Equivalence of Dissolution Profiles

Summary of statistical follow-up activities of the M-CERSI workshop 2019

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Introduction

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Post-approval changes:

- scale-up changes
- manufacturing site changes
- equipment and process changes

FDA Guidance for Industry (2004):
Changes to an Approved NDA or ANDA
Manufacturer must prove that quality, safety and efficacy are not affected by the change

The question

"Is the drug product made after the change
equivalent to
the drug product made before the change?"

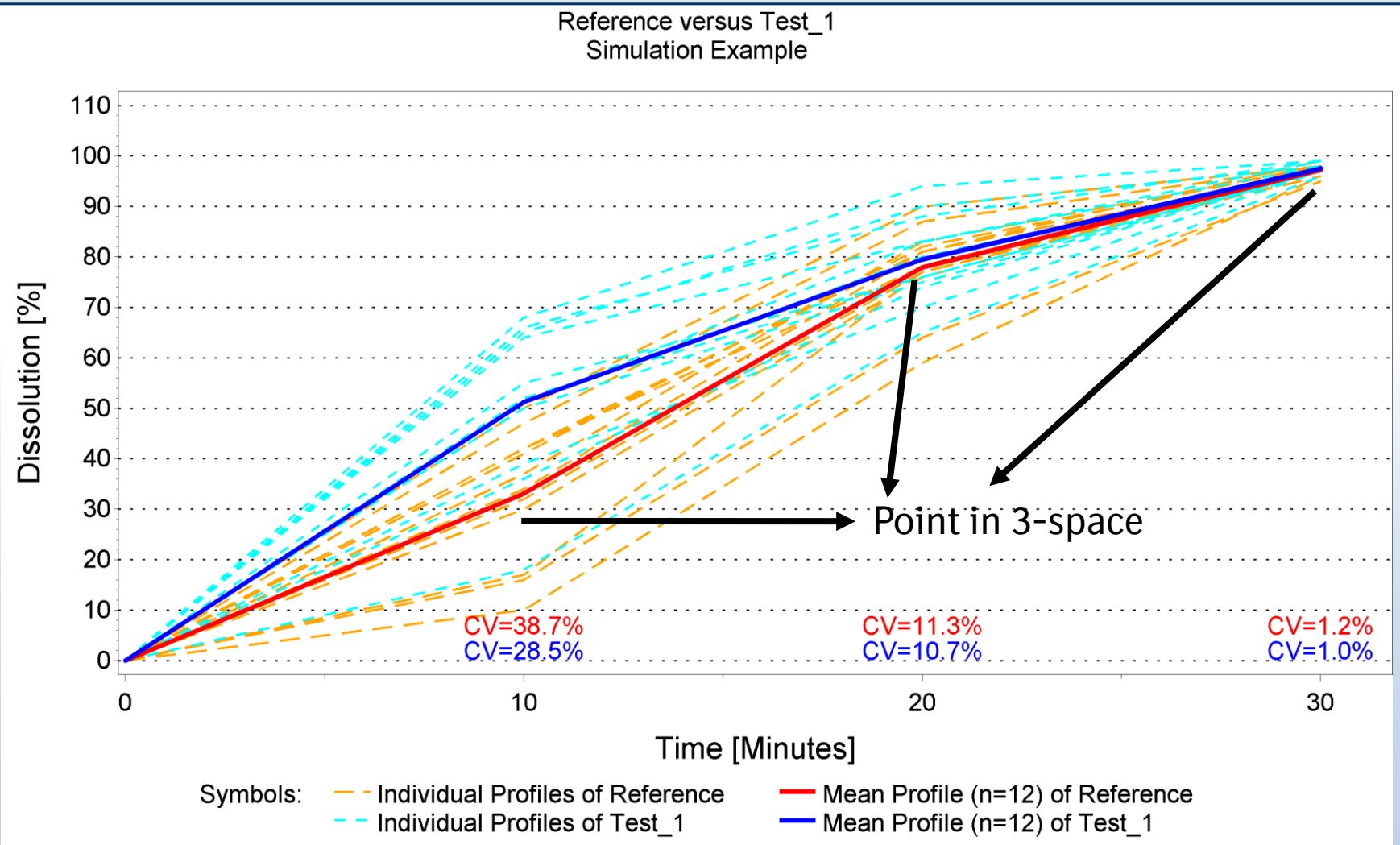
→ TEST product

→ REF product

has to be answered.

Dissolution profile comparison successful ➔ avoid bioequivalence study

Introduction



Dissolution profiles comparison:

- "Similarity" of 2 groups of curves
- Curves <--> Points in p-space

Multivariate equivalence testing

- A distance measure quantifies the dissimilarities
- EM (=equivalence margin) is the acceptance criterion
- **Hypotheses:**
  H_0: Non-equivalence of both dissolution profile groups
  H_1: Equivalence of both dissolution profile groups (goal of study)

Introduction

p: number of time points $\boldsymbol{R} = (R_1, \ldots, R_p)$: REF mean profile $\boldsymbol{T} = (T_1, \ldots, T_p)$: TEST mean profile

QMD is the quadratic mean of the differences between REF and TEST mean profiles.

$$QMD = \sqrt{(1/p)\sum_{t=1}^{p}(R_t - T_t)^2}$$

The regulatory standard approach f2 is a series of monotone transformations of QMD:

$$f_2 = 50\ \log_{10}\left(\frac{100}{\sqrt{1+QMD^2}}\right)$$

Identical acceptance criteria: f2 > 50 ⇔ QMD < 9.95≈10
(and identical alternative hypotheses)

"Average difference < 10"

Introduction

Checking F2 > 50 is the regulatory standard approach

Basic problems:

- point estimates only ➔ no control of Type 1 Error (T1E)!
  ➔ applicable to “low variable” dissolution profiles only (guideline restrictions)
  But: no concrete guidance in case of highly variable profiles.
- In addition: Multiplicity problems due to design of dissolution studies

Goal of the “Day 1 paper” [Hoffelder et al. (2022)]:

- Explain the properties of various equivalence procedures tailored to dissolution profile comparisons
- Suggestion of a decision tree for selecting one of these procedures with at least approximate T1E control
- Design of dissolution studies: Clarifying statements on sample sizes and evaluations of data obtained from several batches per group

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The “day 1 paper” – study design

There is a need of a sufficiently high power for dissolution profile comparisons

Example: Post-approval change, transfer manufacturing site A → manufacturing site B

- 3 pH values
- 4 dosage strengths
- drug product is a fixed-dose combination (tablets) with 3 active ingredients

➔ 3*4*3 = 36 comparisons

For equivalence, all comparisons are required to be successful (Intersection-union principle)

Problem: High number of comparisons ➔ Low overall power

The “day 1 paper” – study design

Use an appropriate design of dissolution profile studies

- Sample size can be increased to n > 12 to obtain a sufficiently high power
  ➔ Increasing the number of samples per batch and/or the number of analyzed batches.
- Danger of pairwise batch-to-batch comparisons!
  - In case of 3 batches for REF and TEST group:
    9 comparisons instead of 1
  - just worsens the multiplicity problems
  - tests batches instead of processes
- **Detailed discussion in Hoffelder et al. (2022)**

REF sample	TEST sample
12 units from Batch R1	12 units from Batch T1
12 units from Batch R2	12 units from Batch T2
12 units from Batch R3	12 units from Batch T3

Conclusion: Avoid pairwise batch-to-batch comparisons

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The “day 1 paper” – decision tree

(source: Hoffelder et al, 2022, Figure 7)

Decision tree for the selection of an appropriate statistical method depending on product characteristics:

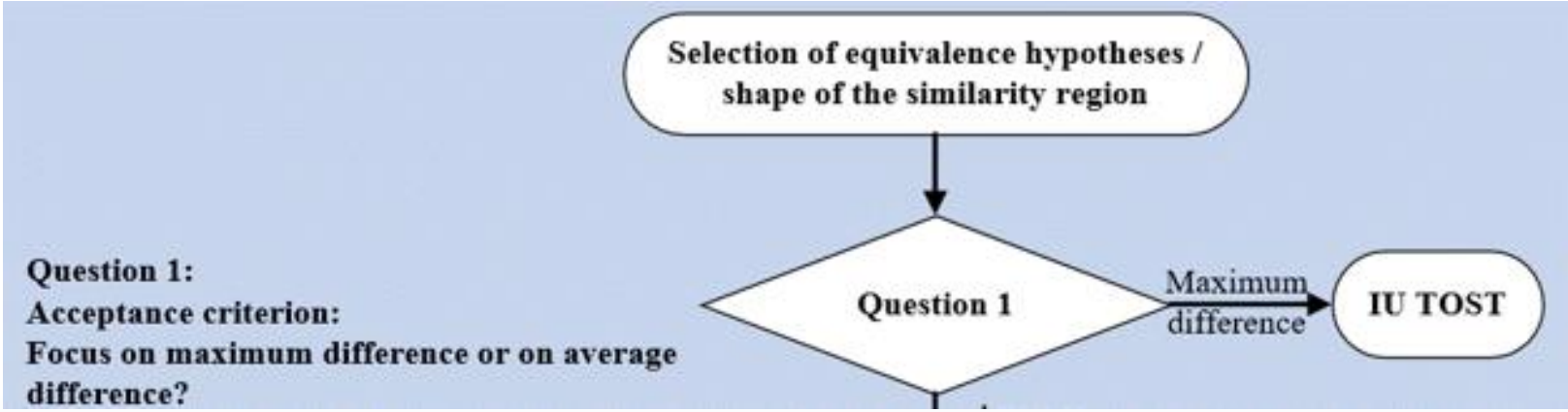
- All methods provide at least approximate Type 1 Error control
- Method selection depends on product characteristics, not data driven

The “day 1 paper” – decision tree

(source: Hoffelder et al, 2022, Figure 7)

Intersection-Union TOST (IU TOST)

- Separate two one-sided t-tests (TOST) for each dissolution time point
- Overall equivalence ⇔ equivalence at each time point (exp. mean < 10)
- For all time points the TOST procedure can be performed at the significance level $\alpha = 0.05$. Using the intersection-union principle, multiplicity adjustment of the significance level is not necessary.
- The intersection union principle implies that the power decreases with an increasing number of time points.
- Strictest test method.
  Votes during Breakout-Session: 0

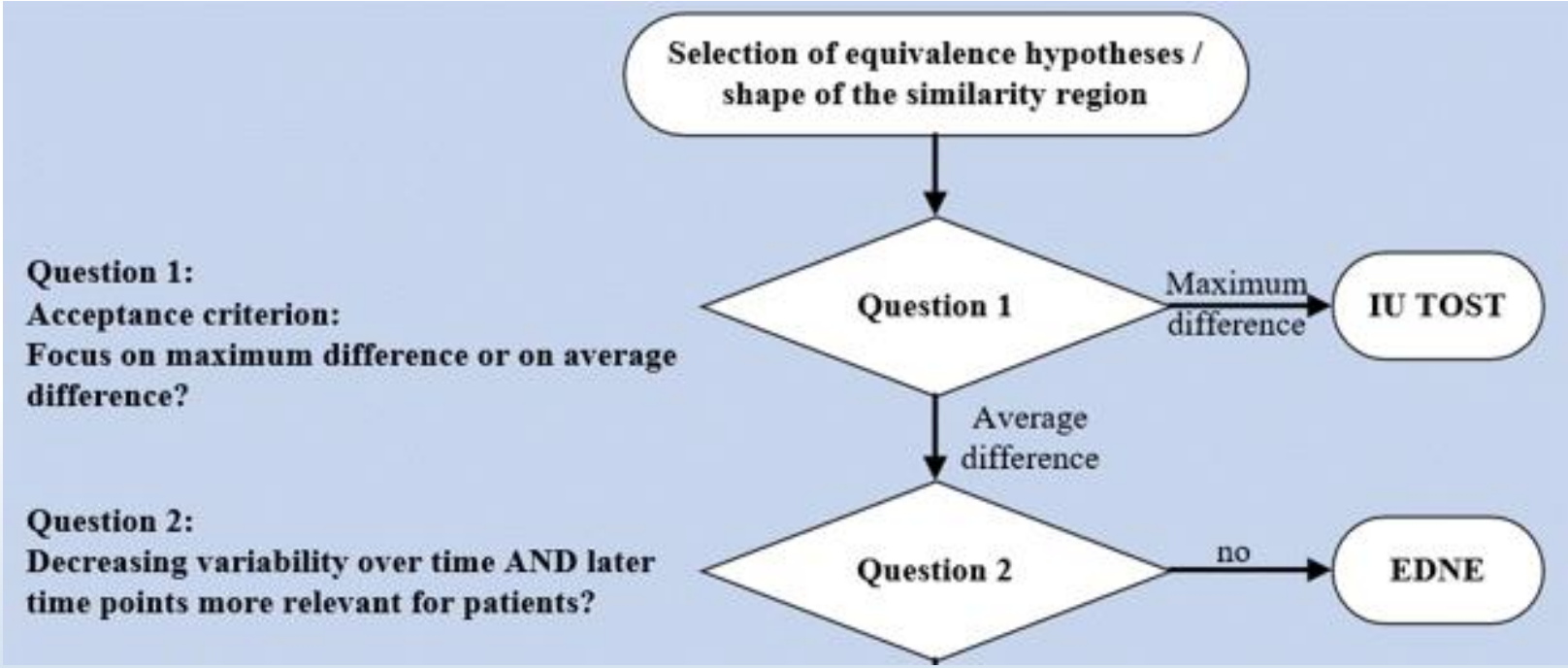


The “day 1 paper” – decision tree

(source: Hoffelder et al, 2022, Figure 7)

Euclidean Distance of the Non-standardized Difference of Expected values (EDNE)

- $ED^2 = \sum_{t=1}^{n}(\mu_{2t}-\mu_{1t})^2$
- Acceptance criterion from f2 hypotheses
- Power strongly depends on the highest variability

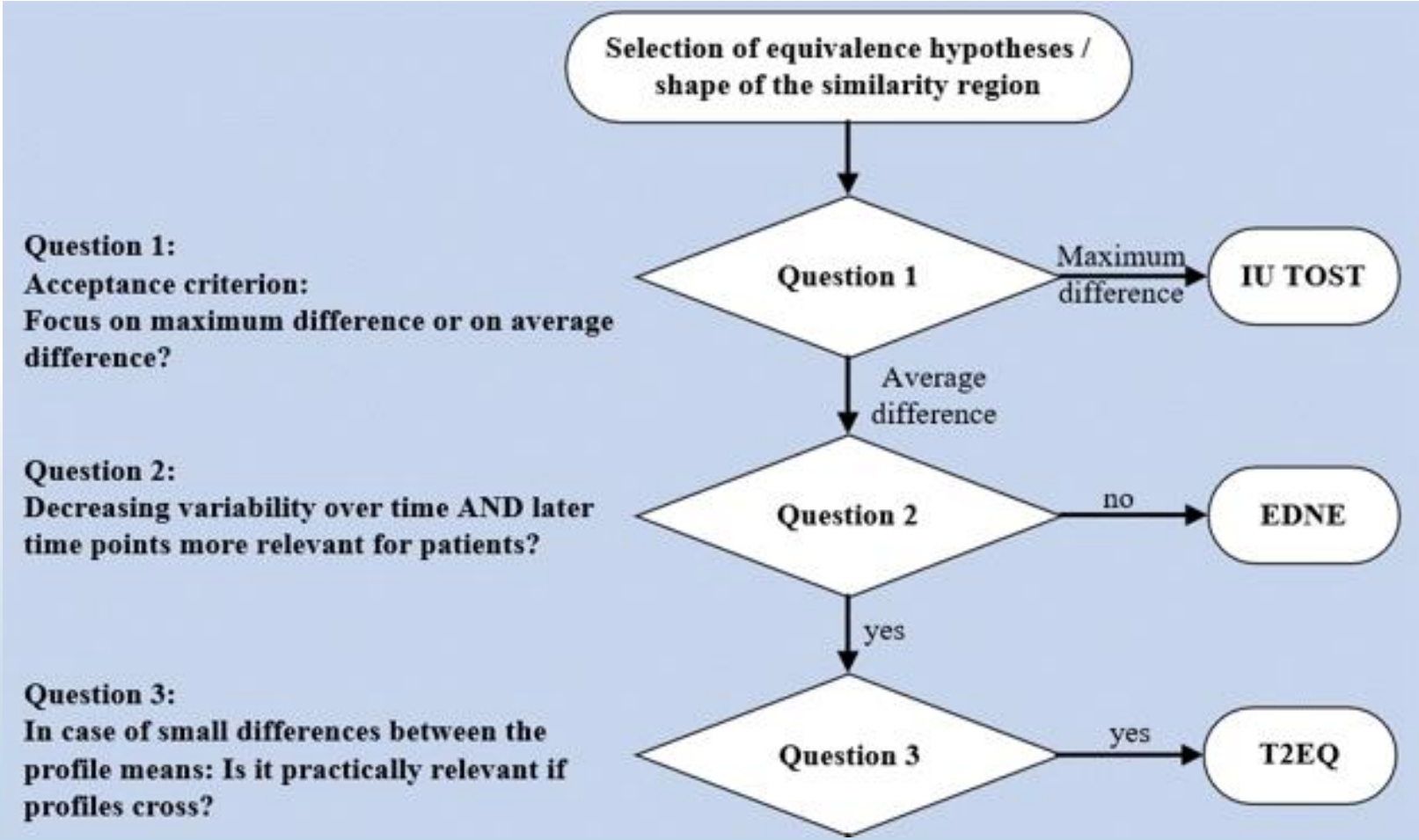


The “day 1 paper” – decision tree

(source: Hoffelder et al, 2022, Figure 7)

T^2-based test for EQuivalence (T2EQ)

- Mahalanobis Distance
  $MD = (\mu_2 - \mu_1)' \sum^{-1} (\mu_2 - \mu_1)$
- Weighted average of differences
- Weights are combinations of correlations and variances
- Correlation phenomen:
  low power for crossing profiles

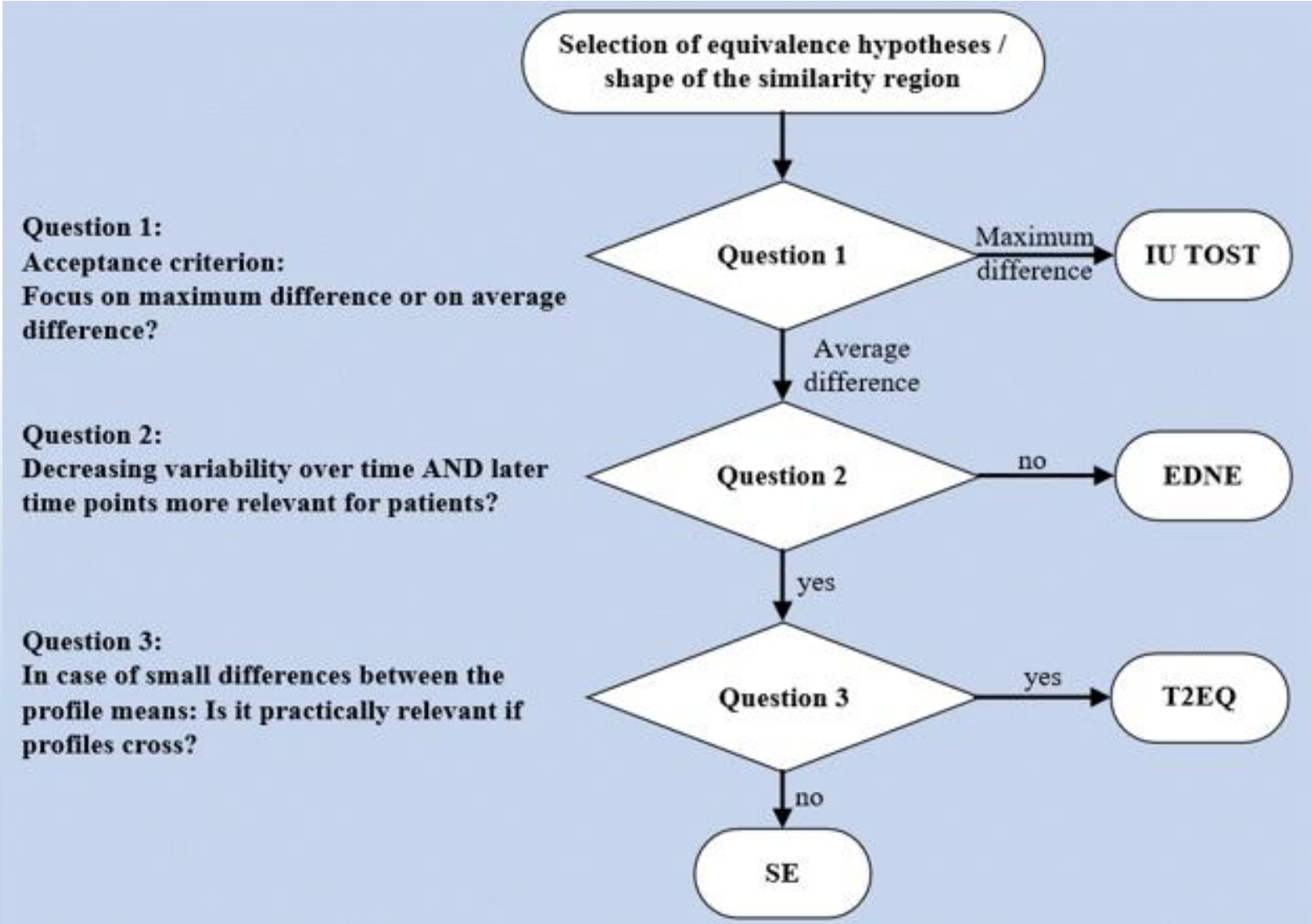


The “day 1 paper” – decision tree

(source: Hoffelder et al, 2022, Figure 7)

Sum of squared Effect sizes (SE)

- $\sum_{t=1}^{n}\left(\frac{\mu_{2t}-\mu_{1t}}{\sigma_t}\right)^2$
- Standardization only by means of variances but not by means of correlations



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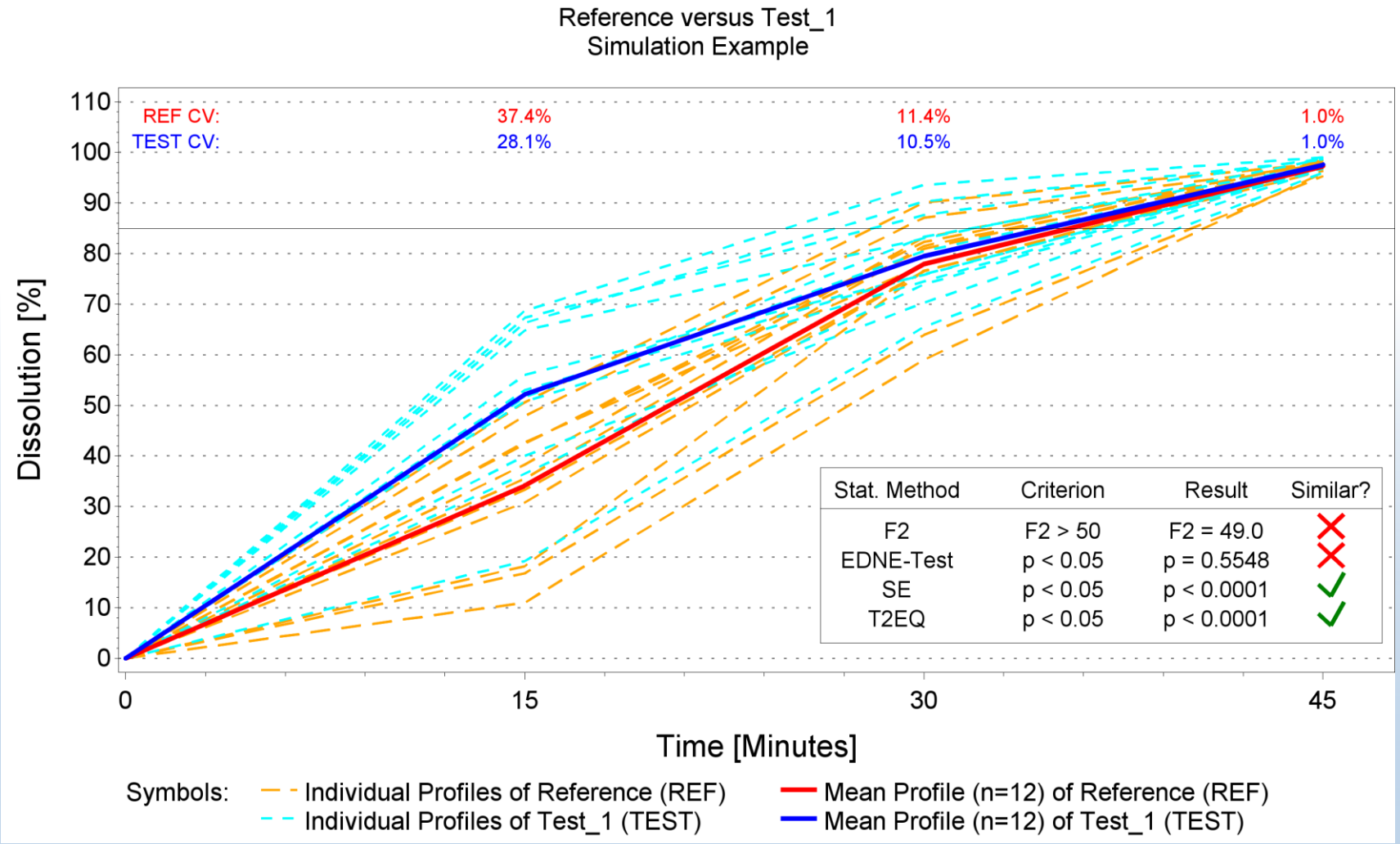

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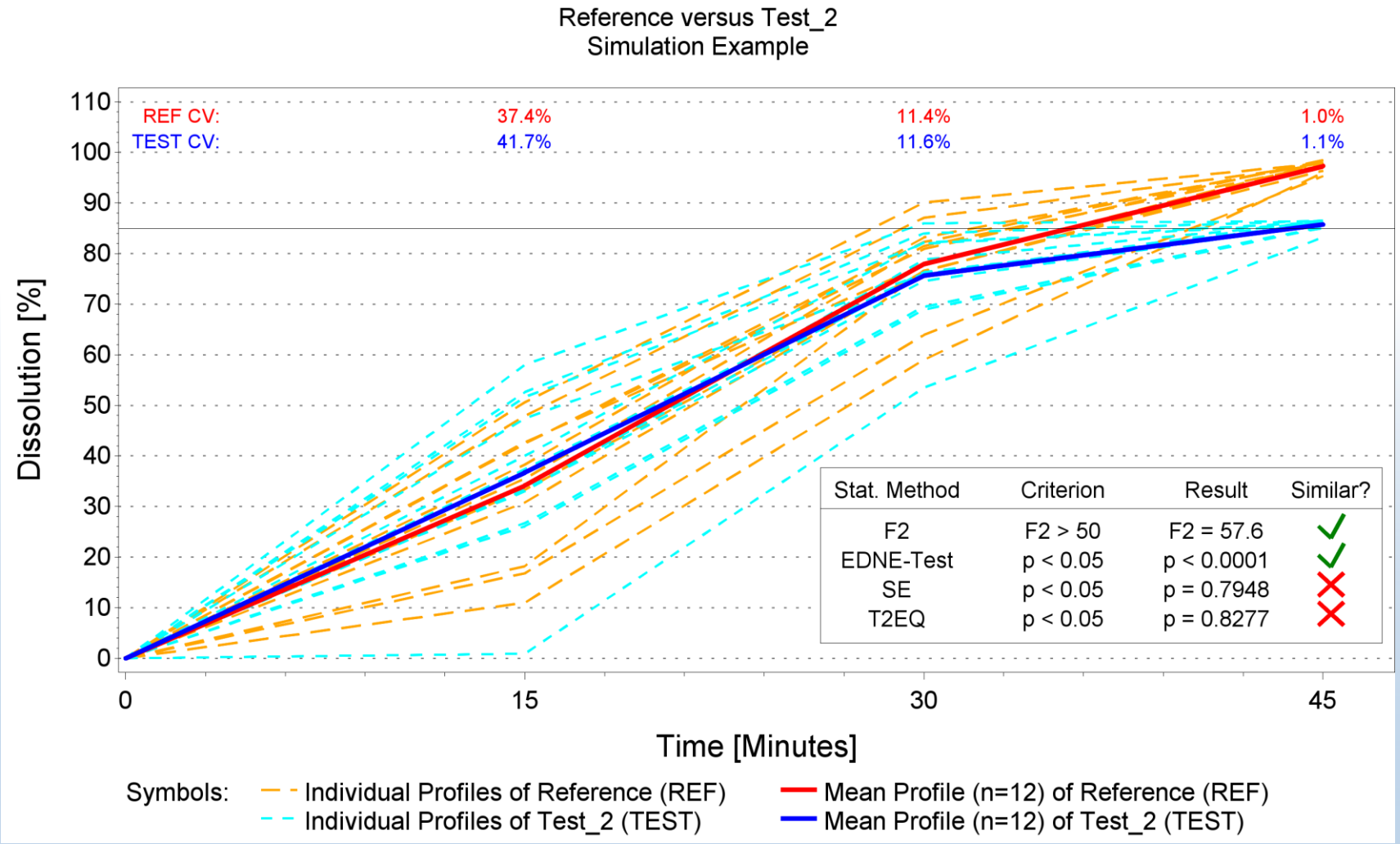

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Summary

- Except for IU-TOST, the methods in the decision tree check whether "**a kind of average difference**" between REF and TEST mean is smaller than 10% LC (recall: f2 acceptance criterion).
  They differ only in the weighting of the differences (none, variances only, variance-covariance matrix)
- The choice of the statistical method should be based on product characteristics.
- Problems regarding **T1E control and power** can be solved via
  - suitable study design
  - suitable sample size
  - suitable statistical method

- **Please avoid pairwise batch-to-batch comparisons**

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End

Thank you