STABILITY IS NOT IMMOBILITY: MOVING STABILITY GUIDELINES FORWARD

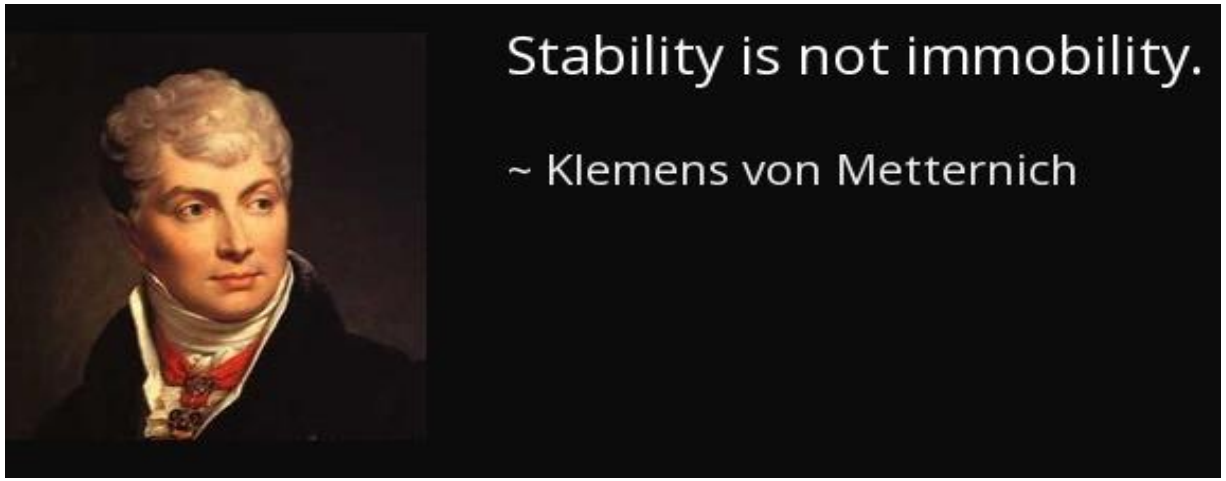
BRIAN K NUNNALLY, HELEN MIHALJEVIC, AND PAUL HEHIR

15 July, 2021

CURRENT STATE

- The stability guidances are some of the best of the ICH guidance series
- They provide detailed and thorough information for how to approach designing stability studies and evaluating data

- So if they are soooooooo good – why even have this talk? What is missing?



ICH Q1 SERIES

ICH Q1A(R2): Stability Testing
ICH Q1B: Photostability
ICH Q1C: New Dosage Forms
ICH Q1D: Bracketing and Matrixing
ICH Q1E: Evaluation of Data
ICH Q1F: Zones III and IV

Seqirus™
A CSL COMPANY

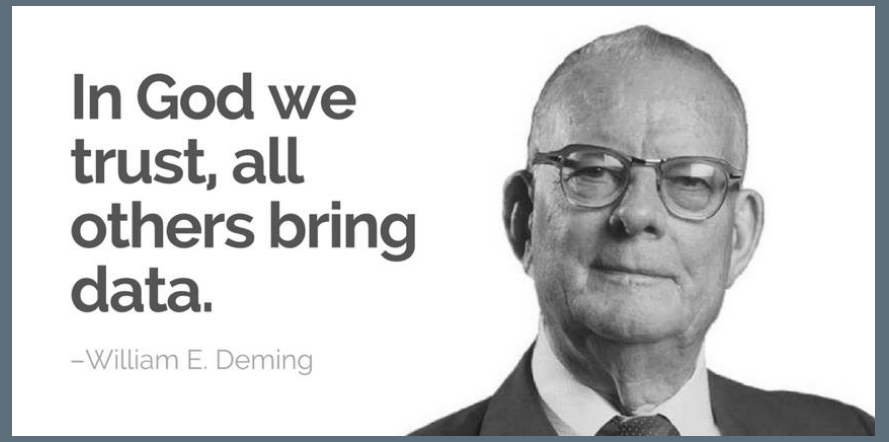
WHAT IS NOT PROVOCATIVE

- Using data to drive your decisions to go outside of ICH **guidelines**
- Picking reasonable temperatures and conditions for stability studies
- Using data to remove non-stability indicating tests from your stability protocols
- Understanding what is “meaningful” – not every statistical change is created equal

- Do we need ICH to tell us about early pulls (☹), testing one timepoint beyond expiry (☹)?!?

RATIONALE

Your stability control strategy should be driven by data



Seqirus™
A CSL COMPANY

WHAT IS MISSING - #1

- Matrixing is an approved concept as part of ICH but is rarely employed in the Biotech industry
- In order to implement, it is expected to have knowledge of data variability (☹), expected stability of the product (☺), availability of supporting data (☺), and stability differences in the product within a factor or among factors (☺)

- We typically have these covered – why, then, is it not more routinely employed???
- We can genericize this to be more flexibility in timepoints for your study

MATRIXING

Matrixing is the design of a stability schedule such that a selected subset of the total number of possible samples for all factor combinations would be tested at a specified time point. At a subsequent time point, another subset of samples for all factor combinations would be tested.

"One-Half Reduction"

Time point (months)			0	3	6	9	12	18	24	36
Strength	S1	Batch 1	T	T		T	T		T	T
		Batch 2	T	T		T	T	T		T
		Batch 3	T		T		T	T		T
	S2	Batch 1	T		T		T		T	T
		Batch 2	T	T		T	T	T		T
		Batch 3	T		T		T		T	T

Key: T = Sample tested

Seqirus
A CSL COMPANY

WHAT IS MISSING - #2

- Bracketing is another concept approved as part of ICH
- Can this be used for different packing types? For instance, can we bracket a staked needle configuration with a luer-lock configuration? This should have no effect on the stability behavior. What data is needed to justify implementing a strategy like this?

BRACKETING

Bracketing is the design of a stability schedule such that only samples on the extremes of certain design factors (e.g., strength, container size and/or fill) are tested at all time points as in a full design.

Table 1: Example of a Bracketing Design

Strength		50 mg			75 mg			100 mg		
Batch		1	2	3	1	2	3	1	2	3
Container size	15 ml	T	T	T				T	T	T
	100 ml									
	500 ml	T	T	T				T	T	T

Key: T = Sample tested

Seqirus
A CSL COMPANY

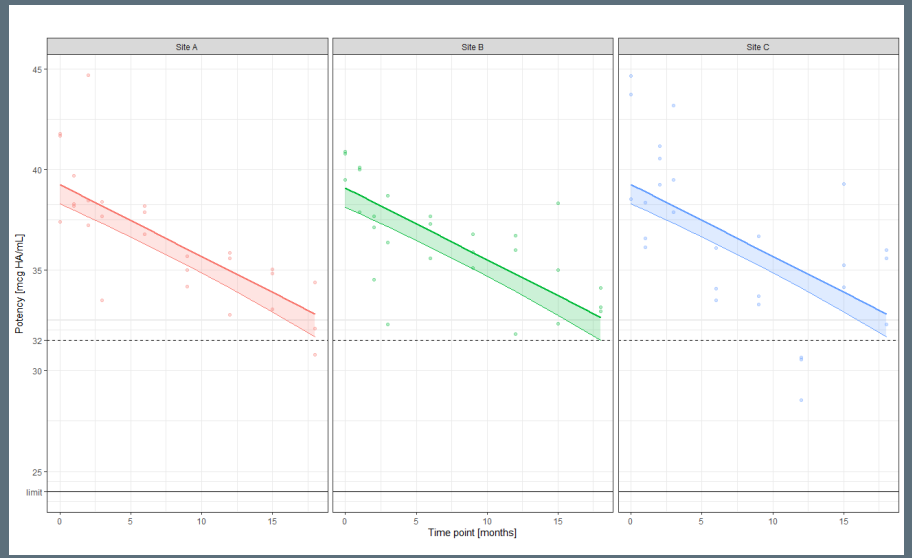
WHAT IS MISSING - #3

- Comparability is not adequately addressed in the stability guidances
- If one fills at multiple sites with comparable processes, do you need stability from all sites every year? Could an accelerated only approach be used for some sites, rotating the long term stability between the sites?
- Well conducted forced degradation studies can be of great utility

- Is there an opportunity to modernize the guidelines and offer some advice based on today's situations?

LEVERAGING OUR DATA

Using the data generated on a product to justify alternative approaches would be a welcome addition to stability guidance's



Seqirus
A CSL COMPANY

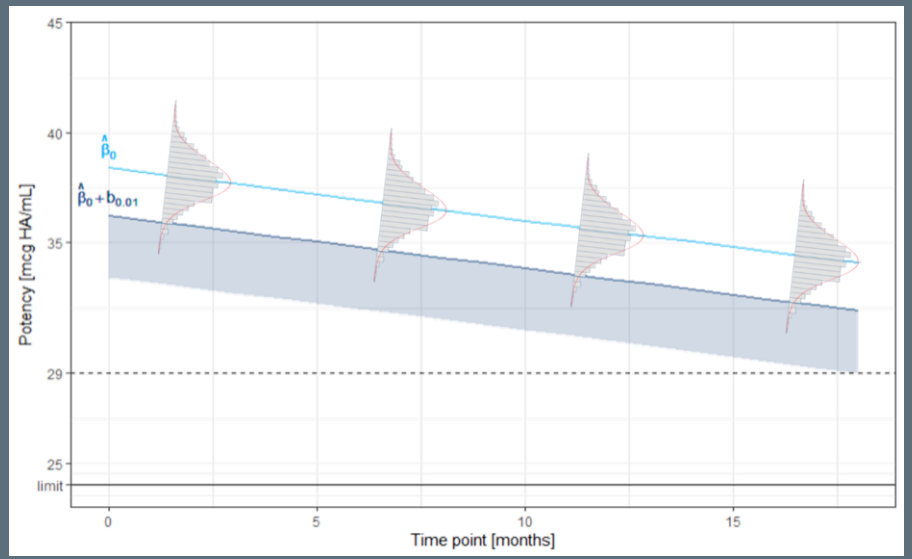
WHAT IS MISSING - #4

- The guidelines focus on using statistical significance tests (p-value < 0.25) to decide whether to pool all available stability data
- Like any tests, these are prone to false positive and false negative conclusions and are dependent on the variability of the stability indicating test method used

- Why are alternative stability data evaluation methods not employed more routinely? Can we update Q1E with some of these techniques?

POOLING STUDIES

With alternative methods (equivalence testing, mixed-effects modelling) common-place in other parts of the pharmaceutical industry, why not in CMC too?



Seqirus
A CSL COMPANY

WHAT IS MISSING - #5

- Some countries require different sets of data
- For certain products like vaccines where the protein composition (strain related) can change like a seasonal influenza or potentially meningitis vaccines, for example, this can be a significant issue and cause delays
- In addition, setting guidance on how to interpret expiry dating could be useful (e.g. formulated product versus filled product)

- Is there an opportunity to agree on a single data package needed to support different requirements (e.g. Annual Strain Update, data formats, etc.)?

ONE OFF REQUESTS

Some countries apply specific requirements related to stability data, from requiring accelerated data to requiring extra signatures / initialing each page. This is frustrating and burdensome and adding no value in others.

Seqirus™
A CSL COMPANY

CONCLUSIONS

- There are opportunities to use a data driven approach to justify a better stability program
- Improvements to the guidances or application guides with case studies could be useful in setting some consistent standards and eliminate nuisance work

- Shall we get started?

THANK YOU!

We would like to acknowledge all of the Seqirus and CSL Stabilitarians who assisted us in preparing this talk!

Seqirus™
A CSL COMPANY