



UNIVERSITY OF GOTHENBURG

Reference Method Certification

JCTLM submission, $A\beta_{42}$

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Joint Committee for Traceability in Laboratory Medicine (JCTLM)

Created 2002 through a cooperation between

- CIPM (the International Committee of Weights and Measures)
- IFCC (the International Federation for Clinical Chemistry and Laboratory Medicine)
- ILAC (the International Laboratory Accreditation Cooperation)

Reference measurement procedure (RMP)

“thoroughly investigated measurement procedure shown to yield values having an uncertainty of measurement commensurate with its intended use, especially in assessing the trueness of other measurement procedures for the same quantity and in characterizing reference materials”

ISO 17511-3.29

Reference measurement procedure (RMP)

In simpler terms, a RMP is a measurement procedures which

- has been validated to measure what it is intended to measure
- provides measurements which have been thoroughly assessed for bias
- provides the results needed

NIST



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Validation

- Calibration – linearity, range
- Specificity
- Accuracy
- Precision
- Detection & quantification limit
- Recovery (spike -)
- Robustness – stability of sample & analytical procedures
- Expanded uncertainty of measurement

Mass Spectrometry–Based Candidate Reference Measurement Procedure for Quantification of Amyloid- β in Cerebrospinal Fluid

Andreas Leinenbach,^{1†} Josef Pannee,^{2†} Thomas Dülffer,¹ Andreas Huber,¹ Tobias Bittner,¹ Ulf Andreasson,² Johan Gobom,² Henrik Zetterberg,^{2,3} Uwe Kobold,¹ Erik Portelius,² and Kaj Blennow^{2*} on behalf of the IFCC Scientific Division Working Group on CSF proteins

BACKGROUND: Cerebrospinal fluid (CSF) amyloid- β ($A\beta_{42}$) is a well-established biomarker for Alzheimer disease. Several immunoassays for $A\beta_{42}$ exist but differ in absolute concentrations and may suffer from matrix interference, thereby hampering interlaboratory comparisons and the use of general cutoff levels. Together with the IFCC Working Group on CSF Proteins, we

cutoff concentrations for CSF $A\beta_{42}$ in clinical trials and practice.

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The cerebrospinal fluid (CSF)⁴ biomarkers total τ , phosphorylated τ , and the 42-amino acid form of am-

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Preparation of Nomination template for submission of RMP (also a “compliance” spreadsheet since 2014)

- Submission of
 - Nomination template
 - Publication (including supplemental data)
 - Additional document for Expanded Uncertainty calculation
 - Additional method comparison with 40 samples

JCTLM Reference Method/Procedures Nominations Template, Version 9, January 2014

WG1-P-02-F-02

- Please:
- 1) complete one line for each analyte-method combination
 - 2) do not merge cells within the table, just copy cells as appropriate if there are multiple analytes with assigned values in an RMP
 - 3) complete one compliance demonstration spreadsheet for each analyte-RM combination/line

For Secretariat Use

For Secretariat Use

Unique Nomination Number	Date Nomination Filed	Analyte/Parameter				Matrix				
		Analyte Category	Analyte Name	IUPAC/IFCC Number	Method capable of traceability of analyte to SI or defined procedure?	Matrix Category 1	Matrix Category 2	Matrix Category 3	Matrix Category 4	Matrix Category 5

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	A	B	C	D	E	F	G
1	Compliance demonstration		Return to Reference Methods Template Spreadsheet				
2	Reference Method Nominated by	Contact Information	Reference Method Identifier / Name	JCTLM Reference Material Nomination Number	Review Team Name	Review Team Leader's Name	Date of review
3							
4	ISO 15193, 2nd Ed 2009-05-01		Compliance demonstration of the nominated reference method with ISO 15193:2009(E) requirements	For Review Team Use			
5	Paragraph number	Title of the paragraph	(Please enter "Yes" or "No" in each of the cells below as appropriate, and add a short description on how the compliance is achieved)	Mandatory element (Yes/No)	Observations	Classification: Critical, Major or Minor non-compliance, or observation	
6	4	Presentation of a reference measurement procedure					
7	4.1	Elements of a written reference measurement procedure					
8	4.2	Warning and safety precautions					
9	4.3	Introduction					
10	4.4	Scope					
11	4.4 a)						
12	4.4 b)						
13	4.4 c)						
14	4.4 d)						
15	4.4 e)						
16	4.5	Terms, definitions, symbols and abbreviated terms					
17	4.5.1						
18	4.5.2						
19	4.5.3						

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- Analyte category (e.g. drugs, enzymes, proteins), name, matrix
- Title & reference to peer-reviewed publication
- Measurement technique(s): ID-LC-MS
- Method range & expected uncertainty range

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Is the method capable of traceability of analyte to SI or defined procedure?

- The concentration of our $A\beta_{42}$ calibrant was measured using LC fluorescence–based amino acid analysis, traceable to NIST¹ SRM²2389a.

¹ *National Institute of Standards and Technology*

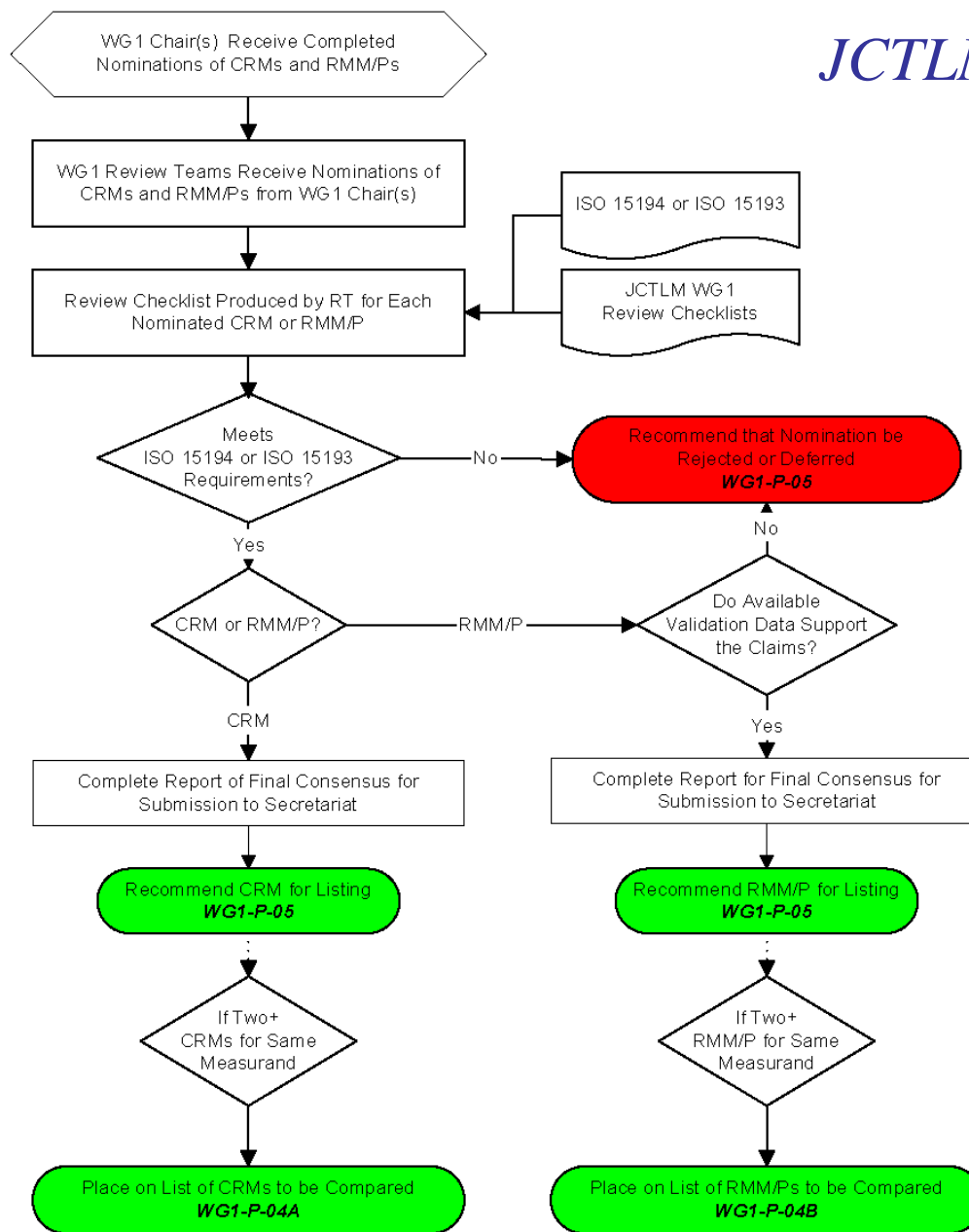
² *Standard Reference Materials*

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Do the method instructions contain all the required items (ISO 15193)?

- The ISO document describes requirements for content and presentation of RMPs.
- Yes or no and a short description/comment

- Introduction (publication).
- Scope: objective (standardization, harmonization of immunoassays, set value of CRM), types of sample (CSF), interfering components (drugs, RBCs), mention allowable modifications of the basic RMP (no), measurement interval (yes)
- Measurement principle and measurement method (MS)
- Reagents and materials: expression of concentration, diluting
- Calibration: procedure (surrogate analyte)
- Method comparison (Triple Quad)



Time schedule

- Launch of the annual call for nominations: February 1st
- Deadline for the submission of nominations: May 30th*
- Distribution of the nominations to the review teams: July 15th
- Deadline for the submission of the review teams' reports: October 31st
- Date for communicating the output of the review to the nominating organizations: January 31st
- Date for the publication of the nominations approved for listing in the JCTLM database: January 31st

*Also possible to send preliminary materials and hand in later (Sept 30th) final documents