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# Equivalence of Dissolution Profiles

Time for the statistical dissolution (r)evolution?

Thomas Hoffelder

*Life forward*

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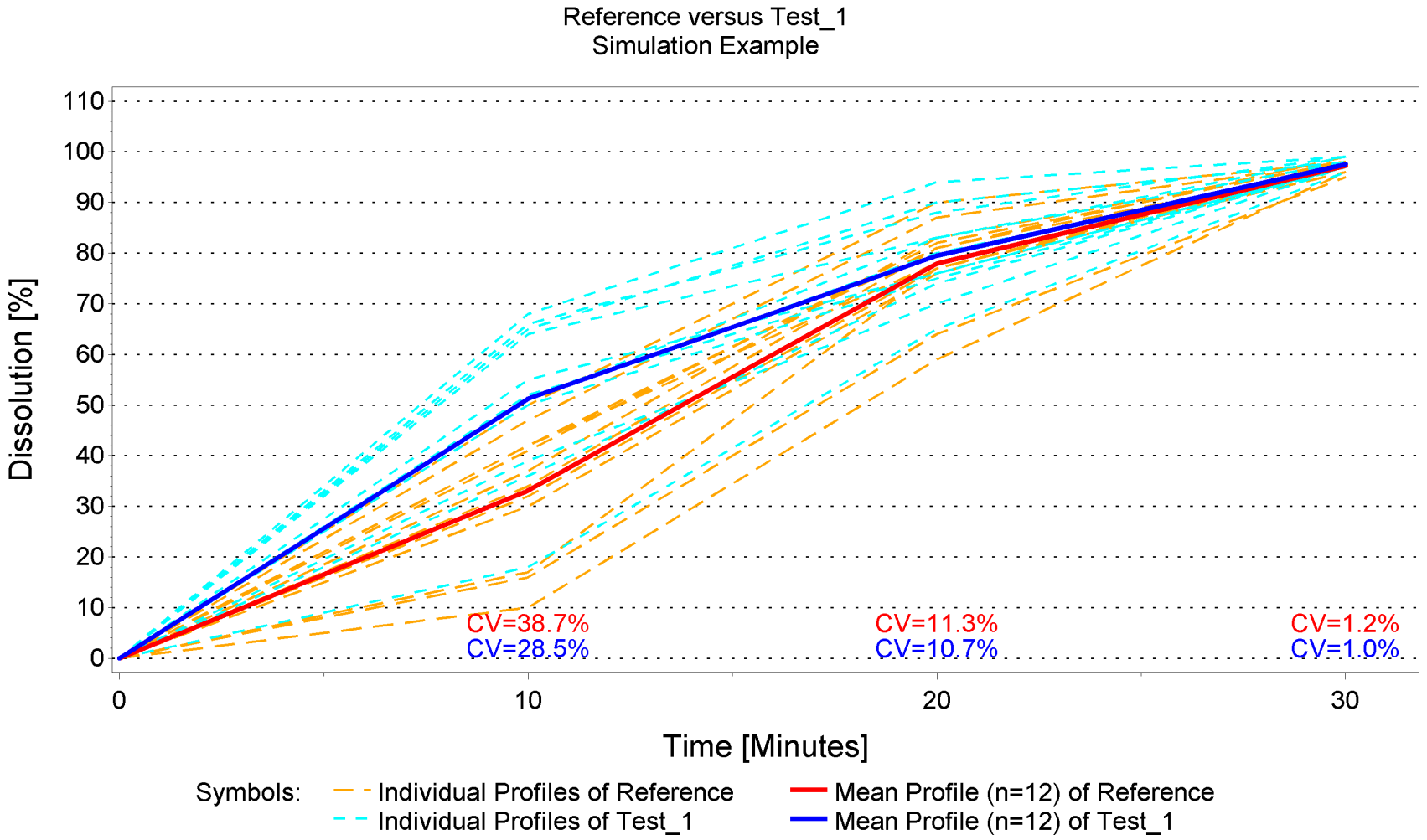
# Introduction

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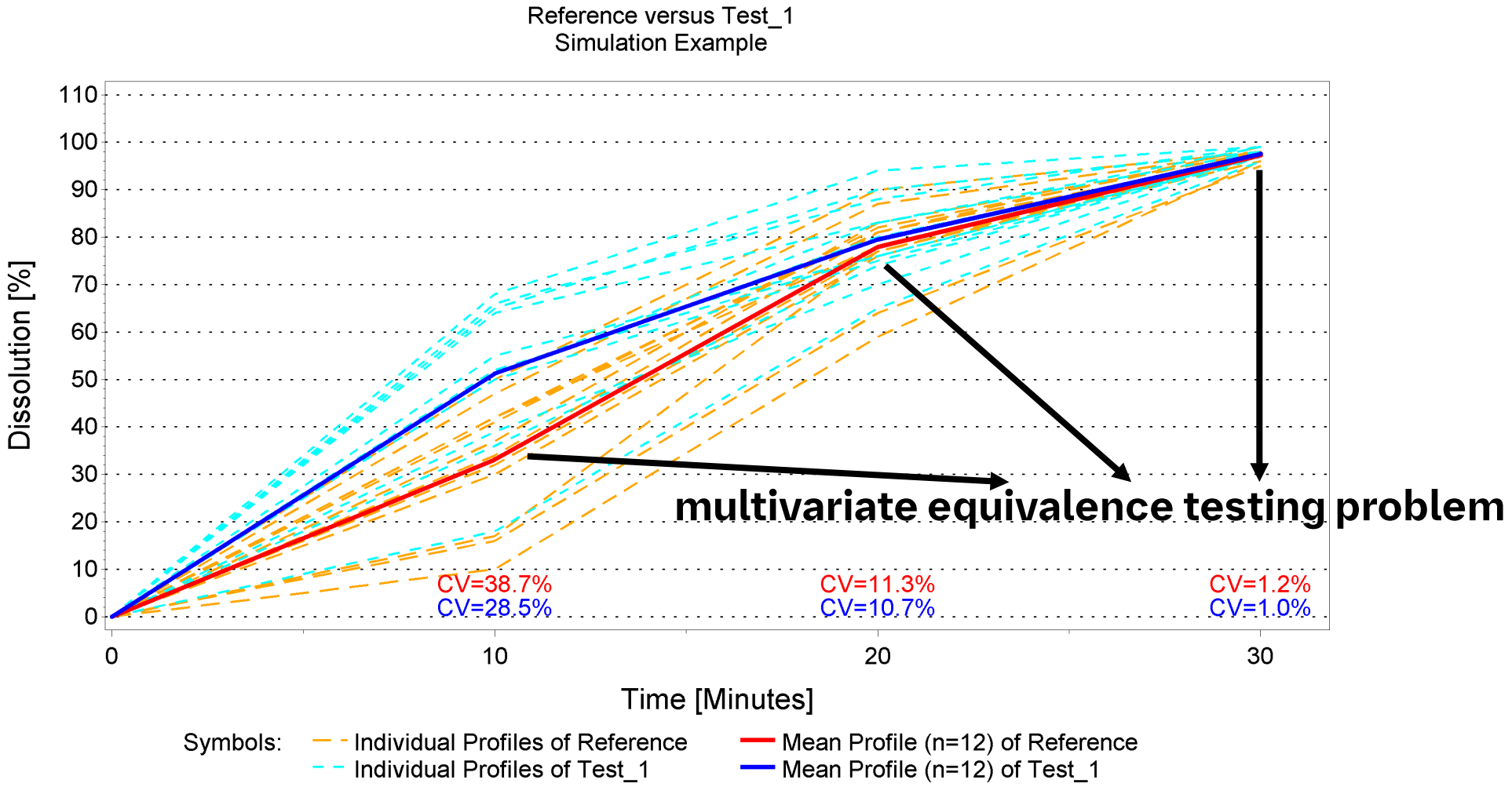
# Introduction

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# Introduction

Context of disso profile studies: surrogates for BE studies (in some cases)

- Biowaiver requests
- Post-approval changes
  - scale-ups
  - manufacturing site changes
  - equipment and process changes

Question of interest: "Is the drug product made after the change equivalent to the drug product made before the change?"

➔ TEST product

➔ REF product

Dissolution profile comparison successful ➔ BE study not necessary

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# Problems with the current situation

**Why should we use statistical methods**

- Foster scientific evidence based decision making
- Balance between T1E control and power
  - appropriate sample size
  - appropriate statistical method

**Current problems in the dissolution profile context**:

- Basic statistical principles (T1E control, sample size determination) not considered in guidances
- The estimand for dissolution profile studies not sufficiently discussed
- Missing harmonization

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# Problems with the current situation – f2

Search for an acceptance criterion/hypothesis for disso profiles:

- p: number of time points  $\boldsymbol{R} = (R_1, \ldots, R_p)$ : REF mean  $\boldsymbol{T} = (T_1, \ldots, T_p)$ : TEST mean
- First idea: "a kind of average difference < 10%" using the **quadratic mean** of the estimated **differences** $\widehat{QMD} = \sqrt{(1/p)\sum_{t=1}^{p}(R_t - T_t)^2}$
- Remark: $\widehat{QMD}$ standardizes the Euclidean distance point estimate $\widehat{ED} = \sqrt{\sum_{t=1}^{p}(R_t - T_t)^2}$ to the number of time points
- ED and QMD are well-known statistical distance measures. An asymptotic equivalence test for ED (and therefore QMD) is available

➔ **Acceptance criterion $\widehat{QMD}$ < 10**

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# Problems with the current situation – f2

Next ideas:

- $\widehat{QMD} < 10$

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# Problems with the current situation – f2

Next ideas:

- $\widehat{QMD} < 10$ ≈

$$\frac{1}{\sqrt{1+\widehat{QMD}^2}} > \frac{1}{10}$$

⟺

$$\frac{100}{\sqrt{1+\widehat{QMD}^2}} > \frac{100}{10}$$

⟺

$$50\ \log_{10}\left(\frac{100}{\sqrt{1+\widehat{QMD}^2}}\right) > 50\ \log_{10}\left(\frac{100}{10}\right)$$

# Problems with the current situation – f2

Next ideas:

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$$\frac{1}{\sqrt{1+\widehat{QMD}^2}} > \frac{1}{10}$$

$$\Leftrightarrow$$

$$\frac{100}{\sqrt{1+\widehat{QMD}^2}} > \frac{100}{10}$$

$$\Leftrightarrow$$

„similarity factor“ f2 := $50\ \log_{10}\left(\frac{100}{\sqrt{1+\widehat{QMD}^2}}\right) > 50\ \log_{10}\left(\frac{100}{10}\right) = 50$

# Problems with the current situation – f2

Next ideas:

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$$\Leftrightarrow$$

„similarity factor“ f2 := $50\ \log_{10}\left(\frac{100}{\sqrt{1+\widehat{QMD}^2}}\right) > 50\ \log_{10}\left(\frac{100}{10}\right) = 50$

the international gold standard for disso profiles: f2 > 50

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# Problems with the current situation – f2

Transformation of „$\widehat{QMD}$ <10“ into „f2>50“ (f2 = $50\ \log_{10}\left(\frac{100}{\sqrt{1+\widehat{QMD}^2}}\right) = 50\ \log_{10}\left(\frac{100}{\sqrt{1+\frac{1}{p}\widehat{ED}^2}}\right)$ )

- Simple criterion
- Non-statisticians loose the understanding for the acceptance criterion
- It is masked that the decision is based on a point estimate ➔ no T1E control!

What does this mean?

- Scientific/statistical update of international standards necessary
- Input of statisticians essential → multivariate equivalence testing problem
- Statistical sections should be written by statisticians

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# Problems with the current situation – The undefined estimand

Guidances:

- f2 point estimate → allowed only if variability is below certain thresholds
- If variability is high: no concrete recommendations

Consequence: lots of papers, lots of method comparisons

Statement: „Method A superior to method B regarding T1E control/power/…“

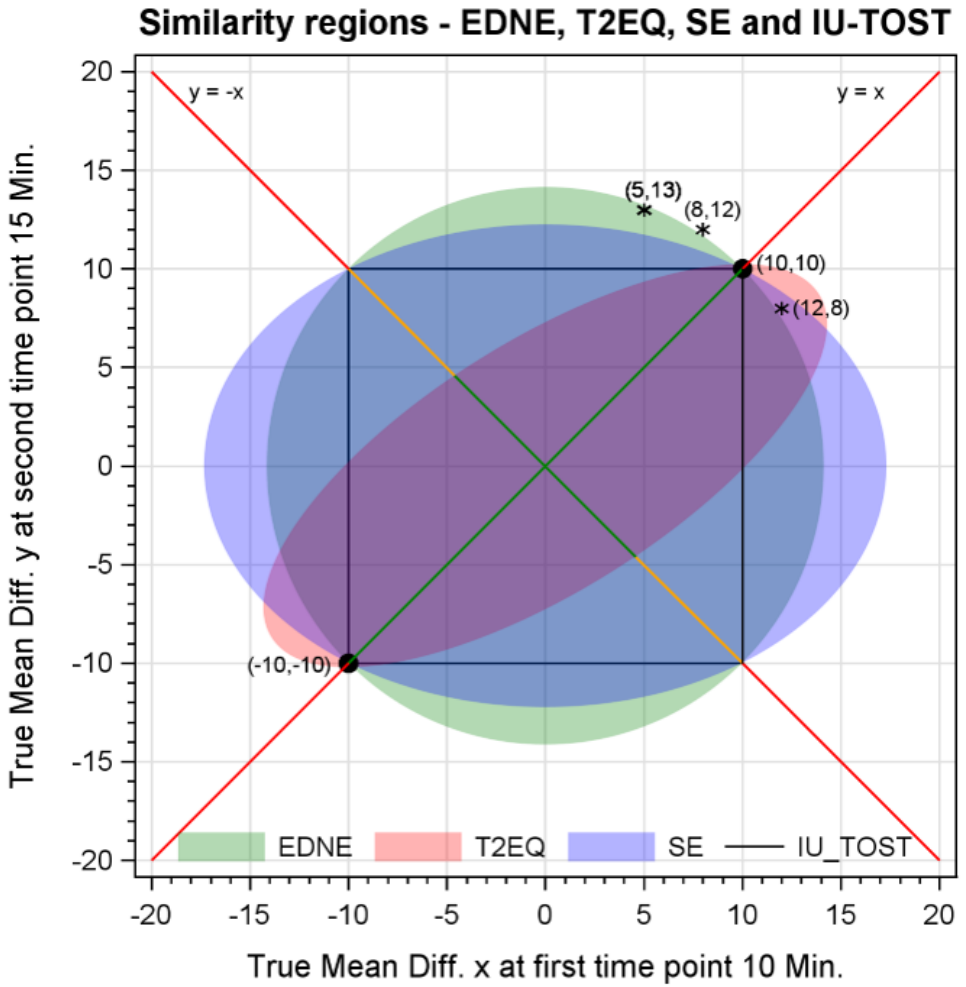
➔ If methods A and B test different hypotheses, what is the meaning of the statement?

# Problems with the current situation – The undefined estimand

Different methods, different distance measures, different equivalence hypotheses:

- How should equivalence be defined?
- What are appropriate equivalence hypotheses?
- Should we use the same equivalence hypotheses for all drug products?
- Are there criteria such that certain hypotheses are preferable for certain products?

Hoffelder et al. (2022): A holy grail / one-size-fits-all approach for disso profiles does not exist




**Source of figure: Hoffelder et al. (2022), Figure 6**

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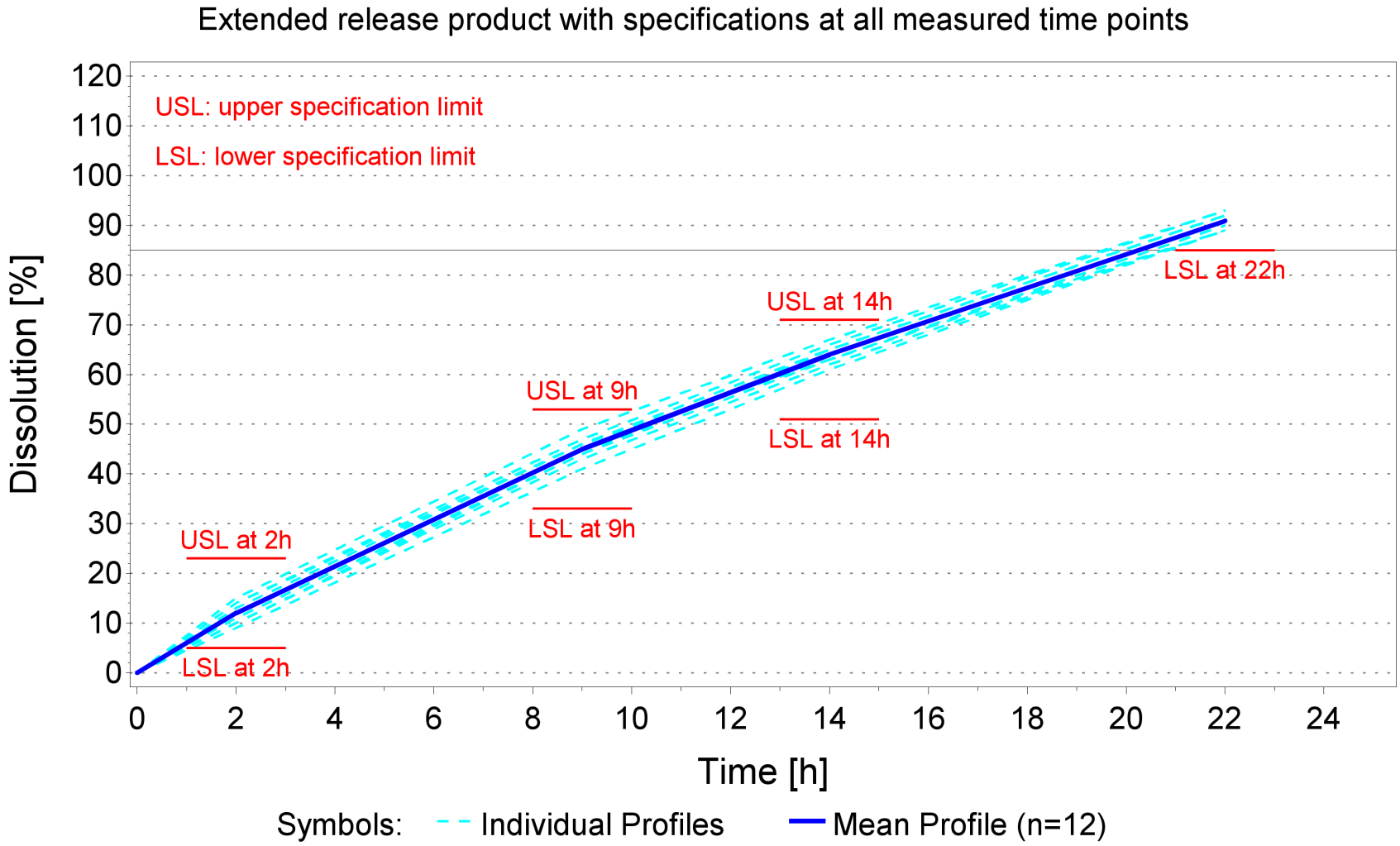
# Problems with the current situation – The undefined estimand

Hypothetical **extended release** product with:

- Several time points (e.g. 2h, 9h, 14h, 22h) relevant for batch release testing
  ➔ specification limits for all time points
- **all time points relevant** for patient/product quality

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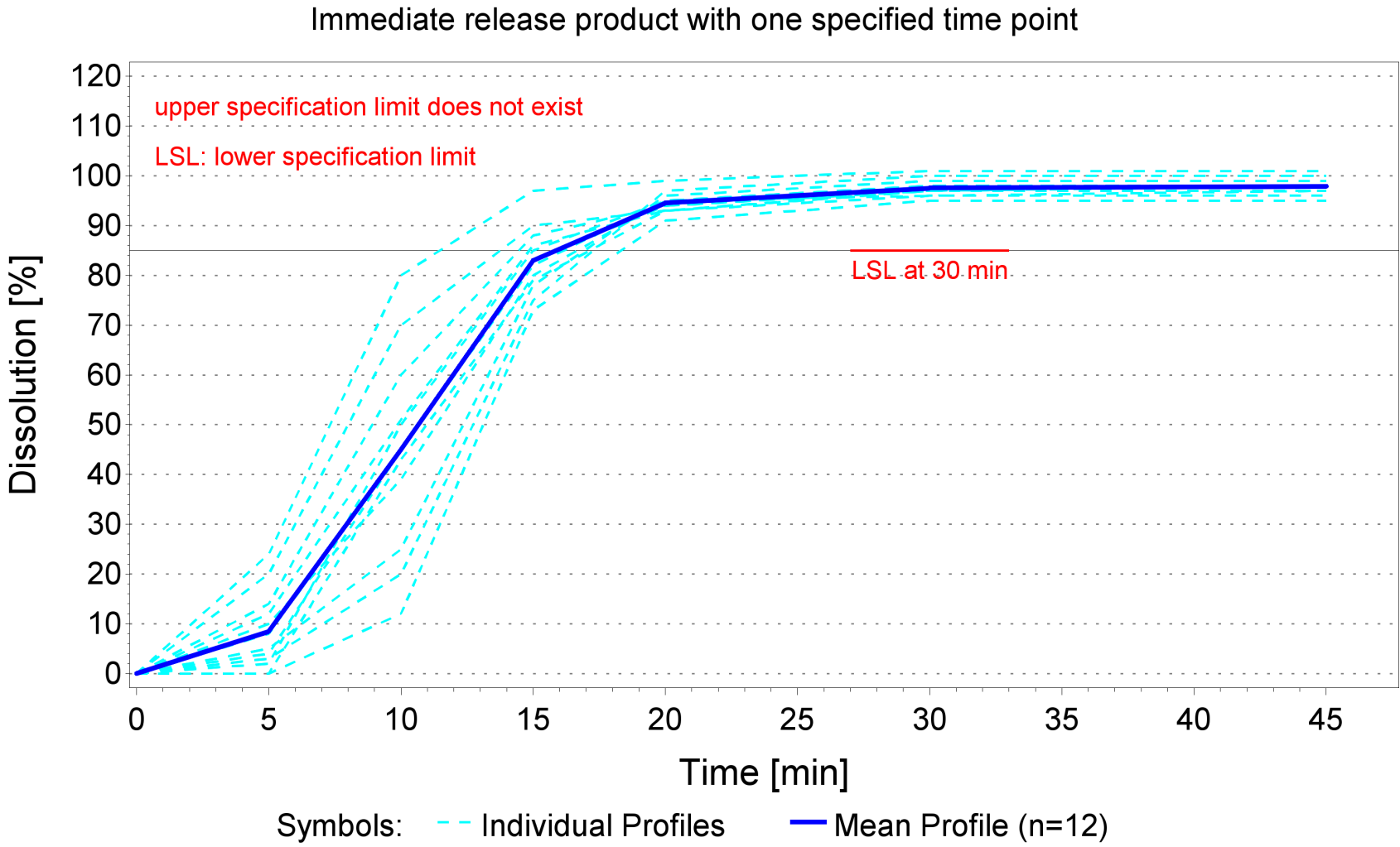
# Problems with the current situation – The undefined estimand

Hypothetical **immediate release** product with:

- Only one time points tested at batch release, e.g. 30 min., one-sided specification
- **Early time points** not tested for batch release, **not relevant** for patients/product quality

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# Problems with the current situation – The undefined estimand

Hypothetical **extended release** product with:

- Several time points (e.g. 2h, 9h, 14h, 22h) relevant for batch release testing
  ➔ specification limits for all time points
- **all time points relevant** for patient/product quality

➔ Equivalence test needed with **equal weight of all time points** in the test decision, e.g. based on the Euclidean distance

Hypothetical **immediate release** product with:

- Only one time points tested at batch release, e.g. 30 min., one-sided specification
- **Early time points** not tested for batch release, **not relevant** for patients/product quality

➔ Equivalence test needed with **higher weight of later timepoints**, e.g. based on a standardized distance measure

# Problems with the current situation – The undefined estimand

Products with different characteristics, different roles of the individual time points:

- Today various multivariate equivalence tests exist which can fulfill the respective needs of different product characteristics

Needed:

Working group to discuss, define and select appropriate equivalence tests for dissolution profile studies

**The estimand for disso profiles should be clarified**

➔ This is a statistical task ➔ **knowledge of equivalence tests needed**

➔ working group of **statisticians**

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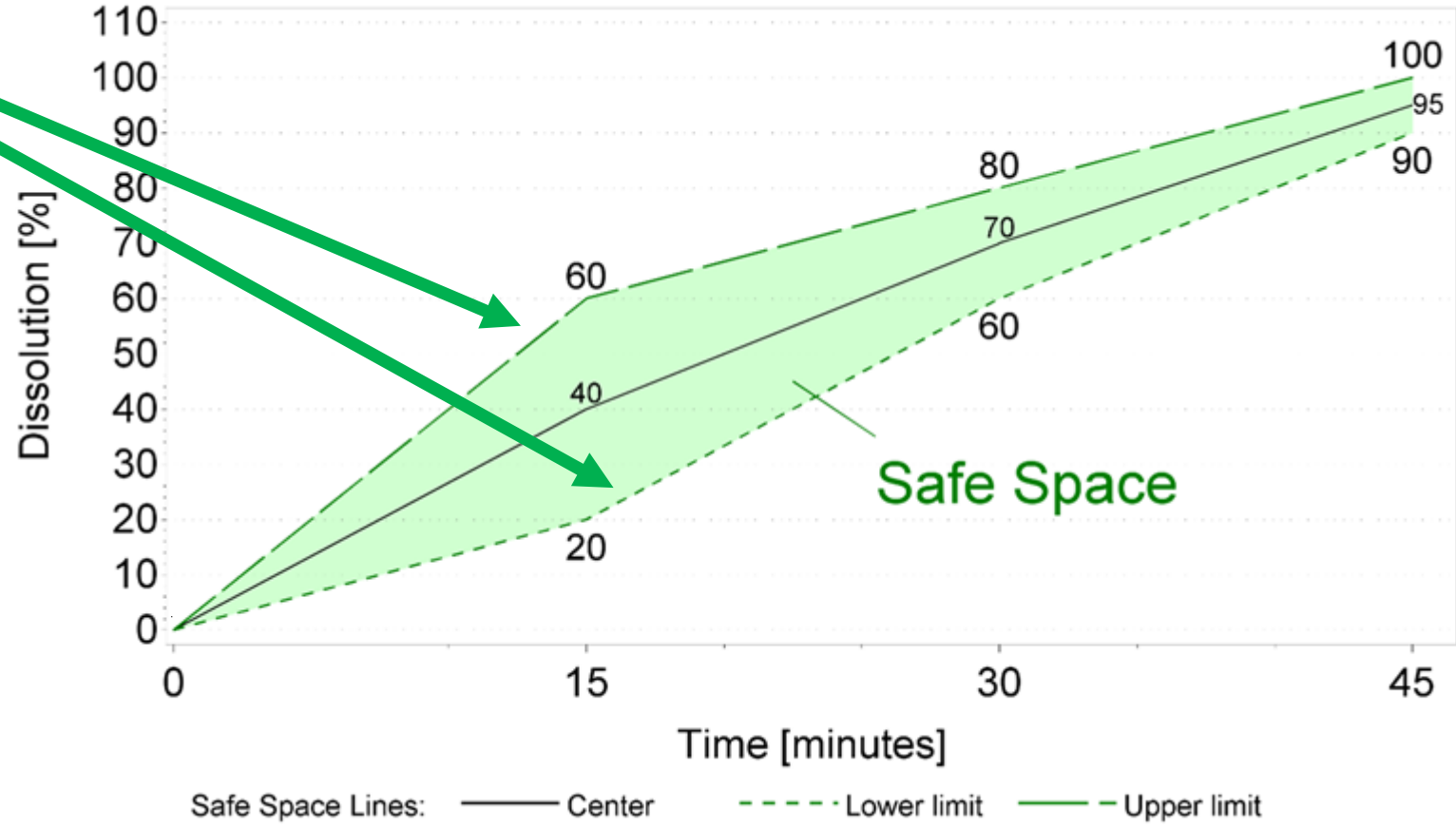
# Problems with the current situation – The safe space

Boundaries of the safe space:

- Disso profile means of two formulations
- BE study result: both formulations are found to be bioequivalent
- Safe space is determined by **in vivo data**!

Consequences for post-approval changes when a safe space exists:




**Source of figure: Abend et al. (2023), Figure 2**

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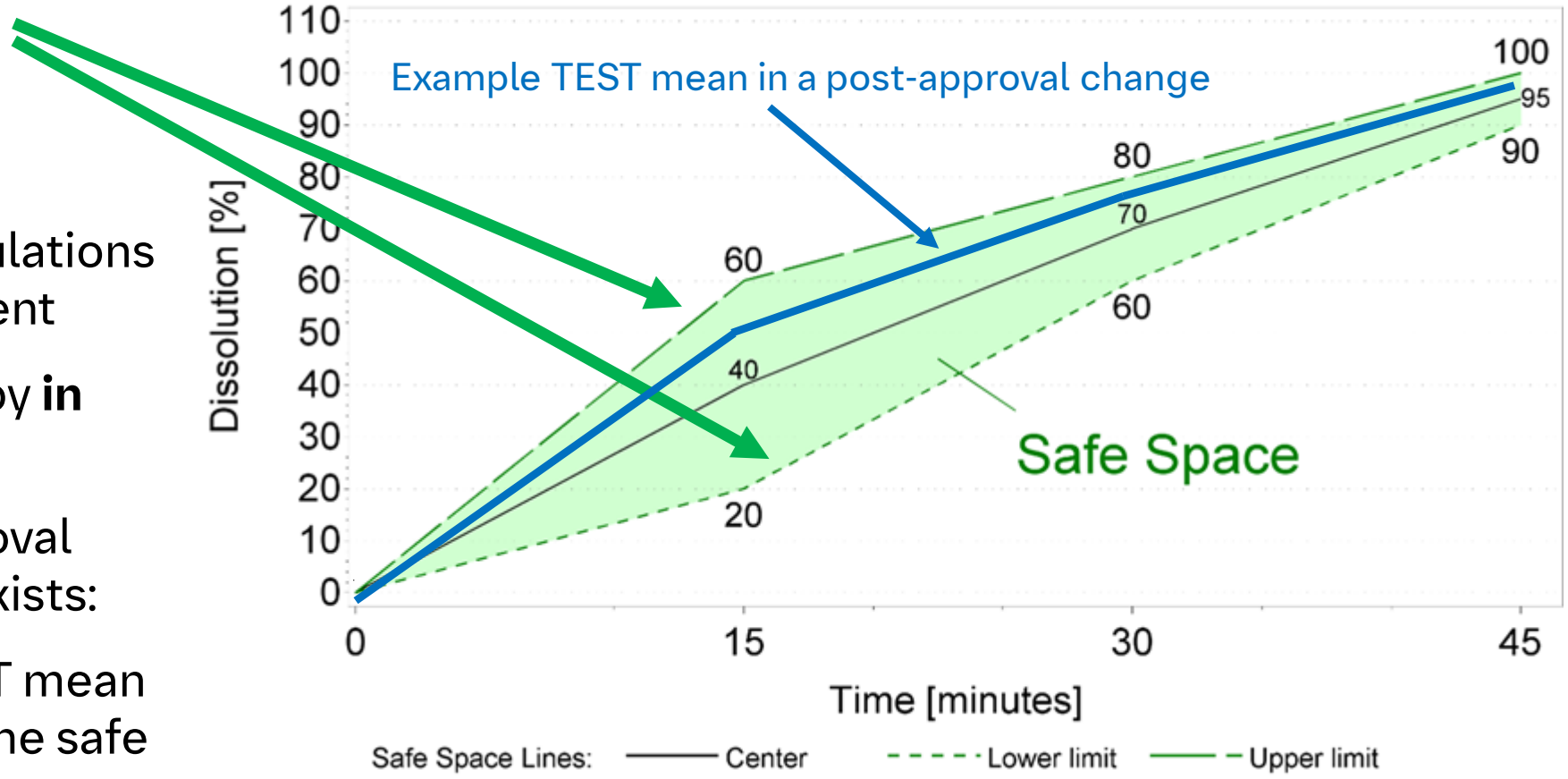
# Problems with the current situation – The safe space

Boundaries of the safe space:

- Disso profile means of two formulations
- BE study result: both formulations are found to be bioequivalent
- Safe space is determined by **in vivo data**!

Consequences for post-approval changes when a safe space exists:

- Acceptance criterion: TEST mean profile completely within the safe space




**Source of figure: Abend et al. (2023), Figure 2**

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# Problems with the current situation – The safe space

| **f2, EDNE, T2EQ, SE, …** | **Safe space** |
|---|---|
| Two-sample equivalence tests | one-sample equivalence test |
| REF and TEST sample | PAC: only TEST sample |
| 10% equivalence margin, arbitrary rule of thumb, no link to in vivo data | equivalence region: safe space **acceptance criterion based on in vivo data!** |
| | T1E control can be easily implemented (IU TOST, one-sample variant) |

Abbreviations:
PAC: post-approval change
IU: intersection-union
TOST: two one-sided tests procedure

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# Problems with the current situation – The safe space

Safe space conclusions:

- Safe space also called “clinically relevant dissolution specification” (Abend et al., 2023), **clinically relevant equivalence region**
- Using the safe space is a **scientific progress** for decision making in contrast to arbitrary rules of thumb (→ the 10% acceptance criterion) as equivalence margins
- This should be recognized and implemented in guidances.

➔ Such a guidance on two-sample and one-sample multivariate equivalence tests needs the input of statisticians!

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# Solution

- We need **more statisticians in the CMC (Chemistry, Manufacturing and Control) area**
- Statistical challenges in the CMC area as e.g. dissolution profile studies should be handled on a professional scientific and statistical level.
- **Working group of statisticians** needed to develop a (draft) **guidance for dissolution profile studies**
  - foster scientific evidence based decision making
  - implement basic statistical principles (balance between T1E control and power, creation of study plan including sample size determination in the planning phase) in the dissolution profile context
  - Clarify the estimand for dissolution profiles (select appropriate equivalence hypotheses for various product characteristics)

# Solution and Conclusion

**Time for the statistical dissolution (r)evolution?**

- Some guidances and the original publication of f2 date from the mid-1990s
  ➔ In the mid-1990s very few knowledge about multivariate equivalence tests was available.
  ➔ This has now changed.
- The current statistical knowledge should be included in current guidances

➔ **Needed: Guidance on the statistical aspects around dissolution profile studies**

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# Thank you for your attention

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