



Palacký University
Olomouc

Pros and cons for the laboratory quality management system in the academic environment

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OUTLINE

- About us – our journey to QMS in the laboratory
- Determination of elemental impurities
- What have we learned?
- Pros & cons
- Conclusion



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About us

- Public university, established in 1573
- 8 faculties ⇒ Faculty of Science
- Department of Analytical Chemistry
 - Bachelor, master and PhD studies of analytical chemistry
 - Close cooperation with pharma industry
 - **Limitation: not certified lab**
 - Is it possible to bring together:
 - Teaching activities (students)
 - Basic research
 - Contract research

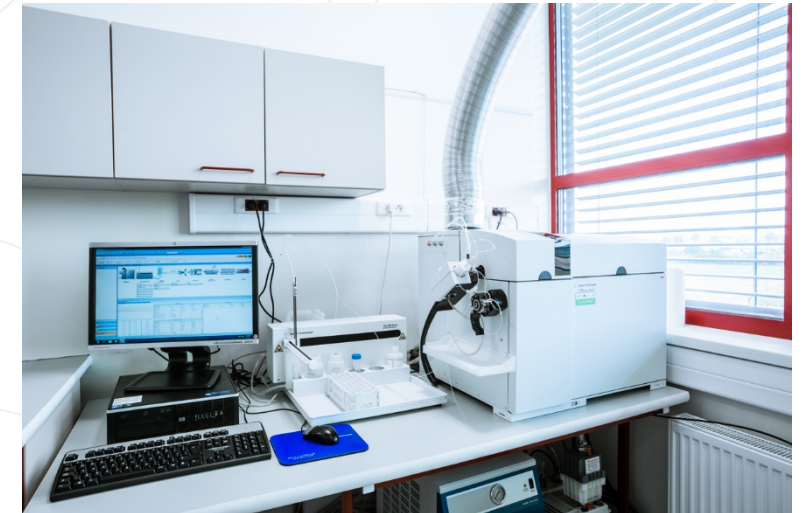




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About us

- 2010 – EU funds:
 - new facilities
 - unique instrumentation interesting to our partners
- Analytical laboratory dedicated only to research
- Which QMS?
 - Accreditation ISO 17025
 - GMP certification
- Preparation started 2013
- Audit for GMP certificate 2015 (2017, 2019)





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Good Manufacturing Practice (GMP)

- Small lab: 8 people
- Experts in different fields of anal. chem.
- Part time job for all of us

- DOCUMENTATION

- Lab structure & philosophy
- SOPs
- Written instructions for *everything*
- NEVER ending process



**State Institute for Drug
Control**



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PRO KONTROLU LÉČIV

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Certificate Ref. No.:

sukls152628/2014

CERTIFIKÁT SVP PRO VÝROBCE Část 1

Vydáný po inspekci v souladu s článkem 111(5) Směrnice 2001/83/ES a s §13, odst. 2, písm. a bod 3 zákona č. 378/2007 Sb., o léčivech a o změnách některých souvisejících zákonů (zákon o léčivech), ve znění pozdějších předpisů.

Příslušný orgán České republiky potvrzuje následující:

Kontrolní laboratoř:
Univerzita Palackého v Olomouci
Křížkovského 511/8
771 47 Olomouc

Adresa místa kontroly jakosti:
Univerzita Palackého v Olomouci
Přírodovědecká fakulta, Katedra analytické chemie, budova

CERTIFICATE OF GMP COMPLIANCE OF A MANUFACTURER Part 1

Issued following an inspection in accordance with Art. 111(5) of Directive 2001/83/EC and Section 13, paragraph 2, letter a, point 3 of the Act No 378/2007 Coll., on Pharmaceuticals and on Amendments to Some Related Acts (the Act on Pharmaceuticals), as amended.

The competent authority of the Czech Republic confirms the following:

The control laboratory:
Univerzita Palackého v Olomouci
Křížkovského 511/8
771 47 Olomouc

Site address:
Univerzita Palackého v Olomouci
Přírodovědecká fakulta, Katedra analytické chemie, budova



Elemental impurities in pharmaceuticals

- Sample preparation (API, final drug products, raw material)
- ICP-MS determination (quad, collision cell)
- Risk assessment of the results (usually 3 batches):



ICH Q3D: Guideline for Elemental Impurities

Permitted Daily Exposures (PDEs) for 24 Elements by 3 Routes of Administration

Class 1		Class 2A		Class 2B		Class 3	
1 H Hydrogen 1.01 G, 7.2	4 Be Beryllium 9.01 S, 1.5	5 B Boron 10.81 S, 7.0	6 C Carbon 12.01 S, 2.0	7 N Nitrogen 14.01 G, 1.2	8 O Oxygen 15.99 G, 1.2	9 F Fluorine 19 G, 4.0	10 Ne Neon 20.18 G
11 Na Sodium 22.99 S, 0.9	12 Mg Magnesium 24.31 S, 1.5	13 Al Aluminum 26.98 S, 1.5	14 Si Silicon 28.09 S, 1.2	15 P Phosphorus 30.97 S, 2.2	16 S Sulfur 32.07 S, 7.0	17 Cl Chlorine 35.45 G, 1.2	18 Ar Argon 39.95 G
19 K Potassium 39.1 S, 0.8	20 Ca Calcium 40.08 S, 1.0	21 Sc Scandium 44.96 S	22 Ti Titanium 47.88 S	23 V Vanadium 50.94 S	24 Cr Chromium 52 S	25 Mn Manganese 54.94 S	26 Fe Iron 55.85 S
27 Co Cobalt 58.93 S	28 Ni Nickel 58.69 S	29 Cu Copper 63.55 S	30 Zn Zinc 65.39 S	31 Ga Gallium 69.72 S, 1.0	32 Ge Germanium 72.64 S, 1.0	33 As Arsenic 74.92 S, 1.0	34 Se Selenium 78.96 S, 1.0
35 Br Bromine 79.9 S, 1.0	36 Kr Krypton 83.8 G	37 Rb Rubidium 85.47 S, 0.8	38 Sr Strontium 87.62 S, 1.0	39 Y Yttrium 88.91 S	40 Zr Zirconium 91.22 S	41 Nb Niobium 92.91 S	42 Mo Molybdenum 95.94 S
43 Tc Technetium [99]	44 Ru Ruthenium 101.07 S	45 Rh Rhodium 102.91 S	46 Pd Palladium 106.42 S	47 Ag Silver 107.87 S	48 Cd Cadmium 112.41 S, 1.7	49 In Indium 114.82 S, 1.7	50 Sn Tin 118.71 S, 1.7
51 Sb Antimony 121.76 S, 2.3	52 Te Tellurium 127.6 S, 2.7	53 I Iodine 126.9 S, 2.7	54 Xe Xenon 131.29 G	55 Cs Cesium 132.91 S, 0.7	56 Ba Barium 137.33 S, 0.4	57 La Lanthanum 138.91 S	58 Ce Cerium 140.12 S
59 Pr Praseodymium [140]	60 Nd Neodymium [144]	61 Pm Promethium [145]	62 Sm Samarium [150]	63 Eu Europium [152]	64 Gd Gadolinium [157]	65 Tb Terbium [159]	66 Dy Dysprosium [163]
67 Ho Holmium [165]	68 Er Erbium [167]	69 Tm Thulium [169]	70 Yb Ytterbium [173]	71 Lu Lutetium [175]	72 Hf Hafnium [178]	73 Ta Tantalum [181]	74 W Tungsten [184]
75 Re Rhenium [187]	76 Os Osmium [190]	77 Ir Iridium [192]	78 Pt Platinum [195]	79 Au Gold [197]	80 Hg Mercury [200]	81 Tl Thallium [203]	82 Pb Lead [207]
83 Bi Bismuth [209]	84 Po Polonium [209]	85 At Astatine [210]	86 Rn Radon [222]	87 Fr Francium [223]	88 Ra Radium [226]	89 Ac Actinium [227]	90 Th Thorium [232]
91 Pa Protactinium [231]	92 U Uranium [238]	93 Np Neptunium [237]	94 Pu Plutonium [244]	95 Am Americium [243]	96 Cm Curium [247]	97 Bk Berkelium [247]	98 Cf Californium [251]
99 Es Einsteinium [252]	100 Fm Fermium [257]	101 Md Mendelevium [258]	102 No Nobelium [259]	103 Lr Lawrencium [260]	104 Rf Rutherfordium [261]	105 Db Dubnium [262]	106 Sg Seaborgium [263]
107 Bh Bohrium [264]	108 Hs Hassium [265]	109 Mt Meitnerium [266]	110 Ds Darmstadtium [271]	111 Rg Roentgenium [272]	112 Cn Copernicium [285]	113 Nh Nihonium [284]	114 Fl Flerovium [289]
115 Mc Moscovium [288]	116 Lv Livermorium [293]	117 Ts Tennessine [294]	118 Og Oganesson [294]				



Metrological Traceability

- Demonstration of traceability in our lab:
 - CRM solutions for calibration – certificate of the CRM;
 - Expiration (shelf life)
 - Mass of a sample – calibration of the balance (certificate);
 - Volumetric flasks – calibration certificate of the manufacturer;
 - Micropipettes – regular „calibration“ and checking (certificate);
 - Microwave digestion units – regular service/qualification;
 - ICP-MS – regular service & qualification (IQ/OQ) – protocols;
 - Performance checks on daily basis
 - Tuning solutions (shelf life)



Validation of Measurement Procedures

- Every procedure used under GMP shall be validated!
 - We have a SOP dealing with validation & acceptance criteria.
 - It is based on **ICH Q2(R1) – Validation of Analytical Procedures: Text and Methodology.**
 - More rigorous approach – parameters, minimum of repeated measurements.

Type of analytical procedure	IDENTIFICATION	TESTING FOR IMPURITIES		ASSAY dissolution (measurement only) content/potency
characteristics		quantitat.	limit	
Accuracy	-	+	-	+
Precision				
Repeatability	-	+	-	+
Interm.Precision	-	+(1)	-	+(1)
Specificity (2)	+	+	+	+
Detection Limit	-	-(3)	+	-
Quantitation Limit	-	+	-	-
Linearity	-	+	-	+
Range	-	+	-	+



Validation of Measurement Procedures

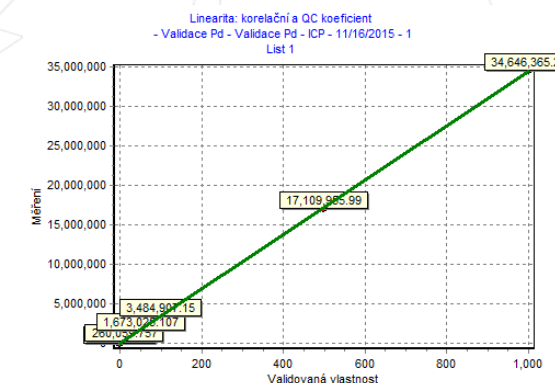
– PROCEDURE:

1. **Validation protocol:** validation experiments, acceptance criteria
2. Perform **validation experiments**
3. **Validation report:** evaluation, compliance with criteria

Characteristic	Acceptance criteria	Experimental data
Linearity	$R \geq 0.99$	$R = 0.9998$
Range	LOQ – 1000 $\mu\text{g}\cdot\text{L}^{-1}$	1.17 – 1000 $\mu\text{g}\cdot\text{L}^{-1}$
LOD	$\leq 0.6 \mu\text{g}\cdot\text{L}^{-1}$	0.57 $\mu\text{g}/\text{L}$ (n = 10)
LOQ	$\leq 1.8 \mu\text{g}\cdot\text{L}^{-1}$	1.17 $\mu\text{g}/\text{L}$ (n = 10)
Accuracy (recovery)	70 – 150 %	104.7 – 109.5 % (3 levels)
Precision (repeatability)	RSD < 20 %	< 5.2 % (n = 6)
Intermediate precision	RSD < 25 %	< 7.9 (n = 2×6)
Specificity	recovery 70 – 150 %	92.9 – 115.3 % (^{105}Pd , ^{108}Pd)
Robustness	recovery 70 – 150 %	107.7 – 119.2 % (modifications in procedure)

Validační zpráva

Stanovení paladia jako nečistoty v aktivních farmaceutických substancích, meziproduktech a výchozích surovinách pomocí ICP-MS



Tab. 6: Přesnost - naměřená data

Měření	Spike 50 ($\mu\text{g}/\text{l}$)	Spike 500 ($\mu\text{g}/\text{l}$)	Spike 800 ($\mu\text{g}/\text{l}$)
1	51,20485347	508,7766914	811,9588187
2	53,01429983	525,2848819	836,6723320
3	54,37651572	527,7519614	836,8858552
4	54,08283967	539,0854652	847,8081330
5	56,76445689	518,6073688	838,9528434
6	59,18893703	539,6886986	851,0177846

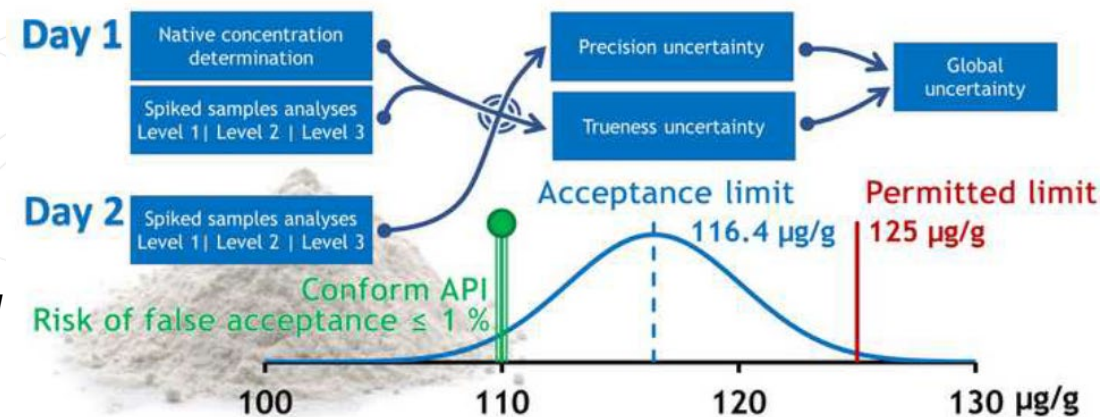


Reporting Results

- Protocols of analysis are prepared for customers.
- Results are presented **WITHOUT** measurement uncertainty.
- Comparison with specification – comparing 2 values (MU not included).
- Out of specification results:
 - Laboratory investigation → re-analysis
 - Discussion with customer

- Our contribution to conformity assessment:

Milde D., Pluháček T., Kuba M., Součková J., Betencourt da Silva R.J.N.: *Measurement uncertainty evaluation from correlated validation data: Determination of elemental impurities in pharmaceutical products by ICP-MS*. Talanta 2020, DOI: 10.1016/j.talanta.2020.121386.





What have we learned?

- Implementation of QMS principles is feasible even in the research lab:
 - It is time consuming and costly.
 - We can rely on measurement results (documentation, data storage, ...).
- It is possible to bring together basic research done in academia & contract research in one lab:
 - “Mix” of personnel (PhD candidates included) in the lab – STRICT RULES
 - Different research topics analysed on same instruments
- Personnel have to be trained regularly, even if qualified.
- PhD graduates better prepared for their career.
- Teaching of QA/QC topics based on experience.



What have we learned – “PROS”

- Gained knowledge:
 - Implementation and running of lab QMS
 - Closer contact with industry
 - Solving of challenging tasks in limited time
 - Carefulness in the lab and results reporting
 - Communication skills
- Regular service of analytical instrumentation.
- Benefits from regular calibration of balances, micropipettes, thermometers.
- Income from customers.



What have we learned – “CONS”

- **EXPENSES:**
 - Service of all instruments and IQ/OQ
 - Data integrity – data storage, audit trail, access to computers, ...
 - Quality manager, office staff – communication with customers
 - Higher running costs (CRMs, chemicals)
- **Regular audits and preparation for them:**
 - State institute for Drug Control, possibly FDA
 - Customers
- **Limited access to laboratory equipment to undergraduate students.**
- **Daily routine checks in the lab may be time consuming.**



CONCLUSIONS

- Laboratory QMS can be implemented in the laboratory of a public university.
- Proper maintenance of QMS is based on regular income from contract research.
- Optimization of expenses needed (e.g. IQ/OQ).
- Contract research can influence university research and vice versa:
 - Scientific publications
 - Invitation to expert committees (e.g. terminology)
- Benefits outweigh difficulties.
- New research topics.



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Acknowledgment



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