WADA IRMS Technical Document update and further documentation guidance

Second IRMS Workshop

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22-23 September 2023
London, UK

ISL
TD IRMS / TD EAAS / TD NA
IRMS Technical Note
IRMS Checklist

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ISL 2021 Art. 1.1.2 – Technical Documents

Mandatory Character of TDs

The implementation of TD requirements into the Laboratory's (…) Management System is mandatory for obtaining and maintaining *WADA* accreditation (…) and for the application of the relevant Analytical Testing Procedure(s) to the analysis of Samples.

A failure by a Laboratory to implement a TD (…) by the effective date may result in the imposition of an Analytical Testing Restriction against the Laboratory for that particular Analytical Testing Procedure or a Suspension of the Laboratory's WADA accreditation (…), as determined by WADA.

Effective Date of a TD

Implementation of the requirements detailed in a TD may occur prior to the effective date for implementation specified in the TD and shall occur no later than the effective date.

The most recently approved TD shall be applied (…) prior to the effective date if it would lead to a result that benefits the Athlete (e.g., increase of a Decision Limit…). Therefore, in the case where an analytical finding does not meet the reporting criteria defined in the new TD, it shall be reported as a Negative Finding.

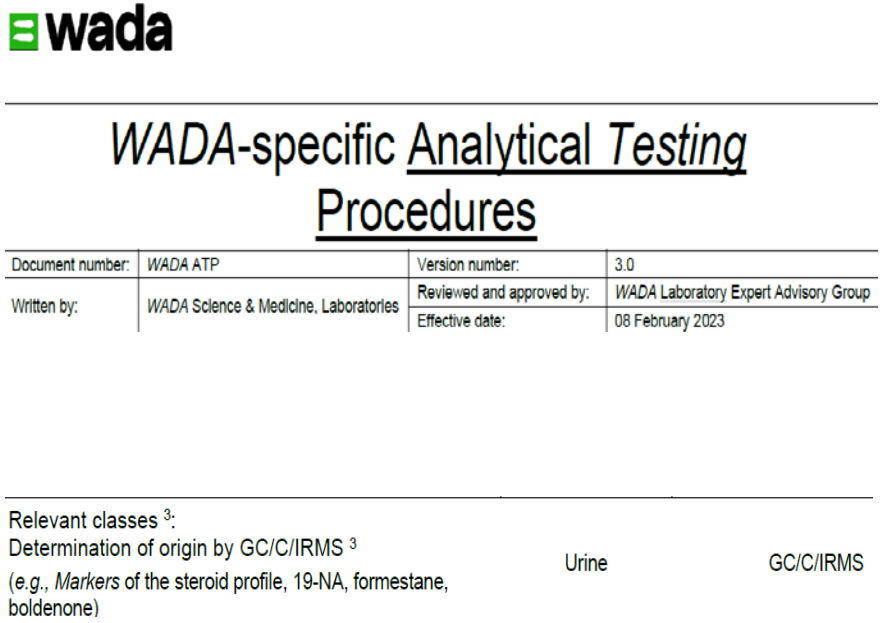
Subject to he above, the analysis of samples or the review of analytical data may occur immediately once a TD has been approved.

ISL 2021 Art. 4.4.2.2 – Flexible Scope of ISO/IEC 17025 Accreditation

WADA-specific Analytical Testing Procedures

WADA may require an extension of the Scope of ISO/IEC 17025 Accreditation to include specific ATPs before application to the analysis of Samples, even if the analytical technique involved is already incorporated in the Laboratory's Scope of ISO/IEC 17025 Accreditation

However, once included within the scope, limited changes to these ATPs may be allowed within the boundaries of a Flexible Scope of ISO/IEC 17025 Accreditation (*e.g., inclusion of new Analytes*). **Nonetheless, this flexibility does not allow the Laboratories to introduce new Analytes within these ATPs if specific method performance and compliance decision criteria (e.g., DLs) are needed and those criteria are not yet defined in an applicable TD (e.g., new target compound(s) for GC/C/IRMS analysis).**



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WADA-specific Analytical *Testing* Procedures

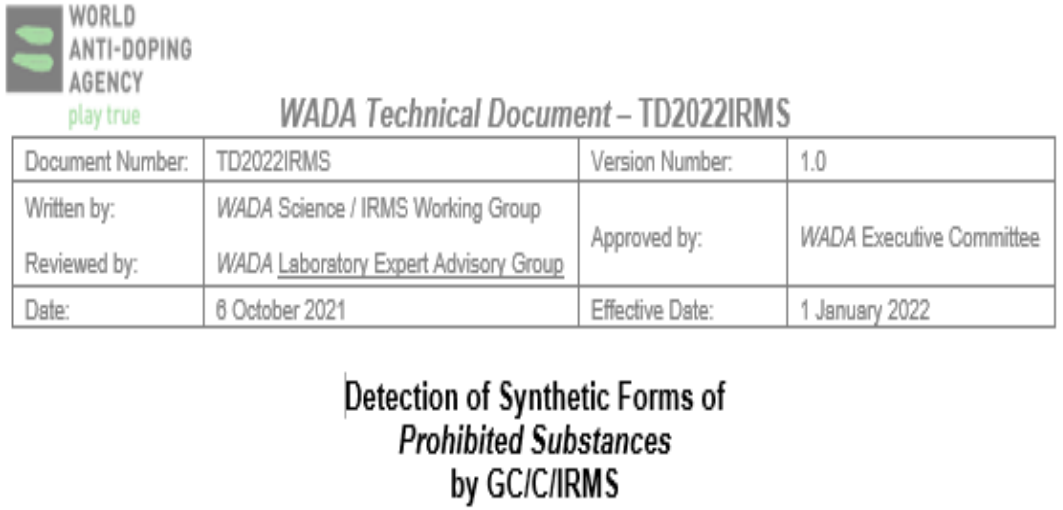
Document number:	*WADA* ATP	Version number:	3.0
Written by:	*WADA* Science & Medicine, Laboratories	Reviewed and approved by:	*WADA* Laboratory Expert Advisory Group
		Effective date:	08 February 2023

Relevant classes [3]: Determination of origin by GC/C/IRMS [3] (*e.g., Markers* of the steroid profile, 19-NA, formestane, boldenone)	Urine	GC/C/IRMS

TD IRMS - Revision Points

- Additional Target Compounds ?
  - S1.1. Adrenosterone (11-oxo)[1]; 1-androstene-steroids (1-androstenediol, 1-androstenedione [1AD], 1-testosterone, 1-androsterone [1AND], and 1-epiandrosterone [1EpiAND])
  - S4.1: Androstatrienedione [TRD] (and its main metabolite 17β-hydroxy-androsta-1,4,6-triene-3-one); 6β-OH-AD.
  - S4.4.1 AICAR
- Expansion of lab analytical capacity for B, BM, Formestane, 19-NA, 6α-OH-AD, EpiA?? Mandatory?
- Issues of sample contamination?

[1] 11-keto-T at > 40 ng/mL should lead to CP for 11-oxo and exclude the use of 11OHA and 11-O-Etio as ERCs for IRMS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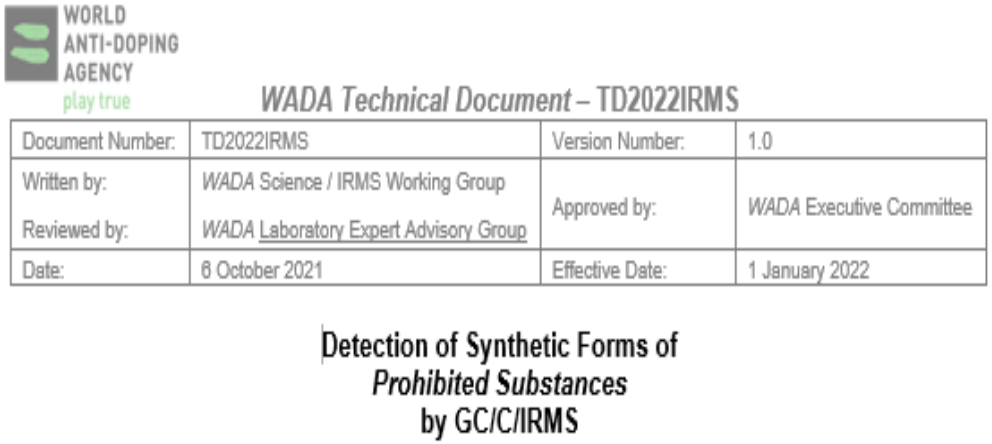
WADA Technical Document – TD2022IRMS

Document Number:	TD2022IRMS	Version Number:	1.0
Written by: Reviewed by:	*WADA* Science / IRMS Working Group *WADA* Laboratory Expert Advisory Group	Approved by:	*WADA* Executive Committee
Date:	6 October 2021	Effective Date:	1 January 2022

Detection of Synthetic Forms of *Prohibited Substances* by GC/C/IRMS

TD IRMS - Revision Points (cont)

- Use of ERCs: Consideration of confounders / synthetic precursors:
  - ERCs with $\delta^{13}C$ values not compatible with an endogenous origin (≤ -25.0 ‰)
  - Pregnenolone, Progesterone – PD : define in SOP a substitute ERC1
  - Adrenosterone (prohibited) - 11-OH-A and 11-oxo-Etio : how to establish use?
  - Cortisol, cortisone (prohibited IC)
  - Make ERC3 mandatory? (e.g. PD not measurable or affected by synthetic precursor)
  - Other confounders?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Detection of Synthetic Forms of *Prohibited Substances* by GC/C/IRMS

TD IRMS - Revision Points (cont)

- Interpretation of IRMS results:
  - Consideration of both GC-MS^n and IRMS results: doping scenario

    T/E > 10; high T: IRMS inconclusive?
  - Positive IRMS results shall prevail
  - Negative / inconclusive IRMS results: pseudoendogenous preparations, use of synthetic precursors of ERCs, populations with naturally depleted $\delta^{13}C$ values.
  - Don't hesitate to ask for 2nd opinion.

TD IRMS - Revision Points (cont)

- Reporting of IRMS results:

Unsatisfactory feedback from TAs: reporting of IRMS results not aligned with other AAF, difficult to understand

• An IRMS AAF is currently reported in the ADAMS report as

AAF – The GC/C/IRMS results are consistent with of the exogenous origin the target compound(s).

Then each TDIRMS criterion met is listed separately such as:

S1.1 Anabolic Androgenic Steroids (AAS)/ The GC/C/IRMS results are consistent with the exogenous origin of Testosterone and at least one of the Adiols (5αAdiol and/or 5βAdiol) when using 11β-hydroxyandrosterone (11-OHA) as ERC.

• Other substances are reported in the ADAMS report as

AAF - Adverse Analytical Finding: S1.1 Anabolic Androgenic Steroids (AAS)/drostanolone

Positive Criteria (Art. 2.3.2)	$\lvert\Delta\delta^{13}C\rvert$ ERC-TC					
	T	E	A	Etio	5αAdiol, 5βAdiol	B, BM1, F 6α-OH-AD, EpiA *
i.	> 3.0 ‰				> 3.0 ‰ (either Adiol)	
ii.					> 3.0 ‰ (both Adiols)	
iii.		> 4.5 ‰				
iv.&			> 2.0 ‰	> 3.0 ‰		
v.			> 2.0 ‰		> 3.0 ‰ (either Adiol)	
				> 3.0 ‰	> 3.0 ‰ (either Adiol)	
vi.					$\lvert\Delta\delta^{13}$(ERC-5α)$\rvert$ > 4.0 ‰ and δ^{13}C(5α) ≤ -27.0 ‰	
vii.						> 4.0 ‰

TD IRMS - Revision Points (cont)

- Reporting of IRMS results:

  TD IRMS Art. 3.0

  • GC/C/IRMS results are consistent with the exogenous administration of the substance(s), **specifying the identity of the relevant TC(s)** that produced a positive GC/C/IRMS finding

  *AAF: GC/C/IRMS results are consistent with the exogenous origin of **T and 5βAdiol***

- Proposed Improvements

  - Remove criteria statements from ADAMS report (intermediate details in TD LDOC)
  - Explicitly name which substance and/or metabolite has been confirmed as exogenous

  E.g., *Presence of testosterone and/or testosterone metabolites (…) of non-endogenous origin, compatible with the exogenous application of testosterone and/or its precursors*

Positive Criteria (Art. 2.3.2)	$\lvert\Delta\delta^{13}C\rvert_{ERC\text{-}TC}$					
	T	E	A	Etio	5αAdiol, 5βAdiol	B, BM1, F 6α-OH-AD, EpiA *
i.	> 3.0 ‰				> 3.0 ‰ (either Adiol)	
ii.					> 3.0 ‰ (both Adiols)	
iii.		> 4.5 ‰				
iv.&			> 2.0 ‰	> 3.0 ‰		
v.			> 2.0 ‰		> 3.0 ‰ (either Adiol)	
				> 3.0 ‰	> 3.0 ‰ (either Adiol)	
vi.					$\lvert\Delta\delta^{13}$(ERC-5α)$\rvert$ > 4.0 ‰ and $\delta^{13}C$(5α) ≤ -27.0 ‰	
vii.						> 4.0 ‰

TD EAAS - Management of IRMS Analyses

- TD2021(v2)EAAS Art. 3.1.1:
  - High T/E (ADAMS) ➡ ATPF-CPR (Lab, TA, APMU)

  Proceed to CP (including IRMS) unless:

  1- Confounding Factors

  Advice from TA (RMA) or Passport Custodian, in writing, within 15 days of ATPF-CPR. If not received ➡ IRMS

  If TA (RMA)/ PC say NO IRMS ➡ Report reasons in ADAMS

  2- AAFs for other substances ➡ Consult TA (RMA)

- TD2021(v2)EAAS Art. 3.1.2:
  - Abnormal values or sequences of A/T, A/Etio, 5αAdiol/5βAdiol, 5αAdiol/E ➡ ATPF-CPR (~~Lab~~, TA, APMU)

  APMU advices TA (RMA) on CP
  IRMS upon written request from TA (RMA)

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***WADA Technical Document* – TD2021EAAS**

Document Number:	TD2021EAAS	Version Number:	2.0
Written by: Reviewed by:	*WADA* Science/EAAS Working Group *WADA* Laboratory Expert Group	Approved by:	*WADA* Executive Committee
Date:	20 May 2021	Effective Date:	1 June 2021

Measurement and Reporting of Endogenous Anabolic Androgenic Steroid (EAAS) *Markers* of the Urinary Steroid Profile

TD EAAS - Management of IRMS Analyses

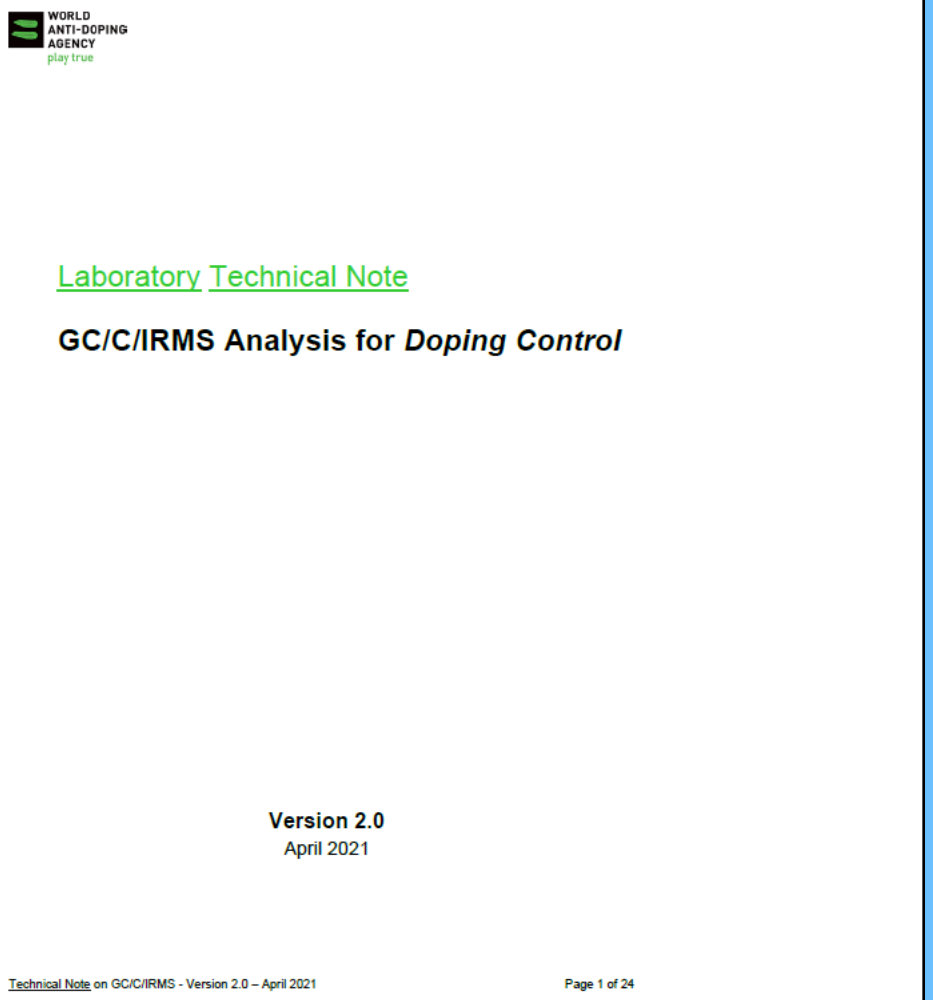
In addition, once IRMS is triggered:

- TD2021(v2)EAAS Art. 3.2.1:
  - GC-MS^n quantitative confirmation of all the Markers of the steroid profile* before IRMS analysis, unless agree with TA to proceed directly to IRMS

    * For T/E, only T may be confirmed (low sample volume, E not detected)
  - ATPF-CPR (T/E): IRMS not mandatory when the confirmed T/E < confirmation T/E cut-off (provided within the ATPF-CPR notification)
  - Other ATPF-CPR: Consult TA before IRMS if CP value ≠ ITP value ($\pm U_{95\%}$)

- TD2021(v2)EAAS Art. 3.3.1:
  - Microbial contamination (T_{free} / T_{total} > 0.05 as determined during CP): shall not preclude the performance of IRMS or invalidate IRMS results.

IRMS TN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Laboratory Technical Note

GC/C/IRMS Analysis for *Doping Control*

Version 2.0
April 2021

Technical Note on GC/C/IRMS - Version 2.0 – April 2021 Page 1 of 24

ISL Art. 1.1.5 - Technical Notes

Implementation of the recommendations detailed in TNs is not mandatory. However, Laboratories are encouraged to follow, to the fullest extent possible, the technical guidance included in TNs.

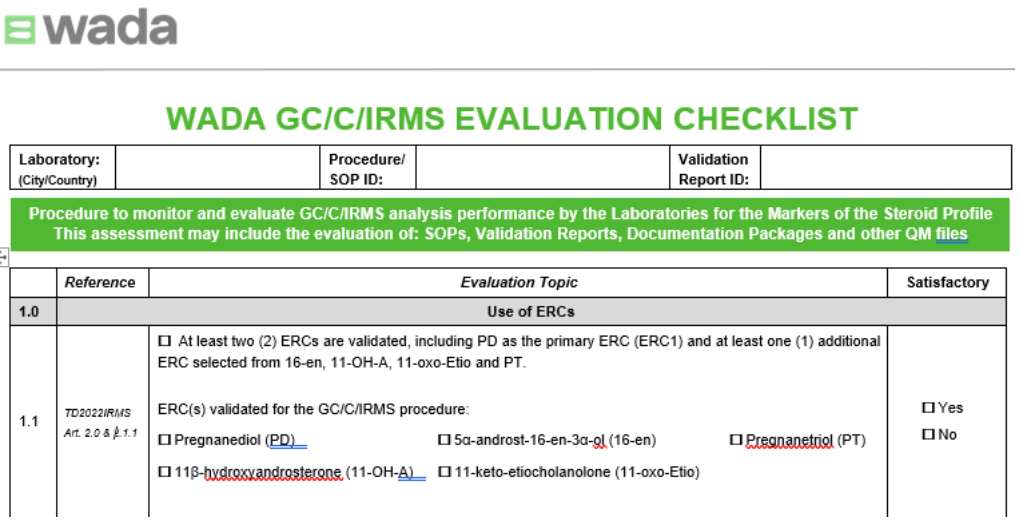
TNs are provided to Laboratories only and are not published on WADA's website (confidential!)

TN IRMS drafted by your colleagues (IRMS WG) – following it will ensure proper validation, implementation, interpretation and reporting of IRMS results

Two Appendices (Measurement Uncertainty)

App1: Intermediate Precision (One-way ANOVA)
Bias (Linear Mixing Model)
App2: Model spreadsheet for calculation of s_w, u_{bias}, and u_c

IRMS Check List



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WADA GC/C/IRMS EVALUATION CHECKLIST

Laboratory: (City/Country)		Procedure/ SOP ID:		Validation Report ID:	

Procedure to monitor and evaluate GC/C/IRMS analysis performance by the Laboratories for the Markers of the Steroid Profile
This assessment may include the evaluation of: SOPs, Validation Reports, Documentation Packages and other QM files

	Reference	*Evaluation Topic*	Satisfactory
1.0		**Use of ERCs**	
1.1	*TD2022IRMS Art. 2.0 & Ĵ.1.1*	☐ At least two (2) ERCs are validated, including PD as the primary ERC (ERC1) and at least one (1) additional ERC selected from 16-en, 11-OH-A, 11-oxo-Etio and PT. ERC(s) validated for the GC/C/IRMS procedure: ☐ Pregnanediol (PD) ☐ 5α-androst-16-en-3α-ol (16-en) ☐ Pregnanetriol (PT) ☐ 11β-hydroxyandrosterone (11-OH-A) ☐ 11-keto-etiocholanolone (11-oxo-Etio)	☐ Yes ☐ No

Developed by WADA Science

Will help WADA and Labs check for proper implementation of IRMS procedure

- Mandatory TD IRMS, TD EAAS, TD NA, TD LDOC requirements
- Best practice TN IRMS recommendations
- To be distributed soon

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