



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



Baume N, Schweizer Grundisch C, Giraud S.,
Kuuranne T.

WADA ABP Symposium

November 5th-7th, 2018

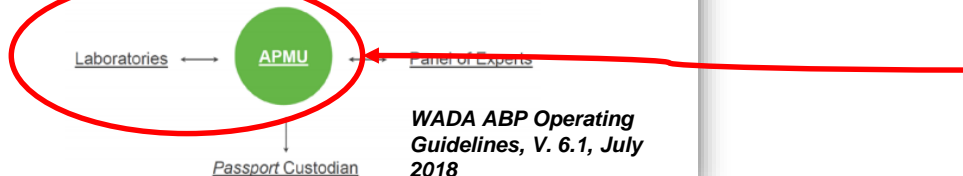
Rome

Athlete Passport Management Unit (APMU)

TD2019APMU

- 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, ...)

Expert panel. Within each Passport in ADAMS, the APMU Report provides a record of these various interactions for efficient follow-up by the Passport Custodian, WADA and other ADOs with whom the Passport is shared through ADAMS.



Independence
≠ ADAMS settings



Invalidity – what does that mean?

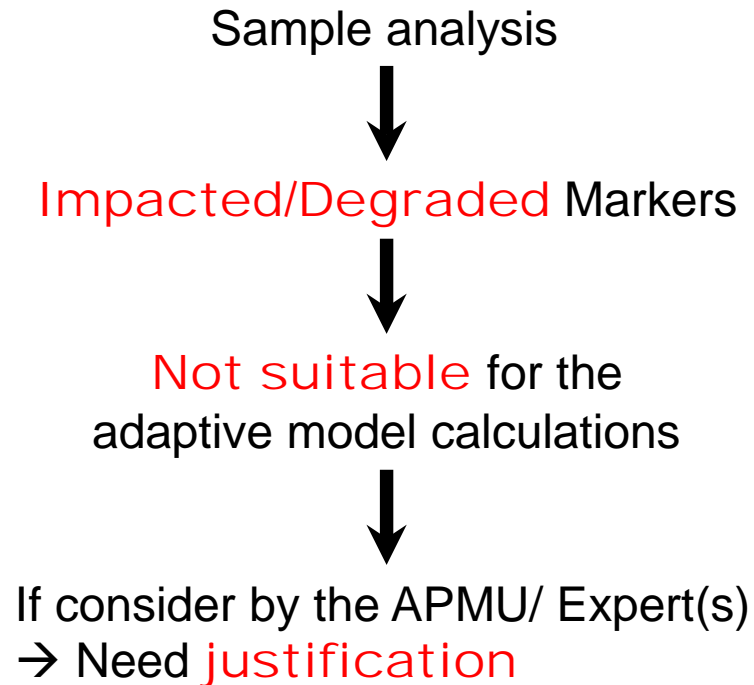
“*Sample is presumed as valid*” (D. Leroux)

L.2.1.4 Departure from WADA ABP requirements

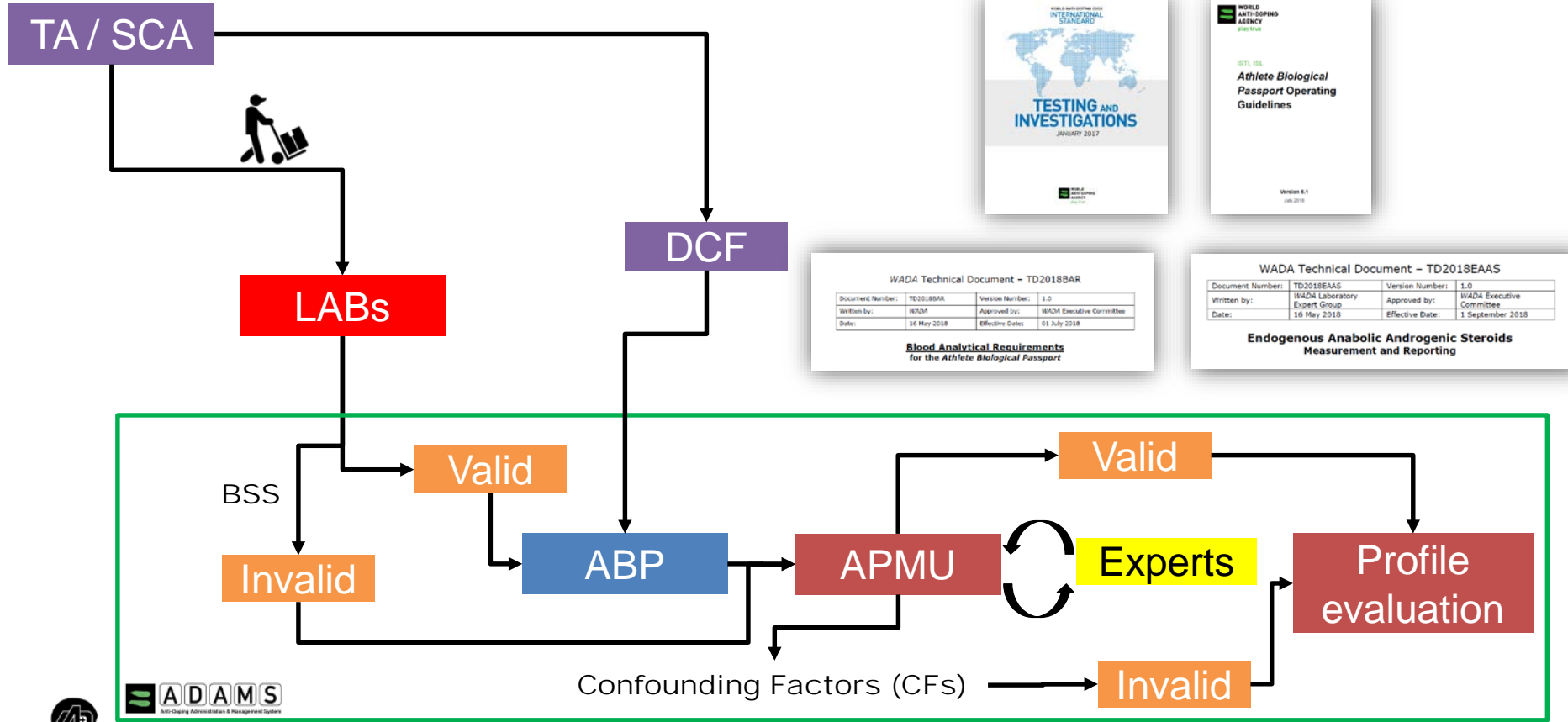
If there is a departure from WADA ABP requirements for *Sample* collection, transport and analysis, the biological result obtained from this *Sample* affected by the non-conformity shall not be considered in the Adaptive Model calculations (for example, reticulocytes are affected but not haemoglobin).

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



From Sample collection to Passport evaluation



From Sample collection to Passport evaluation

Hematological module

Preamalytical
Blood Stability Score (BSS)

$$BSS = 3 \times T + CAT$$



Sysmex (harmonized)
Analytical issues ↓

Intense activity
Valid → Invalid
Invalid → Valid

TA / SCA

LABs

APMU

Experts

Steroid module

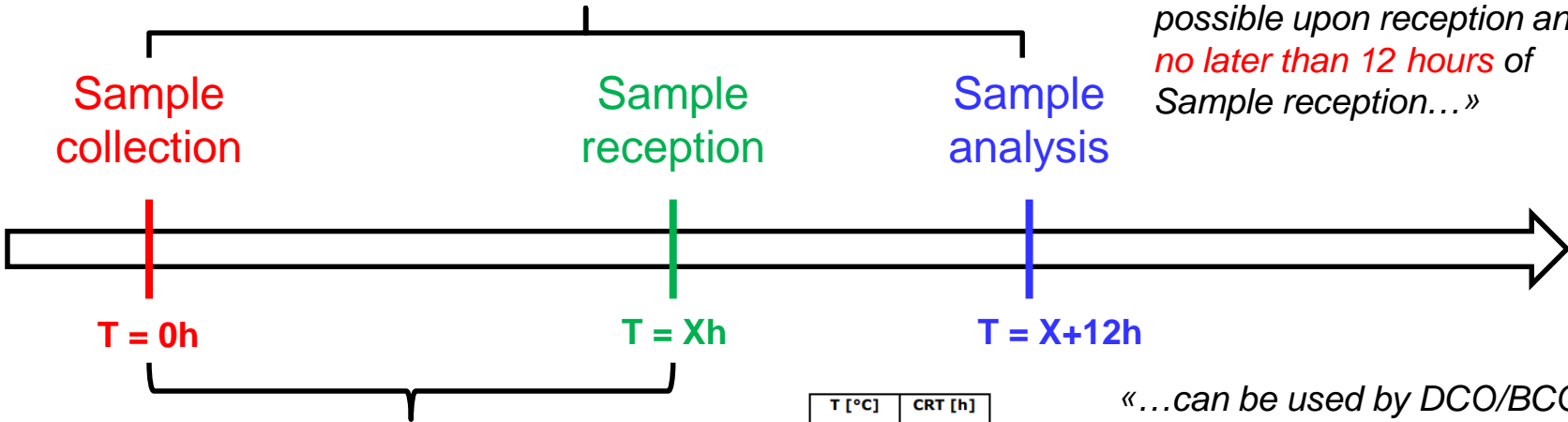
Intense activity
Evaluation of confounding factors (CFs)



Blood Stability Score (BSS)

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

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



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

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

$$BSS = 3 \times T + CAT$$

T [°C]	CRT [h]
15	35
12	41
10	46
9	48
8	50
7	53
6	55
5	58
4	60

International Journal of Laboratory Hematology
ORIGINAL ARTICLE

Validation of a Blood Stability Score as an easy-to-use blood sample quality index
N. ROBINSON*, A. KIRCHBICHLER*, O. BANULS*, M. MADER*, R. AIKIN*, P.-E. SOTTAS*, G. D'ONOFRIO**



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)

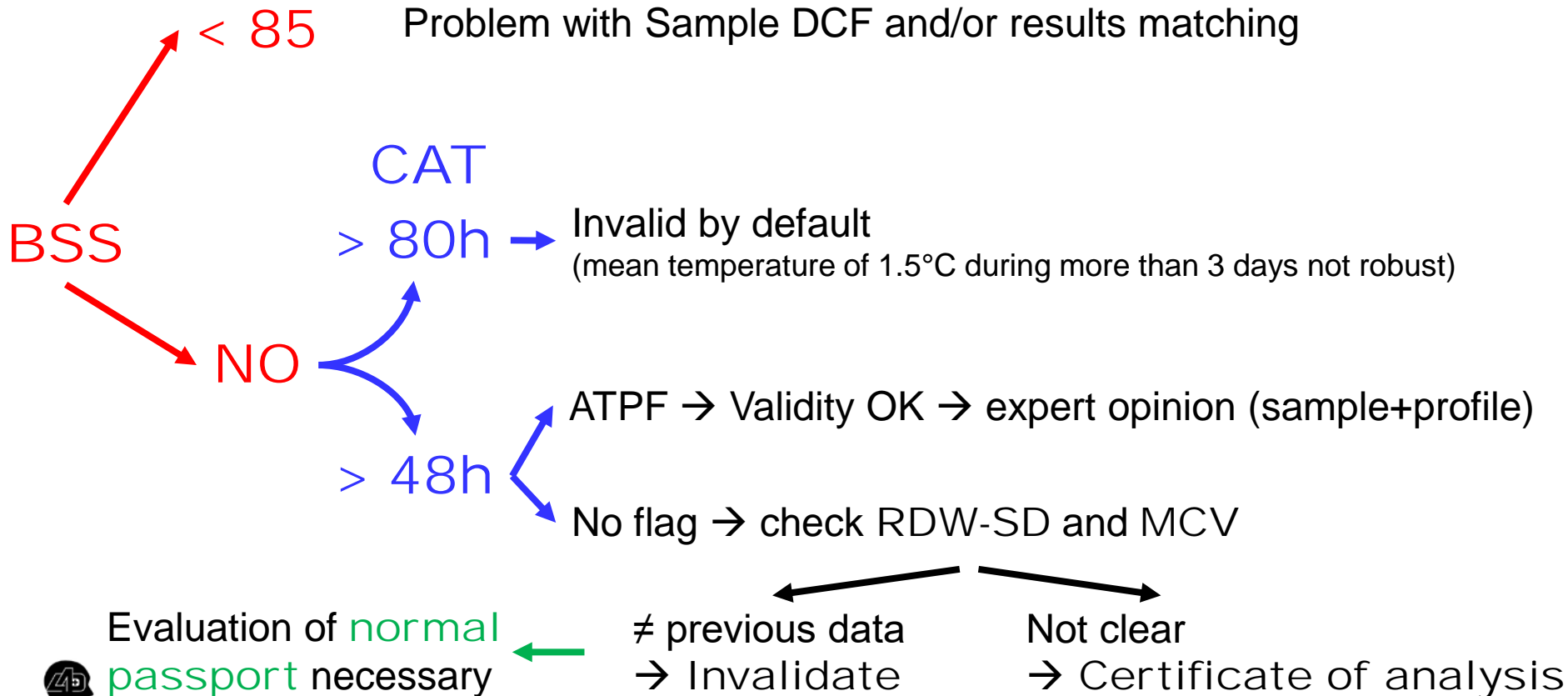


Invalid **blood** data – Role of the APMU to validate

- 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)

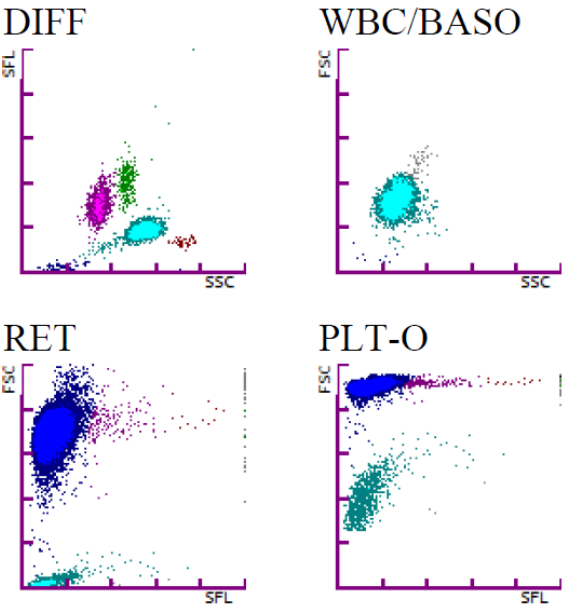


Valid **blood** data – Role of the APMU to invalidate



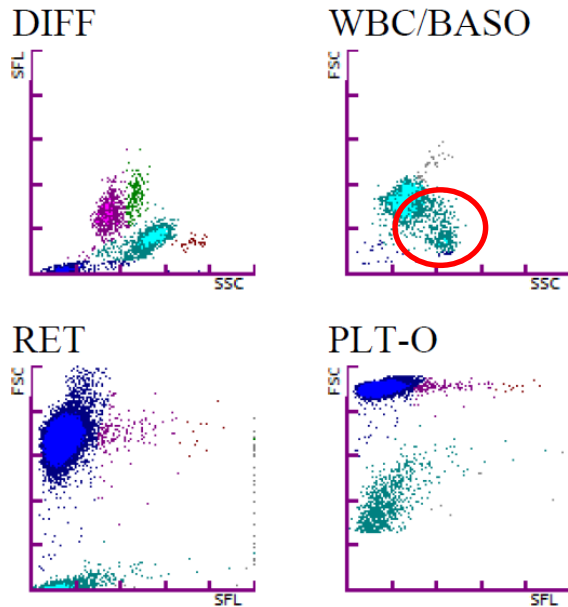
Scattergrams – Valid or Invalid Blood Sample

Optimal Sample



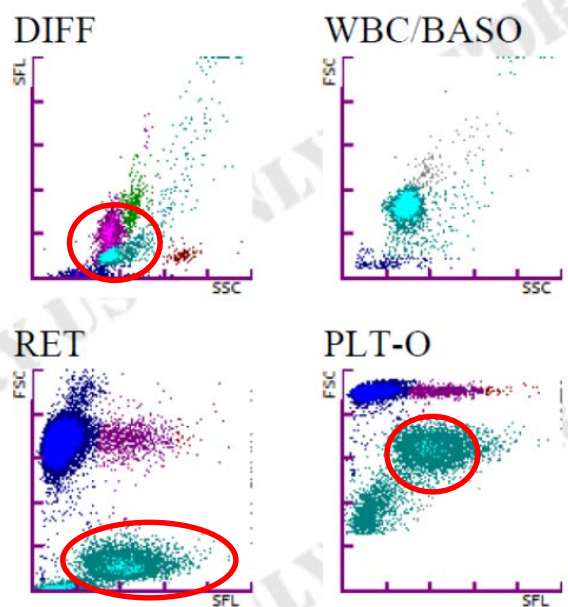
Valid

CRT approx. 60h



Valid or invalid?
Expert opinion

Hemolyzed Sample



Invalid



Urine sample collection and analysis

No acceptance criteria to proceed to analyses but...

WADA Technical Document – TD2018EAAS

Document Number:	TD2018EAAS	Version Number:	1.0
Written by:	WADA Laboratory Expert Group	Approved by:	WADA Executive Committee
Date:	16 May 2018	Effective Date:	1 September 2018

Sample has occurred and the finding be treated as an Anti-Doping Rule Violation.

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 degradation¹³, as determined by:

- $5\alpha\text{AND}/\text{A} \geq 0.1$, and/or
- $5\beta\text{AND}/\text{Etio} \geq 0.1$

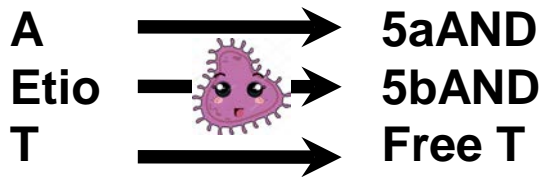
b) **“Valid”**: in all other situations, including:

Excessive T°C and ↑
delivery time
→ Microbial contamination

TA and SCA



Invalid urine data



Specific gravity* 1.009 pH

Validity Invalid

Steroid Profile Data Confirm

Microbial contamination *

	Initial values
5aAND/A	0.20
5βAND/Etio	0.09

Steroid Profile Data

Confirmation Request Status* Approved by TA

Microbial contamination *

	Initial values	Confirmed values
5aAND/A	0.00	0.00
5βAND/Etio	0.00	0.00
Free T/ total T	0.24	

Steroid Profile Variables

	Initial values	Confirmed values	uc
Specific Gravity		1.018	
5a-androstenediol	29.721 ng/mL	26.5 ng/mL	4 ng/mL
5b-androstenediol	11.639 ng/mL	12.1 ng/mL	1.8 ng/mL
androsterone	2301.339 ng/mL	2380 ng/mL	357 ng/mL
epitestosterone	29.293 ng/mL	29.9 ng/mL	3 ng/mL
etiocholanolone	793.909 ng/mL	803.8 ng/mL	120.6 ng/mL
T/E	0.113	0.1	0.01
testosterone	3.32 ng/mL	3 ng/mL	0.3 ng/mL

- ADAMS automatic evaluation
- Reasons (microbial activity)
 - ITP provides
 - $5aAND/A \geq 0.1$ or
 - $5bAND/E \geq 0.1$
 - Confirmation provides
 - $5aAND/A \geq 0.1$ or
 - $5bAND/E \geq 0.1$ or
 - $T_{free} / T_{total} > 0.05$



Valid urine data – Role of the APMU

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

...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



Steroid profile and confounding factors

WADA TD2018EAAS, chapter 1.1

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 5 α -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

JOURNAL OF MASS SPECTROMETRY
J. Mass Spectrom. 2008; **43**: 877–891
Published online 20 June 2008 in Wiley InterScience
(www.interscience.wiley.com) DOI: 10.1002/jms.1457



Review

Factors influencing the steroid profile in doping control

ana Review

Ute N Institute Cologne, Received
Received: 13 September 2017 | Revised: 20 October 2017 | Accepted: 3 November 2017
DOI: 10.1002/dta.2341

OPEI WILEY

Sen dos WILEY

RESEARCH ARTICLE
Received: 25 July 2017 | Revised: 17 October 2017 | Accepted: 5 November 2017
DOI: 10.1002/dta.2338

Jenny Eva Magn WILEY

scrc WILEY

adm WILEY

RESEARCH ARTICLE
Received: 18 December 2017 | Revised: 29 March 2018 | Accepted: 31 March 2018
DOI: 10.1002/dta.2392

Aristo Jordi WILEY

The effect of tea consumption on the steroid profile
Received: 22 November 2017 | Revised: 6 January 2018 | Accepted: 10 January 2018
DOI: 10.1002/dta.2361

Jesús Sergi Clara Rafael WILEY

Pre Bio WILEY

RESEARCH ARTICLE
Received: 25 August 2017 | Revised: 28 November 2017 | Accepted: 13 December 2017
DOI: 10.1002/dta.2351

Jenny Jenny Lena WILEY

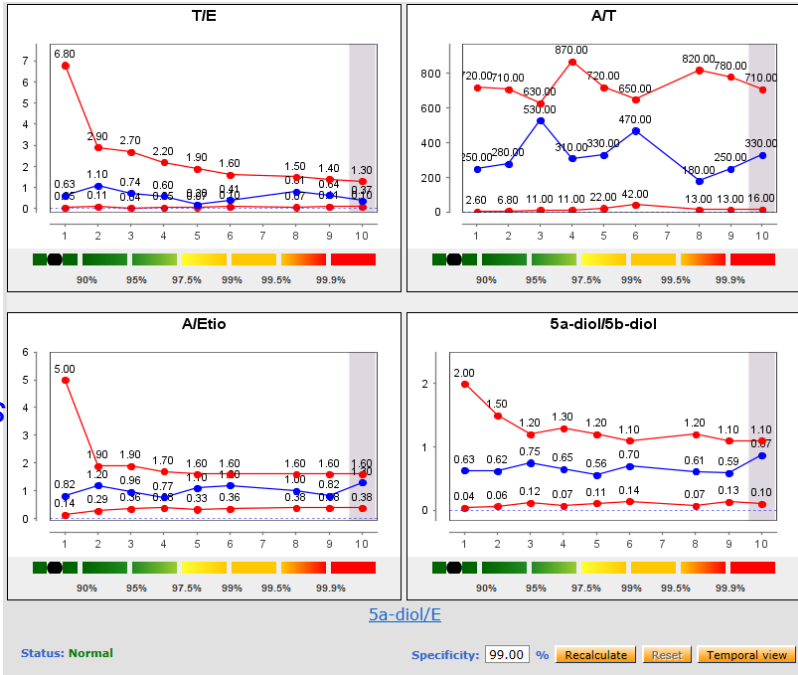
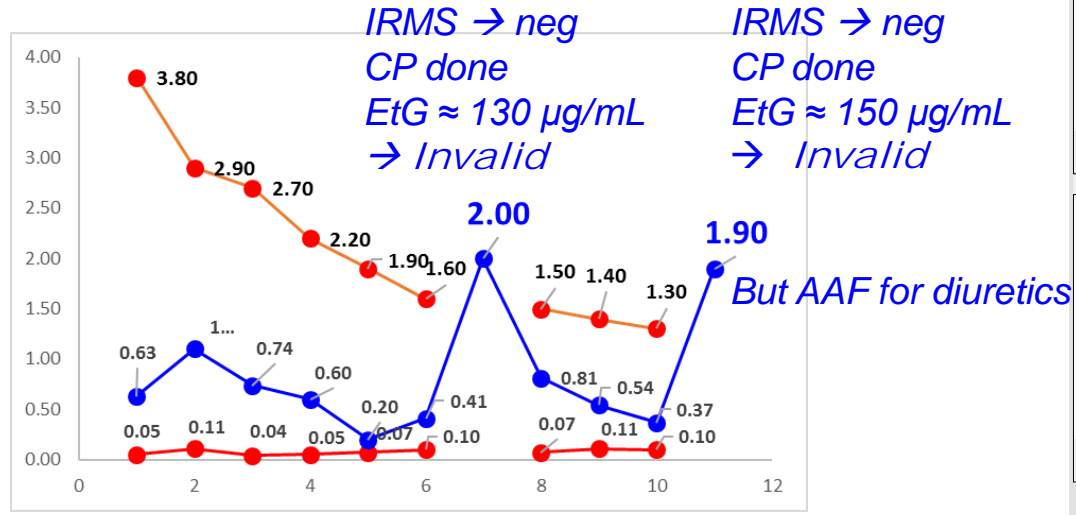
Effect of glucocorticoid administration on the steroid profile
Sergi Coll^{1,2} | Xavier Matabosch¹ | Lorena Garrosta¹ | Clara Perez-Maña^{3,4} | Rosa Ventura^{1,2}



Example of urine invalidation by the APMU

Select#	Test Type	Date of Test	Validity	T [ng/mL]	E [ng/mL]	5a-d [ng/mL]	5b-d [ng/mL]	A [ng/mL]	Etio [ng/mL]	T/E	Cont. T/E	A/T	A/Etio	5a-diol/5b-diol	5a-d/E	Specific Gravity
11	OOC	06-Aug-2018	Invalid	24	13	28	71	1300	1300	1.9	1.9	57	1.0	0.40	2.3	1.014
10	INC	10-Jan-2018	Valid	8.6	23	29	34	2800	2200	0.37	-	330	1.3	0.87	1.3	1.025
9	OOC	29-Dec-2017	Valid	7.3	11	24	41	1800	2200	0.64	-	250	0.82	0.59	2.1	1.027
8	OOC	28-Dec-2017	Valid	14	17	33	54	2500	2400	0.81	-	180	1.0	0.61	1.9	1.011
7	OOC	10-Dec-2017	Invalid	17	8.7	34	53	830	650	2.0	2.0	48	1.3	0.65	3.9	1.024
6	OOC	08-Dec-2017	Valid	3.6	8.7	23	34	1700	1400	0.41	-	470	1.2	0.70	2.7	1.033
5	OOC	17-Mar-2017	Valid	3.9	19	13	23	1300	1200	0.20	-	330	1.1	0.56	0.67	1.016
4	OOC	02-Jan-2017	Valid	4.7	7.9	17	26	1400	1900	0.60	-	310	0.77	0.65	2.1	1.018
3	OOC	27-Oct-2016	Valid	1.6	2.1	15	20	840	880	0.74	-	530	0.96	0.75	7.1	1.025
2	OOC	18-Mar-2016	Valid	3.6	3.5	15	24	1000	820	1.1	-	280	1.2	0.62	4.2	1.022
1	OOC	12-Mar-2014	Valid	18	32	53	84	4400	5300	0.63	-	250	0.82	0.63	1.7	1.017

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



Conclusion

Hematological module

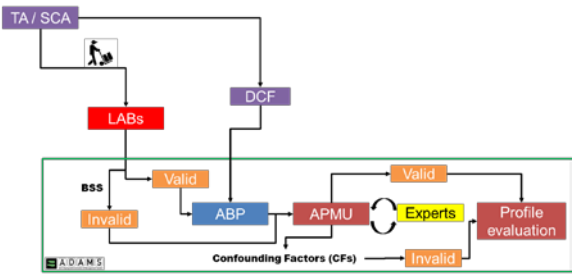
- Validity of Sample needs more information than available by default (ADAMS)
- Long history of markers in clinics
- Confounding factors come from declaration of the athletes (not measurable in the Sample)

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



WADA Technical Document - TD2018BAR

Document Number:	TD2018BAR	Version Number:	1.0
Written by:	WADA Laboratory	Approved by:	WADA Executive Committee
Date:	01 May 2018	Effective Date:	01 July 2018

Blood Analytical Requirements
for the Athlete Biological Passport

WADA Technical Document - TD2018EAAS

Document Number:	TD2018EAAS	Version Number:	1.0
Written by:	WADA Laboratory	Approved by:	WADA Executive Committee
Date:	01 May 2018	Effective Date:	01 September 2018

Endogenous Anabolic Androgenic Steroids
Measurement and Reporting

Case by Case Management



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

