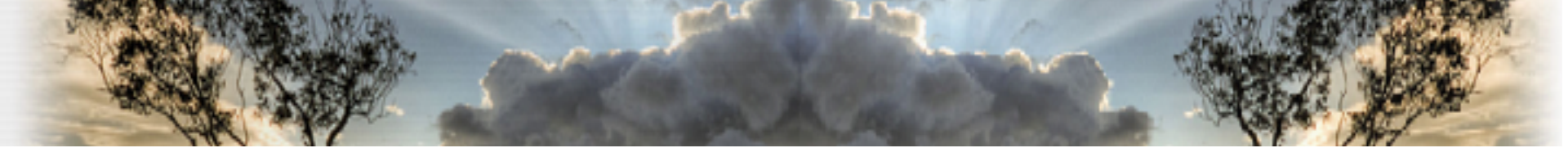

ICH M10 cross validation & documentation: what now?

Tom Verhaeghe, on behalf of the EBF

12th EBF Open Symposium
Imagine! A new bioanalytical Earthrise

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Cross Validation

ICHM10 section 6.2: Cross Validation

- When?
  - Different methods or different labs used within 1 study
  - Different methods used across studies
    - PK data compared to support special dosing regimens or
    - PK data compared to support regulatory decisions re. safety, efficacy, labelling
- How?
  - QCs L,M,H in triplicate and
  - Study samples (n≥30) across concentration range
- Assessment?
  - Bland-Altman plot
  - Deming regression
  - Concordance correlation coefficient
- Criteria?
  - None; assess impact on clinical data in case of disproportionate bias

Cross-validations beyond ICHM10: how to move forward?

- What exactly is Bland-Altman?
- How to deal with the absence of acceptance criteria?

Bland-Altman

Measurement

STATISTICAL METHODS FOR ASSESSING AGREEMENT BETWEEN TWO METHODS OF CLINICAL MEASUREMENT

J. MARTIN BLAND DOUGLAS G. ALTMAN

Department of Clinical Epidemiology and Social Medicine, St George's Hospital Medical School, London SW17; and Division of Medical Statistics, MRC Clinical Research Centre, Northwick Park Hospital, Harrow, Middlesex

Summary In clinical measurement comparison of a new measurement technique with an established one is often needed to see whether they agree sufficiently for the new to replace the old. Such investigations are often analysed inappropriately, notably by using correlation coefficients. The use of correlation is misleading. An alternative approach, based on graphical techniques and simple calculations, is described, together with the relation between this analysis and the assessment of repeatability.

PEFR MEASURED WITH WRIGHT PEAK FLOW AND MINI WRIGHT PEAK FLOW METER

Subject	Wright peak flow meter		Mini Wright peak flow meter	
	First PEFR (l/min)	Second PEFR (l/min)	First PEFR (l/min)	Second PEFR (l/min)
1	494	490	512	525
2	395	397	430	415
3	516	512	520	508
4	434	401	428	444
5	476	470	500	500
6	557	611	600	625
7	413	415	364	460
8	442	431	380	390
9	650	638	658	642
10	433	429	445	432
11	417	420	432	420
12	656	633	626	605
13	267	275	260	227
14	478	492	477	467
15	178	165	259	268
16	423	372	350	370
17	427	421	451	443

PLOTTING DATA

The first step is to plot the data and draw the line of equality on which all points would lie if the two meters gave exactly the same

What is the purpose of a cross validation?

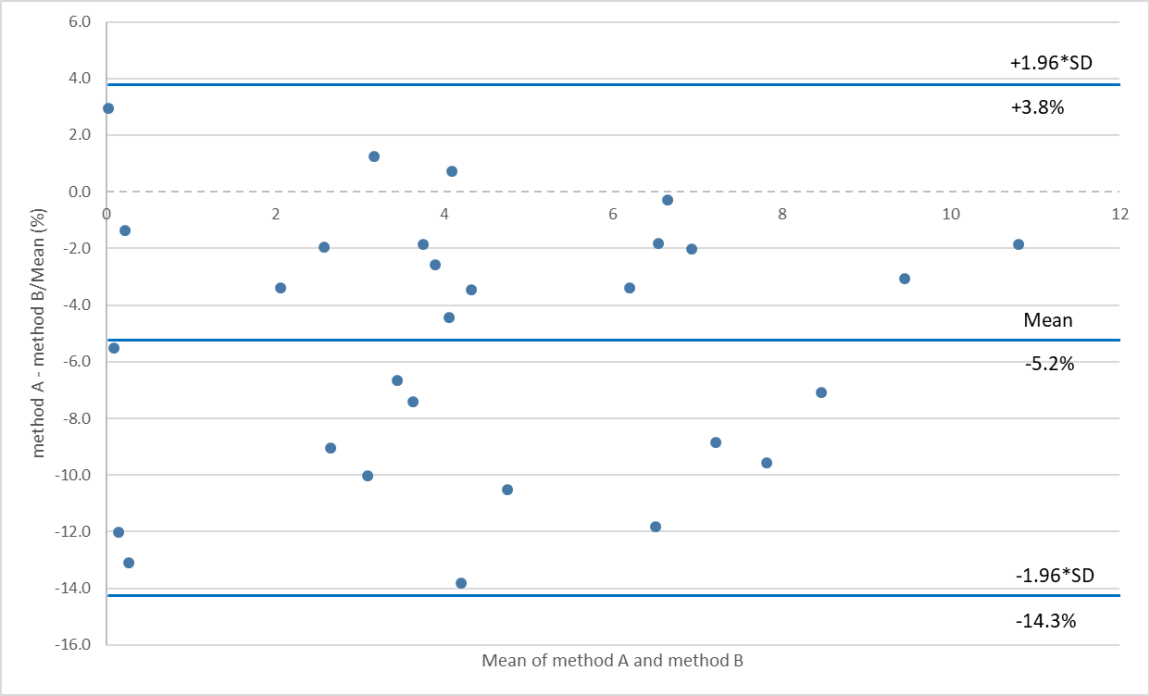
- Unlikely that 2 methods will agree exactly; every method produces an estimate of the true value
- What is the agreement between 2 methods ie by how much does the new method differ from the old?
- If the difference does not impact the clinical interpretation, new method can replace old (or the two be used interchangeably)
- Ideally define in advance what difference is acceptable for the parameter you quantify in order to determine the sample size

What statistical approach for comparing 2 methods?

- Bland-Altman state that correlation coefficient or regression analysis are not appropriate ! High correlation does not imply good agreement.
- Instead propose to plot difference of measurements by 2 methods (absolute or as %) against mean (mean is best estimate as true value is unknown)
- Calculate mean difference and limits of agreement (mean +/- 1.96*SD; 95% differences fall between these limits)
- If differences within limits of agreement have no impact on clinical interpretation, both methods can be used

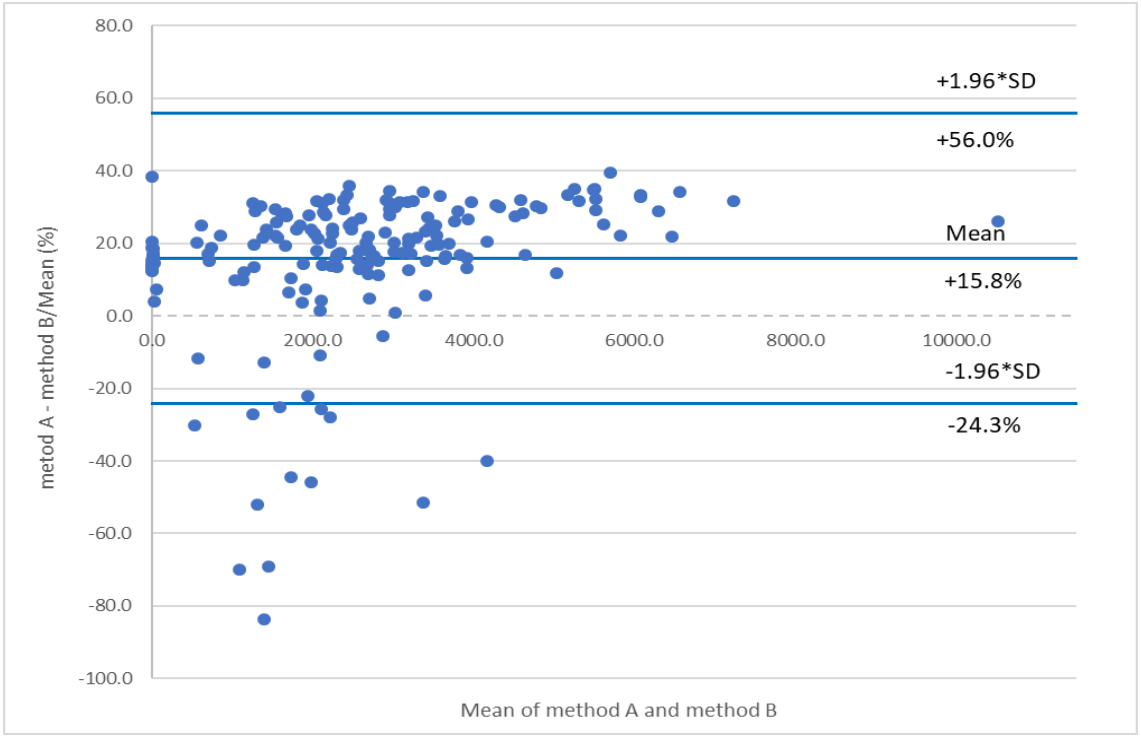
J. Martin Bland, Douglas G. Altman; Statistical methods for assessing agreement between two methods of clinical methods. *International Journal of nursing studies,* 47, 931-936 (2010)

B&A applied to Bioanalysis; example #1



- 2 different labs (Europe & China) used within 1 multi-site study
- 30 study samples selected for cross-validation
- Average difference: -5.2%
- Limits of agreement: -14.3% to +3.8%
- 29/29 samples show difference <20% (1 had no result)

B&A applied to Bioanalysis; example #2



- 2 different labs used across development program
- 200 study samples selected for cross-validation
- Average difference: +15.8%
- Limits of agreement: -24.3% to +56.0%
- 105/178 samples show difference >20% (22 had no result)

Impact assessment

- Major question: “which difference can be tolerated without impact on clinical interpretation (ie PK)?” or “when is the bias disproportionate?”
- Not for BA to decide but needs to be assessed by clinical pharmacology
- Limits of agreement of +/- 20% seem acceptable without impact on PK; this would be in line with ISR criteria
- Example #1: Limits of agreement: -14.3% to +3.8% 
- Example #2: Limits of agreement: -24.3% to +56.0% 
  →impact on PK needs to be assessed by clinical pharmacology

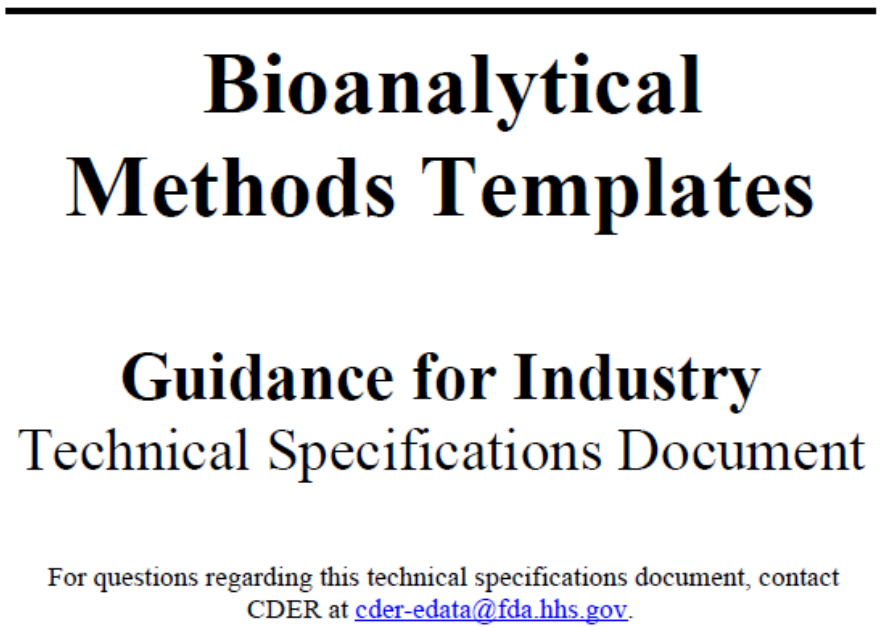
Some thoughts…

- In line with current procedures it would be logical to accept that limits of agreement of +/- 20% have no impact on PK
- When the difference is beyond these limits clinical pharmacology needs to assess the impact on PK
- 2-tiered approach;
  - Tier 1: QCs measured by the 2 methods; compared to nominal
  - Tier 2: incurred samples compared by B-A plot

Documentation

ICH M10 Section 8: Documentation

- 8.1 Summary Information:
  - The information that should be provided in the CTD
  - See also recent FDA Guidance for more clarification on how to report



Bioanalytical Methods Templates

Guidance for Industry

Technical Specifications Document

For questions regarding this technical specifications document, contact CDER at cder-edata@fda.hhs.gov.

ICH M10 Section 8: Documentation

- 8.2 Documentation for validation and Bioanalytical reports; detailed in Table 1:
  - at analytical site
  - in validation report
  - In bioanalytical report

  - 100% of chromatograms BA/BE studies (and corresponding validation report)
  - IS plot
  - Run summary sheet (containing oa. analyte and IS responses, retention times)
  - List of regulatory site inspections including dates and outcomes (in CTD?)
  - Some requests are limited to BA/BE studies

Concerns on Documentation

- Table 1 carries the risk of becoming overinterpreted which may lead to increased resources for industry.
- We suggest to limit the requirements in table 1 to BA/BE-studies, and allow reporting of other studies to be less detailed (i.e. less in reports but allow documentation to be available at the analytical site)

EBF

Acknowledgment

- EBF community
- Delegates to EBF/AAPS/JBF/CBF sister meeting (Barcelona, May, 2019)
- BA Scientists at Janssen for providing the x-validation examples

- Thank you
- Questions?

Contact Information

Questions: info@e-b-f.eu

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