Dissolution curve comparison
Alternative to F2

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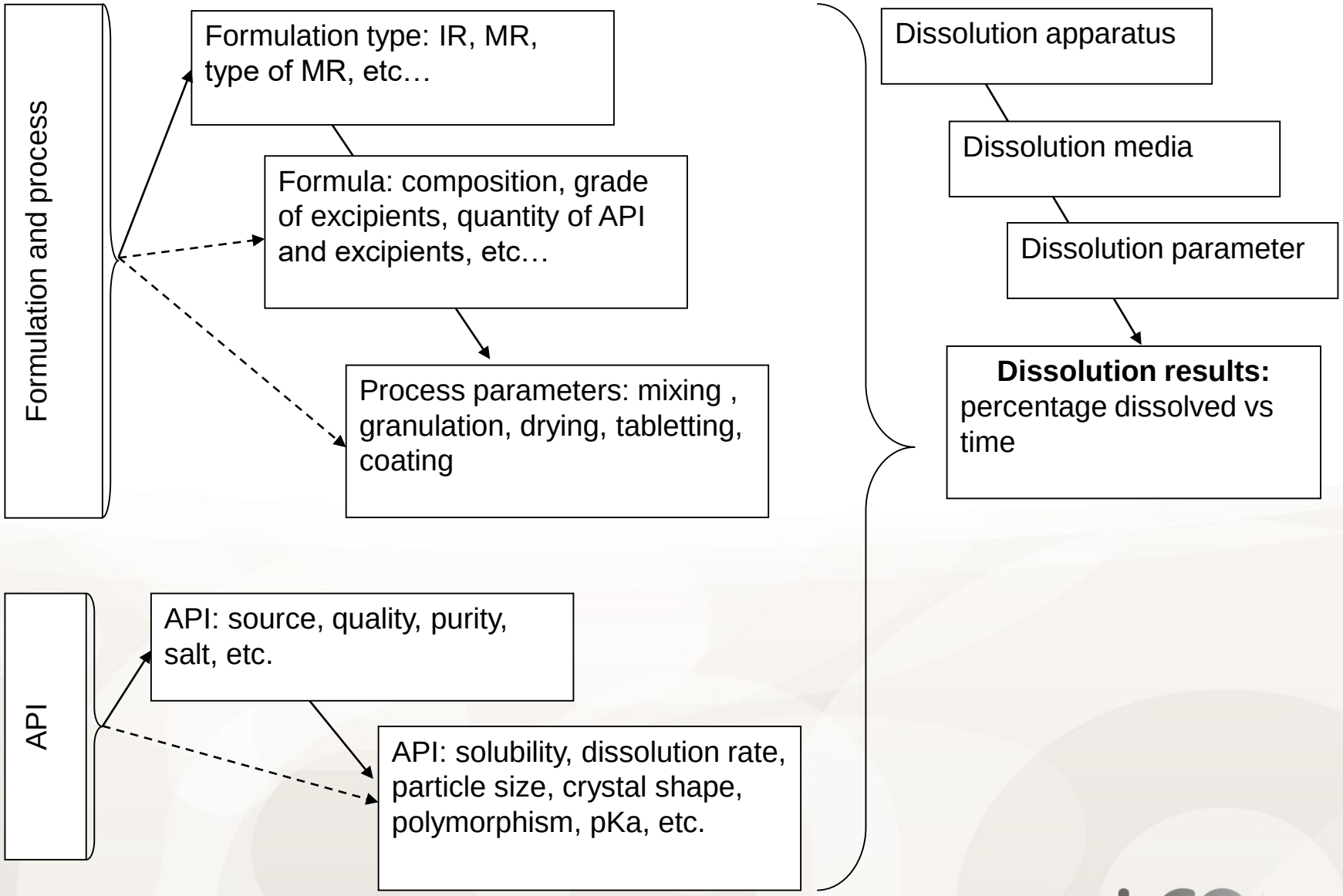
Introduction

Dissolution tests



Dissolution tests

- Use as QC => insure batch to batch consistency
- Use in Biowaivers => surrogate of in vivo
  - BCS based IR solid dosage form
  - Strength IE/MR dosage forms
- Use in life cycle management
  - Support variations

Guidelines/reflection papers EMA

- Bioequivalence
- MR
- ICH Q8
- Variation
- Dissolution
- ICH M9
- Statistical methodology
- Etc…

Dissolution curve comparison

- If >85% dissolved in < 15 for IR solid formulation no statistical test
- If that is not the case
  - F2 but
    - 12 units
    - 3 time points with only one > 85%
    - CV first point < 20% and others < 10%
  - Variability could be due to formulation, process or even reference formulation (and not test formulation)
  - If conditions of F2 not fulfilled for CV => alternative tests … but which one that is not defined

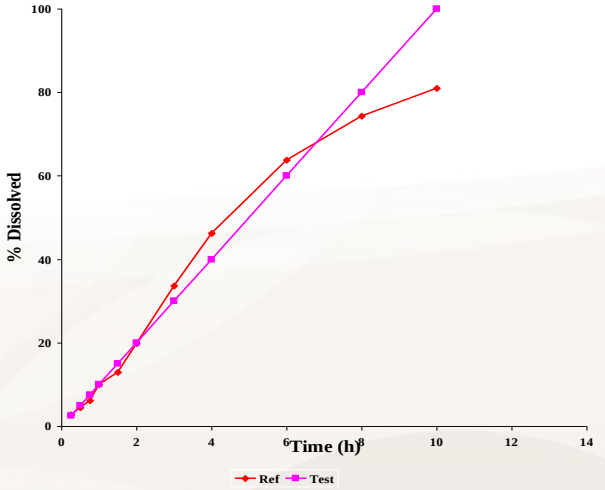
Comparison of curves F2 test

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

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

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



f2

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

- F2=50 => mean R-T=10

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

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

$$10 = \left\{\left[1+\frac{1}{n}\sum_{t=1}^{n}(d_t)^2\right]^{-0.5} \times 100\right\}$$

$$\frac{10}{100} = 0.1 = \left[1+\frac{1}{n}\sum_{t=1}^{n}(d_t)^2\right]^{-0.5}$$

$$0.1 = \frac{1}{\sqrt{1+\frac{1}{n}\sum_{t=1}^{n}(d_t)^2}} \rightarrow \sqrt{1+\frac{1}{n}\sum_{t=1}^{n}(d_t)^2} = \frac{1}{0.1}$$

$$\sqrt{1+\frac{1}{n}\sum_{t=1}^{n}(d_t)^2} = 10 \rightarrow \frac{1}{n}\sum_{t=1}^{n}(d_t)^2 = 99$$

$$\overline{m_d^2} = 99 \rightarrow m_d \approx 10$$

EMA reflection paper on statistical methodology

- F2
  - Use mean, and based on average difference
  - Insensitive to time interval
  - No shape comparison
- When F2 not possible other distance based method used
  - Raw data
  - After modeling ….
- Always based on central parameters … mean value

Reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development

Proposed: dissolution

- F2 no alpha (and of course no beta) risk associated … except after bootstrapping
- F2: not possible to make a simple CI (except if bootstrapping)
- F2 acceptance based on a mean almost 10% difference
- Alternative to F2
  - Limits +/- 10% … of what (ref ?)
  - Limits +/- 10% of bio batch but why
  - What is the in vivo outcome of +/-10%
- How to set alpha risk … problem of multiple comparison R1 vs T1 R1 vs T2 R1 vs T3, R2 vs T1, etc…

Remarks

- Simple to criticize but what to propose ?
- Ideal Target Test Profile
  - Compatible with manual calculation
  - Limits easy to determine
  - Simple selection of points to be used
  - Taking into account if Test less variable than Reference
  - Taking into account shape of curves
  - …

Current alternatives to F2

Alternative tests

- When variability criteria of F2 is not fulfilled
- Not possible when results are not complying with F2>50% but all conditions are fulfilled …

Described

- Multivariate Statistical Distance (MSD) either on raw data or model parameters,
- Bootstrapping F2
- Bootstrapping G1,
- Bayesian extension of f2 metrics,
- Dissolution efficiency DE, associated or not to MDT
- Paired permutated t test,
- GLM: ANOVA, Principal Components Model, and Mixed linear models,
- Etc…

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MSD

- *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***

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MSD

- 2 or n dimension distances which calculations are based on the variance of each variable and the covariance between variables.
- takes into account the relationship and distance between the datasets, the possible different scales and the dispersions of them.
- 90% CI is computed, and the larger bound is compared to a preset value (in the present case, the distance calculated vs the limit)

MSD SAS

- Use proc CANDISC option DISTANCE
  - MSD = $\sqrt{MSD^2}$
  - K=*Fobs/MSD²*.
  - CI=$MSD \pm \sqrt{Fcrit/K}$, where Fcrit is the F value for α=0.1 and 3 (number of parameters), 20 (24 values-3 parameters-1) df

MSD problems: on dissolution curve fitting

- Can be performed on parameters of equation used to fit dissolution curves
  - Is that the right equation
  - Is not the model over-parametrized
  - Often driven by Q dissolved at infinity
  - This high similarity between dissolution at the end of the profile or parameters (such as Fmax) leads to a wrong conditioning of the variance covariance matrix, collinearity, and bias of the common variance estimation.
  - Accomodate non similar sample

MSD problems: on dissolution Raw data

- Can be performed on raw data
  - Which points to take
  - Use time as a factor => Co-linearity problem (dissolution at time 2 depends of dissolution at time 1, etc.), singularity of the pooled covariance matrix, and bias of the common variance estimation
  - Not using time as a factor: best option but must limit sample up to one greater than 85% (as for f2) to avoid insensibility of the results to detect possible differences

Limits … another problem

- 10% of What
- Of Reference seems to be the more logic: Ref vs Ref + or -10%
  - Takes into account the variability of the reference => if test less varaible that is in your advantage
  - Takes into account a reality Ref vs Ref + or – 10% must be in theory equal ….
- Between various batches of the reference => larger difference
  - Possible if greater than the previous option

MSD 2*2 or all batches together

- When 3 test batches (T1, T2, T3) must be compared to a single reference (R) that leads to R vs T1, R vs T2, R vs T3, and R vs limit: 4 tests
- Multiplication of tests is not recommended (alpha inflation)
- MSD could be handle on all the data and then takes into account the variabilities sources

MSD

- Is again a global distance between batches

F2 bootstrapping

Bootstrapping

- Bootstrapping is a random re-sampling technique
- Bootstrapping allows
  - measuring of accuracy to sample estimates
  - estimating of the sampling distribution
- F2 bootstrapping
  - From initial dataset of test and ref sample to create new sets of data
  - Handicap if Ref more variable than Test

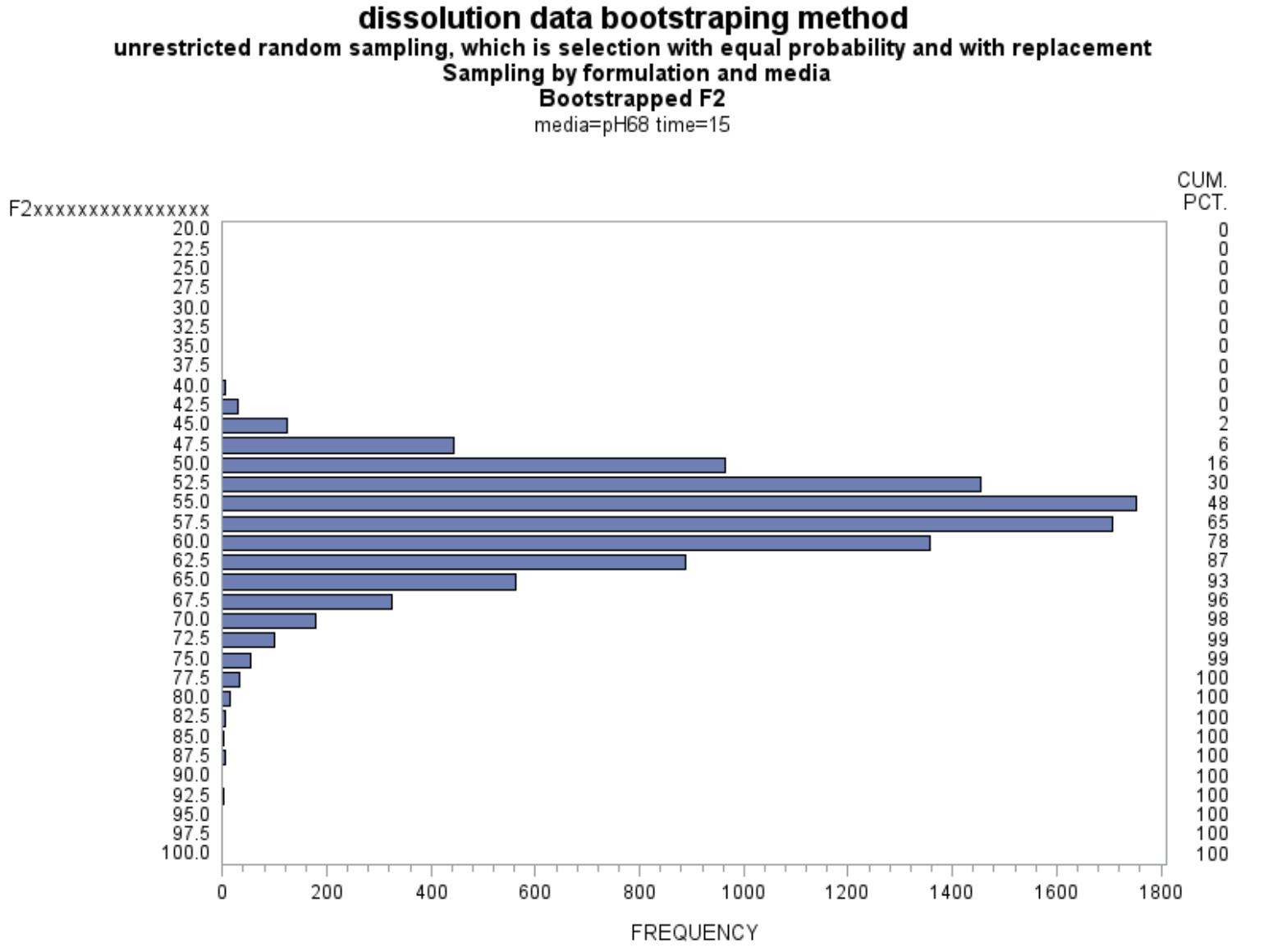
Bootsrapping F2

- SAS procedure SURVEYSELECT for example
- URS method selected => unrestricted random sampling :selection with equal probability and with replacement
- Separate bootstrapping performed for each formulation and for each media two possibilities
  - by curve
  - by time => constraint on the next point ?
- 5 to 10 000 replicated each
- 5^{th} percentile (p5) of all F2 corresponded to the lower limit of F2 and must be > 50% => is that the right limit ?

Bootstrapping and limits

- 50% is a preset limit like for classical F2
- 50% does not take into account the variability especially of the reference => could lead to inconsistent results
- Why not using limit corresponding to reference + or – 10 %?

Graph



Example

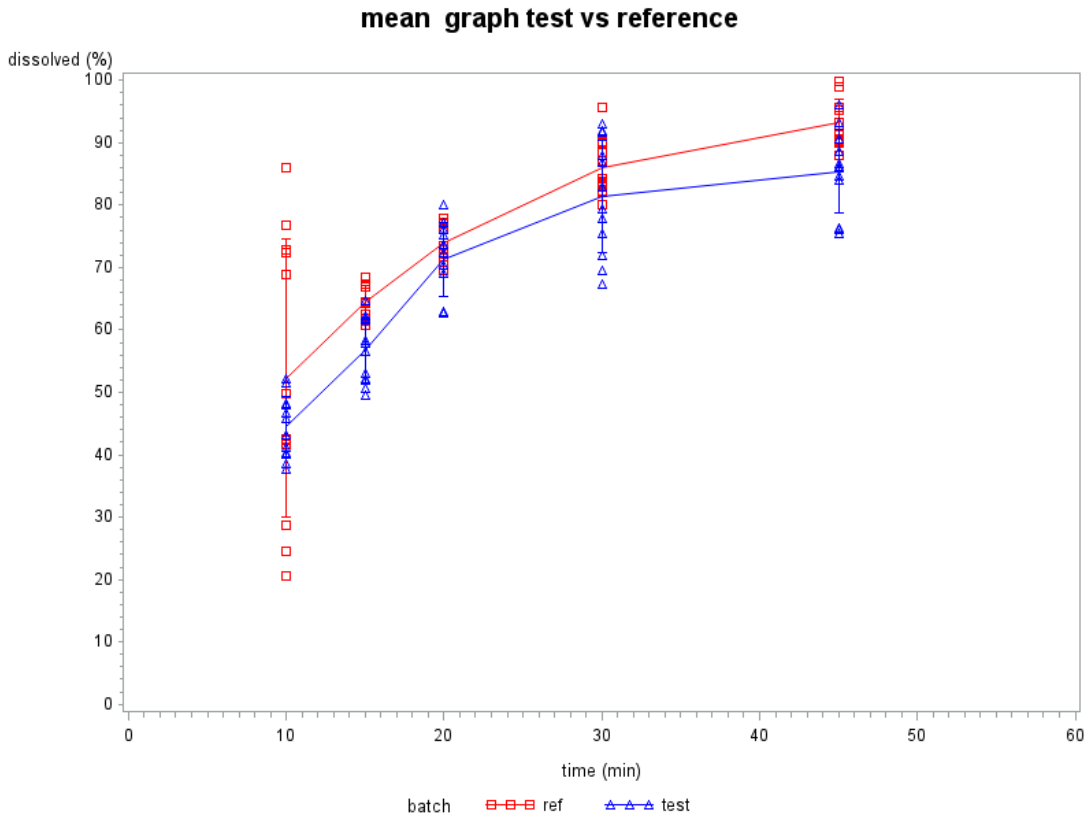
Based on real data

Data

Mean CV

Reference			
time	mean	cv	Flag
10	52	43	>20
15	65	4	
20	74	4	
30	86	5	
Test			
time	mean	cv	Flag
10	44	11	
15	57	9	
20	71	8	
30	81	11	>10

Graph



Initial F2

- F2 (1) test vs ref: 59%
- F2 (2) Ref vs Ref: 100 %
- F2 (3) ref vs Ref ± 10: 50 %

p5 F2 bootstrapping

- F2 (1) test vs ref: 49% => rejected but just at the boarder
- F2 (2) Ref vs Ref: 53 % => limit ….
- F2 (3) ref vs Ref ± 10: 41 % => rejected
- However F2(1) > F2 (3) => must be accepted?

MSD

- Results as follow: accepted

From To↓	limit	ref	test
limit	#DIV/0!	0.94	1.00
ref	0.94	#DIV/0!	0.40
test	1.00	0.40	#DIV/0!

Conclusion

Variability

- As per guideline *"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**"*
- What to do if variability are different between test and reference
  - If test is more variable than reference => not a good batch but what is more?
  - If reference is highly varaible?

Selection of alternative tests

- How to fix limits ?
  - P5>50% for bootstrapping of F2 very conservative
  - Use F2 vs ref ± 10%?
- Function of the test selected results could be different
- Neither bootstrapping of F2 nor MSD fulfill the criteria of an ideal test!

Post meeting note

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 July 2018
EMA/810713/2017
Human Medicines Research and Development Support

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

Aim

Follow up of the statistical reflection paper presented last year

- Provide clarification about the suitability of the Mahalanobis distance (MD)
- Emphasize the importance of confidence intervals to quantify the uncertainty around the point estimate

MD: declared problems

- MD is the multi-dimensional generalisation of the idea of expressing the distance between two points using standard deviation as the unit of measurement.
- 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
- 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.
- Based on these considerations, **the MD metric cannot be supported as a preferred methodological approach** to decide upon similar dissolution

F2 bootstrapping declared advantages

- Any approach based upon **confidence intervals for f2 would, however, be considered appropriate whether the validity criteria outlined in CHMP guidance are met or not**
- Similarity could then be declared if the confidence interval for f2 were **entirely above 50**.
- Properties of the f2 sampling distribution do not allow the derivation of exact confidence intervals
- To address this, bootstrap methodology could be used to derive confidence intervals for f2 based on quantiles of re-sampling distributions
- **This approach could actually be considered the preferred method over f2 and MD**.

Comments 1/4: higher risk to fail, limits

- Variability must be similar for test and ref to declare 2 set of data similar …”In addition, the dissolution variability of the test and reference product data should also be similar” (BE guidance CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **).
- In case of large variability of ref (or ref and test) booptstrapped F2 has all the chance to fail if comparing p5 to 50%. In BE guidance it is clearly specify “lower variability of the test product may be acceptable” => but large variability of ref will penalize the bootstrapped F2 results …..
- Still problem to see how to fix limit

Comments 2/4: strange wording

- **whether the validity criteria outlined in CHMP guidance are met or not => ???**
  - CV only (my guess)
  - number of points <3
  - More than one point > 85%
- **This approach could actually be considered the preferred method over f2 and MD.**
  - Classical f2 not recommended anymore even if possible?

Comment 4/4: Methodology

- Which type of bootstrapping: by curve, by point ?
- Do not forget to fulfill criteria for all of the bootstrap (or not ???)
- Which limit
- Etc…

Comment 4/4: ICH M9

- ICH M9 “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.”
- How to understand “This approach could actually be considered the preferred method over f2 and MD” when no alternative is given in ICH M9 ???

Conclusion

- When variability is high and mainly for reference all the chance to fail bootstrapping if limits at 50%
- Which validity criteria are mentioned
- Could a classical F2 be used when possible ?

=> that is a very restrictive approach if f2 limit could not be adjusted in case of high variability of ref ….

=> no real clarification of what to be done

Thank you

Questions ?

No => perfect ! ☺

Yes => I am ready to answer! ☹ … ☺