2018 PROTEIN AND PEPTIDE THERAPEUTICS AND DIAGNOSTICS: RESEARCH AND QUALITY ASSURANCE INTERNATIONAL WORKSHOP

Measurement and Standards, Quality and Safety

October 10-12, 2018
Chengdu, Sichuan, China

PPTD 2018

Linking ISO 15195 accreditation with the performance of IFCC reference measurement procedures for enzymes

Mauro Panteghini

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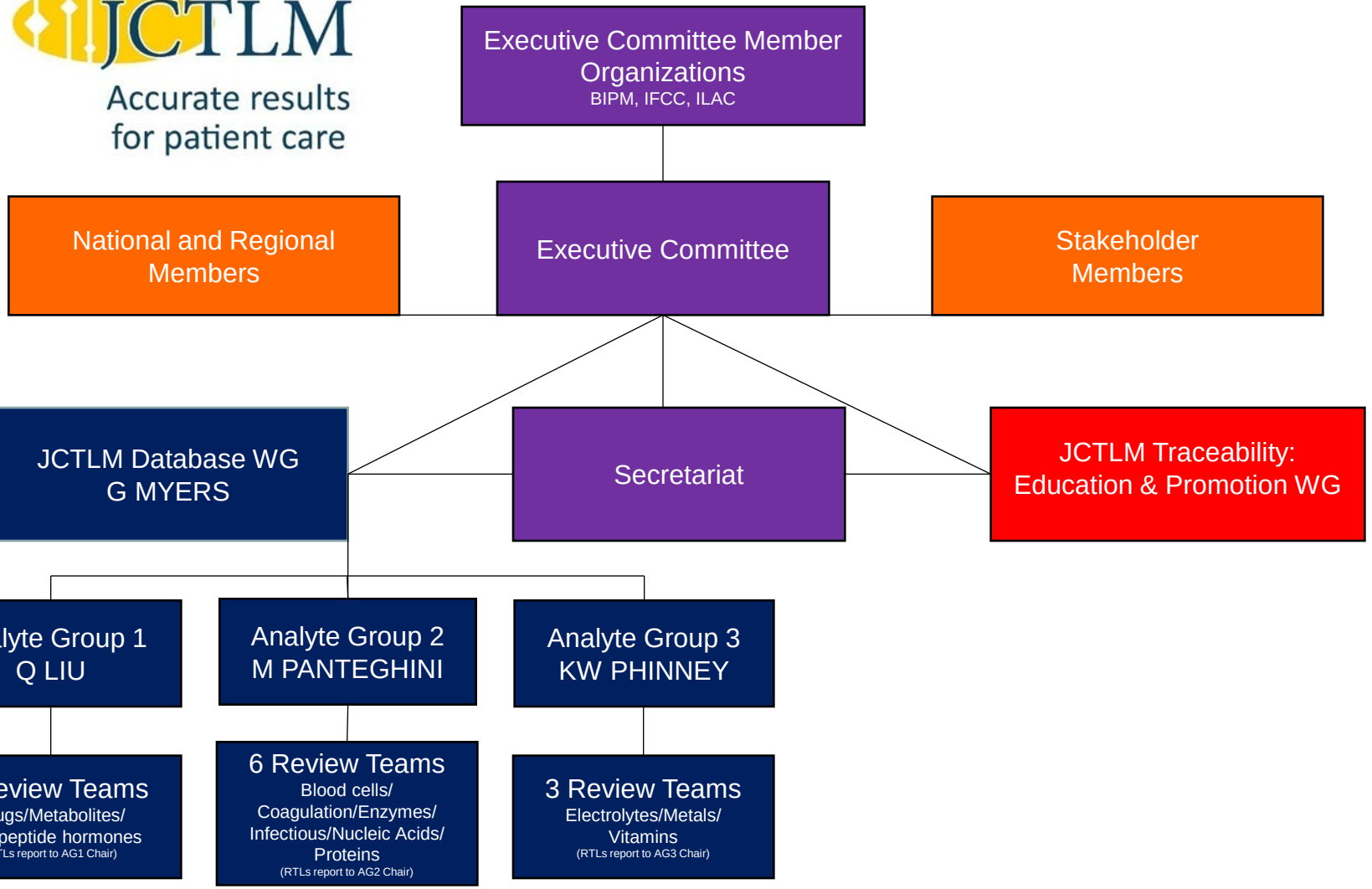
Centre for Metrological Traceability in Laboratory Medicine (CIRME)

site: http://users.unimi.it/cirme

JCTLM

Accurate results for patient care



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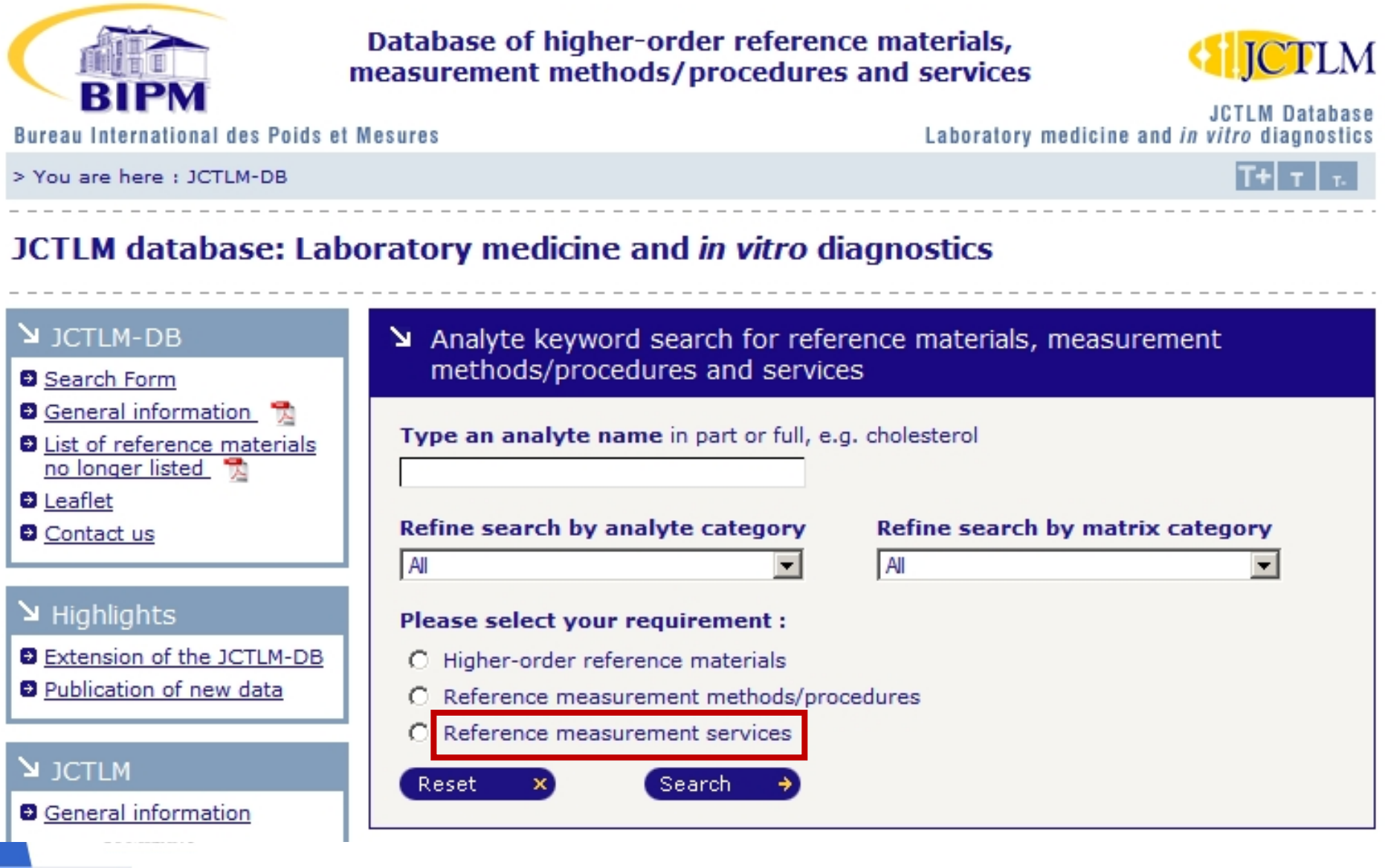
JCTLM Database : www.bipm.org/jctlm/



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‘Enzymes’ Review Team

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Basic principles for reviewing are laid down in the document JCTM DBWG-P-03-B2

Review of Reference Measurement Services from laboratories that are accredited as calibration laboratories (ISO/IEC 17025 and ISO 15195)			JCTLM Accurate results for patient care
JCTLM DBWG-P-03-B2 Version : 5.0	Date : 27 January 2017	Authorized : JCTLM Executive	

Review of Reference Measurement Services from laboratories that are accredited as calibration laboratories (ISO/IEC 17025 and ISO 15195)

1. Purpose

This procedure describes the processes to be followed by review teams for reviewing nominations of reference measurement services provided by reference laboratories that are accredited according to ISO/IEC 17025 and ISO 15195 as calibration laboratories.

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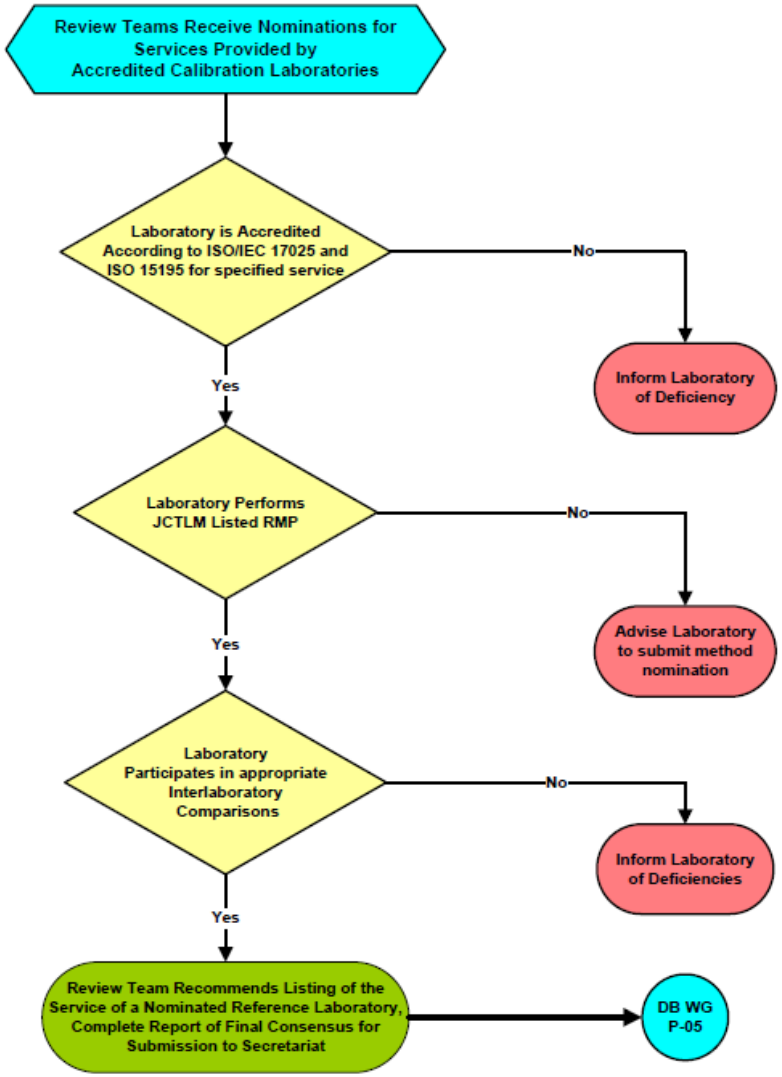
PROCESS FOR REVIEW OF REFERENCE MEASUREMENT SERVICES



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Reference Measurement Services assessed on basis of:

- Metrological level of the reference measurement procedures used (must be listed in the JCTLM database)
- Accreditation to ISO 17025 and ISO 15195 as a calibration laboratory
- Regular (at least annual) participation in inter-laboratory comparisons for reference laboratories

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JCTLM database

Enzymes reference measurement procedures

Enzyme	Reference
ALP	*Clin Chem Lab Med* **2011**;49:1439-46
ALT	*Clin Chem Lab Med* **2002**;40:718-24
Amylase	*Clin Chem Lab Med* **2006**;44:1146-55
AST	*Clin Chem Lab Med* **2002**;40:725-33
CK	*Clin Chem Lab Med* **2002**;40:635-42
GGT	*Clin Chem Lab Med* **2002**;40:734-38
LDH	*Clin Chem Lab Med* **2002**;40:743-48

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Requirements for reference measurement services

Use the following core requirement standards:

- ISO/IEC 17025 (2005, now 2017): General requirements for the competence of testing and calibration laboratories
- ISO 15195 (2003): Laboratory Medicine - Requirements for reference measurements laboratories

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- Regular on-site assessments (ILAC) against ISO/IEC 17025 and ISO 15195
- ISO/IEC 17025 provides general requirements for laboratories (management systems and technical)
- ISO 15195 provides a sector-specific application of ISO/IEC 17025 (i.e. Laboratory Medicine) and provides additional information in relation to the use of reference measurement procedures and appropriate reference materials
- The combination of standards provides the necessary emphasis on metrological aspects, particularly traceability, measurement uncertainty and method validation

Standard under Revision

ISO 15195: 2003

Laboratory Medicine – Requirements for Reference Measurement Laboratories

ISO/DIS 15195 Draft Document

Laboratory Medicine – Requirements for the competence of calibration laboratories using reference measurement procedures

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ISO

ISO TC212 WG2 Project
ISO 15195 Standard under revision

Scope and rationale

- Title revised to avoid ambiguity concerning the types of laboratories covered by this standard
- Specifies requirements for competence in performing reference measurement procedures in Laboratory Medicine, using ISO/IEC 17025: 2017 as a normative reference; lists additional requirements beyond ISO 17025
- Full alignment with ISO 17025: 2017 as normative reference reduces accreditation complexity for covered laboratories (**redundant accreditation to both 17025 and 15195**)

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ISO

WORK IN PROGRESS

ISO TC212 WG2 Project
ISO 15195 Standard under revision

- Robert Wielgosz (BIPM), Project Lead
- Sept 2017 CASCO developing next ed. of normative reference, ISO/IEC 17025: 2017
- Path forward:
  - ISO 15195 revision started when FDIS 17025 document available (Autumn 2017)
  - New draft, fully aligned to FDIS 17025: 2017, was reviewed at the Nov 2017 TC212 WG2 meeting in Brussels
  - Final draft submitted to Draft International Standard (DIS) ballot on April, 2018 for final comments and vote by July 4, 2018
  - Draft 'APPROVED', but further edits introduced and need to check for Vienna Agreement conformity

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Post DIS stage
ISO 15195

Expecting final publication at last by September 2019

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DBWG-P-03-B2 document

"The appropriate JCTLM review team ascertains that the nominated reference laboratory is accredited according to ISO/IEC 17025 and ISO 15195 as calibration laboratory **on the basis of successful, and in general on-site, *assessments* by technical and management *experts* from accreditation bodies which are ILAC members."**

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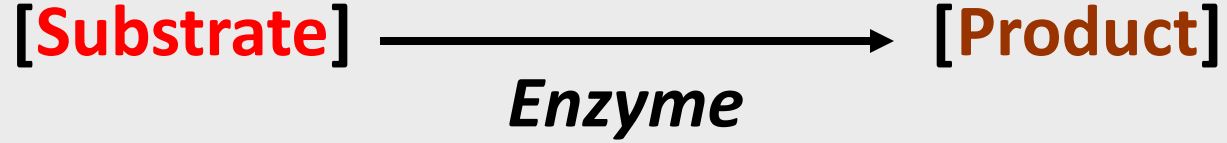
What is different with the measurand "enzyme" compared to glucose or creatinine?

A property of the enzyme is measured, i.e. the catalytic concentration (= catalyzed reaction rate) of the enzyme (not the amount or the mass of the enzyme)



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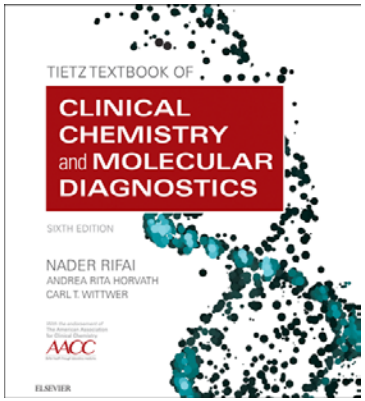
Bais R, Panteghini M. In: "Tietz Textbook of Clinical Chemistry and Molecular Diagnostics". 6th ed. Elsevier Saunders: St. Louis, 2018



As a consequence:

- ✓ There is no procedure for a direct measurement of the catalytic concentration
- ✓ The determination of the catalytic concentration is performed by spectrometric monitoring the reaction rate
- ✓ The catalytic concentration depends strongly on the reaction conditions of the measurement procedure
- ✓ For reference methods, the reaction conditions are defined in a primary reference procedure (IFCC)

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Measurement of enzyme catalytic concentration (activity)

➡ The numerical results are method-dependent (i.e. depend entirely on the experimental conditions under which measurements are made)

Variables:

1. pH and nature of the buffer
2. substrate (nature and concentration)
3. activators and inhibitors
4. measurement temperature

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Definition of Enzyme Catalytic Concentration (Activity)

An enzyme measurand cannot be described only by kind of quantity, name of enzyme and of system, but requires also the specified measurement procedure and especially the indicator component of the measured reaction.

Example:

Rate of conversion of NADH in the IFCC reference measurement procedure for lactate dehydrogenase (LDH)

Reaction:

$$\text{Lactate} + NAD^+ \xrightarrow[\text{LDH}]{} \text{Pyruvate} + NADH + H^+$$

ISO 18153:2003. In vitro diagnostic medical devices - Measurement of quantities in biological samples - Metrological traceability of values for catalytic concentration of enzymes assigned to calibrators and control materials.

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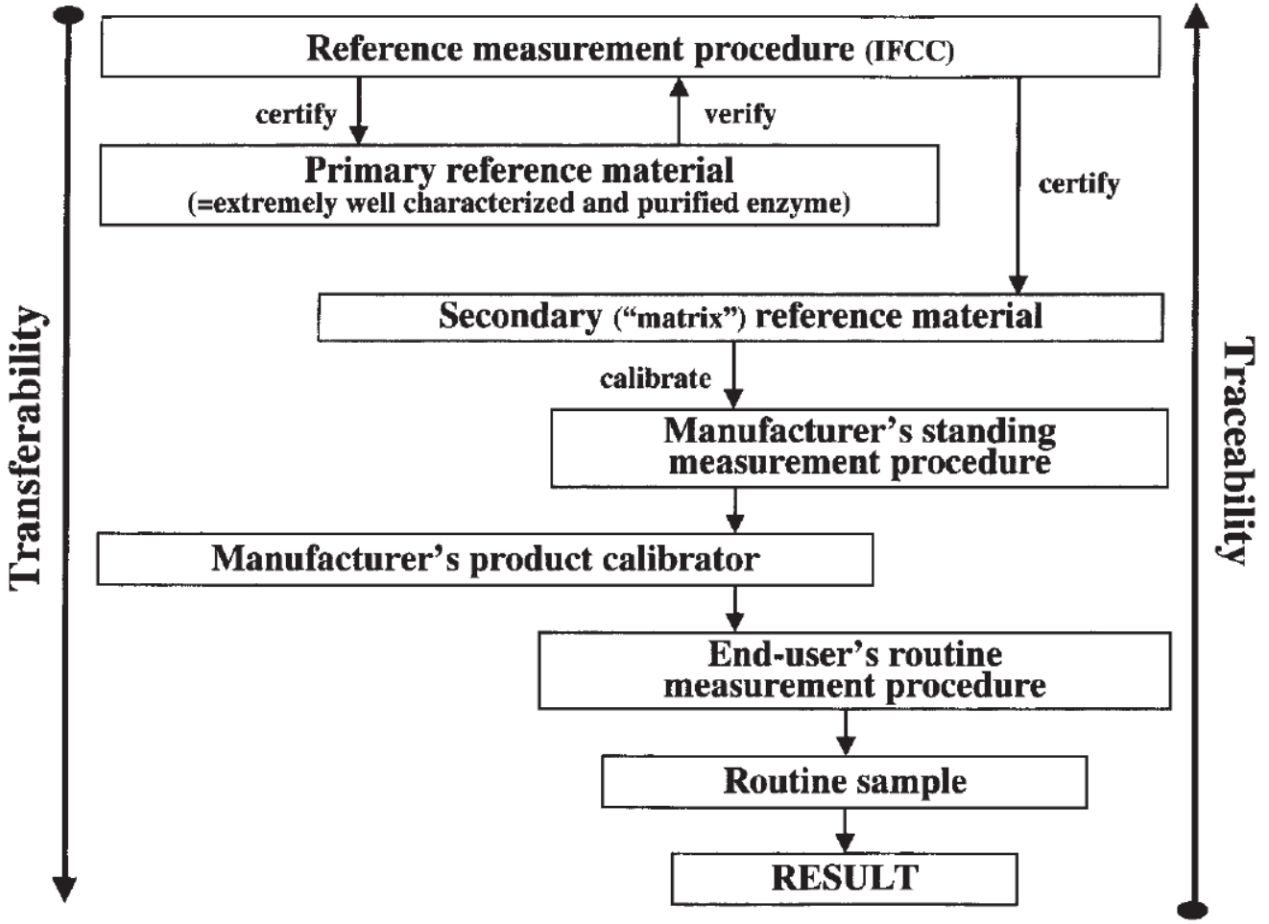
Clin Chem Lab Med 2001; 39(9):795–800

Opinion Paper

Establishing a Reference System in Clinical Enzymology

Mauro Panteghini[1], Ferruccio Ceriotti[2], Gerhard Schumann[3] and Lothar Siekmann[4]



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Example of Reference Measurement Procedure

Quantitation of Catalytic Concentration of Alkaline Phosphatase in Human Serum

Elements of the Measurement Procedure (Clin Chem Lab Med 2011;49:1439)

- Measurement of the catalytic and chemical conversion of 4-nitrophenyl phosphate to 4-nitrophenoxide ion
  -substrate used is a defining characteristic of the RMP
- All enzymatic reaction conditions are thoroughly defined with stated allowable tolerances
  -reaction conditions are defining characteristics of the RMP
  -reaction conditions optimized to maximize repeatability
- Procedure validated through multi-laboratory inter-comparison study
  -thorough evaluation of both the repeatability and reproducibility of the procedure
- Procedure cannot be validated using another method
  -RMPs for catalytic concentrations are procedurally-defined

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Aspects to be controlled in performing reference measurement procedures for enzymes

- ✓ Gravimetry controlled by calibrated test weights
- ✓ Volumetry controlled by gravimetry
- ✓ Temperature controlled by calibrated thermometer
- ✓ pH controlled by calibrated equipment
- ✓ Photometric wavelength controlled by certified filters or solutions of holmium
- ✓ Photometric absorbance checked by certified test solutions

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Infusino I, Schumann G, Ceriotti F, Panteghini M. CCLM 2010;48:301

Measurement of catalytic concentration of enzymes by reference procedures: a synopsis

The enzyme measurand is defined by a set of measurement parameters:

- Kind of substrate and its concentration
- Activators and their concentration
- Direction of the catalysed reaction
- Indicator component
- Buffer system and pH
- Measurement temperature
- Preincubation time
- Material for the starting reaction
- Delay time
- Measurement interval
- Wavelength
- Band width
- Light pass
- Volume fraction of sample

Metrological considerations:

- Gravimetry
- Volumetry
- Thermometry
- Potentiometry
- Photometry

Requirements for a reference service:

- ✓ Publications (IFCC series)
- ✓ Standard operating procedure (SOP)
- ✓ Suited laboratory environment
- ✓ Well trained staff
- ✓ Accreditation (ISO standards)

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QUANTIFYING UNCERTAINTY COMPONENTS OF THE ENZYME REFERENCE PROCEDURE

It is essential establishing a realistic and sound uncertainty budget by identifying the variables that give rise to the uncertainty and their sizes

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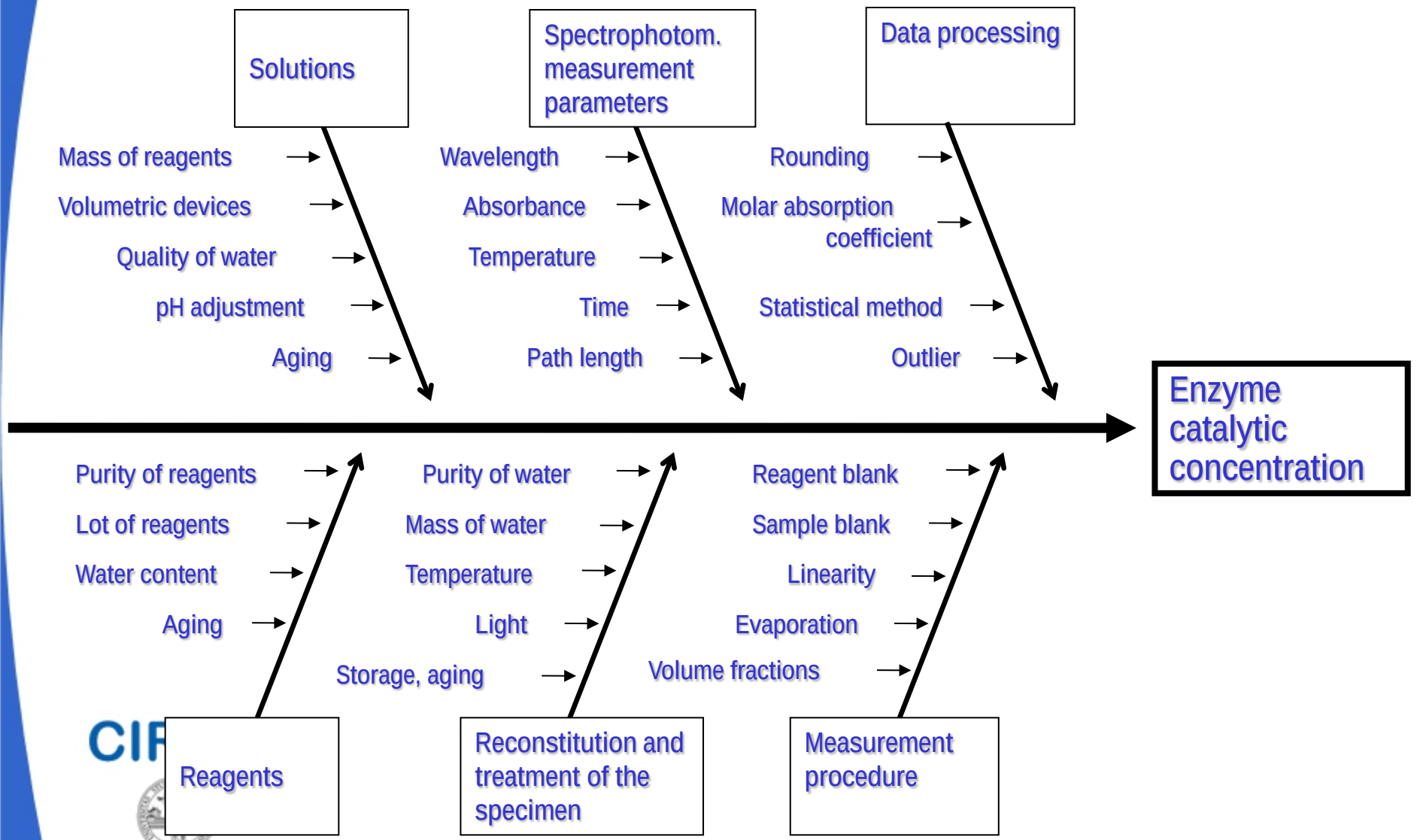
Overview of potentially relevant uncertainty components of the enzyme measurements using reference procedures



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Sources of MU with direct influence on the substrate rate catalyzed by the enzyme

- Measurement temperature
- pH
- Volume fraction of sample
- Final concentration of the reagents in the reaction mixture
- Linearity of the reaction rate
- Evaporation in the cuvette
- Aging of the specimen and aging of the reagent solutions
- Lot of the reagents (impurities)
- Reconstitution of lyophilized materials (e.g. light, temperature)

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Sources of MU influencing the kinetic spectrometry

- Measurement wavelength and band width
- Measurement of absorbance
- Path length of the cuvette
- Time measurement of the kinetic spectrometric signal
- Effects of the matrix of the sample (sample blank)
- Spectrometric stray light and noise, linearity, stability of the baseline
- Reagent blank rate

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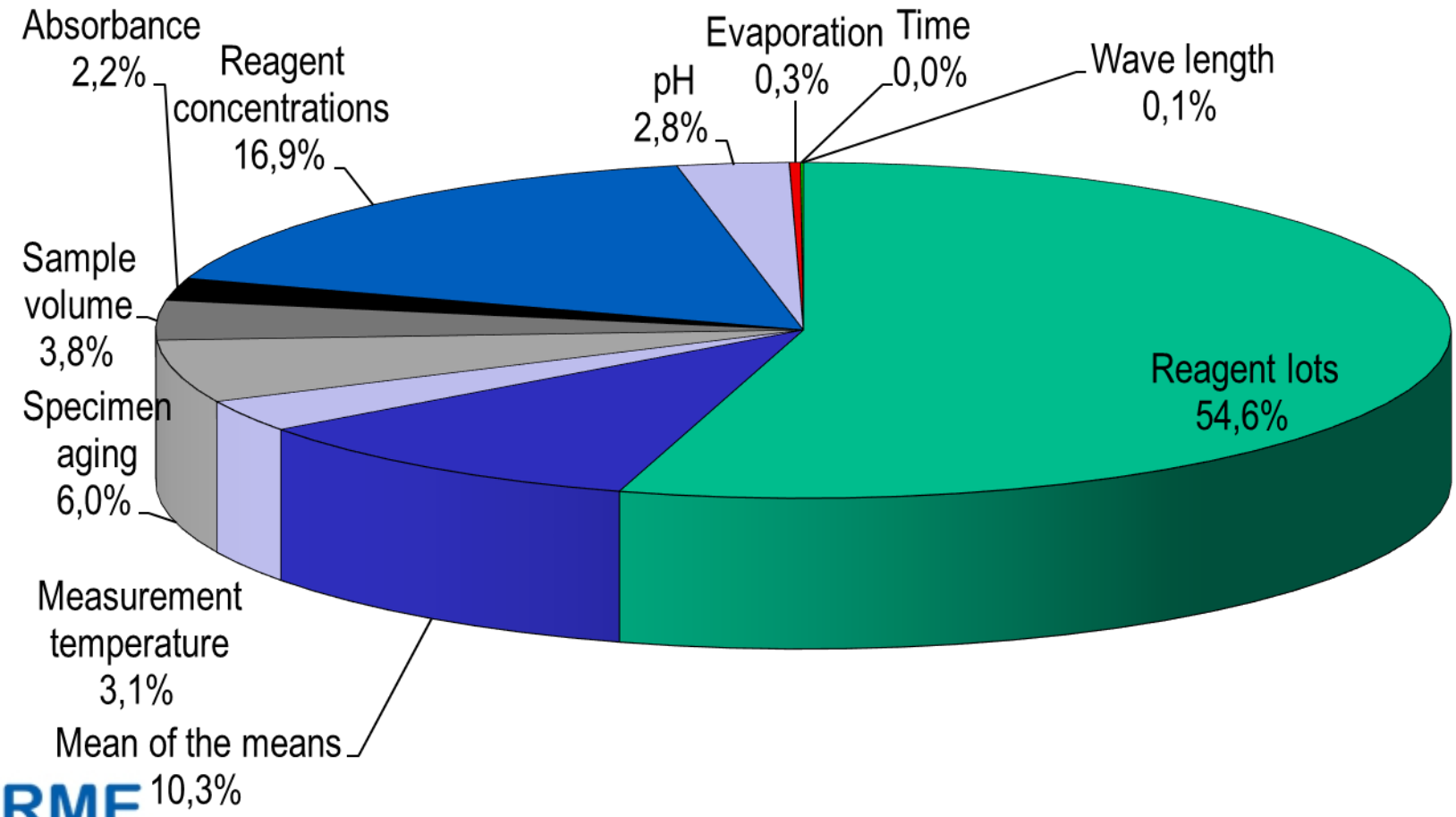
Example of uncertainty budget for ALT reference measurement procedure



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Frusciante E, Infusino I, Panteghini M. Biochim Clin 2011;35:20

QUANTIFYING UNCERTAINTY COMPONENTS OF THE REFERENCE PROCEDURE

Laboratory medicine — Requirements for reference measurement laboratories

3.11 NOTE 2 "Uncertainty of measurement" comprises, in general, many components. Some of these components may be evaluated from the statistical distribution of the results of series of measurements and can be characterized by "experimental standard deviations". The other components … are evaluated from assumed probability distributions based on experience or other information."

QUANTIFYING UNCERTAINTY COMPONENTS OF THE REFERENCE PROCEDURE

- **Type A sources:**
  Random components estimated statistically as standards deviation ⟹ mean of means

- **Type B sources:**
  Components estimated from specific information and additional investigations by the reference laboratory, related to calibration procedures for spectrometry, gravimetry, volumetry, potentiometry, and thermometry.

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Note: While Type A MU is concentration-dependent, Type B MU compounds are constant for all measurement values

TYPE A MU EVALUATION

In this component the estimation of the standard uncertainty (u) is based on the SD derived from the mean of means, considering the number of measurement days (n)

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$$u(\bar{x}) = \frac{SD_{mean}}{\sqrt{n}}$$

MU sources of the standard uncertainty of random components (intermediate imprecision)

Uncertainty source	Reason
Path length of the cuvette	Use of different cuvettes
Measurement of absorbance	Repeated measurements on n days
Temperature adjustment	Continuous temperature control
Volume for reconstitution of lyophilized materials, if any	A new specimen is reconstituted on each of n days
Volume fraction of sample	The sample is independently pipetted 3 x n times

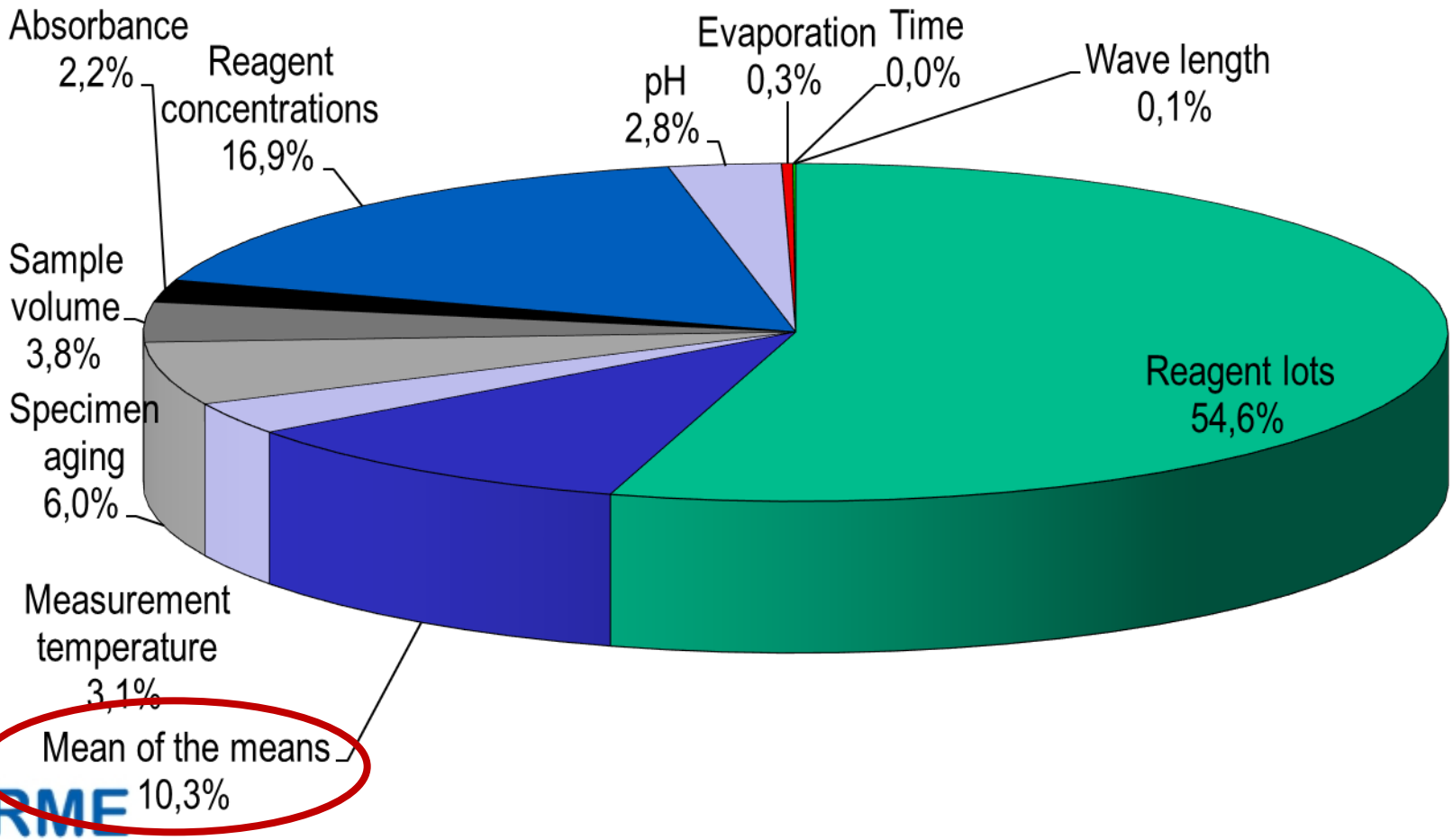
QUANTIFYING UNCERTAINTY COMPONENTS OF THE REFERENCE PROCEDURE

Laboratory medicine — Requirements for reference measurement laboratories

3.11 NOTE 3 It is understood that the result of the measurement is the best estimate of the value of the measurand, and that all components of uncertainty, including those arising from systematic effects, such as components associated with corrections and refe ls, contribute to the dispersion."

Type B sources

Example of uncertainty budget for ALT reference measurement procedure



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Frusciante E, Infusino I, Panteghini M. Biochim Clin 2011;35:20

Type B MU evaluation: uncertainty components due to calibration

- The measurement conditions of the reference measurement procedure are controlled by calibration procedures and are corrected to the target value by adjustment. Consequently all correction factors in the model function can be set to the value 1
- All correction factors have however a standard uncertainty, resulting from the uncertainty of the calibration procedure and the uncertainty of the adjustment or experimentally deduced by the reference laboratory

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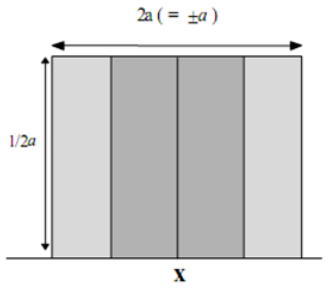
Uncertainty sources for enzyme reference measurement procedures and information origin

Parameter	Type of uncertainty	Distribution of uncertainty	Estimation
Wavelenght	B	Rectangular	Manufacturer's specification
Absorbance	B	Rectangular	Manufacturer's specification
pH	B	Rectangular	IFCC-document
Temperature	B	Rectangular	IFCC-document
Reagent concentration	B	Rectangular	IFCC-document
Lot of reagent	B	Rectangular	Experiment
Volume fraction of sample	B	Rectangular	IFCC-document
Time	B	Rectangular	Experiment
Evaporation	B	Rectangular	Experiment
Aging of specimen	B	Rectangular	Experiment
Linearity	B	Normal	Experiment
Mean of the means	A	Normal	Result of reference method value investigation

Rectangular distribution		
Form	Use when:	Uncertainty
	• A certificate or other specification gives limits without specifying a level of confidence (e.g. 25 mL ± 0.05 mL) • An estimate is made in the form of a maximum range (±a) with no knowledge of the shape of the distribution.	$u(x)=\frac{a}{\sqrt{3}}$

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TYPE B MU EVALUATION

- **Step 1:**
  Definition of the standard uncertainty of each parameter that is considered by a correction factor (=1) in the model function.
- **Step 2:**
  Definition of the sensitivity coefficients (i.e. the rate of change in the final result with the changes of the parameter)
- **Step 3:**
  Estimate of the contribution of each uncertainty source to the overall MU of result

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Example ALT reference procedure: STEP 1

- The IFCC procedure indicates maximum allowable uncertainties for pH and temperature, and the spectrophotometer's manufacturer reports that for wavelength. The calibration procedure of the reference laboratory must assure that these uncertainties are not exceeded.
- There is no information about the distribution of the uncertainties. Therefore, a rectangular distribution is assumed.

Parameter	Mamimum allowable uncertainty	Type	Distribution	Standard uncertainty
pH	0.05 U	B	rectangular	0.03 U
Temperature	0.1 °C	B	rectangular	0.06 °C
Wavelength	0.1 nm	B	rectangular	0.06 nm

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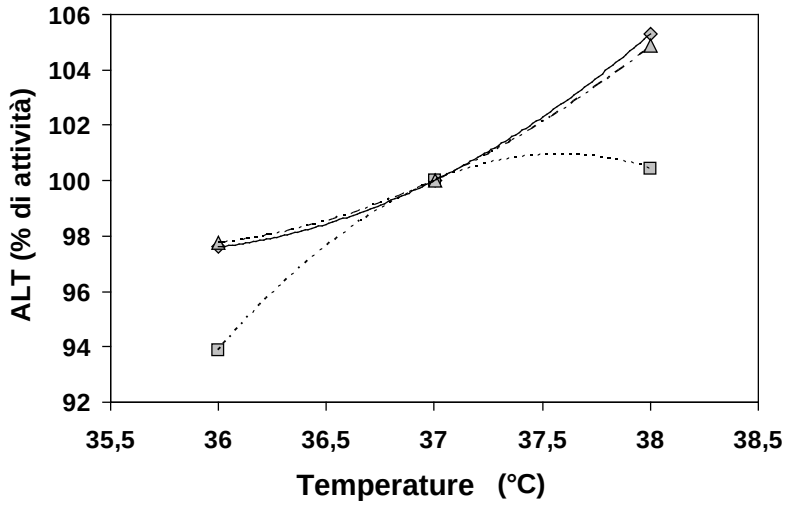
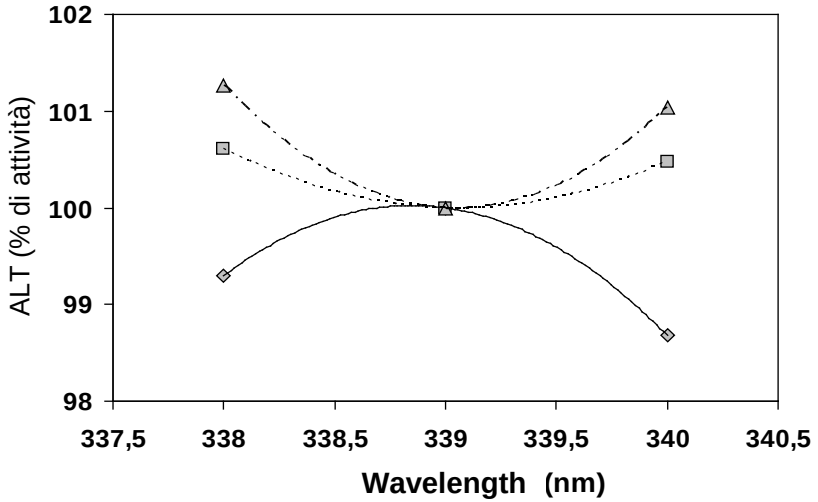
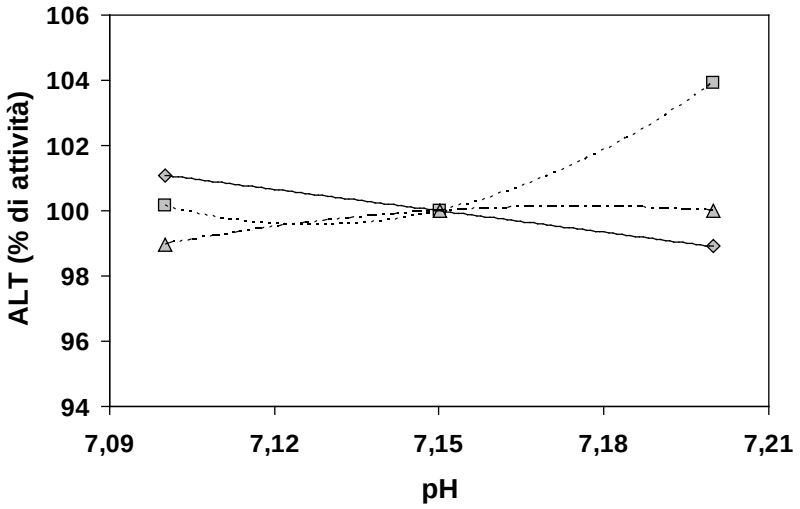
Example ALT reference procedure: STEP 2
Definition of sensitivity coefficients







Parameter	Value	Relative catalytic concentration, %	Sensitivity coefficient
Wavelength	339 nm	100.00	0.39 (for 1 nm)
	338 nm	100.39	
	340 nm	100.07	
Temperature	37 °C	100.00	3.60 (for 1 °C)
	36 °C	96.40	
	38 °C	103.54	
pH	7.15	100.00	0.34 (for 0.05 pH unit)
	7.20	99.66	
	7.10	100.15	

Frusciante E, Infusino I, Panteghini M. Biochim Clin 2011;35:20

Example ALT reference procedure: STEP 3
Standard uncertainty component of the result

standard uncertainty of the component	x	sensitivity coefficent	=	standard uncertainty component of the result
0.03 U pH	x	0.34	=	0.20%
0.06 °C	x	3.60	=	0.22%
0.06 nm	x	0.39	=	0.02%

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EXAMPLE: CALCULATION OF COMBINED MU FOR ALT MEASUREMENT WITH IFCC REFERENCE PROCEDURE

ALT

Parameter	Declared uncertainty		Reference	Distribution of uncertainty	Type of uncertainty	Standard uncertainty	Coefficient of sensitivity	Pro		Relative standard uncertainty
wavelenght	0,1	nm	manufacturer's specification	rectangular	B	0,06	0,14	1	nm	0,01
absorbance	0,3	%	manufacturer's specification	rectangular	B	0,17	1	1	%	0,17
pH	0,05	pH	IFCC-document	rectangular	B	0,03	0,14	0,05	pH	0,08
temperature	0,1	°C	IFCC-document	rectangular	B	0,06	4,14	1	°C	0,24
reagent concentration	1,5	%	IFCC-document	rectangular	B	0,87	0,26	1	%	0,23
lot of reagent	1,5	%	IFCC-document	rectangular	B	0,87	1	1	%	0,87
volume fraction of sample	0,4	%	data basis	rectangular	B	0,22	1	1	%	0,22
time	0,03	%	experiment	rectangular	B	0,02	1	1	%	0,02
evaporation	0,1	%	experiment	rectangular	B	0,06	1	1	%	0,06
aging of specimen	0,5	%	IFCC-document	rectangular	B	0,29	1	1	%	0,29
linearity	0,6	%	experiment	normal	B	0,30	1	1	%	0,30
mean of the means	0,8	U/L	result of the RMV investigation	normal	A	0,40	1	1	U/L	0,40

Combined standard uncertainty = square root of the sum of the variances (calculated from the standard uncertainty components)

$$[u_c]^2 = u(wl)^2 + u(abs)^2 + u(pH)^2 + u(temp)^2 + u(reag)^2 + u(lot)^2 + u(vol)^2 + u(time)^2 + u(evap)^2 + u(aging)^2 + u(lin)^2 + u(mean)^2 = 1.3$$

$$[u_c] = 1.14\ \%$$

$$U\ (k=2) = \pm 2.3\%$$

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ACCREDITATION CERTIFICATE

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In summary:

- ✓ When measuring catalytic concentrations of enzymes by reference procedures, MU is much more than random component and standard uncertainty of the contributing values

- ✓ Each reference laboratory has to establish its own control procedures for type B uncertainty components

- ✓ Each reference laboratory has to establish its individual MU budget

- ✓ Critical review of the MU components and budget on a regular basis is required (including external audit by accreditation assessors)

INTERNATIONAL STANDARD **ISO/FDIS 15195**

Laboratory medicine — Requirements for reference measurement laboratories

Involves:

- on-site assessments on regular basis using technical experts (peers)
- regular use and review of proficiency testing results
- other surveillance techniques (e.g. desk-top review of laboratory internal audits and management reviews)

Example: “An audit procedure shall be established to allow identification of factors affecting uncertainty of the results.” (Clause 4.4)

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Stated uncertainty in the accreditation certificate

- Declared (expanded) uncertainties <1.5% for enzyme measurements using IFCC reference measurement procedures are not realistic!
- Only the type A uncertainty of the contribution values, needed to calculate the reference measurement value as a mean, is at least ~0.8%.
- Furthermore, it would be unlikely that the relative uncertainties at the lower and upper limits of measurement ranges are the same.

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Welcome
login
Registration/ Accou
RELA in progress
order RELA 2017
enter RELA 2017 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), free thyroxine (ft4)
Therapeutic drugs (THER): digoxin, digitoxin, theophylline
Vitamins (VITA): 25-OH-vitamin D3

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The accreditation body should not accept such small MU!

METHOD VALIDATION: Stated measurement ranges

- Some of the nominations of accredited laboratories gave upper (and lower) measurement limits that are significantly different from the limits specified in the IFCC publications.
- **The measurement ranges are fixed by parameters of the published IFCC reference procedures.** So that, published upper measurement limit must be fulfilled in an accredited calibration laboratory and the method validation has to include experiments showing linearity up to those limits.
- The linearity check is the essential proof and the accreditation certificate must show the theoretical values for the upper measurement limit. Exceeding the calculated value for the upper limit of the measurement range by >10% is also unacceptable.

METHOD VALIDATION: Stated measurement ranges

The upper limits of the IFCC reference procedures are defined by the maximum absorbance per min multiplied by the published factors

IFCC upper limit of the measurement range

Enzyme	Abs/time	Factor	Catalytic concentr.	ILAC–member accredited ref lab #1	ILAC–member accredited ref lab #2
ALT	0.150 min^{-1}	1905	286 U/L	200 U/L	286 U/L
ALP	0.250 min^{-1}	2729	682 U/L	350 U/L	NA
AMY	0.235 min^{-1}	3063	720 U/L	454 U/L	270 U/L
AST	0.130 min^{-1}	1905	248 U/L	200 U/L	248 U/L
GGT	0.200 min^{-1}	1382	276 U/L	200 U/L	260 U/L
LDH	0.165 min^{-1}	3651	602 U/L	360 U/L	400 U/L

CIRME

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RT comments to the nomination by ILAC–member accredited ref lab C11 RMS AA-ZZ

IFCC reference measurement procedures and measurement ranges:
There are major problems with the declared linearity limits: the lower measurement limits are often so high to prevent the measurement of most of the samples from healthy subjects, the upper limits (especially for Amylase and CK) are significantly lower than those indicated in the IFCC reference procedure.
The linearity statements should be revised.

Accreditation according to ISO 17025 / ISO 15195:	certified by
Certified measurement uncertainties:	realistic
Participation in RELA:	fulfilled for all 7 enzymes
Recommendation for listing:	**Not recommended**

CIRME

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RT comments to the nomination by ILAC–member accredited ref lab C11 RMS XX-YY

IFCC reference measurement procedures and measurement ranges:
There are major problems with the declared linearity limits: the lower measurement limits appear often so high to prevent the measurement of most of the samples from healthy subjects; the upper measurement limits (especially for AST, 5.24 µkat/L vs 4.13, and for GGT, 4.88 µkat/L vs 4.60) are significantly different from those indicated in the IFCC reference procedure.
The linearity statements should be revised.

Accreditation according to ISO 17025 / ISO 15195:	certified by
Certified measurement uncertainties:	in general, realistic; however, it would be unlikely that the relative uncertainties at the lower and upper limits of the measurement ranges are the same.
Participation in RELA:	fulfilled for all 7 enzymes
Recommendation for listing:	**Not recommended**

The way forward...

a) Identify potential assessors/technical experts that can be expected to do a good job in this difficult area

b) Require specialist knowledge and expertise that existing ILAC accreditation bodies will need to consider on assessment

c) Finalize transparent and sound procedures and practices for JCTLM Database WG

d) Continue good cooperation among all the players to identify problems and look for solutions

CIRME

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Draft Report of the 18th meeting of the JCTLM Executive Committee 11 June 2017, Athens, Greece

Action (A/16-27): R. Wielgosz to contact the Enzymes RT Leader to verify if he would be willing to chair a half-day technical workshop on how to implement the IFCC reference measurement procedures for Enzymes and how accredited laboratories should be declaring their services for inclusion in the JCTLM Database

Dr Wielgosz said that he contacted the Enzymes RT leader who suggested him to postpone the workshop until the PPTD in Chengdu in October 2018 as to ensure a greater involvement/availability of the members of the Enzymes review team in the organization of the technical workshop as well as to reach the right audience, noting that the reference laboratories from Asia had been the major contributors to the nominated calibration reference measurement services in enzymes area in the latest review cycle.

The Committee agreed with the proposal.

CIRME

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