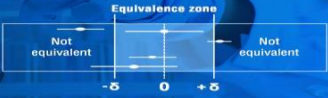


מתי שתי שיטות אנליטיות אקויוולנטיות?
Demonstration of Comparability of Alternative Analytical Procedures
Organized by Raphy Bar

Wednesday, April 10, 2024
Live Online Free Webinar

Webinar language: Hebrew



15:30-15:40 | Opening Notes
Raphy Bar, Ph.D.

15:40-16:20 | Comparability of alternative analytical procedures according to the new Ph. Eur. chapter 5.27
Ina Sigal-Batikoff, Ph.D. Projects & Validations Section Manager in QC KAMADA



16:20-16:30 | Break

16:30-17:00 | Approaches to evaluation of comparability data
Raphy Bar, Ph.D. BR Consulting

17:00-17:40 | Points-to-consider in comparability of biologics/biotechnology products -
Ms. Rivka Zaibel, President & Founder, ADRES, IN'T BIOTECH CNSLT & EXCUT

17:40-18:00 | Q&A
Webinar Speakers

This webinar is sponsored by



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by

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BR Consulting

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3

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1	Understanding Statistical Tools for Pharma R&D and QC Laboratories with Excel and Software practice on real data cases	2 days or 3 days
2	Stability testing of pharmaceuticals and evaluation of stability data for QC, QA and Stability personnel	2 days
3	Sampling Strategies for Finished Products, In-process Materials, Packaging, Medical devices, APIs and Excipients: Sampling standards, Reduced Sampling/Testing	2 days
4	Validation of Analytical methods for cleaning residues in pharmaceutical processes	2 days
5	Analytical Method Transfer with evaluation of method transfer results	1 day
6	Laboratory Data Integrity How to maintain integrity in lab data, record audit trail of chromatographic peaks integration and report results	1 day

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Approaches to Evaluation of Comparability Data
4

Eleven In-house courses

7	Forced Degradations of Pharmaceuticals: for development of stability-indicating methods and Stress Testing for prediction of stability of formulations and shipped finished pharmaceuticals	2 days
8	Pharmacopoeias and Compendial Testing of Pharmaceuticals	2 day
9	Trending of Process Data and Evaluation of Quality Metrics for Annual Product Review (APR) <i>For QA, RA, QC, Project Leaders and Production personnel</i>	2 days
10	Charting and trending of Environmental Monitoring data: from microbial counts to recovery rates in controlled rooms	2 days
11	Validation of Analytical Methods with Uncertainty and Total Analytical Error Considerations in compliance with ICH/FDA/USP	2 days



The Israel Chapter of PDA

העמותה לקידום המדע והטכנולוגיה הפרמצבטית בישראל



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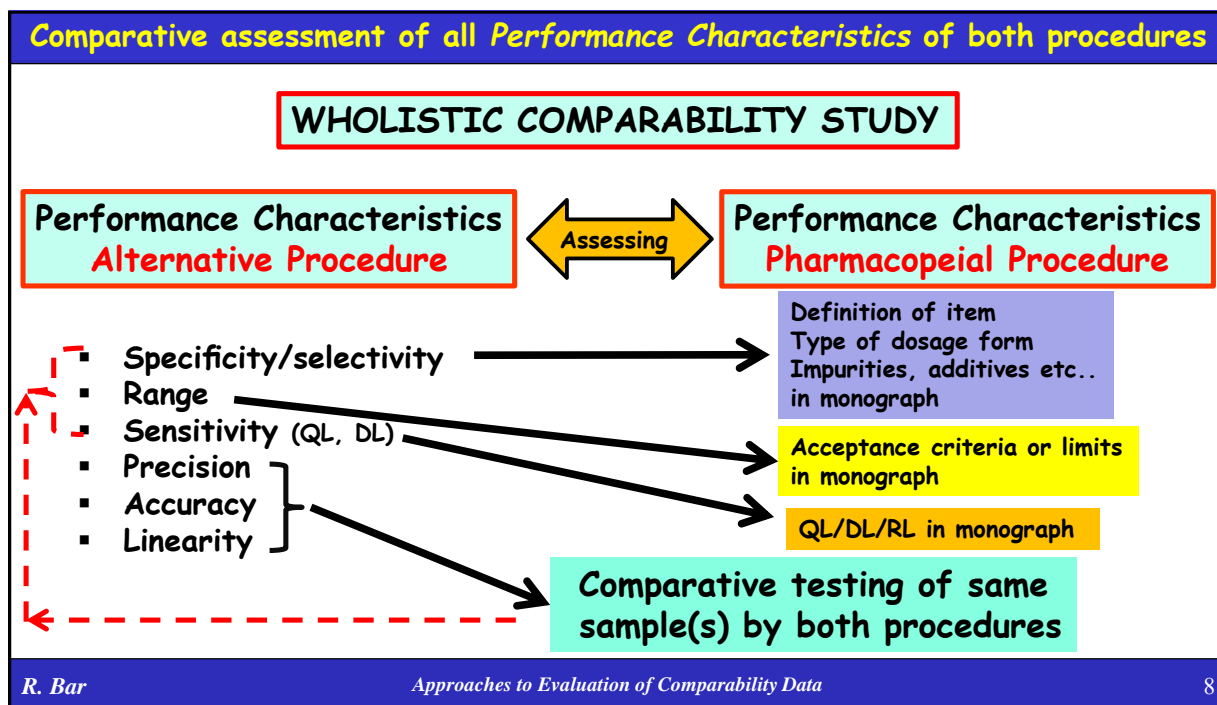
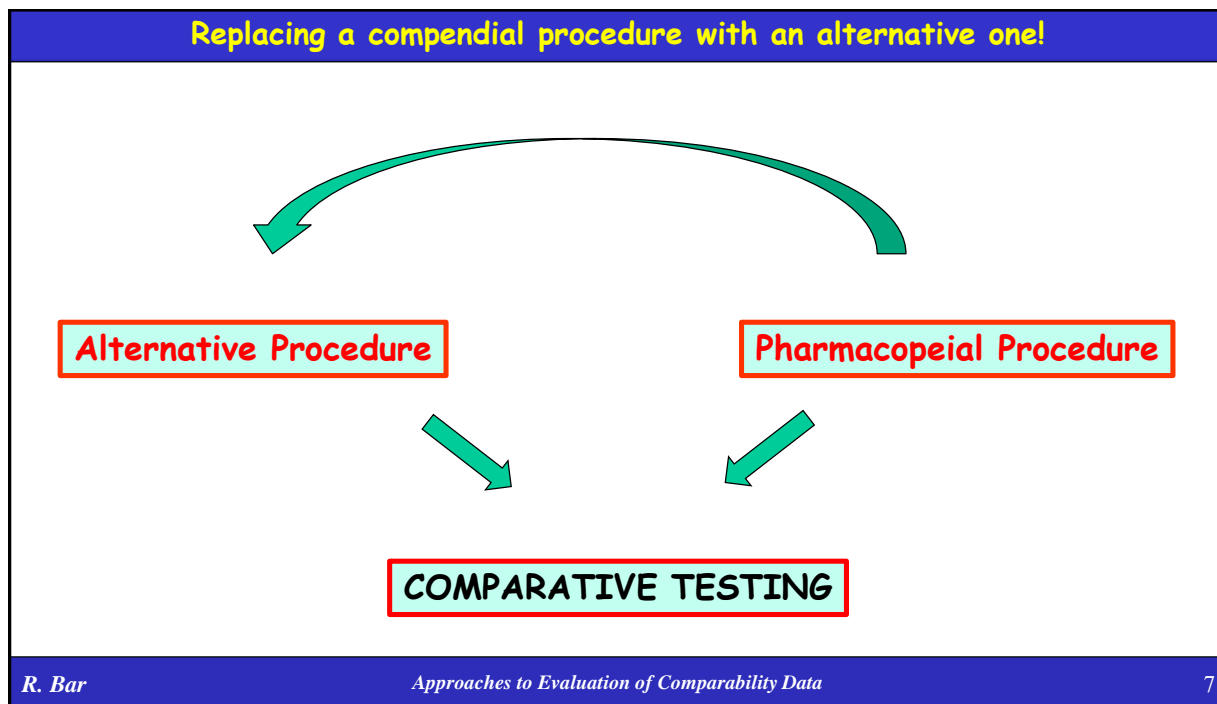
Approaches to Evaluation of Comparability Data

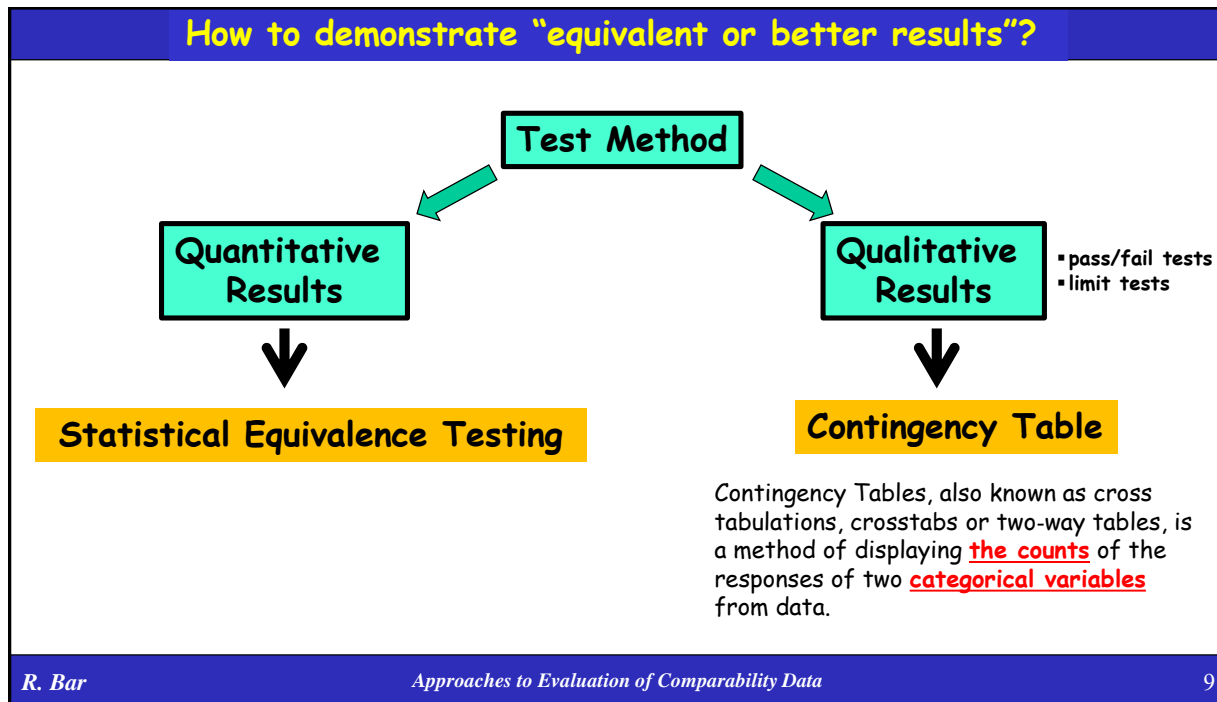
April 10, 2024
15:30 - 18:00h

by
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From manual titration to automated or semi-automated method

Example

Converting a manual titration to automated or semi-automated method

Potassium citrate
The assay of potassium citrate is done by a non-aqueous acid-base titration using perchloric acid in glacial acetic acid as the titrant and crystal violet as the indicator.

USP Compendial Tool, Recommendations for converting a manual titration procedure into an automated titration procedure, Margareth R. C. Marques¹ et al.

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From Pharmacopeial procedure to another pharmacopeial Procedure

Use of Recombinant Factor C (rFC) in the Bacterial Endotoxins Test

New Ph. Eur. 2.6.32

This describes a test for bacterial endotoxins (BET) that can be used as an alternative to the classic limulus amoebocyte lysate (LAL)-based methods for the quantification of endotoxins from gram-negative bacteria. The recombinant factor C (rFC) based on the gene sequence of the [horseshoe crab](#) and fluorimetric detection, in keeping with the kits currently available on the European market.

In Europe and as of January 2021, the **rFC method is now an alternative pharmacopeial method, Ph Eur 2.6.32.**

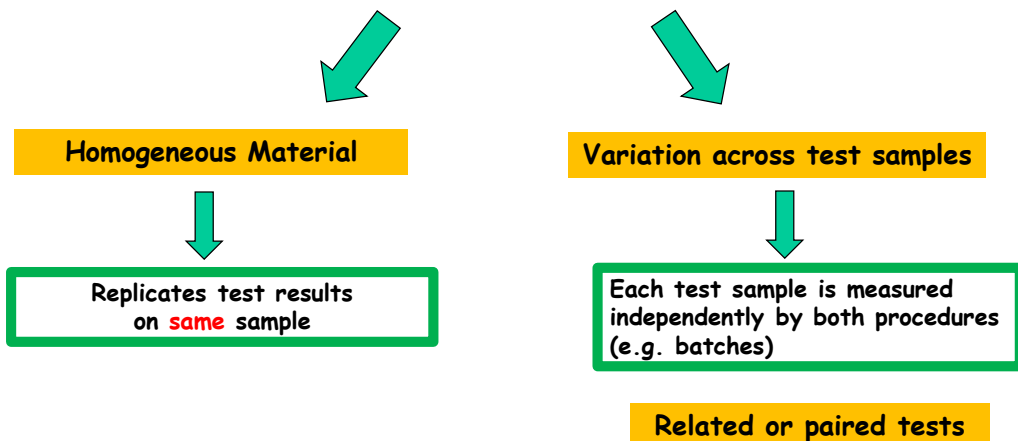
For the bacterial endotoxins test, the monographs still reference Ph. Eur. chapter 2.6.14. Therefore, method 2.6.32 is **considered an alternative to method** 2.6.14 as described in the General Notices.

EDQM

<https://www.edqm.eu/en/-/recombinant-factor-c-new-ph.-eur.-chapter-available-as-of-1-july-2020>

Replicate Sample Testing

Types of test samples



How to demonstrate "equivalent or better results"?

Comparison of two methods

Traditional Way

Direct comparison of:

- * variability (F-test)
- * averages (t-test)

(Difference Test)

Equivalence Test

Two one-sided equivalence test with 95% confidence level for a pre-determined acceptable difference

"For quantitative results, the two one-sided t-tests (TOST) method could be considered for the comparison of the two group means." Ph. Eur. 5.27

- JMP
- Minitab
- StatGraphics
- Etc...

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USP addresses also comparison of analytical procedures

USP Chapter (Official as of 1-Dec-2021) :

(1010) ANALYTICAL DATA—INTERPRETATION AND TREATMENT

5. COMPARISON OF ANALYTICAL PROCEDURES

APPENDIX 3: EQUIVALENCE AND NONINFERIORITY TESTING

Note: It provides more statistical details!

R. Bar Approaches to Evaluation of Comparability Data 14

How to demonstrate "equivalent or better results"?

Plotting of Results

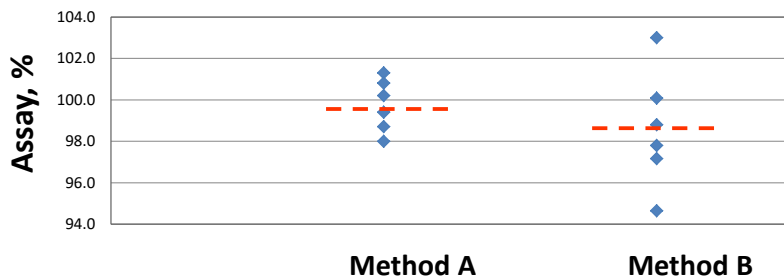
scatter plots and difference plots

Same sample is tested in replicates at 1 Level!

Graphical presentation of test results

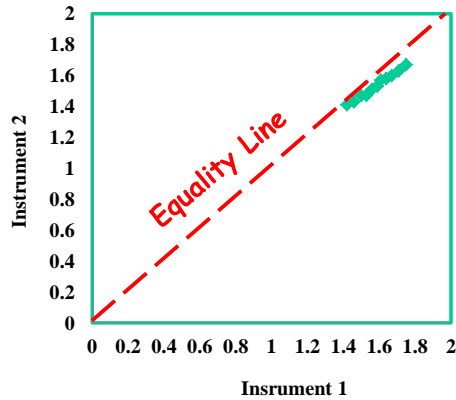
Scatter Plot

Comparison of results



Samples at different levels are tested!

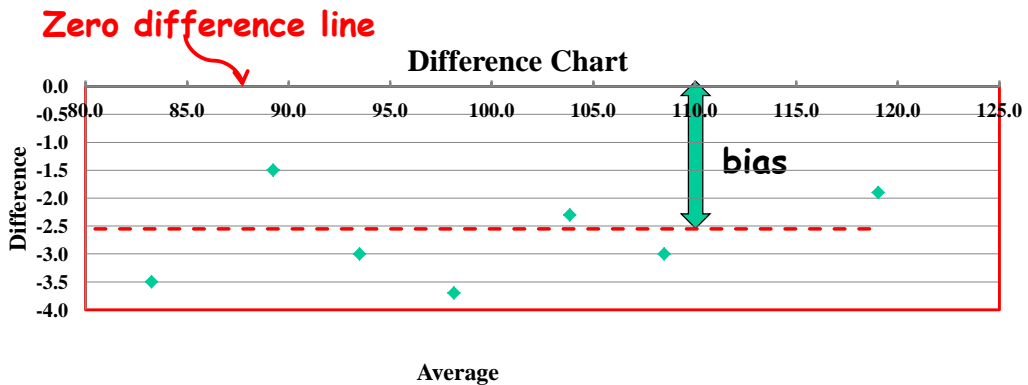
Plotting results of Instrument 1 versus those of Instrument 2:
Comparing with a line with Slope = 1.



Samples at different levels are tested!

Difference Plot

Difference between Assay results of Original and Alternate methods
Systematic error (bias)



Statistical Evaluation of Data

Same sample is tested in replicates at 1 Level!

Statistical Comparison of two sets of measurements

Traditional Way

Separate comparison of:

1. **variances (F-test)** → Do the two methods have a significantly equal variability?
2. **averages (t-test)** → Are the averages of the two methods significantly different?

Statistical Equivalence Testing

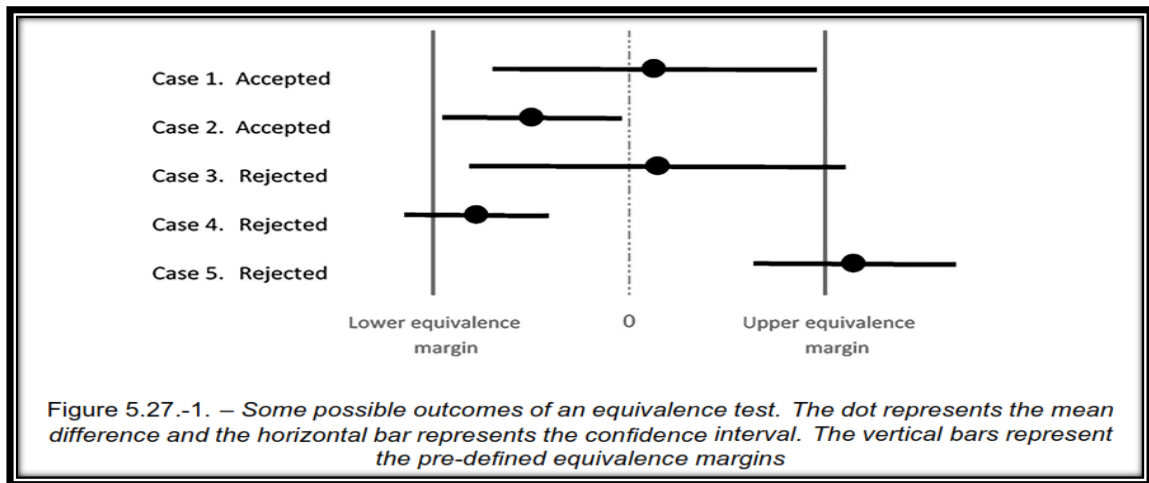
A SPECIAL STATISTICAL TOOL:
Two One t-TEST

H_0 : Non-equivalent
 H_a : Equivalent

It is important to understand that "equivalence" does not mean "equality". Equivalence should be understood as "sufficiently similar" for the use of the new procedure. USP <1010>

The Ph. Eur. equivalence testing approach

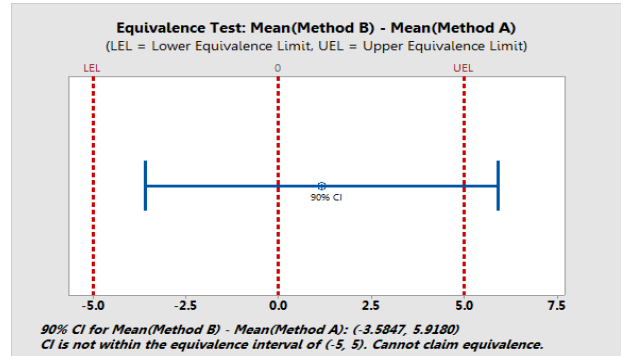
Ph. Eur. 5.27



Equivalence Test at 1 Level

EXAMPLE

Average A	Average B	Difference (B-A)
85.67	86.83	1.17



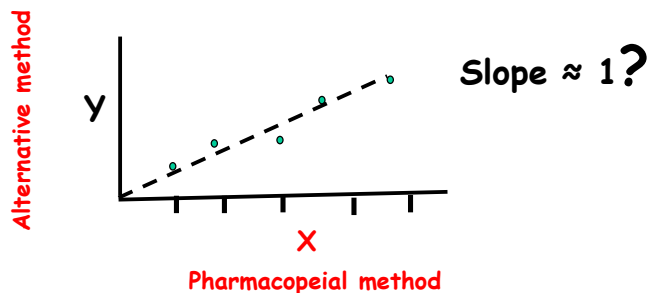
Minitab 18

Conclusion:
Cannot claim equivalence

Comparing results at several levels

But...

Both X and Y are observed with error!



Deming Regression
(for normal data)

"For results spreading over a wider range than those obtained at a single level, a regression approach (e.g. Deming regression, bivariate least squares regression) may be considered instead." Ph. Eur. 5.27

What if the equivalence test is rejected?

“Where **bias** and/or **variability** between the results of two procedures is observed, leading to the equivalence being rejected, the likelihood of subsequently demonstrating equivalence between the two procedures **can be improved** by identifying

the source of the bias and/or variability

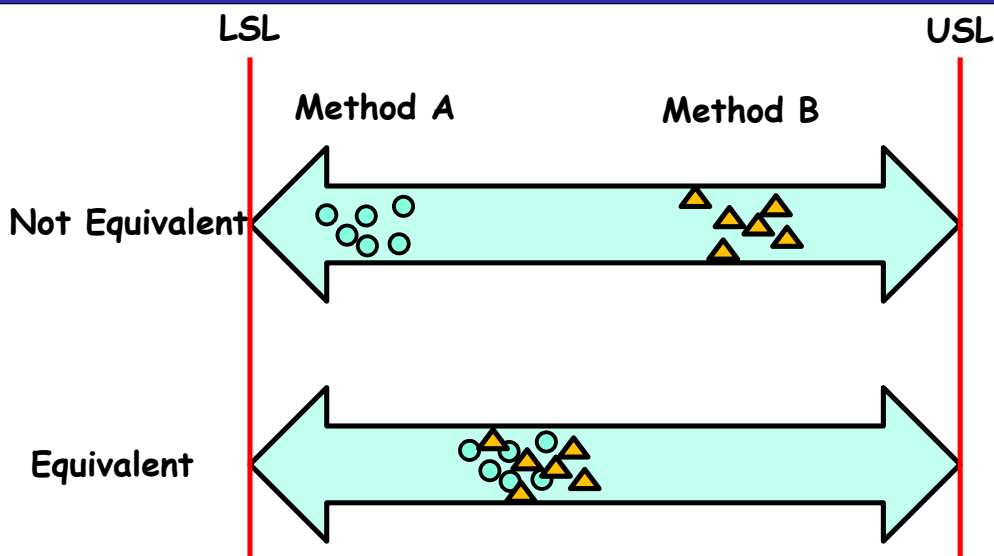
and

taking steps to reduce it

prior to pursuing the assessment.”

Ph. Eur. 5.27

Comparability vs Meeting Specifications



END