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EMA’s current practice and challenges in the evaluation of dissolution profile comparisons in support of minor/moderate product quality changes – Case Studies

M-CERSI workshop
“In Vitro Dissolution Profiles Similarity Assessment in Support of Drug Product Quality”
21-22 May 2019- Baltimore, USA

Presented by Evangelos Kotzagiorgis - Quality Specialist
Human Medicines Research & Development Support Division - Quality Office

An agency of the European Union

Outline

- The f2 similarity factor - a closer look
- General examples and specific cases
- Shortcomings - Other approaches
- Conclusions

Scenarios in which the dissolution profiles of two drug products are compared

- **Bridging studies during development of a product**
- **Variations** of a marketed product
- Application of a **generic** drug product
  - Comparison of the test and reference drug product used in a bioequivalence study (Bioequivalence study)
  - Comparison of the test and reference product used in a bioequivalence study plus extrapolation of the results to the other strengths of a generic product series ("Biowaiver for strengths")
  - Comparison of the dissolution of a generic to the originator drug product under standard conditions ("BCS based biowaiver")

Similarity factor f2 allows 10% difference

Comparison of two dissolution profiles

- More than 85% dissolved after 15 minutes: Similar **without further mathematical evaluation**
- Evaluation of f2-factor:
  - f2 < 50 non similar - mean difference >10% at each time point
  - f2 = **49,9 mean difference of 10% at each time point**
  - f2 > 50 similar - mean difference <10% at each time point
  - f2 = 100 identical

f2 - no blind application

- ✓ **Sampling** sufficient for **meaningful** dissolution **profiles**.
- ✓ For IR formulations, comparison at 15 min is essential to know if complete dissolution is reached before gastric emptying. Where >85% of the drug is dissolved within 15 min, dissolution profiles may be accepted as similar without further mathematical evaluation.
- ✓ Dissolution similarity **may be** determined using the *ƒ*2 statistic-**conditions**.
- ✓ The similarity **acceptance limits** should not be greater than **10%** difference.
- ✓ The **variability of the test and reference** product data should also be similar, however, a lower variability of the test product may be acceptable.

A closer look at the equation for the f2 Similarity factor

Variability related to the data not accounted

Complex equation

$$f_2 = 50 \times \log \left(\frac{100}{\sqrt{1 + \frac{\sum_{t=1}^{t=n} (\overline{R}_{(t)} - \overline{T}_{(t)})^2}{n}}} \right)$$

Scaled to values between 0 and 100

Not linear but exponential relationship

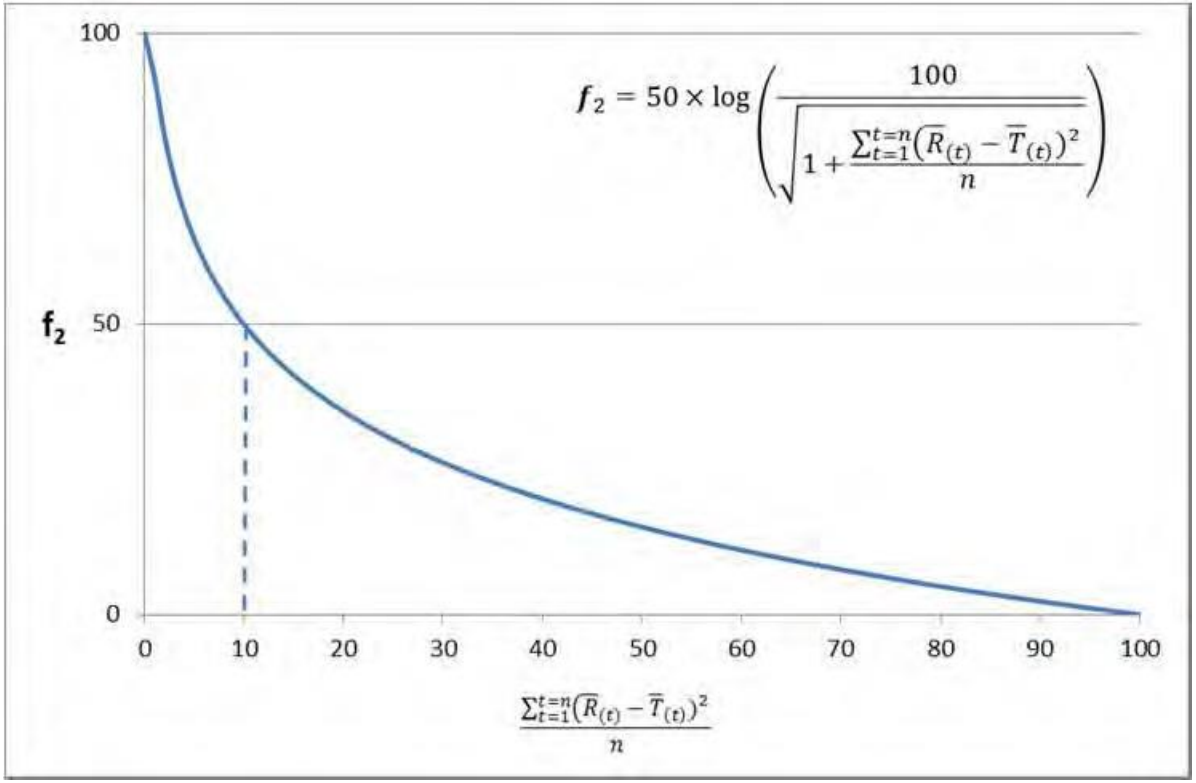
Only variable is the mean difference between reference and test product

- Identical curves: => (R(t)-T(t))²/n is 0, √ of (1+0)=1; 100 /1 is 100, log of 100=2 and 50*2=**100**

- Completely different curves: => (R(t)-T(t))²/n will be 10000, √ of (1+10000)=100; 100/100 is 1, log of 1 = 0 and 50*0=**0**

- Borderline for a non similar curve, i.e. 10% difference: => (R(t)-T(t))²/n will be 100, √ of (1+100)=10.04; 100/10.04=9.95, log of 9.95=0.998 and 50*0.998=**49.9**

f2 as a function of mean difference between amount released of test and reference product over time



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Conditions for calculation of f2

- ✓ a minimum of **three time points** (zero excluded)
- ✓ the time points should be the **same** for the **two formulations**
- ✓ **twelve** individual values for every time point for each formulation
- ✓ **not more than one** mean value of > 85% dissolved **for any** of the formulations
- ✓ relative standard deviation or coefficient of variation of any product should be <20% for the first point and <10% from second to last time point

variability of the test and reference product data should also be similar

Outline

- The f2 similarity factor - a closer look
- **General examples and specific cases**
- Shortcomings - Other approaches
- Conclusions

Example 1: Raw Data for Dissolution of Test and Reference Product

Mean Value and Variability of Dissolution Results

Raw Data Test Product

Time	Vessel 1	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	Vessel 7	Vessel 8	Vessel 9	Vessel 10	Vessel 11	Vessel 12	MEAN	STD
5	19,0	16,3	17,1	17,1	17,7	16,0	16,9	17,7	17,8	17,3	16,8	17,6	17,3	4,45
10	31,7	32,1	30,1	29,5	32,0	29,2	29,8	31,9	30,8	32,0	28,8	31,2	30,8	3,98
15	39,9	42,3	40,3	41,1	41,8	43,6	43,4	39,2	43,2	40,4	42,1	41,0	41,5	3,49
30	66,3	67,1	67,5	64,8	67,4	67,2	69,3	68,7	69,9	64,2	68,9	66,5	67,3	2,58
45	83,1	86,3	79,3	83,2	81,3	81,9	85,5	78,8	84,1	85,4	82,8	81,6	82,8	2,86
60	86,3	93,5	88,0	85,5	86,4	87,0	86,0	90,2	91,2	89,5	78,3	82,8	87,1	4,57

Raw Data Reference Product

Time	Vessel 1	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	Vessel 7	Vessel 8	Vessel 9	Vessel 10	Vessel 11	Vessel 12	MEAN	STD
5	22,1	22,4	22,1	21,3	21,4	21,3	22,5	21,2	22,2	23,9	22,4	20,4	21,9	4,09
10	38,3	40,2	42,3	39,8	39,7	37,8	43,3	38,5	38,5	37,3	42,1	37,9	39,6	4,99
15	50,2	51,6	52,7	47,9	54,2	52,9	51,1	50,7	49,7	52,0	52,7	53,6	51,6	3,46
30	72,1	81,3	79,4	70,1	79,4	74,2	77,9	75,1	72,9	79,7	78,9	77,2	76,5	4,63
45	90,8	88,7	83,6	88,7	89,4	90,1	90,9	86,0	93,1	85,1	82,2	88,8	88,1	3,67
60	88,5	94,0	94,6	90,2	90,2	94,6	98,0	88,7	89,3	90,7	98,7	89,1	92,2	3,93

Example 1: Mean Data for Dissolution of Test and Reference Product

Calculation of f2-Factor and Comments

Raw Data
Test Product

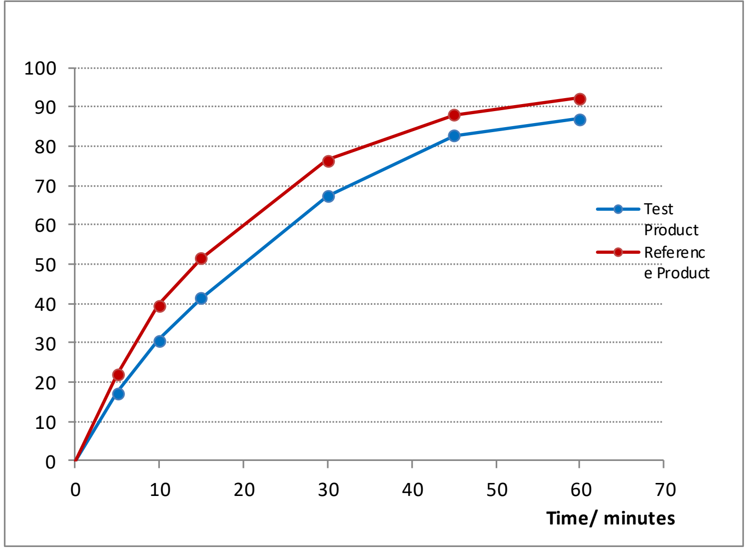
Time	MEAN	STD
5	17,3	4,5
10	30,8	4,0
15	41,5	3,5
30	67,3	2,6
45	82,8	2,9
60	87,1	4,6

Raw Data
Reference Product

Time	MEAN	STD
5	21,9	4,1
10	39,6	5,0
15	51,6	3,5
30	76,5	4,6
45	88,1	3,7
60	92,2	3,9

$(T\text{-}R)^2$
22
79
102
85
29
na

o.K.



$$f_2 = 50 \times \log\left(\frac{100}{\sqrt{1 + \frac{\sum_{t=1}^{t=n}\left(\overline{R}_{(t)} - \overline{T}_{(t)}\right)^2}{n}}}\right)$$

f 2 Factor	54,8
Similar?	yes

Comments:

f2 : Similarity factor
R(t): Average amount dissolved of reference product
T(t): Average amount dissolved of test product
n : number of values

Example 2: Raw Data for Dissolution of Test and Reference Product

Mean Value and Variability of Dissolution Results

Raw Data Test Product

Time	Vessel 1	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	Vessel 7	Vessel 8	Vessel 9	Vessel 10	Vessel 11	Vessel 12	MEAN	STD
5	16,4	16,1	16,9	15,8	15,1	16,1	17,9	16,3	15,8	16,3	16,8	16,2	16,3	4,18
10	29,5	31,3	30,3	30,4	30,8	28,6	33,1	29,0	29,5	29,5	28,0	32,3	30,2	4,97
15	38,8	42,7	40,4	39,1	40,2	37,0	41,4	39,6	41,6	43,7	41,4	41,0	40,6	4,43
30	69,9	66,9	67,0	62,0	66,6	64,9	71,2	65,5	69,0	67,8	69,2	66,2	67,2	3,67
45	86,4	76,8	79,7	73,2	82,9	76,2	78,6	77,1	77,0	81,9	78,5	84,3	79,4	4,80
60	88,5	83,4	88,5	90,4	91,8	85,8	85,5	88,3	89,0	86,7	85,9	84,5	87,4	2,84

Raw Data Reference Product

Time	Vessel 1	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	Vessel 7	Vessel 8	Vessel 9	Vessel 10	Vessel 11	Vessel 12	MEAN	STD
5	22,5	23,9	21,0	22,4	22,5	22,0	24,2	22,8	21,1	22,5	21,6	21,8	22,4	4,32
10	36,9	41,4	39,8	38,8	35,5	39,7	40,7	39,2	40,4	41,9	35,2	42,9	39,4	6,17
15	53,0	48,0	50,9	56,2	51,3	52,9	56,7	55,8	55,0	54,0	50,6	56,9	53,4	5,29
30	77,0	75,6	73,4	81,2	75,6	75,7	76,3	75,2	77,8	74,8	83,5	80,1	77,2	3,83
45	91,4	94,0	89,2	90,2	95,4	93,5	92,5	95,6	87,7	96,6	89,4	86,5	91,8	3,57
60	89,9	98,9	93,5	98,1	96,6	101,6	101,2	98,8	100,3	98,0	95,2	94,3	97,2	3,55

Example 2: Mean Data for Dissolution of Test and Reference Product

Calculation of f2-Factor and Comments

Raw Data
Test Product

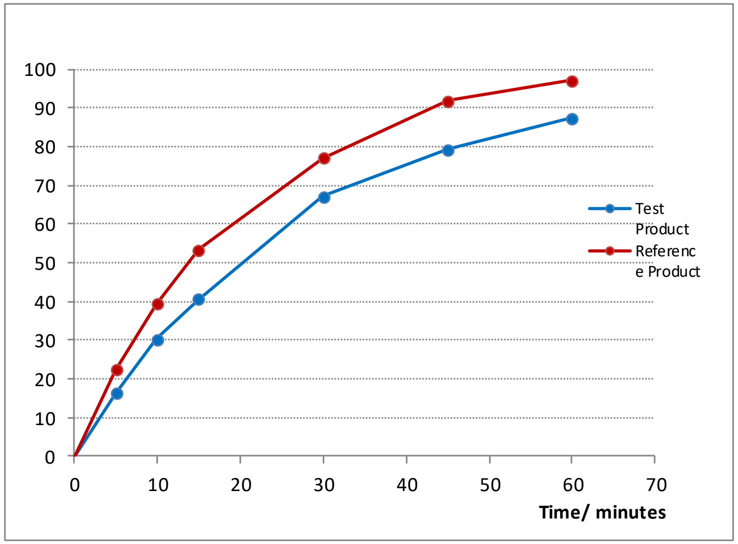
Time	MEAN	STD
5	16,3	4,2
10	30,2	5,0
15	40,6	4,4
30	67,2	3,7
45	79,4	4,8
60	87,4	2,8

Raw Data
Reference Product

Time	MEAN	STD
5	22,4	4,3
10	39,4	6,2
15	53,4	5,3
30	77,2	3,8
45	91,8	3,6
60	97,2	3,5

(T-R)²
37
84
165
100
155
na

o.K.



$$\boldsymbol{f}_2 = 50 \times \log\left(\frac{100}{\sqrt{1 + \frac{\sum_{t=1}^{t=n}\left(\overline{R}_{(t)} - \overline{T}_{(t)}\right)^2}{n}}}\right)$$

f 2 Factor	**49,0**
Similar?	**no**

f2 : Similarity factor
R(t): Average amount dissolved of reference product
T(t): Average amount dissolved of test product
n : number of values

Comments:

Example 3: Raw Data for Dissolution of Test and Reference Product

Mean Value and Variability of Dissolution Results

Raw Data Test Product

Time	Vessel 1	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	Vessel 7	Vessel 8	Vessel 9	Vessel 10	Vessel 11	Vessel 12	MEAN	STD
5	21,5	20,3	18,7	21,0	16,7	19,7	22,6	20,5	19,0	20,7	21,9	23,3	20,5	8,82
10	35,1	34,2	37,9	41,8	38,8	33,9	33,7	37,9	38,7	39,3	41,8	39,2	37,7	7,56
15	54,5	51,3	39,5	46,4	48,5	51,3	59,1	47,6	45,9	49,6	47,0	46,1	48,9	10,05
30	69,1	83,1	80,3	77,9	81,0	82,2	76,8	78,5	90,8	56,5	74,8	68,0	76,6	11,49
45	93,8	77,1	92,9	84,9	82,8	92,5	89,6	104,6	91,3	74,2	91,6	92,5	89,0	9,17
60	98,3	92,0	90,5	95,8	105,7	106,7	103,7	97,6	84,7	88,7	88,7	109,8	96,8	8,46

Raw Data Reference Product

Time	Vessel 1	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	Vessel 7	Vessel 8	Vessel 9	Vessel 10	Vessel 11	Vessel 12	MEAN	STD
5	21,6	23,3	22,0	23,0	21,8	22,4	22,2	21,6	21,8	21,5	21,9	21,6	22,1	2,61
10	39,4	38,3	39,5	40,5	39,8	39,2	39,9	39,7	39,4	39,4	40,3	39,5	39,6	1,42
15	53,5	53,8	52,4	52,5	52,2	51,1	52,2	52,6	53,5	54,8	54,3	56,4	53,3	2,69
30	73,4	77,2	76,9	80,0	76,1	80,9	79,3	75,6	77,8	78,3	80,0	77,0	77,7	2,78
45	89,9	89,2	88,9	89,3	88,7	88,3	87,9	86,7	88,9	89,8	92,1	87,7	89,0	1,53
60	93,3	95,3	94,6	96,4	95,8	97,7	93,7	97,8	93,6	101,5	96,9	94,8	95,9	2,42

Example 3: Mean Data for Dissolution of Test and Reference Product

Calculation of f2-Factor and Comments

Raw Data
Test Product

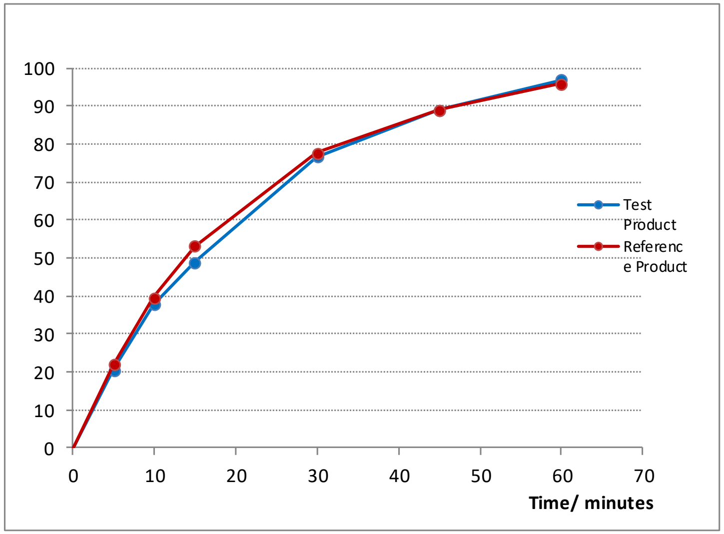
Time	MEAN	STD
5	20,5	8,8
10	37,7	7,6
15	48,9	10,0
30	76,6	11,5
45	89,0	9,2
60	96,8	8,5

Raw Data
Reference Product

Time	MEAN	STD
5	22,1	2,6
10	39,6	1,4
15	53,3	2,7
30	77,7	2,8
45	89,0	1,5
60	95,9	2,4

$(T-R)^2$
2
4
na
na
na
na

FALSCH



$$f_2 = 50 \times \log\left(\frac{100}{\sqrt{1 + \frac{\sum_{t=1}^{t=n}\left(\overline{R}_{(t)} - \overline{T}_{(t)}\right)^2}{n}}}\right)$$

f 2 Factor	not allowed
Similar?	yes

f2 : Similarity factor
R(t): Average amount dissolved of reference product
T(t): Average amount dissolved of test product
n : number of values

Comments:
Interogate the variability of the test product

Outline

- The f2 similarity factor - a closer look
- General examples and **specific cases**
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Example 4: exactly 10% difference at every time point

Raw Data
Test Product

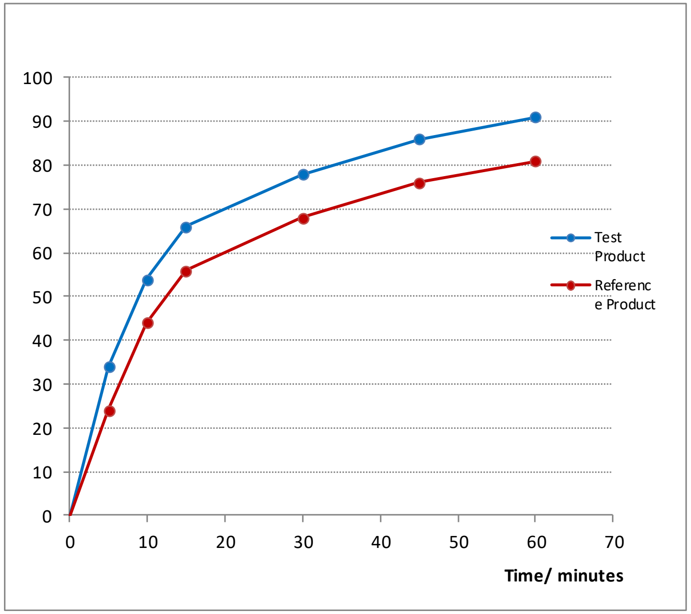
Time	MEAN	STD
5	34,0	3,7
10	54,0	5,3
15	66,0	5,8
30	78,0	3,4
45	86,0	9,9
60	91,0	4,7

Raw Data
Reference Product

Time	MEAN	STD
5	24,0	4,2
10	44,0	8,0
15	56,0	9,0
30	68,0	5,8
45	76,0	5,3
60	81,0	4,3

$(T\text{-}R)^2$
100,00
100,00
100,00
100,00
100,00
100,00

o.K.



$$f_2 = 50 \times \log\left(\frac{100}{\sqrt{1 + \frac{\sum_{t=1}^{t=n}(\overline{R}_{(t)} - \overline{T}_{(t)})^2}{n}}}\right)$$

f 2 Factor	49,9
Similar?	no

f2 : Similarity factor
R(t): Average amount dissolved of reference product
T(t): Average amount dissolved of test product
n : number of values

Comments:

Example 5: exactly 5% difference at any time point

Raw Data
Test Product

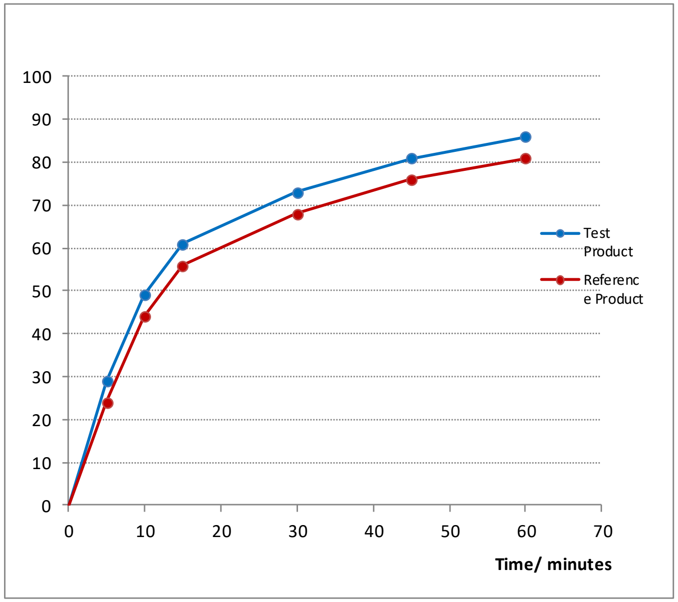
Time	MEAN	STD
5	29,0	3,7
10	49,0	5,3
15	61,0	5,8
30	73,0	3,4
45	81,0	9,9
60	86,0	4,7

Raw Data
Reference Product

Time	MEAN	STD
5	24,0	4,2
10	44,0	8,0
15	56,0	9,0
30	68,0	5,8
45	76,0	5,3
60	81,0	4,3

$(T-R)^2$
25,00
25,00
25,00
25,00
25,00
25,00

o.K.



$$f_2 = 50 \times \log\left(\frac{100}{\sqrt{1 + \frac{\sum_{t=1}^{t=n}(\overline{R}_{(t)} - \overline{T}_{(t)})^2}{n}}}\right)$$

f 2 Factor	64,6
Similar?	yes

f2 : Similarity factor
R(t): Average amount dissolved of reference product
T(t): Average amount dissolved of test product
n : number of values

Comments:

Example 6: 5% difference with intersection of curves

Raw Data
Test Product

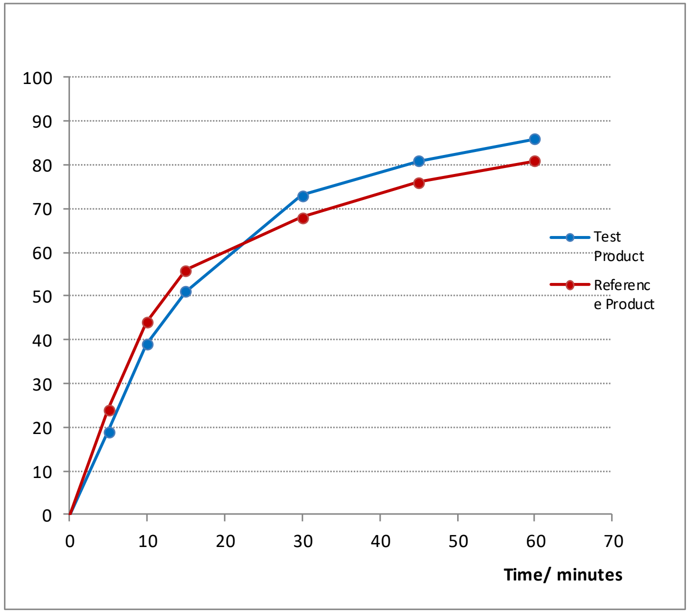
Time	MEAN	STD
5	19,0	3,7
10	39,0	5,3
15	51,0	5,8
30	73,0	3,4
45	81,0	9,9
60	86,0	4,7

Raw Data
Reference Product

Time	MEAN	STD
5	24,0	4,2
10	44,0	8,0
15	56,0	9,0
30	68,0	5,8
45	76,0	5,3
60	81,0	4,3

$(T-R)^2$
25,00
25,00
25,00
25,00
25,00
25,00

o.K.



$$f_2 = 50 \times \log\left(\frac{100}{\sqrt{1 + \frac{\sum_{t=1}^{t=n}(\overline{R}_{(t)} - \overline{T}_{(t)})^2}{n}}}\right)$$

f 2 Factor	64,6
Similar?	yes

f2 : Similarity factor
R(t): Average amount dissolved of reference product
T(t): Average amount dissolved of test product
n : number of values

Comments: **f2 intersecting curves = f2 exactly 5% difference at any time point - UNAFFECTED**

Example 7: average difference of 5% (10, 8, 6, 4, 2 and 0)

Raw Data
Test Product

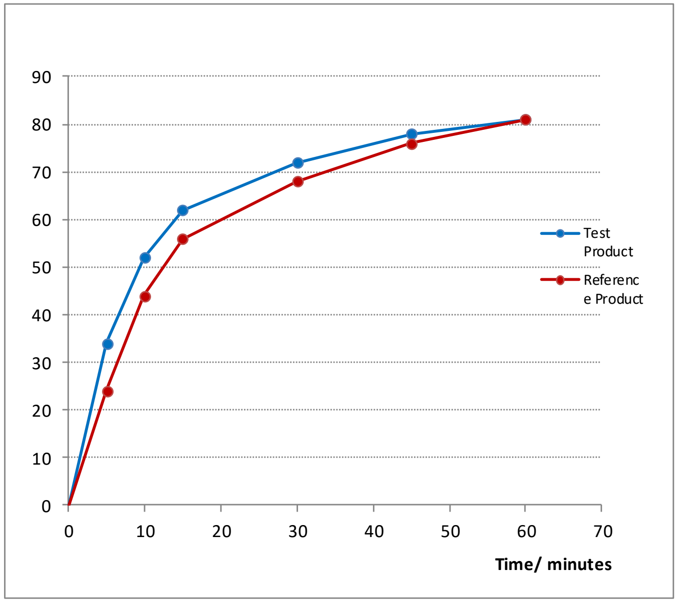
Time	MEAN	STD
5	34,0	3,7
10	52,0	5,3
15	62,0	5,8
30	72,0	3,4
45	78,0	9,9
60	81,0	4,7

Raw Data
Reference Product

Time	MEAN	STD
5	24,0	4,2
10	44,0	8,0
15	56,0	9,0
30	68,0	5,8
45	76,0	5,3
60	81,0	4,3

(T-R)²
100,00
64,00
36,00
16,00
4,00
0,00

o.K.



$$f_2 = 50 \times \log\left(\frac{100}{\sqrt{1 + \frac{\sum_{t=1}^{t=n}\left(\overline{R}_{(t)} - \overline{T}_{(t)}\right)^2}{n}}}\right)$$

f 2 Factor	60,6
Similar?	yes

f2 : Similarity factor
R(t): Average amount dissolved of reference product
T(t): Average amount dissolved of test product
n : number of values

Comments:
f2 average difference of 5% < f2 exactly 5% difference at any time point

Example 8: average difference of 7.5 % (3 x 10% and 3 x 5%, i.e. none >10%)

Raw Data
Test Product

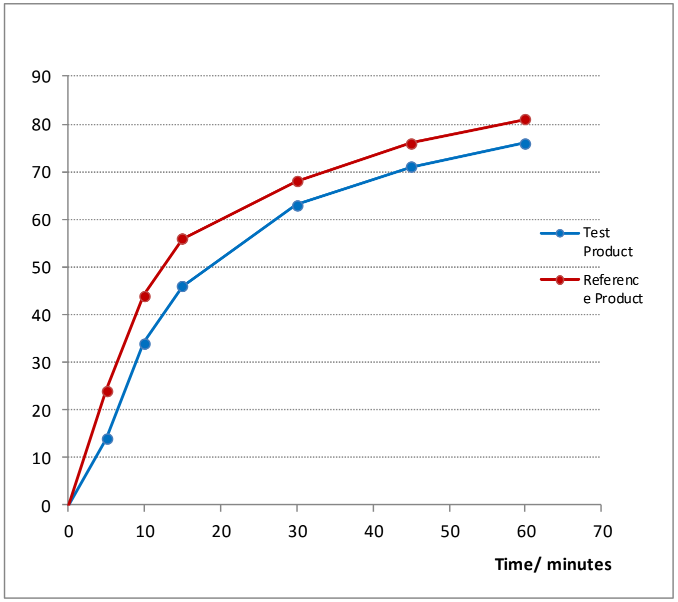
Time	MEAN	STD
5	14,0	3,7
10	34,0	5,3
15	46,0	5,8
30	63,0	3,4
45	71,0	9,9
60	76,0	4,7

Raw Data
Reference Product

Time	MEAN	STD
5	24,0	4,2
10	44,0	8,0
15	56,0	9,0
30	68,0	5,8
45	76,0	5,3
60	81,0	4,3

(T-R)²
100,00
100,00
100,00
25,00
25,00
25,00

o.K.



$$f_2 = 50 \times \log\left(\frac{100}{\sqrt{1 + \frac{\sum_{t=1}^{t=n}\left(\overline{R}_{(t)} - \overline{T}_{(t)}\right)^2}{n}}}\right)$$

f 2 Factor	54,9
Similar?	yes

f2 : Similarity factor
R(t): Average amount dissolved of reference product
T(t): Average amount dissolved of test product
n : number of values

Comments:

Example 9: average difference of 7.5 % (14, 18, 9, 4, 0, 0 – two time points >10%)

Raw Data
Test Product

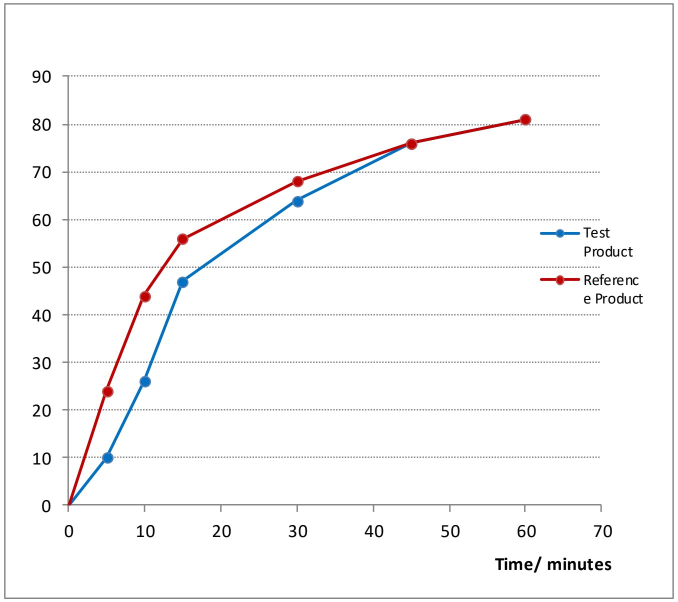
Time	MEAN	STD
5	10,0	3,7
10	26,0	5,3
15	47,0	5,8
30	64,0	3,4
45	76,0	9,9
60	81,0	4,7

Raw Data
Reference Product

Time	MEAN	STD
5	24,0	4,2
10	44,0	8,0
15	56,0	9,0
30	68,0	5,8
45	76,0	5,3
60	81,0	4,3

$(T-R)^2$
196,00
324,00
81,00
16,00
0,00
0,00

o.K.



$$f_2 = 50 \times \log\left(\frac{100}{\sqrt{1+\frac{\sum_{t=1}^{t=n}\left(\overline{R}_{(t)}-\overline{T}_{(t)}\right)^2}{n}}}\right)$$

f 2 Factor	49,6
Similar?	no

f2 : Similarity factor
R(t): Average amount dissolved of reference product
T(t): Average amount dissolved of test product
n : number of values

Comments:
f2 average difference of 7.5% < f2 exactly 7.5% difference at any time point- NON Similar

Example 10: One “outlier” 15%

Raw Data
Test Product

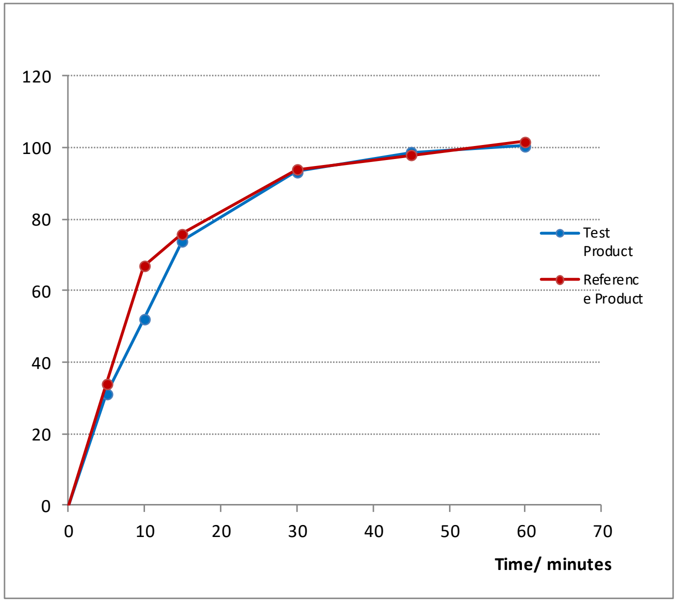
Time	MEAN	STD
5	31,0	3,7
10	52,0	5,3
15	74,0	5,8
30	93,3	3,4
45	98,7	9,9
60	100,6	4,7

Raw Data
Reference Product

Time	MEAN	STD
5	34,0	4,2
10	67,0	8,0
15	76,0	9,0
30	94,0	5,8
45	98,0	5,3
60	101,7	4,3

(T-R)²
9,00
225,00
4,00
na
na
na

o.K.



$$f_2 = 50 \times \log\left(\frac{100}{\sqrt{1 + \frac{\sum_{t=1}^{t=n}\left(\overline{R}_{(t)} - \overline{T}_{(t)}\right)^2}{n}}}\right)$$

f 2 Factor	52,4
Similar?	yes

f2 : Similarity factor
R(t): Average amount dissolved of reference product
T(t): Average amount dissolved of test product
n : number of values

Comments:

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Outline

- The f2 similarity factor - a closer look
- General examples and specific cases
- **Shortcomings - Other approaches**
- Conclusions

Is everything OK with f2? Shortcomings

The **uncertainty** (variability) related to the f2 sampling distribution is not accounted for.

The **shape** of dissolution profiles not taken into account.

The **time correlation** is not taken into account.

While a difference of less than 10% <u>at each time point</u> ensures a value of f2 >50, the reciprocal is not true – *clinical relevance*?

What about processes, sampling, population considerations?

Suitability of dissolution method

Other approaches-when $f2$ is not suitable

Guideline on the Investigation of Bioequivalence

Similarity may be compared using **model-dependent** or **model-independent** methods e.g. by statistical multivariate comparison of the parameters of the Weibull function or the percentage dissolved at different time points.

Alternative methods are considered acceptable, if statistically valid and satisfactorily justified - *but none specified*.

Similarity acceptance limits should be pre-defined, justified and <10% difference.

The dissolution variability of the test and reference product data should also be similar.

EMA - Biostatistics Working Party - Q&A

The adequacy of the Mahalanobis distance (MD) to assess the comparability of drug dissolution profiles

https://www.ema.europa.eu/en/adequacy-mahalanobis-distance-assess-comparability-drug-dissolution-profiles

Published 19 September 2018

- Also emphasises the importance of confidence intervals to quantify the uncertainty around the point estimate of the chosen metric (e.g. the f2 factor or the Mahalanobis distance)

The adequacy of the MD to assess the comparability of dissolution profiles

Under some assumptions, the MD becomes smaller, indicating similar dissolution profiles, with increasing variability observed in the data.

This property makes its use undesirable for deciding upon similarity in dissolution, in particular with regard to the additional criterion that similarity limits should not be greater than a 10% difference at any time point is satisfied.

Depending on the variability observed it is quite possible to have an observed difference of over 10% at some time point, yet MD-based criteria could declare the difference to be unimportant.

EMA - Biostatistics Working Party - Q&A

The adequacy of the Mahalanobis distance to assess the comparability of drug dissolution profiles

MD metric cannot be supported as a preferred methodological approach to decide upon similar dissolution, even in situations where the f2 statistic should not be used in the way outlined in the CHMP bioequivalence guideline.

Bootstrap methodology could be used to derive **confidence intervals for f2** based on quantiles of resampling distributions, and this approach could actually be considered the preferred method over f2 and MD.

Other approaches

Regulatory assessment of drug dissolution profiles comparability via maximum deviation. Statistics in Medicine. 2018;1–14.

According to the authors the method :

- works if the validity criteria of the f2 are not met
- incorporates variability and the time dependency of the measurements
- it takes the shape of the profiles into account
- it gives a proper inferential framework by calculating a test statistic and a p-value
- the resulting test shows high power and the type I-error is controlled

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Conclusions

- f2 remains a simple widely accepted method
- Not perfect but acceptable balance of simplicity and regulatory requirements vs “statistical orthodoxy”
- Not an absolute criterion- provides an indication
- Other things are/should be looked at/considered
  - Variability and its source (manufacturing process)
  - Clinical considerations/ relevance
  - Representativeness and selection of batches to be tested
  - Sampling (scheme, number, timepoints, units selected etc)

C’tnd Conclusions

- Guidelines allow alternative methods
- Alternative methods should be applied with caution
- Prior agreement with authorities is recommended- regulatory/development decisions
- Debate is ongoing

THANK YOU FOR YOUR ATTENTION QUESTIONS?

Evangelos.Kotzagiorgis@ema.europa.eu
European Medicines Agency
Domenico Scarlattilaan 6 | 1083 HS |Amsterdam |The Netherlands
Telephone +31 (0)88 781 7308

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Back-up I

Method steps

1. fit parametric regression curves to the dissolution samples data by two regression models from a candidate set (*First-order model, Higuchi model, Hixson-Crowellmodel, Weibull model and a logistic model*) and choose the best fit for each group. This gives m_1 and m_2.
2. Hypothesis of similarity: H_0: d_∞ $(m_1,m_2) \geq 10\%$ vs. H_1: d_∞ $(m_1;m_2) < 10\%$
3. calculate the test statistic $\hat{d}_\infty = \max_{t \in T} |m_1(t, \hat{\beta}_1) - m_2(t, \hat{\beta}_2)|.$
4. generate new data using a bootstrap procedure
5. either compare the test statistic with (alpha-quantile which we get from the generated bootstrap data (B repetitions)

   or obtain the test decision by calculating the corresponding p-value. The p-value is obtained by evaluating the empirical distribution function at the value of the test statistic.

Back-up II

- Figure below: comparison of the classical f_2-bootstrap and the new procedure

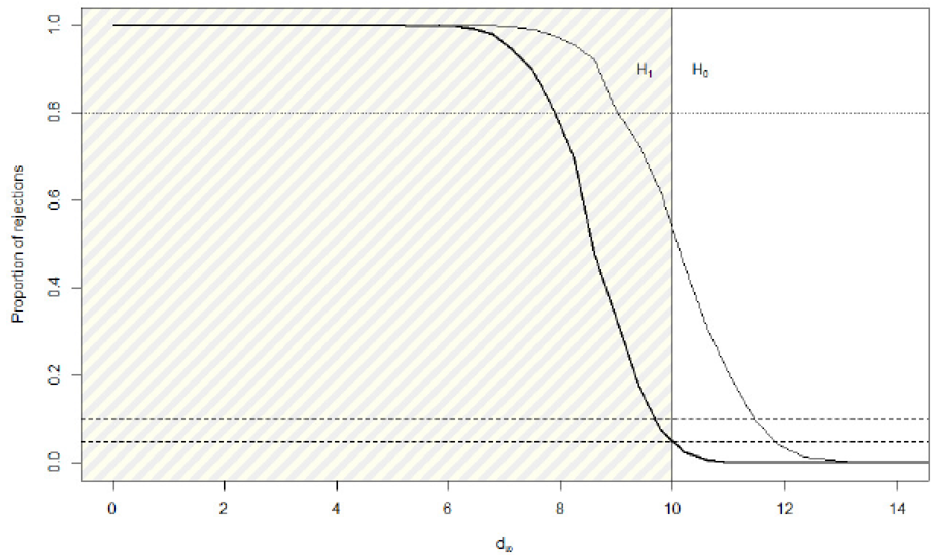

Figure: Artificial data: proportion of rejections of H_0 for the new approach using the maximum deviation (thick line) and the bootstrap f_2 (thin line) over 10000 simulations as d_∞ varies using a level of $\alpha = 0.05$. The horizontal dashed lines correspond to 0.1, 0.05 and 0.80, solid vertical line: $d_\infty = \varepsilon = 10\%$. The shaded region left of the solid line corresponds to the alternative, the region right of this line to the null hypothesis.