A fit-for-purpose perspective on Shelf-Life and Internal Release Limits determination: objectives and models

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PHARMALEX

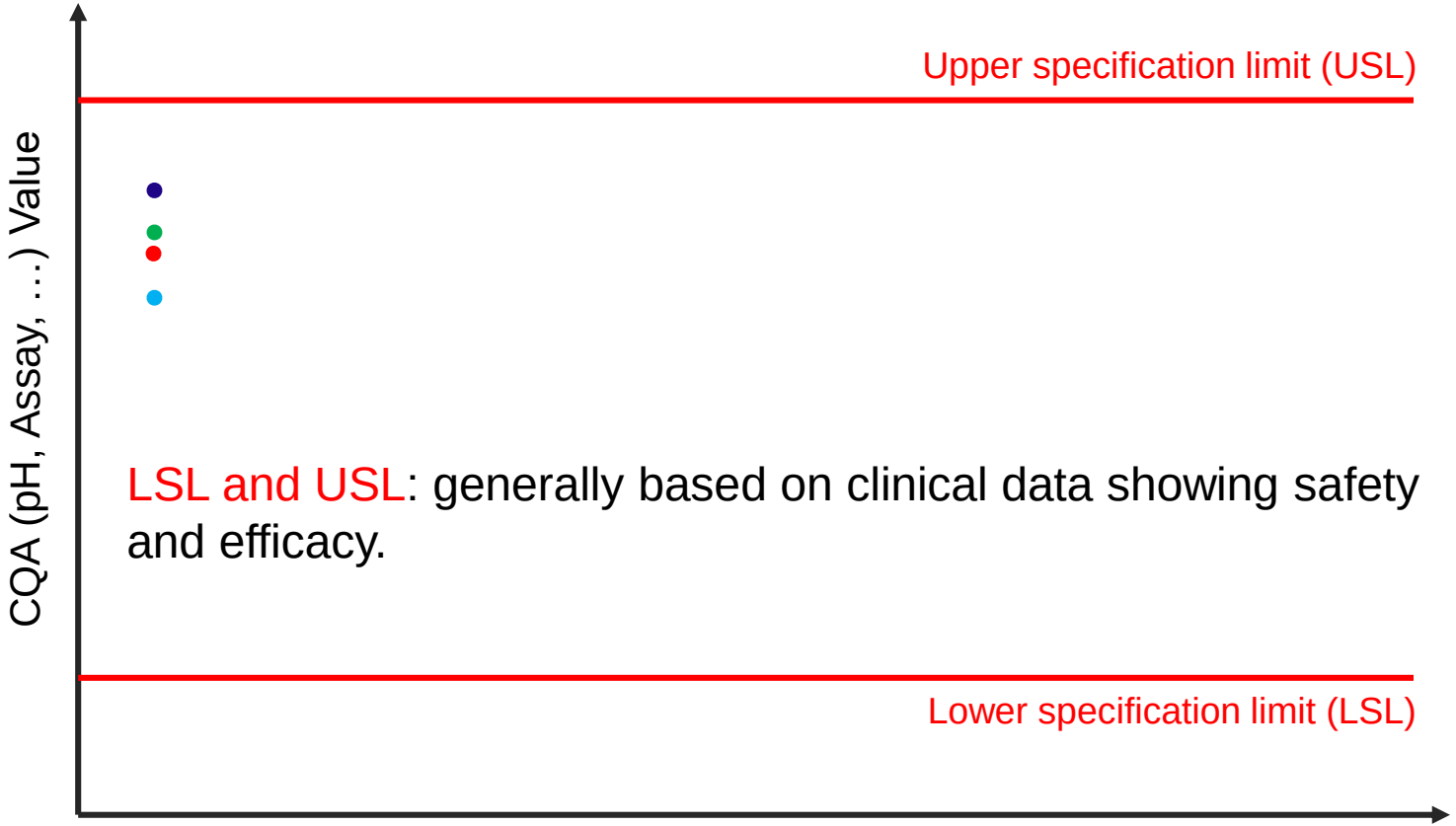
What is behind a drug expiry date?

HOW MILK CONTAINERS SHOULD BE

- **Expiry date:** The date after which a consumable product should not be used because it may be spoiled, damaged or ineffective

- For drugs = based on the risk of critical quality attributes (CQAs) running out of predefined specifications

Specifications are (generally) based on clinical data



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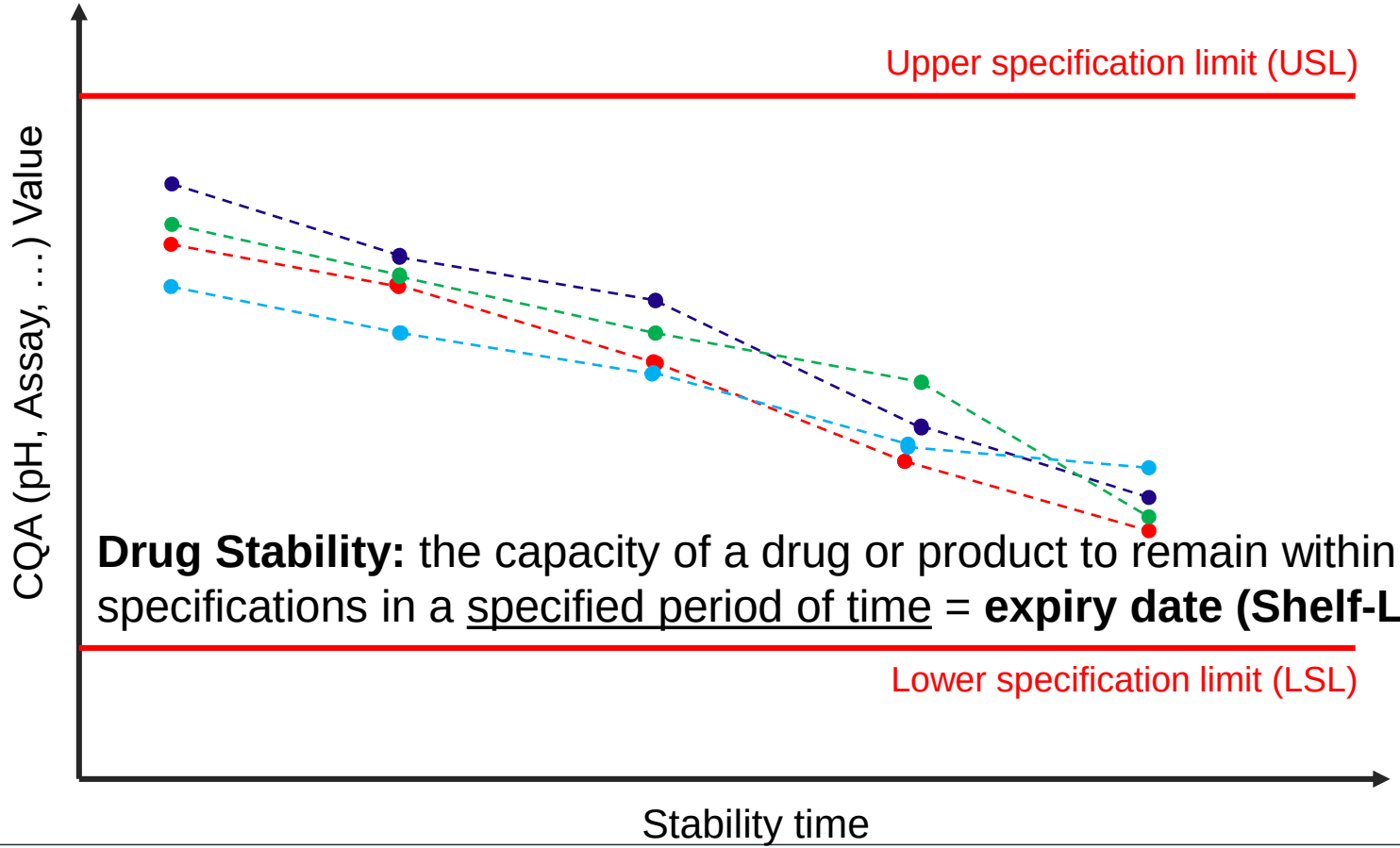
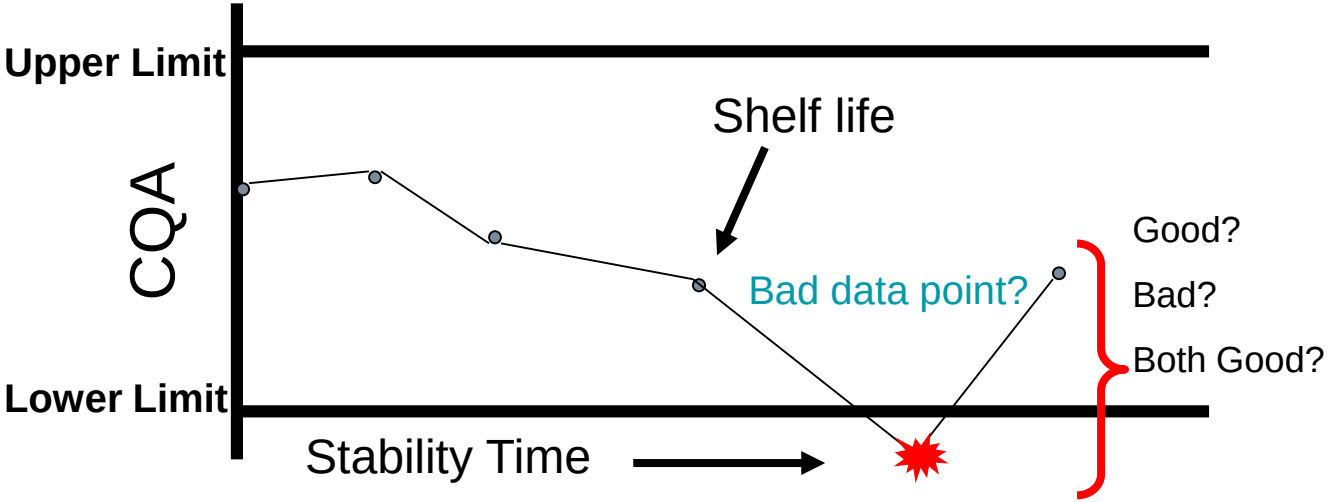


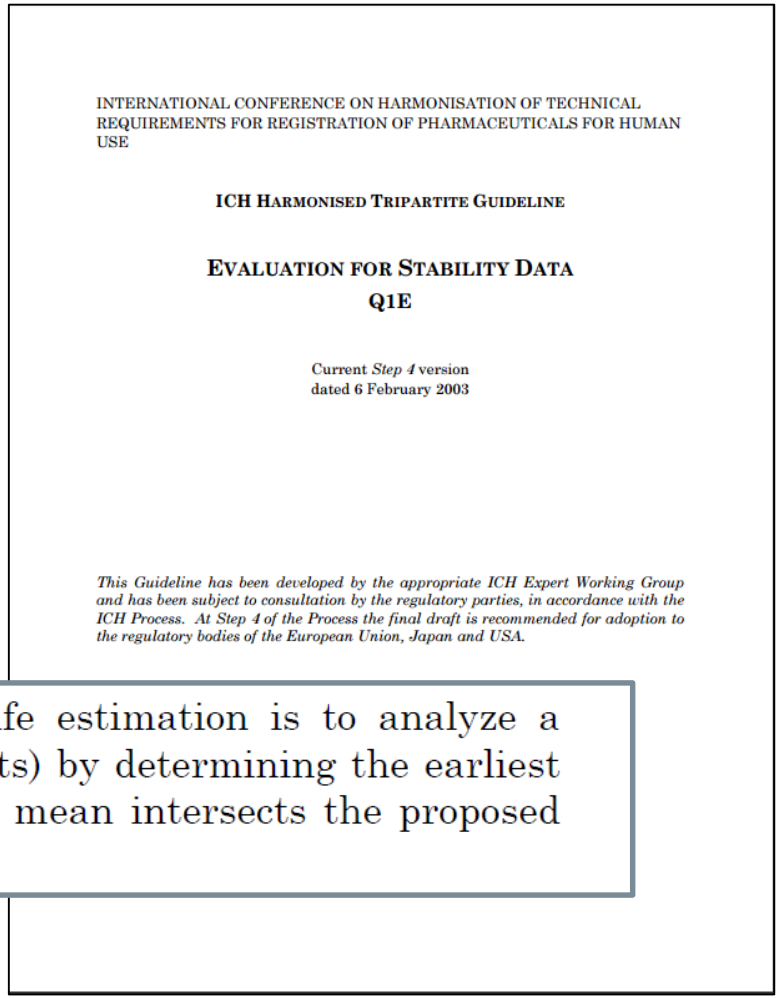
Shelf-life: Compliance approach



- Not necessarily a good stability estimate
- The “confidence” in the shelf life is not defined
- Conceptually flawed; more data = greater risk
- No possible risk assessment at release

Shelf-life : regulatory approach

- **ICH Q1E:** defines shelf-life as the time where the **bound on the confidence interval intersects the specification limit**



INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

EVALUATION FOR STABILITY DATA
Q1E

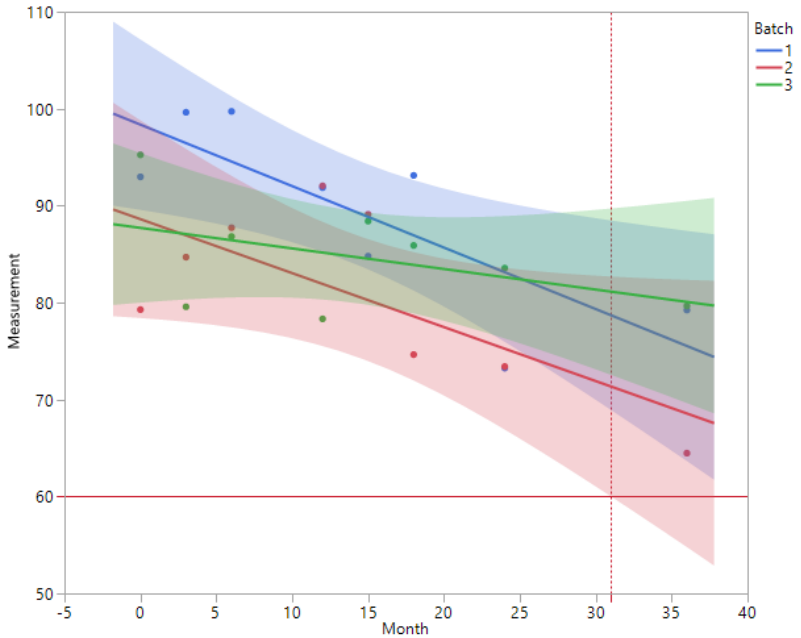
Current *Step 4* version
dated 6 February 2003

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

An appropriate approach to retest period or shelf life estimation is to analyze a quantitative attribute (e.g., assay, degradation products) by determining the earliest time at which the 95 percent confidence limit for the mean intersects the proposed acceptance criterion.

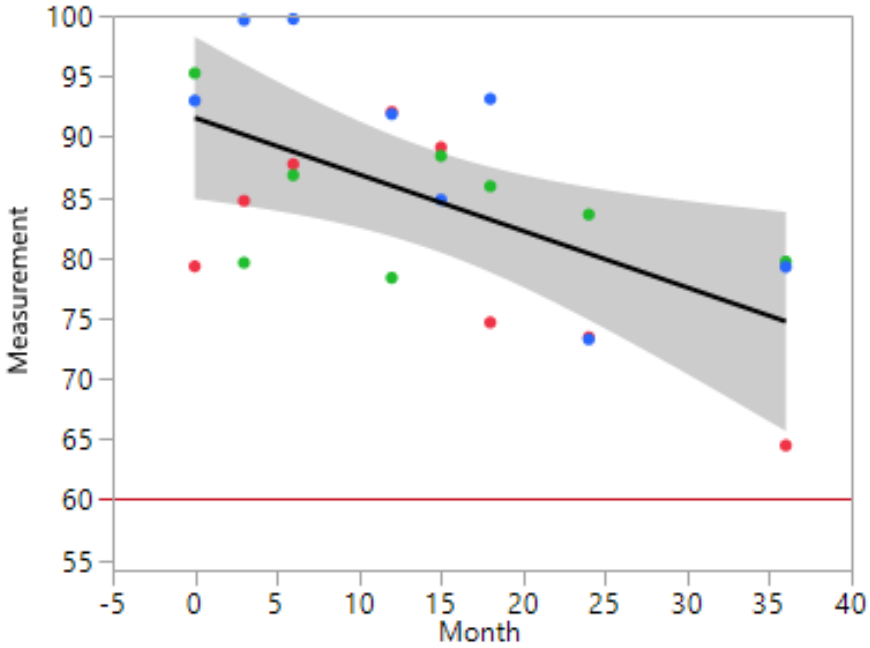
Model based confidence interval

- Q1E suggests that we calculate CI and Shelf Life for each batch separately.
- The shortest Shelf Life is the selected one.
- So, the more batch you measure, the higher chance you get to fail to meet your expected Shelf Life!
- Also, possibility to pool the batches if both slope and intercept are non-significant at a 0.25 α level.

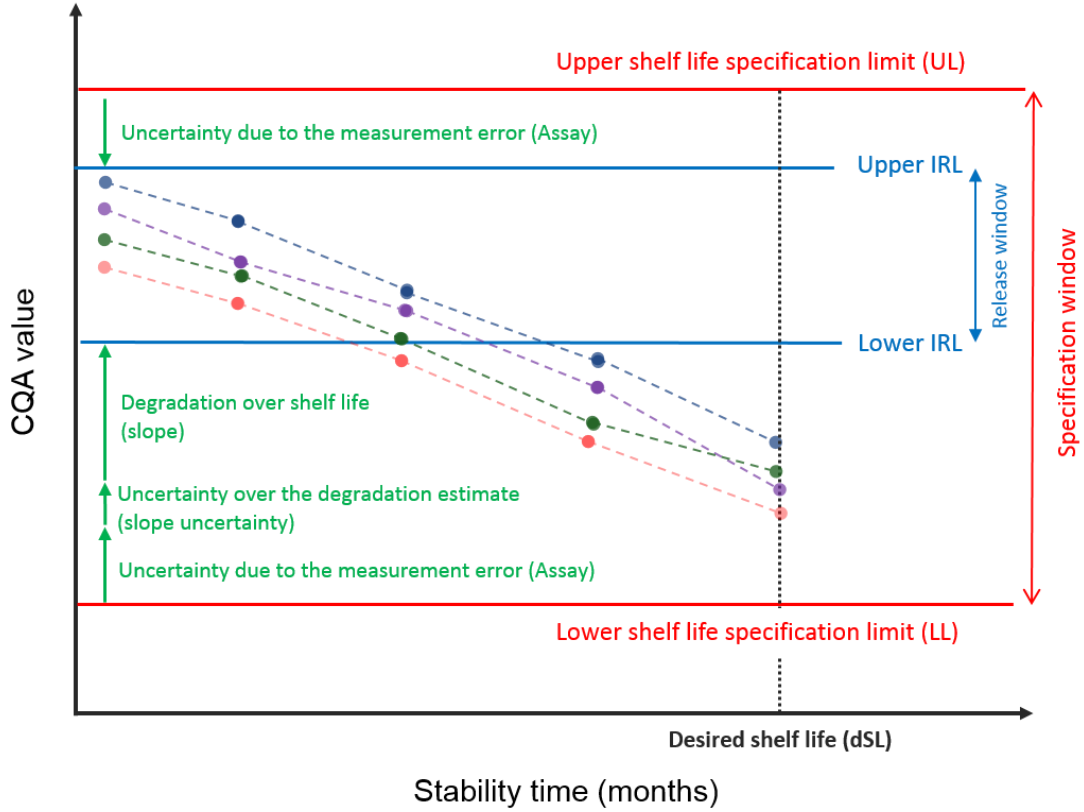


Use mixed models instead

- While this is not in the guidance, it is now accepted by the FDA to use mixed models for Shelf Life estimation.
- Careful when calculating the confidence interval: take the batch to batch variability into account!
- This may not anyways be a good idea when the amount of batch is too small.



Internal Release Limit (IRL), the general concept



IRL : Definition

- **No regulatory definition**
  (not mentioned in ICH Q1E)

- **Business definition:**
  Application of an Internal Release Limit at the time of batch release guarantees with a defined level of confidence (generally 95%) that a batch remains within specifications throughout its entire shelf-life while stored at the labeled storage condition(s).

IRL computation, the main ideas

1. No change overtime

LRL = LSL + assay uncertainty

URL = USL - assay uncertainty

} Maybe not such a good idea ?

2. Decay over time

LRL= LSL + expected decline + uncertainty assay (and/or slope)

URL = USL - assay uncertainty

3. Increase over time

LRL = LSL + uncertainty assay (and/or slope)

URL = USL - expected increased - assay uncertainty

IRLs, some details

Lower Release Limit:

Lower Specification Limit

$$LRL = LSL - \hat{\beta}_1 \cdot x_{SL} + t_{df_L} \sqrt{\hat{\sigma}^2_{\hat{\beta}_1} \cdot x^2_{SL} + \hat{\sigma}^2_{assay}}$$

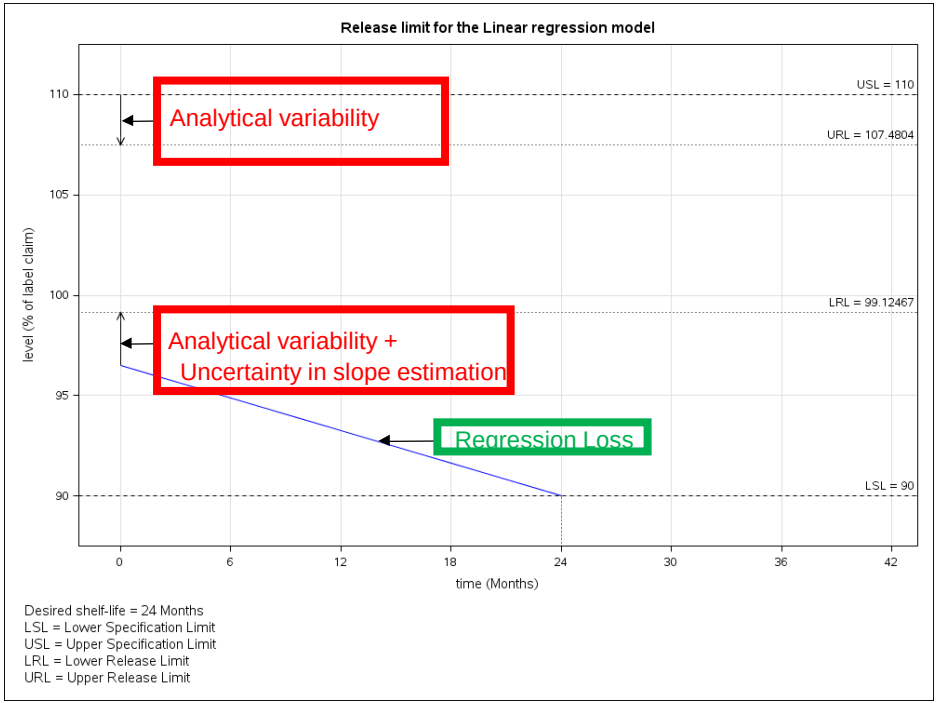
slope

Desired shelf-life

Uncertainty in slope estimation

$\hat{\sigma}^2_B + \hat{\sigma}^2_W$

Analytical variability



Upper Release Limit:

$$URL = USL - t_{df_U} \hat{\sigma}_{assay}$$

Upper Specification Limit

… With df_t and df_U being approximated using Satterthwaite (Allen et al., 1991), or using more simple approaches (Egan and Schofield, 2009)

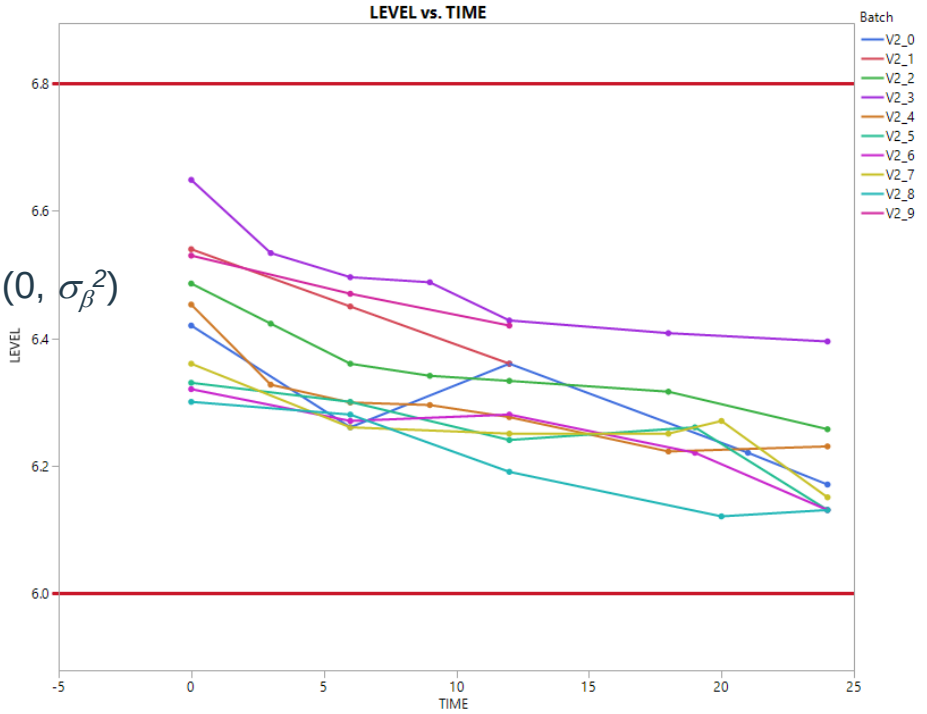
Limitations of the current approach

- Difficulties to compute the *df* (Satterthwaite, etc.)
- How to get the right σ^2_{slope}? In case of high batch-to-batch variability, current approximation can fail
- Works with linear profiles, but how to compute IRLs for non-linear profiles?
- And finally, the question sounds very Bayesian, doesn't it?
  - *What is the probability to be out of specifications at SL, given the observed value at release, the precision of measurement system and the historical data observed with previous batches and the corresponding models?*

Let's do it the Bayesian way! Application to a linear mixed model

$$y_{ij} = A + \alpha_i + B \times T_{ij} + \beta_i \times T_{ij} + \varepsilon_{ij}$$

- y_{ij} = Value for i^{th} batch at j^{th} time point
- A = overall Intercept
- α_i = random effect of the i^{th} batch: ~ N(0, σ_α^2)
- B = overall Slope
- β_i = random effect of the slope of the i^{th} batch: ~ N(0, σ_β^2)
- T_{ij}= j^{th} stability time point for i^{th} batch
- ε_{ij} = Residual Variability ~ N(0, σ_ε^2)
- With uncorrelated α_i and β_i

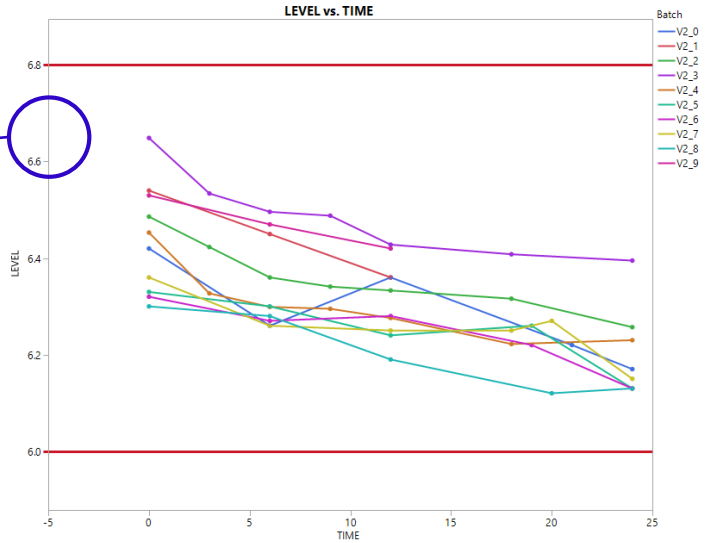


First compute your posterior distributions

How to compute IRLs?

- For each Release value, predict batch value at both Release and end of Shelf-Life for each posterior sample

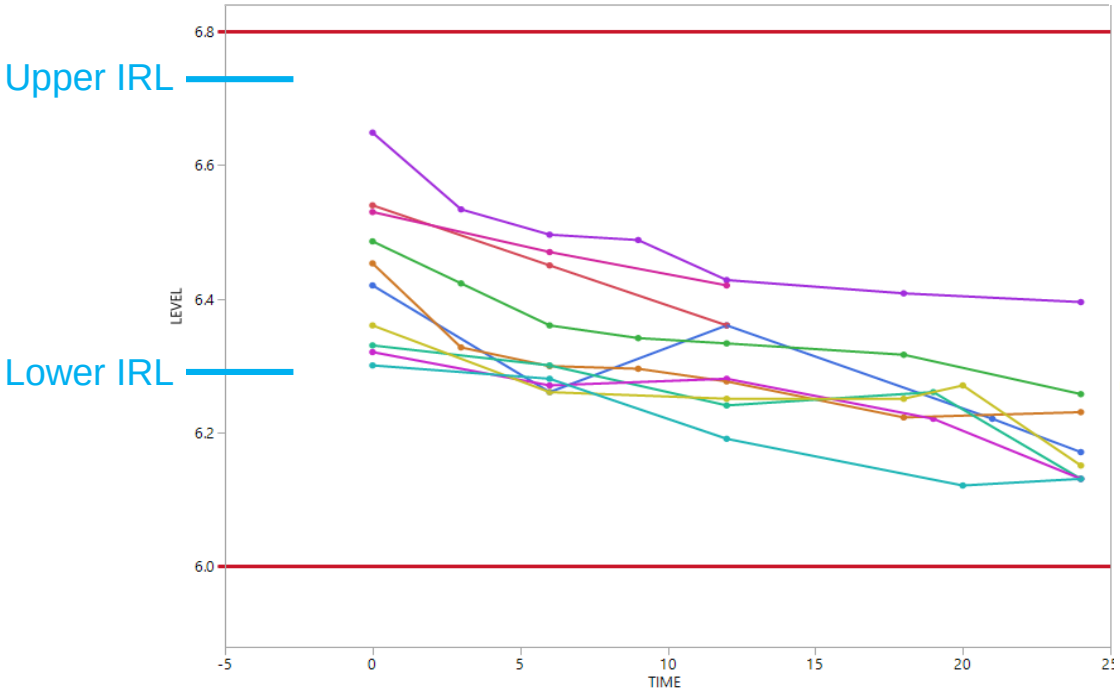
```
predictions_RL = rnorm(n = Nsim,
                       mean = z ,
                       sd = sigma_LEVEL)

predictions_dSL = rnorm(n = Nsim,
                        mean = predictions_RL +
                        rnorm(n = Nsim, mean = b_TIME,
                              sd = sd_Batch_TIME)*dSL,
                              sd = sigma_LEVEL)
```

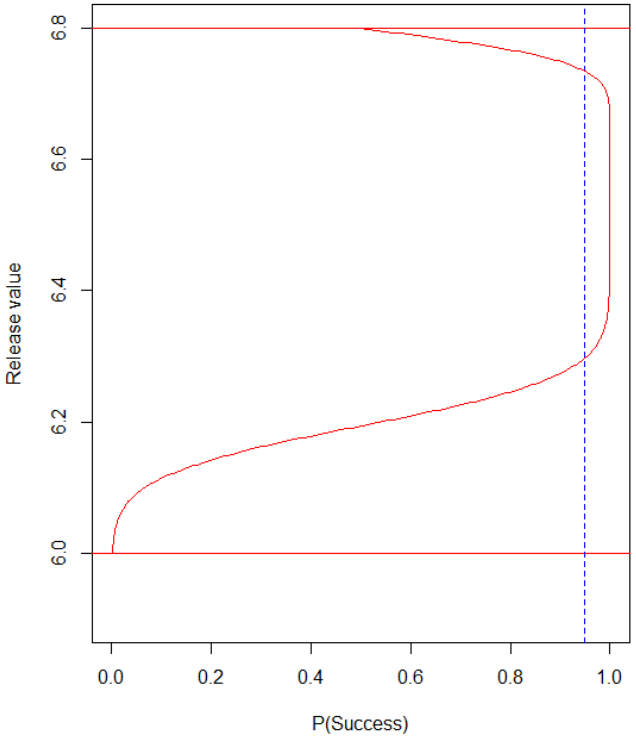


- For each Release value, compute the overall probability to be within the specifications

Computation of the IRLs based on the PoS plot

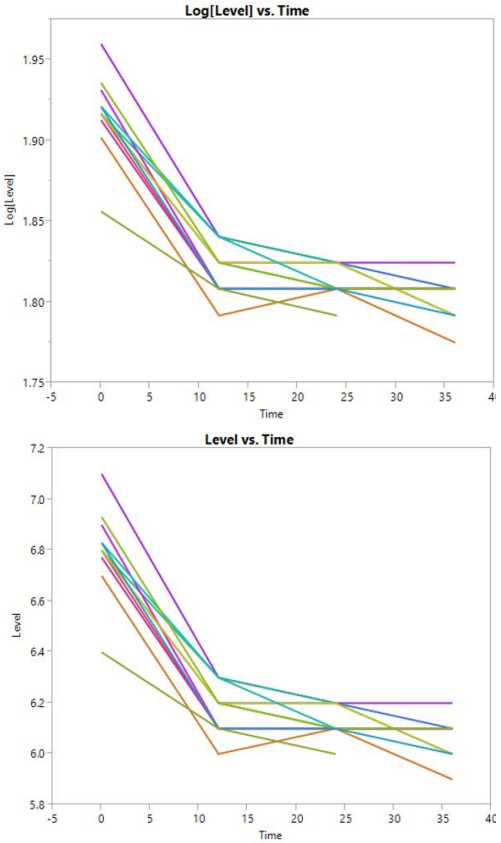
- IRLs is the release window where the joint probability of success at both release and end of shelf-life is above a given value (let's say 95%)





Application to non-linear profiles

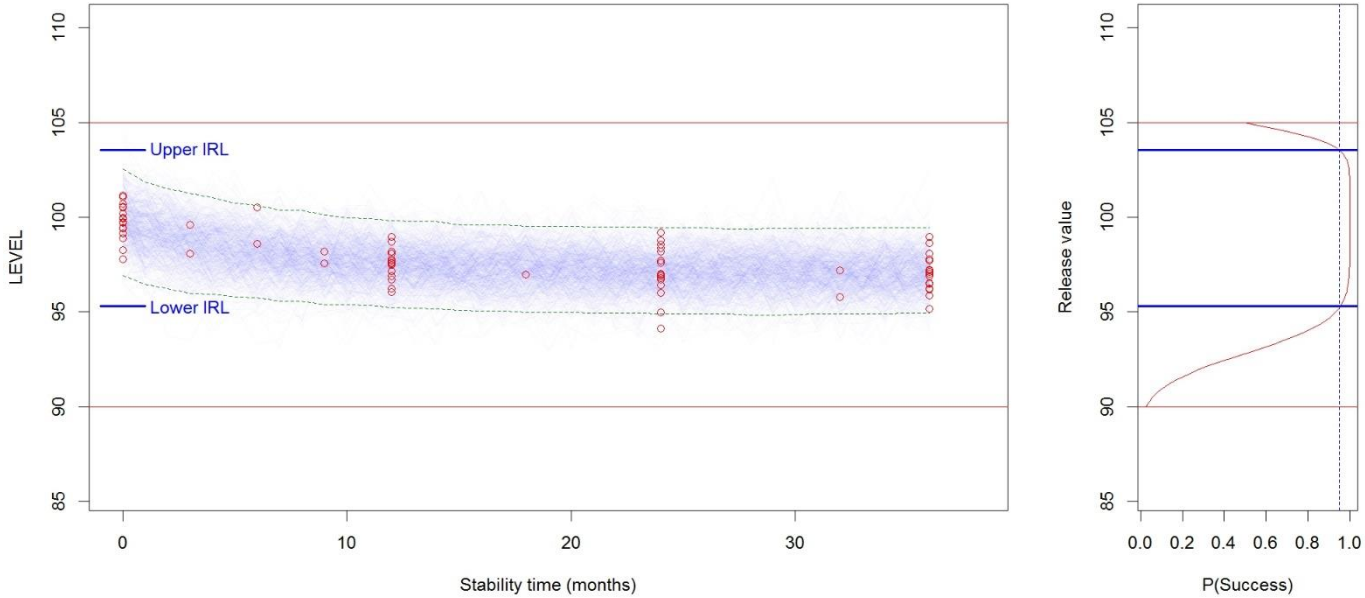
- In some cases (typically pH), transformations will not help! Required to use non-linear model(s)
- No published way to calculate IRLs for non-linear profiles
- Prediction intervals for such profiles can be tricky to compute in a frequentist way



IRLs for nonlinear models

- For non-linear(izable) models, there is no approximate formulas available for the computation of IRLs

- We developed a specific methodology based on a Bayesian approach:



Fit a mono-exponential model to the data

$$y_{ijk} = a_i + s_i \times e^{r_i \times t_j} + \epsilon_{ijk}$$

with,

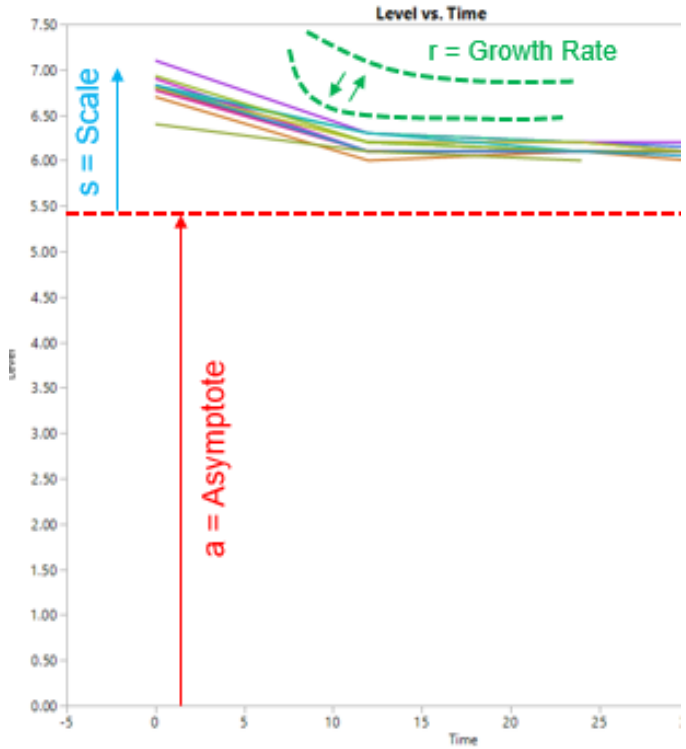
— a_i, the equilibrium state, assumed distributed as $\mathcal{N}(a, \sigma_a^2)$, where σ_a^2 is the batch-to-batch variance

— s_i, the scale, the difference between the release value and the equilibrium, assumed distributed as $\mathcal{N}(s, \sigma_s^2)$, where σ_s^2 is the batch-to-batch variance

— r_i, the growth rate, the curvature of the curve, assumed distributed as $\mathcal{N}(r, \sigma_r^2)$, where σ_r^2 is the batch-to-batch variance

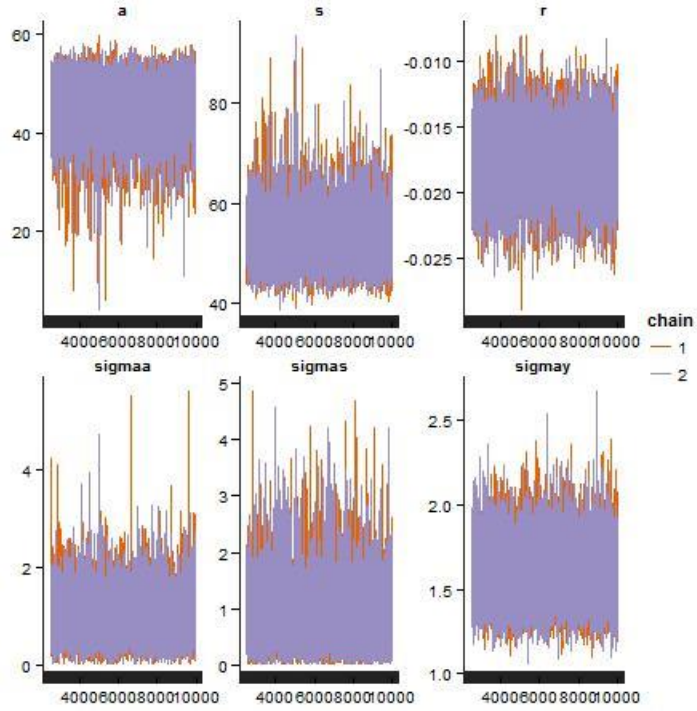
— ϵ, the residuals, assumed distributed as $\mathcal{N}(0, \sigma_\epsilon^2)$, where σ_ϵ^2 is the residual variance

— t, the storage time



In practice, a function generating STAN code is used

```
USL_RL = USL = 110
LSL_RL = LSL = 105
dsl <- 36

U <- exponential_decay_STAN( data = SC_data,
                             Y = "LEVEL",
                             X = "TIME",
                             group = "Batch",
                             RA = T,
                             RS = T,
                             RR = F,
                             side.slope = "decrease",
                             warmup = 10000,
                             iter = 60000,
                             thin = 4,
                             chains = 2,
                             trace = "SC_131_RS_RA",
                             results_directory = "summary_report/")
                             save_chains = T,
                             project_name = "MyProject",
                             print.model = F)
```

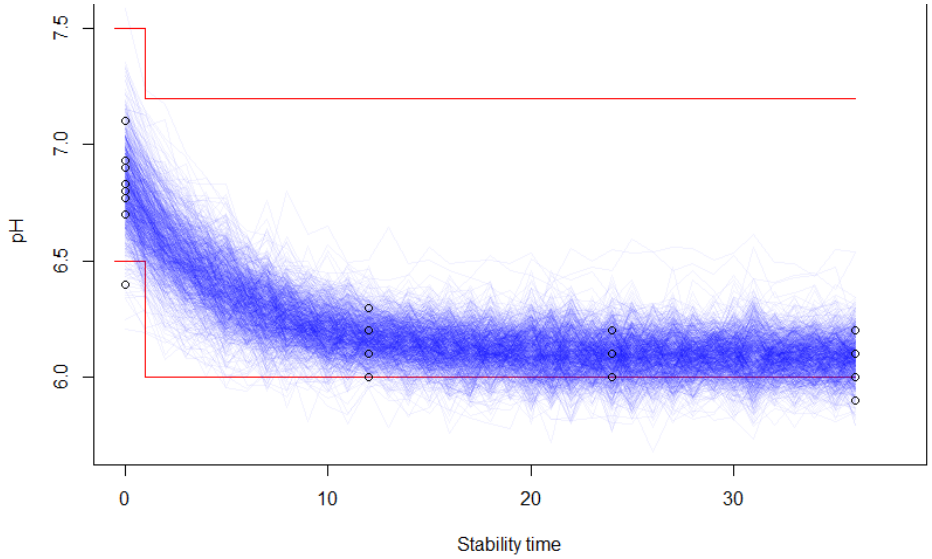


The function returns traceplots and posterior distributions of the parameters (a, s, r, σ_y, and σ_a, σ_s, σ_r , if applicable)

Compute posterior predictive distribution of y

The posterior distributions of the model parameters have been used to predict the full stability profile over time ($pred_{y,t}$) as follows :

$$pred_{y,t} \sim \mathcal{N}(pred_a + pred_s \times e^{pred_r \times t}, \sigma^2_{\epsilon|y}) \quad (2)$$



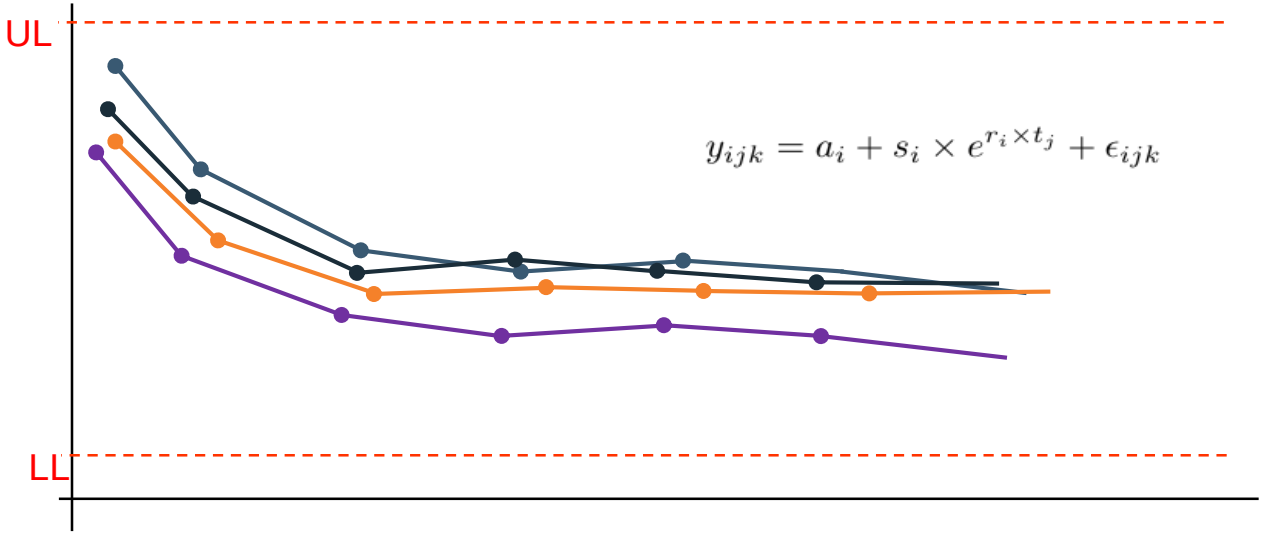
With,

$$pred_a \sim \mathcal{N}(a, \sigma^2_{a|y})$$
$$pred_s \sim \mathcal{N}(s, \sigma^2_{s|y})$$
$$pred_r \sim \mathcal{N}(r, \sigma^2_{r|y})$$

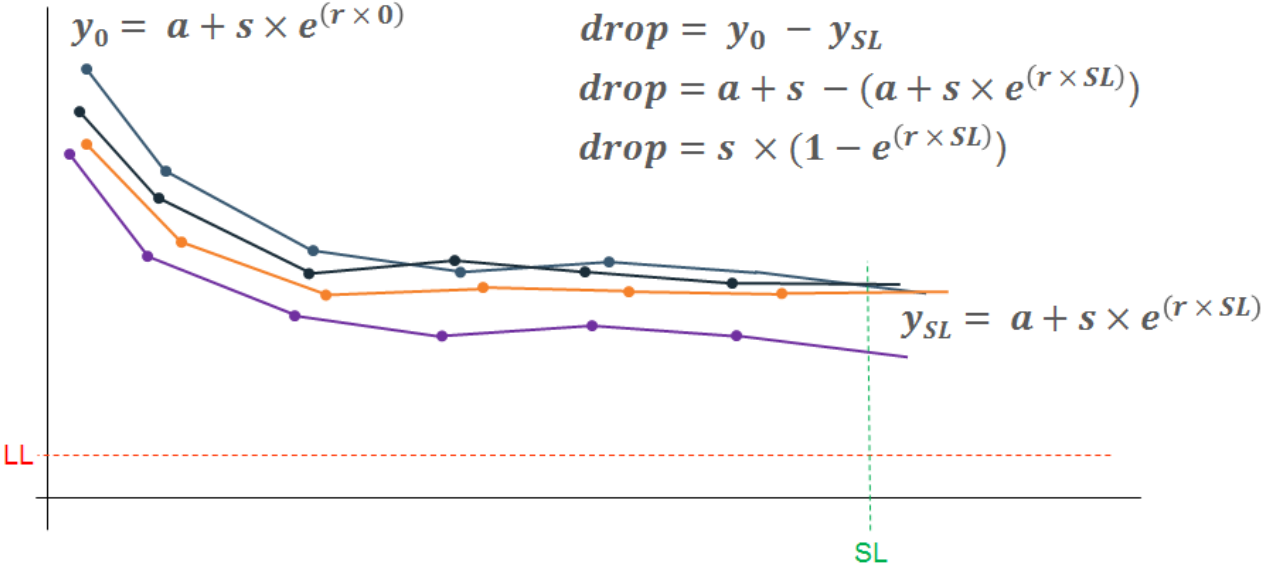
Compute the IRLs

Mono-exponential model has been found to be appropriate in describing the stability profile but it cannot be assumed that there is a true chemical equilibrium

→ batches released at low levels will reach lower steady state at shelf life than batches released at higher levels



Compute the IRLs



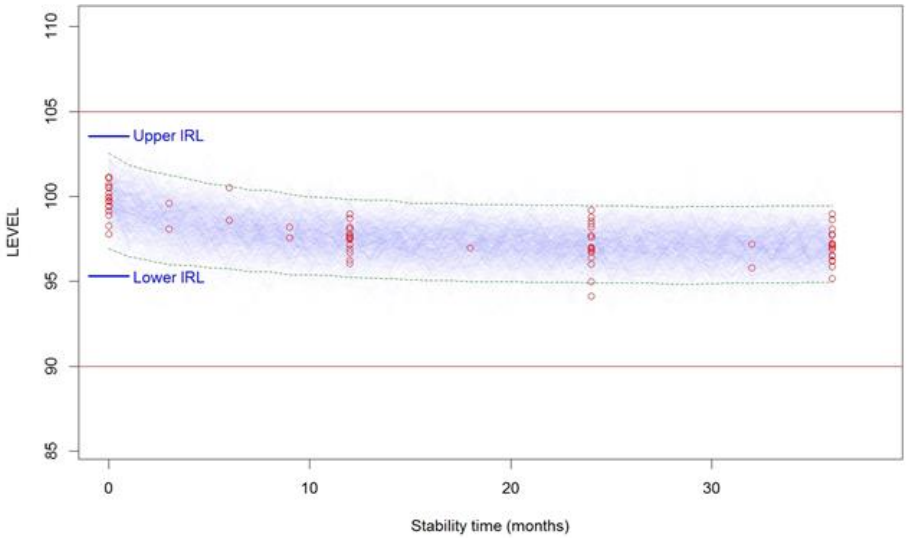
The posterior distribution of the increase/decrease occurring between the time of release and the shelf life ($pred_d$) can be obtained from equation (9).

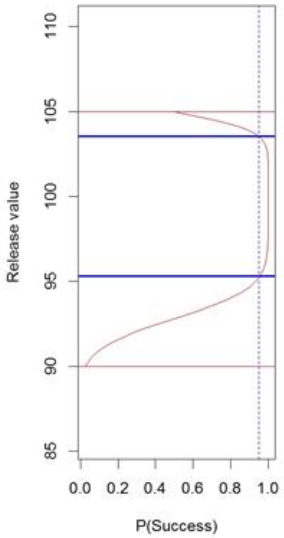
$$pred_d \sim \mathcal{N}(pred_s \times (1 - e^{pred_r \times SL}), \sigma^2_{\epsilon|y}) \quad (9)$$

Compute the PoS plot and the IRLs

The posterior distribution of the measured values at shelf life ($pred_{SL}$) is

$$pred_{SL} = pred_{RL} - pred_d \qquad \textit{with,} \qquad pred_{RL} \sim \mathcal{N}(RL, \sigma^2_{\epsilon|y})$$





(*degradation example)

Conclusions

- Current technology allows the application of a Bayesian approach in a direct and uncomplicated way
- Bayesian approach with PoS plot addresses directly the scientists' key question
- Predictive posterior distribution of future batches can be easily generated, possibility to handle other questions from scientists
- Possibility to compute IRLs for non-linear profiles
- Prior knowledge (from validation reports, or accelerated stability studies) may be integrated into a prior distribution

Thank you !

- Thanks to the **ARLENDA** team (for doing all the work for me):
  Laurent Natalis, Jean-François Michiels, Eric Rozet, Pierre Lebrun, Fabrice Nollevaux, Thomas De Marchin, Cédric Dubourg, Jean-Yves Célis, Dan Castro, Bruno Boulanger

- Thanks to our **CLIENTS** for the collaboration of that topic

- **QUESTIONS** ?