

Review on validation of liquid chromatography–mass spectrometry methods

... and more!

Ivo Leito

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Euro Mass Spectrometry 2017



Tutorial
Tutorial review on validation of liquid chromatography–mass spectrometry methods: Part II
 Anneli Kruve^a, Riin Rebane^a, Karin Kipper^a, Maarja-Liisa Oldekop^a, Hanno Evard^a, Koit Herodes^a, Pekka Raviö^b, Ivo Leito^{a,*}

HIGHLIGHTS

- The status of validation of LC-MS methods is comprehensively reviewed.
- Clarity is brought into validation-related terminology.
- Recommendations on difficult validation-related issues in LC-MS are given.

GRAPHICAL ABSTRACT



ARTICLE INFO

ABSTRACT

This is the part II of a tutorial review intending to give an overview of the state of the art of method validation in liquid chromatography mass spectrometry (LC-MS) and discuss specific issues that arise with MS (and MS-MS) detection in LC (as opposed to the “conventional” detectors). The Part II starts with briefly introducing the main quantitation methods and then addresses the performance related to quantification: linearity of signal, sensitivity, precision, trueness, accuracy, stability and measurement uncertainty. The last section is devoted to practical considerations in validation. With every performance characteristic its essence and terminology are addressed, the current status of treating it is reviewed and recommendations are given, how to handle it, specifically in the case of LC-MS methods.

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LC-MS as technique

- The most powerful technique for determination of **low levels** of organics in **difficult matrices**
- LC-MS: **many adjustable parameters**
 - In LC
 - In MS


Checking that the method performs as required is not trivial!

Validation is BIG in LC-MS!


Guidelines?

NordVal Protocol Document 9

NordVal Protocol No. 2, Approved 26 May 2010



Guide in Validation of Alternative Proprietary Chemical Methods



The Fitness for Purpose of Analytical Methods

A Laboratory Guide to Method Validation and Related Topics

2nd Edition 2014

Pure Appl. Chem., Vol. 74, No. 5, pp. 835–855, 2002.
© 2002 IUPAC

INTERNATIONAL UNION OF PURE AND APPLIED CHEMISTRY
ANALYTICAL, APPLIED, CLINICAL, INORGANIC, AND
PHYSICAL CHEMISTRY DIVISIONS
INTERDIVISIONAL WORKING PARTY FOR HARMONIZATION OF
QUALITY ASSURANCE SCHEMES FOR ANALYTICAL LABORATORIES*

HARMONIZED GUIDELINES FOR SINGLE-LABORATORY VALIDATION OF METHODS OF ANALYSIS

(IUPAC Technical Report)

VALIDATION AND EVALUATION OF QUALITATIVE PROPRIETARY METHODS 2

METHOD COMPARISON STUDY 5

INTERMEDIATE STUDY 9


INTERPRETATION 9

PART 2: VALIDATION AND EVALUATION OF QUANTITATIVE PROPRIETARY METHODS 10

A. METHOD COMPARISON STUDY 10

B. INTERMEDIATE STUDY 14

REFERENCES 15



European Medicines Agency

London, 19 November 2009
Doc Ref: EMEA/CHMP/ENP/192217/2009

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

DRAFT

GUIDELINE ON VALIDATION OF BIOANALYTICAL METHODS

DRAFT AGREED BY THE EFFICACY WORKING PARTY

ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION

END OF CONSULTATION (DEADLINE FOR COMMENTS)

Comments should be provided using the template to EDPs@ec.europa.eu

KEYWORDS: CHMP, EMEA, Guideline, validation, bioanalytical method, analyses

September 2009
19 November 2009
31 May 2010

Prepared for publication by
D. THOMPSON¹, STEPHEN L. R. ELLISON², AND ROGER WOOD^{3,4}

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³Institute of Food Research, Norwich Research Park, Colney, Norwich, NR4 7UA, UK

HARMONISED TRIPARTITE GUIDELINE ON HARMONISATION OF TECHNICAL VALIDATION OF PHARMACEUTICALS FOR HUMAN USE

VALIDATION OF ANALYTICAL PROCEDURES: TEXT AND METHODOLOGY Q2(R1)

Current Step 4 version
Parent Guideline dated 27 October 1994
(Complementary Guideline on Methodology dated 6 November 1996 incorporated in November 2005)

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

Guidance for Industry

Bioanalytical Method Validation

Additional copies are available from:
Office of Communications
Division of Drug Information, FDA, Room 2201
Center for Drug Evaluation and Research
Food and Drug Administration
10901 New Hampshire Ave., Silver Spring, MD 20993
Phone: 301-796-3400, Fax: 301-847-8714
druginfo@fda.hhs.gov
<http://www.fda.gov/oc/communications/Information/CustomerSupport.htm>

and/or
Communications Staff, HPT-12
Center for Veterinary Medicine
Food and Drug Administration
7519 Standish Place, Beltsville, MD 20855
(301) 240-3760
<http://www.fda.gov/cvm/Information/Communications/Information/CustomerSupport.htm>

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Veterinary Medicine (CVM)

September 2013
Biopharmaceutics

Revision 1

Validation guidelines

- Generally very useful, but ...
 - Often **inconsistent** terminology
 - e.g. accuracy vs trueness, ...
 - Often very **general**
 - Choosing concentrations? How many replicates? Spiking levels? How many days? ...
 - Sometimes **conflicting** recommendations
 - Usually **LC-MS is not addressed**
 - Except e.g. 2002/657/EC

Our aims were:

1. Give a **critical overview** of the state of the art of LC-MS method validation
 - Including comparisons of the relevant guidance materials
2. Draw attention to the **LC-MS specific aspects**
 - e.g., ionization suppression by matrix effects
3. Give **recommendations on problematic issues** in validation of LC-MS methods

Outcome:

Two-part tutorial review in *Anal. Chim. Acta*



- Tutorial review on validation of liquid chromatography-mass spectrometry methods: Part I. A. Kruve, R. Rebane, K. Kipper, M.-L. Oldekop, H. Evard, K. Herodes, P. Raviio, I. Leito. *Anal. Chim. Acta* 2015, 870, 29-44.

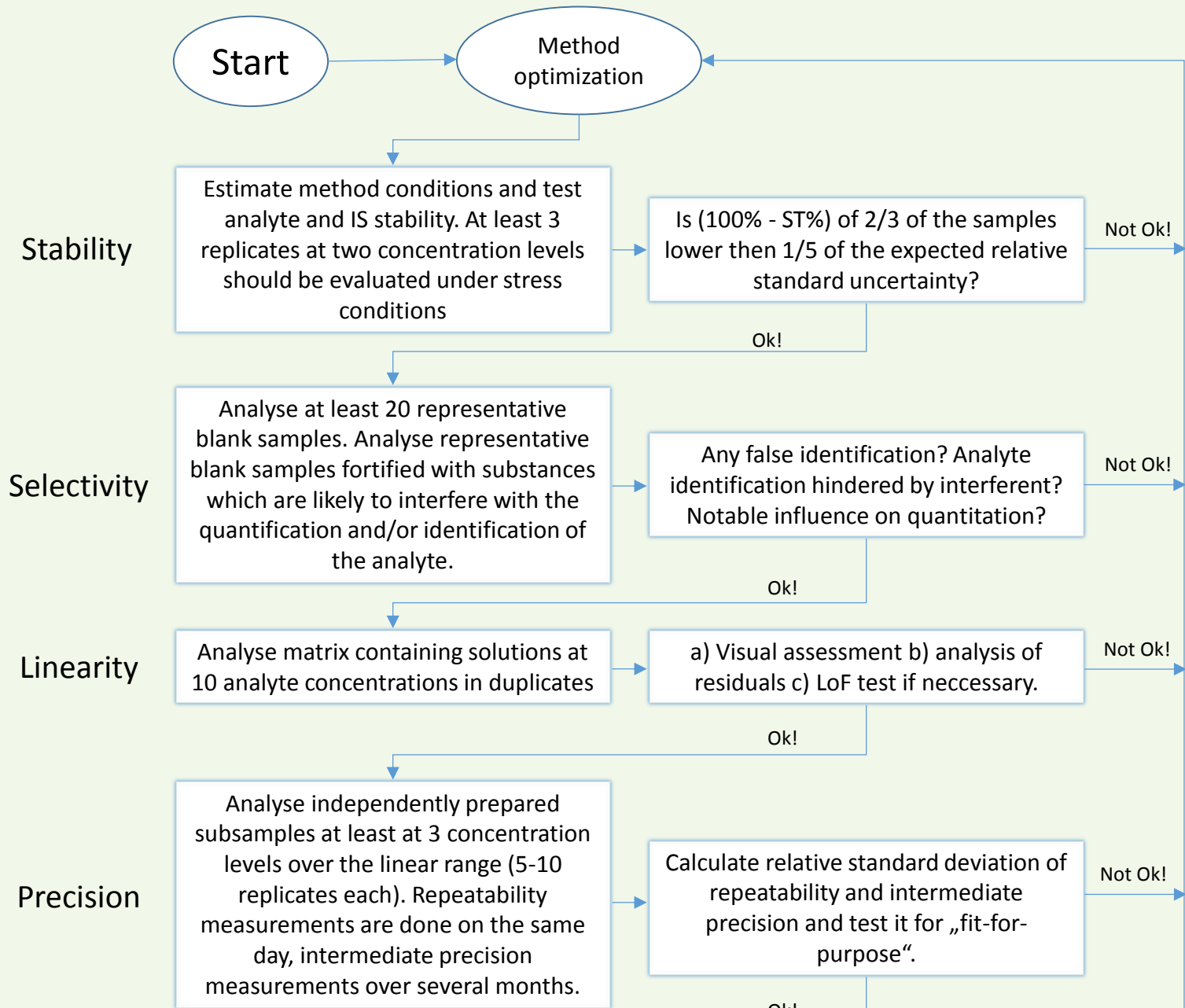
<http://dx.doi.org/10.1016/j.aca.2015.02.017>

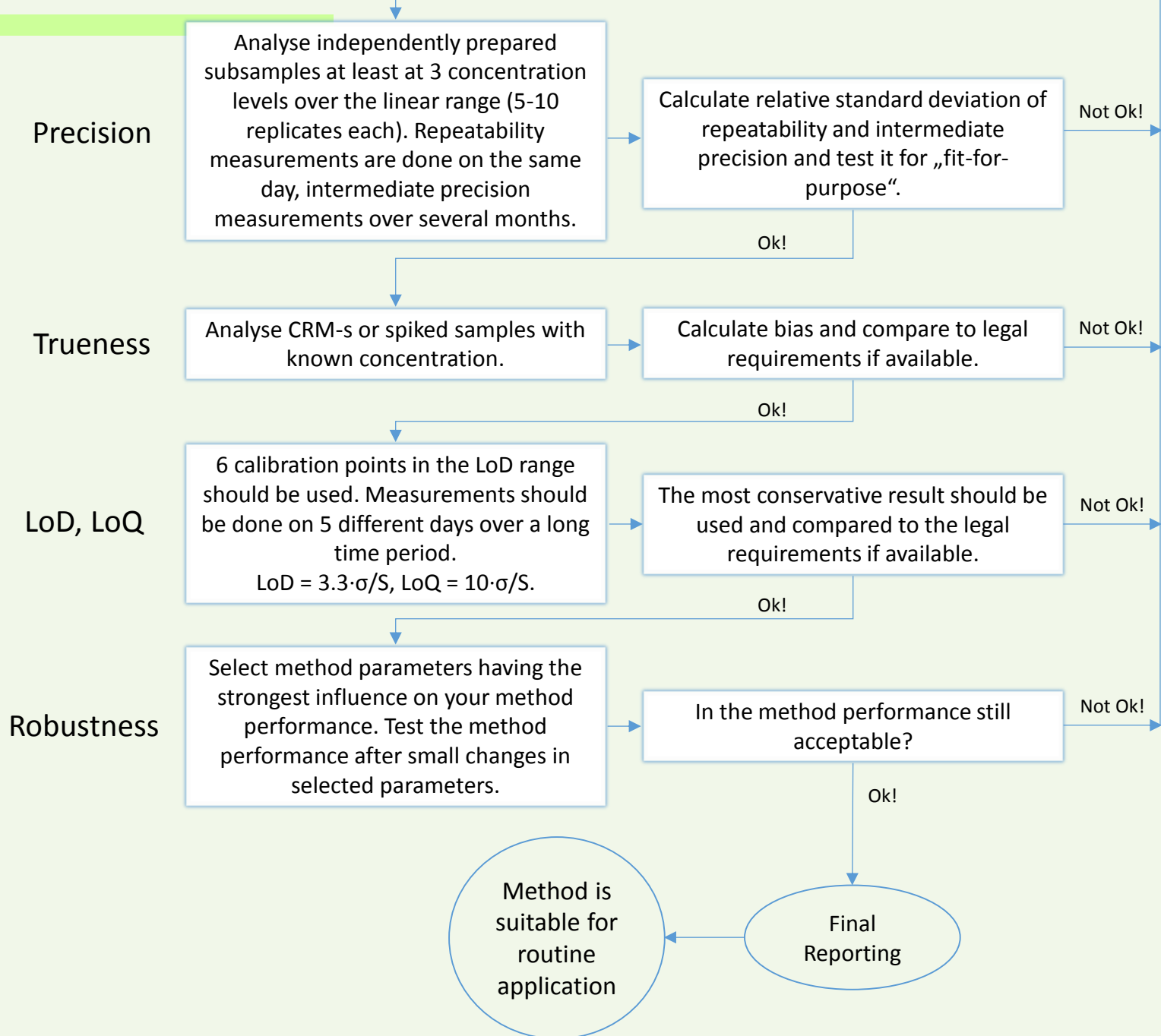
- Tutorial review on validation of liquid chromatography-mass spectrometry methods: Part II. A. Kruve, R. Rebane, K. Kipper, M.-L. Oldekop, H. Evard, K. Herodes, P. Raviio, I. Leito. *Anal. Chim. Acta* 2015, 870, 8-28.

<http://dx.doi.org/10.1016/j.aca.2015.02.016>

Features

- Specific **LC-MS issues**
 - Ionization, matrix effects, MSⁿ selectivity, ...
- Main validation guidelines are **reviewed** and **compared**
 - With every performance parameter
- **Recommendations** are given how to determine performance parameters
 - Synthesis from guidelines and our experience
- **General workflow** of LC-MS method validation is presented





Tutorial review on estimating LoD on the example of LC/MS

Analytica Chimica Acta 942 (2016) 23–39

Contents lists available at ScienceDirect
Analytica Chimica Acta
journal homepage: www.elsevier.com/locate/aca

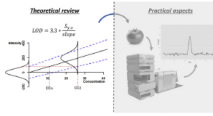
Tutorial
Tutorial on estimating the limit of detection using LC-MS analysis, part I: Theoretical review

Hanno Evard^a, Anneli Kruve, Ivo Leito
^aUniversity of Tartu, Institute of Chemistry, Ravila 14a, Tartu, 50411, Estonia

HIGHLIGHTS

- The concept of limit of detection (LOD) is thoroughly explained.
- Statistical basis of LOD is comprehensively reviewed.
- Mathematical foundations of different LOD determination approaches are compared.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
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Keywords:
Limit of detection
Detection limit
Liquid chromatography
Mass spectrometry
Decision limit
Detection capability

Abstract
A large body of literature exists on the limit of detection (LOD), but there is still a lot of confusion about this important validation parameter. This confusion mainly stems from its statistically complex background. The goal of this two-part tutorial is to discuss and clarify the topic of LOD for practitioners. The two main conclusions of this tutorial are: (1) the choice of how to estimate LOD should be based on the purpose of the analytical method that is being validated (e.g. considerable effort should not be made to estimate LOD for a method that is not used for detecting traces in the vicinity of LOD), and (2) LOD estimates are strongly dependent on different assumptions and the approach used, and therefore caution must be exercised when using the estimate or when comparing different estimates. Part I of the tutorial contains a theoretical discussion (without excessively sophisticated statistics) and part II contains examples based on experimental data. In Part I, LOD and other definitions related to it are reviewed, and their estimation and use are discussed. The assumptions and practicality of different approaches to estimate LOD are compared. Different aspects of the analytical method that strongly influence LOD estimates (e.g. linearity, selectivity and day-to-day variability of LOD) together with experimental design considerations when estimating LOD are discussed. In part II, LOD is estimated for the LC-MS/MS analysis method to detect pesticides on separate days. The performance of different tests on the data necessary for LOD estimation are discussed and the results of different approaches under review in this tutorial are compared. In conclusion, a decision tree is proposed for estimating and monitoring LOD. A detailed working procedure for estimating LOD is presented. Several topics are pointed out in which further research and discussion is needed.

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Abbreviations: LOD, Limit of detection; CC₅₀, Decision limit; CC₉₀, Detection capability; LC-MS/MS, Liquid chromatography tandem mass spectrometry; MRL, Maximum residue limit; SN, Signal-to-noise ratio; S₉₀, Standard deviation of residuals; RSD, Relative standard deviation; CF, Calibration function; SL, Supplementary Information; OLS, Ordinary least-squares regression; WLS, Weighted least-squares regression; 3R, ESI ionization source with additional nebulization capillary.
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E-mail addresses: evardhanno@gmail.com (H. Evard), anneli.kruve@ut.ee (A. Kruve), ivo.leito@ut.ee (I. Leito).

<http://dx.doi.org/10.1016/j.aca.2016.08.043>
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Tutorial
Tutorial on estimating the limit of detection using LC-MS analysis, part II: Practical aspects

Hanno Evard^a, Anneli Kruve, Ivo Leito
^aUniversity of Tartu, Institute of Chemistry, Ravila 14a, Tartu, 50411, Estonia

HIGHLIGHTS

- Different LOD determination approaches are compared from practical LC-MS viewpoint.
- Specific aspects of LC-MS/MS are addressed.
- Recommendations and a flow-chart of LOD determination in LC-MS are given.

GRAPHICAL ABSTRACT



ARTICLE INFO

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Available online 6 September 2016

Keywords:
Limit of detection
Detection limit
Liquid chromatography
Mass spectrometry
Decision limit
Detection capability

Abstract
In part II of this tutorial, the investigated approaches of estimating the limit of detection (LOD) are applied to experimental data from LC-MS measurements. Important practical aspects specific to LC-MS and related to LOD are reviewed. The results of different tests of estimating linearity and selectivity are compared. LOD estimates obtained with different approaches (for both simple characterization of the analysis method and accurate interpretation of the results) are applied to the data and the obtained values are compared. As a conclusion, a decision tree is proposed for estimating LOD for analytical methods using the LC-MS technique.

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2. Important aspects of LC-MS/MS when estimating LOD 41
- 2.1. Fragmentation and identification 41

Abbreviations: LC-MS/MS, Liquid chromatography tandem mass spectrometry; LOD, Limit of detection; SN, Signal-to-noise ratio; RSD, Relative standard deviation; SL, Supplementary Information; MRL, Maximum residue limit; CC₅₀, Decision limit; CC₉₀, Detection capability; CF, Calibration function; OLS, Ordinary least-squares regression; WLS, Weighted least-squares regression; S₉₀, Standard deviation of residuals; ANOVA, Analysis of variance; 3R, ESI ionization source with additional nebulization capillary; y, Signal strength of sample; y₀, Signal strength of blank sample; S, Standard deviation; a, Intercept; b, Slope.
* Corresponding author.
E-mail addresses: evardhanno@gmail.com (H. Evard), anneli.kruve@ut.ee (A. Kruve), ivo.leito@ut.ee (I. Leito).

<http://dx.doi.org/10.1016/j.aca.2016.08.042>
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- Tutorial on Estimating Limit of Detection on the example of LC-MS analysis: Part I. H. Evard, A. Kruve, I. Leito. *Anal. Chim. Acta* 2016, 942, 23-39. <http://dx.doi.org/10.1016/j.aca.2016.08.043>

- Tutorial on Estimating Limit of Detection on the example of LC-MS analysis: Part II. H. Evard, A. Kruve, I. Leito. *Anal. Chim. Acta* 2016, 942, 40-49. <http://dx.doi.org/10.1016/j.aca.2016.08.042>

On-line course: LC/MS Method Validation



Validation of liquid chromat... x

https://sisu.ut.ee/lcms_method_validation/

UNIVERSITY OF TARTU

LC-MS METHOD VALIDATION

- Course introduction
- 1. Validation: General
- 2. Selectivity and identity confirmation
- 3. Linearity of signal, linear range, sensitivity
- 4. Precision
- 5. Trueness
- 6. Precision and trueness: some additional aspects
- 7. Accuracy
- 8. Stability
- 9. LoD and LoQ
- 10. Ruggedness, robustness

VaLChrom

Acknowledgements

References

Glossary

What our participants say?

0:00 / 2:23

Course introduction

<http://www.utv.ee/naita?id=23245>

<https://www.youtube.com/watch?v=jbdA8PnPdLY>

Short description of the course

This is a practice-oriented on-line course on validation of analytical methods, specifically using LC/MS as technique. The course introduces the main concepts and mathematical apparatus of validation, covers the most important method performance parameters and ways of estimating them. The course is largely based on the recently published two-part tutorial review:

Online LC/MS Validation course

- Validation: General
- Performance parameters
 - **Selectivity, Identity**
 - Incl specifics of LC/MS
 - **Linearity**, linear range, **sensitivity**
 - **Precision, Trueness, Accuracy**
 - Including matrix effects
 - **Stability**
 - **LoD, LoQ, CC_{α} , CC_{β}**
 - Including specifics of LC/MS
 - **Ruggedness, Robustness**
- Glossary
- Literature

Course contents

- **Theoretical** basis as well as **practical** skills
- **Detailed** and **example**-based treatment
- More than **50** short **video lectures** by **6 teachers**



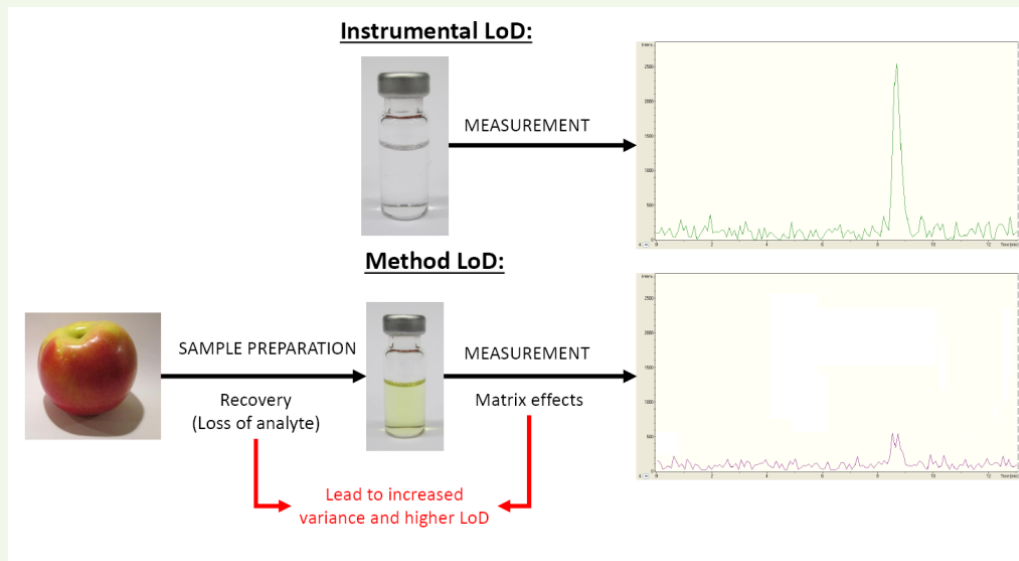
- Excel videos demonstrating calculations
- Numerous **tests** and **calculation exercises**
 - Understanding of main concepts
 - Calculation exercises from **real life** situations
 - **Feedback** is given
- **On-line software** (some functionality)



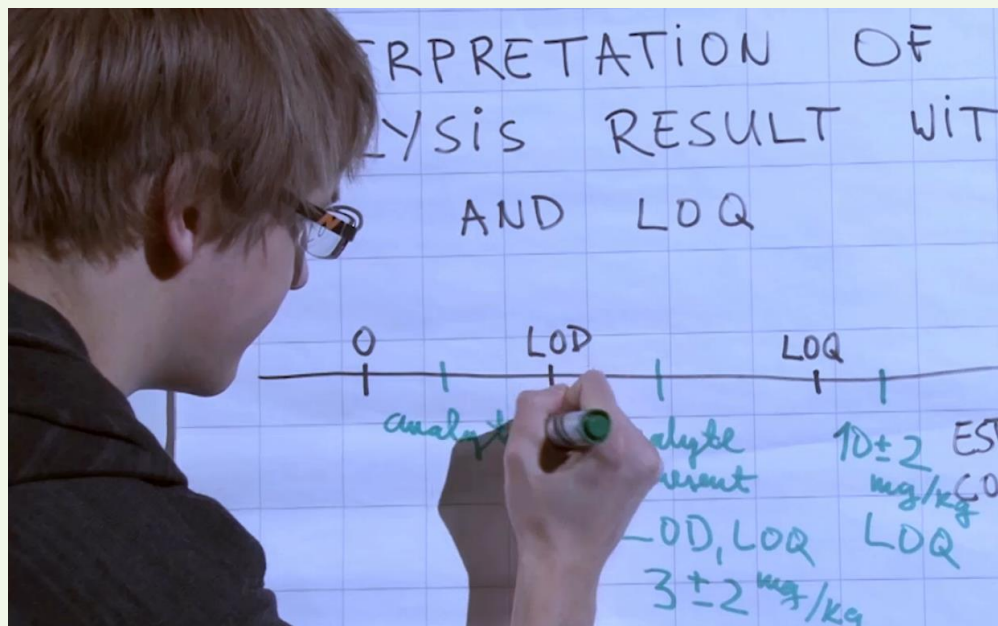
Videos ...

- Using slides:

... or ...



- Pen and whiteboard:

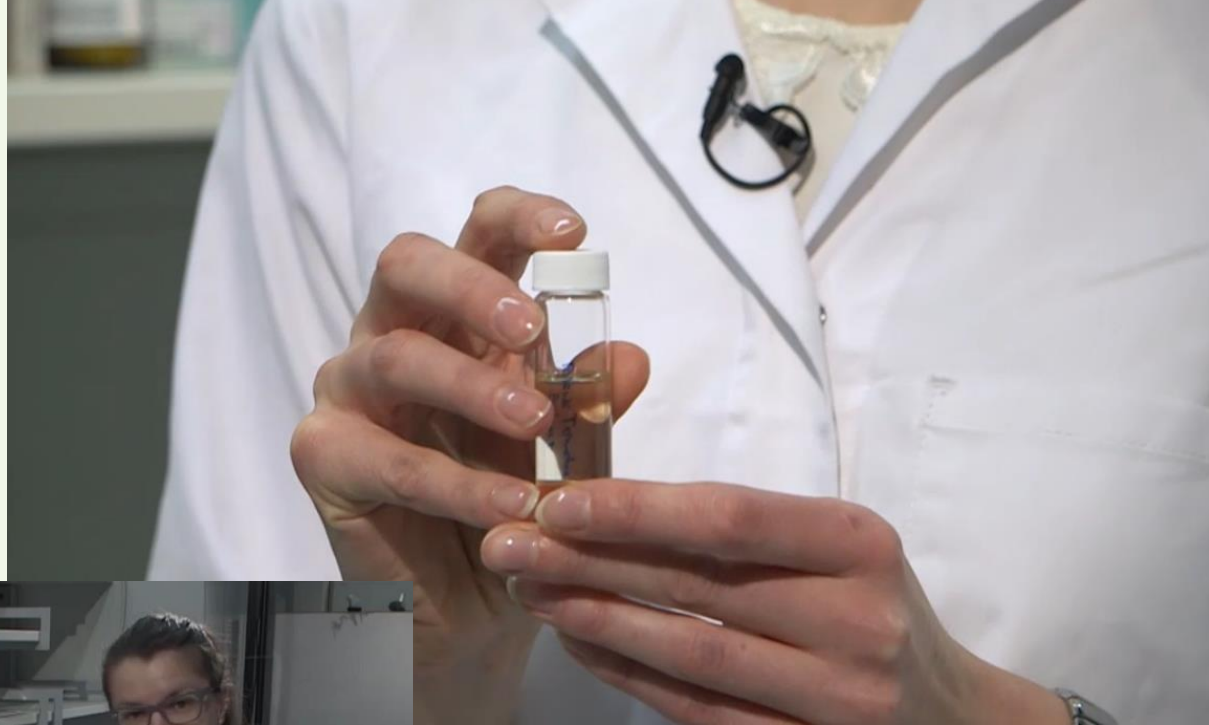


Discussion dialogues

- Two professionals discuss a problematic situations: one asks for help and the other one gives suggestions



Lab videos



Excel videos for calculations

- Initial calculation files can be downloaded

9.3. Estimation of LoD | Va x

https://sisu.ut.ee/lcms_method_validation/93-estimating-lod

BM Ivo M OS U_MOOC OS V_MOOC AK AK EACH AMS AKKI Puhkused GA Gmail Other bookmarks

Excel spreadsheet showing data for 'Chart 2' with columns: Concentration, Intensity, Absolute residuals.

Concentration	Intensity	Absolute residuals
0	1671	-1027.10
3.1E-05	2446	687.508
0.00037	3575	145.78
0.00197	3743	2834.11
0.00454	7579	-8263.99
0.01069	23120	-635.552
0.02317	44792	-3164.78
0	2428	-270.193
3.1E-05	2625	-133.402
0.00037	4701	1271.78
0.00197	6698	120.886
0.00454	16438	4795.01
0.01069	21868	-1887.55
0.02317	48175	-201.781
0	1271	-1227.10
3.1E-05	2457	-301.402
0.00037	4698	1268.78
0.00197	6989	411.886
0.00454	8890	-2752.99
0.01069	24055	2296.45
0.02317	52517	3960.22
0	3101	402.807
3.1E-05	3268	509.598
0.00037	3538	-71.2204
0.00197	6462	-115.114
0.00454	14381	2738.01
0.01069	24049	1193.45
0.02317	47738	-618.781

Chart Title

3:26 / 8:48

Calculating LoD

<http://www.uttv.ee/naita?id=24440>

<https://www.youtube.com/watch?v=u7LCGkFuUFE>

Worked examples

2.3. Selectivity examples

Secure | https://sisu.ut.ee/lcms_method_validation/23-selectivity-examples

Course introduction

1. Validation: General

2. Selectivity and identity confirmation

2.1. Selectivity: LC selectivity

Self-test 2.1

2.2. Selectivity: detector-side (MS) selectivity

Self test 2.2

2.3. Selectivity examples

2.4. Introduction to identity confirmation

Self test 2.4

2.5. Identity confirmation: retention time

2.6. Identity confirmation by MS

2.7. Identity confirmation examples

Self test 2.7

3. Linearity of signal, linear range, sensitivity

4. Precision

5. Trueness

6. Precision and trueness: some additional aspects

7. Accuracy

8. Stability

9. LoD and LoQ

10. Ruggedness, robustness

ValChrom

Acknowledgements

References

Glossary

What our participants say?

2.3. Selectivity examples

Example 1

Not all validation guidelines explicitly specify a required limit for chromatographic peak resolution (R_s). In LC-MS incomplete chromatographic separation of analyte peak from neighboring peaks may or may not cause problems. Often m/z of analyte differs from that of neighboring peaks or unique MRM transition is used. This way the presence of any potentially overlapping peak is simply neglected. However, even though the analytical signals of these interfering compounds are not registered, they can cause matrix effects. Therefore, it is customary to seek for peak resolution of at least $R_s \geq 1.5$.

Chromatogram in Figure 1 was recorded while developing method for compounds A, B, C and D analysis. One MRM trace is presented for each compound and shown in different color. If one hadn't recorded the transition shown in green, this peak would have missed from the chromatogram and one wouldn't have known that compound C (RT 5.33 min) – is present. But this compound could interfere with detection of other compounds, regardless of whether or not its signal is recorded. Therefore, one should make sure that the peak is adequately separated from others.

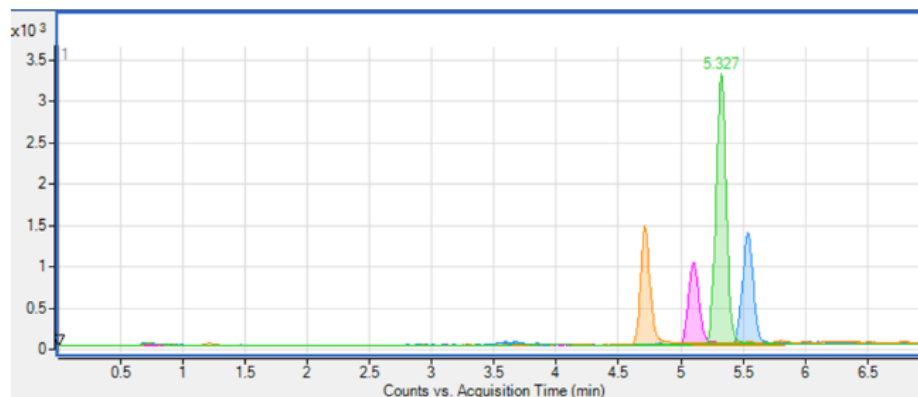


Figure 1. Initial chromatographic separation of compounds A, B, C and D.

Table 1 presents the chromatographic data for above separation. Peak resolution (R_s) from the preceding peak was calculated for the last 3 peaks according to equation 1. It appears that while separation of compounds B and C is at the limit ($R_s = 1.5$), then separation of C and D is not satisfactory ($R_s = 1.4$).

$$R_s = \frac{t_{RB} - t_{RA}}{0.85 \cdot (w_{1/2B} + w_{1/2A})} \quad (\text{Eq 1})$$

Table 1. Peak data of the chromatogram in Figure 1.

Analyte	t_R	$w_{1/2}$	R_s
A	4.710	0.079	
B	5.102	0.094	2.7

Self-tests

Self test 5.2B | Validation

Secure | https://sisu.ut.ee/lcms_method_validation/node/11664/take

★ BM Ivo M U_MOOC V_MOOC AK AK EACH AMS AKKI Puhkused GA Gmail EcoBalt Doodle GP G Radar ModelPr Ilm Other bookmarks

- Course introduction
- 1. Validation; General
- 2. Selectivity and identity confirmation
- 3. Linearity of signal, linear range, sensitivity
- 4. Precision
- 5. Trueness
 - 5.1 Bias and its constituents
 - 5.2 Determining bias in practice
 - Self-test 5.2A
 - Self test 5.2B**
 - 5.3 Qualitative estimation of matrix effect
 - 5.4 Quantitative estimation of matrix effect, recovery and process efficiency
 - Self-test 5.4A
 - Self-test 5.4B
 - Self-test 5.4C
- 6. Precision and trueness: some additional aspects
- 7. Accuracy
- 8. Stability
- 9. LoD and LoQ
- 10. Ruggedness, robustness
- ValChrom
- Acknowledgements
- References
- Glossary
- What our participants say?

Self test 5.2B

You are validating a LC/MS analysis of L-PFOS in ground water and for trueness evaluation, you are analyzing a commercial CRM sample.

CERTIFICATE OF ANALYSIS

	Mass Concentration	
	Certified value ²⁾ [ng/L]	Uncertainty ³⁾ [ng/L]
Perfluorobutane sulfonate (PFBS) ¹⁾	5.5	1.4
Perfluorohexane sulfonate (PFHxS) ¹⁾	3.6	1.0
Linear perfluorooctane sulfonate (L-PFOS) ¹⁾	9.6	1.7
Perfluoropentanoic acid (PFPeA) ¹⁾	4.0	1.0
Perfluorohexanoic acid (PFHxA) ¹⁾	7.4	1.0
Perfluoroheptanoic acid (PFHpA) ¹⁾	3.7	0.7

1) As defined by using liquid chromatography mass spectrometry.
2) Certified values are values that fulfil the highest standards of accuracy and represent the unweighted mean value of the means of accepted sets of data, each set being obtained in a different laboratory with a method of determination including liquid chromatography mass spectrometry. Sulfonates mass concentrations are expressed on anion basis. The certified values and their uncertainties are traceable to the International System of Units (SI).
3) The uncertainty of the certified values is the expanded uncertainty with a coverage factor $k = 2$ corresponding to a level of confidence of about 95 % estimated in accordance with ISO/IEC Guide 98-3, Guide to the Expression of Uncertainty in Measurement (GUM:1995), ISO, 2008.

This certificate is valid for one year after purchase.

You are using matrix matched calibration.

Your analysis data is:

Number of result	C (ng/L)
1	13.96
2	14.00
3	12.51

- Calculate bias:
Answer:
Enter your answer here
- Relative bias:
Answer:
Enter your answer here

Online validation software (some functionality is available)



Adding new or editing existing validation.

When adding new validation or opening existing validation for editing, the following screen appears. Required fields are marked accordingly.

Validations

Caffeine

VALIDATION PARAMETERS EXPERIMENTAL RESULTS REPORT

VALIDATION PARAMETERS I VALIDATION PARAMETERS II

VALIDATION PARAMETERS I

Save and reload Go level up

Name

Caffeine

Status

in work

Validation guide

NordVal EMEA FDA ICH AOAC EuroChem IUPAC

Parameters for validation

Linearity	LoD	LoQ	Precision	Trueness	Specificity	Uncertainty
<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Comment

0/2000

Select unit of concentration

ppb

Select unit of signal

cps

Select unit of time

Select unit of mass

Select unit of volume

Next >

„Usage modes“

**LC/MS Method
Validation**
sisu.ut.ee/lcms_method_validation/

**On-line course for
independent
learning**
*available any time
anywhere*

Course material
*for running training
courses e.g. by labs*

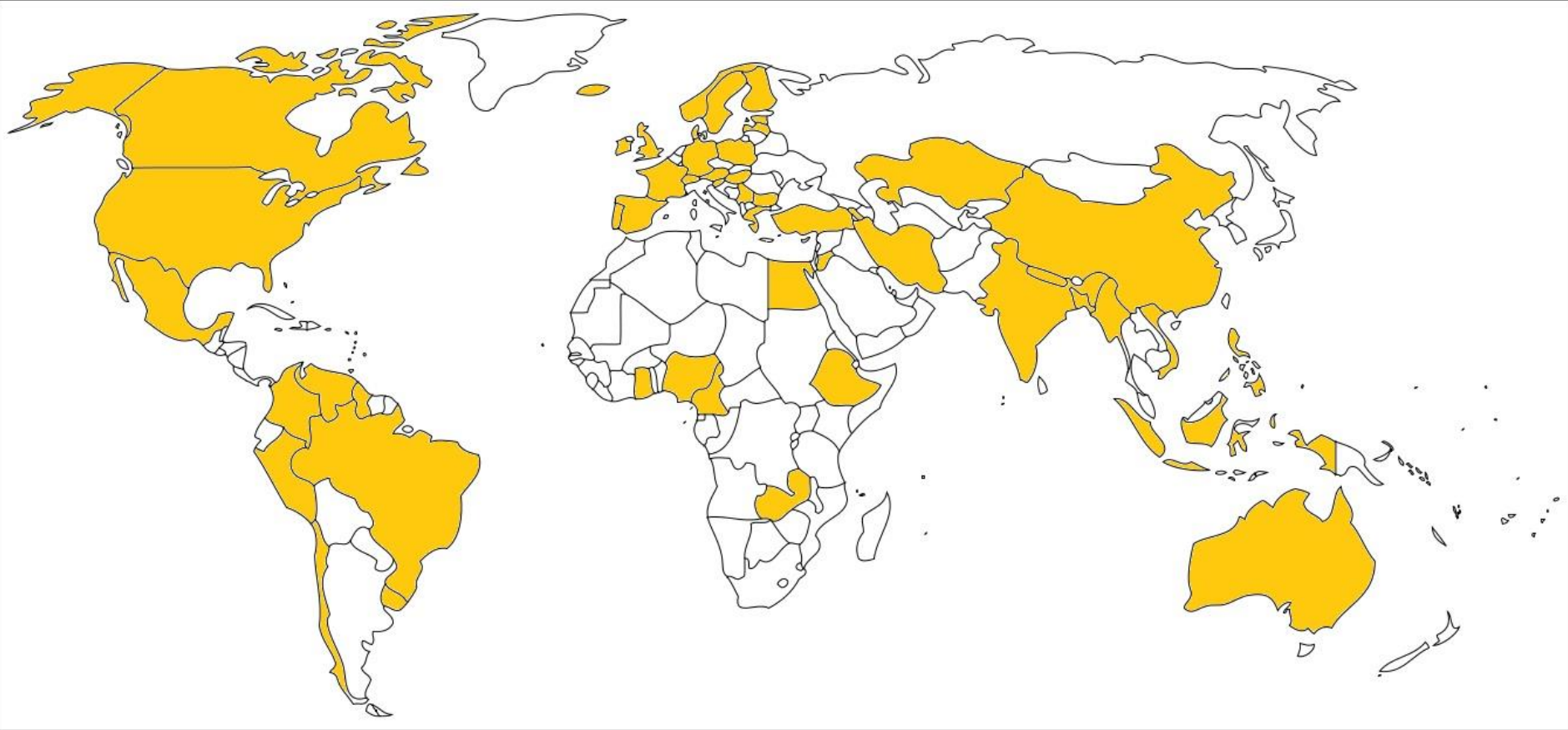
**On-line reference
point**
*of terminology,
explanations and
self-testing
possibilities*

**Support to
university teaching**
*Students can be
directed here e.g. for
self-testing*

**Running as
MOOC**
*with registered
participation, on-line
counseling, graded
tests and certificate*

MOOC: Autumn 2016 edition

303 registered participants from 61 countries



Overall completion rate: 55%

Completion rate of those who started: 75%

Interested?

- Without registration: the materials are freely available 24/7

sisu.ut.ee/lcms_method_validation/

- Registered participation:
 - Forums
 - Graded tests
 - Certificate

LC/MS Validation MOOC – second edition: Winter 2017-2018
Registration will open in autumn 2017

Many thanks to the team!

Course development:



Anneli
Kruve



Koit
Herodes



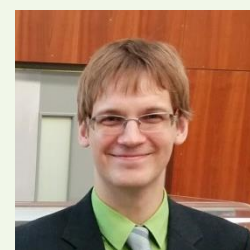
Maarja-Liisa
Oldekop



Riin
Rebane



Karin
Kipper



Hanno Evard

Video, web design, admin:



Irja Helm



Triin Marandi



Lehti Pilt



Esta Pilt



Toomas Petersell
Juho Jalviste

Thank you for your attention!

LC/MS Validation MOOC – second edition: Winter 2017-2018
Registration will open in autumn 2017

sisu.ut.ee/lcms_method_validation/

Questions, requests:
Ivo.leito@ut.ee