Webinar Series

Webinar Series: Enhancing Pharma Processes with X-ray, Thermal, and Raman Analysis Tools

Episode 3 – Formulation Development

1. **Streamline Your Pharmaceutical Formulation Chemistry Process with EDXRF Analysis**
   Presenter: Scott Fess

Starting at 1 pm CDT

- *You will be muted during the workshop*
- *You can ask questions using the Q&A tool.*
- *You should hear music if your sound is working*

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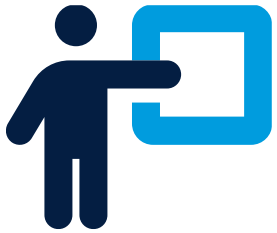
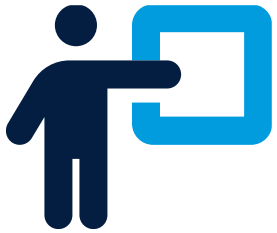
We are starting now



Presenter:
Scott Fess
EDXRF Product Manager



Co-Presenter:
Simon Bates, PhD
VP of Science and Technology

Host:
Aya Takase
Head of Global Marketing

You can ask questions during the presentation. Please use the Q&A to ask questions.

Recording will be available tomorrow.

Target Identification ▶ Lead Generation ▶ Lead Optimization ▶ Preclinical ▶ Clinical ▶ Approved Drug

Discovery ▶ Development Pre-formulation ▶ Formulation ▶ Manufacturing

1

Streamline Your Pharmaceutical Formulation Chemistry Process with EDXRF Analysis

presented by Scott Fess

You will learn

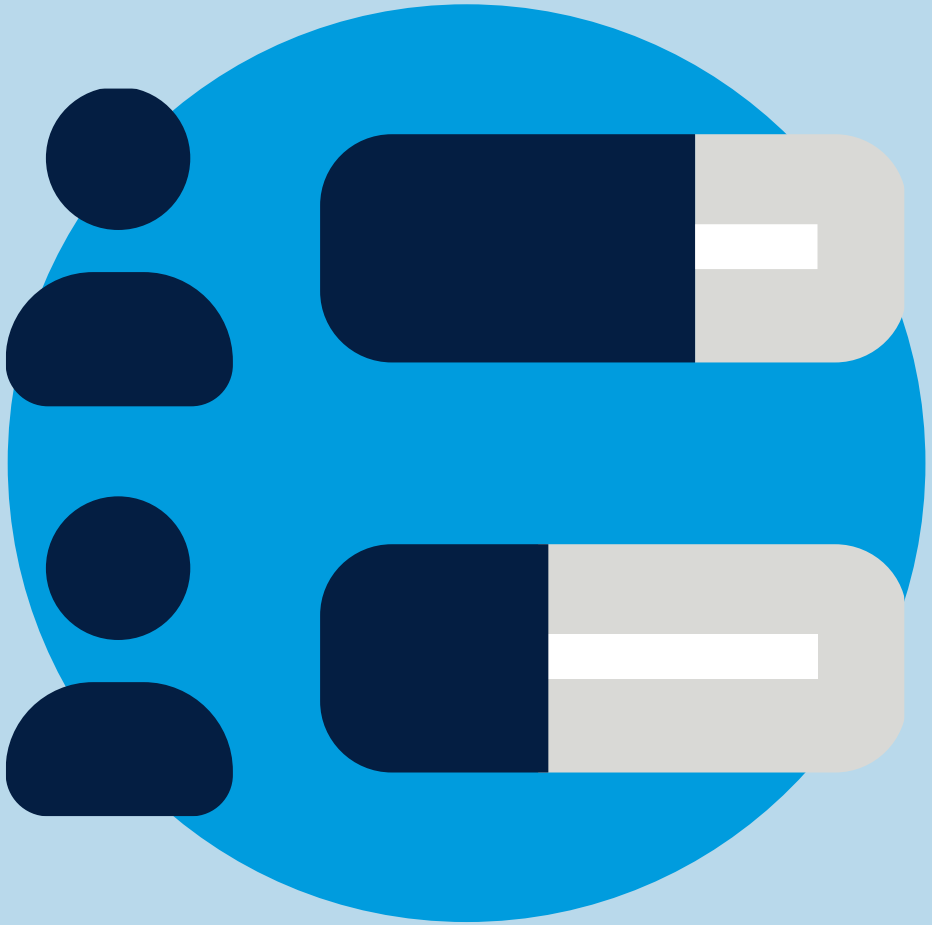
1. Fundamentals of EDXRF technology
2. How EDXRF fits in the formulation development process
3. Real-world applications and examples
4. Key benefits of EDXRF for process chemistry
5. Summary

Why EDXRF is a valuable tool for formulation development

- Non-destructive
- Minimal sample prep
- Fast measurements
- Traceable to ICP
- Optimize yield
- Monitor catalyst residues
- Ensure product safety
- Meet regulatory requirements

Polling Question

#1

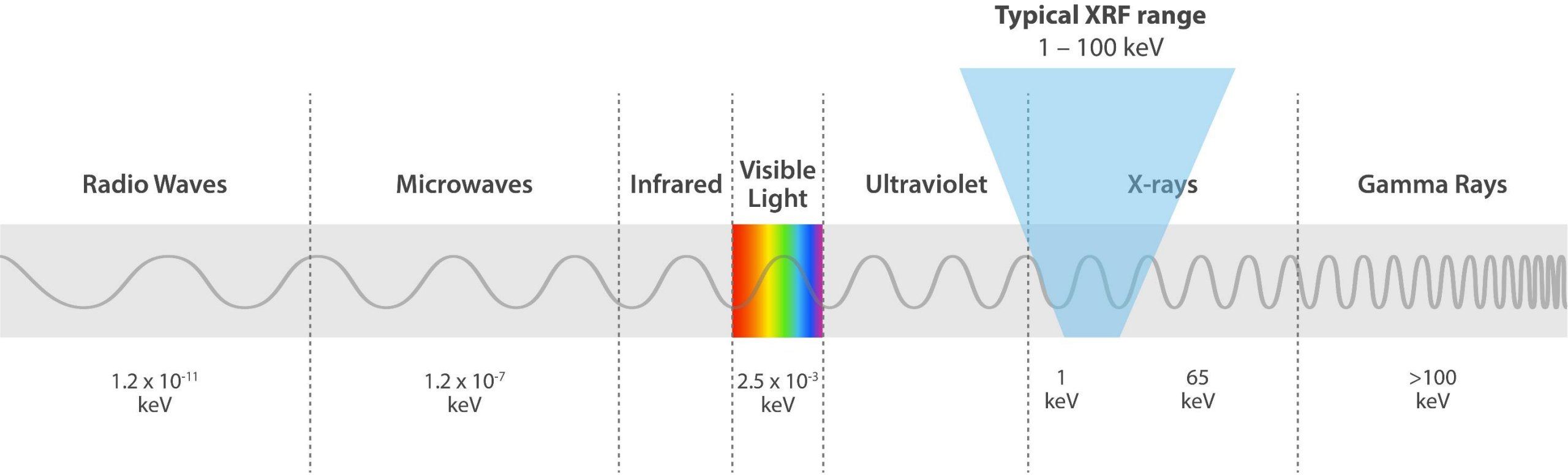


1. Fundamentals of EDXRF technology

Energy dispersive X-ray fluorescence (EDXRF) measures the energies of the detected elements.

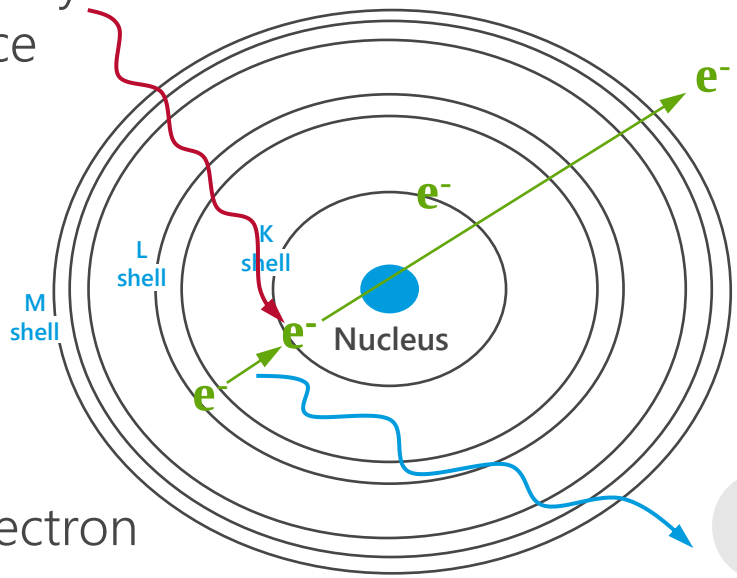
Benchtop EDXRF products

Electromagnetic spectrum



The photoelectric effect

1 Incident X-ray from source



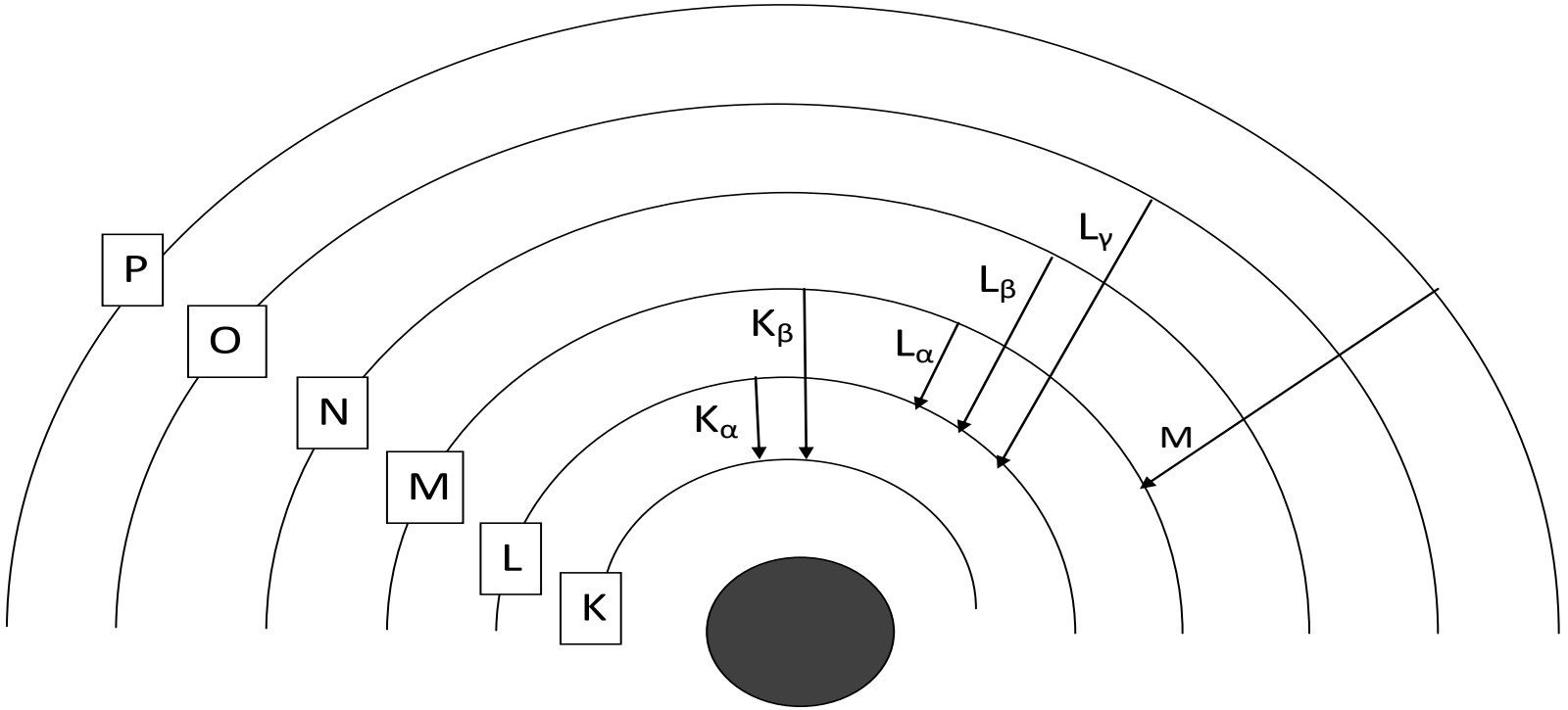
2 Inner shell electron is ejected

3 Outer shell electron fills the vacancy

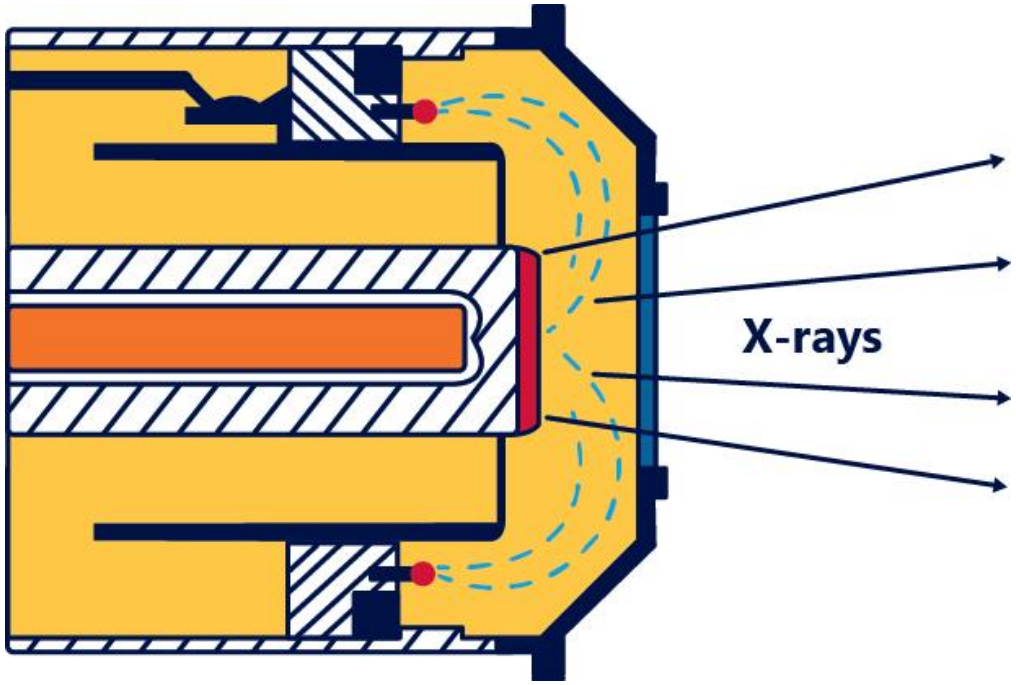
ATOM

4 Energy difference escapes as an X-ray with energy **unique to the element**

Atomic shells and X-ray lines (element peaks)



What does X-ray power mean to your sample?



- Power W = V x I
  - More power, more X-rays
- Low current, low heat
- No damage to sample

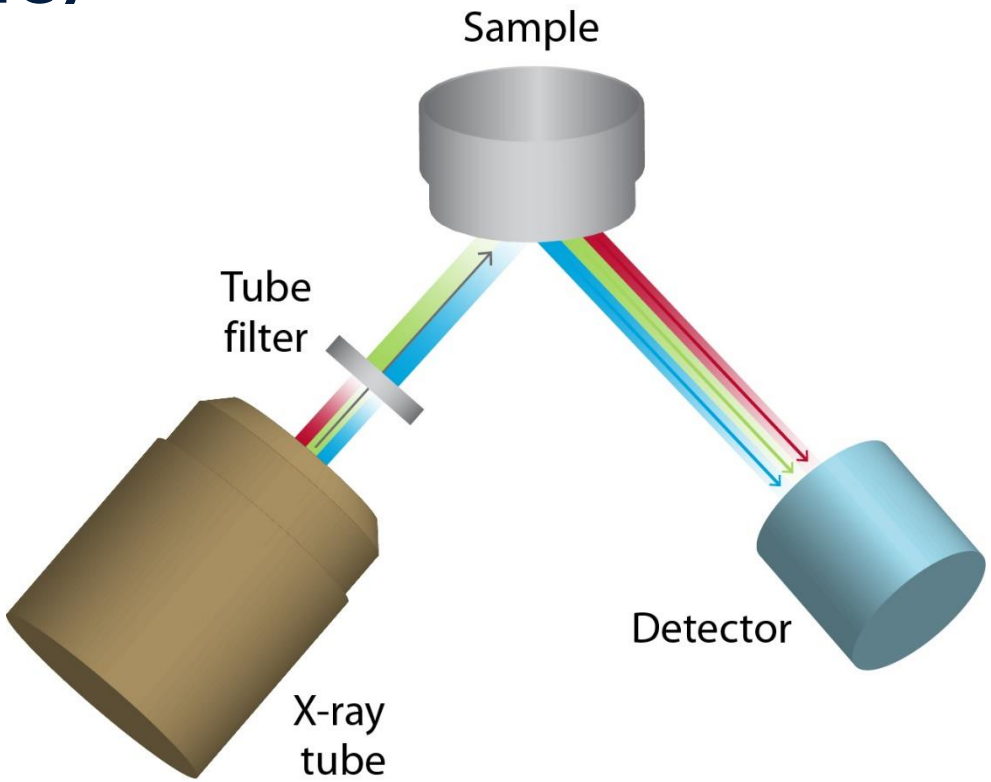
Direct excitation (polychromatic)

Strengths

- Lower price point
- Compact, smaller footprint

Considerations

- More background X-rays
- Lower sensitivity
- Higher LODs for light elements



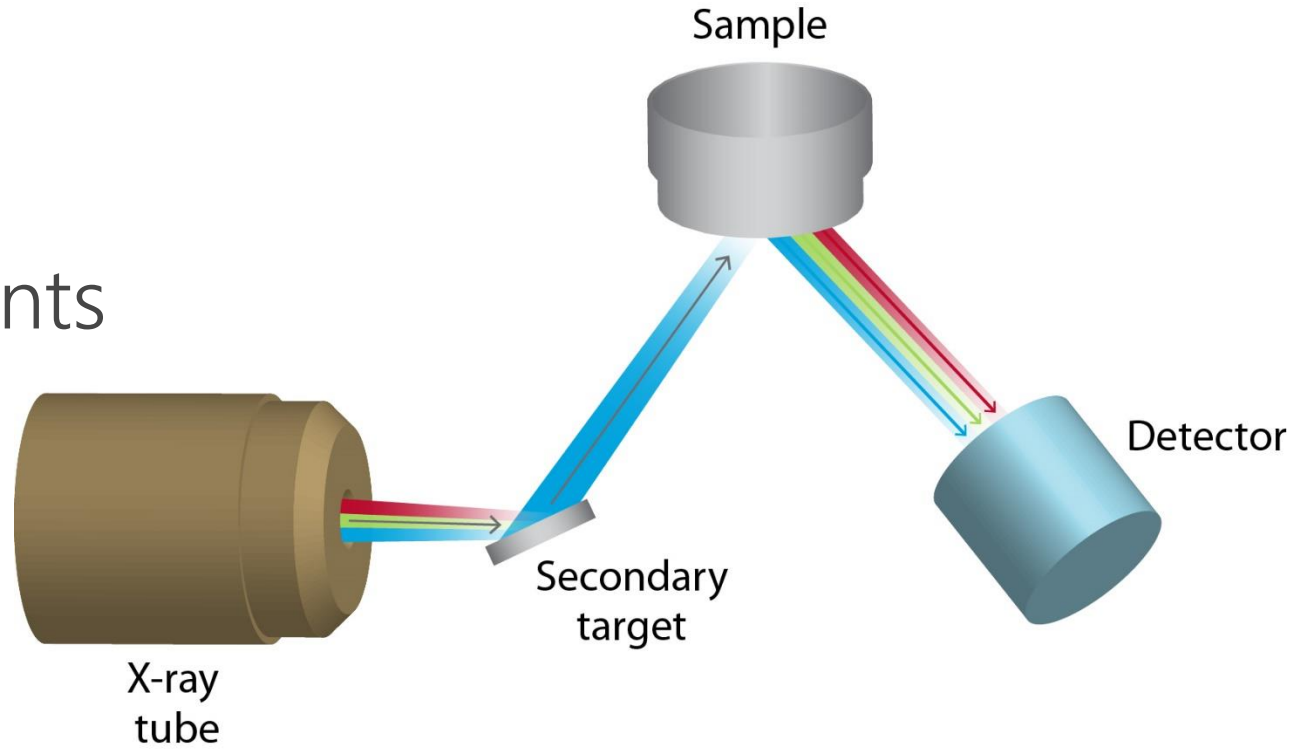
Indirect excitation (monochromatic)

Strengths

- No background
- Higher sensitivity
- Lower LOD for light elements

Considerations

- Higher price point
- Larger footprint

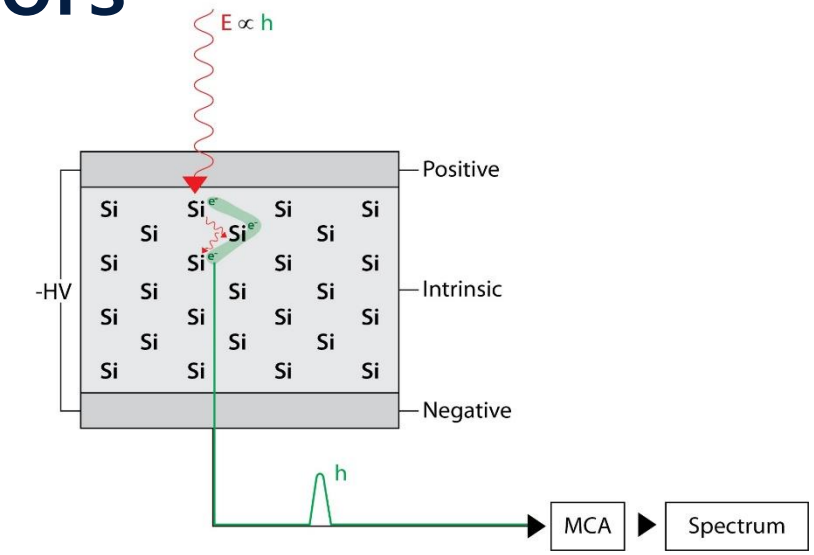


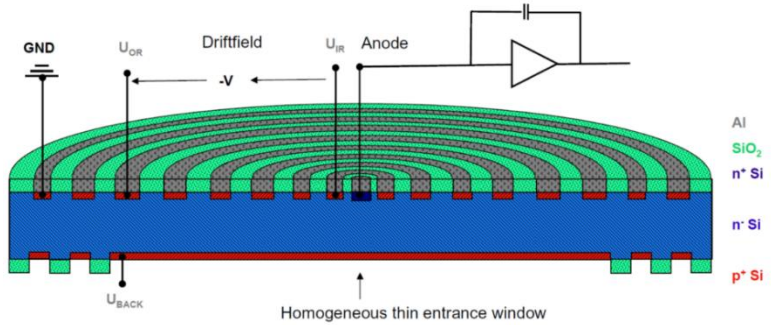
Key differences at a glance

EDXRF type	Power	Damage sample	Price point	Bench footprint	Sensitivity	Light element LOD
Direct	Lower	No	Low	Smaller	Good	Low
Indirect	Higher	No	Slightly higher	Slightly larger	Best	Lowest

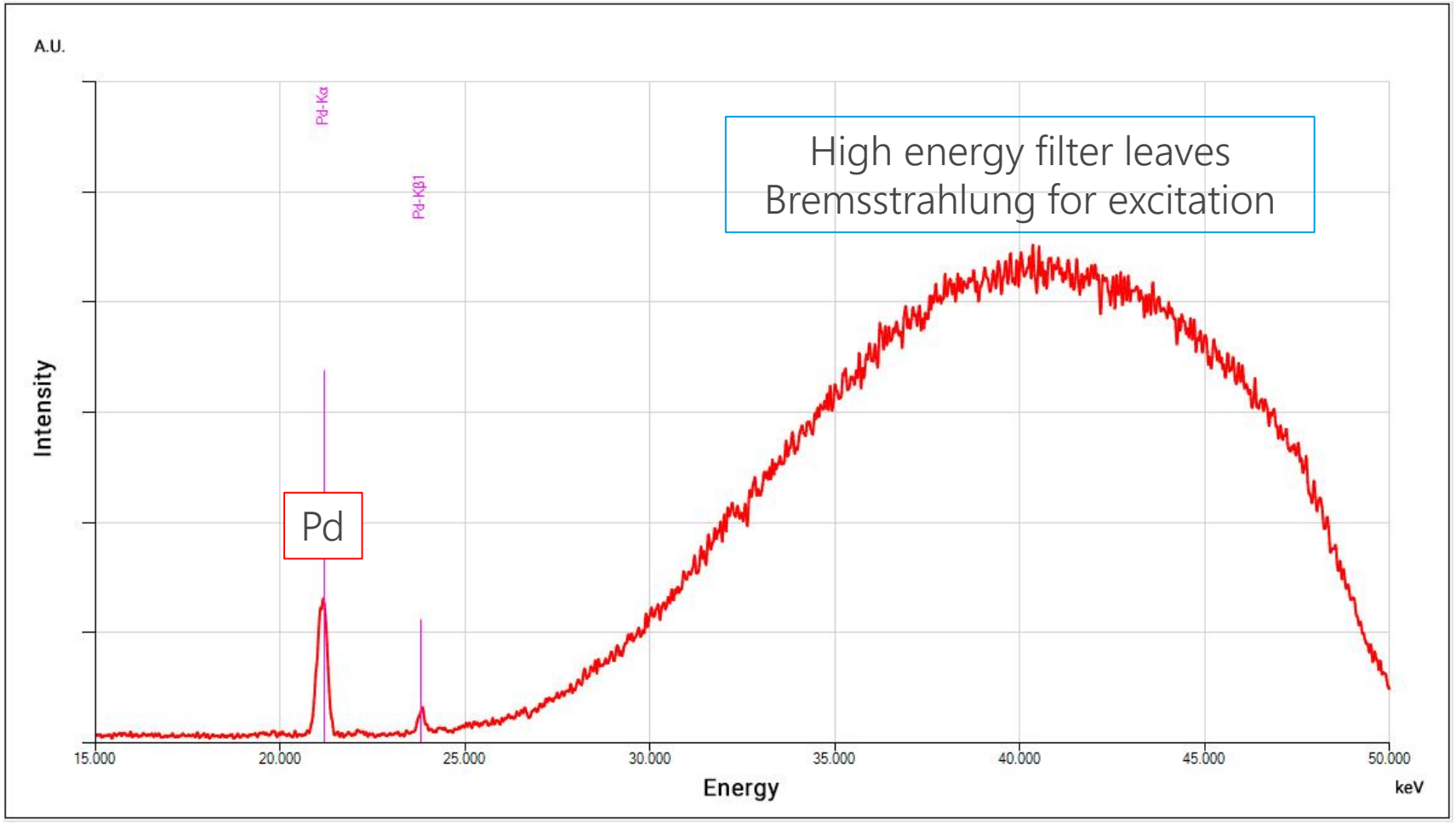
EDXRF silicon semiconductor detectors

- Changes light to electricity
- Detects all X-rays simultaneously
- Makes spectrum

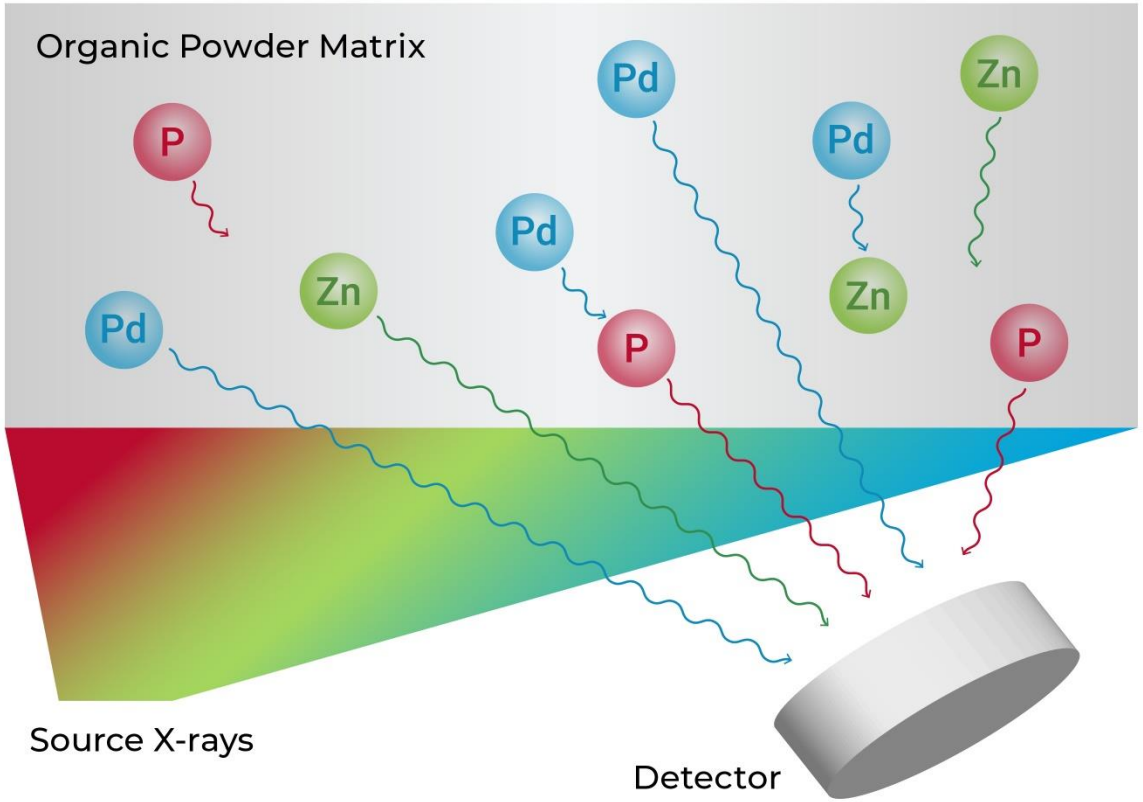




Pd EDXRF spectrum

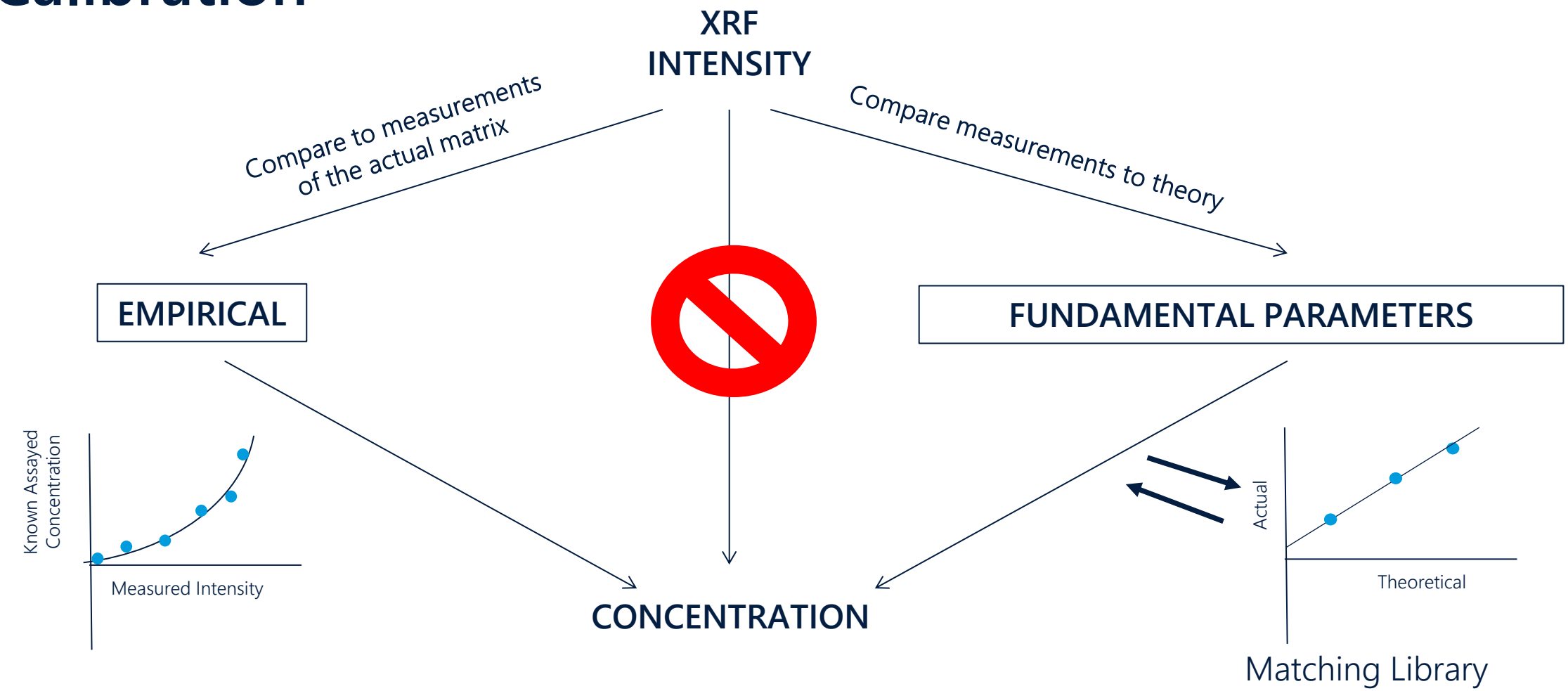


Matrix effects



- Absorption/enhancement
  - Alpha corrections
- Escape depth
  - X-ray energy increases by atomic number
- Homogeneous sample

Calibration



Samples

Types

- Powders and pellets
- Liquids and oils
- Metals and solids
- Polymers and plastics
- Filters
- Thin films

Rules

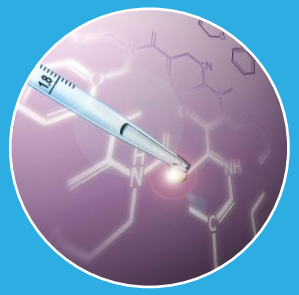
- Homogeneous
- Stable
- Flat surface
- Consistent sample prep

Questions?

2. How EDXRF fits in the formulation development process

Pre-formulation and formulation

Mixing

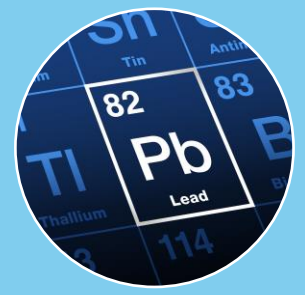


Optimize reactions

Catalysts and catalyst recovery

Increase yield

Salts



Heavy metal initial screening

Process chemistry

Applications

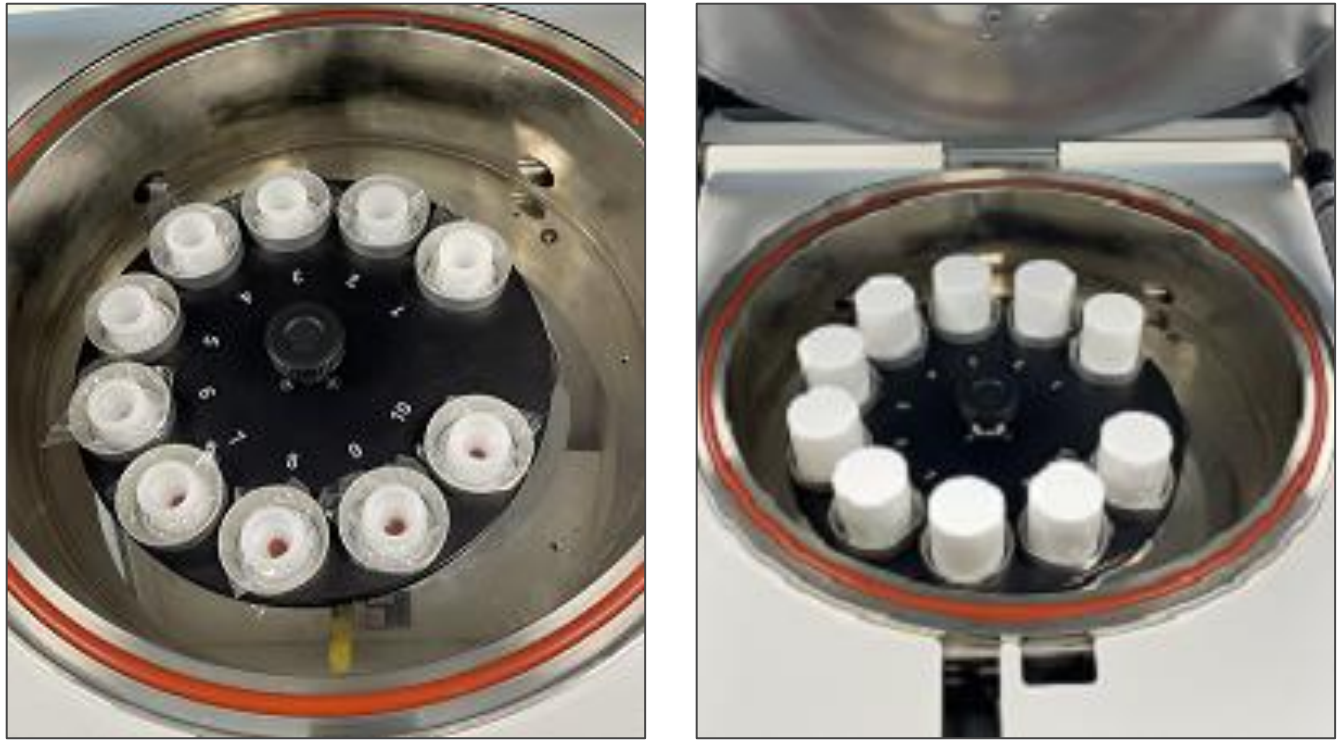
- Monitor catalyst residue
  - Pd, Ru, Rh, Ir, Pt, Al
- Heavy metal screening
  - Cd, Pb, Hg, As, Cr, Ba, Se, Ag
- Content uniformity

Sample preparation

- Homogeneous
- Bulk analysis
  (1 – 6 g)
- Limited quantity
  (0.05 – 1 g)
  - Micro funnel cups

Sample presentation

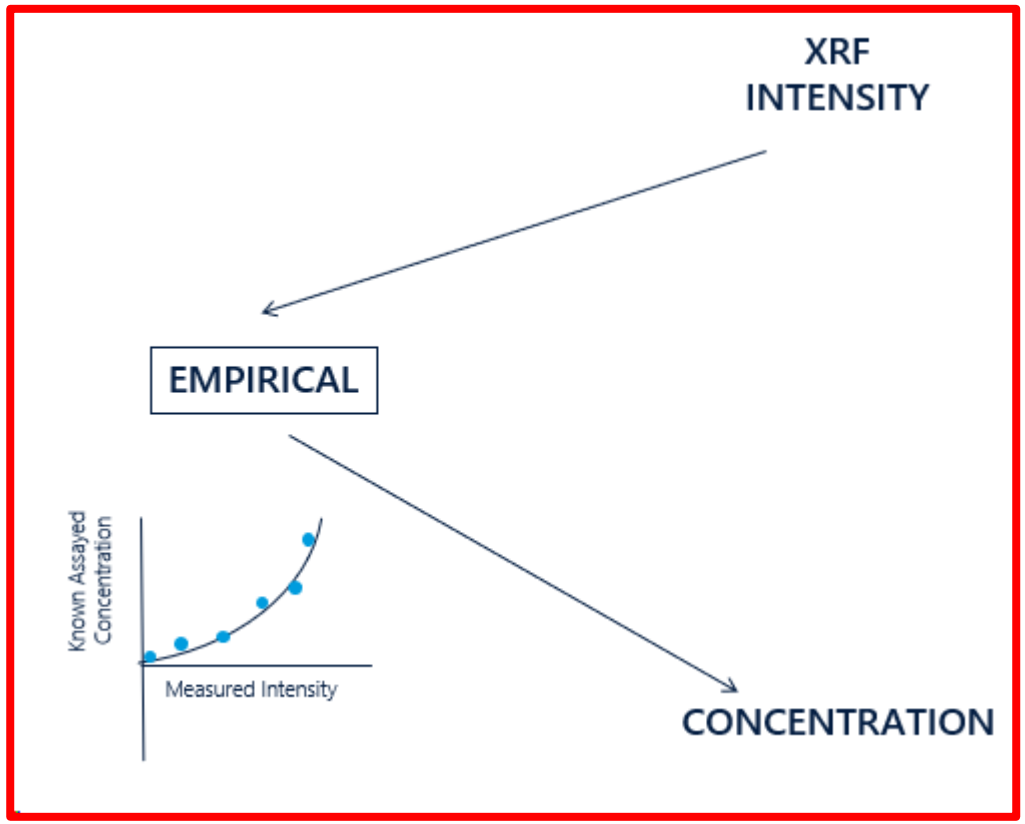
- Batch analysis using automatic sample tray
- Teflon® cup covers for micro funnel cups



Tablets in position for batch analysis with Teflon® cup covers

Teflon is a registered trademark of E.I. du Pont de Nemours and Company and its affiliates.

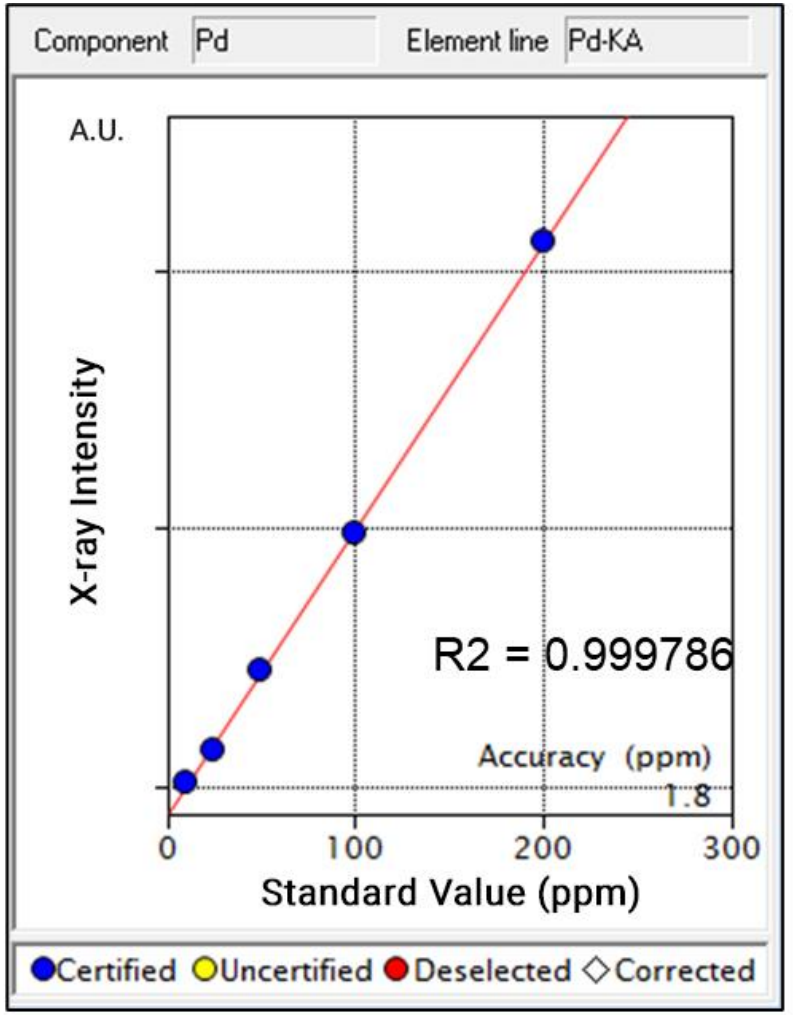
Methodology Empirical best-fit regression (EMP)



- Suite of standards with known concentration
- Matrix-matched
- Teach intensity vs. concentration

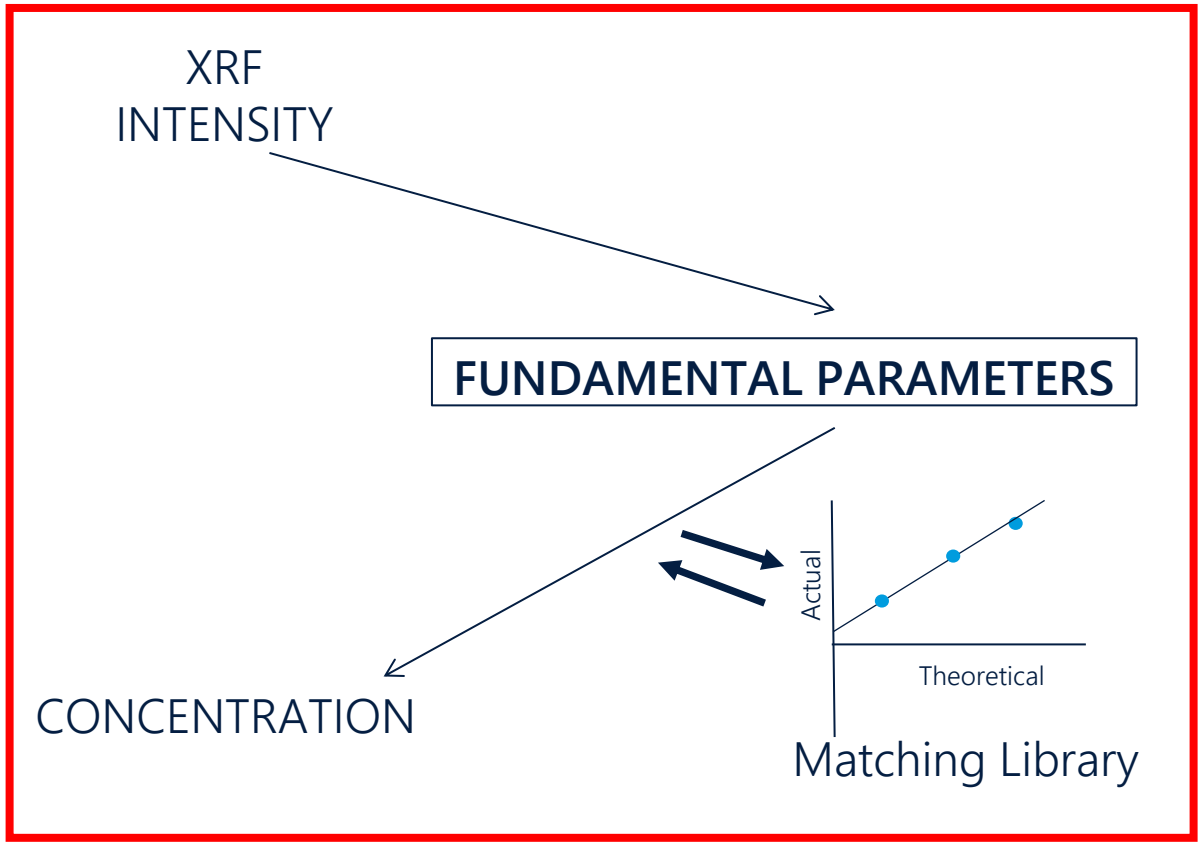
Example of EMP calibration for Pd

- 5 standards with known Pd
- Commercially available or make your own
- Most accurate for a single formulation



60 mg std. sample in 10 mm sample board

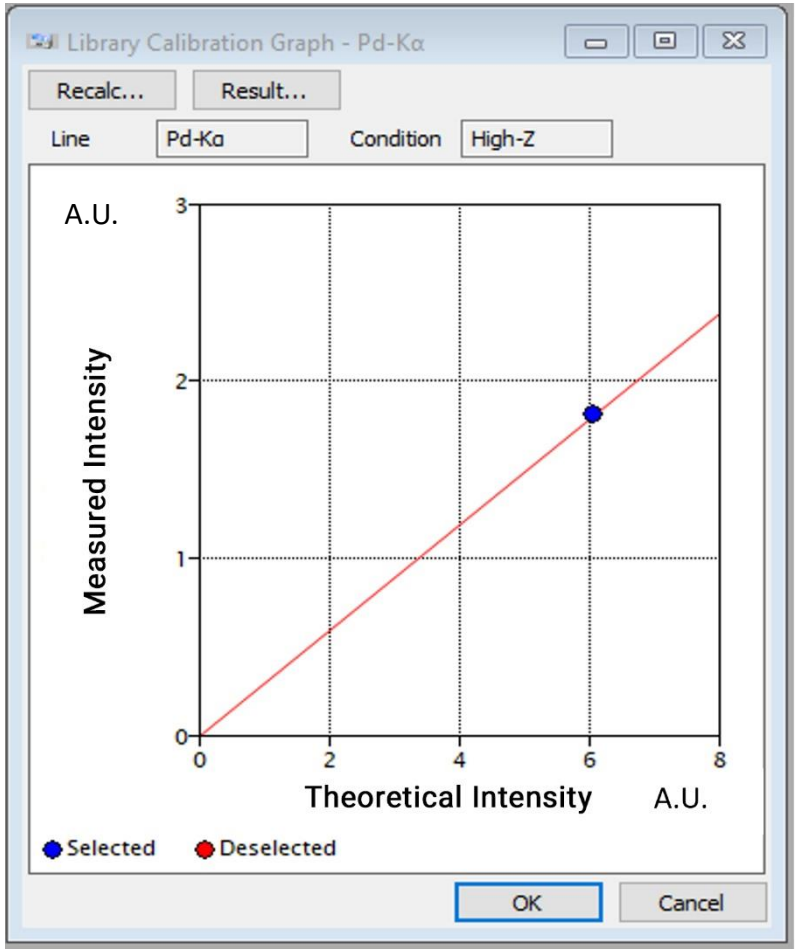
Methodology Fundamental Parameters (FP)



- No standards required
- Estimation of concentration
- Screening
- Multiple formulations

Example of Matching Library for Pd

- FP method alone is OK but can be better
- Matching Library optimizes FP
  - Fewer standards than empirical
- Empirical adjustment
- XRF matches ICP



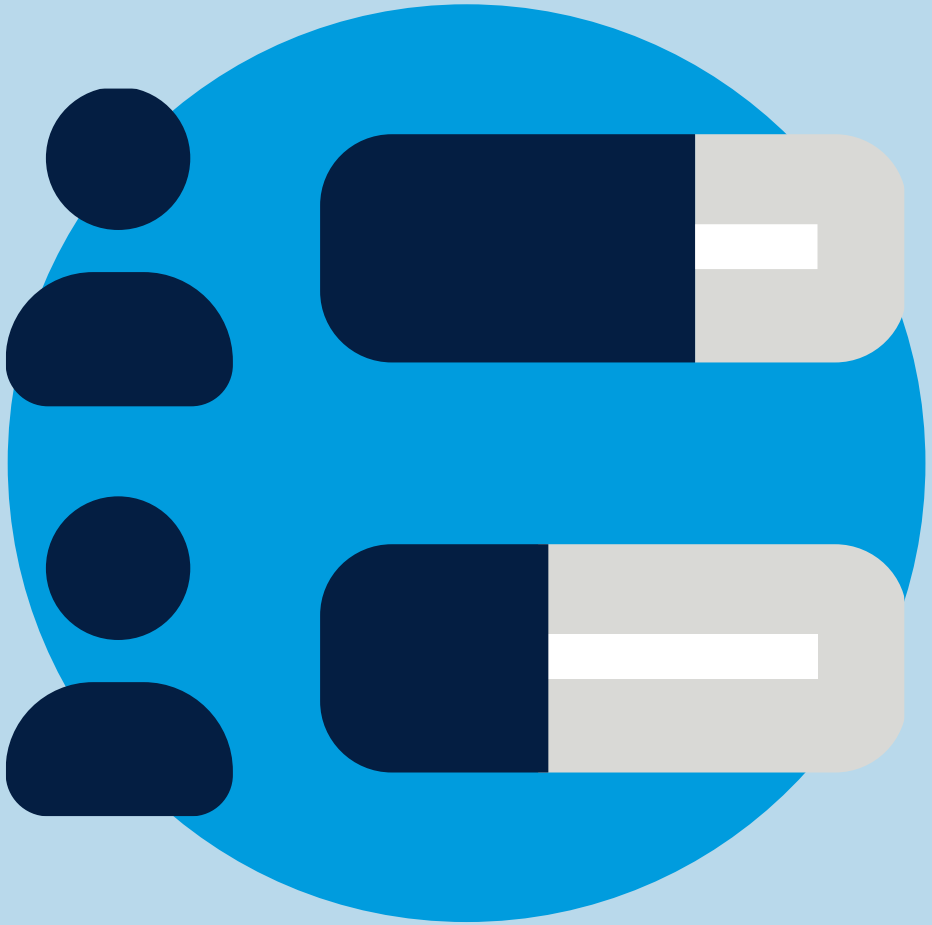
Measurements

- Short measurement times
  100 sec to 10 minutes
- Real-time feedback
- Non-destructive, no damage

Questions?

Polling Question

#2



3. Real-world applications and examples

Demonstration of Pd catalyst residue testing and heavy metal screening

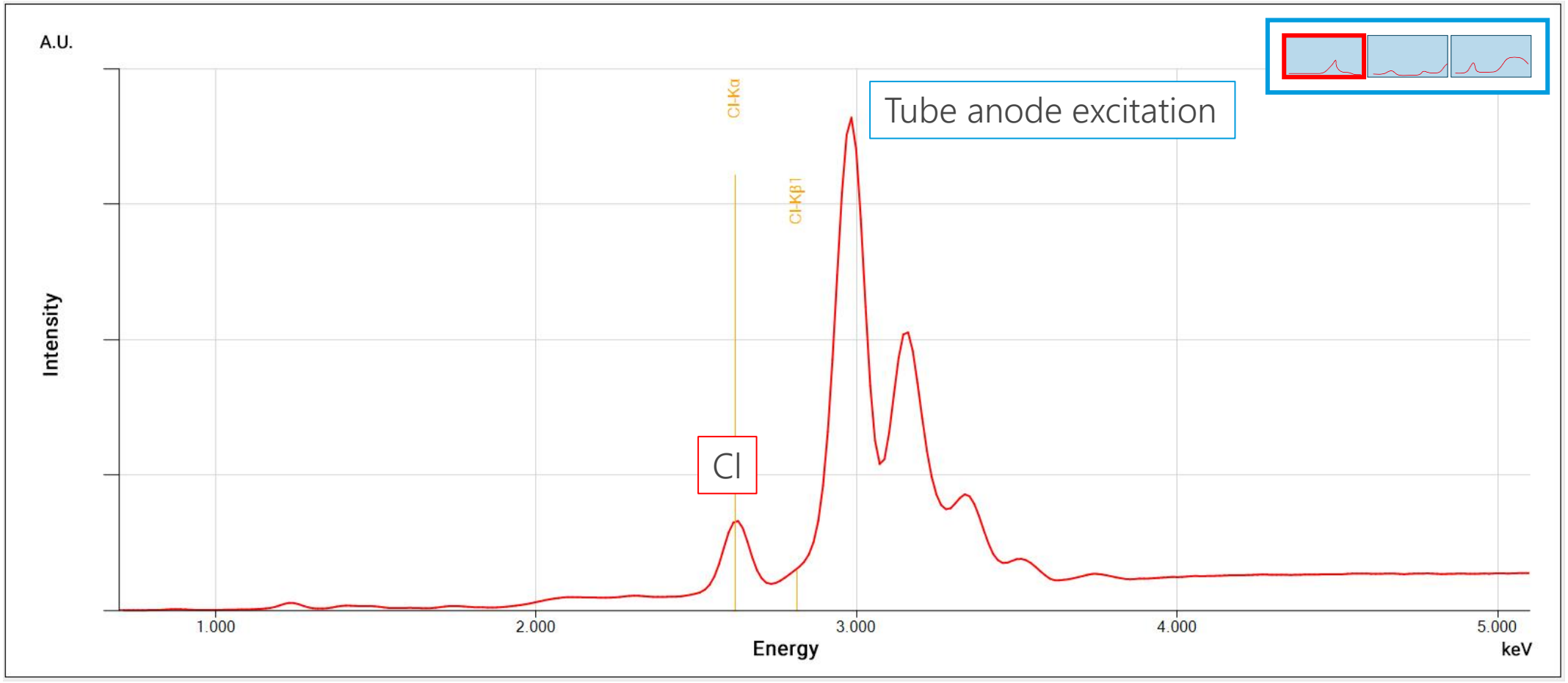
Results and data using direct excitation EDXRF

- Pd catalyst residue
- Heavy metal screening

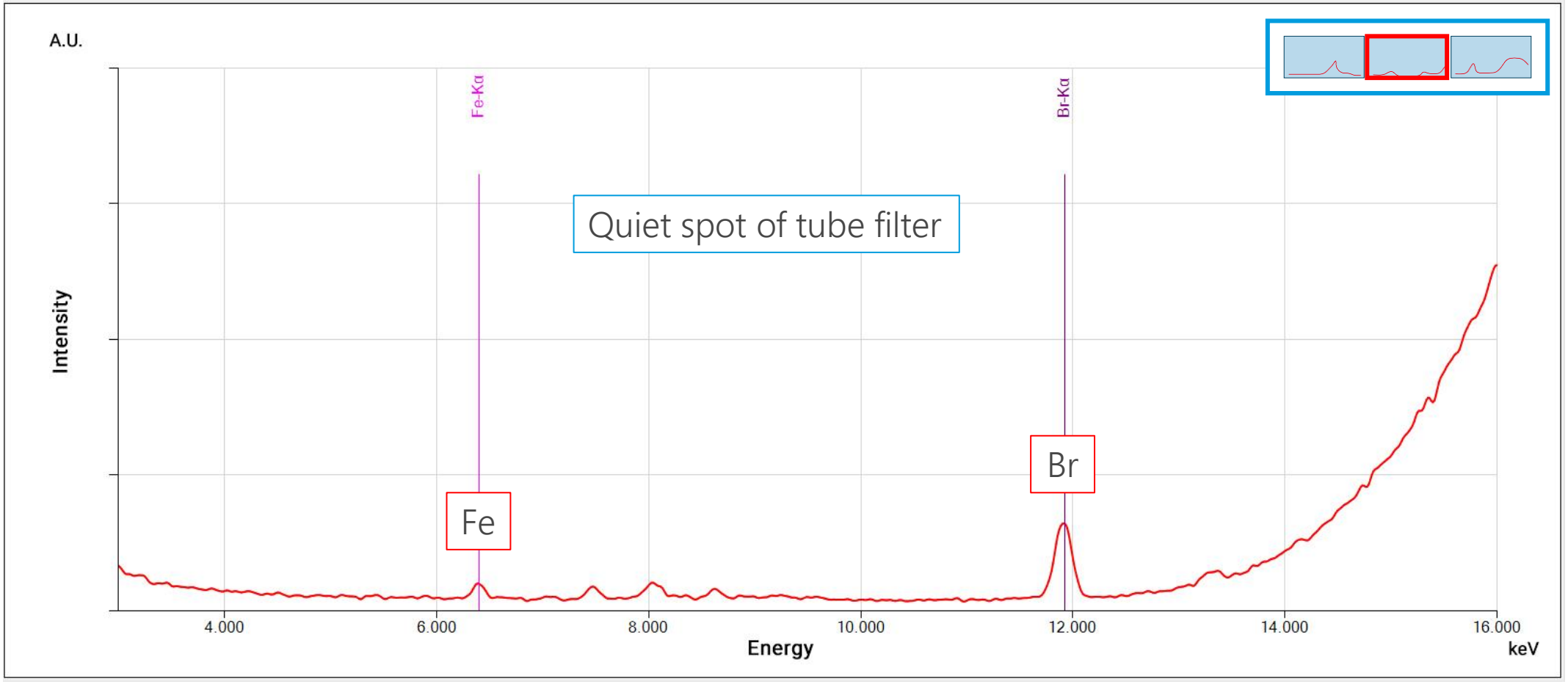
NEX DE VS

- 12 W 60 kV
- Direct excitation
- Small spot 10, 6, and 3 mm beam collimators

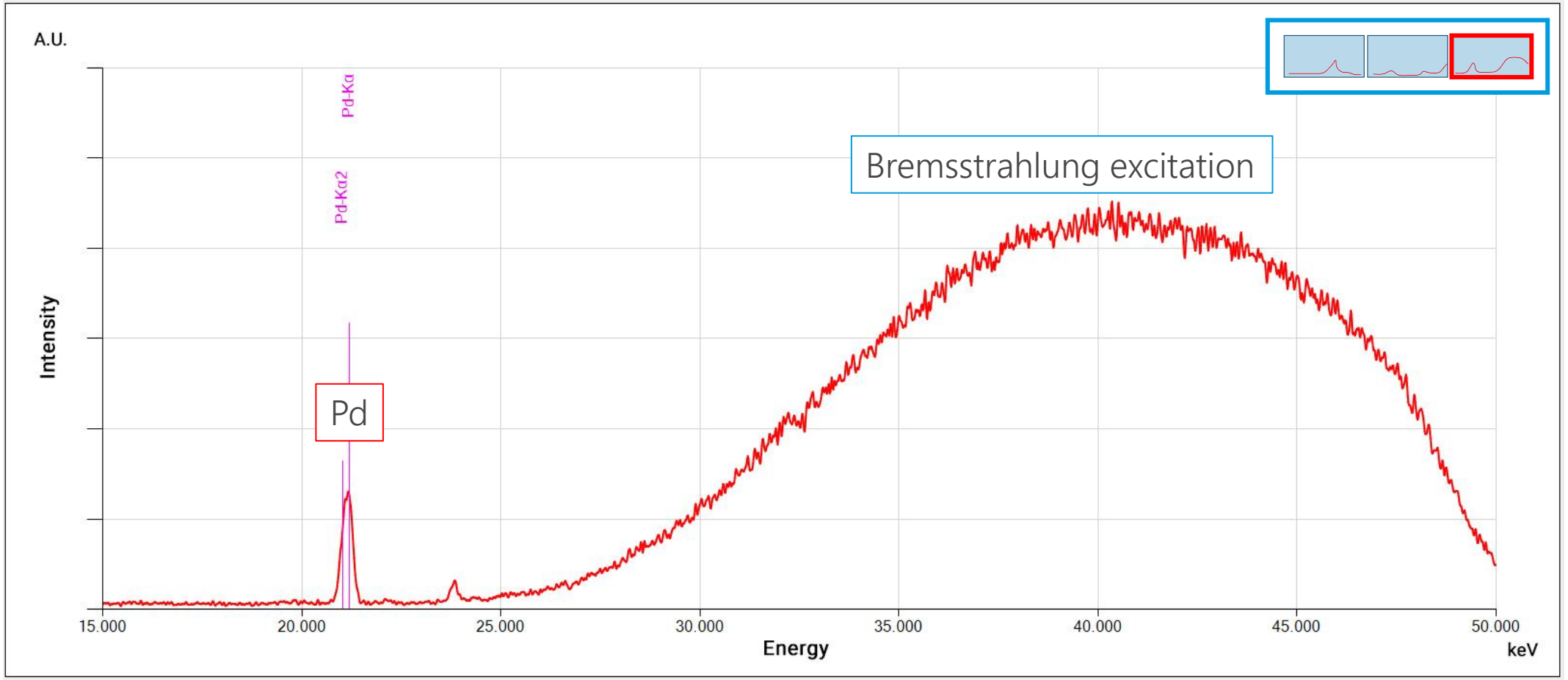
Catalyst residue Cl direct excitation low energy setting



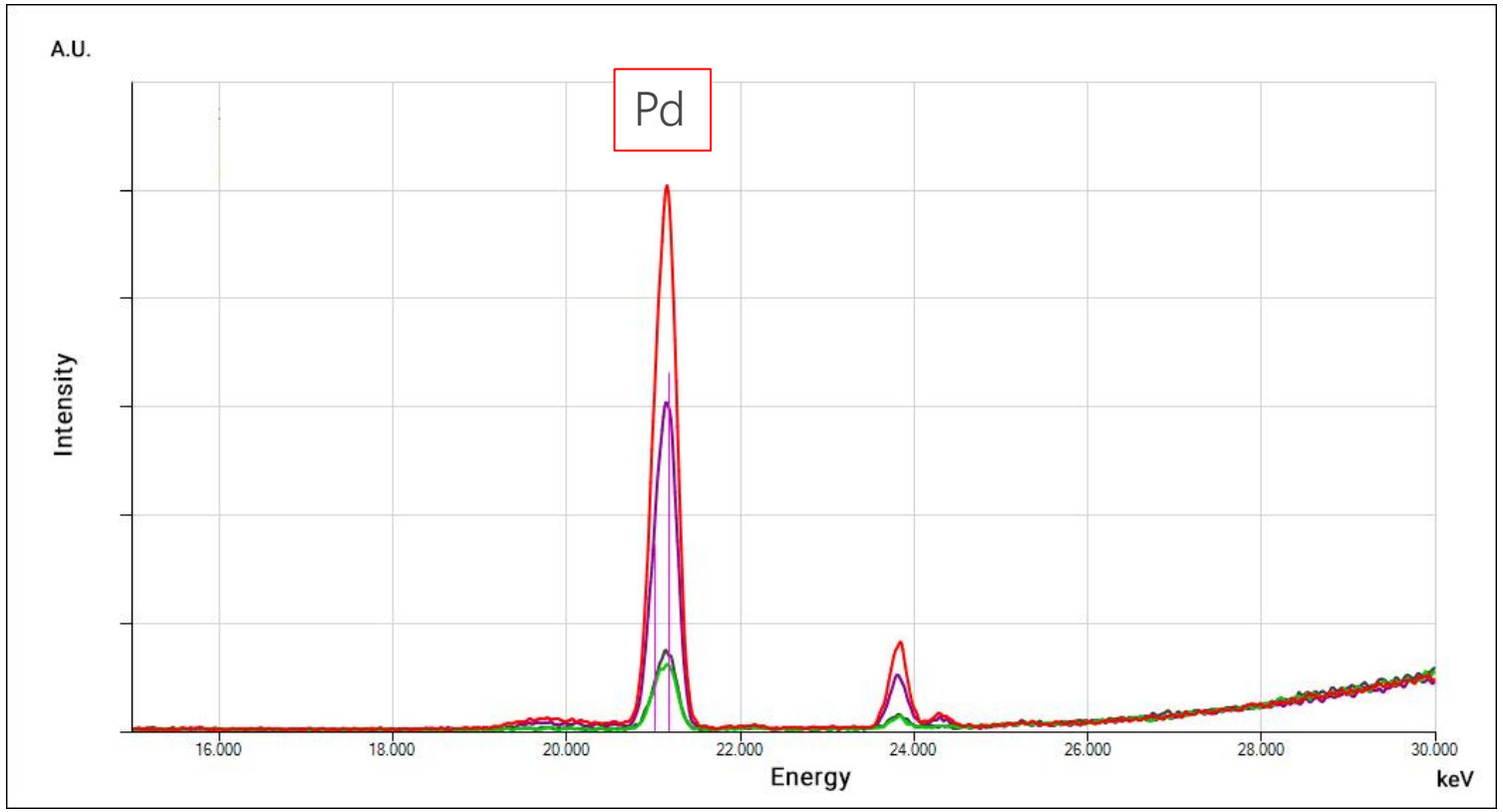
Catalyst residue Fe, Br direct excitation middle energy setting



Catalyst residue Pd direct excitation high energy settings



Catalyst residue Comparative look at several samples



- Several samples overlapped
- 1000 – 50 ppm
- Down to <2 ppm

Catalyst residue sample results Medium Pd

Element	ICP Value (ppm)	NEX DE Value (ppm)	Stat. Error (ppm)	LOD (ppm)
Pd	245	248	1.7	0.3
P	N/A	149	2.2	5.6
Cl		121	1.0	2.6
Fe		ND	0.5	1.4
Br		2.3	0.1	0.1

Catalyst residue sample results Low Pd

Element	ICP Value (ppm)	NEX DE Value (ppm)	Stat. Error (ppm)	LOD (ppm)
Pd	45	47	0.8	0.3
P	N/A	ND	2.2	5.6
Cl		303	1.2	2.0
Fe		2.0	0.5	1.4
Br		3.5	0.1	0.1

Heavy metal screening using direct excitation

Cellulose

Element	LOD (ppm)
Cd	0.4
Pb	0.2
Hg	0.3
As	0.1

Element	LOD (ppm)
Cr	3.1
Ba	1.3
Se	0.1
Ag	0.3

Note: FDA guidance for 1 g daily dosage is Cd < 5 ppm

Demonstration of instrument precision and content uniformity testing

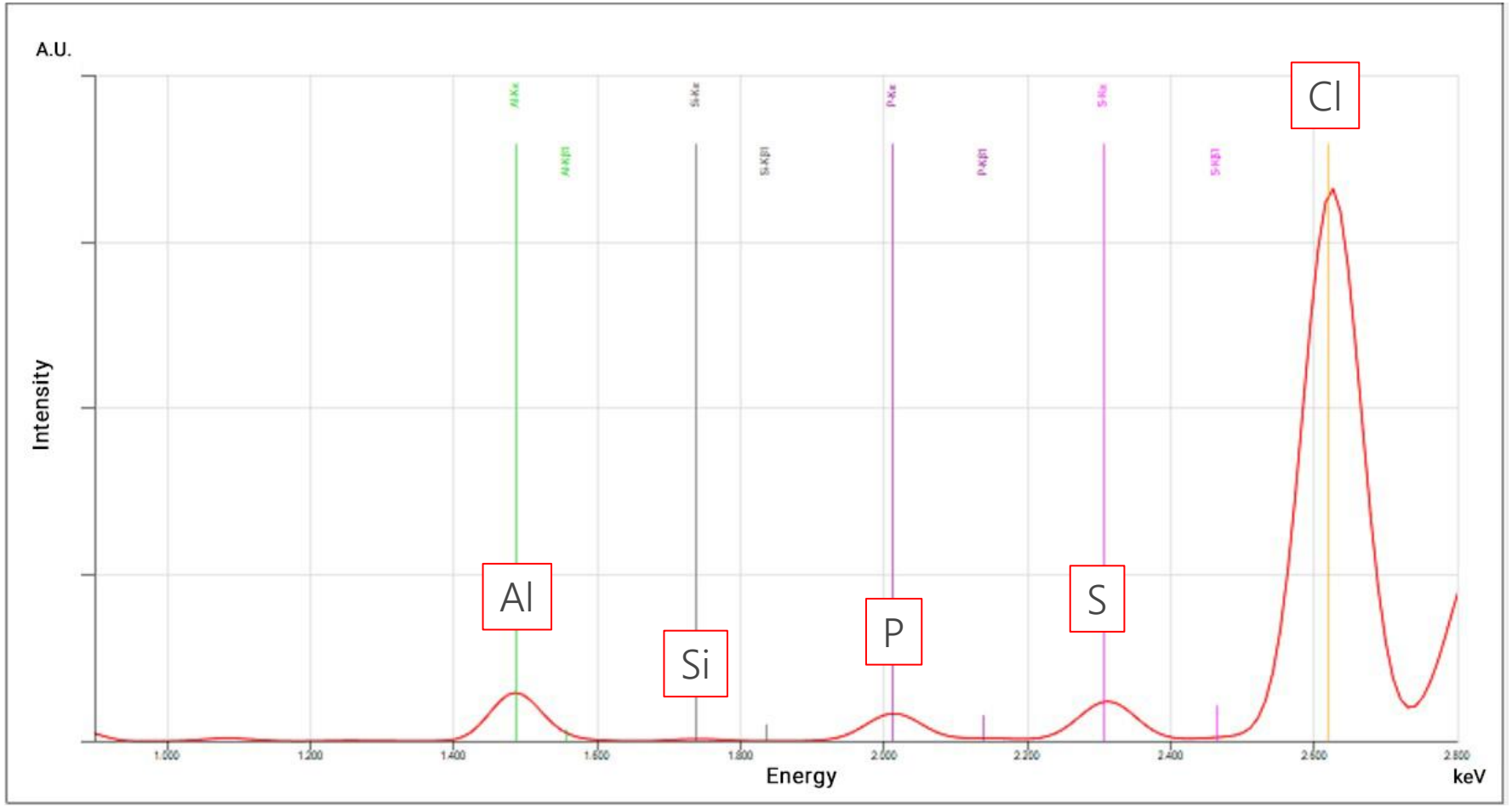
Results and data using indirect excitation EDXRF

- OTC Diphenhydramine HCl (antihistamine)
  - Cl and expedients
- **OTC Ferrous sulfate** (iron supplement)
  - Fe and expedients

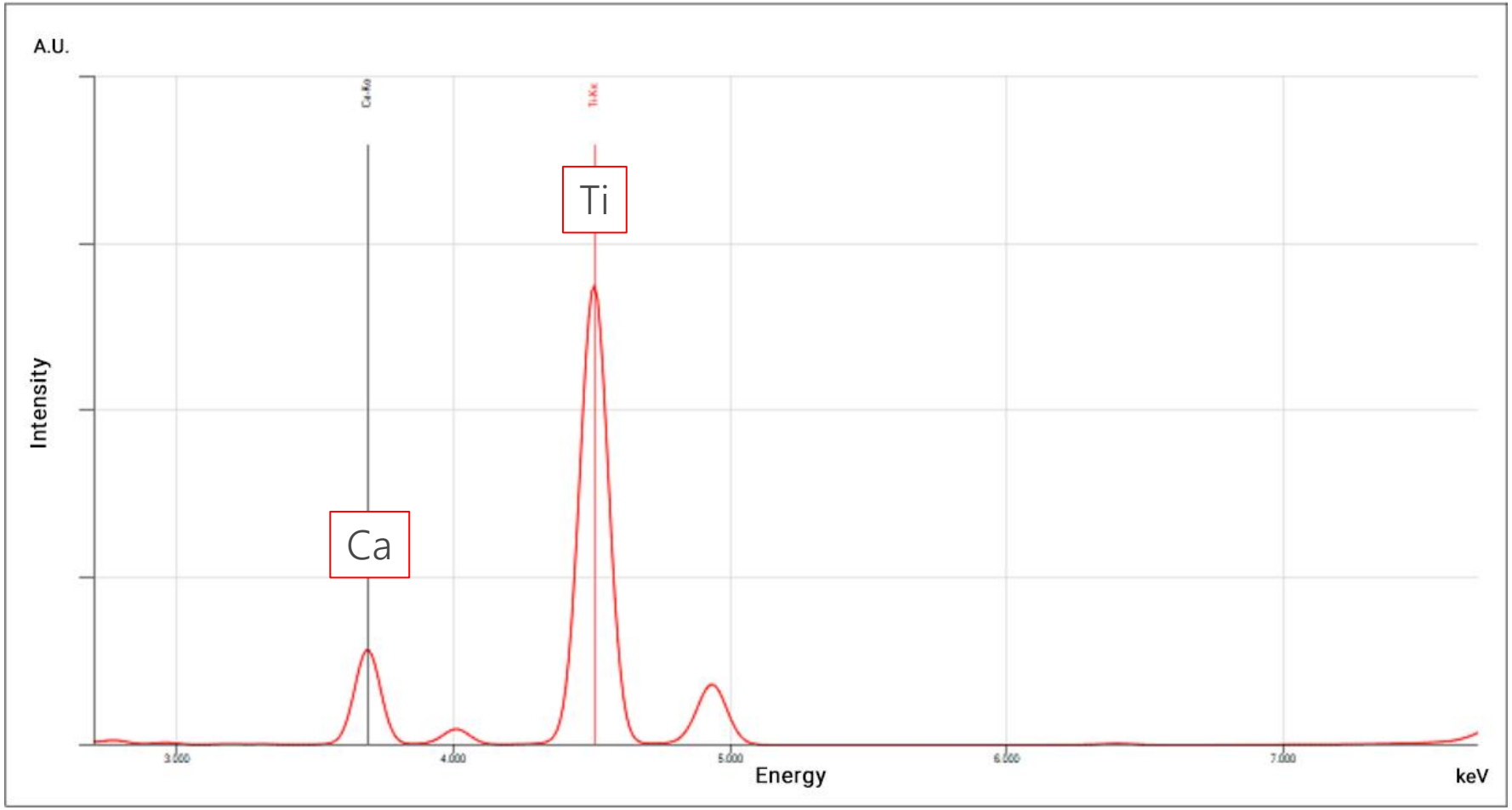
NEX CG II

- 50 W 50 kV
- Indirect excitation
- Helium purge

Diphenhydramine HCl Al, Si, P, S, Cl low energy settings



Diphenhydramine HCl Ca, Ti medium energy settings



Diphenhydramine HCl Measurement precision

Tablet form	Cl	Al	Si	P	S	K	Ca	Ti
Avg. value	1392	2107	24.7	204	177	8.37	3710	8144
Std. Dev.	8	17	0.8	2	1	1.42	12	15
RSD	0.5%	0.8%	3.2%	1.0%	0.6%	17%	0.3%	0.2%

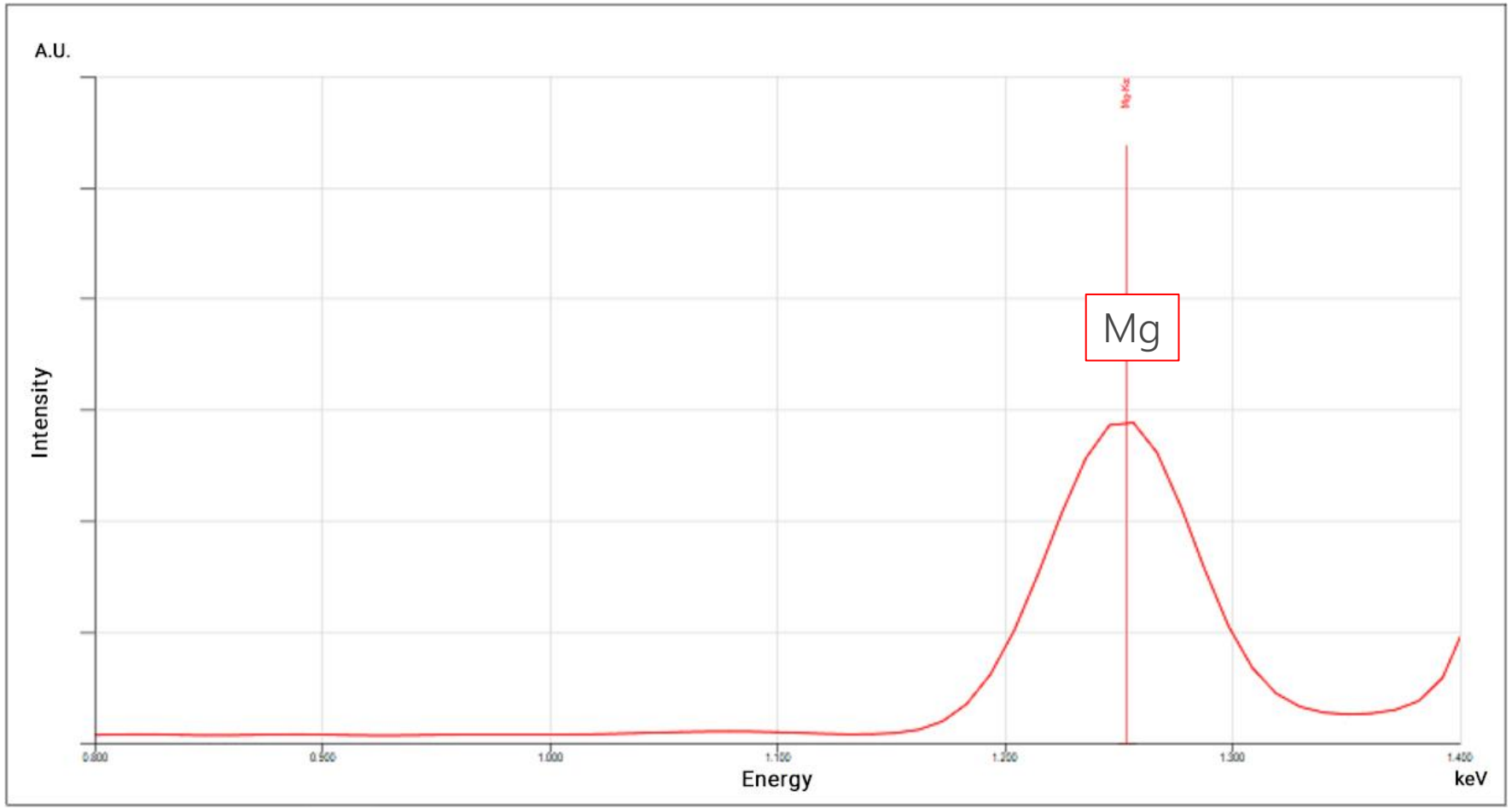
1 tablet measured 10x repeat analyses.
Units: mg/kg
Total measurement time per analysis 600 sec.

Diphenhydramine HCl Content uniformity across 10 tablets

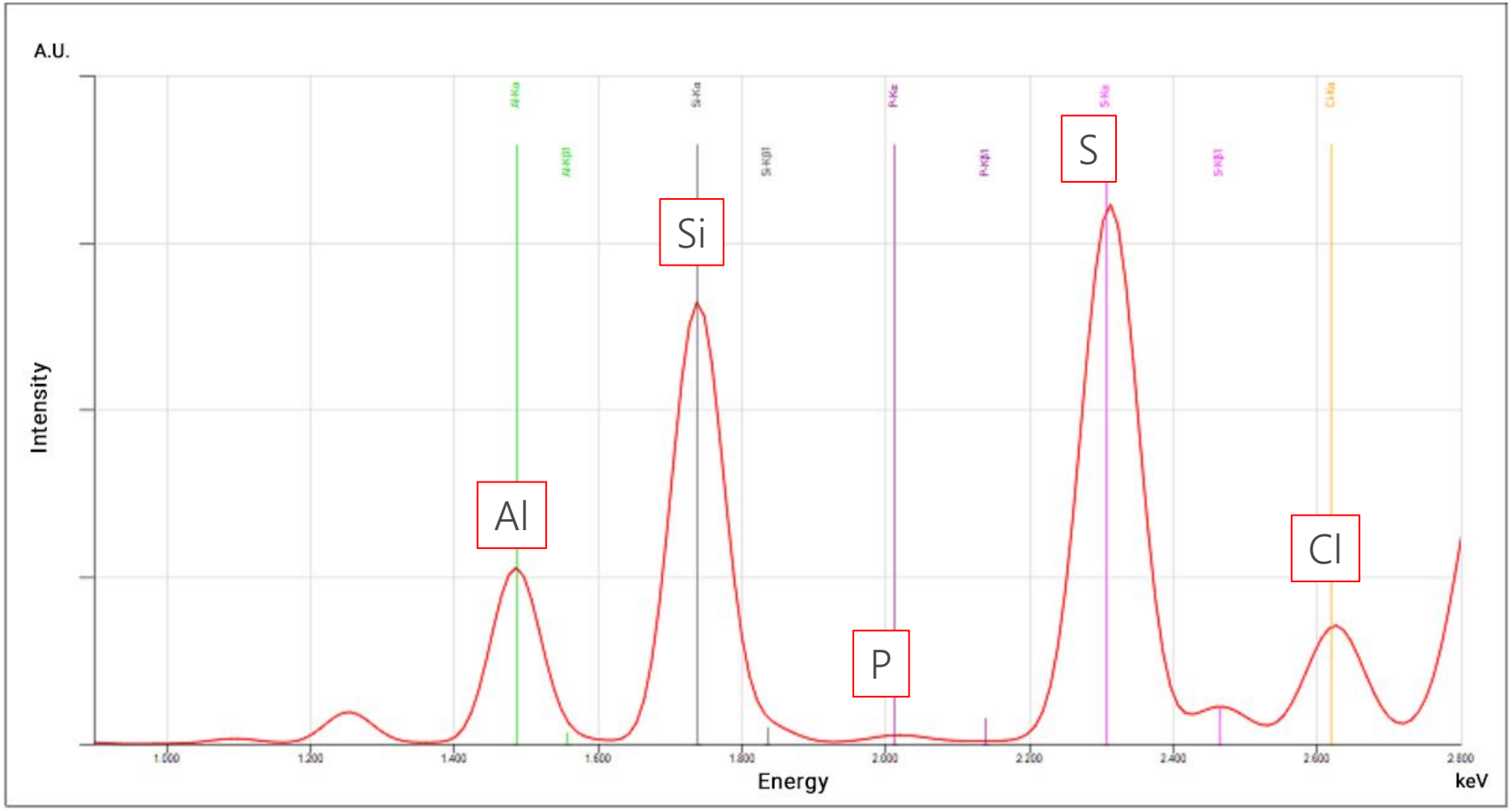
Tablet #	Cl	Al	Si	P	S	Ca	Ti
1	1374	2070	26.3	201	174	3686	8144
2	1382	2067	24.7	203	176	3701	8182
3	1377	1730	5.2	326	137	4072	8638
4	1574	2052	4.1	252	168	3806	8399
5	1219	2130	12	149	183	3512	9809
6	1266	2079	8.9	218	173	3538	8604
7	1288	2050	7.6	161	171	3437	8887
8	1503	1669	3.2	437	130	3876	8903
9	1400	2124	24.6	206	175	3729	8196
10	1400	2103	24.8	206	177	3706	8186
Avg. value	**1378**	2007	14	236	166	3706	8595
Std. Dev.	**106**	165	10	86	18	186	516
RSD	**7.7%**	8.2%	40%	36%	11%	5%	6%
Expected	**1364**	N/A					

10 tablets measured once each. Units: mg/kg. Total measurement time per analysis 600 sec.

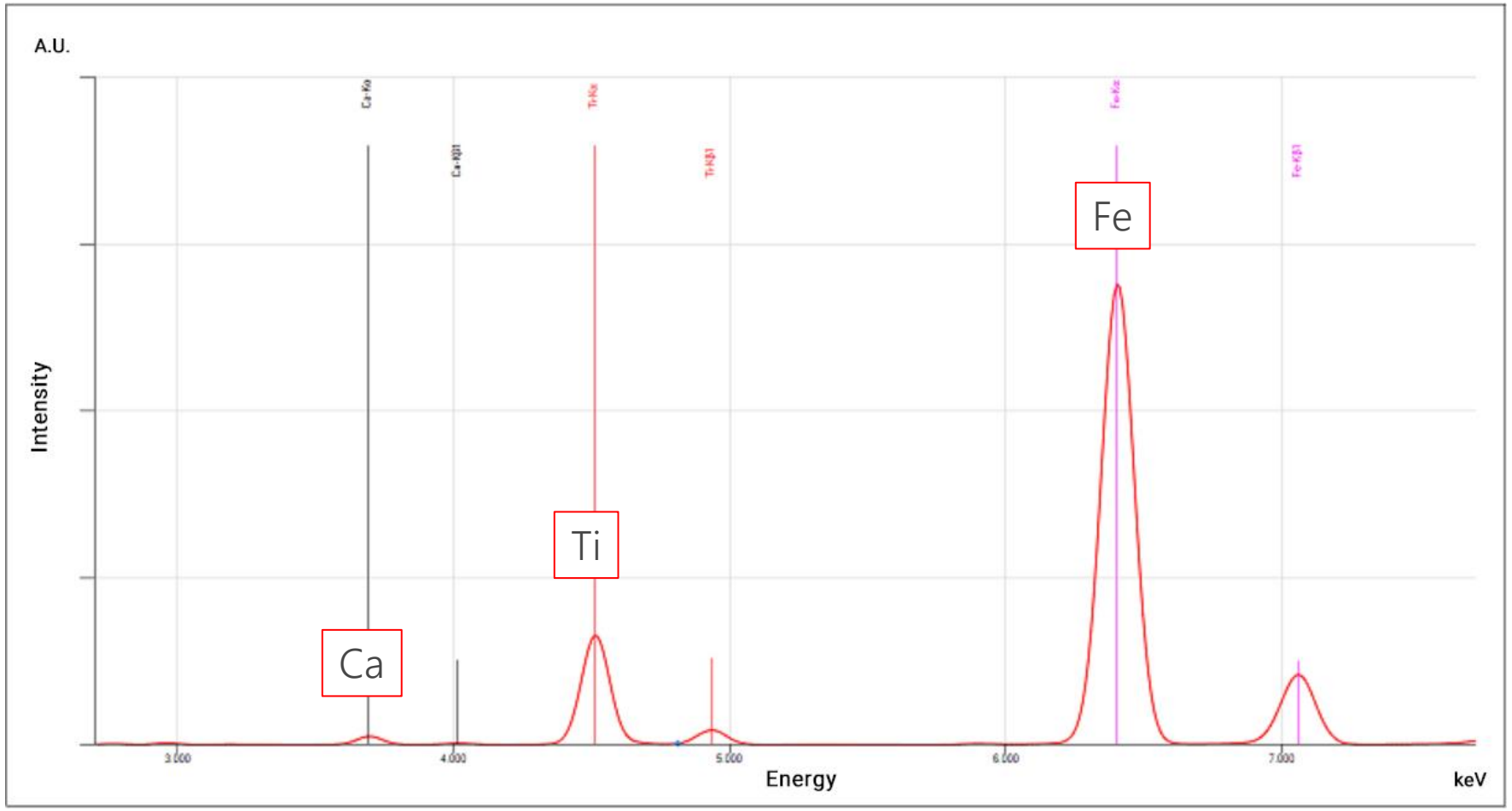
Ferrous sulfate Mg ultra-low energy settings



Ferrous sulfate Al, Si, P, S, Cl low energy settings



Ferrous sulfate Ca, Ti, Fe middle energy settings



Ferrous sulfate Measurement precision

Tablet form	Fe	Mg	Al	Si	P	S	Cl	Ca	Ti
Avg. value	4018	1845	3816	4902	35.1	1299	1158	670	3822
Std. Dev.	32	76	52	56	0.5	16	2	7	33
RSD	0.8%	4.1%	1.4%	1.1%	1.4%	1.2%	1.0%	1.0%	0.9%

1 tablet measured 10x repeat analyses.
Units: mg/kg
Total measurement time per one sample: 900 sec.

Ferrous sulfate Content uniformity across 10 tablets

Tablet #	Fe	Mg	Al	Si	P	S	Cl	Ca	Ti
1	3818	1766	4178	5431	45	1356	183	973	4937
2	5836	2524	5241	6756	57	1743	235	1037	6026
3	4099	2093	4026	5391	48	1284	183	694	4162
4	6367	2716	5595	7420	63	1941	267	890	5228
5	6260	2281	5401	6746	65	1904	249	933	4672
6	6946	2113	4413	5746	51	1393	174	762	5061
7	5880	2531	5584	7232	60	1894	259	995	5038
8	5245	2565	5425	7045	51	1702	202	644	6235
9	5320	2977	6208	8291	62	1998	236	973	6763
10	3932	1820	3697	4774	34	1266	155	654	3742
Avg. value	**5370**	2339	4977	6483	54	1648	214	856	5186
Std. Dev.	**1098**	392	831	1102	10	293	40	152	930
RSD	**20%**	17%	17%	17%	18%	18%	18%	18%	18%

10 tablets measured once each. Units: mg/kg. Total measurement time per tablet: 900 sec.

4. Key benefits of EDXRF for process chemistry

Why EDXRF is a valuable tool for formulation development

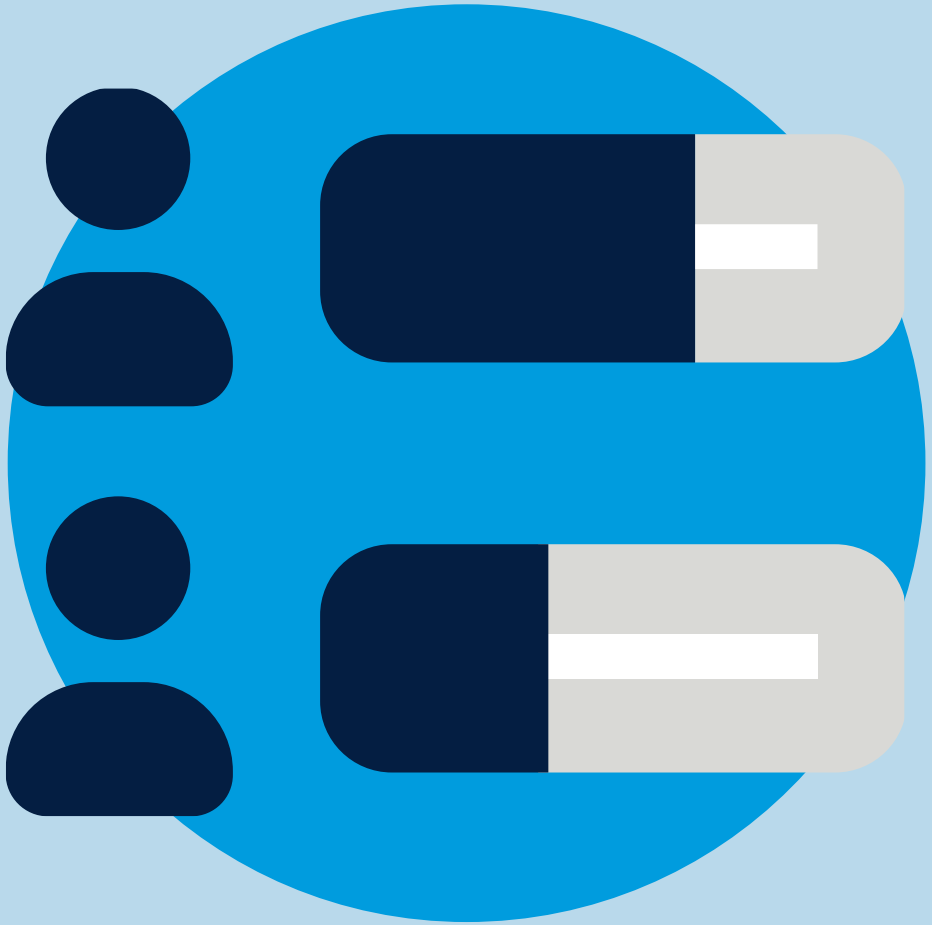
- Non-destructive
- Minimal sample prep
- Fast measurements
- Traceable to ICP
- Optimize yield
- Monitor catalyst residues
- Ensure product safety
- Meet regulatory requirements

EDXRF and 21 CFR Part 11

- Supports data integrity for regulated lab environments
- Fast results without compromising data security
- Systems can be configured to support your needs

Polling Question

#3



5. Summary

EDXRF

- Fast, reliable decision-making
- Compact and cost-effective
- Non-destructive testing
- ICP traceability
- Regulatory compliance

Questions?

We'll follow up with your questions.

Recording will be available tomorrow.

Register for the next episode.

Webinar Series

Webinar Series: Enhancing Pharma Processes with X-ray, Thermal, and Raman Analysis Tools

Episode 4 – Manufacturing and QC

1. **Characterization and quality control of pharmaceutical products using X-ray Computed Tomography**
   Presenter: Angela Criswell, PhD
2. **Real-time Pharmaceutical Quality Analysis and Control using Handheld Raman Spectroscopy**
   Presenter: Suzanne Schreyer, PhD

Starting Wednesday, June 18 at 1 pm CDT

Don't forget to register for the next episode!