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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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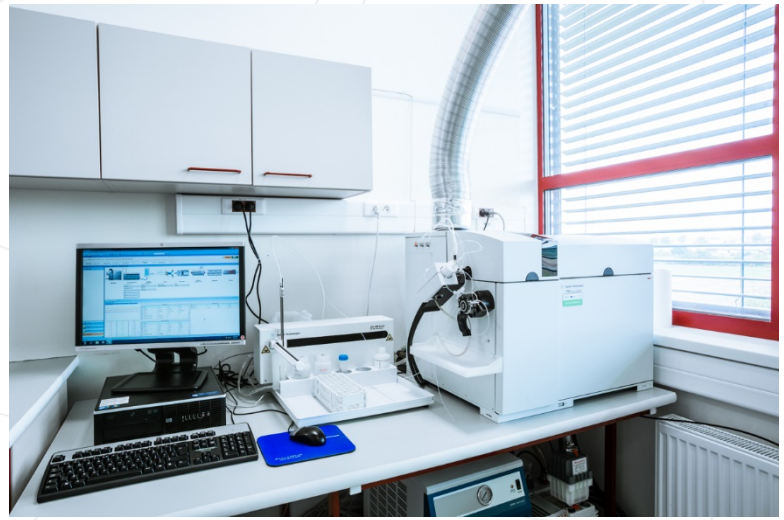
About us

- 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

SÚKL **State Institute for Drug Control**

SÚKL

STÁTNÍ ÚSTAV PRO KONTROLU LÉČIV
Šrobárova 48
100 41 Praha 10
Telefon: +420 272 185 111
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E-mail: posta@sukl.cz
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Certifikát spisová zn.: / Certificate Ref. No.: sukls152628/2014

CERTIFIKÁT SVP PRO VÝROBCE
Část 1

Vydaný 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

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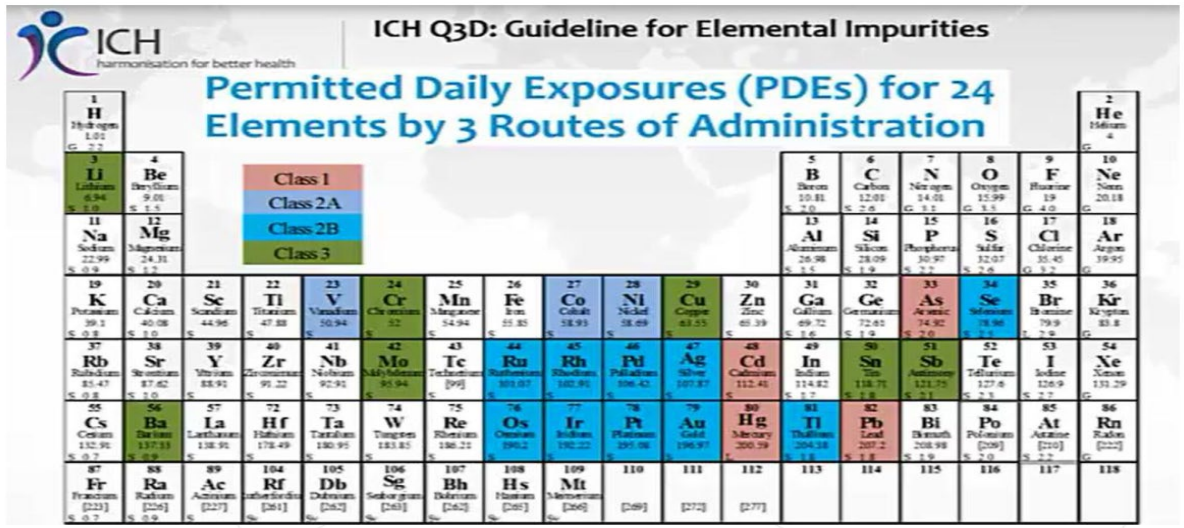
Elemental impurities in pharmaceuticals

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



Decock G.: Eurofins Pharma Presentation 17/11/2015

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

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Přírodovědecká fakulta

R-lab

Validation of Measurement Procedures

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

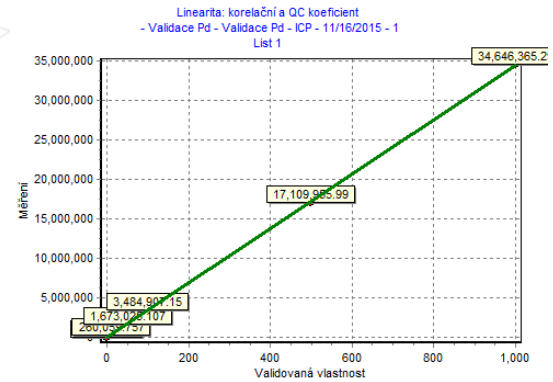
Characteristic	Acceptance criteria	Experimental data
Linearity	R ≥ 0.99	R = 0.9998
Range	LOQ – 1000 µg.L^{-1}	1.17 – 1000 µg.L^{-1}
LOD	≤ 0.6 µg.L^{-1}	0.57 µg/L (n = 10)
LOQ	≤ 1.8 µg.L^{-1}	1.17 µg/L (n = 10)
Accuracy (recovery)	70 – 150 %	104.7 – 109.5 % (3 levels)
Precision (repeatability)	RSD < 20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

VAZ-AS-001

Počet příloh: 5

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 (µg/l)	Spike 500 (µg/l)	Spike 800 (µg/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

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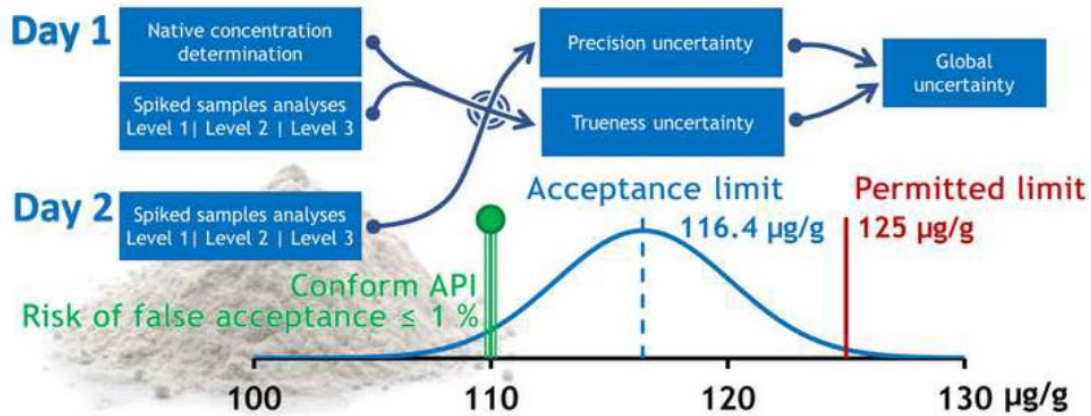
Reporting Results

- 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.

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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.

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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.

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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

Thank You for Your kind attention!

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