WADA Technical Document – ISL TD2027MRPL

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Written by: Reviewed by:	*WADA* Science / MRPL Working Group *WADA* Laboratory Expert Advisory Group	Approved by:	*WADA* Executive Committee
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MINIMUM REQUIRED PERFORMANCE LEVELS FOR NON-THRESHOLD SUBSTANCES ANALYZED BY CHROMATOGRAPHIC - MASS SPECTROMETRIC ANALYTICAL METHODS

1.0 Introduction

The objective of this *Technical Document* (*TD*), which constitutes an integral part of the *International Standard* for Laboratories (*ISL* [1]), is to harmonize, to the extent possible, the Laboratories' analytical capabilities to apply chromatographic-mass spectrometric Analytical *Testing* Procedures (ATPs) to the analysis of Non-Threshold Substances.

ATP performance differences, which can affect the detection capability for specific Analytes, may arise among Laboratories, for example, from the use of different *Sample* preparation procedures, instrumentation, or the application of different analytical techniques. Therefore, to ensure that Analytes of Non-Threshold Substances can be detected and identified consistently by Laboratories, Minimum Required Performance Levels (MRPLs) have been established as a mandatory requirement of Laboratory technical performance.

2.0 Minimum Required Performance Levels

a) The MRPL is a mandatory analytical parameter of technical performance that the Laboratory shall comply with when *Testing* for the presence of Analyte(s) of a particular Non-Threshold Substance in routine operations, during both Initial Testing Procedures (ITPs) and Confirmation Procedures (CPs).

b) The MRPL is not a Limit of Detection (LOD) (see ISL *TD* VAL [2]), nor is it a Threshold or a *Decision Limit* (*DL*) (see ISL *TD DL* [3]).

An *Adverse Analytical Finding* (*AAF*) may result from the identification in a *Sample,* in accordance with the ISL *TD* IDCR [4] and/or other applicable ISL *TD* or ISL *Technical Letter (*ISL *TL*) of Analyte(s) of a Non-Threshold Substance not subject to a *Minimum Reporting Level* (*MRL*) [5] at concentrations below the established MRPL (see also ISL *TD MRL* [5]).

c) The MRPL is established for relevant Analyte(s) of Non-Threshold Substances, depending on the extent of the Non-Threshold Substance's metabolism, pharmacokinetics, pharmacodynamics and/or stability in the *Sample* matrix.

[Comment to Article 2.0: Since the metabolic and excretion patterns of a substance may vary substantially with time after administration, the Laboratory shall include in their chromatographic-mass spectrometric ATPs, which are applied to the analysis of Non-Threshold Substances without MRL, those relevant Analyte(s) that would ensure the detection of the Use of the Prohibited Substance as extensively as possible (i.e., along the whole excretion period).]

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3.0 List of Minimum Required Performance Levels per Class of *Prohibited Substances*

a) Table 1 specifies the MRPLs applied to Analyte(s) of Non-Threshold Substances (either *Prohibited Substances* or *Markers* of *Use* of *Prohibited Methods*).

b) Except otherwise specified in Table 1, the MRPLs are applied to the analysis of urine *Samples*.

c) For the ITPs, the Laboratory shall be aware of the relevant Analyte(s) that have to be monitored so that the analysis covers, as much as possible, the kinetic profile of substance metabolism and/or excretion for a suspicious finding to be detected and subjected to a CP.

d) For the CPs, the Laboratory may include additional target Analyte(s) (*e.g.,* additional *Metabolite*(s) that were not initially included in the ITP), which could strengthen the interpretation of the test results. However, the MRPLs are not necessarily applied to all possible target Analyte(s) of a given Non-Threshold Substance, but only to those that have been determined as relevant to ensure the optimal detection of past substance *Use*.

e) The Laboratory should include in its validated CPs, and attempt to confirm, as many target Analyte(s) of Non-Threshold Substances as possible in order to report an *AAF* or *Atypical Finding* (*ATF*), including any additional target Analyte(s) necessary to correctly interpret the CP results (see Table 2 - MRPLs for Confounding Factors (Non-Prohibited Substances) that May Affect the Interpretation of Findings for *Prohibited Substances*).

f) Where applicable, the Laboratory shall record in the *ADAMS* Test Report the Non-Threshold Substance(s) that were identified in the *Sample* using the same nomenclature utilized in the *Prohibited List* [6]. In addition, wherever possible, relevant Analytes of the Non-Threshold Substance(s) identified in the *Sample* shall be recorded in the *ADAMS* Test Report using the same nomenclature as detailed in the relevant literature. The use of ambiguous or putative names for Analytes (for example, *Metabolite* M1) should be avoided to the extent possible. If this cannot be done (for example, because the structure of the Analyte has not been elucidated), then the Laboratory should indicate the original references for the name of the Analyte in the *ADAMS* Test Report.

g) For Non-Threshold Substances subject to *MRLs*, if the MRPL has not been specified in Table 1, the MRPL is assumed to be equal to the *MRL* (see ISL *TD MRL* [5]).

4.0 List of Confounding Factors

a) Table 2a includes a list of non-prohibited substances that may affect the interpretation of findings for *Prohibited Substances*, including the relevant target Analyte(s) and the applicable MRPLs for their detection.

b) Table 2b lists the confounding factors that may affect the urinary *Markers* of the Steroidal Module of the *Athlete Biological Passport* (*ABP*) and their respective MRPLs.

c) The ATPs for the analysis of Confounding Factors shall be validated in compliance with the *ISL* [1] and the applicable ISL *TD*s (*e.g.,* ISL *TD* VAL [2]), ISL *TLs* or Laboratory Guidelines (LGs) prior to their application to the analysis of *Samples*.

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Table 1. MRPLs per class of *Prohibited Substance*

Prohibited Class (Specific Exemptions)	**MRPL** (ng/mL)	**Comments**
S0. Non-Approved Substances		
BPC-157	20	
2,4-Dinitrophenol	20	
Ryanodine receptor-1-calstabin complex stabilizers (Rycals)	20	*e.g.,* S-107, S48168 (ARM210), JTV-519, ARM036.
Troponin Activators	20	*e.g.,* Reldesemtiv, Tirasemtiv.
S1.1 Anabolic Androgenic Steroids	**2.5**	Refer also to ISL *TL*08 [7], ISL *TL*10 [8] and ISL *TL*20 [9].
4α-chloro-18-nor-17β-hydroxymethyl-17α-methyl-5α-androst-13-en-3α-ol	0.4	Long-term *Metabolite* (LTM) of dehydrochlormethyltestosterone (DHCMT) and other related precursor steroids.
6α-hydroxy-androstenedione (6α-OH-AD)	10	Refer to *TD MRL* [2], ISL *TD* IRMS [10], ISL *TL*21 [11].
17β-hydroxymethyl-17α-methyl-18-nor-androst-1,4,13-trien-3-one	1	LTM of metandienone.
19-norandrosterone (19-NA), 19-noretiocholanolone (19-NE)	2.5	Refer to the ISL *TD MRL* [5] and ISL *TD* NA [12].
Boldenone	2.5	Refer to ISL *TD MRL* [5] and ISL *TD* IRMS [10].
Stanozolol	1	
S1.2 Other Anabolic Agents	**1**	• For andarine, refer to ISL *TL*07 [13]. • For enobosarm (ostarine), refer to ISL *TL*12 [14].
Clenbuterol	0.2	• Refer to ISL *TD MRL* [5] and ISL *TL*23 [15]. • For zeranol, refer also to ISL *TL*04 [16].
Ractopamine, zeranol, zilpaterol	1	
S2.1.1 Erythropoietin-Receptor Agonists (ERAs)		Refer to ISL *TD* EPO [17].
S2.1.2 HIF Activating Agents	**2**	
S2.2.1 Gonadotrophin (CG/LH) Releasing Factors	**2**	

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Prohibited Class (Specific Exemptions)	**MRPL** (ng/mL)	**Comments**
S2.2.3 Growth Hormone (GH), its Analogues and Fragments		
GH Fragments	2	
S2.2.4 Growth Hormone Releasing Factors		
GH-Releasing Hormone (GHRH) and its Analogues	1 Urine 0.3 Plasma / Serum	
GH Secretagogues (GHS) and its Mimetics	2	
GH-Releasing Peptides (GHRPs)	1	
S2.3 Growth Factors and Growth Factor Modulators		
IGF-I analogues	0.3 Urine 2 Plasma / Serum	
TB-500 (N-Ac LKKTETQ)	2	
S3. Beta-2 Agonists	**20**	• For formoterol and salbutamol, which are Threshold Substances, refer to ISL *TD DL* [3]. • For higenamine, salmeterol, tretoquinol and vilanterol, which are Non-Threshold Substances subject to *MRL*, see ISL *TD MRL* [5]. • For tulobuterol, refer to ISL *TL*17 [18].
S4.1 Aromatase Inhibitors	**20**	• For 6-oxo, refer to ISL *TL*21 [11]. • For testolactone, refer to ISL *TL*18 [19]. • For other aromatase inhibitors, refer to ISL *TL*20 [9]
Formestane	50	Refer to ISL *TD MRL* [5] and ISL *TD* IRMS [10].
S4.2 Anti-estrogenic Substances and SERMS	**20**	
Clomifene	**2**	Refer to ISL *TD MRL* [5] and ISL *TL*26 [20].

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Prohibited Class (Specific Exemptions)	**MRPL** (ng/mL)	**Comments**
S4.4 Metabolic Modulators	**10**	For trimetazidine, refer to ISL *TL*13 [21].
GW1516 and GW0742	2	
Insulins	0.05 Urine 0.3 Plasma / Serum	
Meldonium	100	Refer to ISL *TD MRL* [5]
S5. Diuretics and Masking Agents		
Diuretics	**200**	For chlorazanil, refer to ISL *TL*06 [22].
Acetazolamide, bumetanide, furosemide, hydrochlorothiazide, torasemide, triamterene	20	Refer to ISL *TD MRL* [5] and ISL *TL*24 [23].
Masking Agents	**200**	
Desmopressin and analogs	2	
HES	200 000 (200 µg/mL)	
M1.2 Artificially Enhancing the Uptake, Transport or Delivery of Oxygen		
Efaproxiral (RSR13)	10	
S6. Stimulants **S7. Narcotics** **S8. Cannabinoids** **S9. Glucocorticoids**	**All *Prohibited Substances* within these classes are prohibited *In-Competition* only.** **Therefore, specific *MRLs* apply, and the MRPL equals the corresponding *MRL* value – See ISL *TD MRL* [5]** For methylephedrine, ephedrine, canthine, pseudoephedrine, morphine and carboxy-THC, which are Threshold Substances, refer to ISL *TD DL* [3].	
P1. Beta-Blockers	50	Beta-blockers are Non-Threshold Substances prohibited at all times [8] and shall be reported if their presence is confirmed in a *Sample* at any concentration (in compliance with the identification criteria established in the ISL *TD* IDCR [2]). However, an *MRL* for beta-blockers is applied in those sports where the substance is prohibited *In-Competition* only. Refer to the ISL *TD MRL* [5] and *Prohibited List* [8].

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Table 2a. MRPLs for Confounding Factors (Non-Prohibited Substances) that May Affect the Interpretation of Findings for *Prohibited Substances*

Confounding Factor	***Prohibited Substance* affected**	**Common Metabolic Pathway or Degradation Product**	**Relevant Target(s)** (Analyte(s) that should be monitored by the Laboratory)	**MRPL (ng/mL)**	**Normative Document**
Bicalutamide	Enobosarm (Ostarine)	O-dephenyl-ostarine	Ostarine and/or Ostarine glucuronide	1	ISL *TL*12 [14]
Chlorphenesin	Meclofenoxate	4-chlorophenoxyacetic acid (4-CPA)	Chlorphenesin (glucuronide and/or sulfate) 3-(4-Chlorophenoxy)-2-hydroxypropanoic acid (4-CPP)	50	ISL *TL*01 [24]
Chlorphenesin carbamate			Chlorphenesin carbamate (glucuronide and/or sulfate) 4-CPP carbamate		
Codeine (C)	Morphine (M)	C metabolizes into M	C + C-glucuronide	500	ISL *TD DL* [3]
Ethylmorphine (EtM)		EtM metabolizes into M	EtM + EtM-glucuronide Nor-EtM + Nor-EtM-6-glucuronide	500 50	
Flutamide	Andarine	O-Dephenylandarine, O-Dephenylandarine glucuronide	Andarine and/or Andarine glucuronide and/or Desacetyl-hydroxy-Andarine and/or Andarine hydroxylated Metabolites and/or Andarine bishydroxylated *Metabolites*	1	ISL *TL*07 [13]
Hydrocodone (HC)	Hydromorphone (HM)	Metabolization of HC or C into HM	Hydrocodone Norhydrocodone	25	ISL *TL*15 [25]
Lomerizine	Trimetazidine (TMZ)	Lomerizine may metabolize into TMZ	Lomerizine 1-Bis-(4-fluorophenyl)-methylpiperazine	10	ISL *TL*13 [21]
Mebeverine	Amfetamine Selegiline Famprofazone	*para*-Hydroxy-amphetamine (*p*-OH-A).	Mebeverine acid Desmethyl mebeverine acid	50	ISL *TL*02 [26]
Methylnaltrexone (MTNX)	Oxymorphone	Oxymorphone as a degradation artifact of MTNX	Methylnaltrexone	50	ISL *TD MRL* [5]
Morazone	Phenmetrazine	Phenmetrazine	Morazone	50	n/a
Norethisterone	19-NA	19-NA is a minor *Metabolite* of norethisterone	5β-Estran-17α-ethynyl-3α,17β-diol	2.5	ISL *TD* NA [12]
O-desmethyl-venlafaxine	Tramadol	O-desmethyl-venlafaxine may interfere with tramadol detection under certain chromatographic conditions [27]	O-desmethyl-venlafaxine	20,000 (*i.e.,* 20 µg/mL)	ISL *TD MRL* [5]

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Confounding Factor	***Prohibited Substance* affected**	**Common Metabolic Pathway or Degradation Product**	**Relevant Target(s)** (Analyte(s) that should be monitored by the Laboratory)	**MRPL (ng/mL)**	**Normative Document**
Oxethazaine	Phentermine, Mephentermine	Phentermine and mephentermine as minor *Metabolites* of oxethazaine	β-hydroxyphentermine; and/or β-hydroxymephentermine	50	ISL *TD MRL* [5]
Proguanil	Chlorazanil	Proguanil is metabolized into N-(4-chlorophenyl)-biguanide, which is a chemical precursor of chlorazanil	N-(4-Chlorophenyl)-biguanide and either Proguanil or Cycloguanil	200	ISL *TL*06 [22]
Zearalenone	Zeranol and *Metabolites*: Zearalanone and Taleranol	Zeranol	Zearalenone α-Zearalenol β-Zearalenol	5	ISL *TL*04 [16] ISL *TL*23 [15]

Table 2b. MRPLs for Confounding Factors (Non-Prohibited Substance) that May Affect the Urinary *Markers* of the Steroidal Module of the *Athlete Biological Passport*

Confounding Factor	***Markers* of the Steroid Profile affected**	**Target Substances**	**MRPL (ng/mL)**	**Normative Document**
Ethylglucuronide (EtG)	Testosterone (T) Androsterone (A) Etiocholanolone (Etio 5α-Androstane-3α,17β-diol (5αAdiol) 5β-Androstane-3α,17β-diol (5βAdiol) Epitestosterone (E).	EtG	5,000 (*i.e.,* 5 µg/mL)	ISL *TD* USM [28]
Inhibitors of 5α-reductase:				
• Finasteride		Carboxy-finasteride	5	
• Dutasteride		4-hydroxy-dutasteride 6-hydroxy-dutasteride		

5.0 References

[1] The World Anti-Doping *Code International Standard* for Laboratories (ISL).

[2] *WADA Technical Document* ISL *TD* VAL: Minimum Requirements for Validation of Analytical *Testing* Procedures for *Doping Control.*

[3] *WADA Technical Document* ISL *TD DL*: *Decision Limits* for the Confirmatory Quantification of Exogenous Threshold Substances.

[4] *WADA Technical Document* ISL *TD* IDCR: Minimum Criteria for Chromatographic-Mass Spectrometric Confirmation of the Identity of Analytes for *Doping Control* Purposes.

[5] *WADA Technical Document* ISL *TD MRL*: *Minimum Reporting Levels* Applied in *Doping Control*.

[6] The World Anti-Doping *Code International Standard Prohibited List*

[7] *WADA Technical Letter* ISL *TL*08: Use of Internal Standards.

[8] *WADA Technical Letter* ISL *TL*10: In situ Formation of Exogenous Compounds

[9] *WADA Technical Letter* ISL *TL*20: Specific substances with a steroid structure

[10] *WADA Technical Document* ISL *TD* IRMS: Detection of Synthetic Forms of *Prohibited Substances* by GC/C/IRMS.

[11] *WADA Technical Letter* ISL *TL*21: *In Situ* formation of 4-Androstene-3,6,17-trione (6-oxo) and *Metabolites.*

[12] *WADA Technical Document* ISL *TD* NA: Harmonization of Analysis and Reporting of 19-Norsteroids.

[13] *WADA Technical Letter* ISL *TL*07: Andarine – Flutamide.

[14] *WADA Technical Letter* ISL *TL*12: Enobosarm.

[15] *WADA Technical Letter* ISL *TL*23: Growth Promoters (meat contaminants).

[16] *WADA Technical Letter* ISL *TL*04: Zeranol.

[17] *WADA Technical Document* ISL *TD* EPO: Harmonization of Analysis and Reporting of Erythropoietin (EPO) and other EPO-Receptor Agonists (ERAs) by Polyacrylamide Gel Electrophoretic (PAGE) Analytical Methods.

[18] *WADA Technical Letter* ISL *TL*17: Detection of Tulobuterol in the presence of Bupropion.

[19] *WADA Technical Letter T* ISL *L*18: Testolactone.

[20] *WADA Technical Letter* ISL *TL*26: Clomifene.

[21] *WADA Technical Letter* ISL *TL*13: Trimetazidine.

[22] *WADA Technical Letter* ISL *TL*06: Possible Metabolism of Proguanil into Chlorazanil.

[23] *WADA Technical Letter* ISL *TL*24: Diuretics (contaminants of pharmaceutical products)

[24] *WADA Technical Letter* ISL *TL*01: Meclofenoxate

[25] *WADA Technical Letter* ISL *TL*15: Hydromorphone

[26] *WADA Technical Letter* ISL *TL*02: Mebeverine Metabolism

[27] Allen KR. Interference by Venlafaxine Ingestion in the Detection of Tramadol by Liquid Chromatography Linked to Tandem Mass Spectrometry for the Screening of Illicit Drugs in Human Urine. Clin Toxicol, 44:2, 147-153, 2006.

[28] *WADA Technical Document* ISL *TD* USM: Analytical and Reporting Requirements for the Urinary *Markers* of the Steroidal Module of the *Athlete Biological Passport.*

[Current versions of WADA's ISL, Technical Documents and Technical Letters may be found at https://www.wada-ama.org/en/what-we-do/international-standards]