Setting specifications…

… or when statisticians can play the Good, the Bad, and the Ugly…

Laurent NATALIS[1], PhD | Associate Director Statistics
Jean-François MICHIELS[1], Pierre LEBRUN[1], and Hans COPPENOLE[2]

[1] Pharmalex Belgium
[2] Janssen Pharmaceutica

NCS
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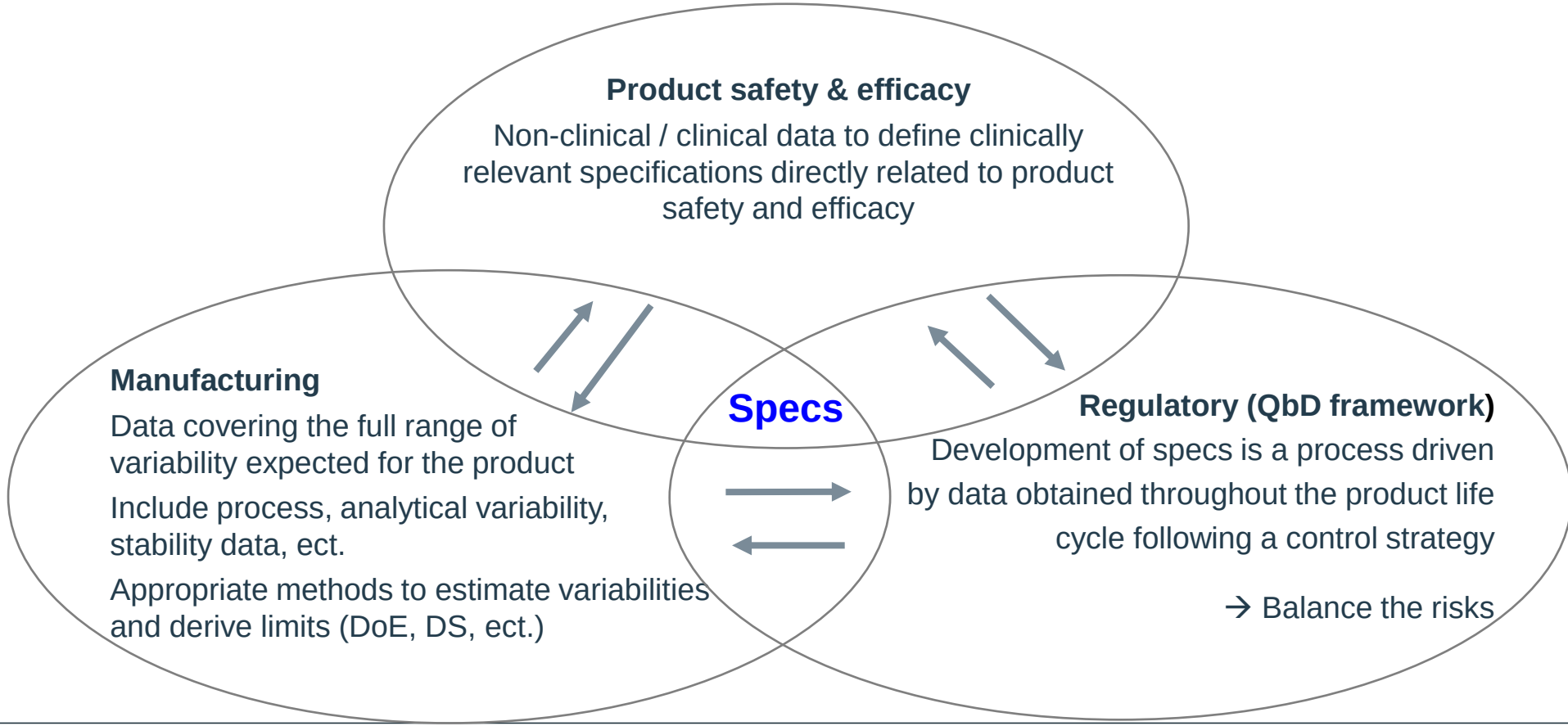
What's good, what's bad?

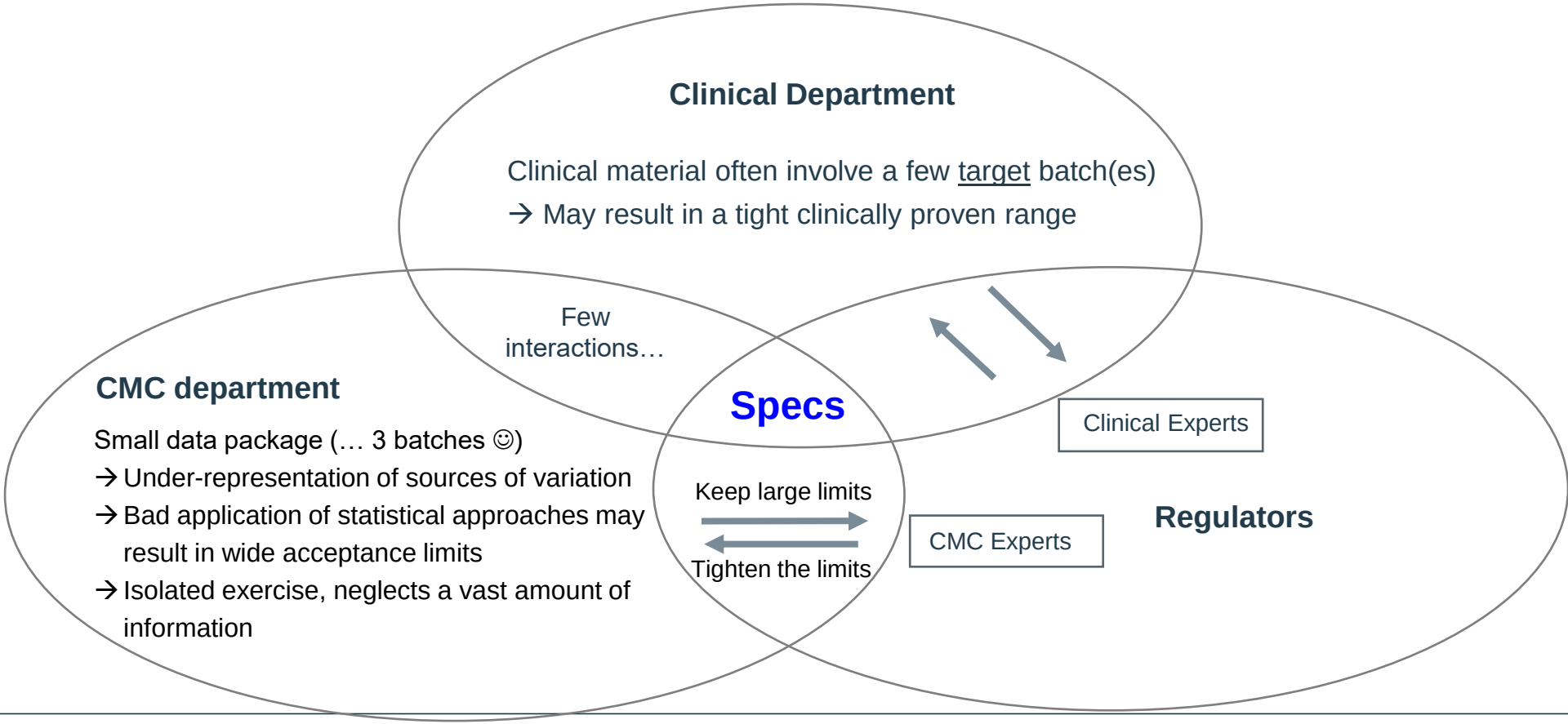
- Setting specifications = define a threshold which determine what is good and what is bad…
- As statisticians, we can derive intervals, probabilities, but to determine what is good and what is bad is over our scope
- Very high risks in case of bad choice… High pressure from scientists, process owners and authorities
- Lack of worldwide agreement on principles and practices

Setting specifications limits, in theory



(Burdick et al. 2017).

Setting specifications limits, in practice



(Burdick et al. 2017).

Setting specifications limits, a Mexican standoff…

Clinical Department

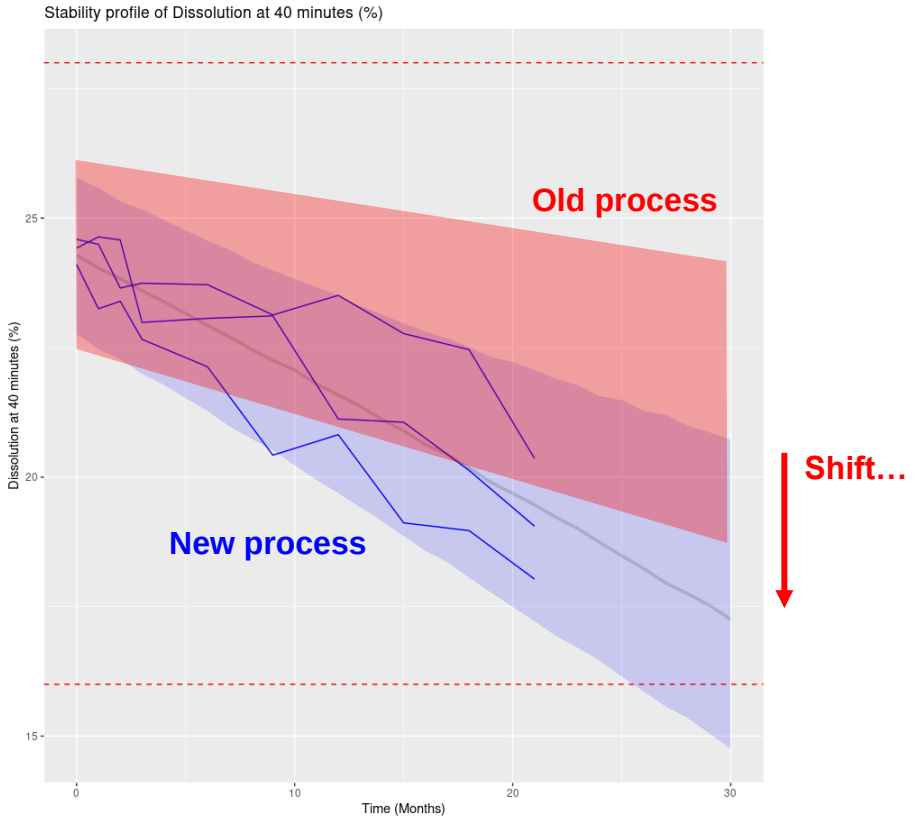
CMC department

Regulators

REAL STORY, BUT ALL RESULTS AND FIGURES BASED ON SIMULATED DATA FOR CONFIDENTIALITY PURPOSES

Illustration of a (hot) request about specifications limits

- After a change in the manufacturing process, a shift in dissolution was observed in stability
- New batches degrade quicklier than those before the change…
- Is there a risk of Out-Of-Specification?



Prediction using a hierarchical model (Bayesian implementation)

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

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)

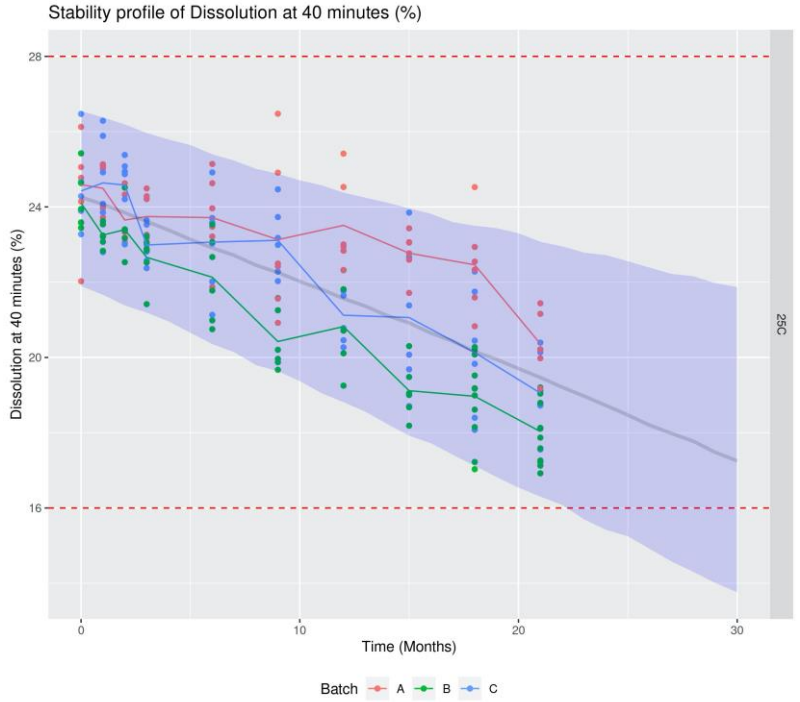
B = overall Slope

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



High chances of OOS in one year…

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

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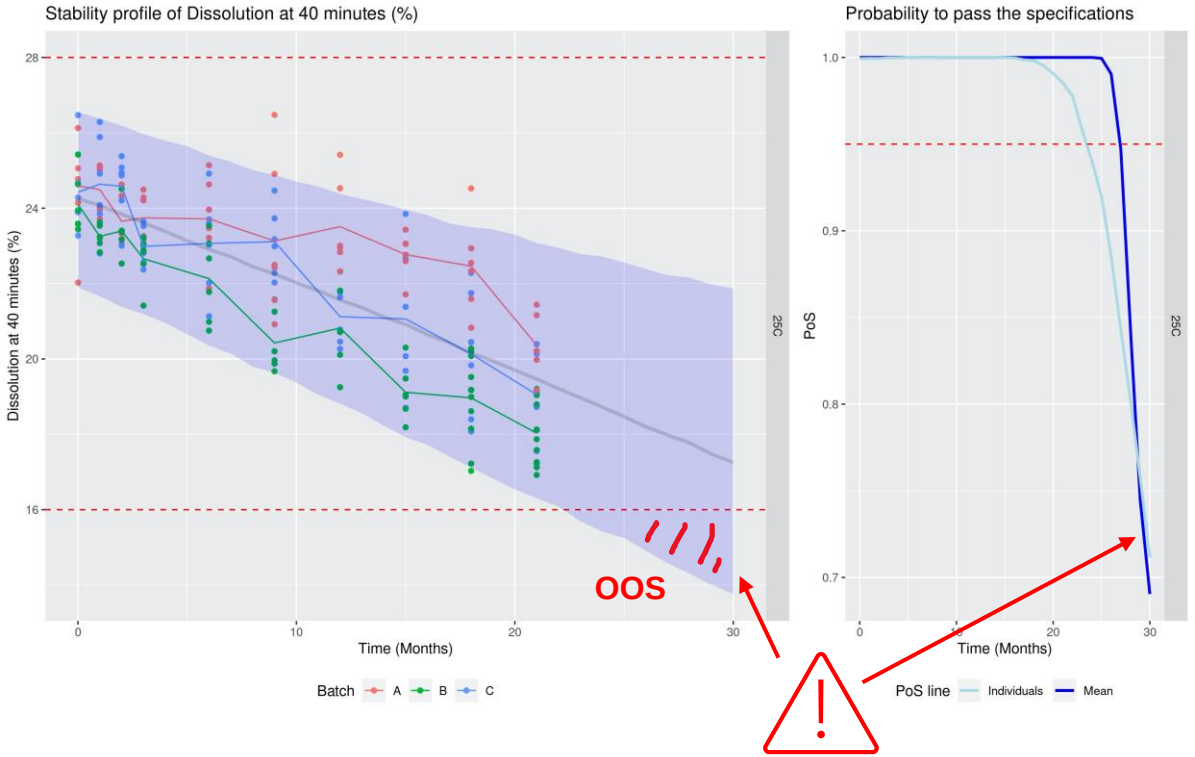

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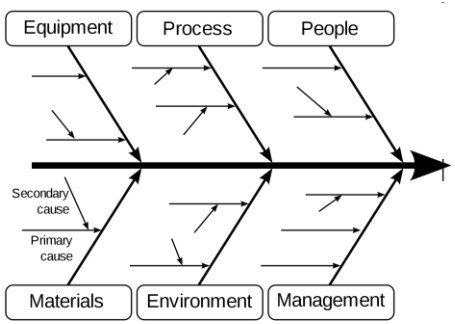
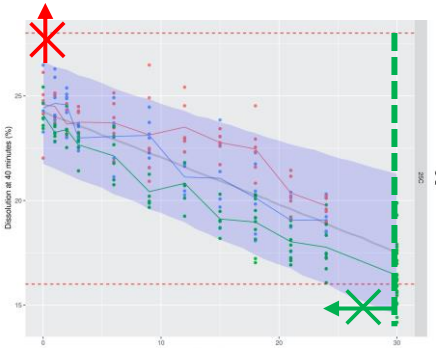
How to avoid OOS with the new process?



No root cause identified despite extensive investigations…



Not possible to release batches higher because of technical limitations

No lower historical batches available

Not possible to shorten the SL

Need to update specifications limits

What are the solutions left?

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Product safety & efficacy at risk

Show that the product is safe after the process change…

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Process capability at risk

A Bioequivalence study was initiated to establish product safety

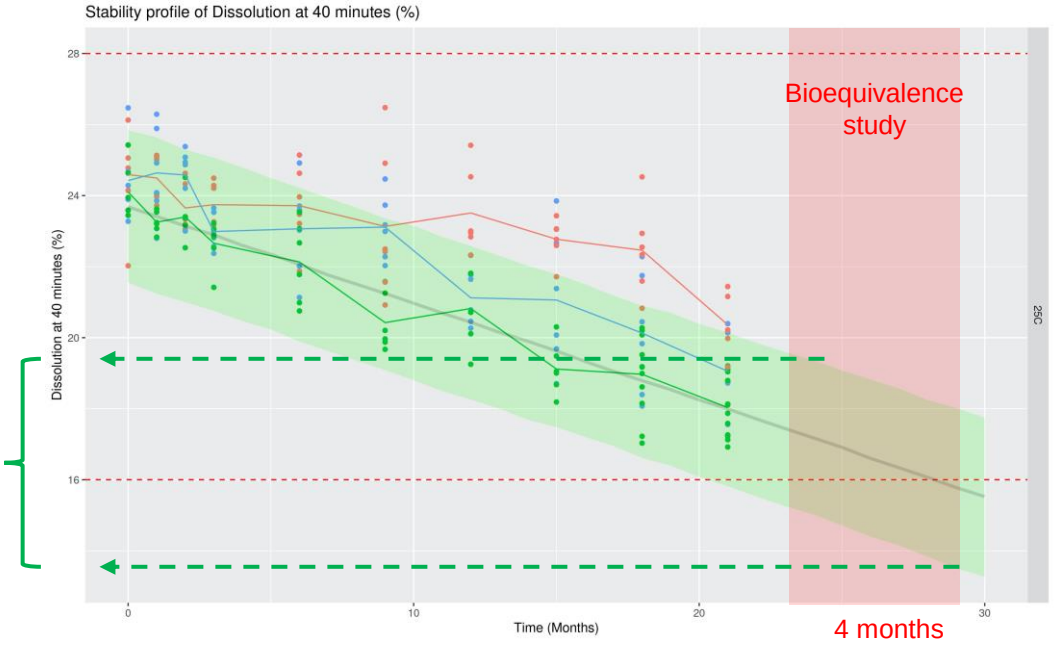
- A clinical Bioequivalence study was initiated
- The study included ~ 70 subjects
- The study was performed using the **batch with the steepest degradation path**
- The study duration was ~ 4 months

Linking patient and stability data, the strategy

Patients will be exposed to the batch **A** in the clinical trial when that batch will be aged between 24 and 28 months

→ Back predict the dose range patients have been exposed during the whole study

→ If there is no concern in both safety and efficacy in the BA study: we have a good rationale to redefine the specs ☺

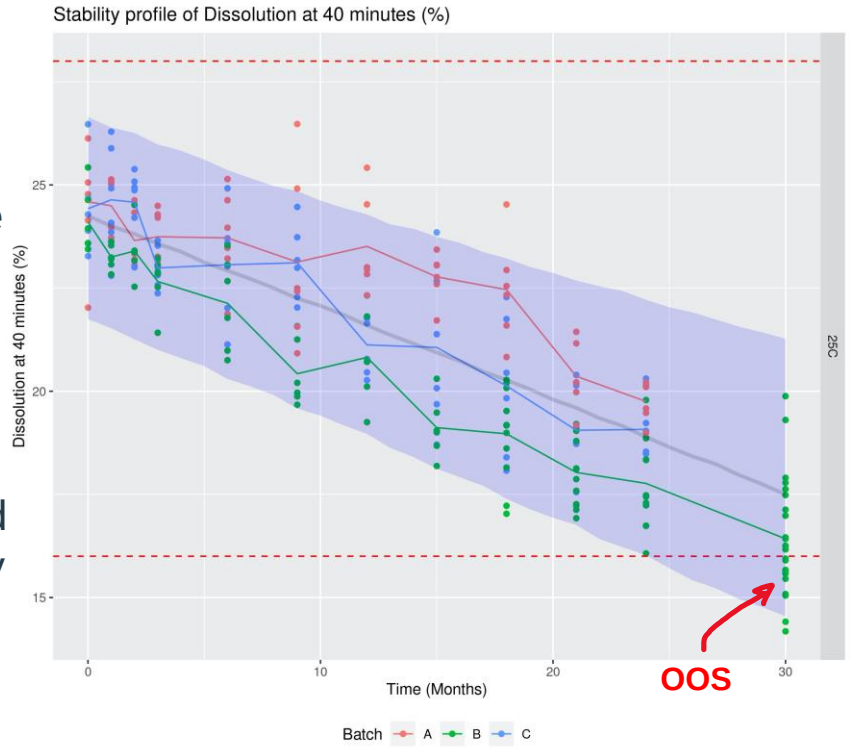


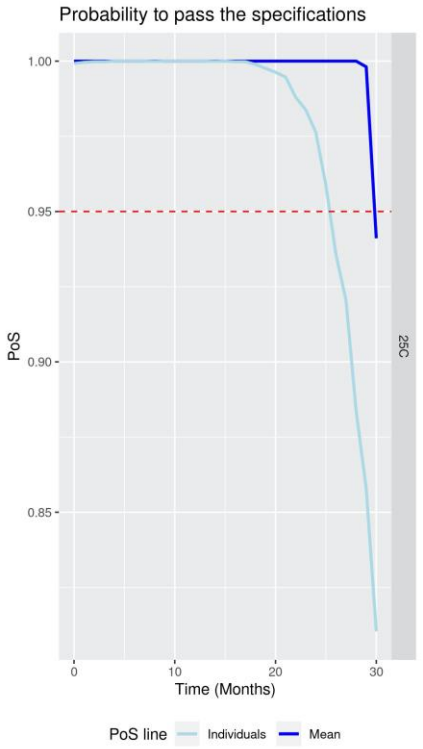
And indeed at 30 months…

- Predictions were proven accurate
- OOS were observed for the Batch A at 30 months

BUT

- The BA study was achieved without any safety / efficacy concern ☺

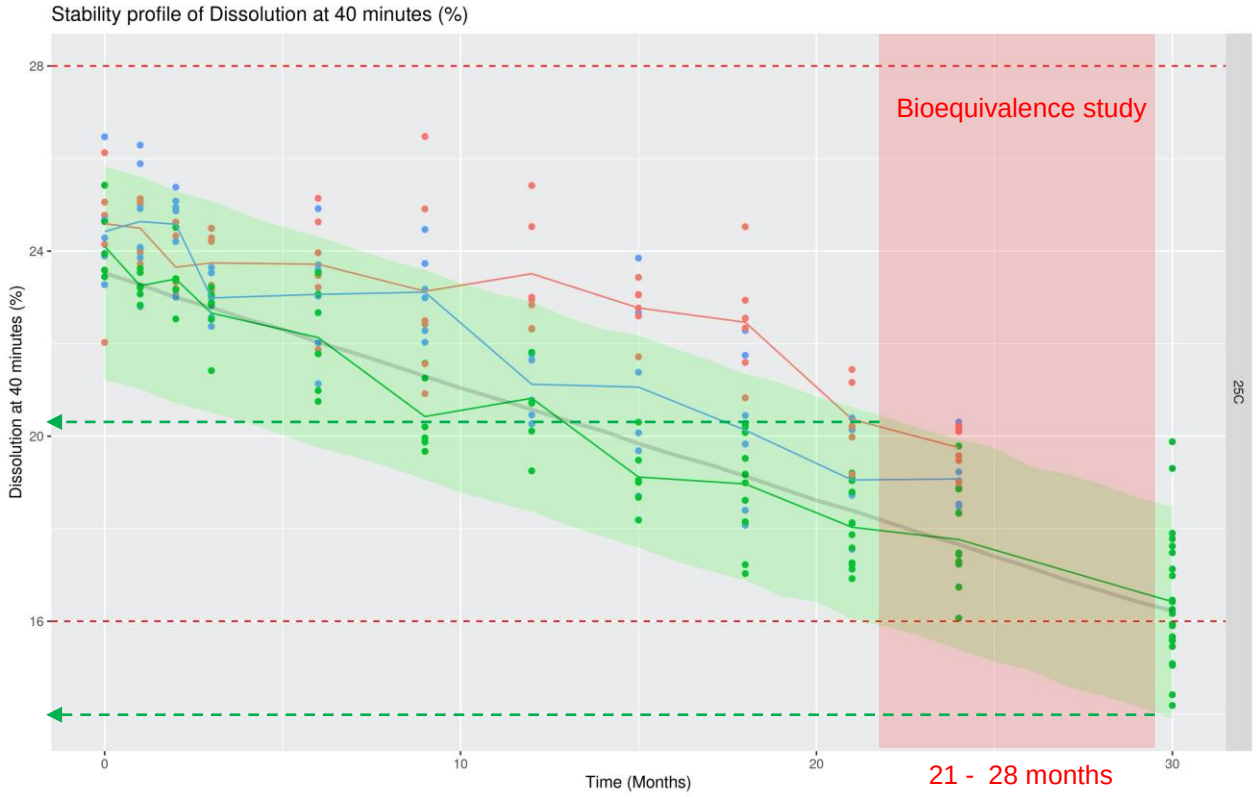




First step: get a clinically relevant dissolution range

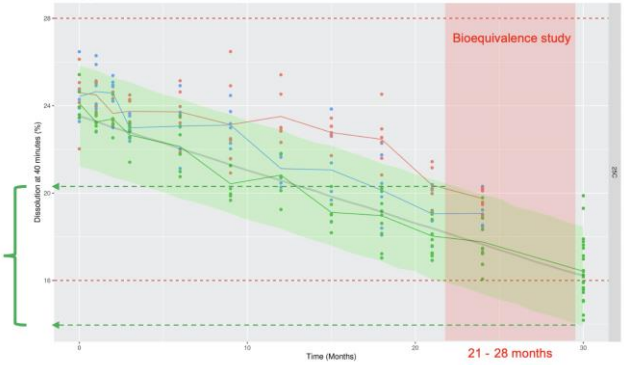
The dose range patients have been exposed during the whole BA study is back-predicted

Dissolutions values ranging from 14 to 20% are clinically safe and efficient ☺



Second step: based on the predicted dissolution values, compute the Q-value following on USP-711

IVR time	LSL ('Stated range' in the USP-711 acceptance table 2)
40 minutes	?



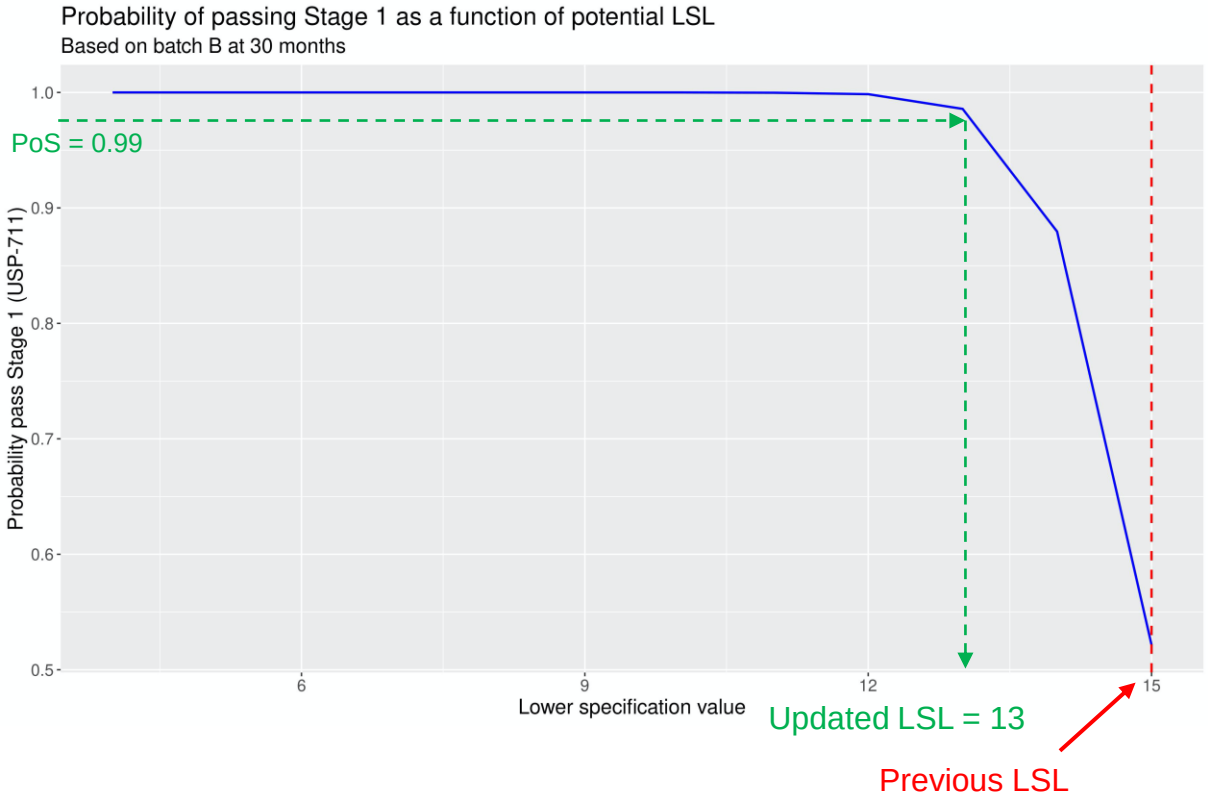
Acceptance Table 2

Level	Number Tested	Criteria
L_1	6	No individual value lies outside each of the stated ranges and no individual value is less than the stated amount at the final test time.
L_2	6	The average value of the 12 units ($L_1 + L_2$) lies within each of the stated ranges and is not less than the stated amount at the final test time; none is more than 10% of labeled content outside each of the stated ranges; and none is more than 10% of labeled content below the stated amount at the final test time.

Second step: Back-computation of the Q-value

- The new LSL (i.e Q-value) is back-predicted using simulations

- The new LSL is designed to be
  - clinically-relevant
  - process-wise achievable
  - USP-711 compliant



And last but not least, convince regulators…

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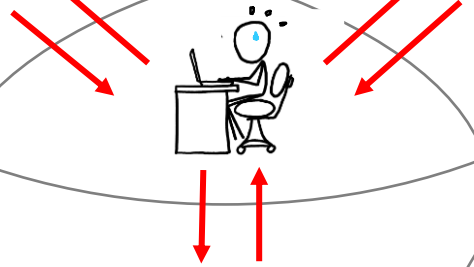


Enlarge the specs?

?

Regulators

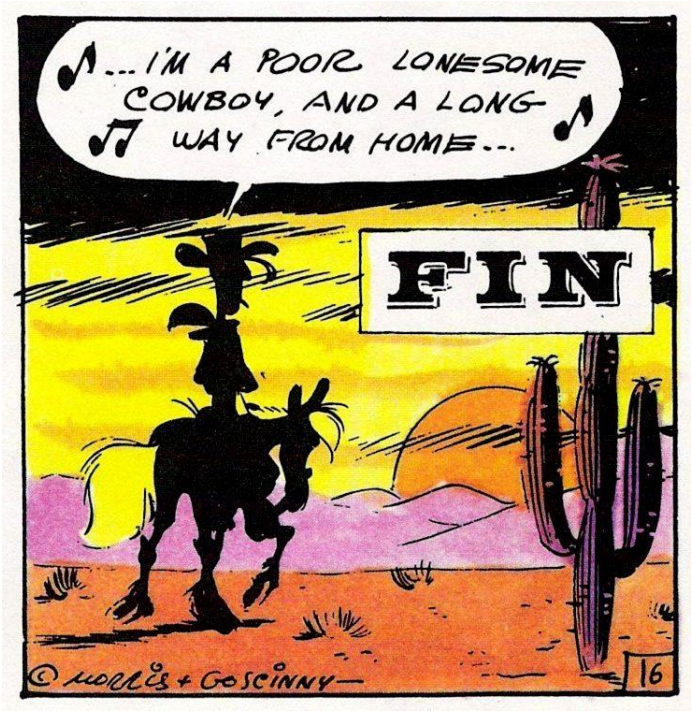
? ? ? ?

Take home messages

- Authorities are moving from **compliance-driven** specifications limits to a **risk-based life cycle approach**
- But still there is no a globally harmonized guidance available on the topic… But this gives you a great flexibility!
- … Flexibility to **use all available data to balance the producer and consumer risks**
- … Flexibility to set provisional limits and to update the limits based on data from post-marketing

Regulatory (QbD framework)
Development of specs is a process driven by data obtained throughout the product life cycle following a control strategy

Many thanks for your attention! Any questions?



Laurent NATALIS, PhD
Associate Director Statistics
+32 494 88 79 90
Laurent.Natalis@Pharmalex.com