

WADA Technical Document – ISL TD2027DL

Summary of Major Modifications

This document summarizes the major modifications in the TD2027DL. In addition, a redline version against the TD2022DL, which is the current version in force, is also presented for reference.

Key updates and modifications include:

1. **Effective Date:** The effective date is 01 January 2027.
2. **Title:** The term “by Chromatography-based Analytical Methods” has been removed, since the analysis of exogenous Threshold Substances may also be performed with alternative techniques.
3. **Table 1:** Inorganic Cobalt (Co^{2+}), a Hypoxia-Inducible Factor (HIF) Activating Agent, has been introduced as a new Threshold Substance with a Threshold of 60 ng/mL and a Decision Limit (DL) of 80 ng/mL. In addition, a new column “Target Analytes” has been included to specify the target analytes of each of the Threshold Substances to which the corresponding DL is applied.

Salmeterol, which had been preliminary introduced in the document draft shared for stakeholder consultation, has been removed from this final version due to the absence of available Certified Reference Material needed for the quantitative confirmation procedure. Therefore, salmeterol remains for the moment a Non-Threshold Substance subject to a Minimum Reporting Level (MRL).

4. **Article 2.0. “A” vs “B” Sample Confirmation Procedures:** This new Article clarifies that the “A” Sample Confirmation Procedure (CP) is based on a combination of quantitative (for measuring the concentration) and qualitative (for identification of relevant analytes, as per ISL TD IDCR)), while for the “B” Sample confirmation of an exogenous Threshold Substance, only the identification of the relevant target analyte(s) is required for the Adverse Analytical Finding (AAF) to be valid.
5. **Quantitative statistics and Quality Control:** The revised document introduces and clarifies statistical requirements for the validity of the measurement, such as the evaluation of the Standard Error of the Mean (SEM) of replicate determinations against the combined standard uncertainty of the measurement. In addition, it includes a requirement for the use of QC samples in the same analytical run, which shall be assessed by either QC-charts or through a comparison with expected QC values to decide on the acceptance/rejection of the results.
6. **Article 3.1 Cobalt:** This Article provides examples of analytical techniques suitable for the CP of Cobalt. In addition, it clarifies that the CP shall separate inorganic Co^{2+} from organic cobalt (cobalamin) and specifically quantify Co^{2+} for the reporting of an AAF. The Initial Testing Procedure (ITP) may target total cobalt but must establish a cut-off to trigger the Co^{2+} CP. The Cobalt Analytical Testing Procedure (ATP) is not mandatory.
7. **Article 3.2 Cathine:** A clarification has been added regarding chromatographic resolution requirements for the separation of cathine from its non-prohibited diastereoisomer phenylpropanolamine (norephedrine). In addition, specific reporting guidance is provided when pseudoephedrine is co-detected at levels below its DL.
8. **Article 3.3 Morphine:** A clarification is provided on the decision rules and interpretation of morphine findings potentially arising from permitted codeine or ethylmorphine administration (previously described in ISL TL22),

including conditional criteria and results interpretation guidance (e.g., ratios/thresholds, hydrolysis considerations).

- 9. Article 4.0 Detection of Exogenous Threshold Substances in the Co-Presence of Diuretics or Masking Agents:** This Article changes the analytical criteria for reporting exogenous threshold substances when detected in a sample at levels lower than the DL in the co-presence of a diuretic or masking agent. Now, the concentration of the threshold substance shall be adjusted for a Specific Gravity (SG) = 1.020 if there is an indication of possible diuretic/masking effect (i.e., in samples with $SG \leq 1.018$). In such cases, the Laboratory shall report the finding as an *AAF* for the Threshold Substance only if the adjusted concentration of the Threshold Substance is higher than the corresponding DL, and the diuretic or masking agent is either not subject to an MRL or, where applicable, its estimated concentration is higher than the corresponding MRL.
- 10. Article 7.0 Adjustment of the DL for a High Specific Gravity of the Sample:** Further clarifications have been added regarding the adjustment of the DL when the SG of a sample is higher than (>) 1.018, including that the DL_{adj} shall be calculated for “A” sample quantitative results only; the adjustment is not needed for “B” Sample confirmations.
- 11. Annex A - Estimation and Verification of Measurement Uncertainty:** Annex A has been revised to address MU estimation approaches, focusing on top-down methods based on intra- and inter-laboratory evaluations. Article 2. emphasizes the verification/monitoring of MU using QC samples and EQAS results.