# Biennial activity report

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| **Organization Name: Joint Research Centre, JRC, European Commission** |
| **JCTLM Member status: National and Regional Member** |
| **Author(s):** Liesbet Deprez |
| **Author(s) email(s):** Liesbet.deprez@ec.europa.eu |
| **Period covered: 2024 – 2025** |

1. **Major achievement(s) in support of standardization in laboratory medicine**

a. CRMs for haemoglobin A2 (ERM®-DA485/IFCC and ERM®-DA486/IFCC)

The JRC has developed and released two CRMs for the quantification of the ratio haemoglobin $A_2$ (HbA2) over total haemoglobin ($Hb_{tot}$) in collaboration with the members of the IFCC working group on standardisation of haemoglobin A2 (WG-HbA2). The starting material was blood haemolysate from healthy donors with normal or elevated $HbA_2/Hb_{tot}$ levels. Each CRM batch has been tested for homogeneity, stability and commutability. The materials have been valued assigned based on the measurements results obtained from 2 different laboratories: Physikalisch-Technische Bundesanstalt, (PTB) and INSTAND. Both laboratories applied an isotope dilution mass spectrometry (ID-HPLC-MS/MS) method calibrated with recombinant forms of $HbA_2$ and $HbA_0$. These two CRMs were released in September 2024 and nominated for listing in the JCTLM database as certified reference materials of higher metrological order, list I, in May 2025.

References:

Certification report: : G. Auclair, A. Muñoz-Piñeiro, J. Charoud-Got, R. Paleari, P. Kaiser, C. Arsene, S. Trapmann, A. Mosca and L. Deprez, Certification of the amount-of-substance fraction of haemoglobin A2 versus total haemoglobin in blood haemolysate: ERM®-DA485/IFCC and ERM®-DA486/IFCC, Publication Office of the European Union, Luxembourg 2024, doi:10.2760/877530, JRC137824

A. Mosca, C. Arsene , R. Paleari, P. Kaiser, K. Harteveld, Y. Daniel, C. Amano, A. Murakami, G. Auclair. Standardization of hemoglobin A2 and hemoglobin F: Achievements and perspectives. Clinica Chimica Acta, 2025;567, art. no. 120087, doi: 10.1016/j.cca.2024.120087

b. CRMs for elements in blood (ERM®-DA634, ERM®-DA635 and ERM®-DA636)

The JRC has developed and released 3 human blood reference materials certified for their mass concentrations of cadmium, chromium, mercury, nickel, lead and thallium. These CRMs were produced to replace the existing CRMs BCR-634, BCR-635 and BCR-636, currently listed in the JCTLM database. The starting material was human blood from healthy donors which was lysed and spiked with the six elements. For each CRM batch, the between-unit homogeneity was confirmed and stability during transport and storage was assessed in accordance with ISO 33405:2024. The value assignment was based on the results of an interlaboratory comparison including eight laboratories with demonstrated competence and adhering to ISO/IEC 17025:2017. These three CRMs were released in January 2025 and they have been nominated for listing in the JCTLM database as certified reference materials of higher metrological order, list I, in May 2025.

References:

Certification report: T.P.J. Linsinger, L. Deprez, G. Auclair, Certification of the mass concentrations of Cd, Cr, Hg, Ni, Pb and Tl in human blood ERM-DA634, ERM-DA635 and ERM-DA636, Publications Office of the European Union, Luxembourg, 2025, https://data.europa.eu/doi/:10.2760/4057065, JRC138775.

T.P.J. Linsinger, L. Deprez, G. Auclair. Commutability study on three CRMs evaluating their suitability for calibration, trueness verification and statistical quality control of methods measuring metal concentrations in human blood. Analytical and Bioanalytical Chemistry, 2025;417(12): 2617 – 2627. doi: 10.1007/s00216-025-05751-0

c. CRM for the catalytic activity concentration of aspartate aminotransferase (ERM®-AD457k/IFCC)

The JRC has released a new CRM for the catalytic activity concentration of aspartate aminotransferase (AST). The starting material was recombinant AST cytosolic isoform (originating from human liver) in a buffered solution. Between-unit homogeneity of the whole batch and stability during transport and storage were assessed in accordance with ISO 33405:2024. The value assignment was based on the results of an interlaboratory comparison including twelve laboratories all applying the primary reference measurement procedures (PRMP) for the measurement of catalytic activity concentrations of AST at 37 °C established by the IFCC. The laboratories had demonstrated competence and adhering to ISO/IEC 17025:2017. This CRM was released in February 2025 and nominated for listing in the JCTLM database as a certified reference material of higher metrological order, list I, in May 2025.

References:

Certification report: E. Luque-Perez and L. Deprez, Certification of the catalytic activity concentration of aspartate transaminase in buffered solution: ERM®-AD457k/IFCC, Publications Office of the European Union, Luxembourg, 2025, doi:10.2760/6491531, JRC140606.

d. CRM for antibodies targeting tissue transglutaminase in human serum (ERM®-DA487/IFCC)

The JRC has developed and released a CRM for antibodies targeting tissue transglutaminase (anti-tTG IgG and IgA) in human serum in collaboration with the Medicines and Healthcare products Regulatory Agency (MHRA). The starting material was human serum obtained from a donor with coeliac disease. One large batch of reference material was produced and the between-unit homogeneity and stability during transport and storage were assessed in accordance with ISO 33405:2024. Afterwards the batch was split into two parts. The first part was transferred to MHRA and labelled as 23/274. During its 80th meeting in October 2024, the Expert Committee of Biological Standardisation (ECBS) of the WHO established 23/274 as the first WHO standard for anti-tTG IgA antibodies with an assigned value of 200 IU/vial and for anti-tTG IgG antibodies with an assigned value of 100 IU/vial. These assigned values were directly transferred from 23/274 to ERM-DA487/IFCC without any additional value transfer measurement procedure. To fulfil the requirements of ISO17034 and ISO15194, the certified values of ERM-DA487/IFCC are accompanied by assigned uncertainties consisting of uncertainty components relating to potential between-unit heterogeneity, and potential degradation during transport, and storage. This CRM was released in May 2025 and nominated for listing in the JCTLM database as certified reference materials of higher metrological order, list II, in May 2025.

References:

L. Deprez, E. Monogioudi, G. Pinski, Certification of the concentration of anti-tissue transglutaminase IgA and IgG antibodies in human serum: ERM®-DA487/IFCC, Publications Office of the European Union, Luxembourg, 2025, https://data.europa.eu/doi:10.2760/0544207, JRC141842.

L. Deprez, E. Monogioudi, G. Pinski, J. Sheldon, G. Auclair, S.Trapmann, P. Rigsby, K. Malik, P. Matejtschuk, C. Thelwell, D. Vara, Report on the collaborative study to establish the First WHO International Standard for Tissue Transglutaminase Immunoglobulin autoantibodies (human serum). WHO/BS/2024.2477. available on https://www.who.int/groups/expert-committee-on-biological-standardization.

**2. Planned activity(ies) in support of standardization in laboratory medicine**

a. CRM for the catalytic activity concentration of alkaline phosphatase (ERM®-AD458/IFCC)

JRC is working on a new CRM for the catalytic activity of alkaline phosphatase (ALP). The most suitable candidate RM was selected based on the results of a preliminary commutability study. The material has been produced and the between-unit homogeneity over the whole batch and stability during transport and storage were assessed in accordance with ISO 33405:2024. The value assignment will be based on the results of an interlaboratory comparison included multiple laboratories all applying the primary reference measurement procedures (PRMP) for the measurement of catalytic activity concentrations of ALP at 37 °C established by the IFCC. The CRM is planned to be released in the first half of 2026.

b. CRMs for 17β-estradiol in human serum (ERM®-DA576, ERM®-DA577 and ERM®-DA578)

JRC is working on three new CRMs for 17β-estradiol in human serum. These new CRMs will replace the CRMs BCR-576, BCR-577 and BCR-578 from which the sales stocks are (almost) exhausted. The candidate CRM batches have been assessed for between-unit homogeneity and stability during transport and storage in accordance with ISO 33405:2024. These new materials are the study materials in the ongoing CCQM key comparison on estradiol in 2024-2025. The CRMs are planned to be released in 2026.

c. CRM for IgG autoantibodies targeting glomerular basement membrane (ERM®-DA484/IFCC)

The JRC has developed a candidate RM for IgG antibodies targeting glomerular basement membrane (anti-GBM IgG) in human serum in collaboration with MHRA. The candidate RM was produced in a large batch, which is also split into two parts. The first part is intended to become the first WHO international standard (IS) for anti-GBM IgG with arbitrary values in IU/ml and will be distributed by MHRA. The second part will be the CRM ERM-DA484/IFCC with an assigned value directly transferred from the WHO IS.

d. New CRM for Cystatin C (ERM ®-DA471k/IFCC)

The sales stock of the CRM ERM®-DA471/IFCC, certified for the mass concentration of cystatin C in human serum, is running low. This material will be replaced with new batch that will be produced in a very similar way. The equivalence between the assigned values of the old and the new batch will also be guaranteed.

e. New calibrator set for HbA1c/ HbA0 (ERM®-AD500k/IFCC)

The sales stock of the CRM ERM®-AD500/IFCC, which is a set of 6 ampoules containing haemoglobin (with different levels of HbA1c) in a buffer solution is running low. This set is certified for the amount-of-substance fraction of HbA1c versus the sum of HbA0 and HbA1c according to the reference methods for the measurement of HbA1c in human blood developed by the IFCC and listed in the JCTLM database. This set of materials will be replaced with new batch that will be produced in a very similar way. The equivalence between the assigned values of the old and the new batch will also be guaranteed.

## 3. Promoting traceability in laboratory medicine

During the past years, the JRC continued the distribution of the established CRMs in the field of laboratory medicine to laboratories and IVD manufacturers all over the world. Around 6000 units of IVD –CRM are distributed every year.

Staff members of the JRC have contributed to the drafting and review for important international standards like the ISO15194 and ISO15195 within the ISO TC212/WG2.

During the Euromedlab meeting in Brussels two oral presentations were given by staff members of the JRC:

“Certified Reference Materials in Clinical Chemistry: do they fulfil their purpose?” Liesbet Deprez

"A new certified reference material in preparation for Anti-glomerular Basement Membrane (Anti-GBM) Immunoglobulin autoantibodies in human serum" Carolina Aznar-Lopez

4. **Reference laboratory networks /collaborations focusing on developing /implementing reference measurement systems**

a. Collaborations with IFCC

A staff member of the JRC is an observer in the Executive Committee of the Scientific Division of the IFCC.

Several staff members of the JRC are members in the following IFCC working groups:
- Standardisation of Haemoglobin A2 and Foetal Haemoglobin (WG-HbA2/HbF)
- Biomarkers of Neurodegenerative Diseases (WG-BND)
- Commutability in Metrological Traceability (WG-CMT)
- Apolipoproteins by Mass Spectrometry (WG-APO MS)
- Faecal Immunochemical Testing (WG-FIT)

In addition, the JRC supports the IFCC Working group on Harmonization of Autoimmune Tests (WG-HAT), and the working group on Pancreatic Enzymes (WG-PE) by the production of CRMs as mentioned before.

b. Collaboration with Consultative Committee for Amount of Substance: Metrology in Chemistry and Biology (CCQM)

Two staff members of the JRC are members in the following CCQM working groups
- CCQM Working Group on Organic Analysis (CCQM-OAWG)
- CCQM Working Group on Protein Analysis (CCQM-PAWG)

c. Collaboration with Euramet's European metrology networks (EMN) and projects

The JRC has joined the EMN for Traceability in Laboratory Medicine (TraceLabMed).

The JRC has joined the NeuroBioStand project on the Standardisation of measurements of neurodegenerative disease biomarkers.

5. **Open questions and suggestions to be addressed by JCTLM**

(Suggestions on issues related to standardization and metrological traceability that should be considered by the JCTLM)

none