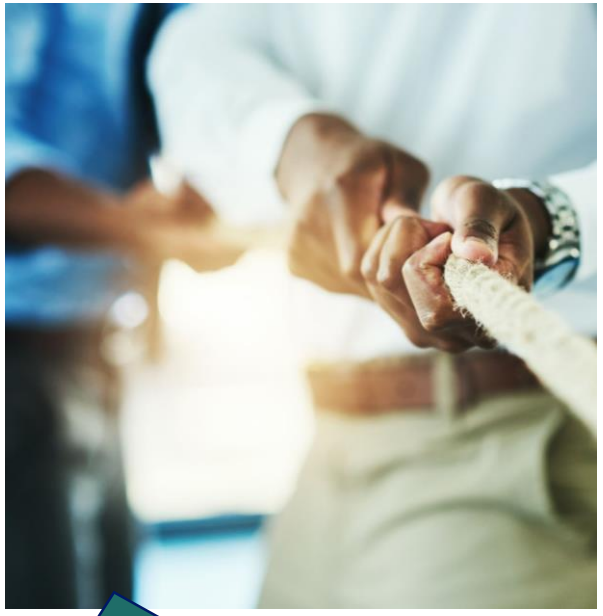
Main basis for justification of specification – current state

- **Regulatory guidance**
- **Manufacturing variability of batches especially for phase 3 clinical trials (& their stability)**
- **Exposure in clinical trials**
- **Scientific arguments**
- **Prior knowledge incl. data**

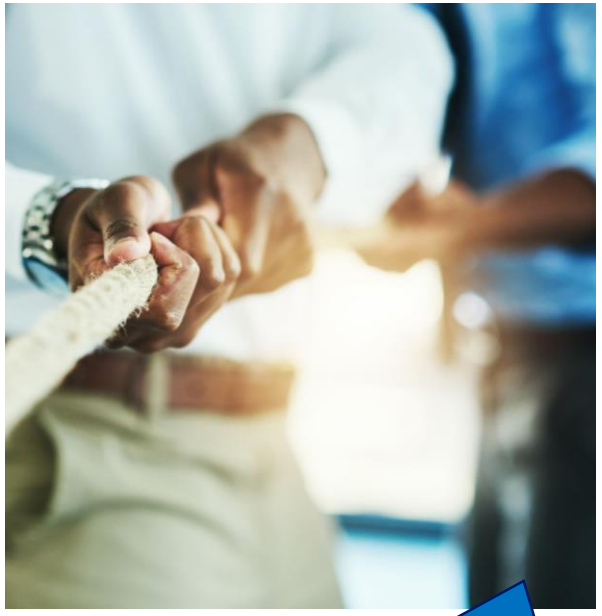
Emphasis on the above vary depending on type of parameter / CQA (Critical Quality Attribute)

The role of the statistician in this process



We want a good relationship with the authorities and fast non-complicated approval -> **thus safe & realistic limits not too wide**

The statistician may provide risk calculations and data-based advice as input for discussions.



Sounds great! We want to be able to produce effectively with low risk of out-of-specification product -> thus safe & realistic limits not too narrow

Specification setting is more than process capability

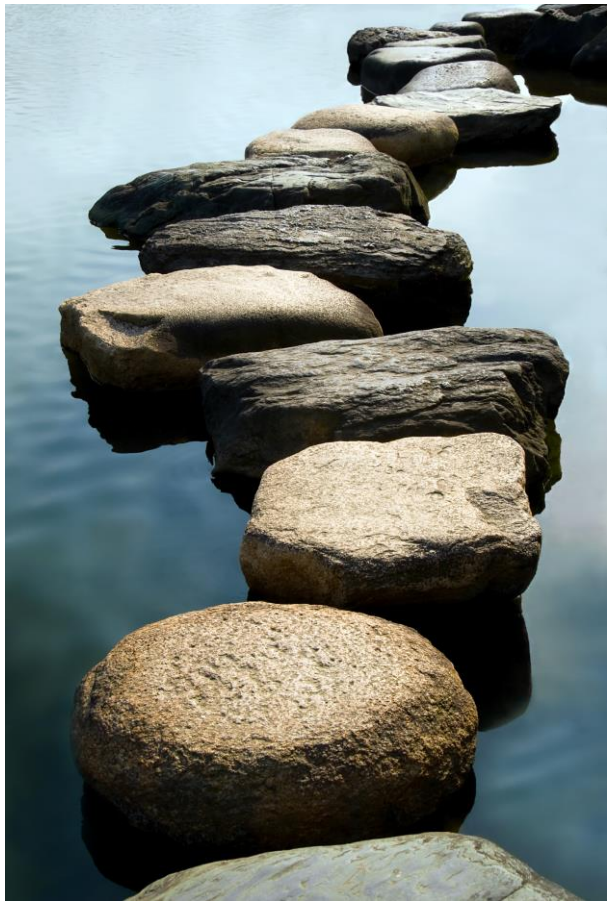
Why reduce current emphasis on manufacturing variability?

1. The batches for assessment of manufacturing variability do not usually reflect expected variations during routine production for the future marketed product. Reasons:
   a. limited number of batches
   b. usually produced during a short time period
   c. often at optimal conditions
   d. often in campaigns
2. Having very tight limits for many parameters (approximately 15 - although not independent) leads to very high risk of out of specification due to multiplicity
3. Risk of unnecessarily tight limits with suboptimal allocation of company resources – better focusing on relevant limits allowing for process improvements and consistent supply

How to change?

In steps:

- More advanced approaches such as in vitro / in vivo models may apply for some parameters such as dissolution and potency
- More emphasis on other arguments than manufacturing variability, such as
  - Scientific arguments
  - Prior knowledge incl. data



Summary

- Patient centric specifications are promising and highly useful
- Justification approach may be different for different parameters

PhD Trine Kvist, Principal specialist, Novo Nordisk

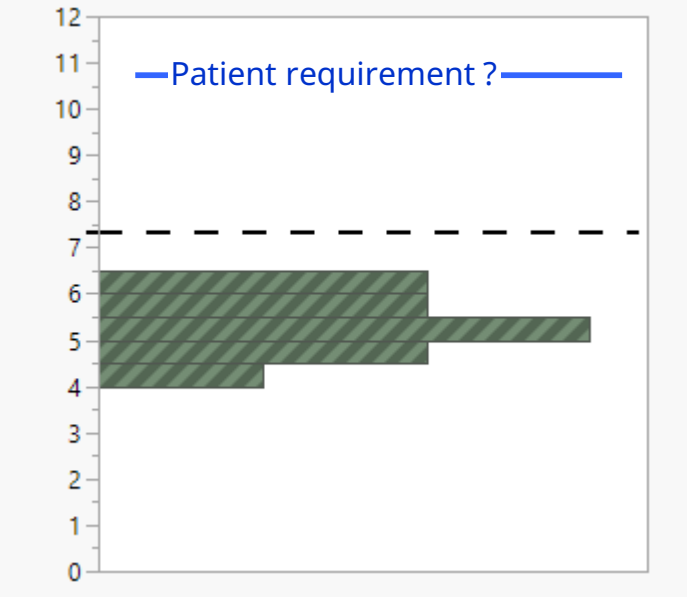
PhD Trine Kvist is MSc in Engineering from the Technical University of Denmark, 1993 and PhD from the same university from Department of Mathematical modelling in 2000.
She started working in the pharmaceutical industry for Novo Nordisk in 1994 and most of her working life has been within this industry. She has worked in the areas of CMC, Quality and Clinical development. She has vast experience with specification setting in practice.

BACK-UP

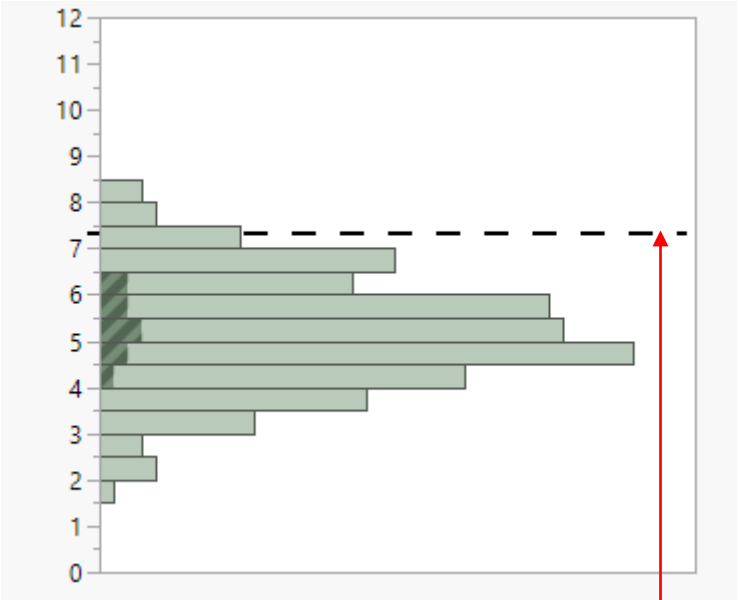
What to do for the parameters where manufacturing variability and exposure plays a role in specification setting?

Example:

Limits based on limited No. of phase 3 batches



Actual manufacturing data with higher variability



Limits based on phase 3 batches alone:

- ✓ Clinical exposure good
- – Risk of unstable supply due to random loss of batches
- – Unnecessarily high manufacturing costs

Other arguments for wider limit from previous slide:

- ✓ Wider limit
- ✓ Avoid risk of unnecessarily poor batches and unstable supply
- – Clinical exposure often from few patients and short time period
- – If arguments too weak we end here.

Mimic future manufacturing variability by deliberately varying setpoints etc. within operating ranges:

- ✓ Wider limit
- ✓ Clinical exposure good
- – Potential risk of manufacturing unnecessarily poor batches for clinical trials