Prague

J-M. Cardot

NEWS IN DISSOLUTION 2020-2022

Sept 2022

ICH M9

EFFECTIVE 30/07/2020

DISSOLUTION

Usual experimental conditions are e.g.:

- Apparatus: paddle or basket
- Volume of dissolution medium: 900 ml or less (if possible as QC)
- Temperature of the dissolution medium: 37±1 °C
- Agitation: paddle apparatus - usually 50 rpm (except if coning=>, the use of sinkers or other appropriately justified approaches)
- basket apparatus - usually 100 rpm
- Sampling schedule: noting said but assume e.g. (5,) 10, 15, 20, 30 and 45 min
- Buffer: pH 1.0 – 1.2 (usually 0.1 N HCl or SGF without enzymes), pH 4.5, and pH 6.8 (or SIF without enzymes)=> see pharmacopeia + media in minimum solubility and in some region water
- Other conditions: no surfactant; in case of gelatin capsules or tablets with gelatin coatings the use of enzymes may be acceptable.
- Samples should be filtered during collection

- QC if different (but no surfactant needed in QC as class I/III!)

PROFILE COMPARISON

The coefficient of variation should not be more than 20% at early time-points (up to 10 minutes), and should not be more than 10% at other time points.

No stat is > 85% of the drug is dissolved within 15 minutes, => CLASS I and III

F2 if > 85% of the drug is dissolved between 15 and 30 minutes NOT FOR CLASS III, CLASS I ONLY

In case the coefficient of variation is too high, f2 calculation is considered not accurate and reliable and a conclusion on similarity in dissolution cannot be made.

MEDIA ?

- *ICH M9* Three buffers: pH 1.2, pH 4.5, and pH 6.8. Pharmacopoeia buffers should be employed.
- Which Buffers those described in
  - Dissolution section of Ph.Eur. 5.17.1? If yes PBS are only potassium dihydrogen phosphate based (for example for pH 6.8)
  - In Buffer section 4.1.3 If yes how to justify that Ph.Eur. 5.17.1 is not followed?
- What in case of incompatibility with excipient … and if this latest is only present in the test or ref formulation?
- It is stated in ICH M9 Q&A that common ion effect is not seen to be a problem.

DISSOLUTION FOR STRENGTH BIOWAIVERS OF DELAYED RELEASE

MAY 2020

DELAYED RELEASE

It is a formulation with a delay in the release !

The simplest one are gastro resistant (entero coated) formulation:

- Resist to acidic pH of the stomach with and without food: 1.2 and 4.5
- Release as soon as they reach a pH > than stomach one

But that not the only delayed release for example colonic delivery is a delayed release.

WHAT MUST DISSOLUTION PROVE

For gastro resistant formulations

- Resit at least 2h in acidic media (<10% dissolved)
- Release in pH 6.8

Sometime 2 tests are made the resistance test in acidic and and the release test in pH 6.8

DISSOLUTION IN PHARMACOPEIA 5.17.1

Gastro-resistant dosage forms require at least

- 2 specification points in a sequential test and
- 2 different specifications in a parallel test.

In a sequential test, the 1st specification point represents an upper limit and is set after 1 h or 2 h in acidic medium, and the 2nd after a pre-set time period of testing in an adequate buffer solution (preferably pH 6.8)

METHOD A 2.9.3

- **Acid stage**. Place 750 mL of 0.1 M hydrochloric acid in the vessel, and assemble the apparatus. Allow the medium to equilibrate to a temperature of 37 ± 0.5 °C. Place 1 dosage unit in the apparatus, cover the vessel and operate the apparatus at the specified rate. After 2 h of operation in 0.1 M hydrochloric acid, withdraw an aliquot of the fluid and proceed immediately as directed under Buffer stage. Perform an analysis of the aliquot using a suitable assay method.
- **Buffer stage**. Complete the operations of adding the buffer and adjusting the pH within 5 min. With the apparatus operating at the rate specified, add to the fluid in the vessel 250 mL of a 0.20 M solution of trisodium phosphate dodecahydrate R that has been equilibrated to 37 ± 0.5 °C. Adjust, if necessary, with 2 M hydrochloric acid R or 2 M sodium hydroxide R to a pH of 6.8 ± 0.05. Continue to operate the apparatus for 45 min, or for the specified time. At the end of the time period, withdraw an aliquot of the fluid and perform the analysis using a suitable assay method.

METHOD B 2.9.3

- **Acid Stage**. Place 1000 mL of 0.1 M hydrochloric acid in the vessel and assemble the apparatus. Allow the medium to equilibrate to a temperature of 37 ± 0.5 °C. Place 1 dosage unit in the apparatus, cover the vessel, and operate the apparatus at the specified rate. After 2 h of operation in 0.1 M hydrochloric acid, withdraw an aliquot of the fluid, and proceed immediately as directed under Buffer stage. Perform an analysis of the aliquot using a suitable assay method.
- Buffer stage. For this stage of the procedure use buffer that has previously been equilibrated to a temperature of 37 ± 0.5 °C.
    - Drain the acid from the vessel and add 1000 mL of pH 6.8 phosphate buffer, prepared by mixing 3 volumes of 0.1 M hydrochloric acid with 1 volume of a 0.20 M solution of trisodium phosphate dodecahydrate R and adjusting, if necessary, with 2 M hydrochloric acid R or 2 M sodium hydroxide R to a pH of 6.8 ± 0.05.
    - This may also be accomplished by removing from the apparatus the vessel containing the acid and replacing it with another vessel, containing the buffer and transferring the dosage unit to the vessel containing the buffer. Continue to operate the apparatus for 45 min, or for the specified time. At the end of the time period, withdraw an aliquot of the fluid and perform the analysis using a suitable assay method.

2.9.3 TIME

All test times stated are to be observed within a tolerance of ± 2 per cent, unless otherwise specified.

REMARKS

A time separate the acidic phase from the neutral phase:

- Add new media in acid and equilibrium as well as pH adjustment
- Change media: remove media and add the new one media
- Change media: remove the formulation and transfer it to a new vessel

<u>What is the time zero for the pH 6.8 phase?</u>

Volume 1000 mL

DR RELEASE DISSOLUTION SEE EMA Q&A

3.8 What are the recommendations for a biowaiver of an additional strength for gastro-resistant preparations (e.g. omeprazole)? July 2010, March 2018 (updated April 2018) and May 2020

The dissolution profiles should be compared not only in Pharmacopoeial conditions (2 hours at pH 1.2 followed by 45 minutes at pH 6.8), but also at more neutral pHs in the range 2-5, both for single unit non disintegrating and disintegrating dosage forms with multiple units.

Hence, at least, two dissolution tests in two steps are required.

- First, a comparison at pharmacopeial conditions, 2 hours at pH 1.2 followed by 45 minutes in pH 6.8 and then, a
- second separate dissolution test at a higher initial pH mimicking fed state, e.g. 2 hours at 4.5 followed by 45 minutes in pH 6.8.

Concluding similarity if dissolution of more than 85% is obtained within 15 minutes is not applicable for gastro-resistant formulations. In case of gastro-resistant formulations the release occurs after gastric emptying (median approx. 13-15 min).

Therefore, the comparison of dissolution profiles should be performed even if dissolution is more than 85% before 15 min in either products or strengths.

Hence, a tight sampling schedule is recommended after the product has been investigated for 2 hours in media mimicking the gastric environment (pH 1.2 or 4.5) since profile comparison (e.g. using the f2 calculation) is required

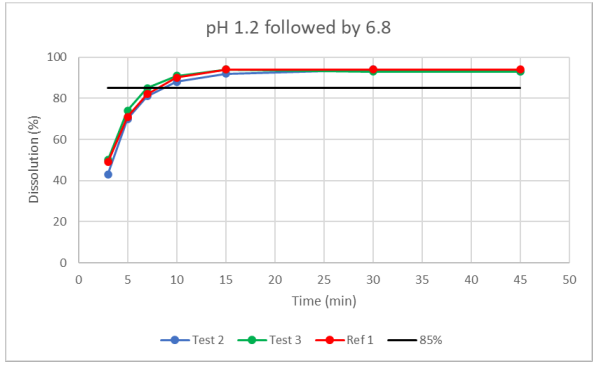
REAL EXAMPLE

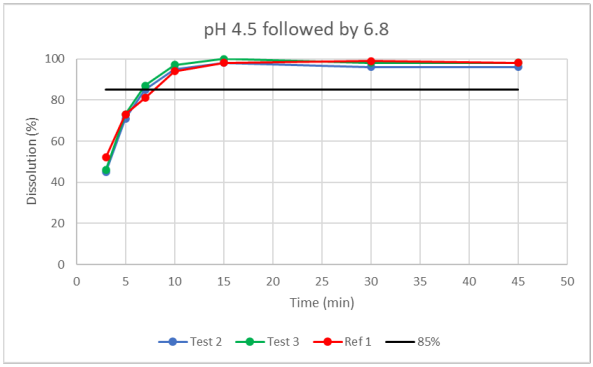
- Method : USP 2 apparatus
- Rpm: 50 rpm,
- Dissolution medium
  1. 2h at pH 1.2 followed by 45 min in pH 6.8
  2. 2h at pH 4.5 followed by 45 min in pH 6.8
  3. Phosphate Buffer pH 6.8
- Medium temperature 37 ± 0.5°C
- Volume
  1. pH 1.2 750ml then pH adjusted to 6.8 final volume 1000ml
  2. pH 4.5 750ml then pH adjusted to 6.8 final volume 1000ml
  3. 1000 mL
- Number of test 12 units
- Complete sampling time 1 and 2. in pH 6.8: 3, 5, 7, 10, 15, 30 and 45 minutes

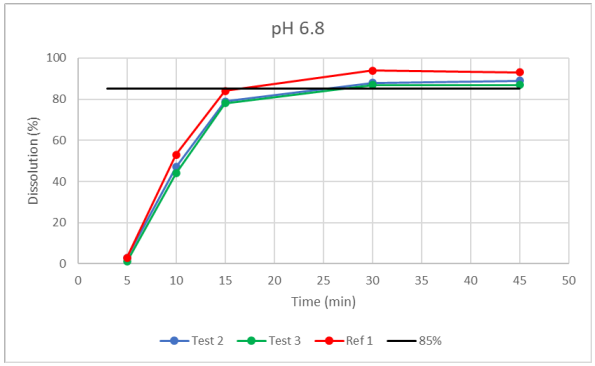
  3. pH 6.8 alone: 5, 10, 15, 30, and 45minutes

RESULTS

			pH 1;2-6.8		pH 4.5-6.8		pH 6.8	
type	batch	Time	Mean	CV	Mean	CV	Mean	CV
		(min)	(%)	(%)	(%)	(%)	(%)	(%)
Test	2	3	43	11	45	16		68
		5	70	8	71	6	3	
		7	81	4	85	3		
		10	88	3	95	2	47	18
		15	92	2	98	1	79	6
		30	94	2	96	1	88	2
		45	93	1	96	1	89	2
	3	3	50	11	46	16		
		5	74	4	73	6	1	153
		7	85	4	87	3		
		10	91	4	97	1	44	33
		15	94	3	100	1	78	10
		30	93	3	98	1	87	2
		45	93	2	98	1	87	1
Ref	1	3	49	14	52	20		
		5	71	10	73	8	3	118
		7	82	5	81	6		
		10	90	3	94	3	53	18
		15	94	2	98	2	84	6
		30	94	2	99	1	94	2
		45	94	2	98	1	93	1







F2 AND BOOTSTARP

The tests must be performed only one value >85%

For test 2 in pH 4.5 followed by 6.8 only 3 points could be used

Ref	Batch	Media	F2 INI	P 5	Bca
1	2	*Ph1.2_6.8*	73	*62*	*60*
		Ph4.5_6.8	68	*56*	*60*
		pH6.8	65	54	55
	3	*Ph1.2_6.8*	81	*64*	*69*
		Ph4.5_6.8	65	*55*	*58*
		pH6.8	59	48	48

In italic bootstrap not needed as CV within limits.

COMPARISON OF CURVES

FEBRUARY 2022

EMA

CPMP/EWP/QWP/1401/98 Rev. 1/ Corr ** Guideline on the investigation of bioequivalence

EMA/810713/2017 Question and Answer on the adequacy of the Mahalanobis distance to assess the comparability of drug dissolution profiles

Q&A 3.11 Expectations for bootstrapping to calculate the 90% confidence interval for the f2 similarity factor **New February 2022**
https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/clinical-pharmacology-pharmacokinetics/clinical-pharmacology-pharmacokinetics-questions-answers#4.-product-specific-bioequivalence-section

EMA/CHMP/138502/2017 Reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development
ICH M9

DISSOLUTION CURVE COMPARISON CLASSICAL F2

If >85% dissolved in < 15 minutes for IR solid formulation no statistical test (see later)

If that is not the case

- F2
- If conditions of F2 not fulfilled **for CV** => alternative tests

BE GUIDELINE EMA

When the f_2 statistic is not suitable, then the 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 … The ***similarity acceptance limits*** *should be pre-defined and justified and* ***not be greater than a 10% difference****. In addition, the* ***dissolution variability of the test and reference product data should also be similar****, however, a* ***lower variability of the test product may be acceptable***

CPMP/EWP/QWP/1401/98 Rev. 1/ Corr ** page 21/27

WHAT IS MODEL INDEPENDENT F2

F2 is a calculation of a mean distance between Ref (R) and Test (T)

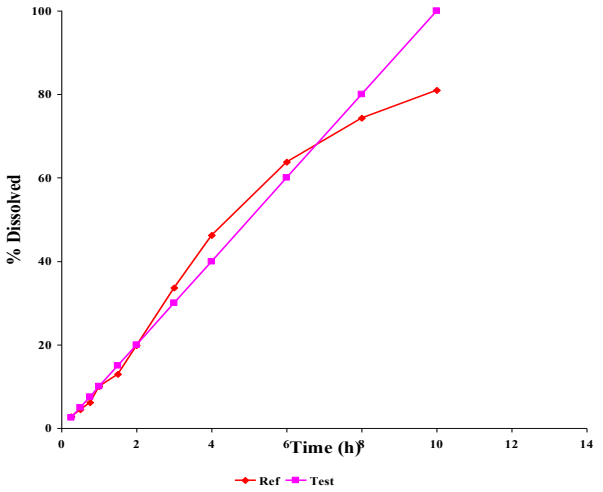
Does not take into account shape

But is simple / robust

To be accepted > 50% (correspond to 10% difference)

$$f_2 = 50 \cdot \log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} \times 100\right\}$$

R(t) % of dissolved dose of reference formulation
T(t) % of dissolved dose of test formulation
n number of sampling time



COMPARISON US-FDA EMA

US-FDA

N≥3 points

Use mean value

CV< 15% (usually CV < 20% first point, < 10% others)

Only one time where both test and reference > 85%

EMA

N≥3 points

Use mean value

CV < 20% first point, < 10% others

Only one time where either test or ref > 85%

E(F2) BOOTSTRAPPING NEW (FEB 2022)

BOOTSTRAPPING F2

Bootstrapping is a random re-sampling technique

Bootstrapping allows

- measuring of “accuracy” to sample estimates
- estimating of the sampling distribution
- Calculate CI for a specific alpha

SOME PRECISIONS IN THE TEXT

- High variability of the dissolution results > 20% RSD at time-points ≤ 10 minutes, > 10% RSD in the later phase for a sample size of 12.
- A tendency to avoid early sampling times (e.g. at 5 min) has been observed, which might cause an incomplete characterisation of the profile, to avoid excessive variability in more than one sampling time (e.g. at 5 and 10 min). Therefore, this modification should be taken into account.
- Furthermore, all sampling times pre-defined in the dissolution study protocol until the sampling time where one of the products reaches > 85% dissolved should be considered in f_2 calculation.

PROTOCOL

The dissolution study protocol should indicate

- the study objectives,
- pre-specify the batches to be compared,
- the dissolution test conditions (apparatus, media composition, agitation rate), media de-aeration, sample filtration and analytical methodology, sampling approach, sampling times,
- the full description of methodology employed for dissolution profile comparison (e.g. f_2 if variability conditions are met and bootstrap 90% CI of expected f_2 with a percentile method for bootstrap 90% CI calculation if variability conditions are not met, including software to be used, number of bootstrap samples, seeds, etc.).

FORMULA

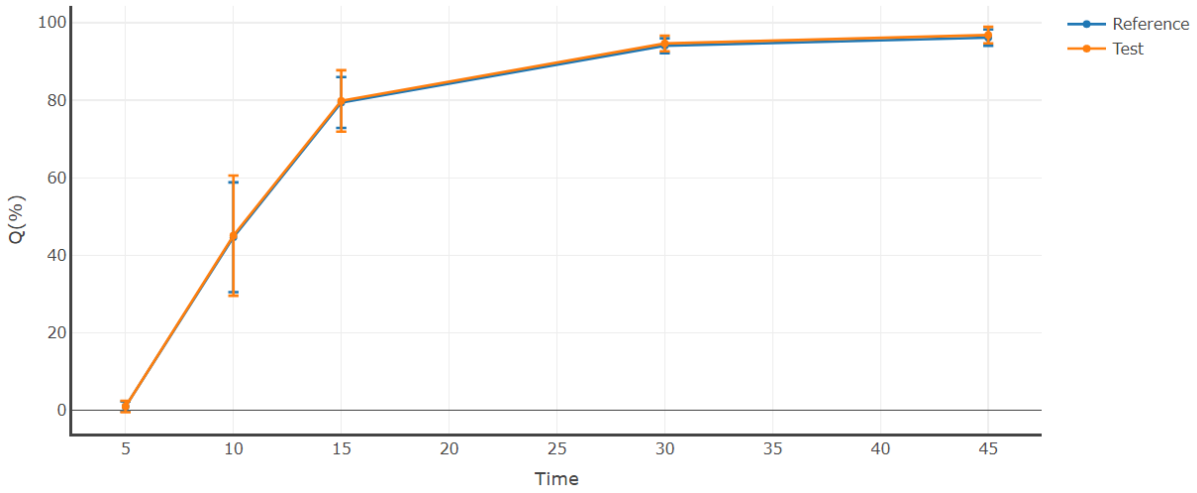
Propose not to use bootstrapped E(F2)

$$\hat{f}_{2,\mathrm{EXP}} = 100 - 25\log\left(1 + \frac{1}{P}\left(\sum_{i=1}^{P}\left(\tilde{X}_{\mathrm{T},i} - \tilde{X}_{\mathrm{R},i}\right)^2 + \frac{1}{n}\sum_{i=1}^{P}\left(S^2_{\mathrm{T},i} + S^2_{\mathrm{R},i}\right)\right)\right),$$

Variability in re-introduced in addition the difference between T and R

That is conservative => more complicated to show equivalence in majority of the cases

EXAMPLE 1



Classical F2

Initial = 98

P5=59

BCA = 99

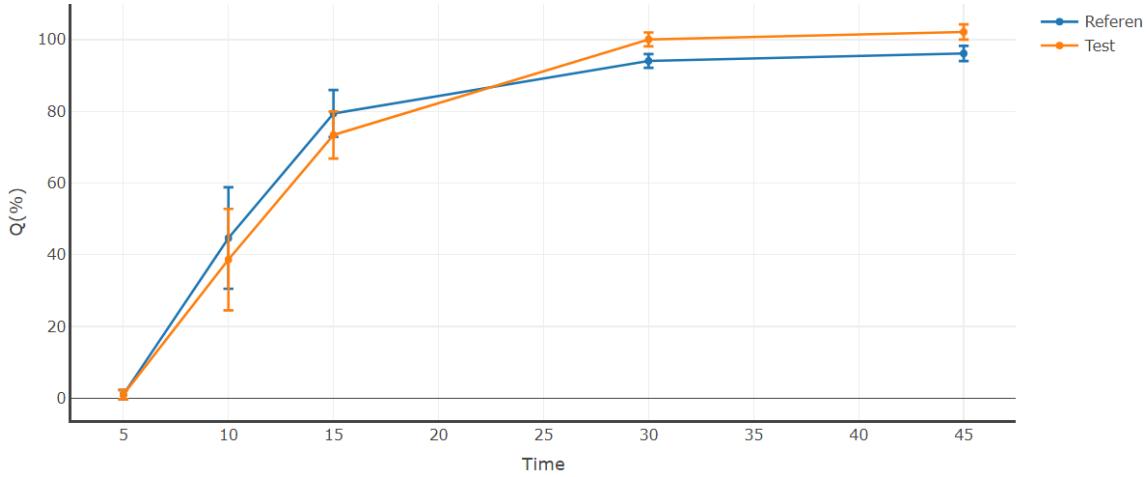
E(F2)

Initial = 72

P5 = 57

BCA = 68

EXAMPLE 2



Classical F2

Initial = 63

P5=51

BCA = 51

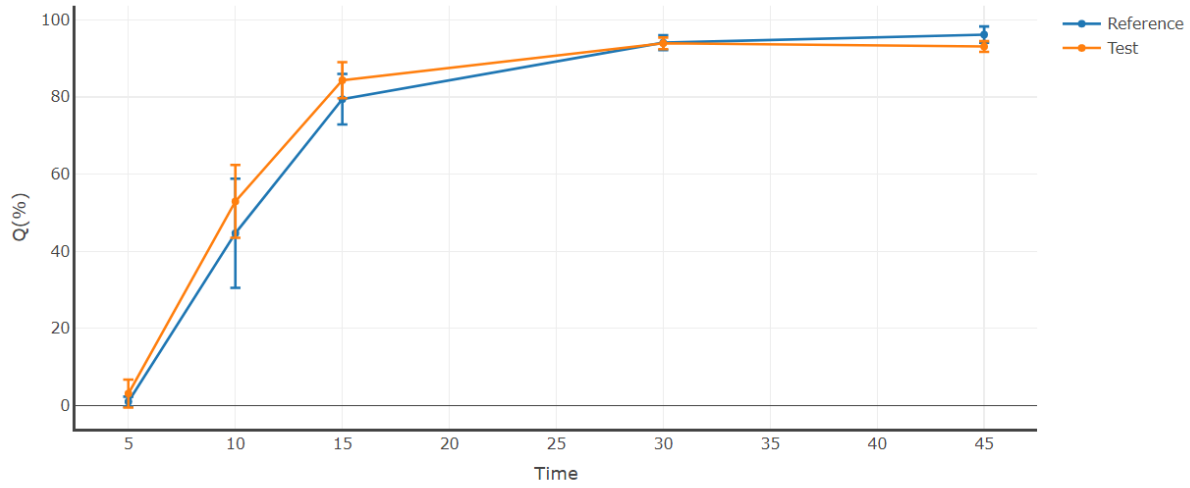
E(F2)

Initial = 59

P5 = 50

BCA = 49

EXAMPLE 3



Classical F2

Initial = 64

P5=50

BCA = 52

E(F2)

Initial = 59

P5 = 49

BCA = 51

BOOTSTRAP

At least 5000 replicates

Use any of the percentile calculation methods described in Hyndman and Fan publication => 9 definitions certain are criticized!

P5 only must be used? No P5, BC, BCa, etc… could be used are they are all based on percentile approach

All sampling times pre-defined in the dissolution study protocol should be considered in the calculation until the sampling time where one of the products reaches >85% dissolved => by bootstrap!

the lower limit is equal or above 50 (≥ 50)

The results should be reported rounded to the next integer without decimal units => 49.56 lead to 50 ????

That is in contradiction with current approach, Shah paper and Mahalanobis distance reflection paper : lower limit is entirely above 50 (>50)

Modify null hypothesis … implication must be evaluated such as on Alpha ….

REPORTING

When reporting dissolution profile comparisons, the applicant should provide individual results of the percentage dissolved at the different sampling times pre-defined in the protocol as well as mean percentage dissolved with its variability (CV(%)) in order to allow the replication of the calculations.

REPORTING

In addition, the applicant should discuss the basis for the similarity conclusion: dissolution is > 85% in 15 min for oral products with systemic action, f_2 similarity factor calculation (e.g. acceptable variability, no more than one sampling time above 85% dissolved, etc.) is needed, or if the 90% confidence interval of f_2 is required ….

In case of bootstrapping, similarity in dissolution profiles will be concluded when the lower limit of the 90% confidence interval for the Expected f_2 is ≥ 50. The results should be reported rounded to the next integer without decimal units => *49.56 lead to 50 ????*

SOFTWARE

In any case, the software should be adequately documented.

In the case of specific software packages, the selected options (e.g. whole vectors, one profile, number of bootstrap samples, seed number, if available) should be described.

In the case of in-house platforms, the code of the platform should be provided and it should be demonstrated that the employed software is able to calculate the 90% confidence interval of f_2,*EXP* correctly. See [NOCE] for examples of datasets and results. => *Validation*

SOFTWARE

Based on Statistical package: R, SAS, WPS, etc… validated and provide code

Based on available softwares: Bootf2bca and Pheq_bootstrap (question in come cases), DDSolver (Not following EMA truncation rule)

Warning:

- should provide clear truncation rules
- should be possible to validate them if in house,
- should provide more than one approach: percentile, BC, Bca, …
- calculation algorithm are different between software

NOCE PAPER

According to Q&A Validation must be done using data proposed in NOCE

L. Noce, L. Gwaza, V. Mangas-Sanjuan, A. Garcia-Arieta. Comparison of free software platforms for the calculation of the 90% confidence interval of f2 similarity factor by bootstrap analysis. Eur J Pharm Sci. 2020;146:105259. https://doi.org/10.1016/j.ejps.2020.105259.

Both V Mangas Sanjuan and A Garia Arieta are members of PKWP ….

Article in which errors are existing in equations 2 and 3 (sum of variances must be divided by nP) That was mentioned but will not be corrected! Hope that calculation are correct!

Seed not mentioned

Rounding non mentioned

$$E(f_2) = 50 \cdot log\left\{\left[1 + \frac{1}{P}\sum_{j=1}^{P}(R_j - T_j)^2 + \sum_{j=1}^{P}(s_{Rj}^2 + s_{Tj}^2)/n\right]^{-0.5} \cdot 100\right\}$$

Noce's concluded

"In conclusion, the 90% confidence interval of Expected f2 should be employed to conclude on the similarity of dissolution profiles with excessive variability because it is the most conservative unbiased estimation of f2 and it is always defined. It can be calculated with Pheq_bootstrap or Bootf2bca, since the differences caused by the uncontrolled seed employed by Pheq_bootstrap are negligible, except in borderline cases since the results differ only in the decimal units when the number of runs is at least 500. The method of 90% CI estimation based on the percentile bootstrap using at least 500 bootstrap replicates is acceptable. Finally, both platforms use the truncation rules required by regulatory agencies."

two softwares are proposed but it seems one of the two (to be confirmed) is not fully complying with the proposed rules of minimum number of points i.e. at least 3, (that was not mentioned in the paper as that was not tested) as in some bootstrap it keeps only 2 values….

it does not control its seed …. That could create problems in « borderline cases »

what to do ?

EXAMPLE NOCE DATA AS REPORTED VS OTHER SOFTWARE

E(F2)		Noce P	WPS W			W vs P %	Bootf2BCA: B			B vs P %	W vs B %		
1 vs 3	Initial E(F2)	44.54	44.54			0.01	44.53			0.02	0.01		
			M	LL	HL	LL	M	LL	HL	LL	Mean	LL	HL
	BP	35.82	45.54	35.56	58.11	0.74	45.32	35.62	57.61	0.56	0.48	-0.18	0.87
	BCa			35.13	57.09			35.62	57.61			-1.39	-0.92
	Normal			32.16	54.91			32.75	54.76			-1.84	0.27
	Basic			30.96	53.52			31.47	53.45			-1.65	0.13
2 vs 3	Initial E(F2)	55.70	55.70			0.00	55.69			0.02	0.02		
			M	LL	HL	LL	M	LL	HL	LL	Mean	LL	HL
	BP	47.92	56.89	48.05	62.82	-0.27	55.64	48.17	63.17	-0.52	2.19	-0.25	-0.56
	BCa			48.28	63.21			47.88	62.90			0.83	0.49
	Normal			48.33	63.36			48.20	63.30			0.28	0.10
	Basic			48.58	63.35			48.23	63.23			0.73	0.19

EXAMPLE CITED BY NOCE SHAH DATA

1000			Shah		Noce		BootF2Bca			WPS		
		mean	LL	UL	LL	UL	*mean*	LL	HL	*mean*	LL	HL
1	PI	*60.22*	53.01	68.34	52.64	67.85	*59.94*	53.03	68	*59.71*	52.93	67.55
	BCA		53.89	70.24	51.7	67.06		51.65	66.71		52.47	67.07
2	PI	*51.01*	48.25	53.69	48.03	53.83	*50.86*	48.15	53.73	*50.84*	48.15	53.66
	BCA		48.37	53.74	48.08	53.93		48.29	53.9		48.32	53.91
3	PI	*51.29*	48.54	54.56	48.28	54.02	*51.07*	48.27	53.94	*51.11*	48.21	53.95
	BCA		48.41	54.22	48.6	54.58		48.3	54.06		48.21	53.95
4	PI	*49.99*	48.38	51.59	48.35	51.4	*49.85*	48.27	51.55	*49.88*	48.28	51.50
	BCA		48.47	51.73	48.54	51.56		48.42	51.68		48.39	51.64
5	PI	*48.01*	46.05	50.04	45.96	49.96	*47.97*	45.98	50.14	*47.99*	45.87	50.04
	BCA		46.15	50.17	45.91	49.91		46.05	50.17		45.87	50.03

DELTA %

1000		delta Noce % vs Shah		delta WPS % vs Noce		delta BootF2Bca % vs Noce		delta % WPS vs bootF2Bca		
		LL	UL	LL	UL	LL	UL	mean	LL	UL
1	PI	0.70	0.72	-0.55	0.44	-0.74	-0.22	0.38	0.19	0.66
	BCA	4.06	4.53	-1.48	-0.02	0.10	0.52		-1.58	-0.54
2	PI	0.46	-0.26	-0.25	0.31	-0.25	0.19	0.05	0.00	0.12
	BCA	0.60	-0.35	-0.50	0.04	-0.44	0.06		-0.06	-0.02
3	PI	0.54	0.99	0.15	0.14	0.02	0.15	-0.09	0.13	-0.01
	BCA	-0.39	-0.66	0.81	1.16	0.62	0.95		0.19	0.21
4	PI	0.06	0.37	0.14	-0.19	0.17	-0.29	-0.05	-0.02	0.10
	BCA	-0.14	0.33	0.30	-0.16	0.25	-0.23		0.05	0.07
5	PI	0.20	0.16	0.19	-0.16	-0.04	-0.36	-0.04	0.23	0.20
	BCA	0.52	0.52	0.10	-0.24	-0.30	-0.52		0.40	0.28

REMARK

- In some cases could have problems as you must fulfill by run the truncation rule i.e. only one mean dissolution > 85% for either test or ref and a minimum of 3 points
- Seed must be controlled
- Percentile calculation tule must be defined
- Rounding of F2 applied without digits (but where for each F2 or only the P5)
- Software must be validated (… and revalidated in case of version modification)

So Pandora box still opened …

THANK YOU

Email: jean-michel.CARDOT@wanadoo.fr

OTHER REFERENCES

- Cardot JM, Roudier B, Schütz H. Dissolution comparisons using a Multivariate Statistical Distance (MSD) test and a comparison of various approaches for calculating the measurements of dissolution profile comparison AAPS J. 2017 Jul;19(4):1091-1101
- Islam, MM. & Begum, M. (2018). Bootstrap confidence intervals for dissolution similarity factor f2. Biom Biostat Int J. 7(5): 397–403.
- Ma MC, Wang B, Liu JP, Tsong Y Assessment of similarity between dissolution profiles Journal of Biopharmaceutical Statistics, 2000, 10(2), 229–249
- Mangas-Sanjuan V, Colon-Useche S, Gonzalez-Alvarez I, Bermejo M, Garcia-Arieta A., Assessment of the Regulatory Methods for the Comparison of Highly Variable Dissolution Profiles. AAPS J. 2016 Nov;18(6):1550-1561. doi: 10.1208/s12248-016-9971-5
- Tsong Y, Hammerstrom T, Sathe P, Shah V. Statistical assessment of mean differences between two dissolution data sets, Drug Inf J. 1996;30(4):1105–12.
- Noce L, Gwaza L, Mangas-Sanjuan V, Garcia-Arieta A Comparison of free software platforms for the calculation of the 90% confidence interval of f 2 similarity factor by bootstrap analysis Comparative Study Eur J Pharm Sci 2020 Apr 15;146:105259. doi: 10.1016/j.ejps.2020.105259