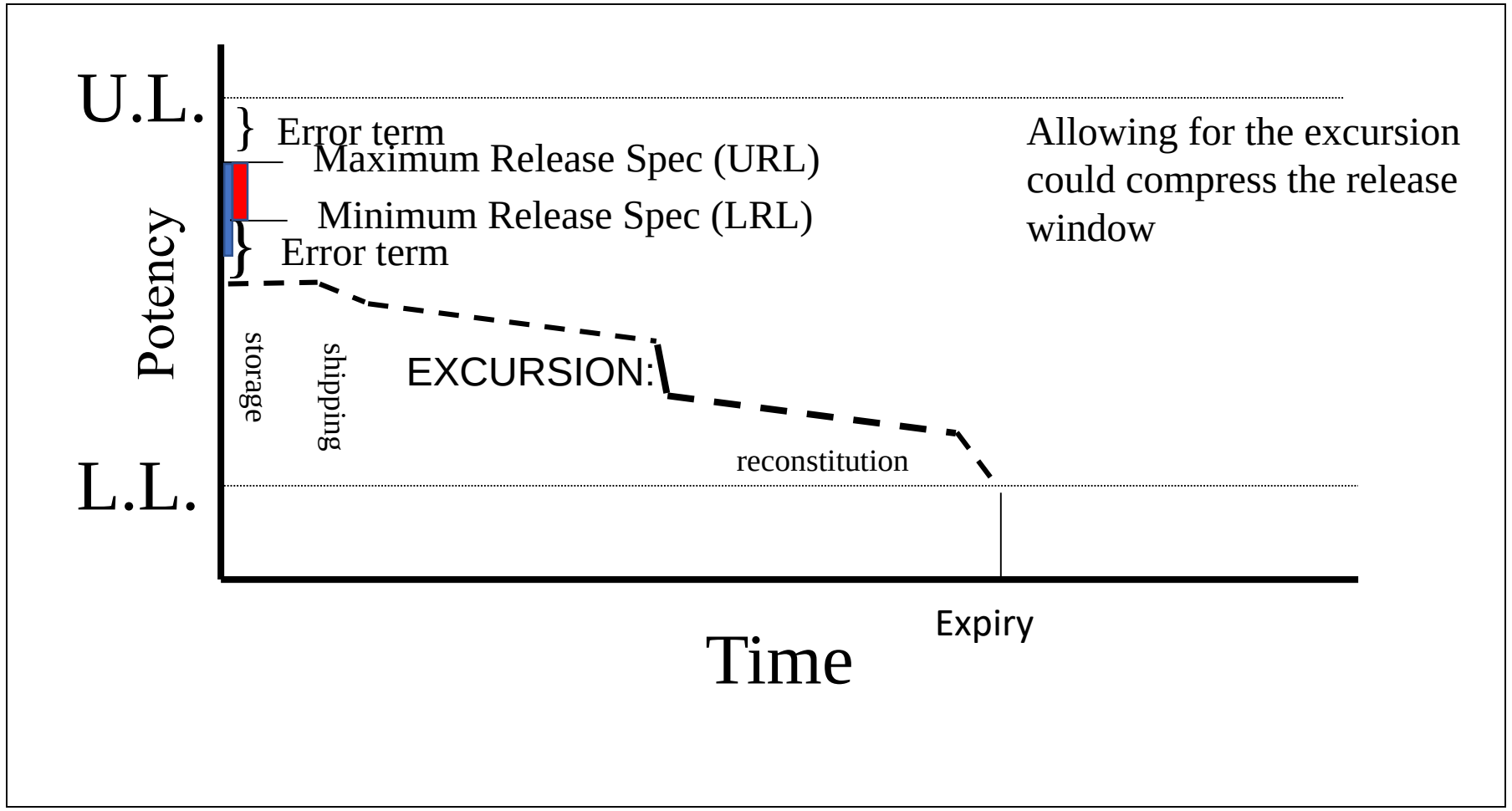


Release model is most robust when:

- Assay precision is high
  - When assay precision is high, error term is lower and 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
- Therapeutic index (between LL and UL) is wide

Adding excursions to the model



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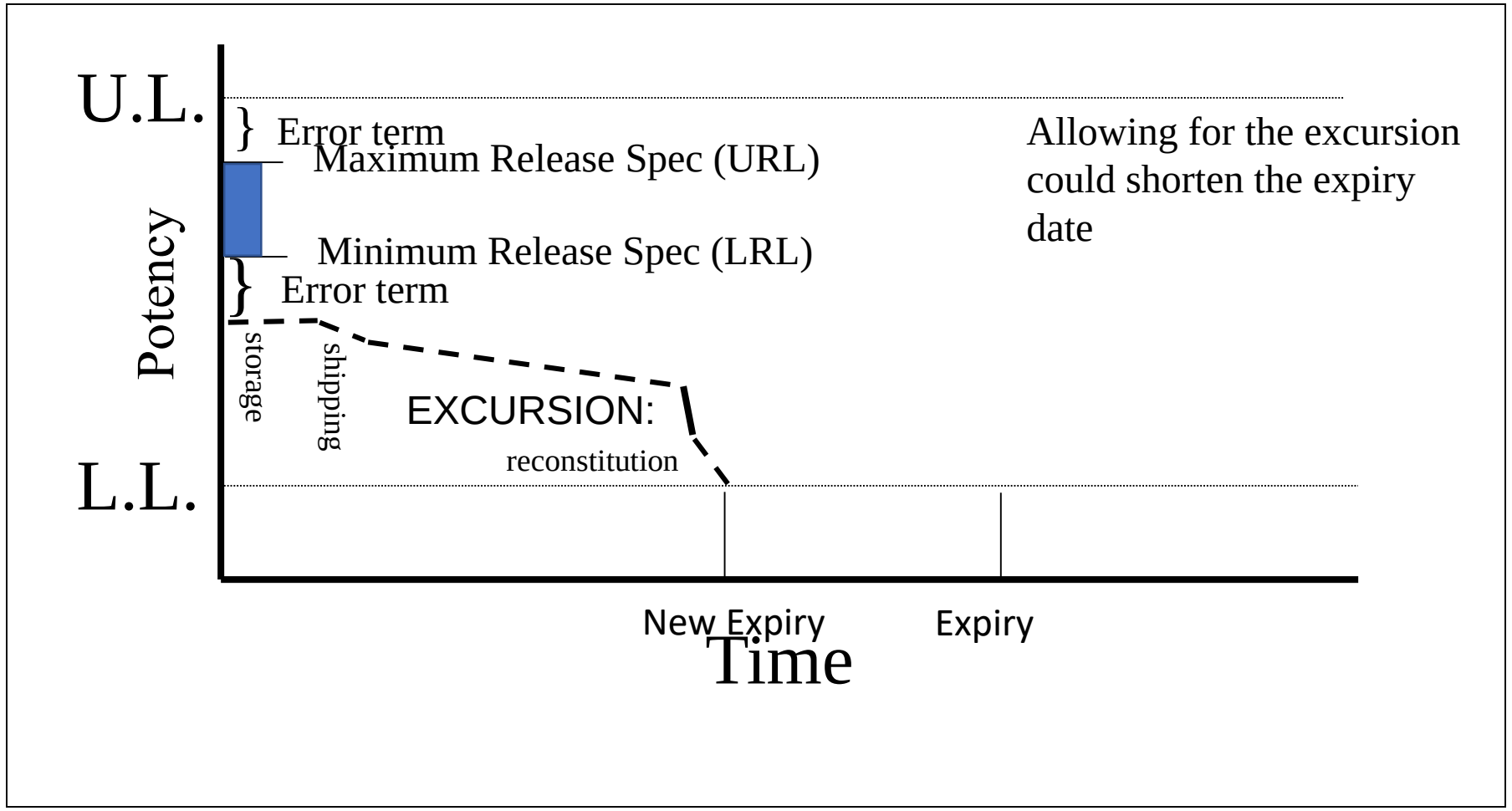
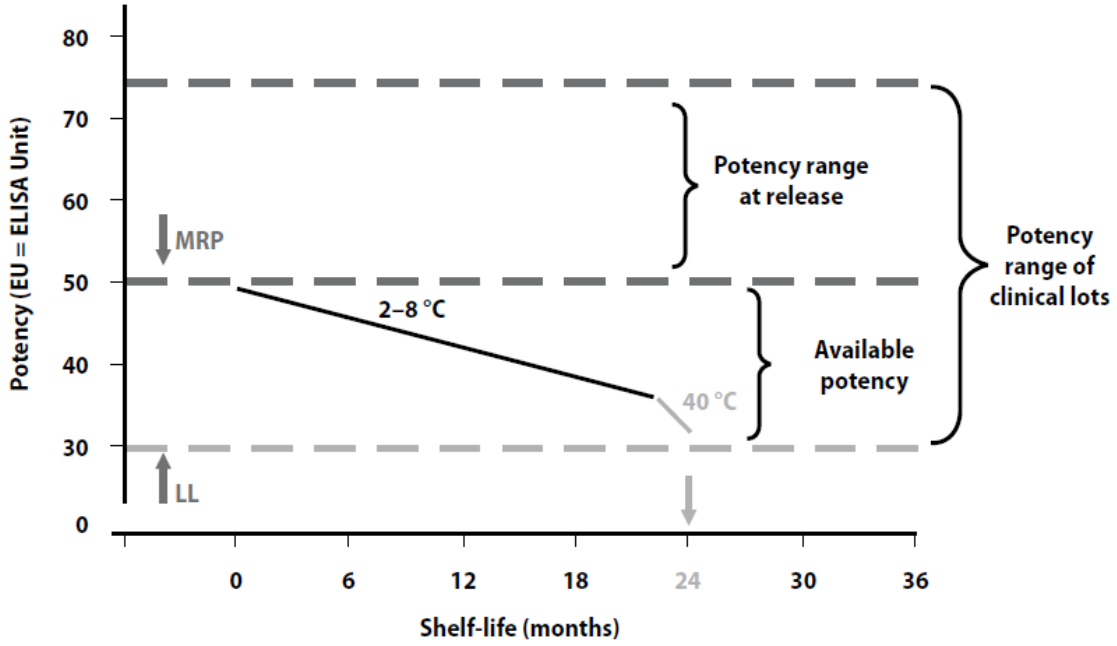


WHO Guidelines on the stability evaluation of vaccines for use under extended controlled temperature conditions (ECTC)

- Provides guidance for developing vaccines intended for temporary storage, directly before use, at temperatures higher than typically used for long-term storage

Fig. 1
Graphic representation of a product-release model for an ECTC application



Conclusions

- Accelerated stability studies can provide critical information to support development, manufacturing changes, and product use under unusual conditions
- Statistical modeling of stability is critical for interpreting accelerated stability studies
- Assay precision is a critical element of stability assessment, including for accelerated stability studies