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IRMS management and organization for the Olympic Games

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22-23 Sept 2023, Workshop IRMS, London

Olympic Games: Consequences for the lab

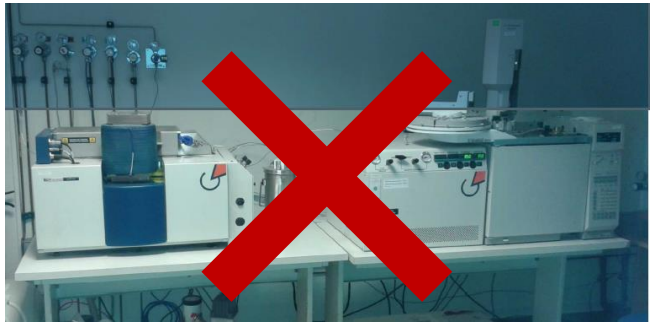
= ½ year of work in few weeks

Consequence 1: analysis for OG not feasible in the current laboratory: need to move

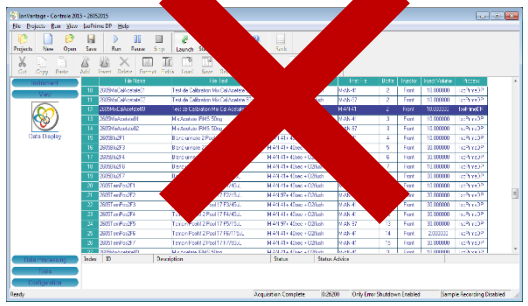
Consequence 2: getting ready for high throughput and efficiency in a short time: need for instrument change and (re)validation

Olympic Games: Consequences for IRMS analysis

What we had….



IonVantage



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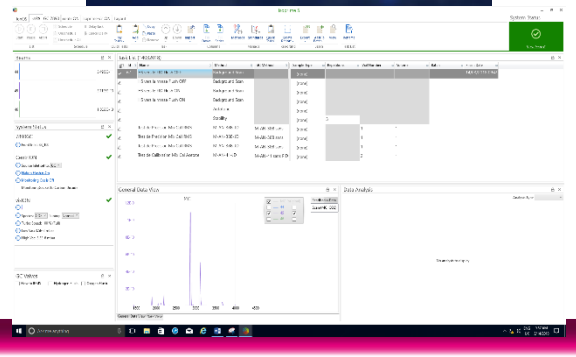
SOFTWARE SUITE BY ELEMENTAR



What we need for OG….

X 4 and lyticOS® SOFTWARE SUITE BY ELEMENTAR

→ Need to purchase/rent 2 GC-C-IRMS and 1 IRMS

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Olympic Games: Consequences for IRMS analysis

What we had….

2 x Ultimate 3000 (Dionex !)

System too old: spare parts may be not available in case of problem

1 x Vanquish™ Core

What we need for OG….

4 x Vanquish™ Core

Need to purchase/rent 3 HPLC systems

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Olympic Games: Consequences for IRMS analysis

What we had….

Gilson XL4
SPE extraction:
4 cartridges at the same time

What we need for OG….

2 x Biotage® Extrahera™ HV-5000
SPE extraction:
24 cartridges at the same time

➡ Need to purchase 2 SPE systems

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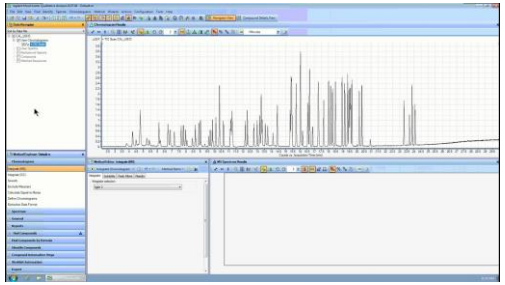
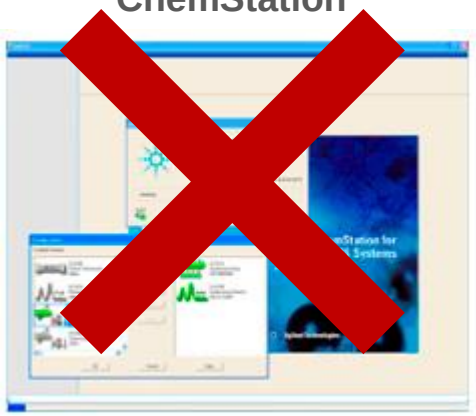
Olympic Games: Consequences for IRMS analysis

What we have….

MassHunter



ChemStation



What we need for OG….

X 2 and MassHunter

Need to upgrade software

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Olympic Games: Consequences for IRMS analysis

- New laboratory
  - Moving in March 2023
  - Start of routine operations May 2023
  - Four floors, 2600 m^2

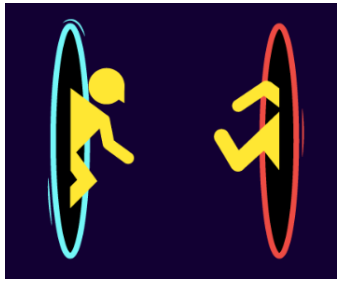
➡ 1 year and few months before OG

Moving organization

Moving in March/May 2023: organizing around this important milestone

What to do before moving (from 2022 to march 2023):
- Purchase of new IRMS instruments + initial validation in the “old” lab
- Purchase of the new SPE system + method development + initial validation
- Purchase of the new HPLC to be delivered in the new lab

What to do during the transition period (from march to may 2023):
- Moving of 1 GC-C-IRMS + new SPE system and delivery of the new HPLC system = validation of sample prep + IRMS analysis in the new lab
- IRMS analysis continuation in the old lab with the current method



What to do after final moving (may 2023)
- Validation of the moving of the 2 other IRMS instruments
- preparing the purchase of another new SPE system + 2 new HPLC (to be installed in September!)
- Preparing purchase/rent of the 4th GC-C-IRMS

Validation strategy: old lab

Validation of new GC-C-IRMS instruments in the "old" lab: **Validation according to TN + risk assessment to evaluate steps required:**

✗ Selectivity not necessary: same sample prep + same instrument than initial validated method

✓ Validation of the working range of the method (performances of the instrument, linearity, LOQ)

✓ Measurement uncertainty determination (linear mixing model)

✓ Robustness (only of the IRMS system, done with uc)

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Validation strategy: old lab

Implementation and performances evaluation of new SPE system in the “old” lab:

- ✓ Optimization of the parameters for SPE
- ✓ Recovery – isotopic fractionation evaluation
- ✓ Comparison study with old system

➡ Pre-validation only => Full validation will be done in the new lab

Validation strategy: new lab

Validation of IRMS instruments after relocation

Repeatability intra and inter day

Reproducibility of CQs analysis

Validation strategy: new lab

Validation of new HPLC + new SPE system and GC-C-IRMS after relocation

- ✓ Repeatability intra and inter day (HPLC system)
- ✓ Recovery – isotopic fractionation (full sample prep: SPE and HPLC)
- ✓ Check of Selectivity (GC-MS analysis)
- ✓ Carry over
- ✓ Robustness (CQs repeatability and reproducibility)
- ✓ Accuracy (QCs, RM and CRMs analysis) and uc assessment (control charts)

IQAS performed successfully 

Validation results

Validation of new HPLC system: stability of RT

	Repeatability Intra Day (n=6)			Repeatability Inter Day (n=6)		
	Mean RT (min)	SD RT (min)	RSD (%)	Mean RT (min)	SD RT (min)	RSD (%)
a-Trenbolone (ISTD)	7.807	0.005	0.06%	7.813	0.003	0.04%
11bOH Ac/11KetoE Ac	15.950	0.012	0.08%	15.965	0.010	0.06%
Bold Ac	17.064	0.013	0.08%	17.082	0.011	0.06%
E Ac	19.192	0.015	0.08%	19.210	0.012	0.06%
Testo Ac	21.242	0.017	0.08%	21.263	0.012	0.06%
Bold M1 Ac	25.025	0.018	0.07%	25.049	0.015	0.06%
Etio Ac/A Ac	27.008	0.018	0.07%	27.031	0.016	0.06%
5adiol diAc	39.661	0.014	0.03%	39.673	0.011	0.03%
5bdiol diAc	39.868	0.014	0.04%	39.881	0.011	0.03%
Pdiol diAc	43.479	0.018	0.04%	43.493	0.013	0.03%

Validation results

Validation of relocated GC-C-IRMS: accuracy (in house prepared RMs (with δ13C values traceable to a CRM))

	-30.08	-31.95	-19.91	-32.11	-33.81	-35.31	-31.96	-16.30	-33.80	-29.67	-22.58	-30.56	-32.29	
	16en Ac	SI	Etio Ac	Andro Ac	5bdiol diAc	5adiol diAc	Bold M1 Ac	11KetoE Ac	EpiT Ac	Testo Ac	Pdiol diAc	Bold Ac	11bOH A Ac	RSQ
M-AN-41	-30.98	-32.00	-20.07	-32.35	-33.93	-35.52	-32.44	-16.32	-34.28	-30.05	-22.09	-30.77	-32.81	0.9988
	-30.70	-32.22	-20.06	-31.98	-33.79	-35.30	-32.37	-16.54	-34.08	-30.03	-22.64	-30.94	-32.09	0.9992
	-30.71	-32.05	-20.20	-32.37	-33.60	-35.66	-32.45	-16.41	-34.12	-30.17	-22.74	-30.93	-32.34	0.9993
	-30.70	-32.05	-20.15	-32.02	-33.49	-35.23	-32.38	-16.49	-34.15	-30.29	-22.52	-31.04	-32.25	0.9987
	-30.57	-32.66	-19.96	-32.20	-33.86	-35.70	-32.41	-16.29	-34.39	-30.05	-22.43	-30.80	-32.21	0.9992
M-AN-97 (B/BM1)	-30.59	-32.41	-20.26	-32.43	-33.59	-35.24	-32.35	-16.29	-34.28	-30.06	-22.91	-31.34	-32.61	0.9990
	-30.77	-32.25	-20.20	-32.69	-33.70	-35.03	-32.51	-16.43	-34.38	-30.20	-22.96	-31.18	-32.72	0.9987
	-30.34	-32.08	-20.03	-32.20	-33.26	-35.06	-32.26	-16.43	-34.03	-29.81	-22.43	-30.71	-32.42	0.9992
	-30.70	-32.43	-19.86	-31.83	-33.69	-35.58	-32.25	-16.22	-33.91	-29.54	-22.64	-30.75	-32.38	0.9991
	-30.81	-32.22	-19.96	-32.52	-33.67	-35.57	-32.33	-16.33	-34.22	-29.87	-22.68	-30.99	-32.69	0.9994
M ‰	**-30.69**	**-32.24**	**-20.08**	**-32.26**	**-33.66**	**-35.39**	**-32.37**	**-16.37**	**-34.18**	**-30.01**	**-22.60**	**-30.94**	**-32.45**	
SD ‰	**0.17**	**0.21**	**0.13**	**0.27**	**0.19**	**0.25**	**0.08**	**0.10**	**0.15**	**0.22**	**0.25**	**0.20**	**0.24**	
CV %	**0.5%**	**0.7%**	**0.6%**	**0.8%**	**0.6%**	**0.7%**	**0.3%**	**0.6%**	**0.4%**	**0.7%**	**1.1%**	**0.7%**	**0.7%**	
Ecart	**0.61**	**0.29**	**0.17**	**0.15**	**-0.15**	**0.08**	**0.41**	**0.07**	**0.38**	**0.34**	**0.02**	**0.38**	**0.16**	

Validation results

Validation of new HPLC + new SPE system and GC-C-IRMS after relocation

Experimental design for robustness

QC 1 old_SPE	QC 2 old_SPE	QC 1 Extra 05	QC 2 Extra 05	QC 3 Extra 05	QC 4 Extra 05
HPLC 9	HPLC 8	HPLC 9	HPLC 9	HPLC 9	HPLC 8
Isop 7	Isop 5	Isop 7	Isop 7	Isop 7	Isop 5

Results

Old lab

QCN	Etio	Andro	11KétoE	11bOH Andro	E	Testo	5b Adiol	5a Adiol	Pdiol
Control Chart mean value	-22.46	-21.91	-21.61	-21.80	-22.88	-22.48	-22.80	-22.77	-22.08
uc (initial validation)	0.5	0.4	0.3	0.6	0.7	0.7	0.6	0.7	0.7
QCN 1 old_SPE Isop 7	-22.57	-22.19	-20.17	-22.09	-23.84	-22.96	-23.52	-23.42	-20.95
QCN 2 old SPE Isop 5	-22.30	-21.93	-21.61	-21.64	-22.56	-21.52	-22.19	-22.45	-21.96
QCN 1 Extra05 Isop 7	-22.23	-21.61	-21.32	-21.91	-23.44	-22.84	-22.73	-22.87	-21.99
QCN 2 Extra05 Isop 7	-22.14	-22.00	-21.22	-22.25	-23.00	-22.58	-22.67	-22.51	-20.71
QCN 3 Extra05 Isop 7	-21.90	-21.78	-20.97	-22.16	-22.19	-22.68	-22.91	-22.70	-20.72
QCN 4 Extra05 Isop 5	-22.40	-21.73	-21.32	-21.55	-22.35	-21.80	-22.12	-22.14	-21.85
Mean Old_SPE	-22.43	-22.06	-20.89	-21.86	-23.20	-22.24	-22.86	-22.93	-21.46
SD Old_SPE	0.19	0.19	1.02	0.32	0.91	1.02	0.94	0.69	0.72
Mean Extra 05	-22.17	-21.78	-21.21	-21.97	-22.75	-22.48	-22.61	-22.56	-21.32
SD Extra 05	0.21	0.16	0.16	0.31	0.58	0.46	0.34	0.31	0.70
Diff (Old_SPE – Extra 05)	**-0.26**	**-0.28**	**0.31**	**0.10**	**-0.45**	**0.24**	**-0.25**	**-0.37**	**-0.14**

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Olympic Games Prerequisites

- Number of samples

	OG	ParaOG
• Urine IC	3099	1200
• Urine OOC	1551	800
• Serum	577	300
• Whole blood	578	300
• DBS	200	100

- Hub model
  - Samples to be collected and gathered in a “sample hub” organized by Paris2024
  - One major delivery from the hub to the laboratory per day
  - Late coming samples are welcomed in a narrow time window after the large delivery, a few hours.
- Reporting time
  - 36-48 h
  - ESA 72h
  - IRMS 72H

Olympic Games preparations

- Staff and shifts

	Total staff	Comment
Sample reception, aliquotage	30	Lab staff and students,
EPO	10	lab staff and experts
IRMS prep	4	Lab staff, experts (and students)
IRMS analysis and LC-UV prep	6	Labb staff and experts
PIIINP, hCG, Sysmex, pH/SG, hGH, Transfusion	8	lab staff students and experts
Gene doping	2	Labb staff and experts
hGH isoforms	4	Labb staff and experts
LC-HRMS prep	5	Lab staff, experts and students
LC-HRMS peptide prep	5	Lab staff, experts and students
GC-MS/MS prep	5	Lab staff, experts and students
Large peptides prep	2	Lab staff, experts and students
DBS prep	2	Lab staff, experts and students
IGF-1 prep	2	Lab staff, experts and students
Steroids in blood prep	2	Lab staff, experts and students
LC-HRMS instrument and evaluation	10	Lab staff and experts
LC-HRMS peptide instrument and evaluation	10	Lab staff and experts
GC-MS/MS instrument and evaluation	10	Lab staff and experts
Large peptides instrument and evaluation	4	Lab staff and experts
DBS instrument and evaluation	2	Lab staff and experts
IGF-1 instrument and evaluation	2	Lab staff and experts
Confirmation MS	3	Lab staff
Steroids in blood instrument and evaluation	2	Lab staff and experts
Reporting negative	2	Lab staff
Reporting positive samples	1	Director + director panel
Director panel	4	Lab directors
	137	

Shift Reception	04h00-10h00
Shift preparation MS	08h00-16h00
Shift 1 analysis Chemistry	8h00-17h00
Shift 2 analysis Chemistry	16h00-01h00
Shift 1 analysis bio	8h-17h00
Shift 1 EPO	7h-15h00
Shift 2 EPO	12h30-20h30
Shift 1 IRMS	7h-15h00
Shift 1 IRMS	12h30-20h30
Shift 1 Conf MS	8h00-17h00
Shift 1 Conf MS	16h00-01h00
Shift Guard for instruments	24h00-8h00

Need help for :

IRMS prep (SPE/hydrolyse/LLE) and/or HPLC prep and Elementar instrument (lyticOS)

Olympic Games organization: conclusion

What is ready today

- ✓ New lab = lab for OG validated!
- ✓ 3 GC-C-IRMS for T, B and metabolites validated
- ✓ 1 GC-C-IRMS validated for 19NA and Formestane
- ✓ 1 SPE system validated
- ✓ 2 HPLC systems validated

Analyte	LOQ (ng/mL)	u_{c_Max} (δ) (‰)
ERCs	50	0.7
T, 5αAdiol	10	0.7
5βAdiol	20	0.7
EpiA	20	1.0
E, F	50	1.0
A, Etio	100	0.7
B / BM1	2.5	1.0
6α-OH-AD	10	1.0

Olympic Games organization: conclusion

What remains to be done …

- Order and validate the fourth (and last!) IRMS system (installation planned early 2024)
- Installation and Validation the 2 new HPLC systems (before end of 2023)
- Installation and Validation the new SPE system (before end of 2023)
- Train a new technician from the lab (in progress …)
- Upgrade of GC-MS software and validation of its use
- Validation of 6aOH-AD (end of 2023 – beginning of 2024)
- Recruiting for OG! (invitation soon …)
- Pass the WADA audit(s)

Merci!