The Israel Chapter of PDA
העמותה לקידום המדע והטכנולוגיה הפרמצבטית בישראל

Live Online Webinar

The ICH concept of 'total analytical error' in validation of analytical procedures of pharmaceuticals

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Test Result Uncertainty

"…no quantitative results are of any value unless they are accompanied by some estimate of the errors inherent in them"

Miller Jane C. and James N. Miller
Statistics for Analytical Chemistry (1993)

Test Result Uncertainty

Reportable Result

Result: $x \pm U$ (units) (k=2)

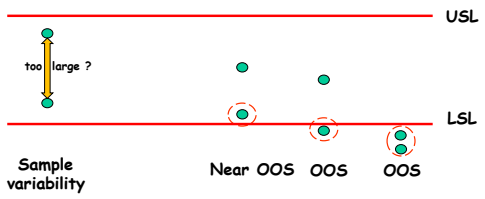
Example

Assay of a drug product: 99.1% ± 1.0% (k=2)

Procedure Precision + Procedure Accuracy → Uncertainty of Result

In the Pharma industry, measurement uncertainty is usually not reported!

When do we particularly consider measurement variability?



Emerging Regulatory Expectation

Two New Draft ICH Guides

ANALYTICAL PROCEDURE DEVELOPMENT Q14
Draft version
Endorsed on 24 March 2022
Currently under public consultation

VALIDATION OF ANALYTICAL PROCEDURES Q2(R2)
Draft version
Endorsed on 24 March 2022
Currently under public consultation

TOTAL ANALYTICAL ERROR

ICH = International council for harmonization of Technical Requirements for Pharmaceuticals for Human Use

TOTAL ANALYTICAL ERROR

Total analytical error (TAE) represents the overall error in a test result that is attributed to imprecision and inaccuracy. TAE is the combination of both systematic error of the procedure and random measurement error. (ICH Q14)

Definitions from VIM, 3rd Ed.

Error
2.16 (3.10)
measured quantity value minus a reference quantity value

random measurement error
2.19 (3.13)
component of measurement error that in replicate measurements varies in an unpredictable manner

systematic error
2.17 (3.14)
component of measurement error that in replicate measurements remains constant or varies in a predictable manner

When to consider error of measurement?

Development/Validation

- Traditional Approach
- Enhanced (QbD) Approach

When to consider error of measurement?

Enhanced (QbD) Approach

Before procedure development:

Analytical Target Profile → ANALYTICAL PROCEDURE DEVELOPMENT Q14 (Draft version, Endorsed on 24 March 2022, Currently under public consultation)

Define allowed Accuracy and Precision criteria or total error in ATP!

The analytical method must be capable of quantifying Atorvastatin in Atorvastatin Tablets from 70% to 130% of the true value with an accuracy of 99.0% - 101.0% and a precision coefficient of variation (CV) of not more than 1.5%.

MHRA Technical Review of MHRA Analytical Quality by Design Project, London, 2019

Note: *"Formal documentation and submission of an ATP is optional but can facilitate regulatory communication irrespective of the chosen development approach."* ICH Q14

When to consider error of measurement?

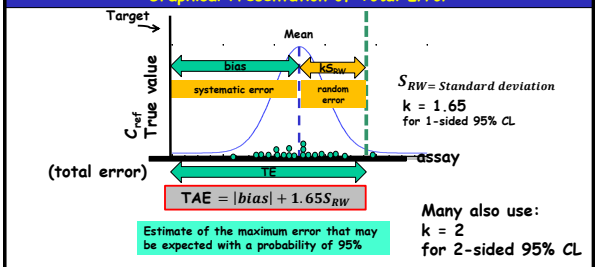
Traditional Approach

During procedure development/validation:

Specify allowed Accuracy and Precision criteria or total error in validation protocol!

Validation Protocol → ANALYTICAL PROCEDURE DEVELOPMENT Q14 (Draft version, Endorsed on 24 March 2022, Currently under public consultation)

Graphical Presentation of Total Error

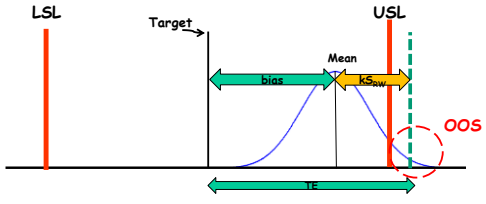


Estimate of the maximum error that may be expected with a probability of 95%

Many also use:
k = 2
for 2-sided 95% CL

James O. Westgard, R N Carey and Svante Wold, **Criteria for Judging Precision and Accuracy in Method Development and Evaluation**, Clinical Chemistry 20(7):825-33, 1974

The allowed TAE should have a limit!



The Purpose of TAE in ICH Documents

Different statistical measures can be used for **evaluation** of the **capability of the method** such as comparison of the TAE (combined accuracy and precision of the measurement) with the specification limit.

Draft ICH Q14

Total analytical error (TAE) ≠ Measurement Uncertainty (MU)

- Analytical procedure
- Single Result

Two Options to evaluate TAE

Draft ICH Q2(R2)

VALIDATION OF ANALYTICAL PROCEDURES Q2(R2)

random error
S

systematic error
$b = \bar{y} - y_{true}$

Accuracy

Precision

Option 1
done as
two separate studies

Option 2
done as
one combined study

Total Analytical Error (TAE)

Evaluation a Combined Accuracy/Precision Study

USP <1210> Example

Assay of main active in a drug substance

Option 2

Option 2

Estimation of TAE

Statistical Intervals

Evaluation a Combined Accuracy/Precision Study

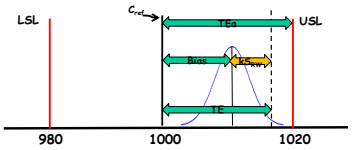
Option 2 Assay of main active in a drug substance

USP <1210> Example: Data

Limits of Individual accuracy:
± 20mg/g of Reference value = 1000mg/g

Lower specification = 980mg/g

Upper Specification = 1020mg/g



Assay, mg/g
996.07
988.43
995.90
987.22
990.53
999.39
996.33
993.67
987.76
Average 992.81
SD 4.440

Estimation of TAE

Option 2 Assay of main active in an a drug substance

Limits of Individual accuracy: ± 20mg/g of Reference value

C_{ref} = 1000mg/g

Lower specification = 980mg/g

Upper Specification = 1020mg/g

Bias = 992.8 - 1000 =-7.2mg/g
(statistically significant)

Assuming as the "true bias":

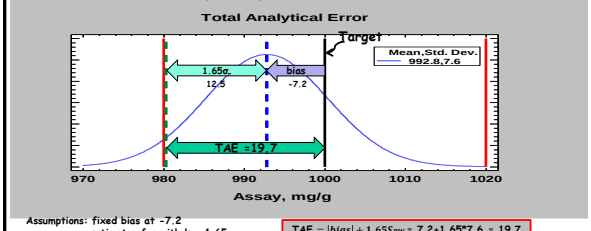
Since n = 9, the expected σ

Assay, mg/g
996.07
988.43
995.90
987.22
990.53
999.39
996.33
993.67
987.76
Average 992.81
SD 4.440
95% Upper confidence bound of SD 7.598

$TAE = |bias| + 1.65S_{RW}$ = 7.2+1.65*7.6 = 19.7

Estimation of TAE

Graphical presentation of TAE



Assumptions: fixed bias at -7.2
estimate of σ with k = 1.65

$TAE = |bias| + 1.65S_{RW}$ = 7.2+1.65*7.6 = 19.7

Conclusion: TAE does not breach the specification limits!

Method of Statistical Intervals

Draft ICH Q2(R2)

Statistical Intervals that include individual test results

Prediction Intervals

they include one future individual measurement

Prediction Interval for Normal Data

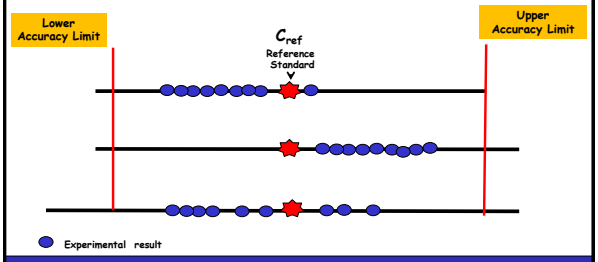
Tolerance Intervals

they include a fixed proportion of individual measurements.

1. Tolerance Interval for Normal Data
2. Tolerance Interval for Non-normal Data

Statistical Intervals

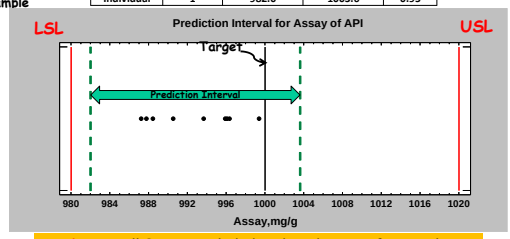
First Requirement: Set Limits for single accuracy results



Method of Statistical Intervals: Prediction Intervals

USP <1210> Example

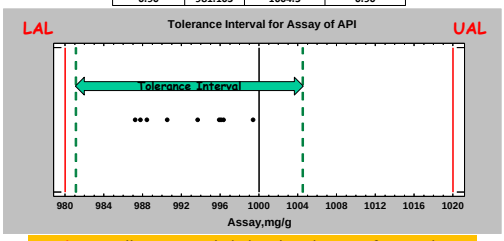
Parameter	Future N	Lower PI	Upper PI	1-Alpha
Individual	1	982.0	1003.6	0.95



Conclusion: all PI are included within the specification limits

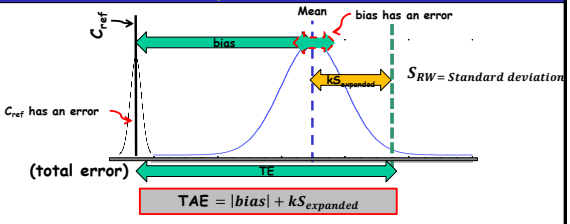
Method of Statistical Intervals: Tolerance Intervals

Proportion	Lower TI	Upper TI	1-Alpha
0.90	981.103	1004.5	0.90



Conclusion: all TI are included within the specification limits

Considering additional variabilities



If uncertainty of C_{ref} and of Bias, then S_{RW} should include the Variabilities of the Cref, the Bias and the Procedure

SUMMARY

- **TAE** reflects the analytical performance of the procedure
- **TAE** is a guiding metric for capability of analytical procedures to provide results within acceptable limits

CONCLUSION

Uncertainty of results should be accounted for in method validation studies

No need to routinely report uncertainty with a test result for a chemical pharmaceutical

For more details

END