Maintenance of vaccine stability through annual stability and comparability studies

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WORKSHOP ON
STATISTICAL ANALYSIS OF STABILITY TESTING

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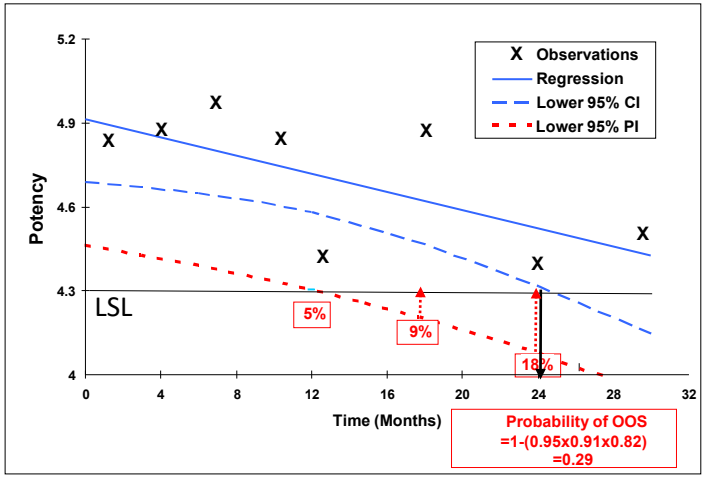
Opportunities for maintenance

- Stability monitoring
  - Annual stability program
- Stability comparability
  - When a process or product change may result in a change in kinetics
- Temperature excursions
  - Expected (LPI) and unexpected excursions in product storage conditions

Stability monitoring

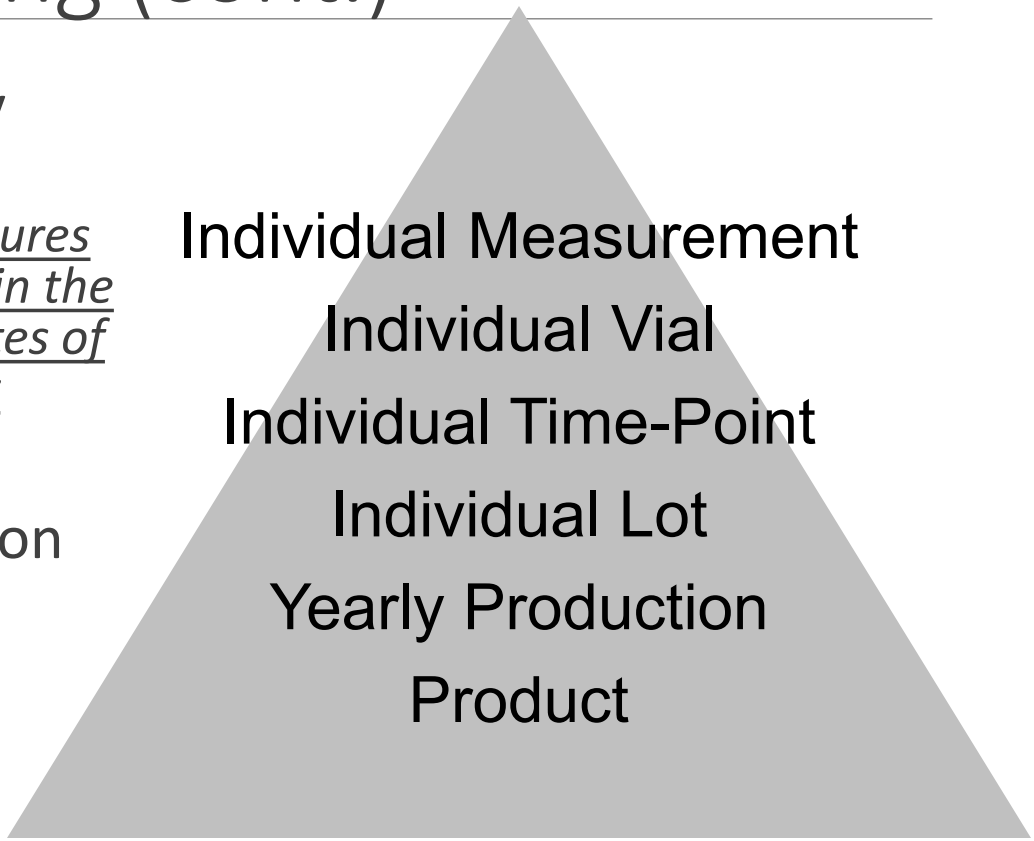
- One lot per year to monitor product stability
- Stability OOS:
  - ICH Q1E advocates for use of a confidence interval to determine shelf life – represents the "*average*" of the stability profile
  - However, "*individual stability measurements*" are bounded by a much wider prediction interval
  - P(OOS) of individual measurements increases throughout shelf life
  - Culminating in ~30% chance of one or more OOS's throughout shelf life



Schofield, *Maintenance*, 2009

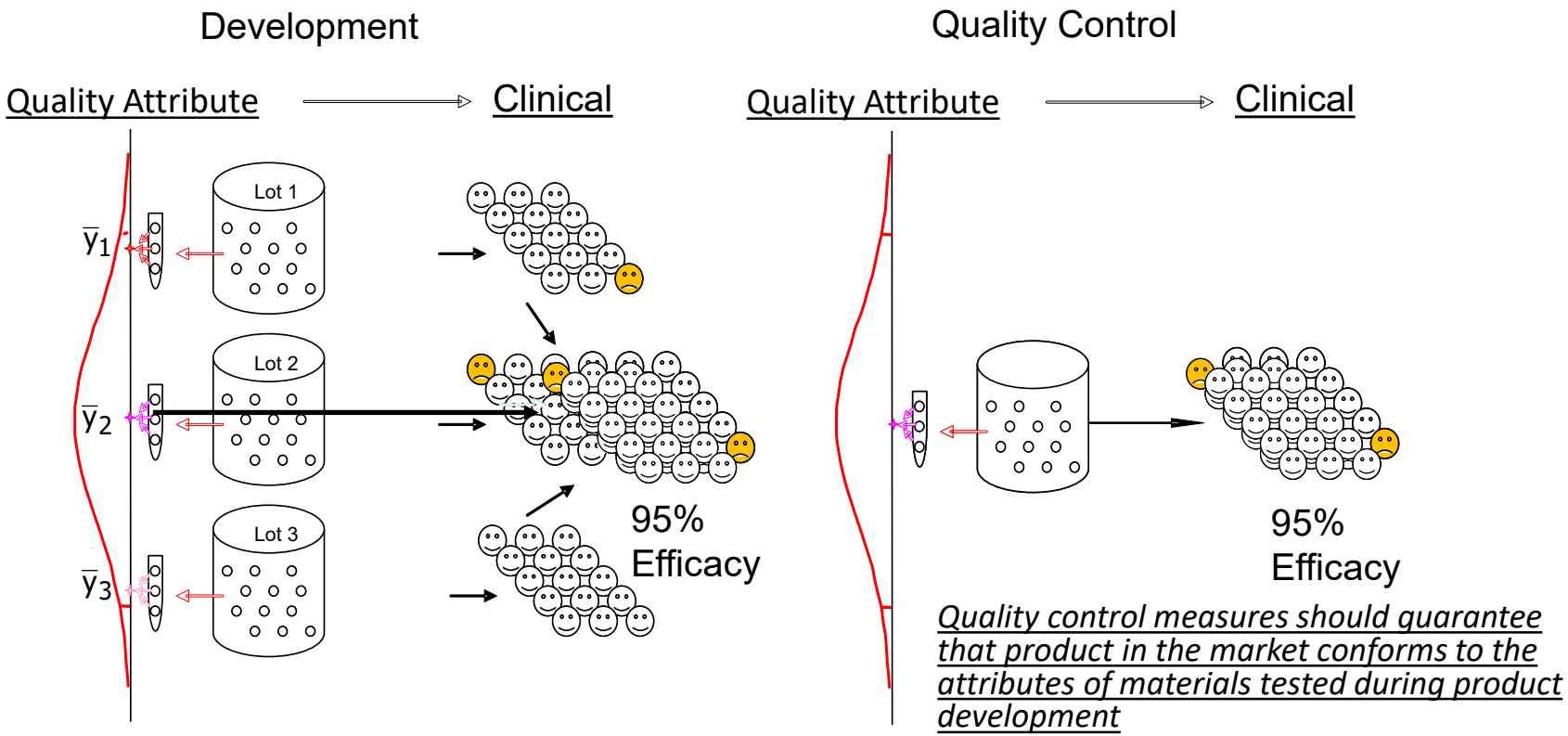
Stability monitoring (cont.)

- What is the goal of stability monitoring?
  - Paradigm: *Quality control measures should guarantee that product in the market conforms to the attributes of materials tested during product development*
- What is the target population
  - What are we studying?



Stability monitoring (cont.)

- Mean versus individual values
  - The mean of the batch is the measure of product quality

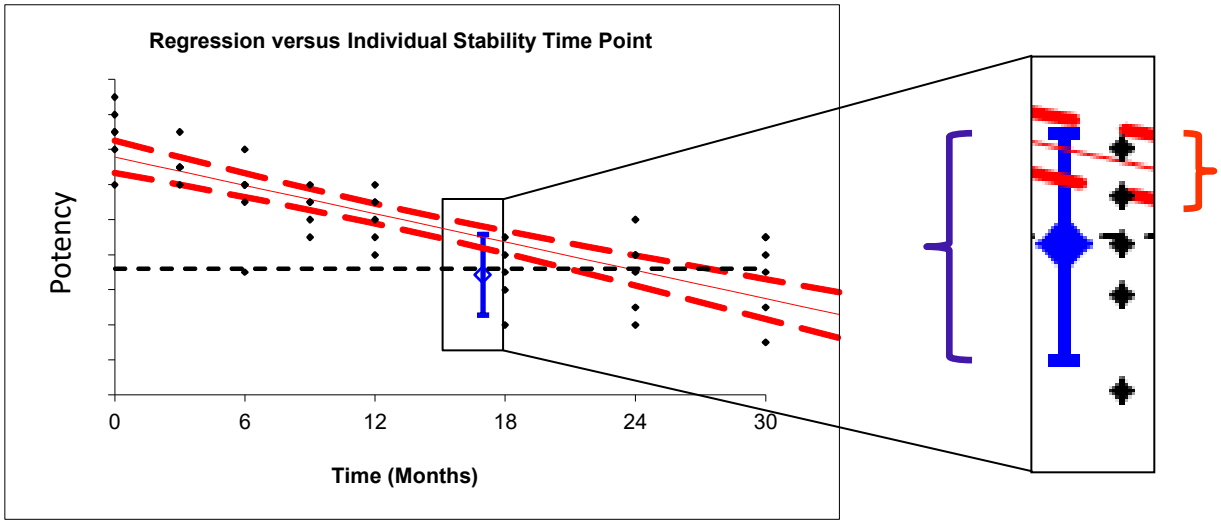


Stability monitoring (cont.)

- Solution: Treat post licensure stability as a form of "process monitoring"
  - Mitigation of stability OOS
  - Continued stability verification:
    - Use post licensure stability modeling
    - Combine data from ongoing post licensure studies to perform an overall analysis
    - Monitor slopes of post licensure studies

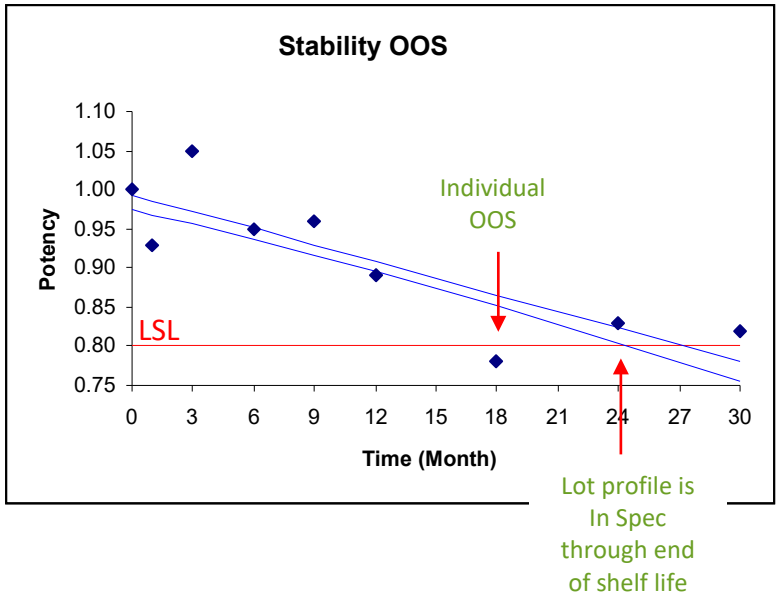
Stability monitoring (cont.)

- Estimate stability using an appropriate kinetics model
- Prediction from the kinetics model is more precise than prediction from individual stability measurements
  - "Smooths" out the long term variability of the potency assay
  - Uses the power of the measurements from other time points



Stability monitoring (cont.)

- Mitigation of stability OOS
  - Establish an OOT process using statistical modeling to demonstrate that the OOS result is not a quality concern, but is due to assay variability
  - Institute a retest plan to verify disposition of the lot
- Utilize the OOT process to predict quality and/or OOT



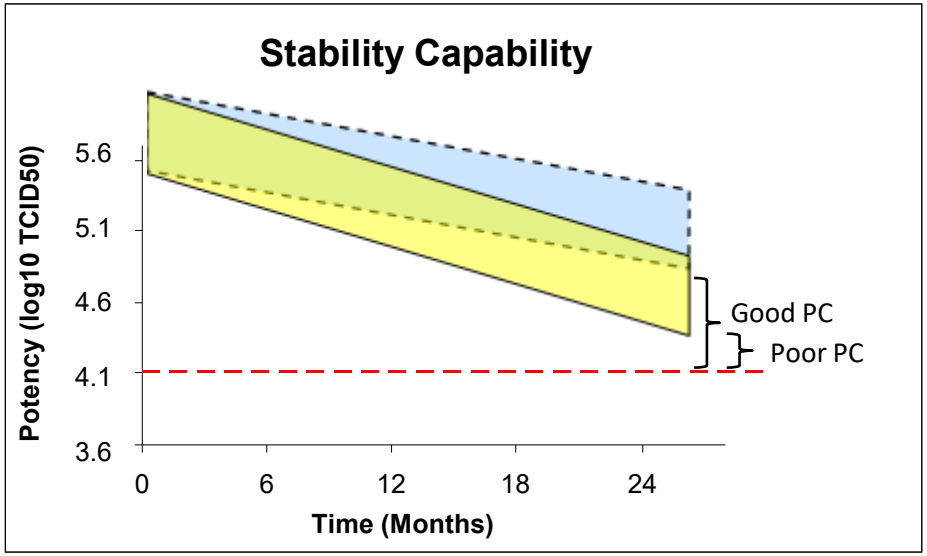
Gorko, 2003

Stability monitoring (cont.)

- Design a stability monitoring program
- Objective:
  - Utilize the post licensure program to bridge product stability performance to development, and to monitor the process for shifts and trends
- Design parameters:
  - Number of lots – Stability intervals – Assay format
- Design criteria:
  - Minimize the risk of missing a change in product stability (false success)
  - Minimize the risk of incorrectly detecting a change (false failure)

Stability monitoring (cont.)

- Select lots on a periodic basis (yearly, quarterly, monthly) based on "stability capability" - proximity of expiry potency to minimum potency
  - Good "SC" → less frequent selection
  - Poor "SC" → more frequent selection
  - Process monitoring:
    - Use combined data from ongoing stability lots to forecast expiry potency
  - Product monitoring:
    - Monitor individual lot slopes for extreme outliers.

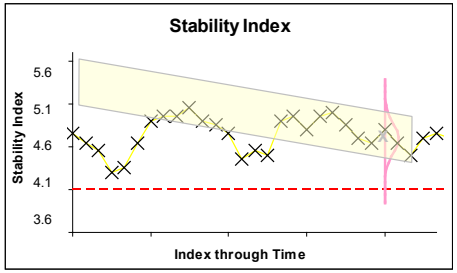


Stability monitoring
Process monitoring

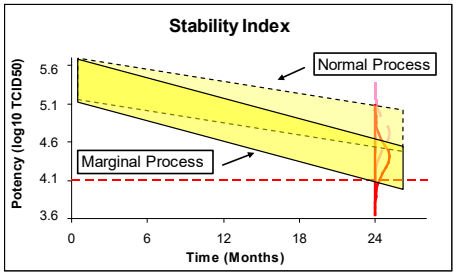
- Combine data from ongoing post licensure studies to perform an overall analysis
  - Appropriate to a shelf life determination approach
  - Formulated as an “Index”
  - Equal to the predicted potency at EOSL from a pooled analysis

Sample calculation of vaccine quality index
4 Lots per Year

Number of months earlier released	Month 0	3	6	9	12	15	18	21	24	w_i=1/var(Y)	Predicted Month 24	w_i*Yhat
0	4.891									NA	NA	NA
3	4.771	4.932								0.009	6.06	0.0086
6	4.932	4.723	4.727							0.040	4.08	0.0264
9	4.926	4.556	4.613	4.934						0.115	4.81	0.0890
12	4.933	5.012	4.334	5.028	5.862					0.263	6.16	0.2608
15	4.846	4.975	4.887	4.245	4.011	3.821				0.528	3.10	0.2635
18	4.811	5.098	5.105	4.576	4.983	5.042	5.271			0.966	5.19	0.8060
21	4.934	4.769	4.545	4.605	4.244	4.770	3.501	5.774		1.647	4.63	1.2284
24	4.894	4.632	4.351	4.668	4.388	5.105	4.586	4.627	3.222	2.647	4.11	1.7511
									Sum=	6.214	Index =	4.4338



Index is monitored over time with acquisition of each new time point



A threshold is determined which distinguishes a normal from a marginal process (predicts failure to meet LSL with 95% confidence.

Fairweather, 2003
Schofield, 2006

Stability monitoring
Process monitoring

Full

Released	Month 0	3	6	9	12	15	18	21	24	w_i=1/var(Y)
0	4.891									NA
3	4.771	4.932								0.009
6	4.932	4.723	4.727							0.040
9	4.926	4.556	4.613	4.934						0.115
12	4.933	5.012	4.334	5.028	5.862					0.263
15	4.846	4.975	4.887	4.245	4.011	3.821				0.528
18	4.811	5.098	5.105	4.576	4.983	5.042	5.271			0.966
21	4.934	4.769	4.545	4.605	4.244	4.770	3.501	5.774		1.647
24	4.894	4.632	4.351	4.668	4.388	5.105	4.586	4.627	3.222	2.647
									Sum=	6.214

Drop 1

Released	Month 0	3	6	9	12	15	18	21	24	w_i=1/var(Y)
0	4.891									NA
3	4.771	4.932								0.009
6	4.932	4.723	4.727							0.040
9	4.926		4.613	4.934						0.112
12	4.933	5.012		5.028	5.862					0.260
15	4.846	4.975	4.887		4.011	3.821				0.494
18	4.811		5.105	4.576	4.983		5.271			0.690
21	4.934	4.769		4.605	4.244	4.770		5.774		1.220
24	4.894	4.632	4.351		4.388	5.105	4.586		3.222	1.944
									Sum=	4.768

Drop 2

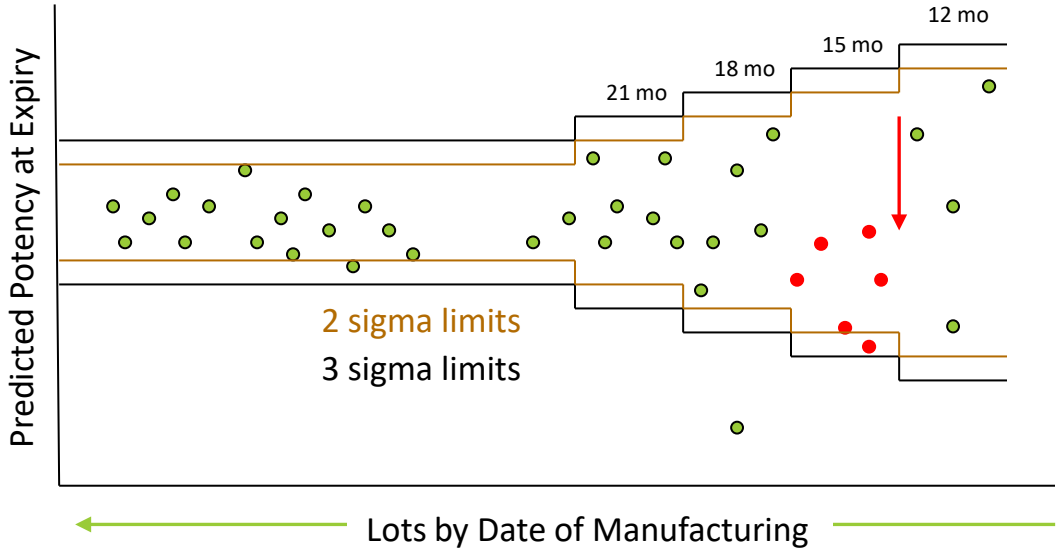
Released	Month 0	3	6	9	12	15	18	21	24	w_i=1/var(Y)
0	4.891									NA
3	4.771	4.932								0.009
6	4.932		4.727							0.040
9	4.926			4.934						0.101
12	4.933	5.012			5.862					0.202
15	4.846		4.887		4.011	3.821				0.472
18	4.811			4.576	4.983		5.271			0.688
21	4.934	4.769			4.244			5.774		1.391
24	4.894		4.351		4.388	5.105			3.222	1.472
									Sum=	4.375

Testing Scheme	#Tests/Yr	%Saving	Index Sigma	%Decrease in Efficiency
Full	24	0%	0.4041	0%
Drop 1	20	17%	0.4580	12%
Drop 2	15	38%	0.4781	15%

- Utilize “matrixing” to decrease stability testing burden
  - Dropping one test per lot in the first and second year results in a 17% saving in test burden, with a 12% drop in Index efficiency
  - Dropping two tests per lot in the first and second year results in a 38% saving in test burden, with a 15% drop in Index efficiency

Stability monitoring
Product monitoring

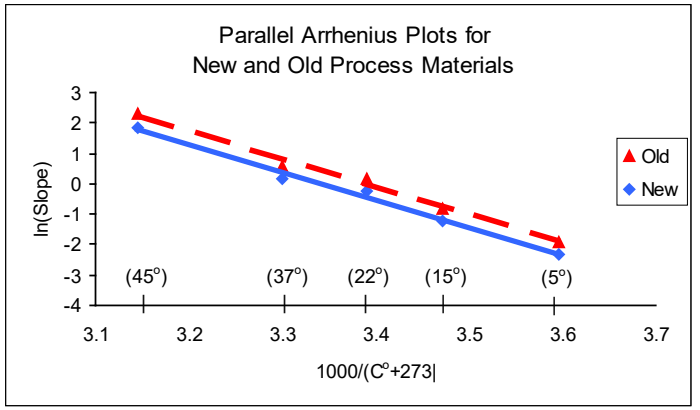
- Monitor slopes of post licensure studies (SPC)
  - Appropriate to a release limit approach
  - Evaluate ongoing lots with > 12 mos. of data. If predicted potency at expiry is outside 3 sigma limits, lot is investigated as an extreme outlier (atypical lot)
  - Address potential shifts in a timely manner



Stability comparability

- Using Arrhenius relationship as a stability "fingerprint"
  - Not as a predictor of slope at the labeled storage temperature
  - With a commitment to monitor routine stability on new process materials
  - Statistical approaches have been proposed using a "stability space" and "equivalence testing"

    . . . or rely upon continuous stability verification (maybe together with accelerated stability)



$$\ln|\text{Slope}| = a + b \cdot \frac{1}{|\text{Temp}|}$$

Schofield, *Maintenance*, 2009
Noël, 2001
Burdick, 2011, 2013
Yu, 2015

Temperature excursions

- Excursions from the labeled storage condition occur for planned and unplanned reasons
  - Planned excursions under the manufacturers control including labeling, packaging, and inspection
    - Managed through a release model
  - Unplanned excursions outside the manufacturers control including equipment failures (e.g., refrigerators), regional practices (e.g., pharmacy to patient to doctor), and ECTC

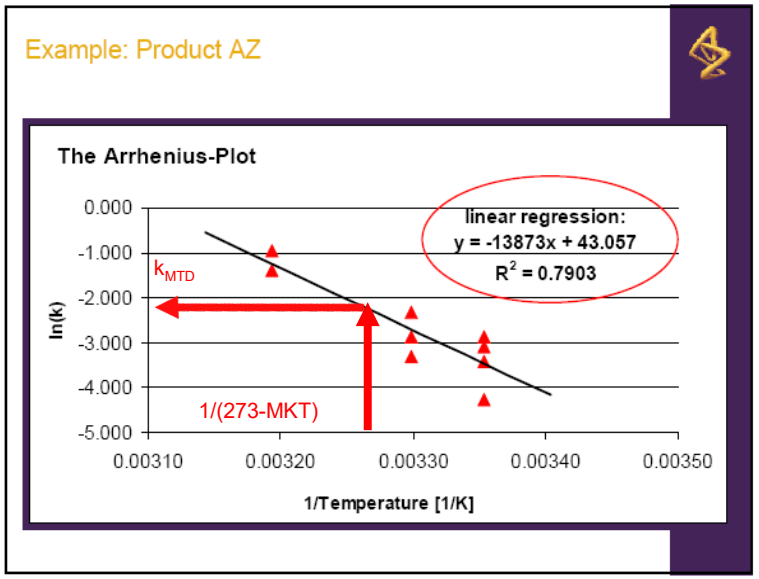
Temperature excursions (cont.)

- An assessment plan can be developed using accelerated stability data and the Arrhenius model:

$$\ln(k) = a + \frac{b}{°K}$$

  - Determine mean kinetic temperature of excursion in °K ($273\text{-}MKT_{°C}$)
  - Interpolate the degradation rate corresponding to mean kinetic temperature from the model – k_{MKT}
  - Determine loss of potency due to excursion:

$$Loss = k_{MKT} \cdot t_{Excursion}$$



MKT is expressed as:

$$-ln\left(\frac{e^{-\Delta H/RT1} + e^{-\Delta H/RT2} + \ldots + e^{-\Delta H/RTn}}{n}\right)^{\Delta H/R}$$

Where.
ΔH = activation energy (typically from 60 to 100 kJ/mol for solids and liquids)
R = 8.314472 J/mol-K (universal gas constant)
T = temperature in degrees K
n = the number of sample periods over which data is collected

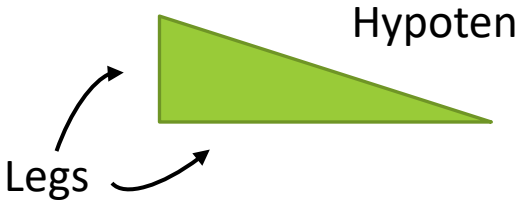
Note : ln is the natural log and e_x is the natural log base.

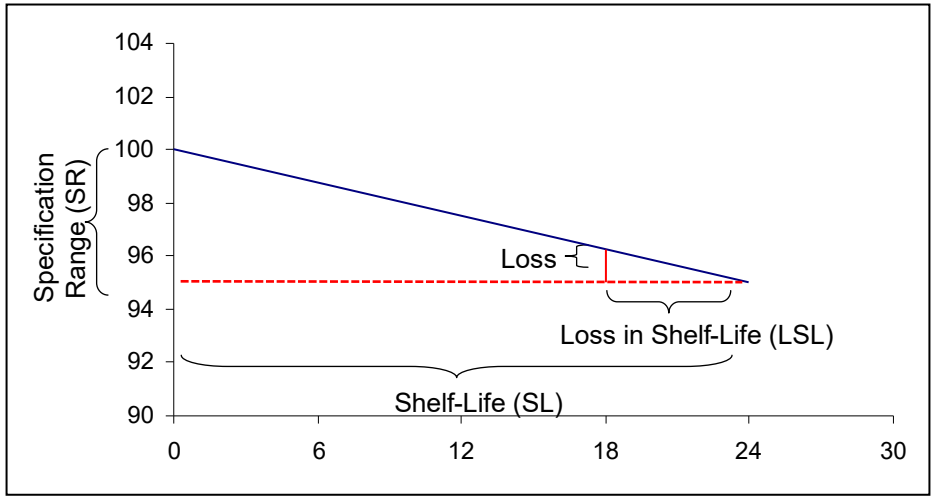
Temperature excursions (cont.)

- Recalculate expiration date
- Use Loss = $k_{MKT} \cdot t_{Excursion}$ to determine the loss in shelf life (LSL) – amount of shelf life lost due to the excursion
  - Using the principle of similar triangles – ratio of "legs" of similar triangles are equal

$$LSL/_{Loss} = SL/_{SR},$$

$$LSL = SL/_{SR} \cdot Loss$$





Temperature excursions (cont.)

- Example: a refrigerated product is subject to MKT exposure of 25°C over a 48-hour period of time.
  - Loss rate at 25°C = 0.0025 from the Arrhenius interpolation
  - Specification Range = Release – LSL = 3.5 – 3.0 = 0.5 log
  - Shelf-life = 24-Months

$$Loss = 0.0025 \log/hr \cdot 48 - hrs = 0.12 \log,$$

$$LSL = \frac{24\ Months}{0.5\ log} \cdot 0.12\ log = 5.8\ Months$$

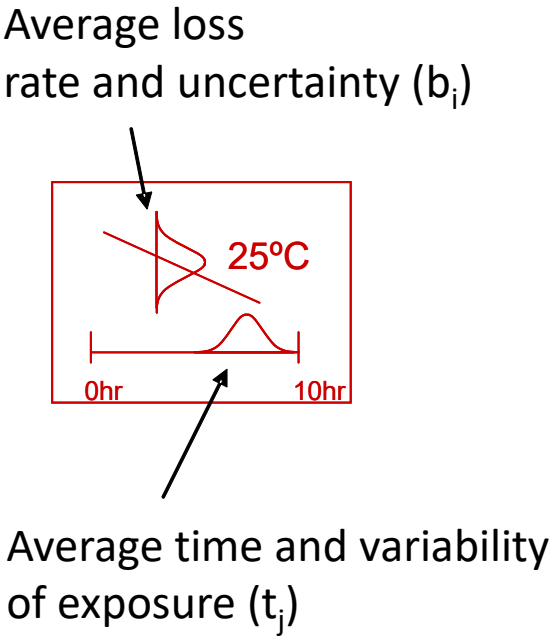
  - Thus, if expiry is 1/1/20, the recalculated expiry is ~7/1/19

Temperature excursions (cont.)

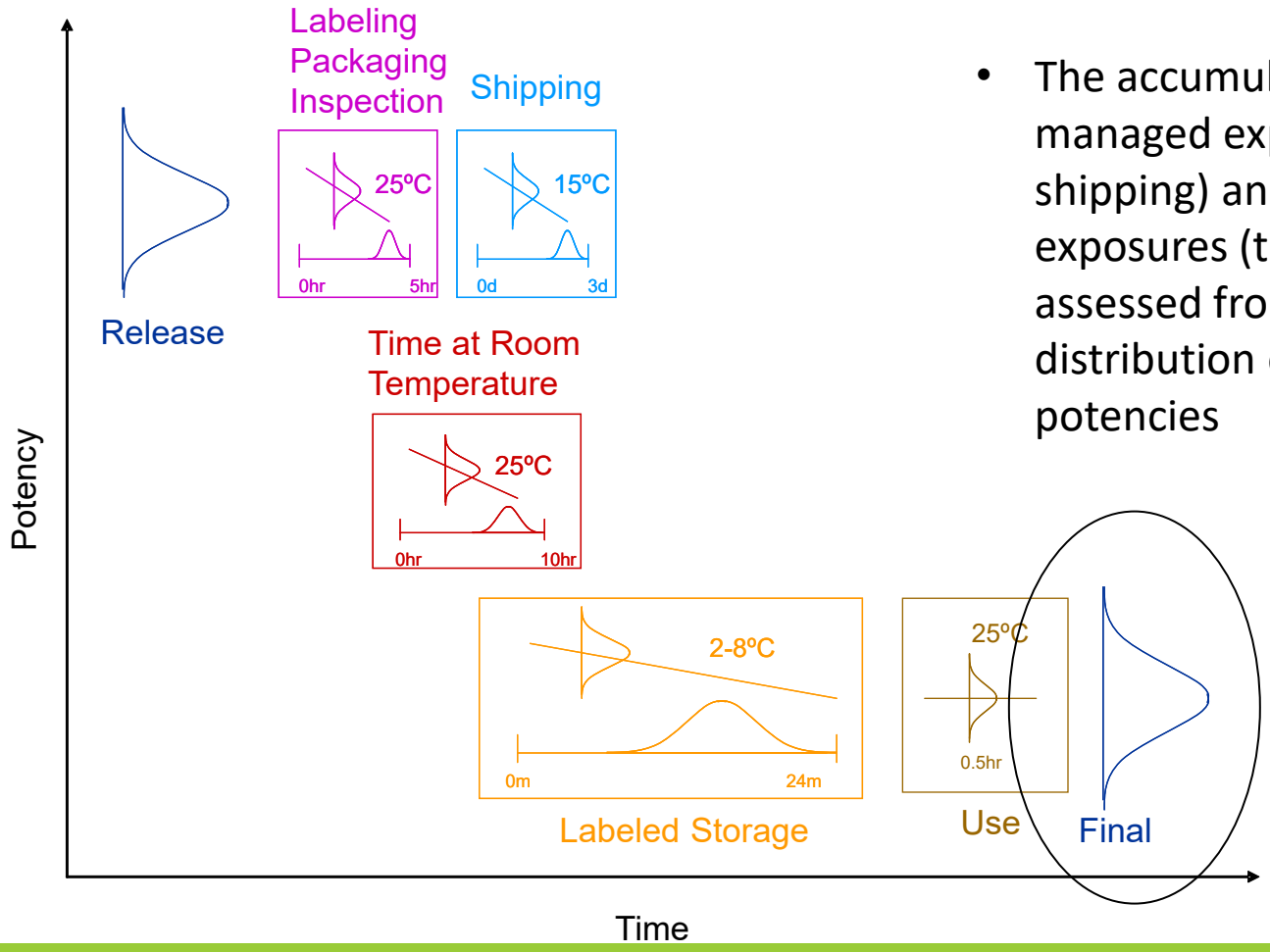
- Assess the risk to a patient of receiving product that is unsafe or subpotent due to exposure to elevated temperatures outside the chain of custody of the manufacturer (e.g., pharmacy to patient to doctor)
  - A release model is built upon “worst case” exposure (i.e., maximum prescribed time of exposure such as product shelf life) to various conditions
  - A risk analysis simulates “real case” outcomes from models and information on the actual product exposures

Temperature excursions (cont.)

- Example of Monte Carlo simulation of expected potencies for material exposed to 25°C up to 10-hours
  - Simulate 10K random lots
  - Randomly pick from distributions of loss rates (b_i) and exposure times (t_j)
  - For each lot calculate the potency at the end of their exposure times
    - $Final = Beginning - b_i \cdot t_j$



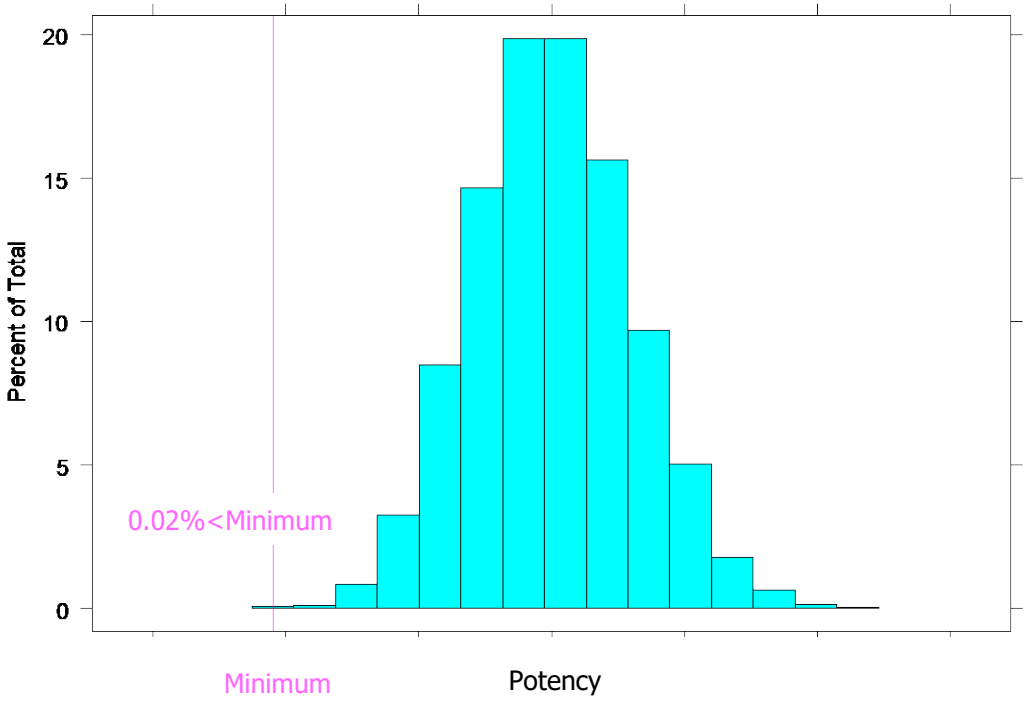
Temperature excursions (cont.)



- The accumulated impacts of managed exposures (LPI and shipping) and unmanaged exposures (time at RT) can be assessed from the simulated distribution of final (expiry) potencies

Temperature excursions (cont.)

- The resulting distribution is used to calculate percent of lots that are predicted to fall below the minimum potency specification at the time of administration
- The conclusion is that there is minimal risk (0.02%) that a patient will receive vaccine from a lot with potency less than the minimum specification
  - Note: the risk that a patient will receive subpotent vaccine is 5% using the release model



Summary

- Product quality is assured through appropriate calculation of shelf-life and release limit
- Stability monitoring can be designed and analyzed to ensure that the “stability process” and “product stability” deliver potent vaccine through the end of shelf life
- Stability comparability can effectively use accelerated temperature conditions to address relevant process changes
- Intended excursions can be managed using the release model; unintended excursions can be managed by reassessing the expiry date from the estimated excursion loss

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Thank you

Questions?

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