

# WADA Technical Document – ISL TD2027MRPL

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Written by:	WADA Science / MRPL Working Group	Approved by:	WADA Executive Committee
Reviewed by:	WADA Laboratory Expert Advisory Group		
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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* <sup>[1]</sup>), 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 <sup>[2]</sup>), nor is it a Threshold or a Decision Limit (DL) (see ISL TD DL <sup>[3]</sup>).

An Adverse Analytical Finding (AAF) may result from the identification in a Sample, in accordance with the ISL TD IDCR <sup>[4]</sup> 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) <sup>[5]</sup> at concentrations below the established MRPL (see also ISL TD MRL <sup>[5]</sup>).

- 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* <sup>[6]</sup>. 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* <sup>[5]</sup>).

## 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* <sup>[1]</sup> and the applicable *ISL TDs* (e.g., *ISL TD VAL* <sup>[2]</sup>), *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
<b>S0. Non-Approved Substances</b>		
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.
<b>S1.1 Anabolic Androgenic Steroids</b>	<b>2.5</b>	Refer also to ISL TL08 [7], ISL TL10 [8] and ISL TL20 [9].
4 $\alpha$ -chloro-18-nor-17 $\beta$ -hydroxymethyl-17 $\alpha$ -methyl-5 $\alpha$ -androst-13-en-3 $\alpha$ -ol	0.4	Long-term <i>Metabolite</i> (LTM) of dehydrochloromethyltestosterone (DHCMT) and other related precursor steroids.
6 $\alpha$ -hydroxy-androstenedione (6 $\alpha$ -OH-AD)	10	Refer to <i>TD MRL</i> [2], ISL <i>TD IRMS</i> [10], ISL <i>TL21</i> [11].
17 $\beta$ -hydroxymethyl-17 $\alpha$ -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 <i>TD MRL</i> [5] and ISL <i>TD NA</i> [12].
Boldenone	2.5	Refer to ISL <i>TD MRL</i> [5] and ISL <i>TD IRMS</i> [10].
Stanozolol	1	
<b>S1.2 Other Anabolic Agents</b>	<b>1</b>	<ul style="list-style-type: none"> <li>For andarine, refer to ISL <i>TL07</i> [13].</li> <li>For enobosarm (ostarine), refer to ISL <i>TL12</i> [14].</li> </ul>
Clenbuterol	0.2	<ul style="list-style-type: none"> <li>Refer to ISL <i>TD MRL</i> [5] and ISL <i>TL23</i> [15].</li> </ul>
Ractopamine, zeranol, zilpaterol	1	<ul style="list-style-type: none"> <li>For zeranol, refer also to ISL <i>TL04</i> [16].</li> </ul>
<b>S2.1.1 Erythropoietin-Receptor Agonists (ERAs)</b>		Refer to ISL <i>TD EPO</i> [17].
<b>S2.1.2 HIF Activating Agents</b>	<b>2</b>	
<b>S2.2.1 Gonadotrophin (CG/LH) Releasing Factors</b>	<b>2</b>	

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Prohibited Class (Specific Exemptions)	MRPL (ng/mL)	Comments
<b>S2.2.3 Growth Hormone (GH), its Analogues and Fragments</b>		
GH Fragments	2	
<b>S2.2.4 Growth Hormone Releasing Factors</b>		
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	
<b>S2.3 Growth Factors and Growth Factor Modulators</b>		
IGF-I analogues	0.3 Urine 2 Plasma/ Serum Plasma/ Serum	
TB-500 (N-Ac LKKTETQ)	2	
<b>S3. Beta-2 Agonists</b>	20	<ul style="list-style-type: none"> <li>For formoterol, <del>and</del> salbutamol <del>and salmeterol</del>, which are <u>Threshold Substances</u>, refer to ISL <i>TD DL</i> [3].</li> <li>For higenamine, <u>salmeterol</u>, tretoquinol and vilanterol, which are <u>Non-Threshold Substances</u> subject to <i>MRL</i>, see ISL <i>TD MRL</i> [5].</li> <li>For tulobuterol, refer to ISL <i>TL17</i> [18].</li> </ul>
<b>S4.1 Aromatase Inhibitors</b>	20	<ul style="list-style-type: none"> <li>For 6-oxo, refer to ISL <i>TL21</i> [11].</li> <li>For testolactone, refer to ISL <i>TL18</i> [19].</li> <li>For other aromatase inhibitors, refer to ISL <i>TL20</i> [9].</li> </ul>
Formestane	50	Refer to ISL <i>TD MRL</i> [5] and ISL <i>TD IRMS</i> [10].

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<b>S4.2 Anti-estrogenic Substances and SERMS</b>	<b>20</b>	
Clomifene	<b>2</b>	Refer to ISL <i>TD MRL</i> <sup>[5]</sup> and ISL <i>TL26</i> <sup>[20]</sup> .
<b>Prohibited Class (Specific Exemptions)</b>	<b>MRPL</b> (ng/mL)	<b>Comments</b>
<b>S4.4 Metabolic Modulators</b>	<b>10</b>	For trimetazidine, refer to ISL <i>TL13</i> <sup>[21]</sup> .
GW1516 and GW0742	2	
Insulins	0.05 Urine 0.3 Plasma Serum	
Meldonium	100	Refer to ISL <i>TD MRL</i> <sup>[5]</sup>
<b>S5. Diuretics and Masking Agents</b>		
<b>Diuretics</b>	<b>200</b>	For chlorazanyl, refer to ISL <i>TL06</i> <sup>[22]</sup> .
Acetazolamide, bumetanide, furosemide, hydrochlorothiazide, torasemide, triamterene	20	Refer to ISL <i>TD MRL</i> <sup>[5]</sup> and ISL <i>TL24</i> <sup>[23]</sup> .
<b>Masking Agents</b>	<b>200</b>	
Desmopressin and analogs	2	
HES	200 000 (200 µg/mL)	
<b>M1.2 Artificially Enhancing the Uptake, Transport or Delivery of Oxygen</b>		
Efaproxiral (RSR13)	10	
<b>S6. Stimulants</b> <b>S7. Narcotics</b> <b>S8. Cannabinoids</b> <b>S9. Glucocorticoids</b>		<b>All Prohibited Substances within these classes are prohibited <i>In-Competition</i> only.</b> <b>Therefore, specific <i>MRLs</i> apply, and the <u>MRPL</u> equals the corresponding <i>MRL</i> value</b> <b>– See ISL <i>TD MRL</i> <sup>[5]</sup></b> <a href="#">For methylephedrine, ephedrine, canthine, pseudoephedrine, morphine and carboxy-THC, which are Threshold Substances, refer to ISL <i>TD DL</i> <sup>[3]</sup>.</a>
<b>P1. Beta-Blockers</b>	50	Beta-blockers are Non-Threshold Substances prohibited at all times <sup>[8]</sup> and shall be reported if their presence is confirmed in a <i>Sample</i> at any

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	concentration (in compliance with the identification criteria established in the ISL TD IDCR <sup>[2]</sup> ). However, an MRL for beta-blockers is applied in those sports where the substance is prohibited <i>In-Competition</i> only. Refer to the ISL TD MRL <sup>[5]</sup> and <i>Prohibited List</i> <sup>[8]</sup> .
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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 TL12 <sup>[14]</sup>
Chlorphenesin	Meclofenoxate	4-chlorophenoxyacetic acid (4-CPA)	Chlorphenesin (glucuronide and/or sulfate)	50	ISL TL01 <sup>[24]</sup>
Chlorphenesin carbamate			3-(4-Chlorophenoxy)-2-hydroxypropanoic acid (4-CPP) Chlorphenesin carbamate (glucuronide and/or sulfate) 4-CPP carbamate		
Codeine (C)	Morphine (M)	C metabolizes into M	C + C-glucuronide	500	ISL TD DL <sup>[3]</sup>
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 TL07 <sup>[13]</sup>
Hydrocodone (HC)	Hydromorphone (HM)	Metabolization of HC or C into HM	Hydrocodone Norhydrocodone	25	ISL TL15 <sup>[25]</sup>
Lomerizine	Trimetazidine (TMZ)	Lomerizine may metabolize into TMZ	Lomerizine 1-Bis-(4-fluorophenyl)-methylpiperazine	10	ISL TL13 <sup>[21]</sup>
Mebeverine	Amfetamine Selegiline Famprofazone	<i>para</i> -Hydroxy-amphetamine ( <i>p</i> -OH-A).	Mebeverine acid Desmethyl mebeverine acid	50	ISL TL02 <sup>[26]</sup>
Methylnaltrexone (MTNX)	Oxymorphone	Oxymorphone as a degradation artifact of MTNX	Methylnaltrexone	50	ISL TD MRL <sup>[5]</sup>
Morazone	Phenmetrazine	Phenmetrazine	Morazone	50	n/a

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Norethisterone	19-NA	19-NA is a minor <i>Metabolite</i> of norethisterone	5 $\beta$ -Estran-17 $\alpha$ -ethynyl-3 $\alpha$ ,17 $\beta$ -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 $\mu$ g/mL)	ISL TD MRL [5]
<b>Confounding Factor</b>	<b>Prohibited Substance affected</b>	<b>Common Metabolic Pathway or Degradation Product</b>	<b>Relevant Target(s) (Analyte(s) that should be monitored by the Laboratory)</b>	<b>MRPL (ng/mL)</b>	<b>Normative Document</b>
Oxethazaine	Phentermine, Mephentermine	Phentermine and mephentermine as minor <i>Metabolites</i> of oxethazaine	$\beta$ -hydroxyphentermine; and/or $\beta$ -hydroxymephentermine	50	ISL TD MRL [5]
Proguanil	Chlorazaniil	Proguanil is metabolized into N-(4-chlorophenyl)-biguanide, which is a chemical precursor of chlorazaniil	N-(4-Chlorophenyl)-biguanide and either Proguanil or Cycloguanil	200	ISL TL06 [22]
Zearalenone	Zeranol and <i>Metabolites</i> : Zearalenone and Taleranol	Zeranol	Zearalenone $\alpha$ -Zearalenol $\beta$ -Zearalenol	5	ISL TL04 [16] ISL TL23 [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) Etiolcholanolone (Etio)	EtG	5,000 (i.e., 5 $\mu$ g/mL)	ISL TD USM [28]
Inhibitors of 5 $\alpha$ -reductase:	5 $\alpha$ -Androstane-3 $\alpha$ ,17 $\beta$ -diol (5 $\alpha$ Adiol)		5	
• Finasteride	5 $\beta$ -Androstane-3 $\alpha$ ,17 $\beta$ -diol (5 $\beta$ Adiol)	Carboxy-finasteride		
• Dutasteride	Epitestosterone (E).	4-hydroxy-dutasteride 6-hydroxy-dutasteride		

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## 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 TL08: Use of Internal Standards.
- [8] WADA Technical Letter ISL TL10: In situ Formation of Exogenous Compounds
- [9] WADA Technical Letter ISL TL20: 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 TL21: *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 TL07: Andarine – Flutamide.
- [14] WADA Technical Letter ISL TL12: Enobosarm.
- [15] WADA Technical Letter ISL TL23: Growth Promoters (meat contaminants).
- [16] WADA Technical Letter ISL TL04: 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 TL17: Detection of Tulobuterol in the presence of Bupropion.
- [19] WADA Technical Letter T ISL L18: Testolactone.
- [20] WADA Technical Letter ISL TL26: Clomifene.
- [21] WADA Technical Letter ISL TL13: Trimetazidine.
- [22] WADA Technical Letter ISL TL06: Possible Metabolism of Proguanil into Chlorazaniil.
- [23] WADA Technical Letter ISL TL24: Diuretics (contaminants of pharmaceutical products)
- [24] WADA Technical Letter ISL TL01: Meclofenoxate
- [25] WADA Technical Letter ISL TL15: Hydromorphone
- [26] WADA Technical Letter ISL TL02: 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>]