WEBINAR SERIES 2021

How to use XRF in Pharma & Cosmetics

Adrian Fiege and Frank Portala

13.10.2021

From Rapid Incoming Raw Material Verification to At-line Heavy Metal Impurity Determination

Frank Portala, Product Manager XRF, Karlsruhe, Germany

Chemical Engineer (Dipl. FH)

2012 Product Management Bruker AXS

Product Management XRF

Karlsruhe, Germany

Adrian Fiege, Product Manager XRF, Karlsruhe, Germany

Ph D, Geology

2019 Product Management Bruker AXS

Product Management XRF

Karlsruhe, Germany

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From Rapid Incoming Raw Material Verification to At-line Heavy Metal Impurity Determination

01 Elemental Analysis: Pharma & Cosmetics

02 Basics about XRF

03 Benefits of XRF vs. other Techniques

04 Analytical Requirements (ICH, USP)

05 Pharma & Cosmetic Applications for EDXRF and WDXRF

06 21 CFR Part 11 and IQ/OQ

07 When to use Standardless Solutions?

08 Summary and Q&A

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Elemental Analysis: Pharma & Cosmetics

- Strict regulations apply to ensure the quality of resulting medications and other products. This makes reliable and precise analysis inevitable.
- **Elemental analysis** is required at all manufacturing steps particularly including
  - verification of incoming **raw materials**
  - monitoring **manufacturing processes** including **catalysts** and **metals residues** analysis
  - **heavy metal impurity** analysis
  - analysis of **active pharmaceutical ingredients (API)**, **intermediates** and final products
- **Cosmetic** and personal care products must meet high product quality standards due to their applications.

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Example for Elemental Analysis in Pharma & Cosmetics Raw Material ID

- NaCl / KCl
  Ensure the correct use of NaCl for physiological saline solutions

- ZnO / TiO_2
  - Sun lotion, wound ointments

- $CaCl_2$ / $MgSO_4$ / $AlPO_4$ / $CaCO_3$
  - $CaCl_2$ and $MgSO_4$ used in infusions
  - $AlPO_4$ for vaccinations
  - $CaCO_3$ as dietary Ca supplement

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ICH Q3D
International Conference on Harmonisation

- Describes technical requirements for registration of pharmaceuticals for human use (ICH) Q3D for elemental impurities
- ICH Q3D guidelines define control thresholds of 30% of the Permitted Daily Exposure (PDE)
- 24 elements included in risk assessment, split into 4 classes
- Typically, AAS / ICP-OES / ICP-MS is used to measure/monitor these elements in raw materials, active ingredients, drugs and final products

Element	Class[2]	Oral PDE µg/day	Parenteral PDE, µg/day	Inhalation PDE, µg/day
Cd	1	5	2	3
Pb	1	5	5	5
As	1	15	15	2
Hg	1	30	3	1
Co	2A	50	5	3
V	2A	100	10	1
Ni	2A	200	20	5
Tl	2B	8	8	8
Au	2B	100	100	1
Pd	2B	100	10	1
Ir	2B	100	10	1
Os	2B	100	10	1
Rh	2B	100	10	1
Ru	2B	100	10	1
Se	2B	150	80	130
Ag	2B	150	10	7
Pt	2B	100	10	1
Li	3	550	250	25
Sb	3	1200	90	20
Ba	3	1400	700	300
Mo	3	3000	1500	10
Cu	3	3000	300	30
Sn	3	6000	600	60
Cr	3	11000	1100	3

Source: ICH guideline Q3D on elemental impurities

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US Pharmacopeia (USP) - Chapters <232>, <233>, & <735>

- USP is a pharmacopeia (compendium of drug information) for the United States
- Chapters define more precise requirements for techniques and methods
- USP<232> and ICH Q3D define the requirements for analysis of elemental impurities (heavy metals) in pharmaceuticals
- USP<233> specifies ICP-OES and ICP-MS techniques for elemental impurities analysis
- **USP<735> enables the use of X-ray fluorescence spectrometry for this analysis**
- Enforcement of the standards is the responsibility of the U.S. Food and Drug Administration (FDA) and other government authorities in the US

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How does current Pharma & Cosmetics Analysis look like?

Atomic Absorption Spectrometry (AAS)

- Spectroscopic technique with wide element range
- Used as flame or graphite furnace AAS
- Sample must be prepared/digested/diluted
- Requires daily instrument calibration
- Usually, single element analysis

Inductively Coupled Plasma Spectrometry (ICP-OES / ICP-MS)

- Spectroscopic technique with wide element range
- Established techniques for elemental analysis in pharma and cosmetics, including heavy metal impurities
- Sample must be prepared/digested/diluted
- Requires daily instrument calibration

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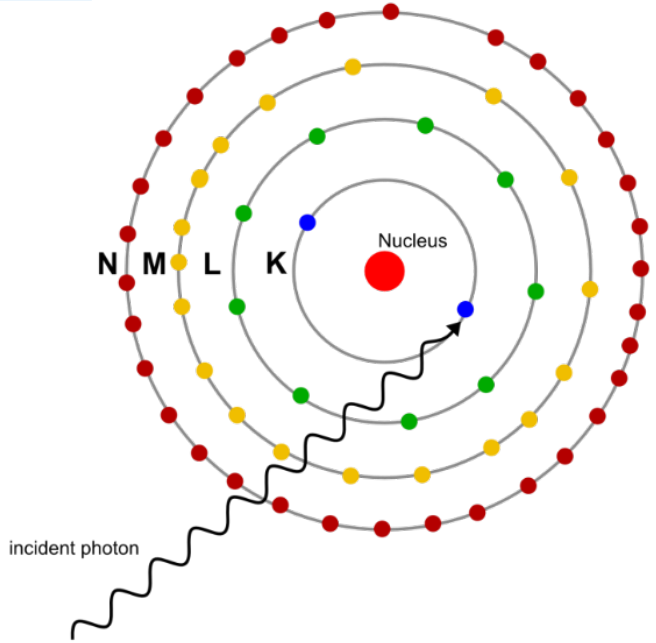
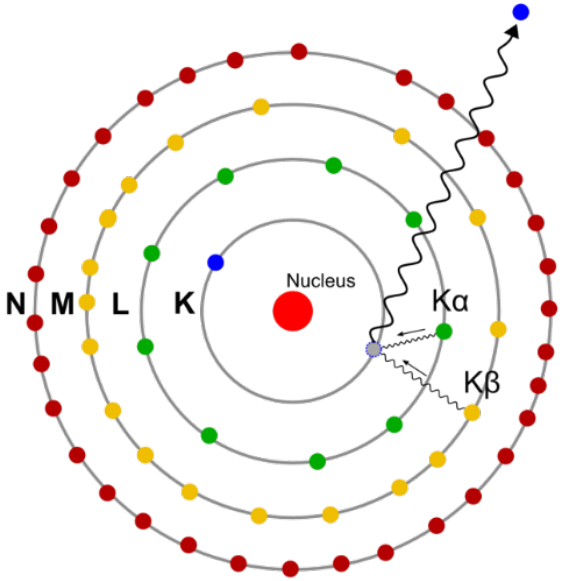
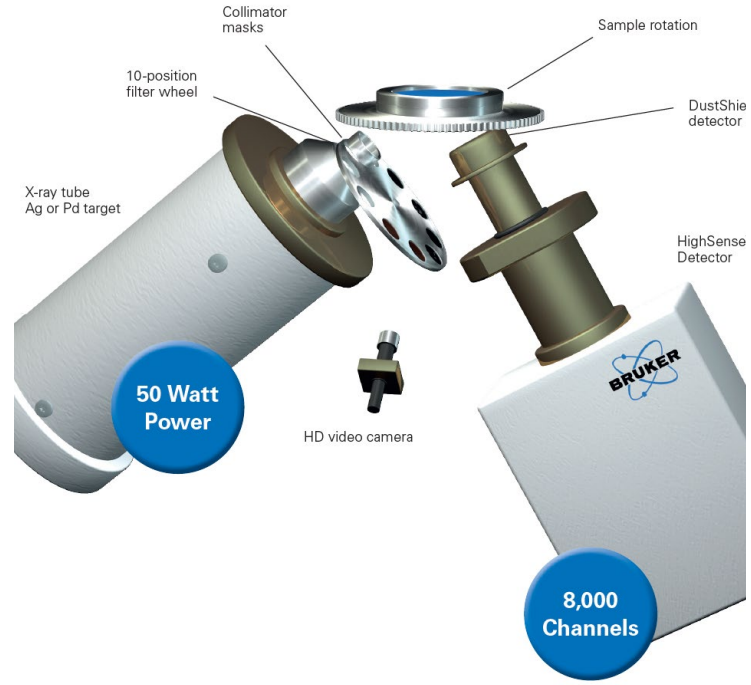
How does X-ray Fluorescence (XRF) Technique works? Photoelectric Effect







- Sample excited with an X-ray beam causing fluorescence
- Electron ejected from an inner shell of its atom
- Electron from a shell farther out falls into the vacancy
- Energy difference is emitted as an X-ray photon
- Discrete energy or wavelength is characteristic for the emitting element / transition
- Intensity of characteristic radiation is proportional to concentration of the element in the sample

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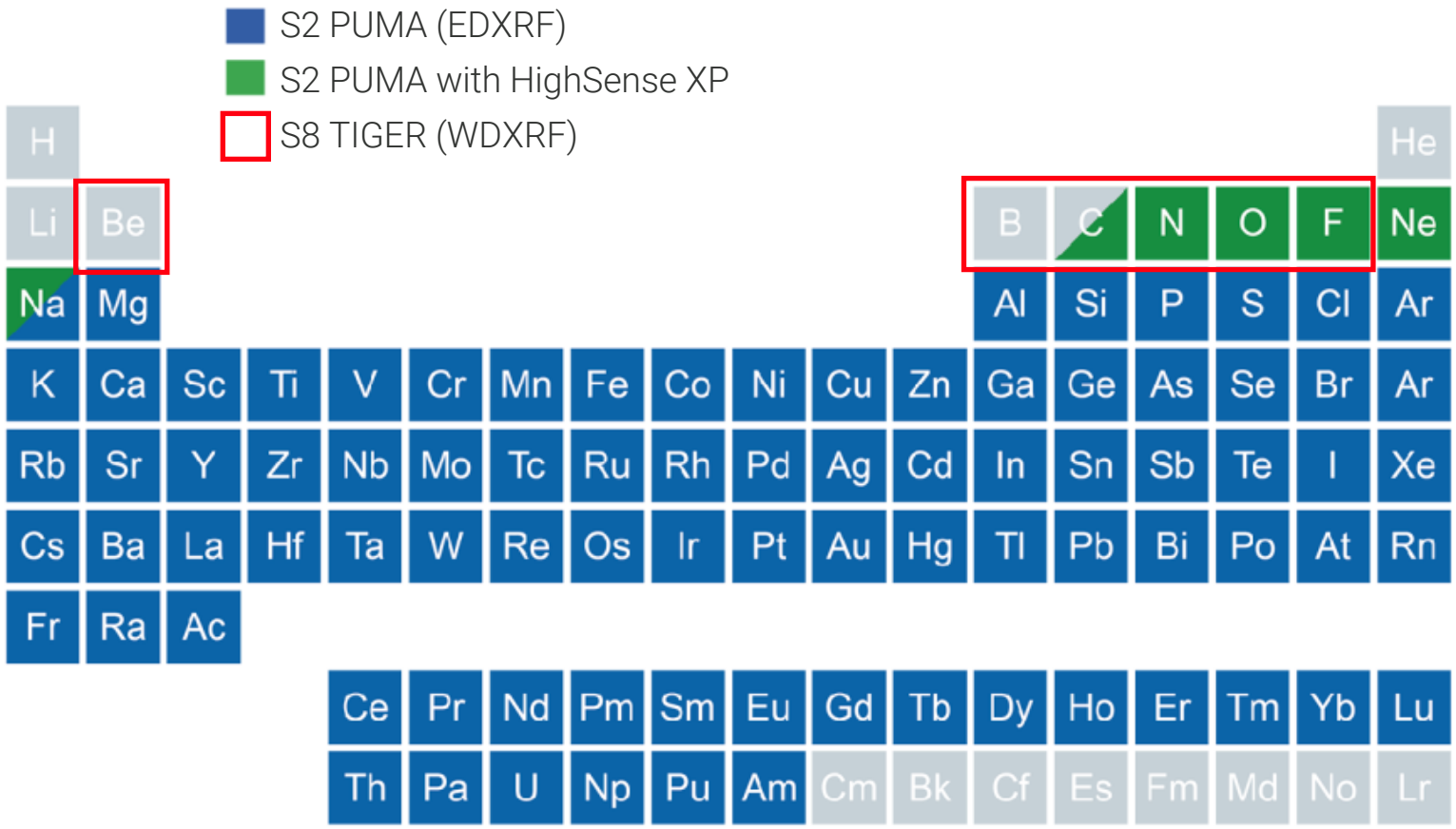
X-ray Fluorescence (XRF) Elemental Range

Elemental Range:

XRF: (B) Be to Am

- Pharma/Cosmetics: F to U



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Sample Types

XRF can be used for all sample types and applications

- Powders, granules, ointments, solids, liquids, bulk

A selection of atmosphere modes ensures optimal performance – even for light elements

- Vacuum, helium, air, nitrogen

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Comparison of EDXRF vs. AAS / ICP-OES / ICP-MS

EDXRF

- Compact instruments
- Sensitivities: down to ppm level
- Records the entire spectrum
- Easy operation
- Low costs of operation
- Able to measure powders or grinded samples directly
- Very short time from sample to result
- Smaller, “can also be brought to the sample”

AAS / ICP-OES / ICP-MS

- Complex instruments
- Sensitivities: down to (low) ppb level
- Multi-element techniques
- Requires trained lab personnel
- Time consuming instrument and sample preparation:
  - Requires daily calibration
  - Solid samples must be dissolved

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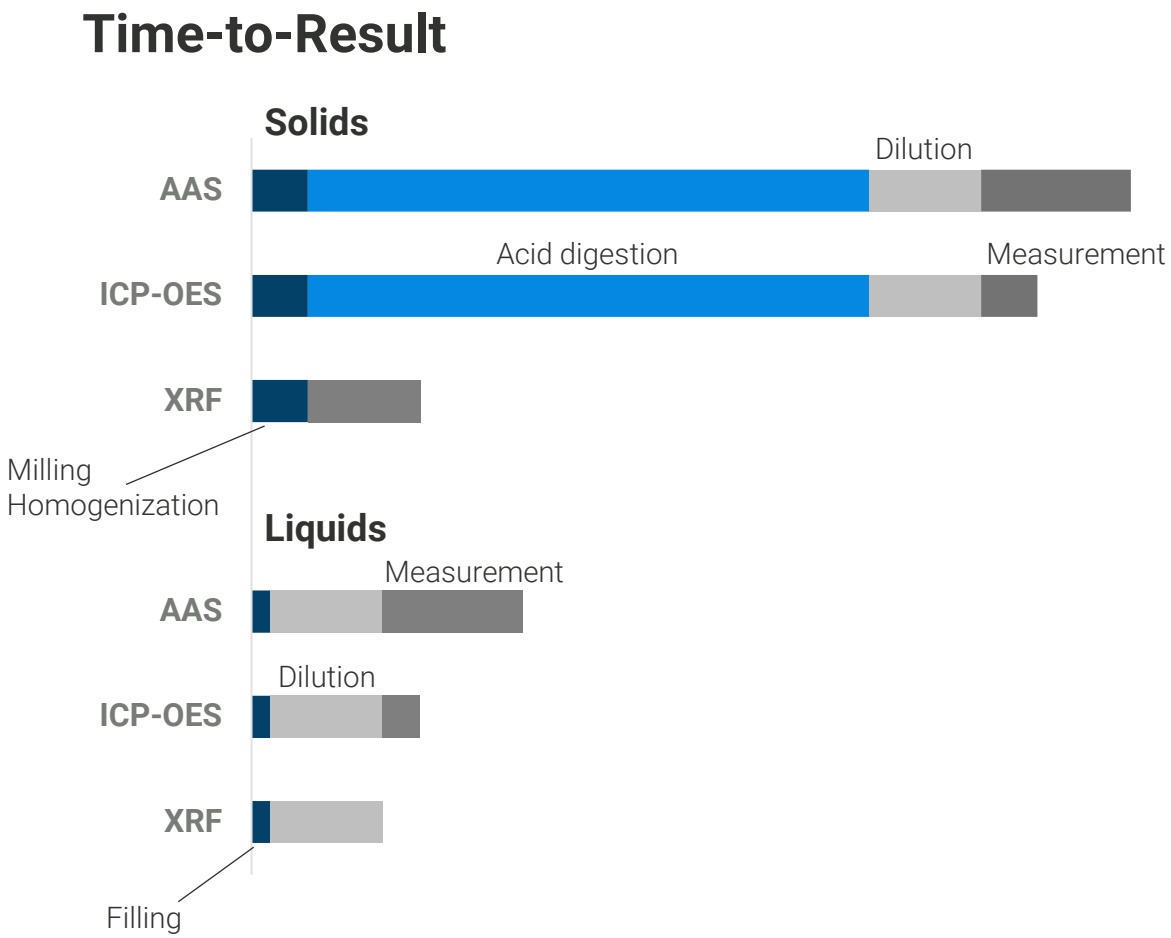
Advantages of XRF
Time-to-Result: XRF vs. AAS or ICP-OES

- Effective quality and process control requires the shortest time-to-result possible
- This is the time needed from sampling to the final quantitative result
- Any advantage results in:
  - Higher sample throughput
  - Stable industrial processes due to immediate feedback
  - Constantly high product quality

XRF has significant advantages for raw material ID and at-line production monitoring



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Pharma & Cosmetic Applications

XRF Elemental Analysis: Pharma & Cosmetics

- XRF is particularly suitable for
  - quick verification of incoming raw material
  - at-line production monitoring (Process Analytical Technology, PAT)
  - foreign body identification (FBI), and
  - heavy metal impurity analysis.

- Cosmetic and personal care products must meet high product quality standards due to their applications.

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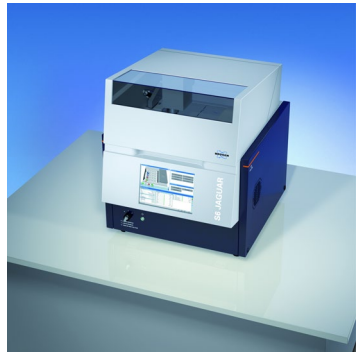
21 CFR Part 11-Compliance

21 CFR Part 11-compliance

- SPECTRA.ELEMENTS is fully compliant

- The Part 11 features are smoothly integrated to ensure ease-of-use and worry-free operation – being always prepared for the next audit

- *Key features:*
  - Audit trailing
  - Electronic signatures / validation
  - Dedicated user levels
  - Customizable views



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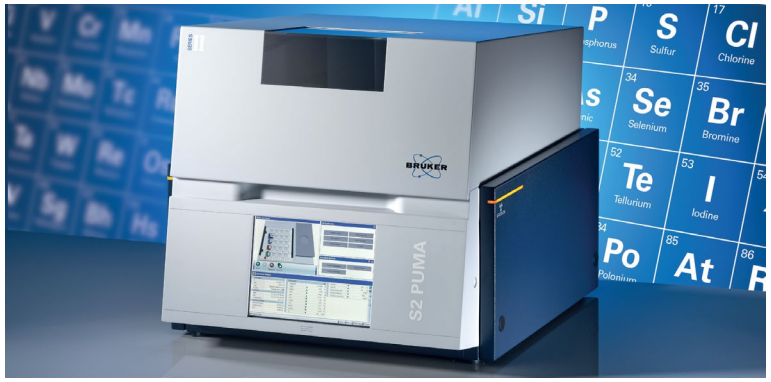
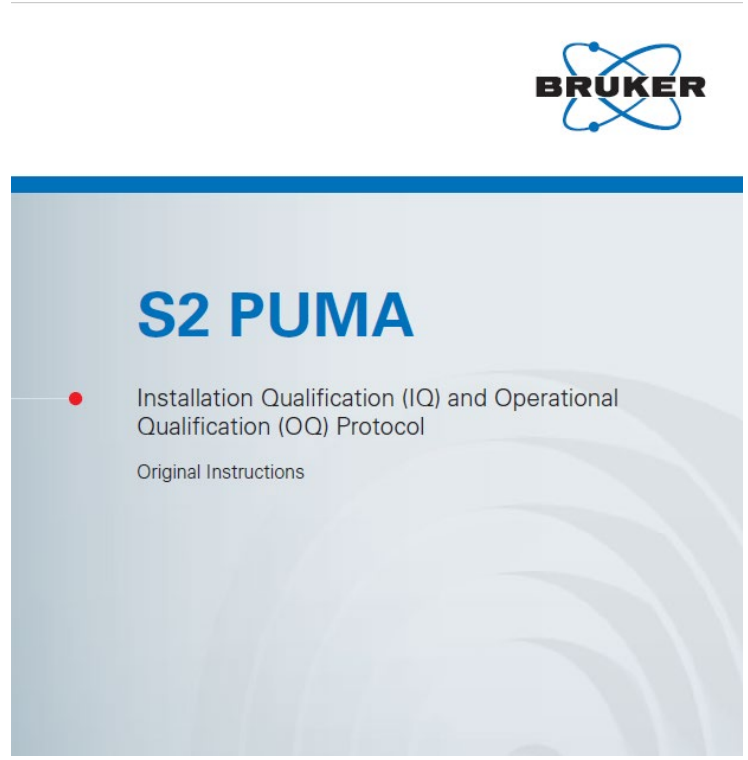
IQ/OQ Documentation and Support

- Installation Qualification:
  Establishes that the instrument is received as designed and specified and that it is properly installed

- Operation Qualification:
  Demonstrates that the instrument will function according to the operational specifications (acceptance testing).

- IQ/OQ: Performed together with our Part 11 trained Service Engineer





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Standardless Analysis SMART-QUANT FP and WD

SMART-QUANT is set up to work in full Fundamental Parameter (FP) mode – this means no calibrations necessary!

Excellent for raw material testing and whenever special samples outside the analytical routing need to be measured.

- Na to Am (FP) / F to Am (WD)
- ppm to 100%
- Air, Helium, Vacuum
- 30 and 50 kV

SMART-QUANT: Push-button solution for quick and reliable analysis of unknown samples

S2 PUMA Series 2 with XY-Autochanger for highest sample throughput

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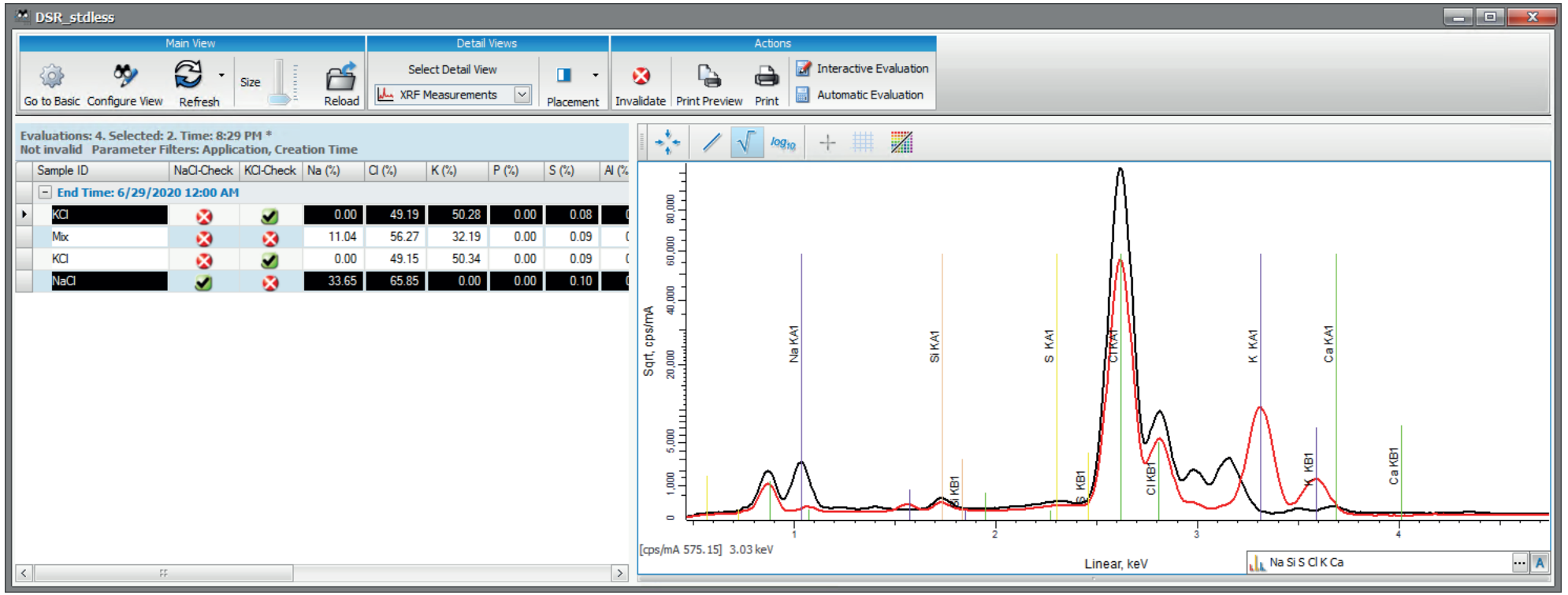
SMART-QUANT FP
Elemental Analysis: Pharma & Cosmetics

- Customizable concentration thresholds and configurable views allow to make a quick decision (reject or accept)



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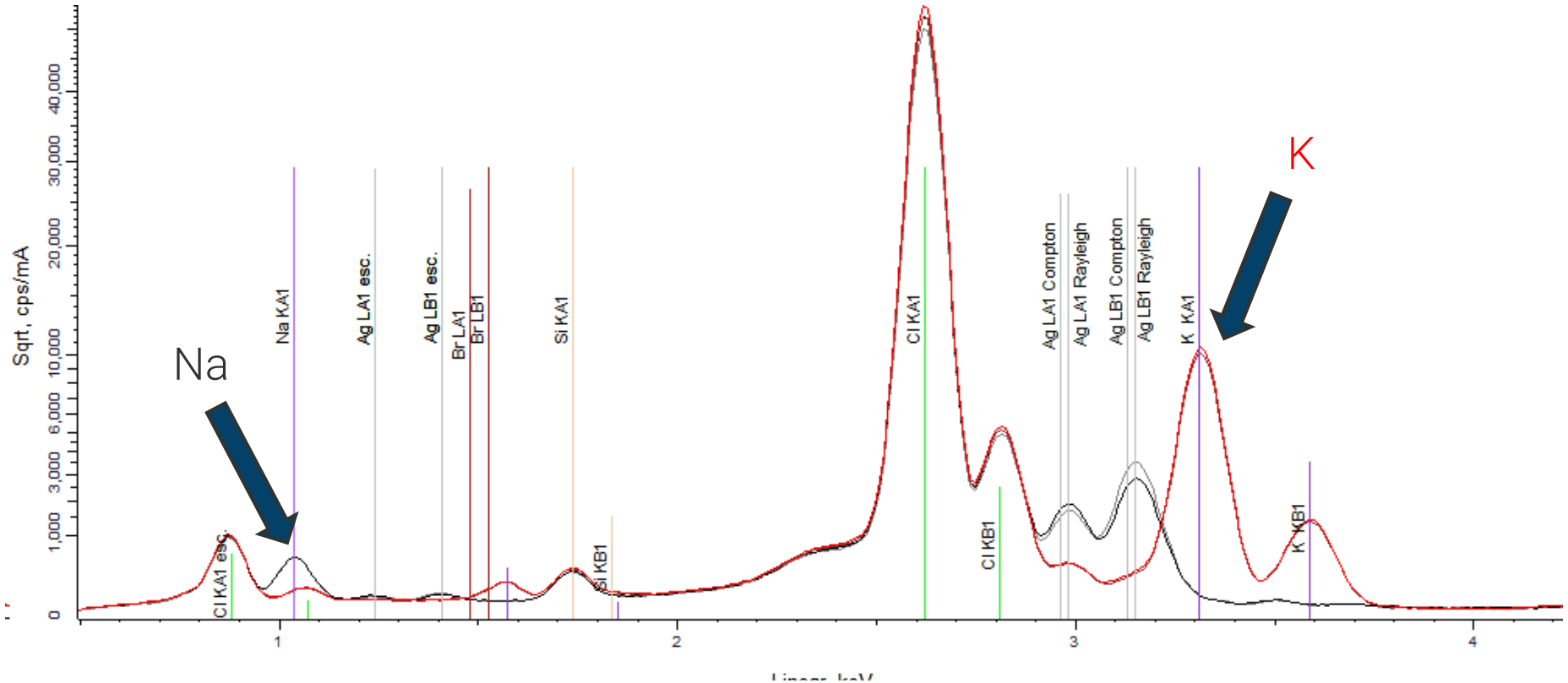
SMART-QUANT FP
Elemental Analysis: Pharma & Cosmetics

- Differentiate quickly between KCl and NaCl



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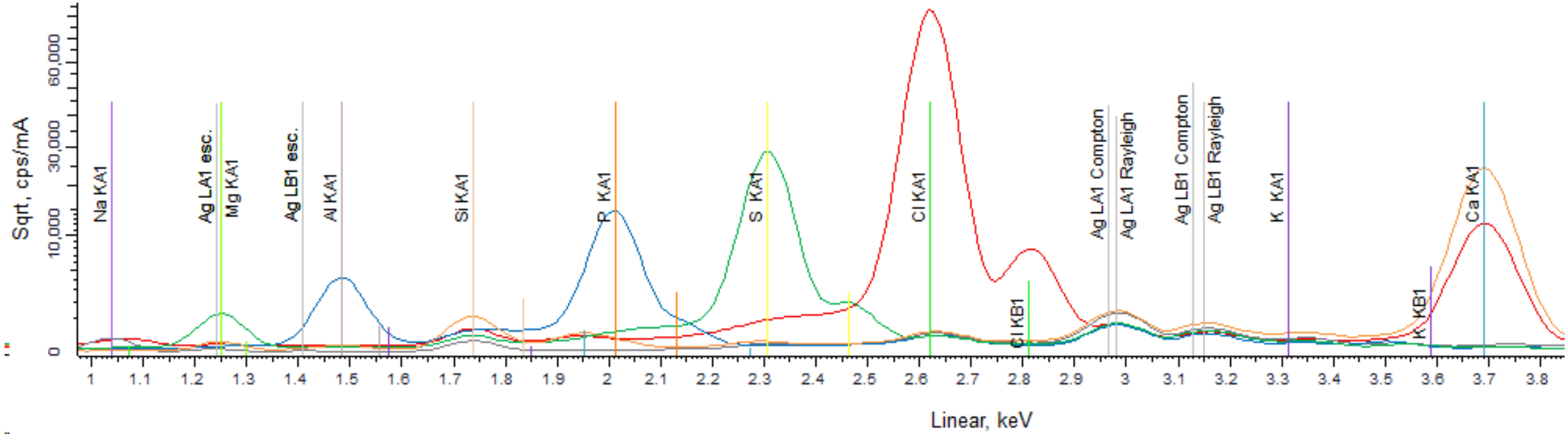
SMART-QUANT FP
Elemental Analysis: Pharma & Cosmetics

- Differentiate quickly between $CaCl_2$, $MgSO_4$, $AlPO_4$, and $CaCO_3$



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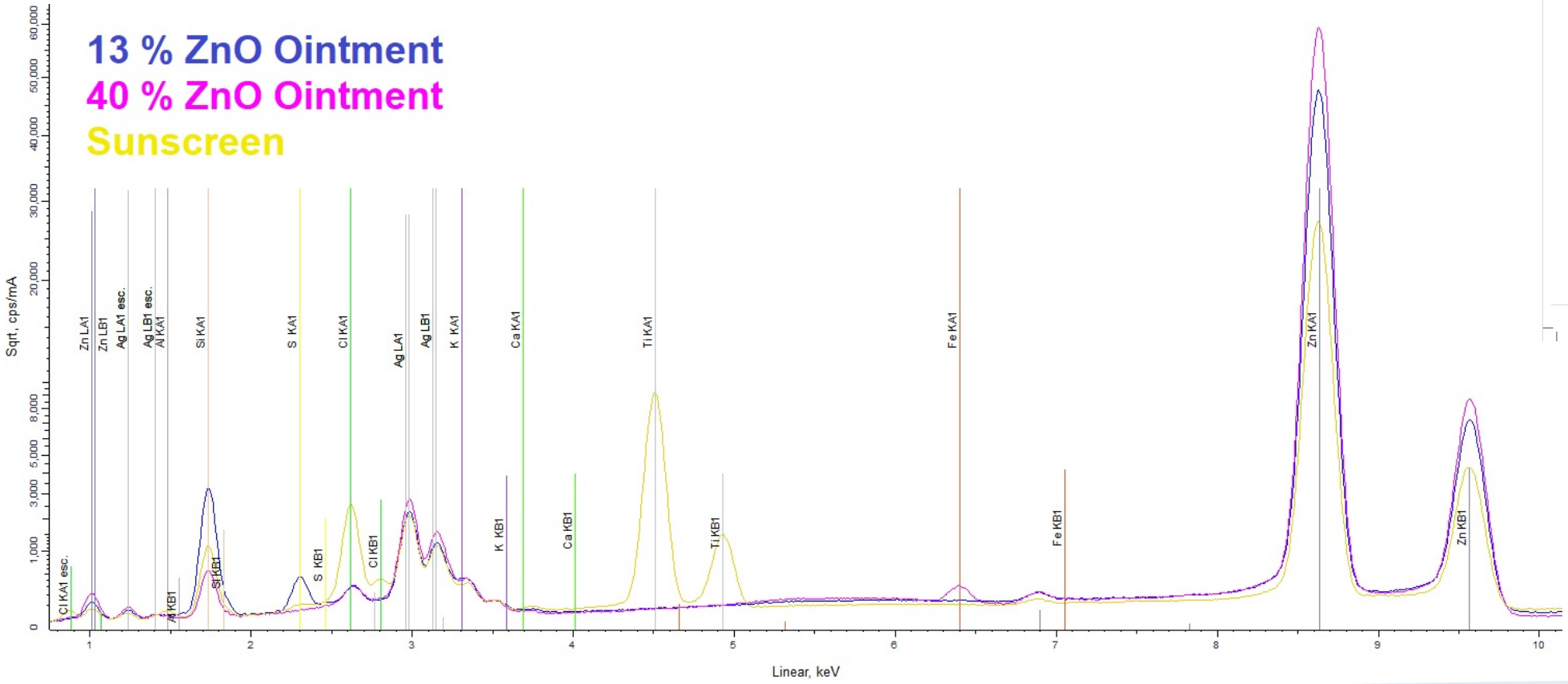
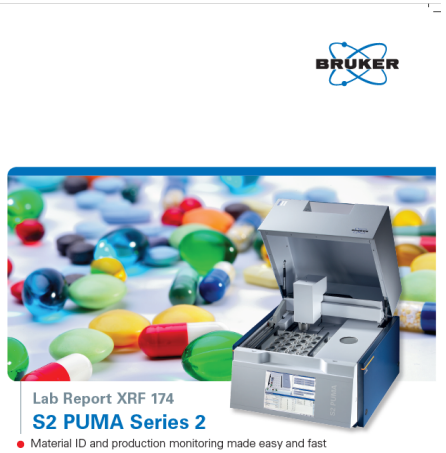
SMART-QUANT FP
Elemental Analysis: Pharma & Cosmetics

- Identify material based on ZnO and/or TiO_2 contents, without providing information about the matrix





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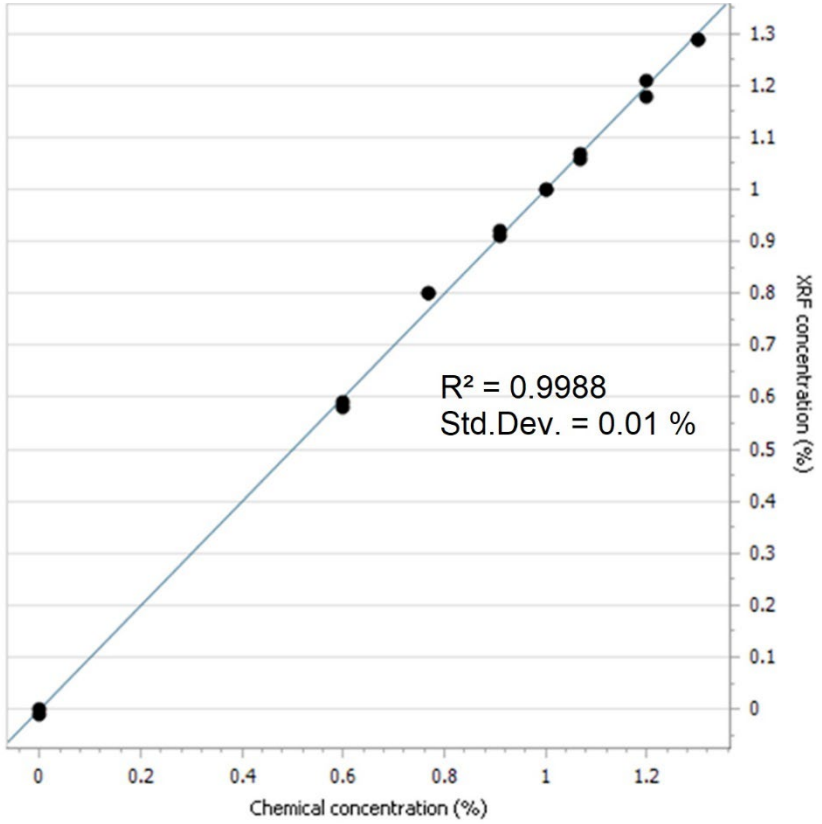
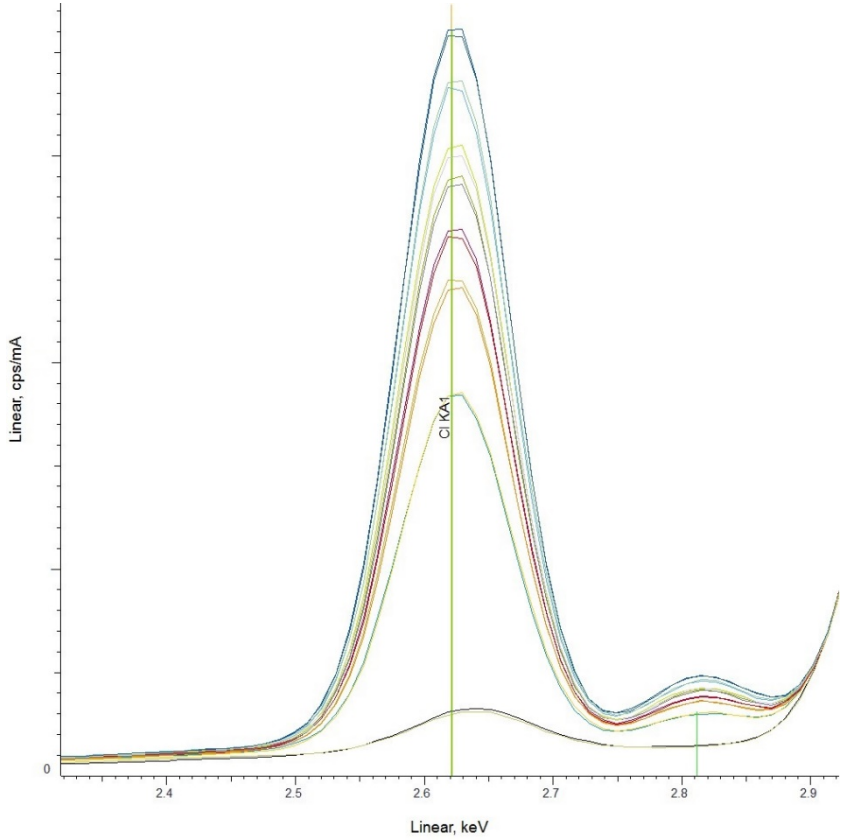
SMART-QUANT FP
Elemental Analysis: Pharma & Cosmetics

- Calibration for NaCl in saline solution. Excellent calibration curve (left) thanks to outstanding signal-to-noise ratio and system stability.





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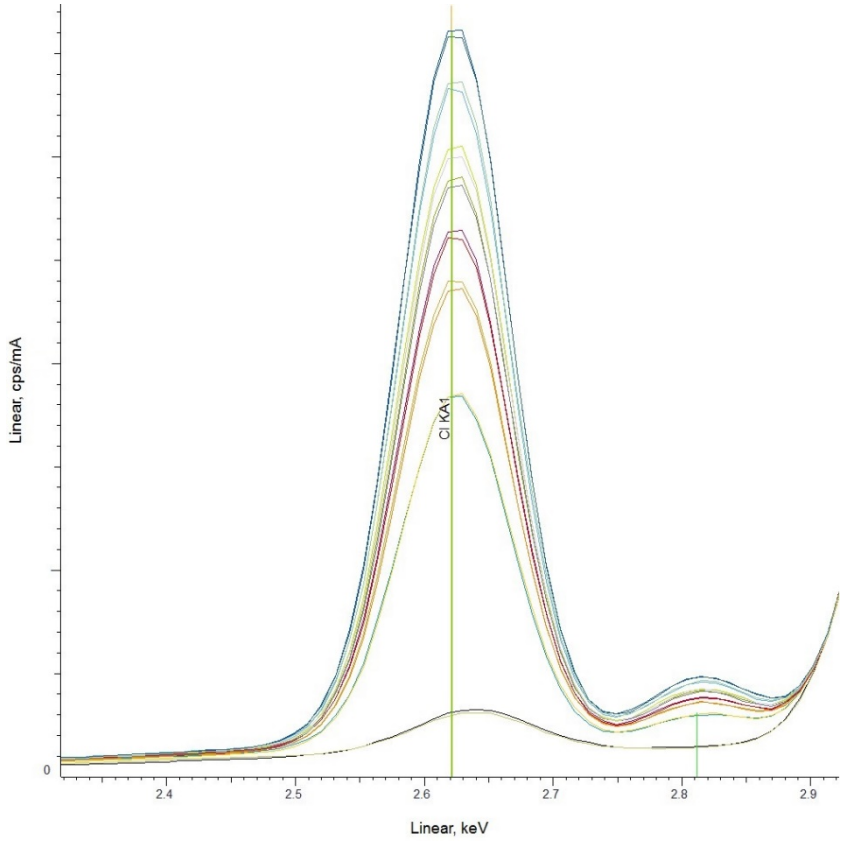
Elemental Analysis: Pharma & Cosmetics S2 PUMA

- Repetition test shows excellent precision, even for light elements.

Measurement #	NaCl [%]
1	1.00
2	0.99
3	1.00
4	0.99
5	0.99
6	1.00
7	1.00
8	0.99
9	0.99
10	1.00
Average	1.00
Abs. Std Dev.	<0.01
Re. Std. Dev.	0.45%



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Sunscreen Products S2 PUMA

- Excellent precision!

Measurement #	TiO_2 [%]	ZnO [%]
1	9.50	1.94
2	9.56	1.93
3	9.61	1.93
4	9.44	1.92
5	9.40	1.90
6	9.46	1.91
7	9.42	1.90
8	9.46	1.91
9	9.50	1.91
10	9.44	1.90
Average	9.48	1.92
Abs. Std Dev.	0.063	0.014
Re. Std. Dev. [%]	0.66	0.71

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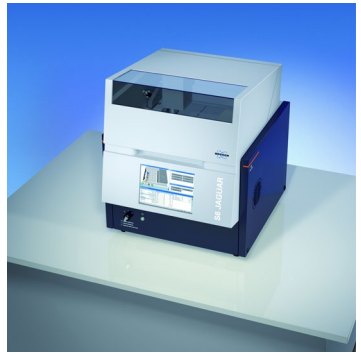
Elemental Analysis: Pharma & Cosmetics S2 PUMA

Heavy metal LLD in pharmaceutical and cosmetic materials

- Cd, Pb, As, Hg, Co, Ni: 1-2 µg/g depending on preparation and measurement time

Examples	LLD (µg/g)
Co	0.4
Ni	0.2
As	0.9
Hg	2.2



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Elemental Analysis: Pharma & Cosmetics S2 PUMA

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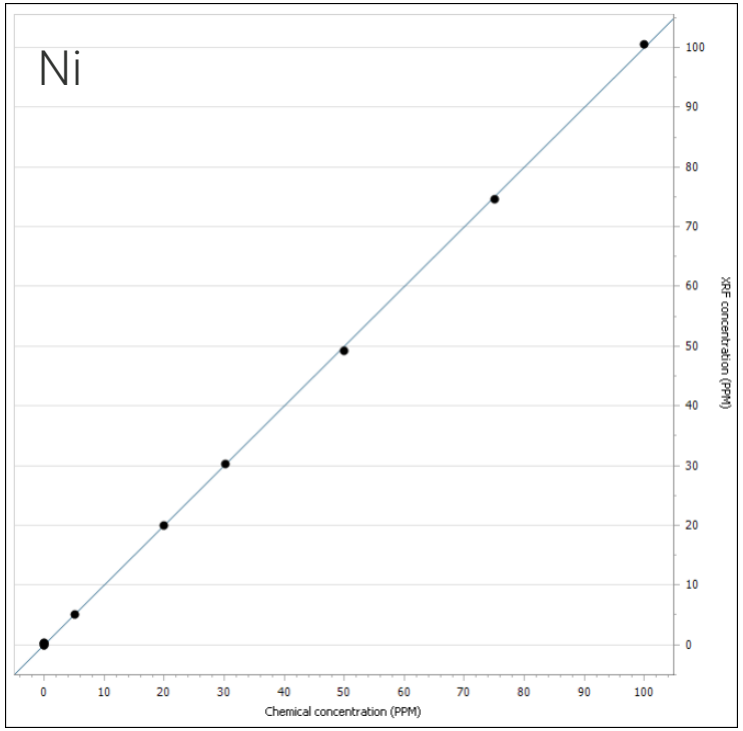

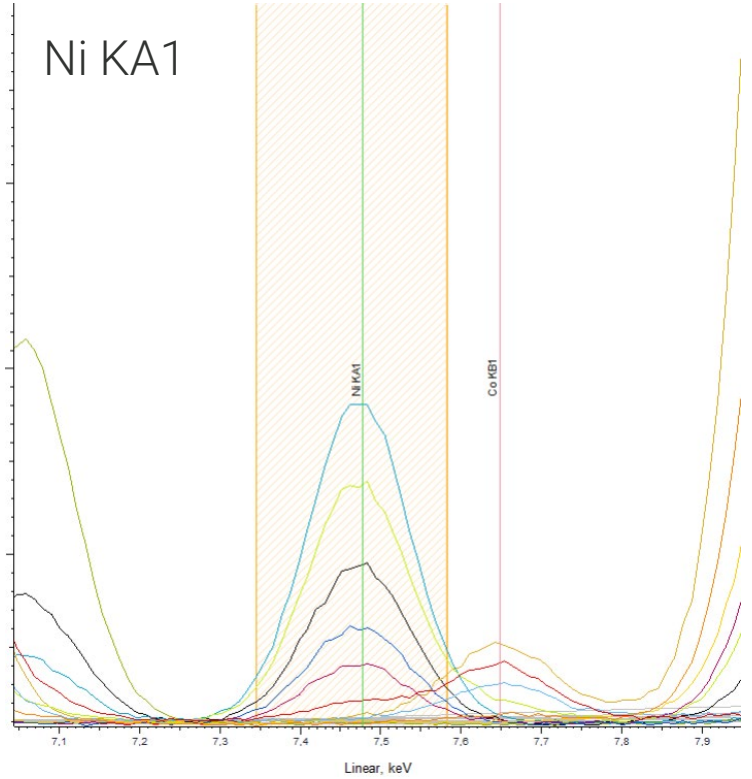

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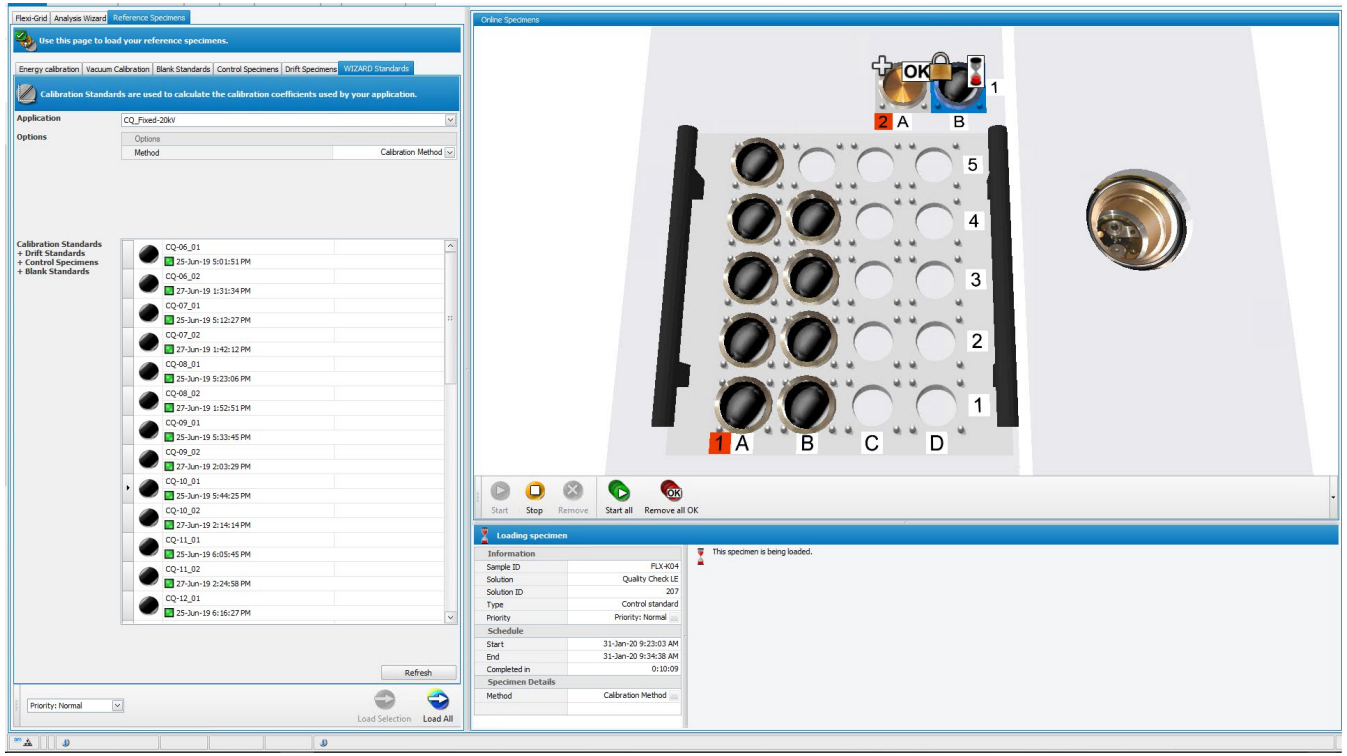
Routine operation made easy
Thanks to SPECTRA.ELEMENTS

Faster. Smarter. Easier.

Easier to use

- Quick learning with new User Interface
- Hints provide help when needed
- WIZARD: the proven tree-structure guide you through the calibration process
- LOADER: Intuitive interface for routine operation
- RESULT MANAGER: Access all your data quickly and get extended reporting



The LOADER: load / unload samples; adjust priorities; start / stop your measurements; view your results.

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Bruker provides tailor-made XRF Solution for your applications S2 PUMA Series 2

State-of-the-art Software and Hardware

- Powerful 50 W X-Ray Tube
- HighSense™ Technology
- SampleCare™ Technology
- SPECTRA.ELEMENTS
- And more…

Ready for all sample types, sizes and throughput requirements

- Single, Carousel, Mapping-Stage, XY-Autochanger, XY-Automation

Various options to ensure optimal performance

- Light element configuration
- Vacuum, He, N_2, and Air mode
- Detector profiling
- TouchControl™
- Sample Rotation
- SMART-QUANT FP
- QUANT Solutions
- 21 CFR Part 11 compliance
- IQ-OQ Documentation
- And more ….

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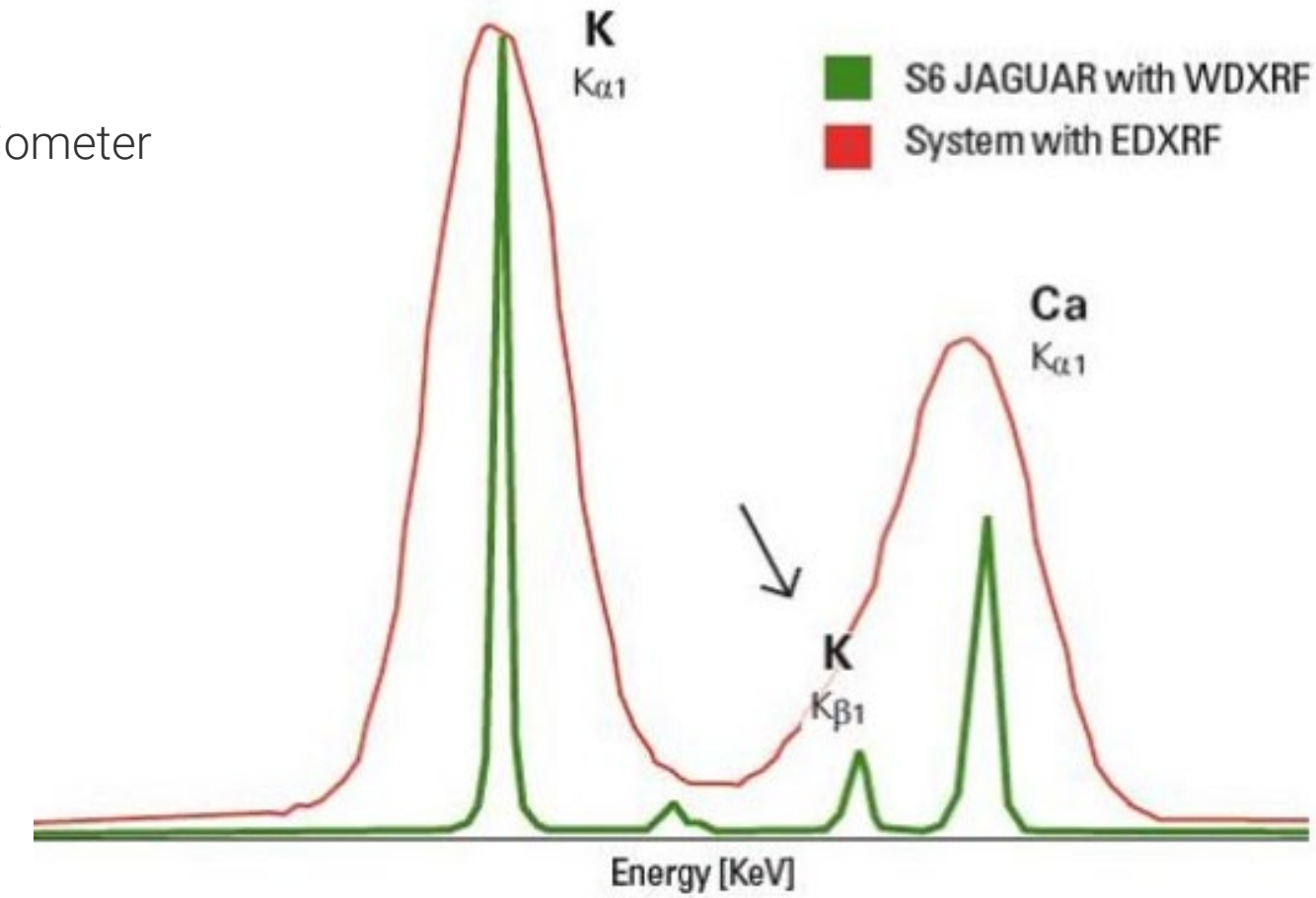
Enhance the Performance for Light and Trace Elements S6 JAGUAR: Benchtop WDXRF

HighSense Goniometer: High Resolution

- The S6 JAGUAR with WDXRF HighSense Goniometer excels
- ED based systems in resolution and analytical precision



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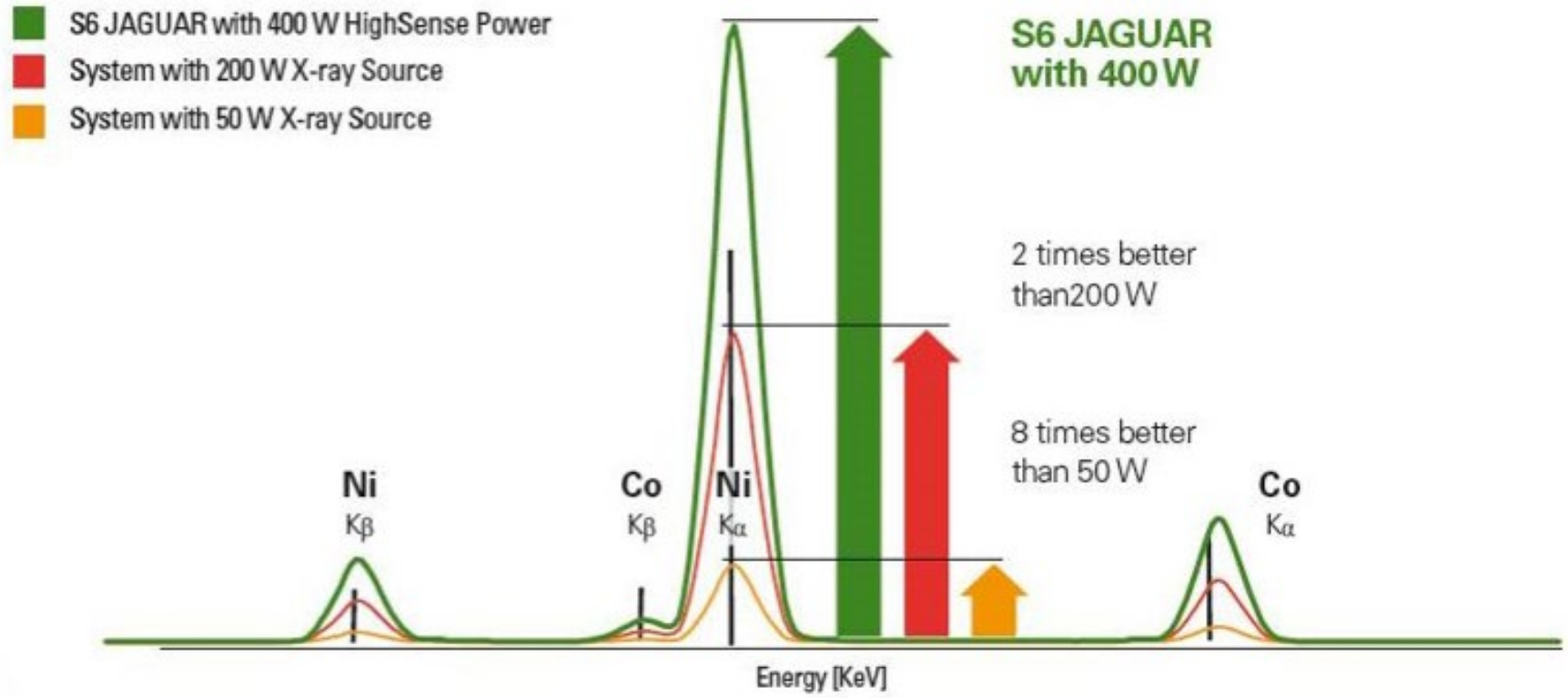
Enhance the Performance for Light and Trace Elements HighSense™: Full 400 W excitation power

S6 JAGUAR is twice as powerful as a 200 W system and 8 times more powerful than a 50 W system



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Enhance the Performance for Light and Trace Elements HighSense™ Goniometer: Impressive versatility

- 400 W excitation
  - 20 – 50 kV
  - 1 – 17 mA
  - Optimal settings for every single element at full power
- 5 position beam filter (optional) for improved peak-to-background ratio
- 4 sample masks (optional for different sample sizes)
- Vacuum seal for low-cost-of-operation
- Up to 4 analyzer crystals for the entire element range and specific demands
- Flow counter and HighSense XE detector for 2 Mcps countrates for high calibration ranges

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“The fast analysis of our drug substances and intermediates of our sunscreen products is vital for us. The S6 JAGUAR is much more sensitive than comparable spectrometers. The ease-of-use and 21CFRPart11 compliance of SPECTRA.ELEMENTS are important to us.”

S6 JAGUAR made its way into Food & Pharma:

- Better light element performance than ED
- Better resolution for clear separation of neighboring elements
- IQ/OQ & 21CFRPart11

HOW TO USE XRF IN PHARMA & COSMETICS

Summary

X-ray Fluorescence (XRF) Spectrometry: An excellent Technique for Pharma & Cosmetics Elemental Analysis

- XRF can be used for a wide range of applications in the pharma and cosmetics industry:
- Key benefits of XRF: Wide range of elements and concentrations, simple sample preparation, ease-of-use, low operation costs, high accuracy & precision, high throughput.
- Bruker offers a full portfolio of laboratory equipment for pharma and cosmetics applications:
  - S2 PUMA Series 2 is the ideal choice for many applications – including raw material and process control analysis powder.
  - S6 JAGUAR is used for very low trace element contents (<10 ppm) and for (low) F
  - Including 21 CFR Part 11 compliance and full IQ/OC support for all instruments

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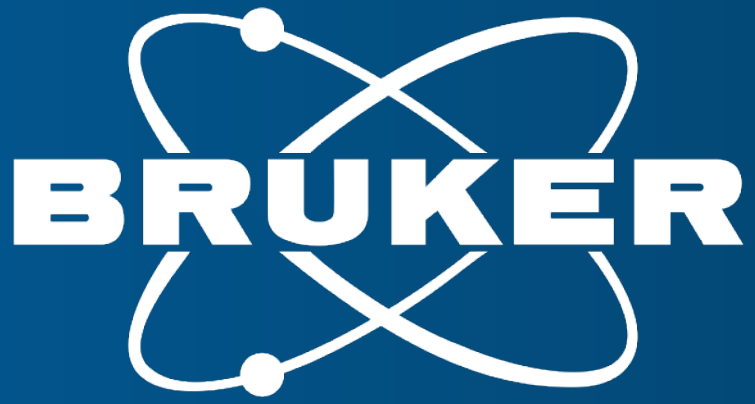
Any Questions?

Learn more about ‘Industrial Minerals’

In our 27.10.2021 webinar – Sign Up Now!

Thank you!

Kai Behrens, Frank Portala, Adrian Fiege



Innovation with Integrity