



World Anti-Doping Program

GUIDELINES

REPORTING & MANAGEMENT of URINARY HUMAN CHORIONIC GONADOTROPHIN (hCG) and LUTEINIZING HORMONE (LH) FINDINGS IN MALE ATHLETES

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1. Objective

These guidelines have been developed to ensure a harmonized approach in the reporting and management of elevated urinary concentrations of human Chorionic Gonadotrophin (hCG) and Luteinizing Hormone (LH).

The finding of the α/β heterodimer of hCG¹ in the urine of male *Athletes* at concentrations greater than the established Decision Limit (DL) may be an indicator of hCG *Use* for doping purposes. However, due to the association of elevated urinary hCG with pathology such as testicular cancer, consideration must be given to possible causes, other than doping, that can produce elevated concentrations of heterodimeric hCG in urine *Samples* from male *Athletes*.

Elevated concentrations of total LH² in urine of male *Athletes* may also be an indication of the administration of this banned substance for doping purposes or of the *Use* of substances that induce the release of endogenous LH, such as gonadotropin-releasing hormone (GnRH) and its synthetic analogs or estrogen blockers (anti-estrogens, aromatase inhibitors). On the other hand, suppressed urinary concentrations of LH in male *Athletes* may also be an indication of, or corroborative finding for, the *Use* of androgens.

These guidelines aim to assist Laboratories to report analytical findings for hCG and LH and *Anti-Doping Organizations (ADOs)* to determine whether an Anti-Doping Rule Violation (ADRV) has occurred.

2. Scope

These guidelines follow the current rules established in the *International Standard for Laboratories* (ISL), whose requirements are still fully applicable and shall be respected.

These guidelines outline the Analytical Testing requirements for Laboratories and provide recommendations to *ADOs* to facilitate the result management of elevated concentrations of hCG and LH in urine *Samples* of male *Athletes*.

¹ The α/β heterodimer of hCG includes the intact α/β heterodimer as well as the ‘nicked’ α/β heterodimer, in which the β -subunit is (usually) cleaved between residues 47 and 48. Although cleaved, the α and β -subunits in the nicked hCG are held together by non-covalent bonds. Immunoassays developed against ‘intact hCG’ usually measure these two forms of the α/β heterodimeric hCG molecule.

² Total LH includes the α/β LH heterodimer as well as the dissociated β -subunit and their degradation products.

3. Responsibility

These guidelines are intended for application by WADA-accredited laboratories and ADOs with result management responsibility.

4. Introduction

- hCG and LH are prohibited in male *Athletes* only;
- hCG and LH are both heterodimeric proteins comprising two polypeptide chains, a common α -subunit and a unique β -subunit (hCG β , LH β). Only the α/β heterodimer has biological activity, which is determined by the hormone-specific β -subunit;
- Both hCG and LH occur in urine in different molecular forms, including the intact and nicked α/β heterodimers as well as the dissociated α - and β -subunits and their degradation products (*e.g.* the β -core fragments, nicked products, *etc.*);
- In men, hCG and LH stimulate production of testosterone by Leydig cells by binding to and activating CG/LH receptors;
- The heterodimeric hCG is either undetectable or found at very low levels (usually below 2 IU/L) in urine from healthy males. However, elevated levels of heterodimeric hCG, free hCG β , hCG β -core fragment are produced by certain malignant tumors, especially testicular cancer. Heterodimeric hCG may also be produced by extra-testicular germ cell tumors. In addition, hCG β may be produced by various non-trophoblastic cancers;
- Endogenous LH is normally detectable in urine from healthy men. LH has a shorter half-time in circulation than hCG. Circulating LH is subject to negative feedback by the production of endogenous testosterone or the administration of androgens.

5. Pre-analytical Procedure

- Before aliquoting for analysis, the urine *Sample* should be homogenized in the *Sample* bottle;
- Aliquots taken for analysis should be analyzed immediately or stored refrigerated for up to 7 days until analysis. Aliquots should not be frozen;
- If stored refrigerated, Aliquots should be re-suspended after removal from storage (*e.g.* by pipetting, vortexing or shaking). Aliquots should be allowed to stand at room temperature for at least 30 minutes before being loaded into the instrument for analysis;

- In case of a Presumptive Adverse Analytical Finding, "A" Samples stored at -20°C should be subjected to the Confirmation Procedure as soon as possible;
- "B" Samples associated with an Adverse Analytical Finding for the "A" Sample should be subjected to the Confirmation Procedure or transferred to -70°C storage as soon as possible;
- For long-term storage when Further Analysis is required, it is recommended that both the "A" and "B" Samples are stored frozen at approximately -70°C to avoid the dissociation and degradation of the α/β heterodimers into free α - and β -subunits and their fragments.

6. Assay Requirements

- For the measurement of heterodimeric hCG and total LH concentrations in urine Samples, Laboratories shall apply assays that have been validated and demonstrated as fit-for-purpose;
- For the measurement of hCG in urine, Laboratories should apply assays which are specific for the α/β heterodimer of hCG^{1, 3};
- Assays for total hCG, *i.e.* those assays that measure other molecular forms (*e.g.* free β subunits or degradation fragments) in addition to the α/β heterodimer of hCG are not recommended to be used. However, a Laboratory may consider the application of a total hCG assay only as an initial pre-screening method for practical reasons (*e.g.* the lack of an automated assay for heterodimeric hCG);
- In contrast, for the estimation of LH in urine, Laboratories shall apply assays for total LH (*e.g.* Siemens Immulite, Delfia), which are capable of measuring the total content of LH immunoreactivity, *i.e.* targeting the α/β heterodimer as well as the free β -chain and the β -core fragment;
- Parameters of heterodimeric hCG¹ quantitative assay performance should be validated on-site, including, for example, the determination of the assay's Limit of Quantification (*LOQ*), Laboratory Repeatability (s_r), Intermediate Precision (s_w), bias (b) and relative standard combined Measurement Uncertainty (u_c %).

³ Men with "familial hCG", an apparently physiological and non-pathological anomaly of hCG secretion, have consistently elevated concentrations of hCG β in serum and urine. This may cause a positive finding if an assay for "total" hCG is used. Therefore, such assays are not recommended to be used for *Doping Control* purposes.

The acceptance values for these parameters of heterodimeric hCG¹ assay performance are specified in the table below:

Validation parameter	Acceptance Criterion
S_r (intra-assay Relative Standard Deviation, <i>RSD</i> %)	$\leq 10\%$ (at 5 IU/L)
S_w (inter-assay <i>RSD</i> %)	$\leq 15\%$ (at 5 IU/L)
LOQ⁴ (IU/L)	≤ 3.0 IU/L
u_{c_Max} (%)	20% (at 5 IU/L)

7. Analytical Testing Strategy

7.1 *Testing* for hCG

Initial Testing Procedure

- Laboratories should apply an immunoassay that specifically detects the α/β heterodimer of hCG¹ (e.g. Roche hCG-STAT, Perkin-Elmer AutoDelfia, Delfia Xpress or any other assay validated to be fit-for-purpose, e.g. LC-MS/MS or LC-HRMS [1]);
- If a total hCG assay is applied as a pre-screening method and produces a suspicious result (greater than 5 IU/L), the *Sample* shall be subjected to an Initial Testing Procedure using an assay specific for heterodimeric hCG;
- The Laboratory should use at least one urine positive quality control (QCP) sample (up to 15 IU/L). The consistency of the hCG measurements of the QCP should be monitored through the use of QC-charts.

Confirmation Procedure

- For the Confirmation Procedure, the Laboratory shall use a negative (less than 5 IU/L) and a positive (up to 15 IU/L) urine QC sample. The consistency of the hCG measurements of the QCP shall be monitored through the use of QC-charts;

⁴ LOQ is defined as the lowest hCG concentration in urine meeting the specified criteria for u_c ($\leq 20\%$).

- For the Confirmation Procedure(s), in accordance with ISL provision 5.2.4.3.1.3 on the application of affinity binding assays, Laboratories shall apply an assay different from that applied for the Initial Testing Procedure and which specifically detects the α/β heterodimer of hCG^{1, 5}. The LC-MS/MS method may be used for both the Initial Testing Procedure and the Confirmation Procedure;
- For *Samples* producing a Presumptive Adverse Analytical Finding for the α/β heterodimer of hCG, the "A" Sample Confirmation Procedure should be performed as soon as possible. Alternatively, the remainder of the "A" Sample and the "B" Sample should be frozen immediately at -70°C until thawing for analysis;
- For both "A" and "B" Confirmation Procedures, three (3) Sample Aliquots shall be measured, except when there is limited Sample volume, in which case a lower maximum number of replicates may be used. When the concentration of hCG, as determined during the "A" Sample Confirmation Procedure, is greater than 15 IU/L (after correction for specific gravity, if applicable), the "B" Sample Confirmation Procedure may be done on a single Aliquot.

7.2 Testing for LH

- Laboratories should estimate the concentrations of total LH² in urine during the Initial Testing Procedure by applying an assay capable of detecting the α/β heterodimer as well as the free β -chain and the β -core fragment (e.g. Siemens Immulite, Delfia);
- The Laboratory should use at least one QC sample with total LH concentration between 5 – 50 IU/L. The consistency of the total LH measurements of the QC should be monitored through the use of QC-charts;
- If the Initial Testing Procedure produces a Presumptive Adverse Analytical Finding for LH, the Laboratory, in consultation with the Testing Authority, should test the Sample for the presence of GnRH analogs (e.g. buserelin, gonadorelin, leuprorelin). Laboratories that do not have the analytical capacity to perform analyses for GnRH analogs should have, upon consultation with the responsible Testing Authority, the Sample shipped to and analyzed by another Laboratory that has such analytical capacity. Testing for anti-estrogenic substances and aromatase inhibitors should be part of the Laboratory's standard Analytical Testing menu.

⁵ Laboratories that do not have the analytical capacity to perform the Confirmation Procedure with a second assay specific for the α/β heterodimer of hCG shall have, upon consultation with the responsible Testing Authority, the Sample shipped to and analyzed by another Laboratory that has such analytical capacity.

8. Interpretation and Reporting of Results

8.1 hCG results

- For urine *Samples* with values of specific gravity (SG) **greater than 1.020**, hCG concentrations shall be adjusted to $SG = 1.020^6$;
- The Laboratory shall report an *Adverse Analytical Finding* for hCG if the Confirmation Procedure confirms the presence of the hCG- α/β heterodimer at concentrations (after adjustment if urine SG is greater than 1.020) greater than the DL of 5 IU/L;
- When reporting an *Adverse Analytical Finding* for hCG, the Laboratory Test Report shall include the mean concentration of the hCG- α/β heterodimer (expressed in international units per liter (IU/L) to 1 decimal place) of the replicate determinations performed during the Confirmatory Procedure as well as the u_c at values close to the DL as determined by the Laboratory during method validation (expressed in IU/L to 1 decimal place);
- In case of an *Adverse Analytical Finding* for hCG, a comment shall be added to the Test Report describing the hCG finding and recommending the *ADO* to advise the *Athlete* to undergo clinical investigations to exclude any pathological cause for the elevated urinary hCG (see Appendix 1);
- In cases when a pre-screening total hCG assay produces a suspicious result not corroborated by an elevated concentration (greater than 5 IU/L) for heterodimeric hCG, the Laboratory shall report the finding as “No *Prohibited Substance(s)* or *Metabolite(s)* or *Marker(s)* of a *Prohibited Method(s)* were detected”. However, the Laboratory shall make a comment on the Test Report recommending the *ADO* to advise the *Athlete* to undergo clinical investigations to exclude any pathological cause for the elevated total urinary hCG (see Appendix 1).

8.2 LH results

- For urine *Samples* with values of SG **greater than 1.020**, LH concentrations shall be adjusted to $SG = 1.020^6$.
- When *Testing* for LH, the Laboratory should report the measured concentration of total LH, as determined during the Initial Testing Procedure. In cases when LH is not detectable, the Laboratory shall report the finding as “the concentration of LH was less than the limit of detection (LOD)” and specify the applicable LOD;

⁶ For urine *Samples* with values of SG higher than 1.020, the hCG and LH concentrations in the *Sample* shall be adjusted according to the formula:

$$\text{Conc.}_{1.020} \text{ (IU/L)} = [(1.020-1) / (SG_{\text{Sample}} - 1)] \cdot \text{Conc.}_{\text{measured}} \text{ (IU/L)}$$

- The Initial Testing Procedure should produce a Presumptive Adverse Analytical Finding if the total LH concentration (after adjustment if urine SG is greater than 1.020) is greater than 60 IU/L when using the Immulite assay or greater than 40 IU/L when applying the Delfia assay;
- When there is a Presumptive Adverse Analytical Finding for LH, and tests are performed to detect the presence of GnRH analogs, anti-estrogenic substances and aromatase inhibitors, the Laboratory shall report an Adverse Analytical Finding if any one of these *Prohibited Substances* is confirmed in the *Sample* (in accordance with the TD IDCR (2]). In addition, the Laboratory shall report the estimated concentrations of LH;
- When there is a Presumptive Adverse Analytical Finding for LH, and tests performed to detect the presence of GnRH analogs, anti-estrogenic substances and aromatase inhibitors produce negative results, the Laboratory shall report the finding as “No *Prohibited Substance(s)* or *Metabolite(s)* or *Marker(s)* of a *Prohibited Method(s)* were detected”. The Laboratory shall report the estimated concentrations of LH (without correction for SG) and specify that the *Sample* was tested and produced negative results for GnRH analogs, anti-estrogenic substances and aromatase inhibitors;
- When there is a Presumptive Adverse Analytical Finding for LH, and tests to detect the presence of GnRH analogs are not performed, the Laboratory shall report the finding as an *Atypical Finding* for LH. The Laboratory shall report the estimated concentrations of LH and specify that the *Sample* has not been tested for GnRH analogs.

9. Results Management

9.1 hCG findings

- When a *Sample* is reported as an *Adverse Analytical Finding* for hCG, the *ADO* should alert the *Athlete* and advise that clinical investigations be performed within a reasonable time frame to exclude pathological causes of the elevated urinary hCG concentrations (see Appendix 1). **No provisional suspension shall be imposed on the Athlete during the course of the clinical investigations.** The *ADO* should advise *WADA* when clinical investigations are conducted on an *Athlete* ⁷;
- It is recommended that the *ADO* conducts at least one (1) follow-up no-notice test within a reasonable time frame (*e.g.* within 2 weeks) following the initial finding. If possible, the follow-up *Sample* should be analyzed at the same Laboratory and using the same assays that produced the initial *Adverse Analytical Finding*. If a different Laboratory is to be used, the same confirmatory assay for hCG should be applied;
- If no clinical evidence is provided or the clinical investigations determine that there is no pathological condition associated with the elevated hCG concentrations, the results management process is followed as in the case for *Use of other Prohibited Substance(s) or Prohibited Method(s)*. The results of the follow-up *Sample* should be considered when evaluating the initial *Adverse Analytical Finding* and the clinical information⁸;
- If medical information is provided by the *Athlete* to support the claim that the result is due to a physiological or pathological condition, such information shall be taken in to account and should lead the *ADO* to stop the result management process of the case as an *ADRV*.

9.2 LH findings

- If the presence of GnRH analogs, anti-estrogenic substances or aromatase inhibitors is reported as an *Adverse Analytical Finding*, the results management process is followed, as in the case for *Use of any other Prohibited Substance(s) or Prohibited Method(s)*;

⁷ An *Adverse Analytical Finding* for the heterodimeric hCG does not exclude the possibility of a pathological cause. Most cases of testicular cancer are associated with elevated serum and urine concentrations of heterodimeric hCG, as well as the presence of free hCG β and hCG β -core fragment in urine. In such cases, it is a responsibility of the *Athlete* to provide medical information or clinical evidence demonstrating that the heterodimeric hCG finding is the result of a pathological condition.

⁸ For example, a negative result for the follow up *Sample* is more consistent with prior *Use* of hCG and the absence of a pathological condition.

- If an *Atypical Finding* for LH is reported (elevated total LH concentration without analyzing for the presence of GnRH analogs), the *ADO* should conduct at least one (1) follow-up no-notice test on the *Athlete* within a reasonable time frame (e.g. within 2 weeks) following the initial finding, unless the *ADO* has longitudinal data for the *Athlete* that indicates a follow-up *Testing* is not warranted;
- The follow-up *Sample* should be preferably analyzed at a Laboratory that applies the same assay for total LH as the one used on the first *Sample* and has the analytical capacity to test for GnRH analogs;
- If the result for the follow-up *Sample* is also suspicious for elevated total LH, the Testing Authority, upon consultation with the Laboratory, should have the *Sample* analyzed for the presence of GnRH analogs. Then, a similar process as for the first *Sample* reporting and management should be followed;
- The *ADO* should consider the results of longitudinal tests for LH in parallel with the evaluation of the longitudinal “steroid profile” of the *Athlete*. This evaluation should be done in consultation with an Athlete Passport Management Unit (APMU).

10. References

1. Woldemariam GA and AW Butch. Immunoextraction-Tandem Mass Spectrometry Method for Measuring Intact Human Chorionic Gonadotropin, Free β -Subunit, and β -Subunit Core Fragment in Urine. *Clin Chem* **60**: 1089-1097, 2014.
2. WADA Technical Document TD IDCR (current version). Minimum Criteria for Chromatographic-Mass Spectrometric Confirmation of the Identity of Analytes for Doping Control Purposes.

[https://www.wada-ama.org/en/resources/search?f\[0\]=field_resource_collections%3A30](https://www.wada-ama.org/en/resources/search?f[0]=field_resource_collections%3A30)

Appendix 1. Medical Evaluation of a Case with Confirmed Positive hCG Test

A confirmed positive urine hCG test in a male *Athlete* should lead to investigation of a non-doping cause before confirming an Anti-Doping Rule Violation for hCG doping. (Note: hCG is not prohibited in female *Athletes*).

Testing for hCG

hCG is a heterodimeric glycoprotein comprised of two subunits, α (hCG α) and β (hCG β). hCG occurs in urine in different molecular forms, including the intact and nicked α/β heterodimers as well as the dissociated α - and β -subunits and their degradation products (e.g. the β -core fragments, nicked products, etc.).

Both hCG, its subunits and their fragments may be detected in urine by hCG immunoassays with wide specificity ("total hCG" assays). Anti-doping tests, however, aim to detect only the hCG- α/β heterodimer (i.e. by applying so-called "intact hCG" assays, which in addition to the intact α/β heterodimer may also detect the "nicked" α/β heterodimer). Among a variety of available commercial hCG immunoassays, only some have been validated for this purpose.

The heterodimeric hCG is either undetectable or found at very low levels (usually below 2 IU/L) in urine from healthy males. However, heterodimeric hCG may be produced by testicular cancers or extra-testicular germ cell tumors. If such tumors can be excluded, the otherwise unexplained presence of elevated levels of heterodimeric hCG in serum or urine is evidence for pharmacological administration of hCG.

A positive urine "intact hCG" test result (> 5 IU/L) in an athlete may be due to an undiagnosed testicular tumor containing trophoblastic elements that synthesize hCG. Rarely, ectopic hCG secretion can arise from extra-testicular germ cell tumors, typically located in the midline of the mediastinum, retro-peritoneum or pineal gland. These extra-testicular tumors have a significantly worse prognosis than testicular germ cell tumors.

Medical Evaluation

Following an AAF for an hCG test, the first step is to promptly exclude a pathological cause by a medical assessment. The importance of this should be communicated to the Athlete who should subsequently be reviewed by a doctor, ideally a urologist or an endocrinologist.

The medical assessment of a potential pathological cause of a positive hCG test must include:

1. History (including cryptorchidism, family history);
2. Physical examination (including testes palpation, testis volume, gynecomastia);
3. Laboratory investigations - serum hCG (intact), alpha fetoprotein (AFP), LDH as tumor marker and serum LH, FSH, testosterone, SHBG (to detect hCG bioactivity);
4. Imaging
 - a. Ultrasound of testes (hypoechoic lesions, microlithiasis)
 - b. If serum hCG (intact) assay remains positive AND there is no palpably enlarged testis or presumptive tumor identified by ultrasound, imaging to exclude an extra-testicular germ cell tumor is indicated by CT scan (alternatively MRI or PET scan) of chest, abdomen and brain.

A palpably enlarged testis requires referral to an urologist or oncologist for further evaluations and treatment of a presumed testis tumor.

If serum hCG (intact) remains elevated and no testis or extra-testicular tumor is identified in the original investigation, the *Athlete* should have clinical follow-up with the same serum hCG (intact) immunoassay, including repeat testis ultrasound (to examine for any new or changed hypoechoic testicular lesions) at 3 months. As some of these tumors may be slow growing, follow-up to exclude a testis tumor may need to be prolonged (up to 2 years).

Although the investigation for testicular tumors/cancers should be pursued without delay, further anti-doping *Testing* during the period of investigation is often required to clarify the situation.

See Section 9 - Results Management of the *Guidelines for Reporting and Management of hCG & LH Findings* for further information about follow-up *Testing* and initiating results management.

Definitions

Code Defined Terms

Adverse Analytical Finding (AAF): A report from a Laboratory or other WADA-approved entity that, consistent with the *International Standard* for Laboratories and related Technical Documents, identifies in a *Sample* the presence of a *Prohibited Substance* or its *Metabolites* or *Markers* (including elevated quantities of endogenous substances) or evidence of the Use of a *Prohibited Method*.

Anti-Doping Organization (ADO): A *Signatory* that is responsible for adopting rules for initiating, implementing or enforcing any part of the *Doping Control* process. This includes, for example, the International Olympic Committee, the International Paralympic Committee, other *Major Event Organizations* that conduct *Testing* at their *Events*, WADA, International Federations, and *National Anti-Doping Organizations*.

Athlete: Any *Person* who competes in sport at the international level (as defined by each International Federation) or the national level (as defined by each *National Anti-Doping Organization*). An *Anti-Doping Organization* has discretion to apply anti-doping rules to an *Athlete* who is neither an *International-Level Athlete* nor a *National-Level Athlete*, and thus to bring them within the definition of "Athlete." In relation to *Athletes* who are neither *International-Level* nor *National-Level Athletes*, an *Anti-Doping Organization* may elect to: conduct limited *Testing* or no *Testing* at all; analyze *Samples* for less than the full menu of *Prohibited Substances*; require limited or no whereabouts information; or not require advance *TUEs*. However, if an Article 2.1, 2.3 or 2.5 anti-doping rule violation is committed by any *Athlete* over whom an *Anti-Doping Organization* has authority who competes below the international or national level, then the *Consequences* set forth in the *Code* (except Article 14.3.2) must be applied. For purposes of Article 2.8 and Article 2.9 and for purposes of anti-doping information and education, any *Person* who participates in sport under the authority of any *Signatory*, government, or other sports organization accepting the *Code* is an *Athlete*.

Atypical Finding (ATF): a report from a Laboratory or other WADA-approved entity which requires further investigation as provided by the *International Standard* for Laboratories or related Technical Documents prior to the determination of an *Adverse Analytical Finding*.

International Standard (IS): A standard adopted by WADA in support of the *Code*. Compliance with an *International Standard* (as opposed to another alternative standard, practice or procedure) shall be sufficient to conclude that the procedures addressed by the *International Standard* were performed properly. *International Standards* shall include any Technical Documents issued pursuant to the *International Standard*.

Sample or Specimen: Any biological material collected for the purposes of *Doping Control*.

Testing: The parts of the *Doping Control* process involving test distribution planning, *Sample* collection, *Sample* handling, and *Sample* transport to the laboratory.

Use: The utilization, application, ingestion, injection or consumption by any means whatsoever of any *Prohibited Substance* or *Prohibited Method*.

WADA: The World Anti-Doping Agency.

ISL Defined Terms

Aliquot: A portion of the *Sample* or biological fluid or tissue (e.g., urine, blood) obtained from the *Athlete* used in the analytical process.

Analytical Testing: The parts of the *Doping Control* process involving *Sample* handling, analysis and reporting following receipt in the Laboratory.

Athlete Passport Management Unit (APMU): A unit composed of a *Person* or *Persons*, designated by the *Anti-Doping Organization*, responsible for the administrative management of the Passports advising the *Anti-Doping Organization* for intelligent, *Targeted Testing* liaising with the Expert Panel compiling and authorizing an *Athlete* Biological Passport Documentation Package and reporting *Adverse Passport Findings*.

Confirmation Procedure: An analytical test procedure whose purpose is to identify the presence or to measure the concentration/ratio of one or more specific *Prohibited Substances*, *Metabolite(s)* of a *Prohibited Substance*, or *Marker(s)* of the *Use of a Prohibited Substance* or *Method* in a *Sample*.

[*Comment: A Confirmation Procedure for a threshold substance shall also indicate a concentration/ratio of the Prohibited Substance greater than the applicable Decision Limit (as noted in the TD DL).*]

Decision Limit (DL): a concentration, accounting for the maximum permitted combined uncertainty, above which an *Adverse Analytical Finding* shall be reported.

Fit(ness)-for-purpose: suitable for the intended purpose and compliant to the ISO/IEC 17025 or 15189, ISL and applicable technical documents.

Further Analysis: Any analysis for any substance or method except where an *Athlete* has previously been notified of an asserted anti-doping rule violation based on an *Adverse Analytical Finding* for that substance or method.

Initial Testing Procedure: An analytical test procedure whose purpose is to identify those *Samples* which may contain a *Prohibited Substance*, *Metabolite(s)* of a *Prohibited Substance*, or *Marker(s)* of the *Use of a Prohibited Substance* or *Prohibited Method* or the quantity of a *Prohibited Substance*, *Metabolite(s)* of a *Prohibited Substance*, or *Marker(s)* of the *Use of a Prohibited Substance* or *Prohibited Method*.

Intermediate Precision: Variation in results observed when one or more factors, such as time, equipment, or operator are varied within a Laboratory.

International Standard for Laboratories (ISL): The *International Standard* applicable to Laboratories.

Laboratory(ies): (A) WADA-accredited laboratory(ies) applying test methods and processes to provide evidentiary data for the detection of *Prohibited Substances*, *Methods* or *Markers* on the *Prohibited List* and, if applicable, quantification of a Threshold Substance in *Samples* of urine and other biological matrices in the context of anti-doping activities.

Measurement Uncertainty (MU): Parameter associated with a measurement result that characterizes the dispersion of quantity values attributed to a measurand.

[*Comment: Knowledge of the MU increases the confidence in the validity of a measurement result.*]

Presumptive Adverse Analytical Finding: The status of a *Sample* test result for which there is a suspicious result in the Initial Testing Procedure, but for which a confirmation test has not yet been performed.

Repeatability, s_r: Variability observed within a Laboratory, over a short time, using a single operator, item of equipment, etc.

ISTI Defined Terms

Testing Authority: The organization that has authorized a particular *Sample* collection, whether (1) an *Anti-Doping Organization* (for example, the International Olympic Committee or other Major Event Organization, WADA, an International Federation, or a *National Anti-Doping Organization*); or (2) another organization conducting *Testing* pursuant to the authority of and in accordance with the rules of the *Anti-Doping Organization* (for example, a National Federation that is a member of an International Federation).