Managing sample validity, analytical and pre-analytical issues in the ABP

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Rome
Athlete Passport Management Unit (APMU)

→ **Timely management of the passports** in ADAMS.
→ **Assessment of passport** for target testing
→ **Management of** atypical passports (APMU reports, liaising with Experts, ABP doc pack, declaring APFs)
→ **Review of sample validity** in consultation with the Experts or Laboratories.
→ **Support the Passport Custodian to set priorities** (costs, special analyses, target testing, …)

Independence ≠ ADAMS settings
Invalidity – what does that mean?

“Sample is presumed as valid” (D. Leroux)

L.2.1.4 Departure from WADA ABP requirements

If there is a departure from WADA ABP requirements for Sample collection, transport and analysis, the biological result obtained from this Sample affected by the non-conformity shall not be considered in the Adaptive Model calculations (for example, reticulocytes are affected but not haemoglobin).

The part of the result which is not affected by the non-conformity can still be considered in the Adaptive Model calculations. In such case, the APMU shall provide the specific explanations supporting the inclusion of the results. In all cases, the Sample shall remain recorded in the Athlete’s Passport. The Experts may include all results in their review provided that their conclusions may be validly supported in the context of the non-conformity.

ISTI, Jan 2017

Sample analysis

Impacted/Degraded Markers

Not suitable for the adaptive model calculations

If consider by the APMU/ Expert(s)
→ Need justification
From Sample collection to Passport evaluation

- TA / SCA
- LABs
- DCF
- BSS
- Valid
- ABP
- Valid
- APMU
- Experts
- Profile evaluation
- Confounding Factors (CFs)
- Invalid

WADA APMU Symposium, Rome November 5th-7th 2018
From Sample collection to Passport evaluation

**Hematological module**

**Preanalytical**
- Blood Stability Score (BSS)
  \[ BSS = 3 \times T + CAT \]

**Sysmex (harmonized)**
- Analytical issues ↓

**Intense activity**
- Valid → Invalid
- Invalid → Valid

**Steroidal module**

**TA / SCA**

**LABs**

**APMU**

**Experts**

**Intense activity**
- Evaluation of confounding factors (CFs)
Blood Stability Score (BSS)

Collection to Analysis Time (CAT)
See chapter 2, TDBAR2018

Collection to Reception Time (CRT)
See chapter 3.1, K.4 of the ABP Guidelines

\[ BSS = 3 \times T + CAT \]

«The blood Sample shall be analyzed as soon as possible upon reception and no later than 12 hours of Sample reception…»

«…can be used by DCO/BCO to estimate the max. transport to Laboratory…»
Invalid blood data

- According to ISTI (Annex L, $L2.1.4$)
  - «…If there is a departure from WADA ABP requirements…”
  - Rules are not clearly defined and leave space for APMU and Expert evaluation

- ADAMS automatic evaluation

- Reasons
  1. If the BSS > 85
  2. If the datalogger is switched **ON too late**, or **OFF too early**
  3. If the temperature goes **below 0°C**
     a) Going below 0°C was at any point before July 2018, even before Sample collection
     b) Since July 2018, going below 0°C must be during the **Collection to Analysis Time (CAT)**
Invalid blood data – Role of the APMU to validate

- **Estimation** of the BSS
  - Temperature plot and CAT not complete

- The **degradation markers** are not always clear

- **Consultation** of the **expert panel**
  - A certificate of analysis is often needed (Sysmex data)

- Process
  - **Time consuming**
  - **Must be documented** (APMU expert report in ADAMS)
Valid blood data – Role of the APMU to invalidate

- **BSS**
  - **< 85**
  - Problem with Sample DCF and/or results matching

- **CAT**
  - **> 80h**
  - Invalid by default
    - (mean temperature of 1.5°C during more than 3 days not robust)

- **NO**
  - **> 48h**
  - ATPF → Validity OK → expert opinion (sample+profile)

- **Evaluation of normal passport necessary**
  - ≠ previous data → **Invalidate**
  - Not clear → **Certificate of analysis**
  - No flag → check **RDW-SD** and **MCV**
Scattergrams – Valid or Invalid Blood Sample

Optimal Sample

CRT approx. 60h

Hemolyzed Sample

DIFF

WBC/BASO

RET

PLT-O

Valid

Valid or invalid?

Expert opinion

Invalid
Urine sample collection and analysis

No acceptance criteria to proceed to analyses but...

2.2.1 Validity of (the “steroid profile” of) the Sample

The validity of the Sample will be determined automatically upon reporting the “steroid profile” in ADAMS in accordance to:

a) “Invalid”: only when the Sample shows signs of extensive degradation\(^{13}\), as determined by:
   - \(5\alpha\text{AND}/\Delta\geq 0.1\), and/or
   - \(5\beta\text{AND}/\text{Etio} \geq 0.1\)

b) “Valid”: in all other situations, including:

Excessive T°C and ↑ delivery time → Microbial contamination
Invalid urine data

A ➔ 5aAND
Etio ➔ 5bAND
T ➔ Free T

- ADAMS automatic evaluation
- Reasons (microbial activity)
  1. ITP provides
     a) $5a\text{AND}/A \geq 0.1$ or
     b) $5b\text{AND}/E \geq 0.1$
  2. Confirmation provides
     a) $5a\text{AND}/A \geq 0.1$ or
     b) $5b\text{AND}/E \geq 0.1$ or
     c) $T_{\text{free}} / T_{\text{total}} > 0.05$
Valid urine data – Role of the APMU

...In addition, following the reporting of the “steroid profile” in ADAMS by the Laboratory, the Sample may be evaluated as “invalid” by the APMU upon review of the “steroid profile” data, for example, by considering the presence of substances that may alter the “steroid profile” in the Sample.
Additionally, alteration of the urinary “steroid profile” can occur for a number of reasons including, but not limited to the following confounding factors:

- the administration of other anabolic steroids (e.g. stanozolol);
- the administration of human chorionic gonadotrophin (hCG) in males;
- the administration of aromatase inhibitors and anti-estrogens;
- the administration of inhibitors of 5α-reductase (e.g. finasteride);
- intake of alcohol (ethanol);
- the administration of ketoconazole or other similar compounds;
- the use of masking agents (e.g. probenecid) and diuretics; or
- microbial growth.

Profile evaluation by APMU
Check for validity

Automatically invalidated in ADAMS
How APMU can evaluate the validity of a urine Sample?

Confounding factors (CFs)
- **Measurable**
- Relation with the **labs** needed
- **Objective** information

Constant evolution of CFs
- **Scientific publications** review
- **Research** projects ongoing
Example of urine invalidation by the APMU

**EtG → T/E ↑ and A/T ↓**
Interaction between APMU and Partners

Which information are available for the APMU in ADAMS

- **Steroid profiles data** (ITP and confirmation)
- **Sample validity** (microbial contamination)
- **GC-C-IRMS data if any**
- **Presence or absence of CFs**

But…

- **No information about the concentrations or identification of the CFs**
- **Importance** for evaluation of the confounding factors impact on the profile

Communication

- **ADAMS expert report sent to Passport Custodian (PC)**
- PC should read and contact the appropriate laboratory (agreement between PC - APMU)
- Feedback from the Laboratories, PC and/or TA are not easily available for the APMU
Confounding factors come from analytical results (measurable)

Hematological module

→ **Validity** of Sample needs more information than available by default (ADAMS)

→ **Long history** of markers in clinics

→ **Confounding factors** come from declaration of the athletes (not measurable in the Sample)

Steroidal module

→ **Validity** clearly defined by TDEAAS

→ **No history** or background of the markers and CFs coming from the clinicians (antidoping related tool)

→ **Confounding factors** come from analytical results (measurable)
Conclusion

Case by Case Management

https://www.knowledgedesk.com/collaboration-trumps-management/