"How can we strengthen statisticians' impact in CMC related ICH guidelines?"

Special focus on ICH M13b concerning dissolution profiles

Thomas Hoffelder, PhD, Boehringer-Ingelheim

Beate Presser, PhD, Boehringer-Ingelheim

Christian Schmid, PhD, Roche

Affiliations: **E**uropean **F**ederation of **S**tatisticians in the **P**harmaceutical **I**ndustry (EFPSI)
CMC **S**tatistics **N**etwork **E**urope (CSNE)

CMC - Chemistry, Manufacturing, and Controls

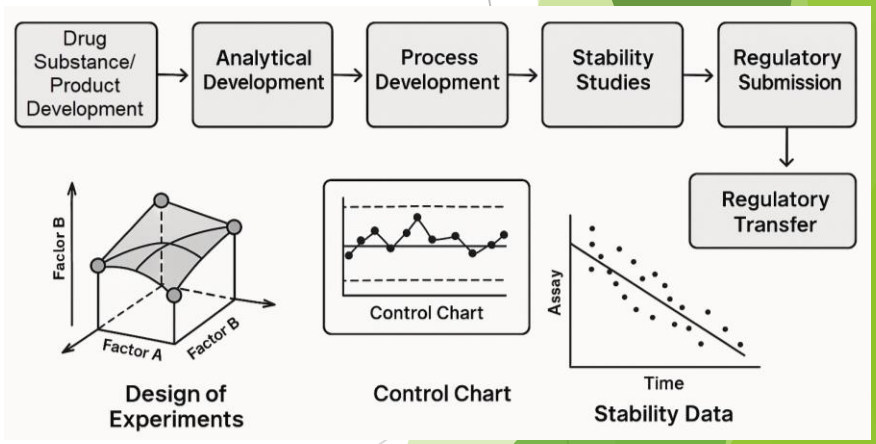
CMC Statisticians in the Pharmaceutical Industry

- Focus Areas:
  - Manufacturing Control
  - Process Development
  - Regulatory Registration
- Core Contributions:

Provide a data-driven foundation ensuring:

- High Quality and Consistency of manufactured drugs to be safe and effective
- Stability and safety compliance through strict quality controls
- Efficient and cost-effective product development

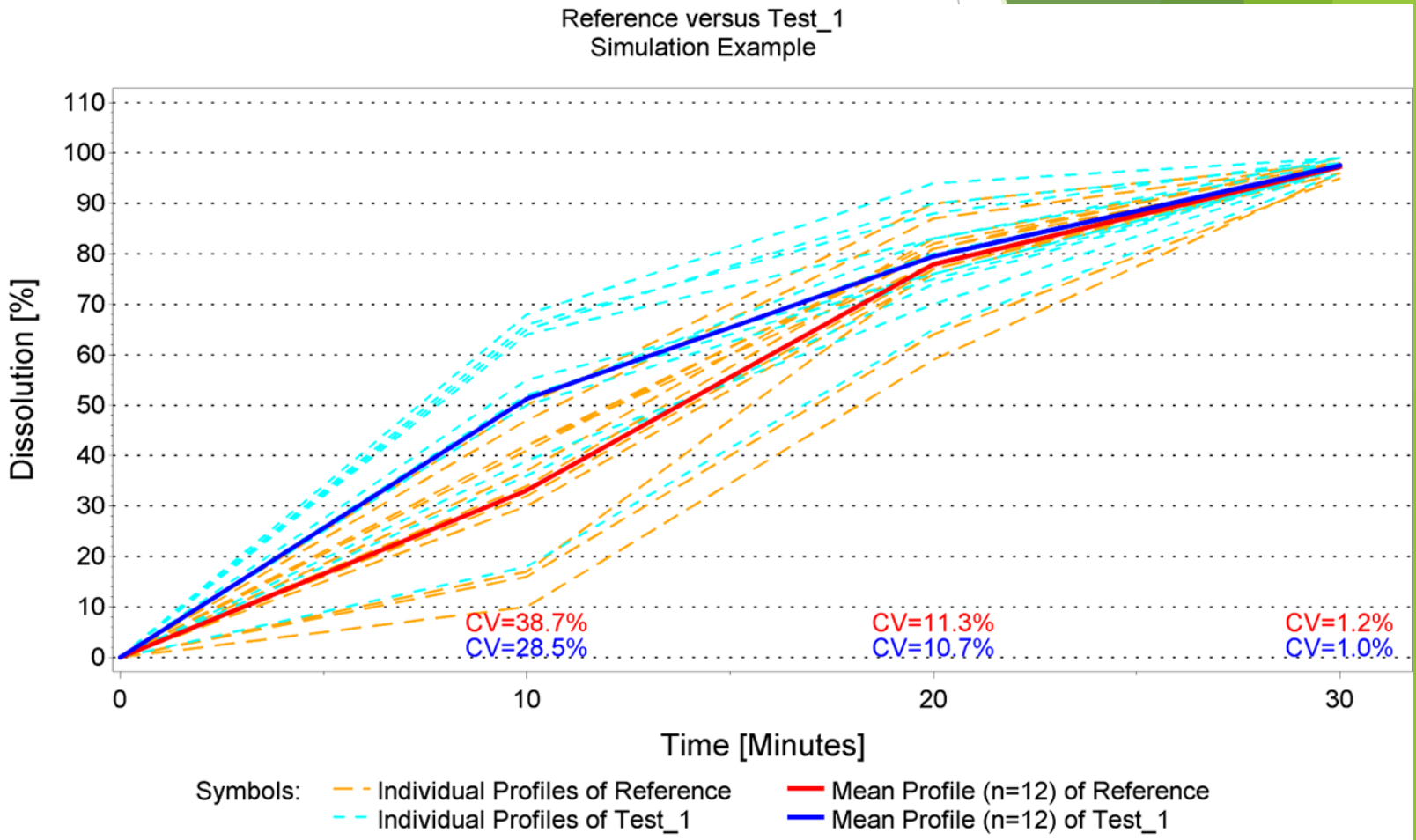
- Key Guidelines:
  - Q1: Stability
  - Q2/Q14: Analytical Method Validation
  - Q6: Specifications
  - Q8: Pharmaceutical Development
  - Q9: Quality Risk Management
  - …



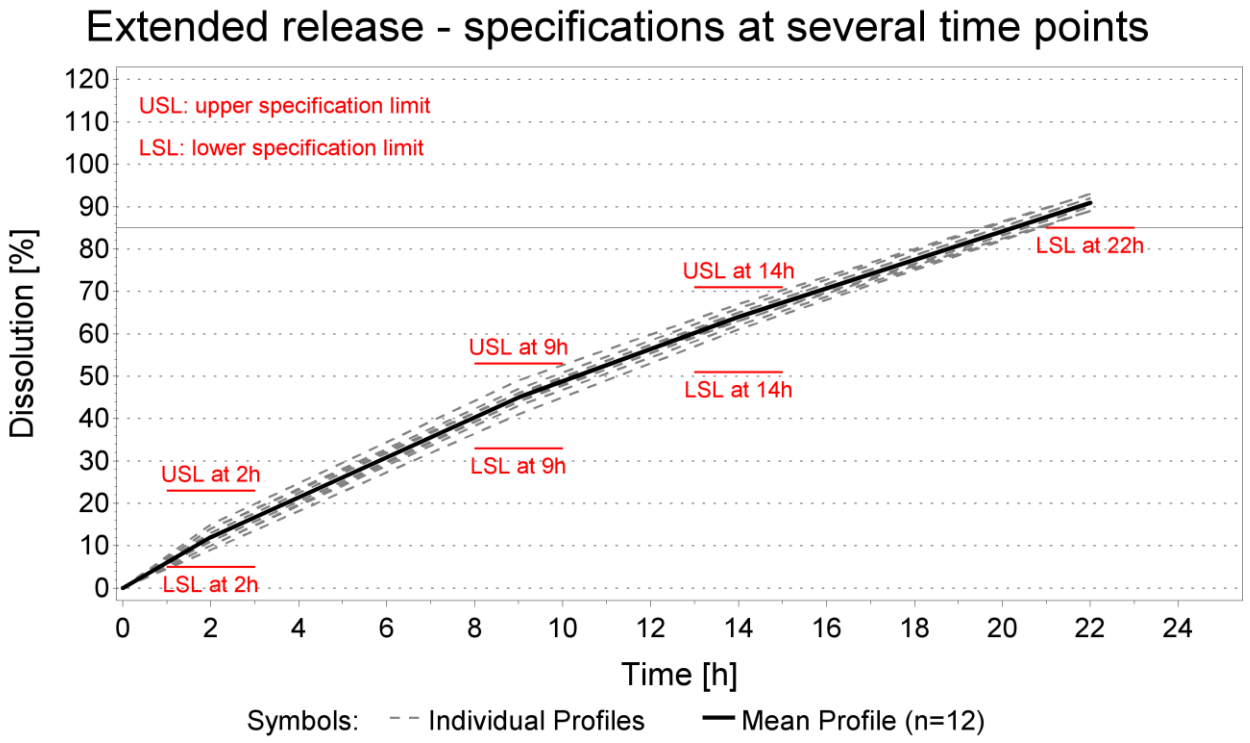
Despite their critical contributions, CMC statisticians hold a limited role in guidelines and regulatory interactions.

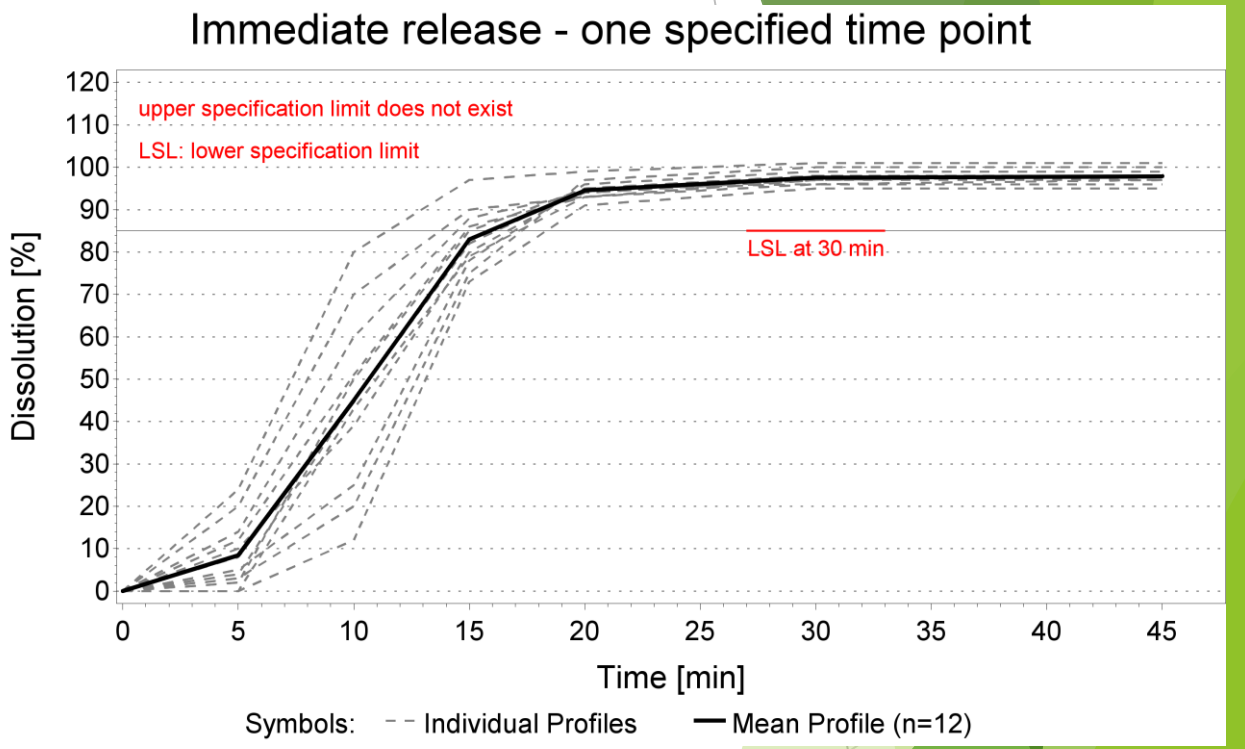
Disso profiles Intro – relationship to BE

- Context: post-approval changes (PACs)
- surrogates for **BE studies:** disso profile study successful --> BE study not necessary
- ICH E6: “avoid unnecessary burden on participants” --> Need for **sufficiently powered** disso profile studies **to avoid unnecessary** BE studies.



Disso profiles Intro – ER and IR products



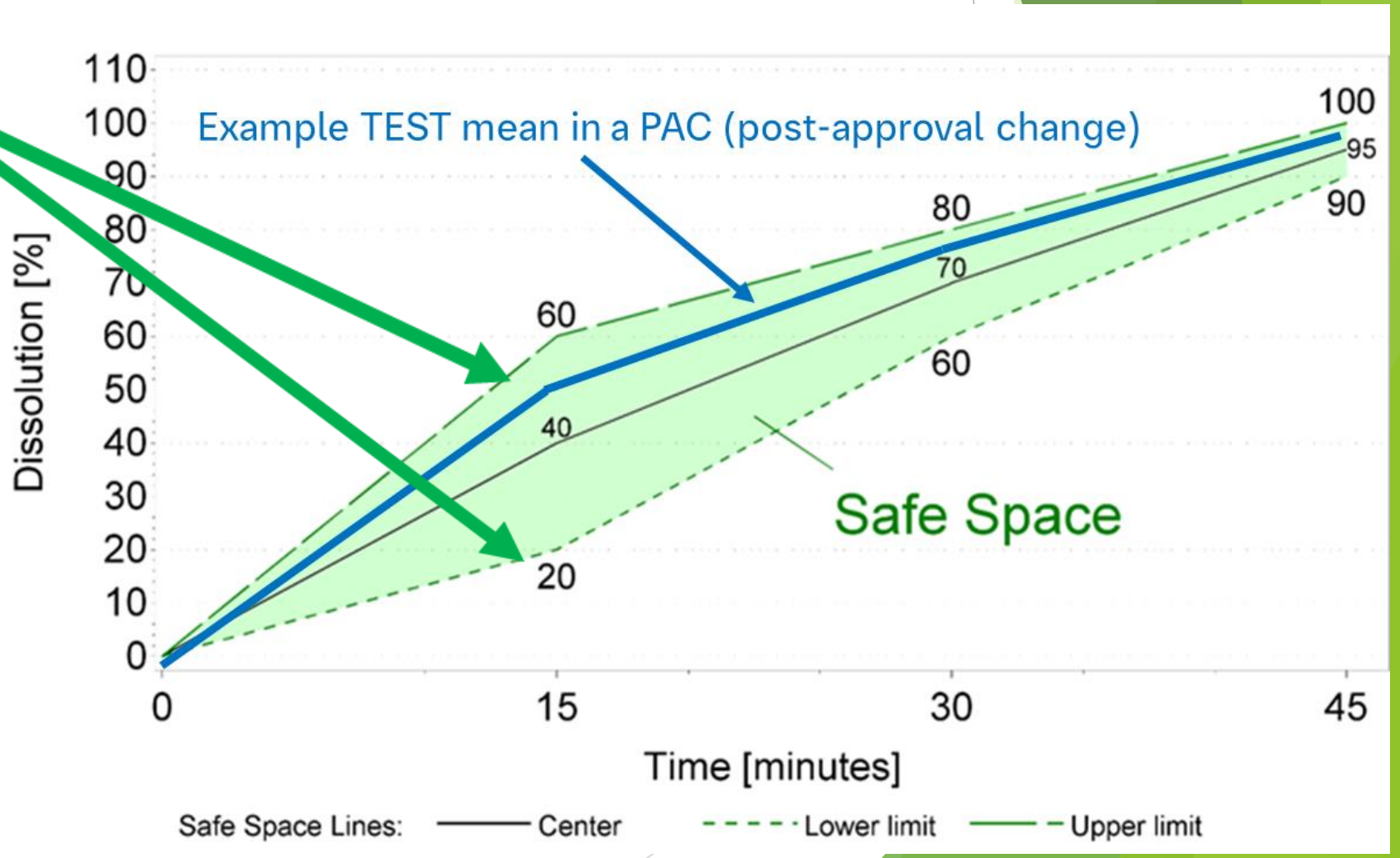


- **all time points relevant** for patient/product quality
- Standard approach: Euclidean distance based --> equal weight to all time points

- **Early time points not relevant** for patients/product quality
- Higher power possible with standardized approaches (higher weight of later time points)

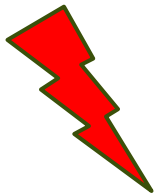
Disso profiles Intro – the "safe space"

- Disso profile means of two formulations
- **BE study** result: both formulations are found to be bioequivalent
  ==> Safe space: area between disso profile means
- Acceptance criterion for PACs: TEST mean within safe space
- One-sample equivalence test, **equivalence margin justified by in vivo data!**



Disso profiles – recent developments

- 2019 M-CERSI workshop on dissolution profile similarity
  - Safe space considered as the preferred approach (when it exists)
  - Estimand discussion, decision tree: different equivalence hypotheses suggested for different drug product types
- 2019 EFSPI RSW: EMA Q&A document on Mahalanobis distance and T2EQ



- 2025 ICH M13b
  5 CMC statisticians (1 FDA, 4 industry) invited to advice the working group, central recommendations:
  - Use of safe space if available --> not considered
  - Appropriate estimands for dissolution profiles needed (select appropriate equivalence test depending on drug product type) --> not considered

Questions

- (ICH E6, M-CERSI workshop 2019, EFSPI RSW 2019) versus (ICH M13b)
  How to solve these conflicts? Suggestion: Establishing a working group of **statisticians** to develop a guidance/white paper/… on the **statistical aspects** of dissolution profile studies. Do you agree?

- Do you agree that statistical methodologies could also be part of the QIG discussions? E.g. stability modelling...
- What opportunities do you see for CMC statisticians to contribute more consistently to guideline development, such as ICH Q6? How do you view the role of statistics in justifying specifications?"
- Could you envision a constructive role for EFSPI – CSNE in contributing to guideline discussions, and if so, what form might that collaboration take?