Mahalanobis Distance Based Approaches, Performance and Limitations

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M-CERSI Workshop

In Vitro Dissolution Profiles Similarity Assessment in Support of Drug Product Quality: What, How, and When

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Contents

Introduction

Equivalence analyses of dissolution profiles - statistical description

- **hypotheses:**
  H_0: Non-equivalence of both dissolution profile groups
  versus
  H_1: Equivalence of both dissolution profile groups (goal of study)

- **type I error:**
  wrong decision in favor of equivalence
  regulatory need: control of type I error

- **power:**
  probability of a correct decision in favor of equivalence
  probability of a successful study in case of no relevant differences
  practitioners' need: sufficiently high power

Introduction

- **Distance measure:** Mahalanobis distance (**MD**)

$$MD = (\boldsymbol{\mu_1} - \boldsymbol{\mu_2})' \, \boldsymbol{\Sigma}^{-1} \, (\boldsymbol{\mu_1} - \boldsymbol{\mu_2})$$

$\boldsymbol{\mu_1}$ and $\boldsymbol{\mu_2}$ are the expected values of both reference and test group and $\sum$ is the common covariance matrix

- MD is a multivariate generalization of the **standardized difference** between the expected values: $\frac{\mu_1 - \mu_2}{\sigma}$

- Note: f_2 is based on the Euclidean distance $\sum_{i=1}^{n} (\mu_{1i} - \mu_{2i})^2$ which is the multivariate generalization of the **non-standardized difference** between the expected values: $\mu_1 - \mu_2$

μ_{1i}: expected value of REF at time point nr. *i*

μ_{2i}: expected value of TEST at time point nr. *i*

n: number of dissolution time points

Introduction

- **Distance measure:** Mahalanobis distance (**MD**)

$$MD = (\boldsymbol{\mu}_1 - \boldsymbol{\mu}_2)' \, \boldsymbol{\Sigma}^{-1} \, (\boldsymbol{\mu}_1 - \boldsymbol{\mu}_2)$$

$\boldsymbol{\mu}_1$ and $\boldsymbol{\mu}_2$ are the expected values of both reference and test group and $\sum$ is the common covariance matrix

- **Equivalence hypotheses:**

$$H_0 : MD \geq EM \quad \text{versus} \quad H_1 : MD < EM$$

EM: Equivalence margin (similarity limit / acceptance criterion)

Contents

1) Introduction: Equivalence hypotheses based on the Mahalanobis distance

2) **Equivalence procedures based on the Mahalanobis distance (MD)**
   - **T^2-test for equivalence, ACLMD approach („MSD-test“), bootstrapped MD, T2EQ approach**
   - **properties of MD based approaches**
   - **Discussion on equivalence margin (similarity limit, acceptance criterion)**
   - **Critical comments on MD in the current literature**

3) Experiences with the T2EQ approach
   - dialogue with regulatory agencies, academia and other companies
   - software

4) The Mahalanobis distance: performance and limitations
   - MD versus (bootstrapped) f2 - comments
   - MD versus model dependent approaches – comments
   - The correlation problem

5) Conclusions

MD based equivalence tests

Approximate procedures:

- ACLMD (Approximate Confidence Limit for Mahalanobis Distance) approach according to Tsong et al. (1996), "MSD-test"
- Bootstrapped MD

➔ approximate procedures may be affected by the bias of the MD point estimate

Exact procedure: The T^2-test for equivalence according to Wellek (2010):

- for normally distributed data: **UMPI-test**
- **robust** under deviations from normal distribution assumption
- statistically equivalent to **exact CI procedure for MD** (→ Hoffelder et al., 2015)

- **Problem**: Determination of a **fixed EM** is **not practically feasible**

MD based equivalence tests

Why is a fixed EM for the Mahalanobis distance not practically feasible?

Regulatory perspective:

- manufacturer benefits from an increased variability
- the higher the variability the higher the allowed difference between the profiles
- would not be compliant with EMA (2010) guideline ("similarity acceptance limits should … not be greater than a 10% difference")
- see EMA (2018)

Practitioners' perspective:

- manufacturer punished by a decreased variability
- the lower the variability the lower the allowed difference between the profiles
  ➔ test very sensitive regarding differences at time points with very low variability

MD based equivalence tests

EMA (2018):

Question and answer on the adequacy of the Mahalanobis distance to assess the comparability of drug dissolution profiles

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MD based equivalence tests

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MD based equivalence tests

Solution: Specific choice of the EM

Tsong et al. (1996):

- "**global similarity limit**" for MD in the context of comparing dissolution profiles
  → product independent, always practically feasible EM.
- EM is defined by a max. allowed constant shift between REF and TEST $\boldsymbol{D} = (d,d,\ldots,d)$
- this max. allowed shift is related to the present variability $\mathrm{EM} = \boldsymbol{D}'\boldsymbol{S}^{-1}\boldsymbol{D}$
  $\boldsymbol{S}$: pooled empirical covariance matrix

EMA (2010):

- "similarity acceptance limits should … not be greater than a 10% difference"

➔ $EM = \boldsymbol{D}'\boldsymbol{S}^{-1}\boldsymbol{D}$, where $\boldsymbol{D}$ = (10,10,…,10)

➔ EM defined by a difference of 10% at all time points
same interpretation as for f_2 !
Acceptance criterion: "Average" profile difference < 10%

MD based equivalence tests

T2EQ approach

- T^2-test for equivalence according to Wellek (2010)
- EM according to Tsong et al. (1996)
- EM restrictions according to EMA (2010)

} **T2EQ approach**

- **p-value of the test** can be calculated
  => "p-value < 0.05" is not more difficult to understand as "$f_2 > 50$"
  => no simulations or numerical methods necessary
- test result can be reported via p-value **or** via upper confidence limit for the Mahalanobis distance

MD based equivalence tests

What about control of type I error and power?

In Hoffelder (2018b) several methods, i.e.

- T2EQ approach
- ACLMD ["MSD-Test"] → Tsong et al. (1996)
- bootstrapped MD
- bootstrapped f_2

were compared regarding **control of type I error, robustness and power.**

Note that all methods use **the same acceptance criterion** (limit between equivalence and non-equivalence is defined by a shift in location of 10% at all dissolution time points).

Most advantageous approach in the simulation study: T2EQ

MD based equivalence tests

Critical comments on MD in the current literature (→ §5.1 in Hoffelder, 2018b)

Mahalanobis distance shrinks when the variance of the experiment increases

- ➔ the higher the variability the higher is the power
- ➔ "poorly designed experiments would be rewarded"
- ➔ not compliant with EMA (2010) because a decision in favor of equivalence might be possible in spite of a profile difference > 10% (see EMA, 2018)

T2EQ approach not affected by these concerns because

- the covariance matrix enters into both sides of the equivalence hypotheses, into **MD as well as into EM.**
  Increased variance ➔ **EM decreases in the same way as MD.**
- EM **defined by a shift in location of 10%** at all dissolution time points.
  ➔ **T2EQ compliant with the EMA guideline** independent of the present covariance matrix
- Remark: Simulations in Hoffelder (2018b): increased variability reduces the power

MD based equivalence tests

Discussion on the equivalence margin $EM = \boldsymbol{D}'\boldsymbol{S}^{-1}\boldsymbol{D}$, $\boldsymbol{D}$ = (10,10,...,10)

- EM is a **random variable** via $\boldsymbol{S}$
- critisized as being **"data driven"** (equivalence margins should usually be pre-defined and fixed so that **no cherry picking** is possible)

But:

- **construction of the T2EQ EM is pre-defined and fixed ➔** No cherry picking possible
- perspective of using a non-standardized distance measure.
  For a standardized distance measure (e.g. MD) it holds:
  EM fixed ➔ maximum allowed constant shift in location between the profiles is "data driven" via empirical covariance matrix $\boldsymbol{S}$
  T2EQ EM being a random variable, not fixed
  ➔ **maximum allowed constant shift in location is fixed to 10%!**
  EMA (2010) and EMA (2018) emphasize that the focus on dissolution profile equivalence is the **shift in location.**

Contents

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5) Conclusions

Experiences with T2EQ

Dialogue with regulators, academia and industry:

- DIA/FDA Statistics Forum 2016:
  - Roundtable discussion „Similarity of Dissolution Profiles“
  - Poster „Comparison of Dissolution Profiles: A Statistician’s Perspective“

  ➔ Paper Hoffelder (2018a)

- CEN-ISBS Vienna 2017:
  - Presentation of T2EQ simulation results on size, robustness, power

  ➔ Papers Hoffelder (2018b,2019)

- T2EQ approach and the evaluation strategy addressed in Hoffelder (2018a) submitted to more than 20 countries/regions

  ➔ Sample size calculations, increased sample size ✓

  ➔ no pairwise batch-to-batch comparisons ✓

  ➔ T2EQ approach ✓

Experiences with T2EQ

T2EQ approach summary

1) „Easy“ to understand for non-statisticians:
   Analogue to f_2 => acceptance criterion, p-value

2) Regulatory perspective: sufficient control of type I error

3) Industry perspective: sufficiently high power, sample size calculations can be done

4) R package T2EQ available on CRAN,
   SAS/IML modules published in Hoffelder (2018b)

=> T2EQ ready for use in pharmaceutical practice

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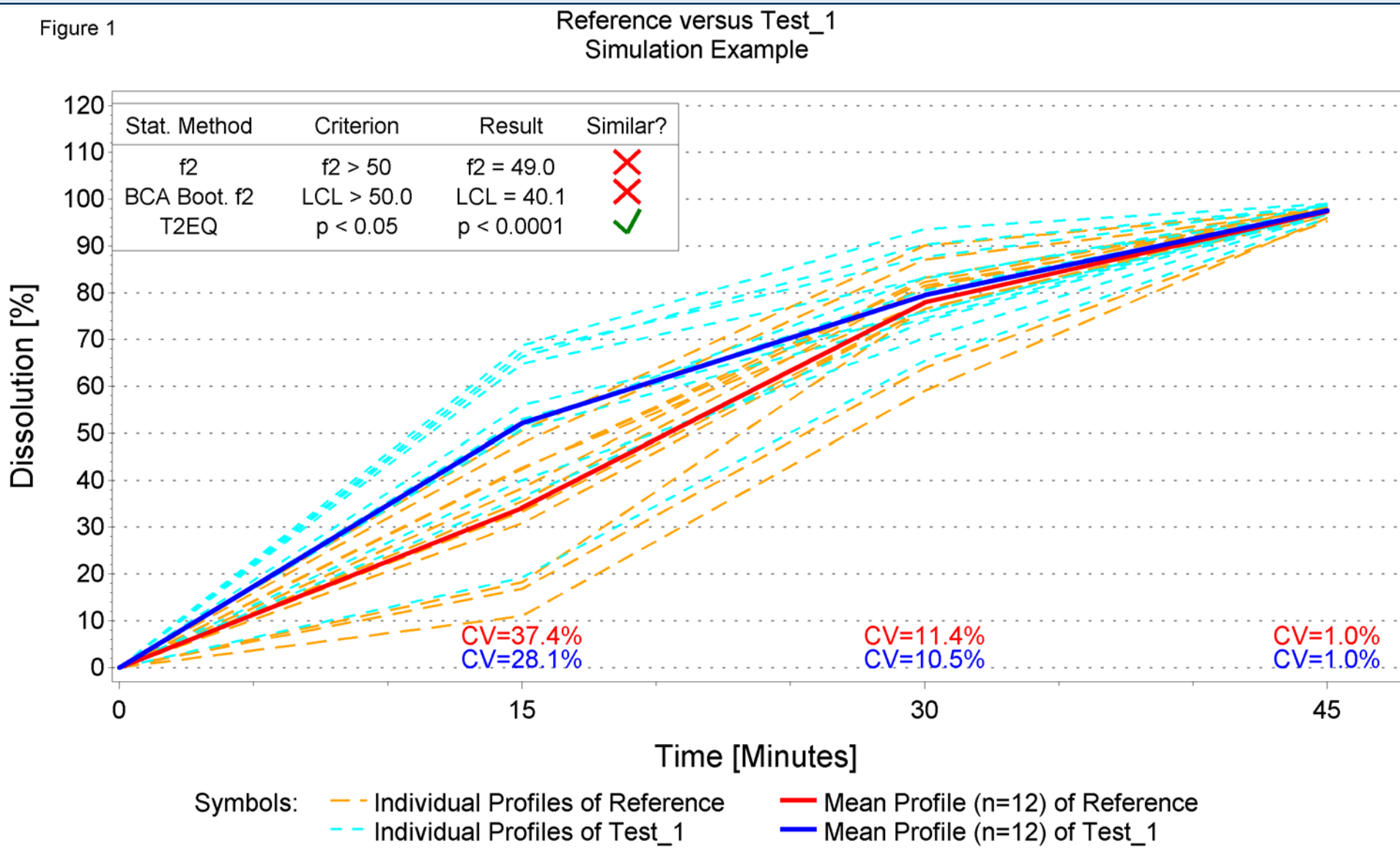
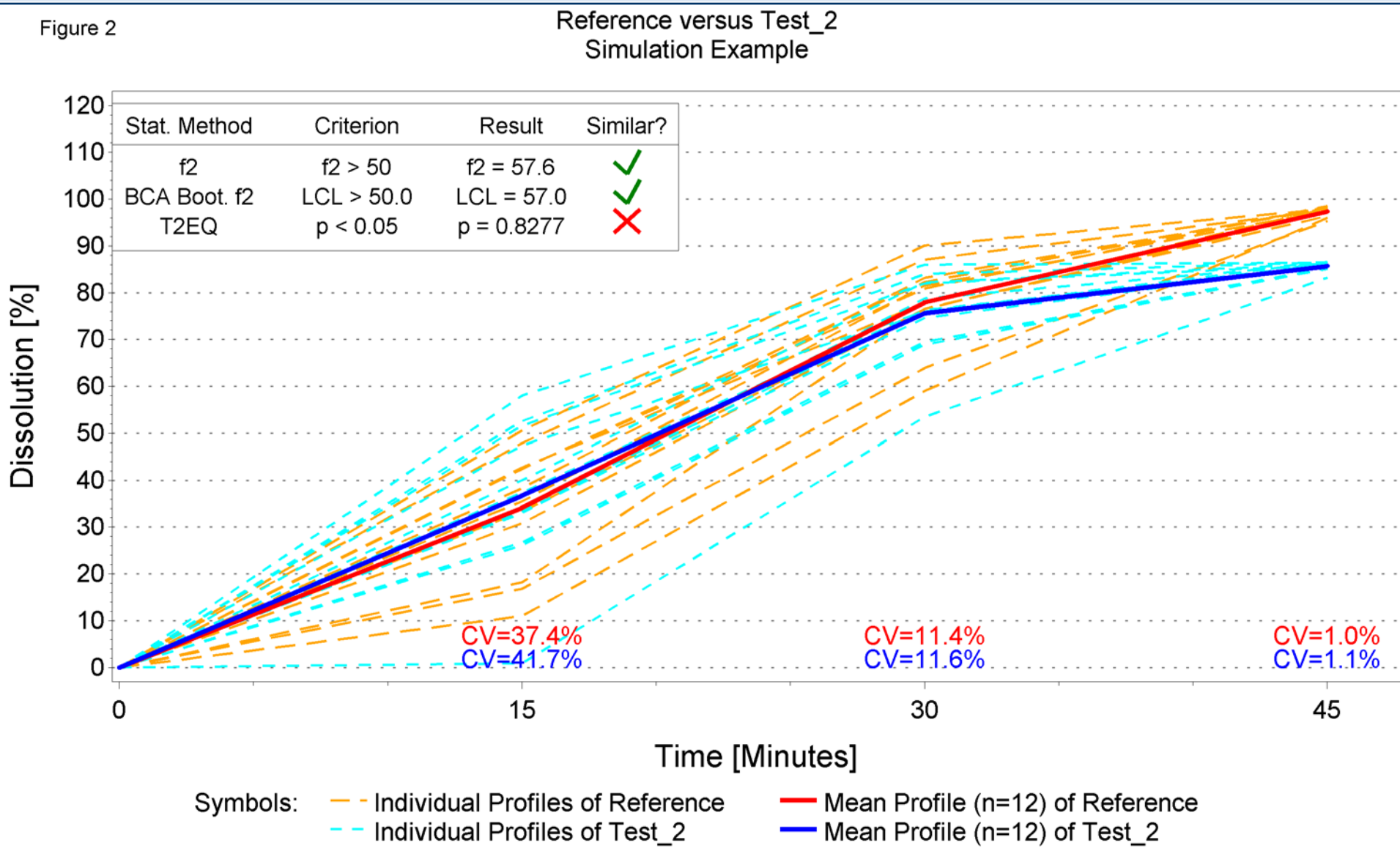
T2EQ versus f_2 (source of figures: Hoffelder, 2018a)



T2EQ versus f_2 (source of figures: Hoffelder, 2018a)



T2EQ versus f_2

Mahalanobis distance versus Euclidean distance (f_2):

- **ED** summarizes **absolute differences** between the mean values.
  - ➔ Differences from time points with maybe considerably **different variabilities** are amalgamated into one distance measure **without any standardization.**
  - ➔ One cannot distinguish whether a certain difference mainly stems from random effects or whether the difference is caused by a systematic effect.
- **MD** summarizes **standardized differences**
  - ➔ allows to distinguish between systematic and random effects as root cause for the profile differences.
- Recall the profile difference in Figure 2
  - ➔ highly significant difference in the last time point ➔ irrelevant for patients?

➔ Compared with ED, a **standardized distance measure as MD** gives a better assessment on the question which differences are ***practically relevant*** and which are not

MD versus Model Dependent Approaches

Mahalanobis distance versus Model Dependent Approaches I:

- for products where only three or four time points are available (e.g. immediate release products completely dissolving within 20 minutes) **sufficient data** for a reliable fit of the profiles might **not be available.**
- a **product-independent** optimal nonlinear model does not exist
- **model selection problems** for Model Dependent Approaches
  → similarity decision might depend on chosen nonlinear regression model
- **Definition of the equivalence criterion** in terms of the parameters of nonlinear functions
  ➔ complex, practically feasible, product-independent equivalence margins / acceptance criteria available?
- In contrast, methods based on MD or ED directly evaluate the dissolution profile data and a **theoretical assumption on the shape of the profiles is not necessary.**

MD versus Model Dependent Approaches

Mahalanobis distance versus Model Dependent Approaches II:

- Maximum deviation based approach (MDBA) from Collignon et al. (2018)
  + Decision in favor of equivalence if **maximum absolute deviation** between both fitted nonlinear regression curves is below a certain acceptance limit, e.g. 10%.
  + The maximum difference between the fitted curves might be at a time point that is not measured (recall example evaluation in Collignon et al., 2018).
  + Possible situation: estimated maximum deviation > 10% but a difference above 10% is not observed at any measured time point.
- In contrast, methods based on MD or ED directly evaluate the dissolution profile data and a theoretical assumption on the shape of the profiles is not necessary.

➔ **Question for BO sessions: Focus of dissolution profile equivalence:**

Average difference or maximum difference?

Limitation of MD based approaches

Limitation: The correlation problem

- One can interpret the T2EQ acceptance criterion as "MD based weighted mean of the profile differences lower than 10%". The **weights** can be interpreted as a **combination of variances and correlations.**

- It is possible that the correlations play an important role in the similarity decision.

- Example: Let $\Sigma = \begin{pmatrix} 120 & 39 & -9 \\ 29 & 146 & 111 \\ -9 & 111 & 113 \end{pmatrix}$ ➔ Difference (3,3,3) ➔ MD = 0.22

  ➔ Difference (3,-3,3) ➔ MD = 2.49

- No practically relevant difference between shifts in location (3,3,3) and (3,-3,3)

➔ strong influence of correlation / hard to understand for non-statisticians.

Limitation of MD based approaches

Limitation: The correlation problem

Possible solution:

- **Standardization with variances only** - not with complete covariance matrix
- Differences (3,3,3) and (3,-3,3) would result in the same (estimated) distance
- **Approach already exists:** SE-test according to Hoffelder et al. (2015)
  EM can be analogically derived as for T2EQ approach
- acceptance criterion can be interpreted as "**weighted mean of the profile differences lower than 10%**". The weights are the variances.
- To-do-list:
  paper with detailed simulation study on type I error, robustness and power.

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5) **Conclusions**

Conclusions

1) **Standardized distance measures (as e.g. MD) are statistically preferable to decide which differences are practically relevant and which are not.**

2) **T2EQ is ready for use in pharmaceutical practice**

3) **Solution of the „correlation problem“: work in progress ➔ teamwork?**

Literature

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End

Thank you!

End

Back up

MD based equivalence tests

Standard approach: similarity factor f_2

- n: number of dissolution time points, $\boldsymbol{R} = (R_1,\ldots,R_n)$: reference mean profile, $\boldsymbol{T} = (T_1,\ldots,T_n)$: test mean profile
  f_2 is a transformation of the quadratic mean (over time) of the differences between reference and test mean:

$$QMD = \sqrt{(1/n)\sum_{t=1}^{n}(R_t - T_t)^2} \quad \Rightarrow \quad f_2 = 50\log_{10}\left(\frac{100}{\sqrt{1+QMD^2}}\right)$$

- acceptance criterion: $f_2 > 50 \Leftrightarrow QMD < \sqrt{99} = 9.95 \approx 10$

  ➔ profiles similar if **<u>average difference between profile means is below 10%</u>**

- f_2 depends on means only, point estimate, no control of type I error

  ➔ the less reliable the higher the variability of the underlying data

  ➔ guideline restrictions for f_2 if variability exceeds certain thresholds

- no guideline recommendation for highly variable dissolution profiles

  ➔ **WANTED: suitable multivariate equivalence procedure**