Developing Reference Measurement Procedures in Compliance with ISO 15193

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Differences between Routine Analysis and RMP

RfB
Referenzinstitut
für Bioanalytik

Lab 1

Lab 2

Definition of RMP

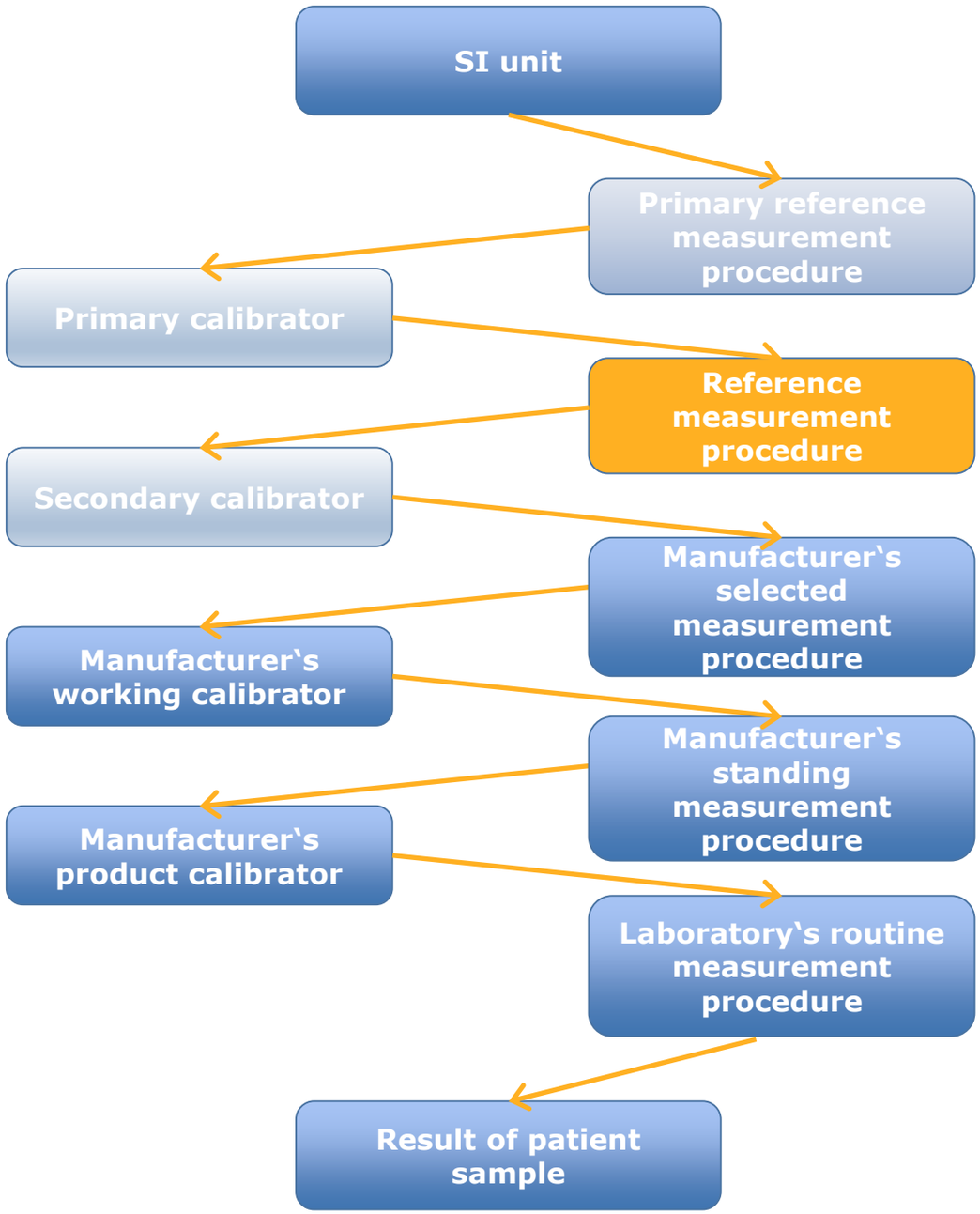
Reference Measurement Procedure

Measurement procedure accepted as providing measurement results fit for their use in assessing measurement trueness of measured quantity values obtained from other measurement procedures for quantities of the same kind, in calibration, or in characterizing reference materials.

(ISO/IEC Guide 99:2007, 2.7)

- The RMP has to be validated for the quantity which is intended to be measured.
- RMP can be part of a reference measurement system to assess measurement trueness of other measurement procedures within a calibration hierarchy.

Role of RMP



RMPs that comprise elements of a calibration hierarchy and that meet the requirements of ISO 15193 has to be considered as MPs of higher metrological order.

ISO 15193

In vitro diagnostic medical devices –

Measurement of quantities in samples of biological origin –

Requirements for content and presentation of reference measurement procedures (ISO 15193:2009)

Mandatory Elements of RMP
according to ISO 15193

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Title page

Warning and safety precautions

Title of RMP

Scope

Measurement principle and method

Reagents

Apparatus

Sampling and sample

Preparation of measuring system and analytical portion

Operation of measuring system

Data processing

Analytical reliability

Validation by inter-laboratory comparisons

Reporting

Quality assurance

Date of authorization and revision

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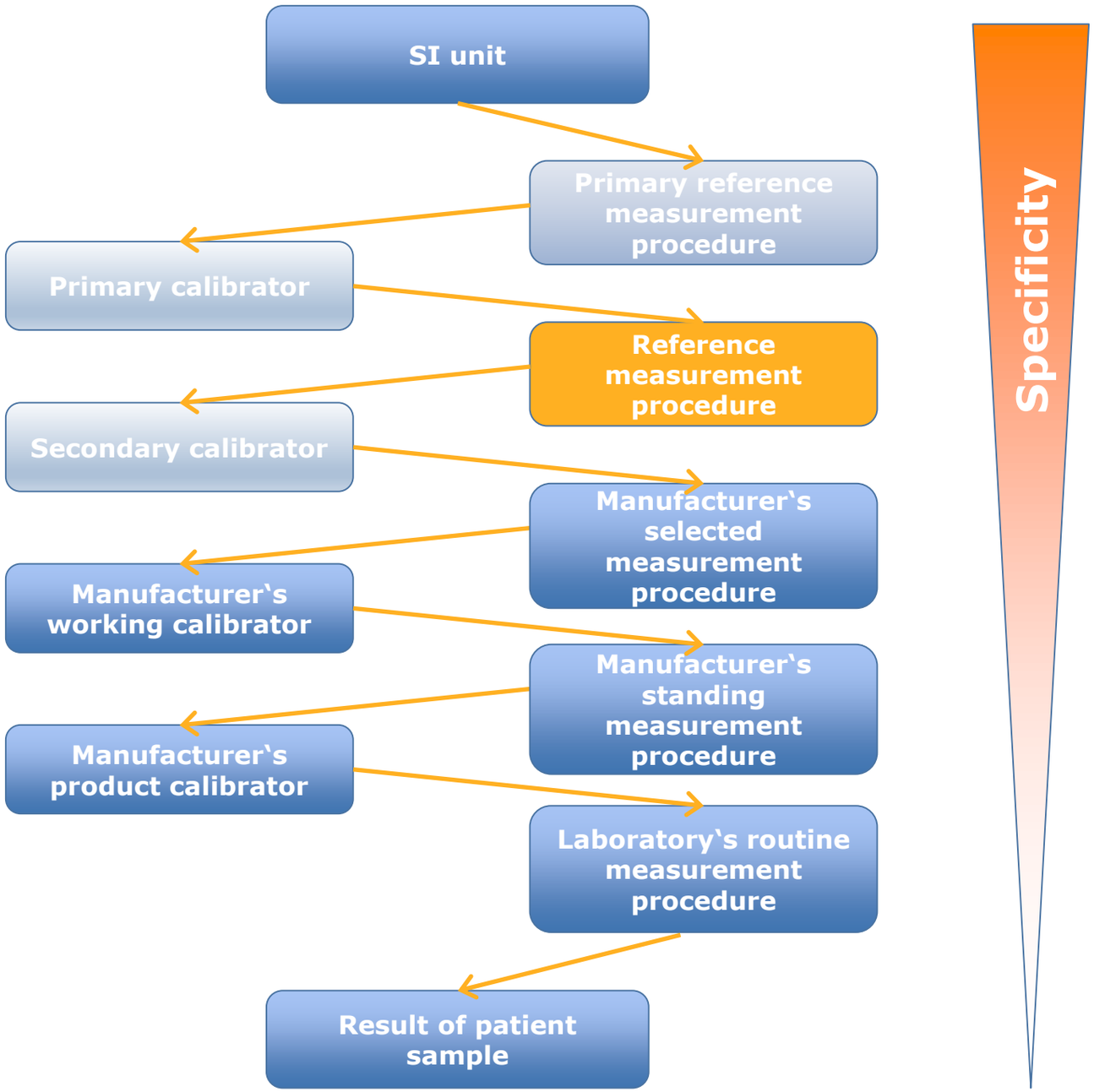
Measurement principle and method



Measurement principle e.g.IDMS

Method description comprises all steps like addition of internal standard, preparation of samples and calibrators, quantitative determination, and calculation.

Preparation of measuring system and analytical portion

Calibration

The principle, materials and steps have to be described in detail:

- choice of calibration procedure (number of calibration points, equation, bracketing, ...)
- suitable calibrators (check for metrological traceability, ...)
- calibrator preparation (e.g. gravimetric/volumetric preparation, standard addition technique, ...)
- measurement of calibrators
- method of computing a monotonic calibration function and the measurement uncertainties of its parameters
- acceptance of calibration function
- time interval of recalibration within and/or between series

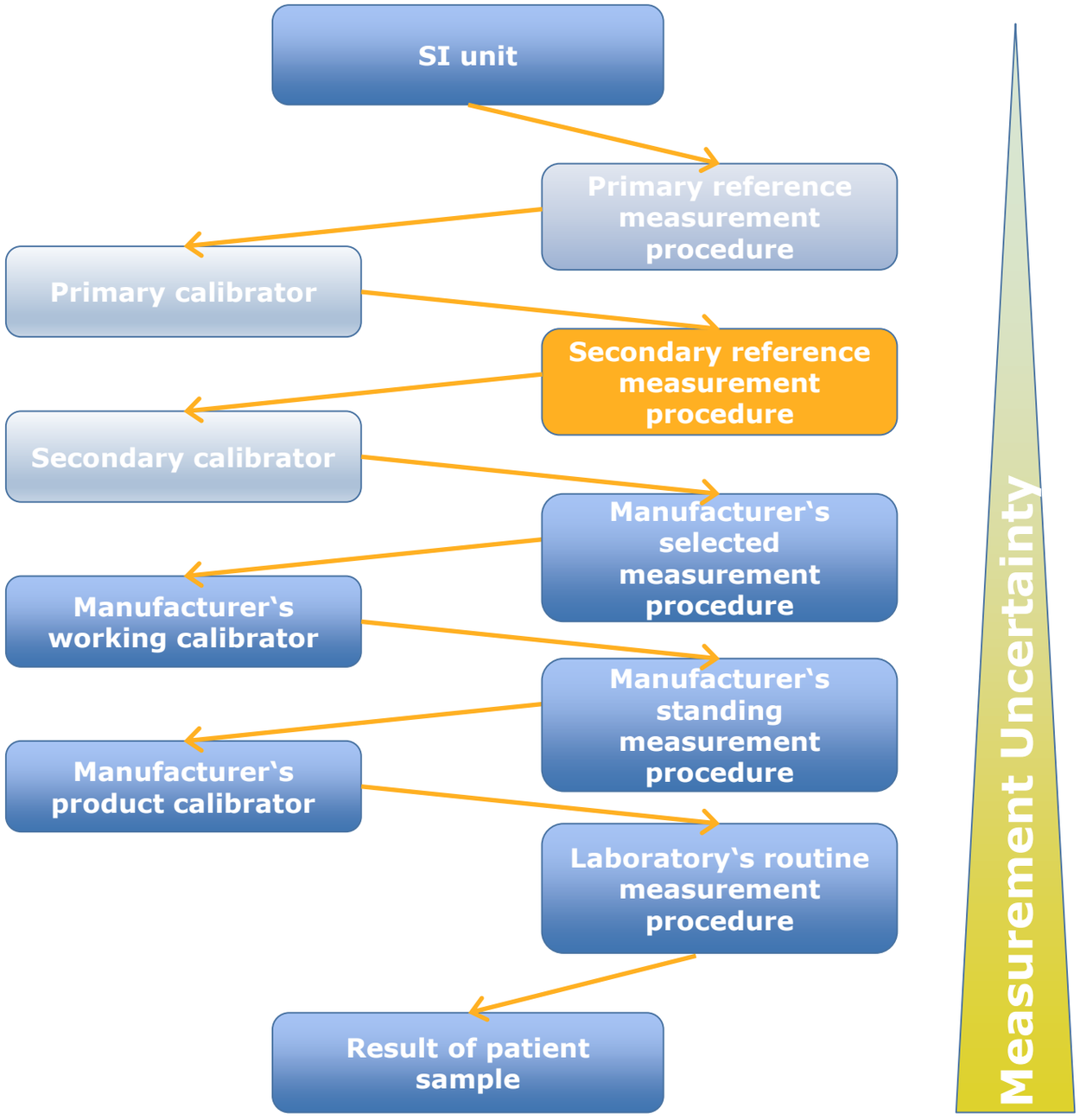
Data Processing

Calculation of measurement results

The procedure for calculation has to include:

- processing of validated initial data (including blank correction, repeated values)
- construction of measuring function
- the quantity and its measurement unit
- the model for statistical treatment
- the complete equation for calculation
- the description of any algorithm used
- the minimum number of points
- the number of replicate measured values
- calculation of measurement uncertainty

Measurement Uncertainty



Each values has its measurement uncertainty.

It should be an objective in developing a RMP to eliminate all known causes of effects as far as possible.

But note:

It's not getting less, if you don't look at.

Analytical reliability

Measurement uncertainty (MU)

MU comprises many components. The MU of random effects should be evaluated from statistical distribution of values from series of measurements.

MUs caused by systematic effects have to be add to the uncertainty budget, e.g. impurity of RM, calibrated volumetric equipment , or balances

Validation of a RMP

A RMP should be validated to show that it is fit for its intended use.

The validation has to be as extensive as necessary and includes:

- comparison of results achieved with other procedures
- interlaboratory comparisons
- performance validation using reference materials (matrix-based CRM)
- assessment of the measurement uncertainty based on scientific understanding and practical experience.

Interlaboratory comparisons

RELA - Homepage
External quality control for Reference Laboratories

Home -

Welcome
- login
- Registration/ Accou

RELA in progress
- order RELA 2018
- enter RELA 2018 results

former RELA results
Choose year...

RELA - IFCC External Quality assessment scheme for Reference Laboratories in Laboratory Medicine

This site gives you all the information you will need for participating in the RELA scheme.

Time schedule for the annual surveys (may vary slightly)

Announcement: September 1
Deadline for ordering: September 30
Shipment of samples: October 15
Deadline for transmission of results: April 15 (following year)
Reporting results to participants: May 15
Publishing results on this website: June 15

Please refer to the navigation area on the left to (for instructions see our new RELA web manual)
- register or log in
- order the survey
- entering your results
- get the evaluation of past surveys

The whole RELA process is described in detail in the **IFCC-RELA-EQAS procedure manual**.

Offered measurands:
Metabolites and substrates (META): total cholesterol, total glycerol, creatinine, uric acid, urea, glucose, total bilirubine
Electrolytes (ELEC): sodium, potassium, chloride, calcium, lithium, magnesium
Enzymes (ENZY): ALT, AP, AST, CK, LDH, GGT, amylase
Glycated hemoglobins (GLYC): HbA1c
Proteins (PROT): total protein
Hormones (HORM): aldosterone, cortisol, progesterone, testosterone, estradiol-17ß, estriol, 17-OH-progesterone
Thyroid hormones (THYR): total thyroxine (TT4), total tri-iodthyronine (TT3),
Therapeutic drugs (THER): digoxin, digitoxin, theophylline
Vitamins (VITA): 25-OH-vitamin D3

Interlaboratory comparisons

Example: Estriol, unconjugated

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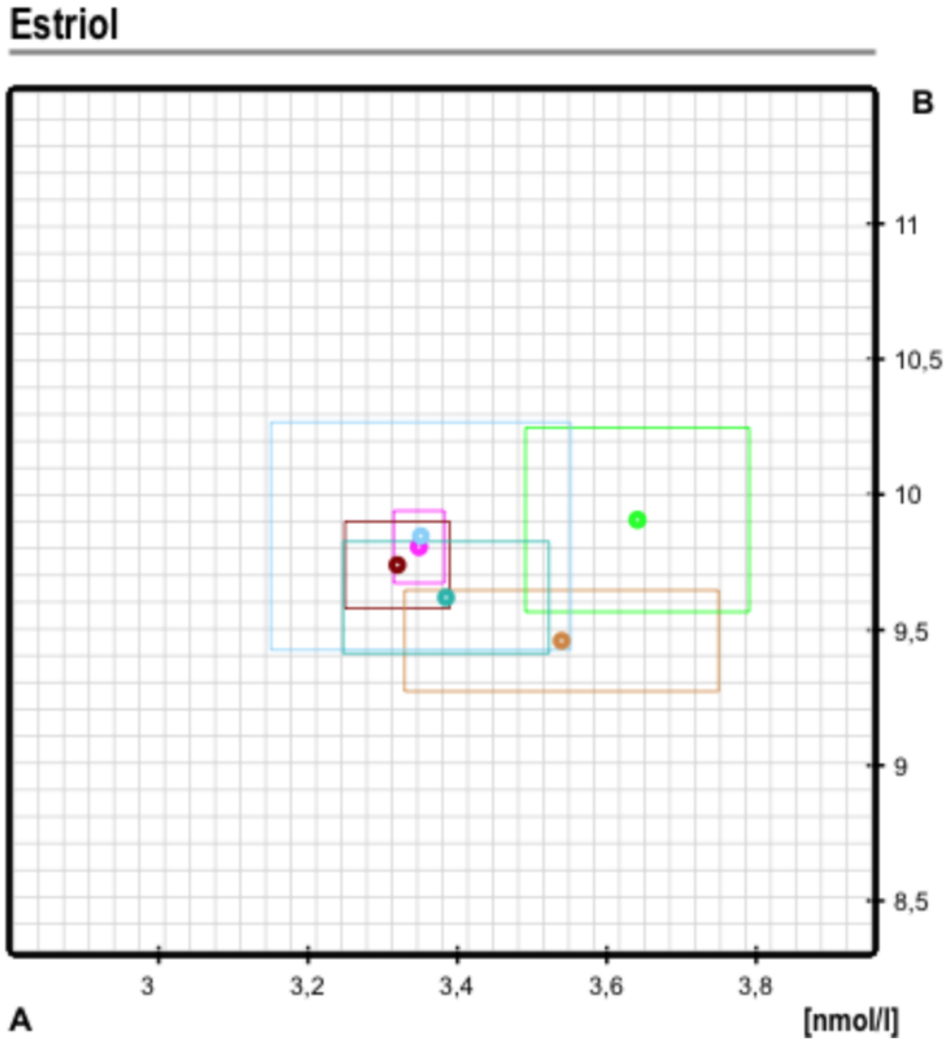
RELA 2017

All or choose Lab ...

select lab analytes | full address

Estriol | show result plot

with limits of equivalence



For highlighting a specific result please click on the corresponding result line.

Result lines printed in bold indicate JCTLM listed services.

Labcode	A	e.u. A	B	e.u. B	Method
1	**3.349**	**0.033**	**9.81**	**0.13**	**ID/GC/MS**
51	3.32	0.07	9.74	0.16	ID/LC/MS/MS
54	3.54	0.21	9.46	0.19	ID/LC/MS/MS
65	**3.64**	**0.15**	**9.91**	**0.34**	**ID/LC/MS/MS**
87	3.35	0.2	9.85	0.42	ID/LC/MS/MS
134	3.385	0.137	9.619	0.206	ID/LC/MS/MS

grey lines indicate a one-percent grid

e.u. - expanded uncertainty

Different RMP

2 labs listed JCTLM

Comparison of MU

A Min 1.0 %
Max 5.9 %

B Min 1.3 %
Max 4.3 %

MUs do not have to be the same. Comparison of MUs can give hints of underestimation ⬇ or errors in processing RMP ⬆.

Results of candidate RMP can be compare to established (and JCTLM listed) RMP, too.

JCTLM and its database

Bureau International des Poids et Mesures

Database of higher-order reference materials, measurement methods/procedures and services

JCTLM
Accurate results for patient care

JCTLM WG reviews nominations of RMP based on ISO Guide 15193 and their individual expertise.

Currently 194 RMP for 81 unique measurands are listed in the JCTLM database; 23 RMP for 20 different peptides.

https://www.bipm.org/en/committees/jc/jctlm/jctlm-nominations-and-review.html

RMP – JCTLM Database Entry

Isotope dilution mass spectrometry methods for amyloid beta 1-42 in other ▸ 2D-UPLC-tandem mass spectrometric method for analysis of amyloid beta 1-42 in human CSF	
Applicable matrice(s)	frozen human cerebrospinal fluid (CSF)
Full description of technique(s)	Liquid chromatography tandem mass spectrometry, solid phase extraction
Quantity	Mass concentration
Applicable range	100 pg/mL to 3000 pg/mL
Expected uncertainty (level of confidence 95%)	14.3 pg/mL to 355.2 pg/mL
Reference(s)	Qualification of a surrogate matrix-based absolute quantification method for Amyloid β_{42} in human cerebrospinal fluid using 2D UPLC-Tandem Mass Spectrometry, Korecka M et al., *Journal of Alzheimer's Disease (JAD)*, 2014, **41**(2), 441-451
Comparability assessment study(ies)	Clinical comparison with immunoassay as cited in: Korecka M et al., *JAD*, 2014, **41**(2), 441-451 Round robin test on quantification of amyloid-β-1-42 in cerebrospinal fluid by mass spectrometry, Pannee J et al., *Alzheimer's and Dementia*, 2016, **12**(1), 55-59
Comment(s)	The reference measurement method, C12RMP1, for quantification of Aβ42 in cerebrospinal fluid was developed and validated by the Biomarker Research Laboratory of Perelman School of Medicine, University of Pennsylvania
JCTLM DB identification number	C12RMP1

Use of RMP

RMP can be used

- to assess performance properties of routine procedures,
- to demonstrate if there is a functional interchangeability of different routine procedures,
- to assign values to reference materials used for calibration or trueness control (e.g. EQA schemes),
- to detect analytical influence quantities in patient samples.

Conclusions

Developing a RMP comprises many different elements:
from the detailed description of the measurement principle and all analytical steps to the estimation of measurement uncertainty, extensive analytical reliability and an unprejudiced validation.

The international standard ISO 15193 gives guidance through this process.

If an experienced laboratory worker applies your written RMP and produces measurement results with the same measurement uncertainty as you did, than the intention of the standard is met.