



# **The use of Field-Portable pXRD for the Rapid Identification of Counterfeit Pharmaceutical Products and Subsequent Excipient Identification and Quantification**

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# Outline of the talk

**Introduction**

**CheMin Spacecraft Instrument**

**Terrestrial prototypes**

**Examples of mineral analysis with field-portable XRD**

**Spacecraft XRD requirements vs. Pharmaceutical  
XRD requirements**

**Counterfeit drugs**

**Future Spaceflight Instruments**

**Conclusions**



# CheMin: CHEMistry and MINeralogy

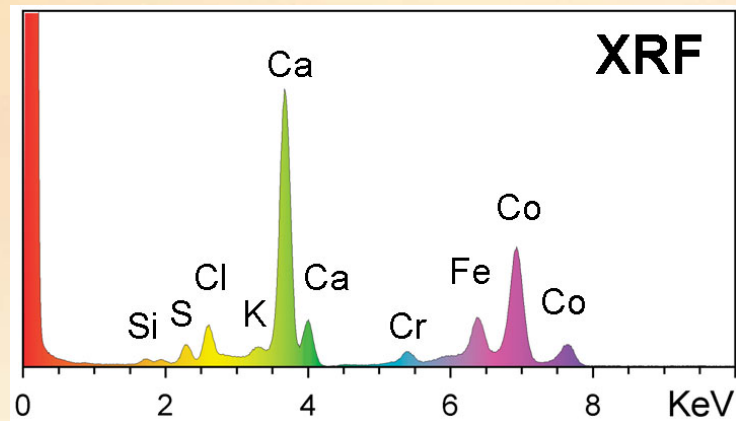
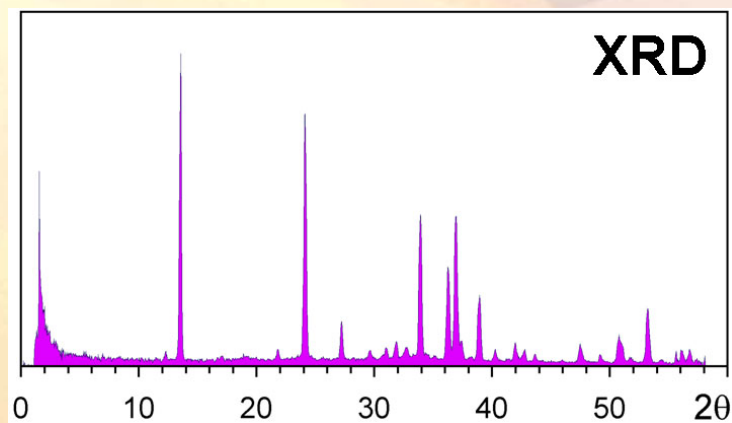
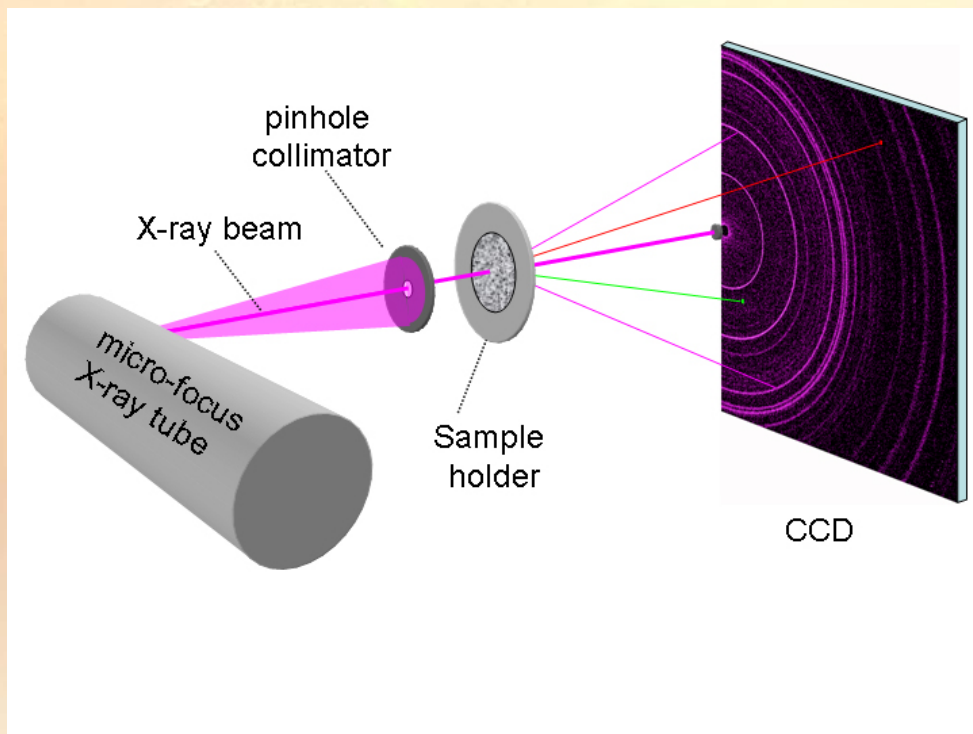
## CheMin principle:

- X-ray diffraction (XRD) for mineralogical characterization
- X-ray fluorescence (XRF) for elemental characterization
- A single detector for both measurements
- 1 moving part (sample wheel), ~20 milligram sample size



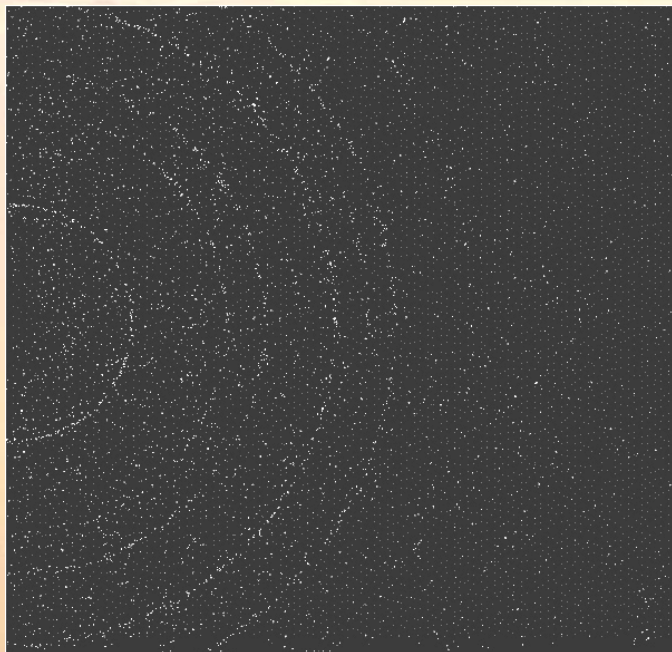
# CheMin Principle of Operation

- ◆ *A single detector measures energy, position and intensity of the X-rays emanating from the sample*

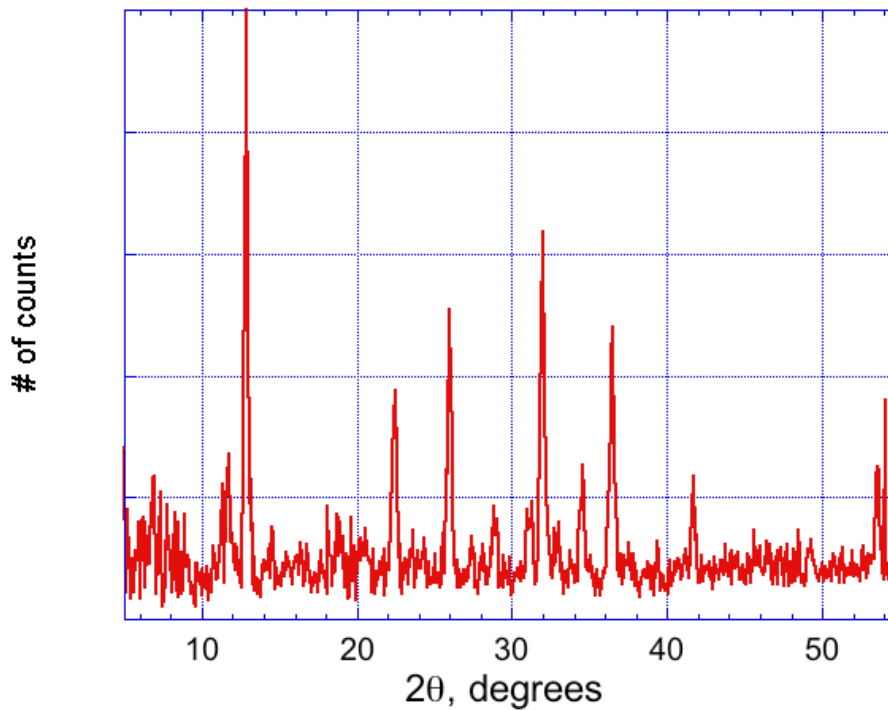




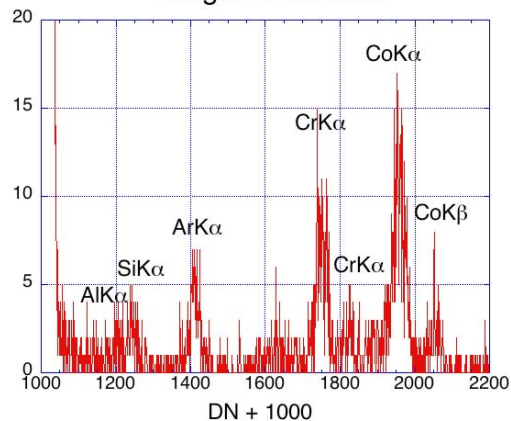
# Single frame of Quartz-Beryl standard data 10 sec. integration



### Single Frame XRD (film mode)



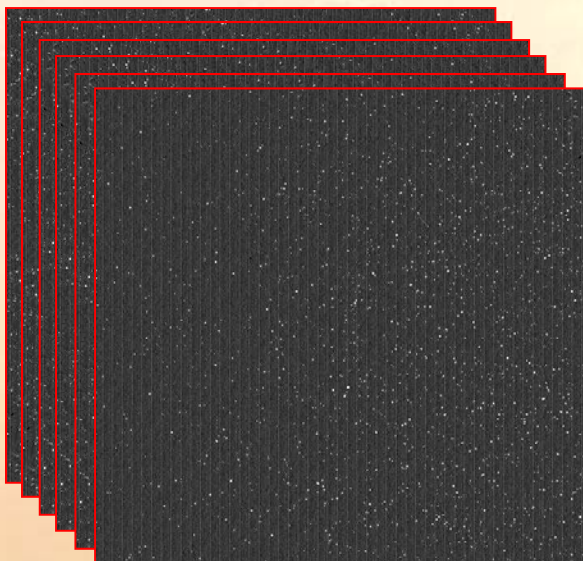
### Single Frame XRF



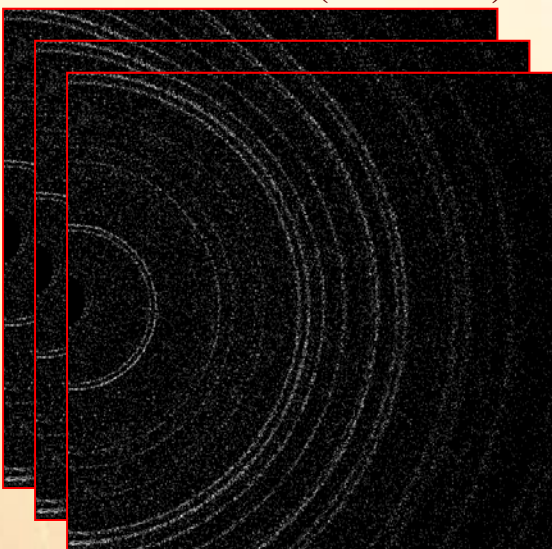


# Summing individual frames for analysis

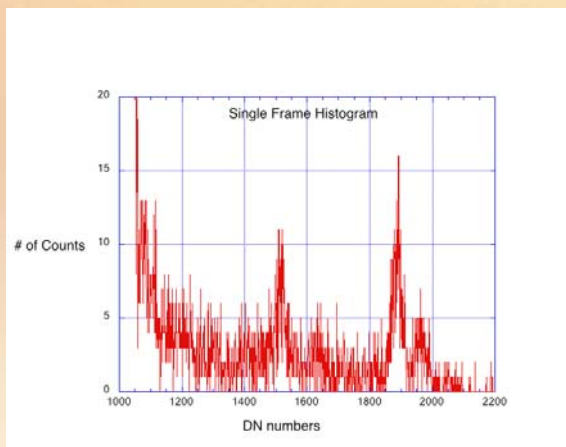
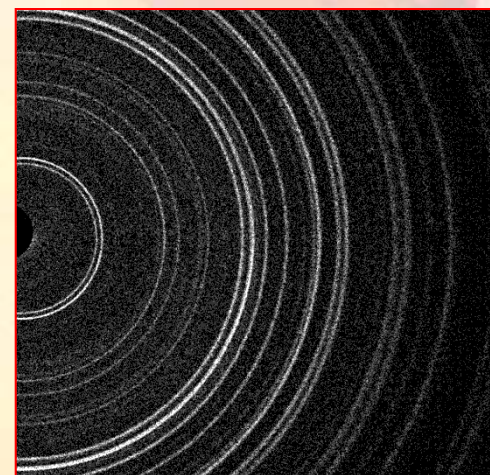
100-200 10 sec. indiv. frames



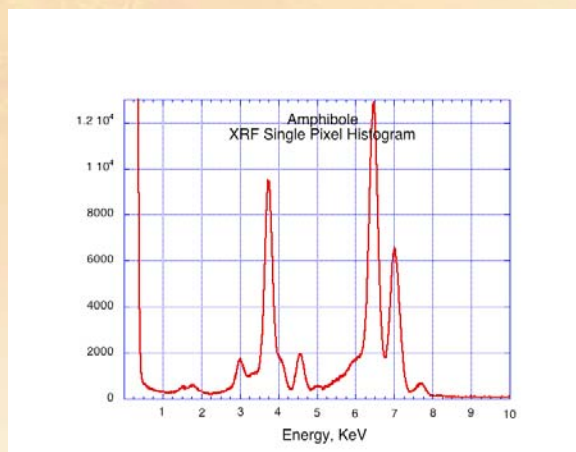
5-10 Minor frames ( $K\alpha$  shown)



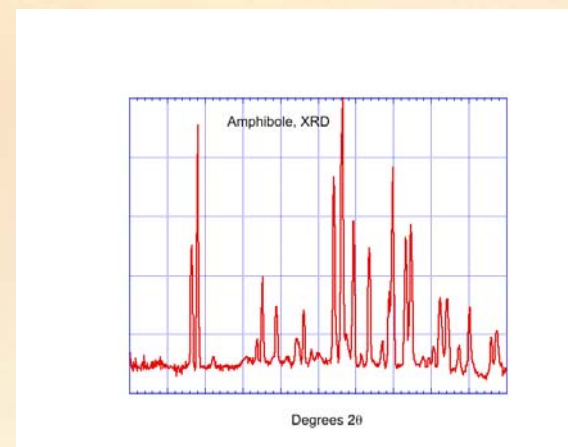
1 Major frame ( $K\alpha$  shown)



Single frame histogram



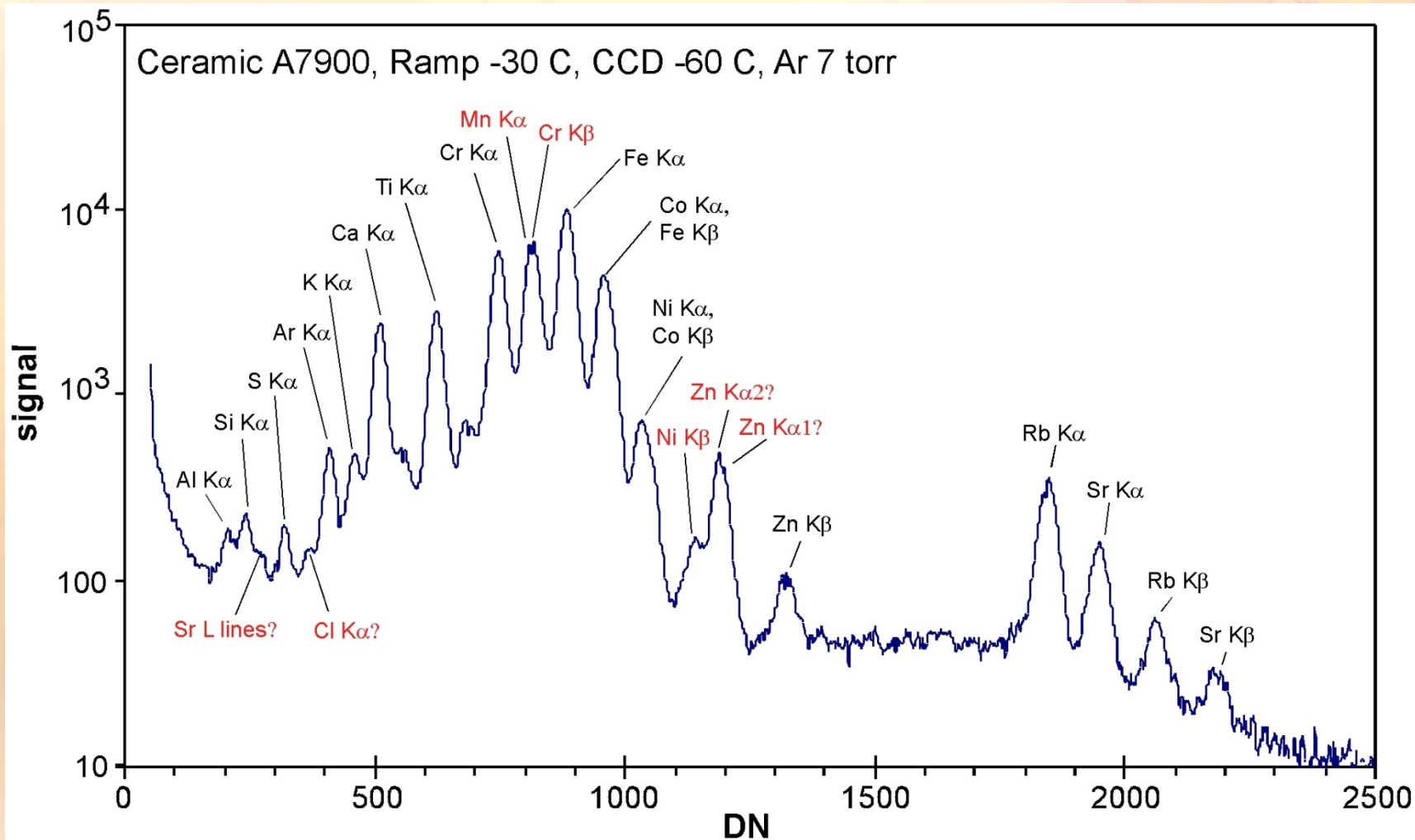
XRF spectrum



$K\alpha$  XRD pattern



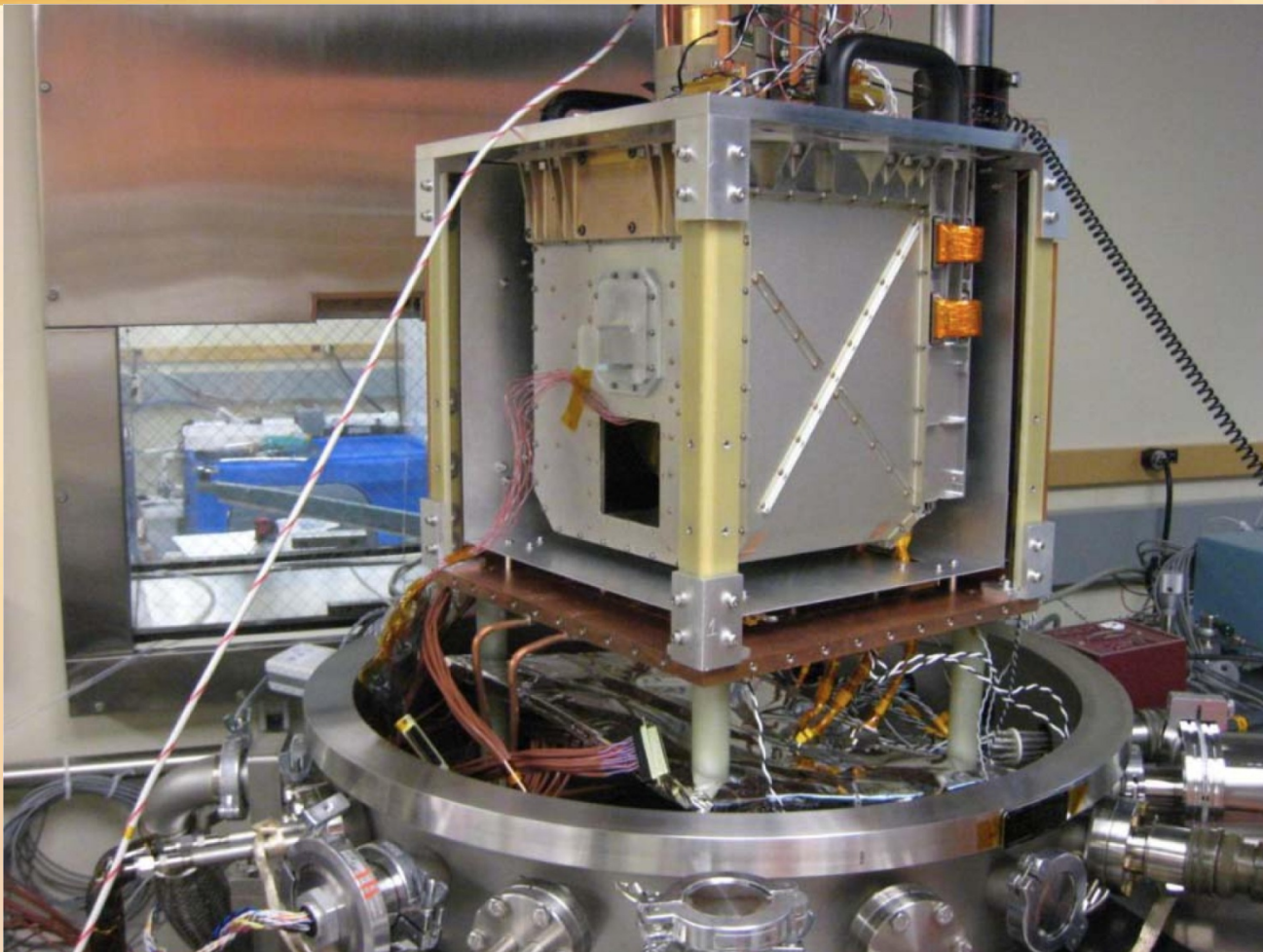
# XRF - multielement ceramic material







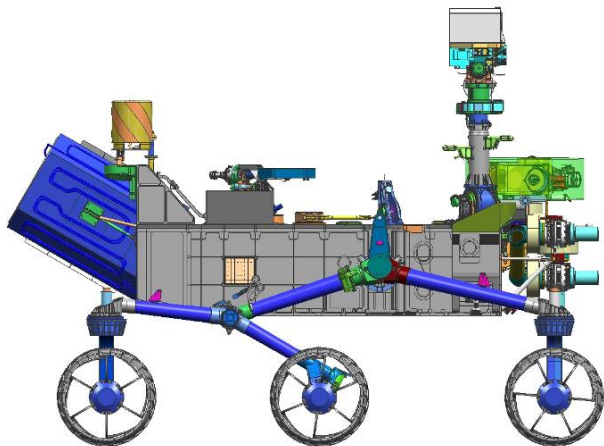
# The CheMin flight instrument



**CheMin Flight Model in thermo-vac tests. 30X30X30 cm, 10 Kg., 40 W**



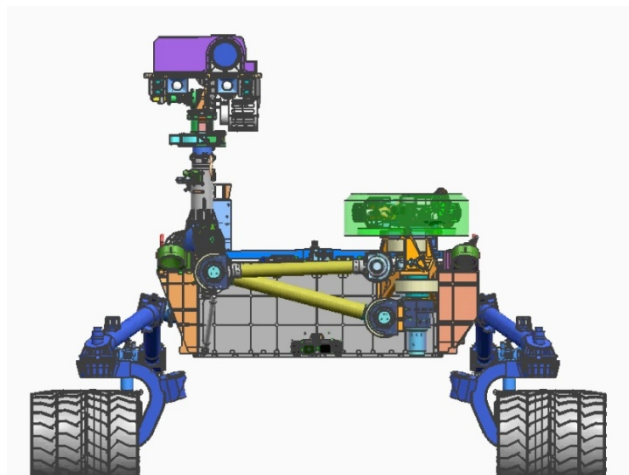
# MSL Size Comparison



**JPL 2011 MSL Rover**



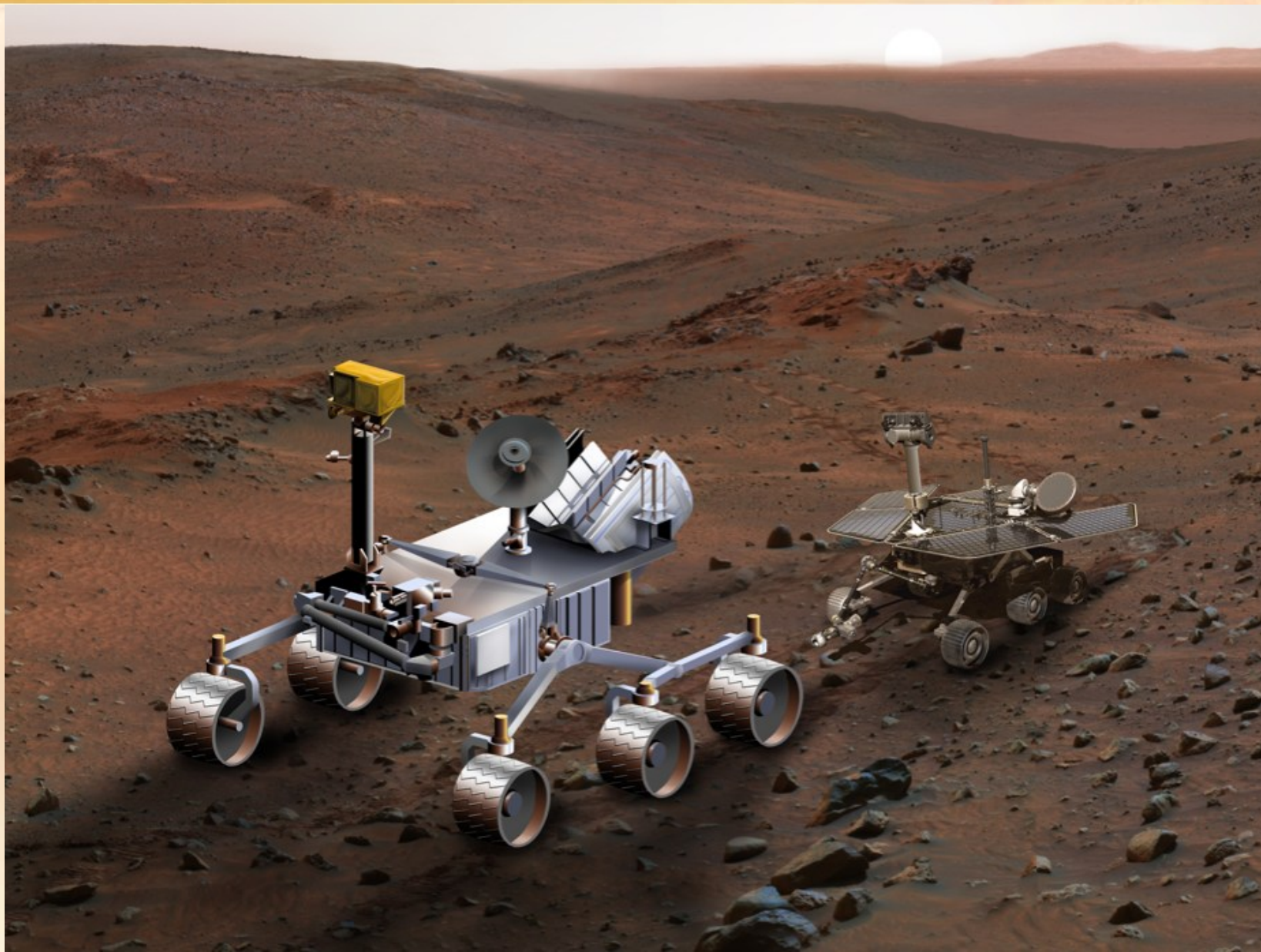
**2005 MINI Cooper S**



The data/information contained herein has been reviewed and approved for release by JPL Export Administration on the basis that this document contains no export-controlled information.

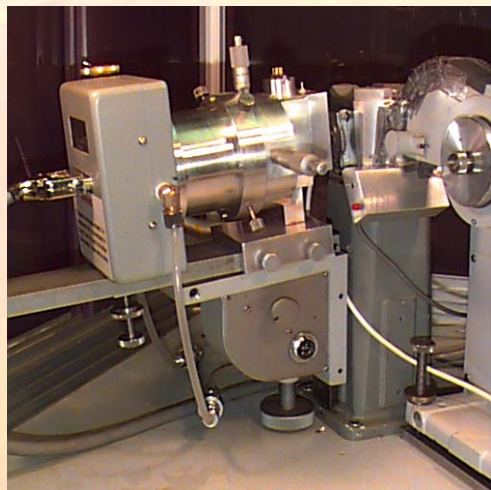


# MSL - MER Comparison

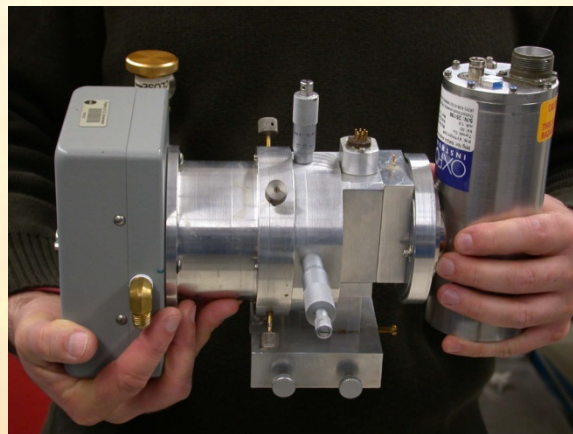




# CheMin Laboratory / Field Prototypes



**CheMin I (1992)**



**CheMin II (2002)**



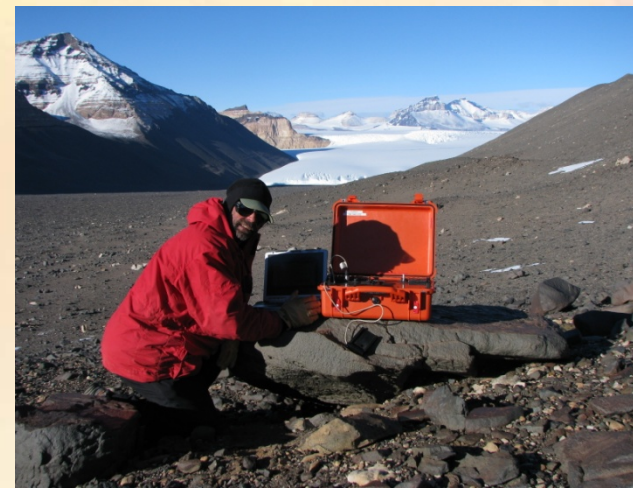
**CheMin III (2003)**



**CheMin III field version (2003)**



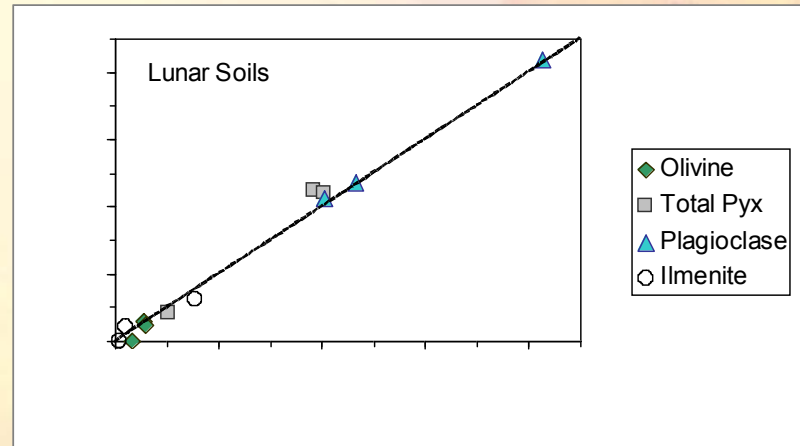
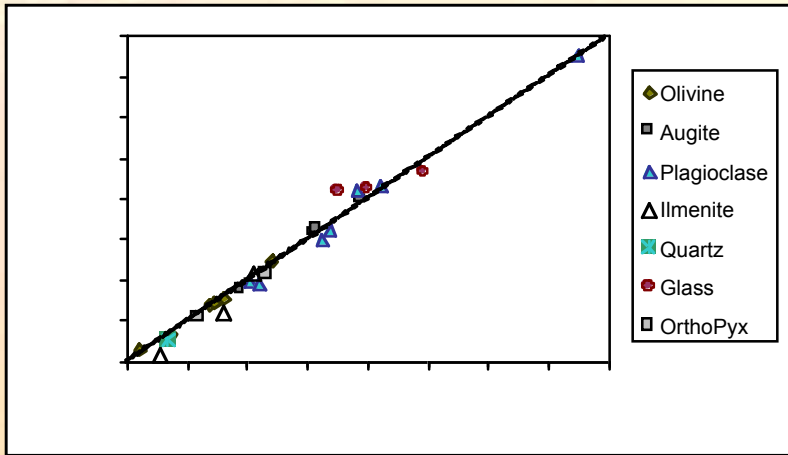
**CheMin IV (2006)**



**Terra (2007-present)**

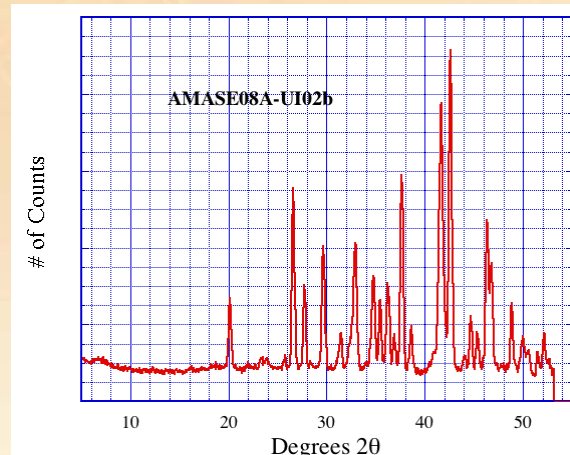
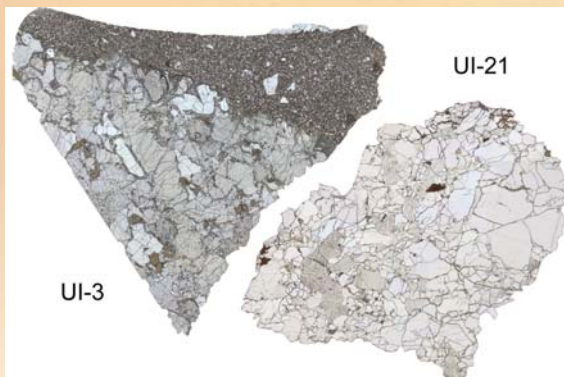


# Quantitative analysis with Terra



Abundances of minerals in seven mixtures versus those determined by quantitative XRD using Rietveld whole-pattern fitting and instrument calibration with binary mixtures.

Comparison of point counting using SEM (L.A. Taylor et al., 2001a,b and 2009) with our results using XRD. Both datasets were obtained on soils sieved to 25-45  $\mu\text{m}$ . Abundances are on a glass-free basis.



Xeno lith, Mineral %	Petrographic mapping	XRD (Terra)
Spinel	1.6	1.4
Plagioclase	~0.3	0.6
Partial Melt	1.1	---
Orthopyroxene	21.	25.
Olivine	65.	66.
Clinopyroxene	10.	6.
Aqueous Alt.	~2.	0.
Amphibole	0.	0.



# Design considerations: robotic XRD:

- 1. Particle size:** *Coarse grains easier to produce, transfer; finer grains clog mechanisms.*  
*Transmission geometry - X-ray beam diameter and sample thickness define  $2\theta$  resolution; sample vibration randomizes the orientation of large grains.*
- 2. Preferred orientation:** *No sophisticated sample preparation is possible.*  
*Sample vibration produces powder flow and random particle motion - “powder Gandolfi.” 2D detector collects large area of Laue cones to homogenize preferred orientations.*
- 3. Sample geometry:** *Difficult to make flat samples robotically*  
*Sample morphology defined by parallel X-ray transparent windows 170  $\mu\text{m}$  apart*
- 4. Diffraction geometry:** *Necessary to detect low  $2\theta$  for large periodicity phases*  
*Transmission geometry - peak detection down to  $3^\circ 2\theta$ , symmetrical peaks, constant resolution in  $5\text{--}50^\circ 2\theta$  region.*
- 5. Sample size:** *Miniaturized instruments - small samples, small mechanisms, less energy.*  
*Sample size for CheMin is  $\sim 20$  mg.*



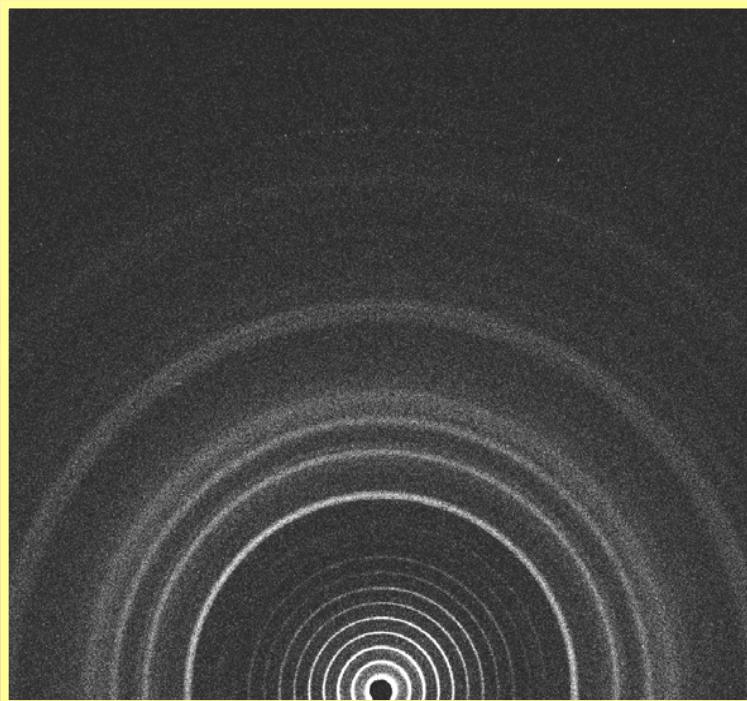
# Design considerations: **Pharmaceutical XRD:**

- 1. Particle size:** *Grain size is typically too large, but grinding may affect phases in sample. Transmission geometry - X-ray beam diameter and sample thickness define  $2\theta$  resolution; sample vibration randomizes the orientation of large grains and increases particle statistics.*
- 2. Preferred orientation:** *Grinding to reduce orientation effects may alter the phases. Sample vibration produces powder flow and random particle motion - “powder Gandolfi.” 2D detector collects large area of Laue cone to homogenize preferred orientations.*
- 3. Sample morphology:** *Coplanarity of sample/sample holder is an issue in reflection geom. Sample morphology defined by parallel X-ray transparent windows 170  $\mu\text{m}$  apart*
- 4. Diffraction geometry:** *Reflection geometry, peak asymmetry at low  $2\theta$ , peak broadening. Transmission geometry, peak detection down to  $3^\circ 2\theta$ , symmetrical peaks, constant resolution in  $5\text{--}50^\circ 2\theta$  region.*
- 5. Sample size:** *Many pharmaceuticals in quantities  $<100$  mg, esp. research products. Sample size for CheMin is  $\sim 20$  mg.*

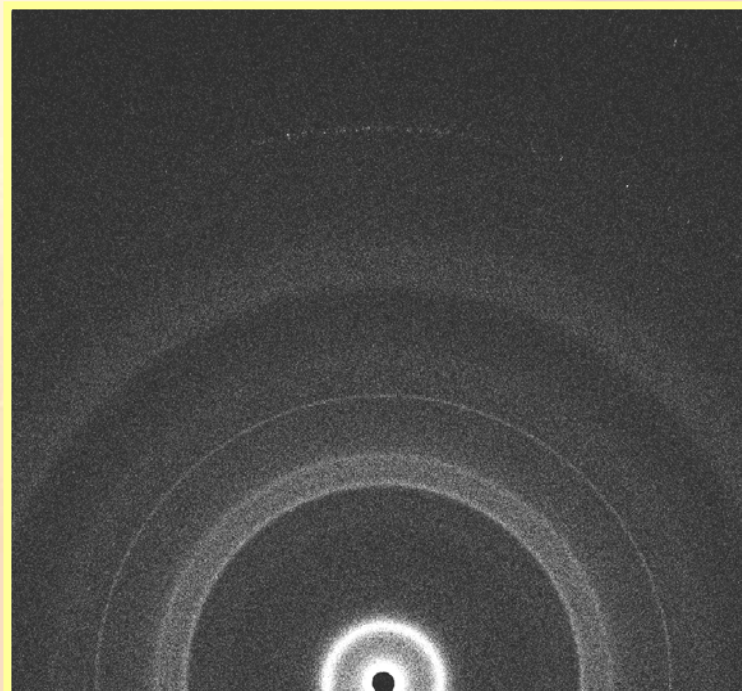


# Angular range: $1.5^\circ$ to $57.5^\circ 2\theta$ , $\text{CoK}\alpha$

Low angle detection is critical for the characterization of clay minerals.



*XRD pattern of non purified Silver Behenate  $\text{CH}_3(\text{CH}_2)_{20}\text{COO-Ag}$ . First ring  $d_{001}=58.38\text{\AA}$ ,  $1.75^\circ 2\theta \text{ Co K}\alpha$*



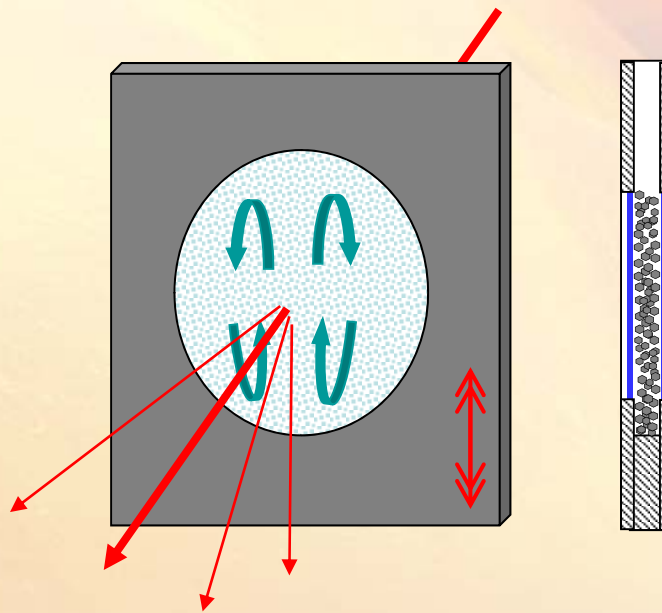
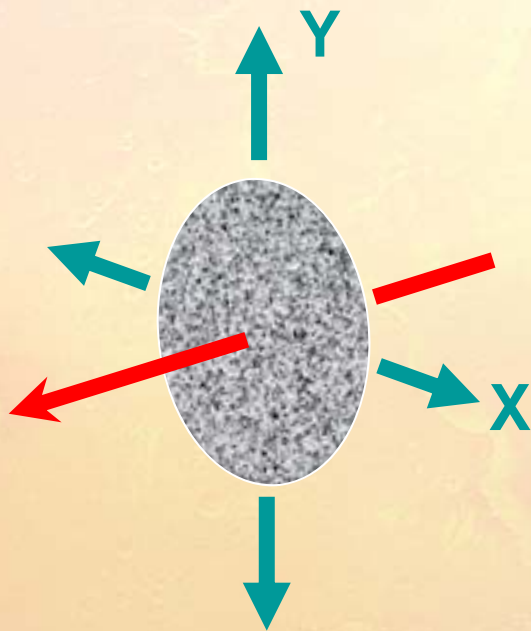
*XRD pattern of a Smectite (SWa-1) with trace of quartz.*





# Sample Movement Through Vibration

Remind me to show the movie!



## Old System:

- 2 movements
- requires fine powder
- sample loading?

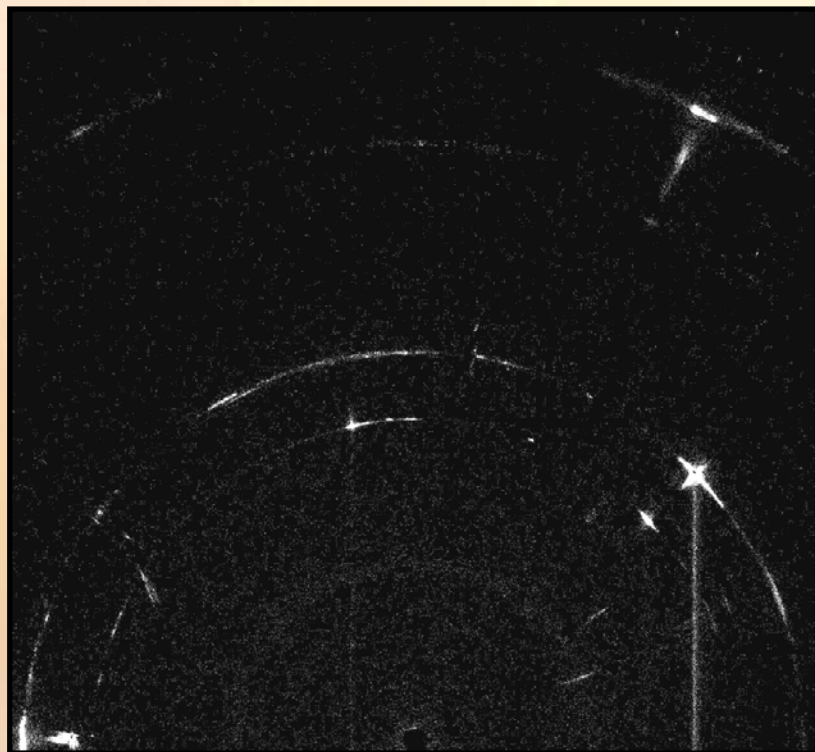
## New System:

- no movements
- coarse powder okay
- easy loading

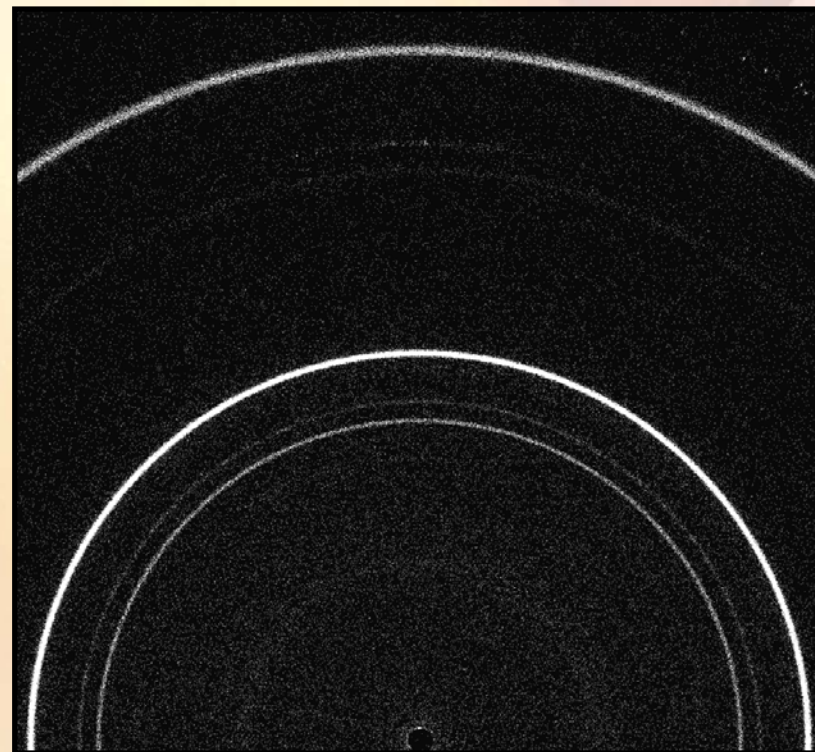


# Sample movement through vibration

NaCl crushed & sieved <150 um



No vibration



Vibrations 1.5kHz



# Active ingredients and Excipients

Genuine drugs have specific active ingredients and excipients

Counterfeit drugs fall into a number of categories:

- Fakes w/ active ingredient (but less or more of it)
  - quantify the active ingredient,
  - identify and quantify the excipients
  - use the excipients to identify the source (?)
- Fakes that have the wrong ingredients
  - identify the ingredients
  - use the ingredients to identify the source (?)



# Textbook example - Excedrin (RIR method)

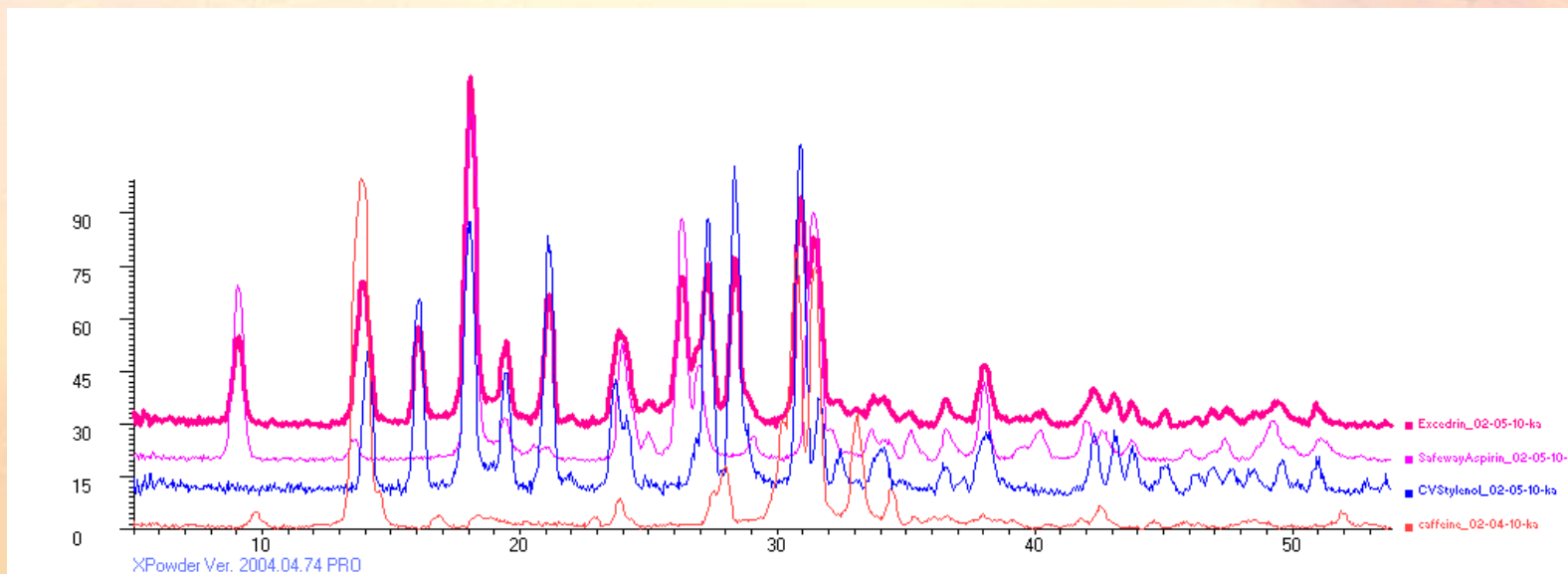


Table I

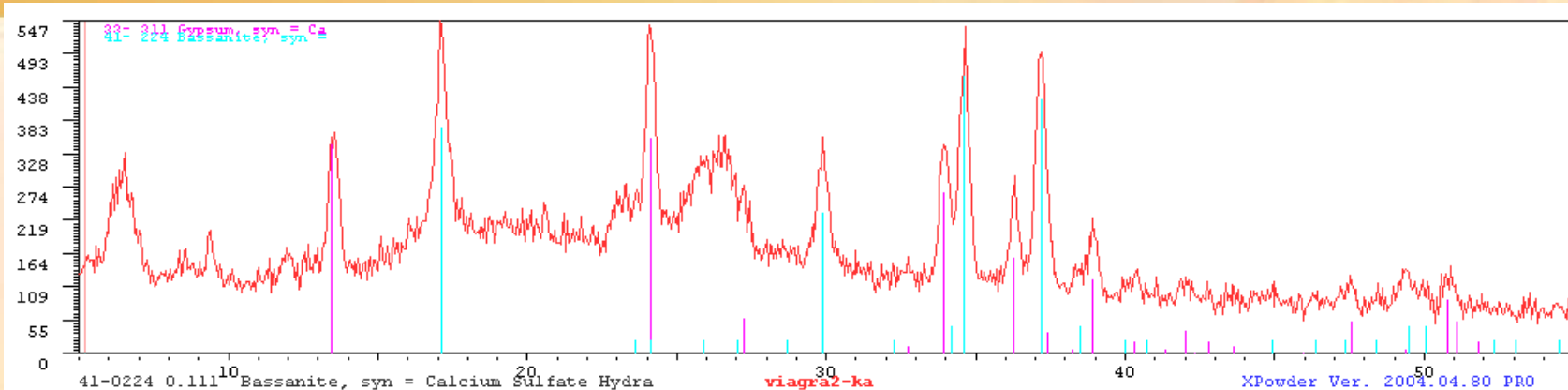
Active Ingredients, Excedrin*	Excedrin listed Package content (%)*	Observed %, XRD (RIR method)**
Tylenol (250 mg)	37.0%	38.2%
Aspirin (250 mg)	37.0%	52.4%
Caffeine (65 mg)	9.7%	9.4%
Excipient (110 mg)	16.6%	-

\*off-the shelf analgesic product contained approximately 17% excipients.

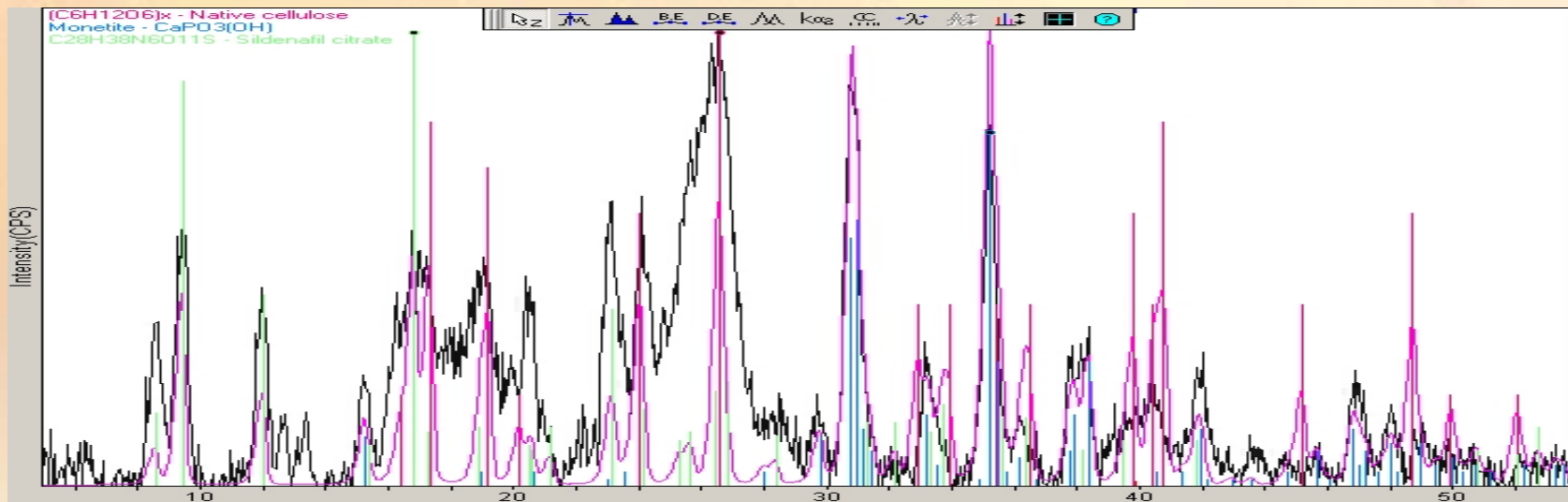
\*\* active ingredients summed to 100%



# Outright Fraud - Viagra



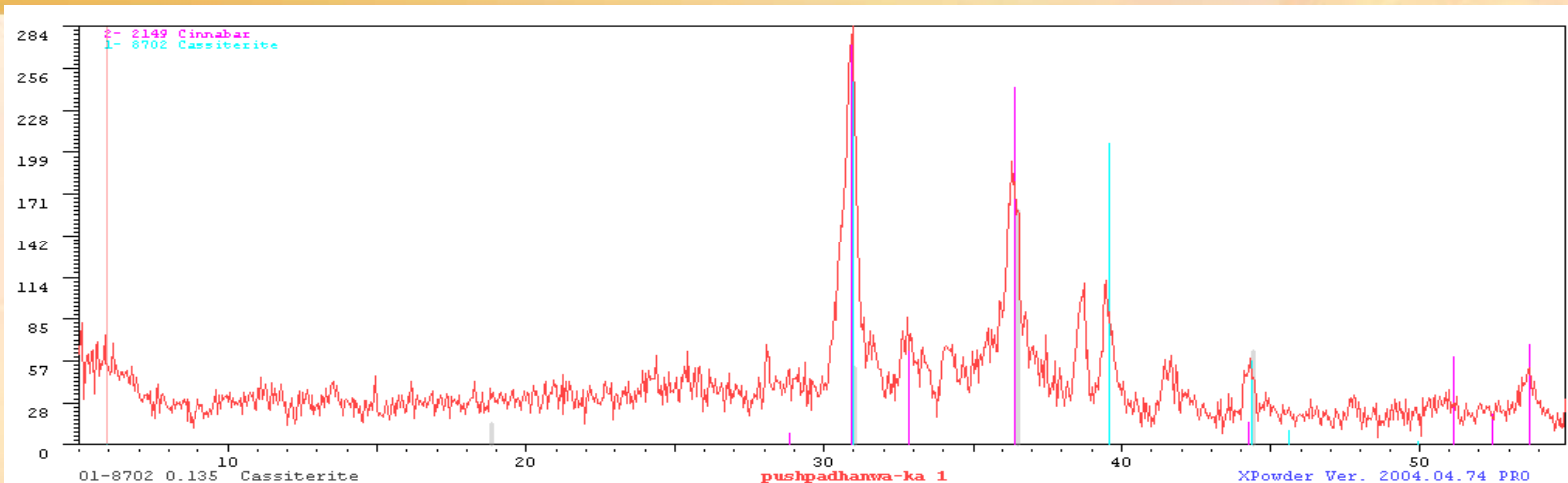
*Fake viagra - contains microcrystalline cellulose (broad peaks at 6.5, 23.5 and 26 degrees), gypsum and bassanite (both are calcium sulfate hydrates) 15 minute acquisition*



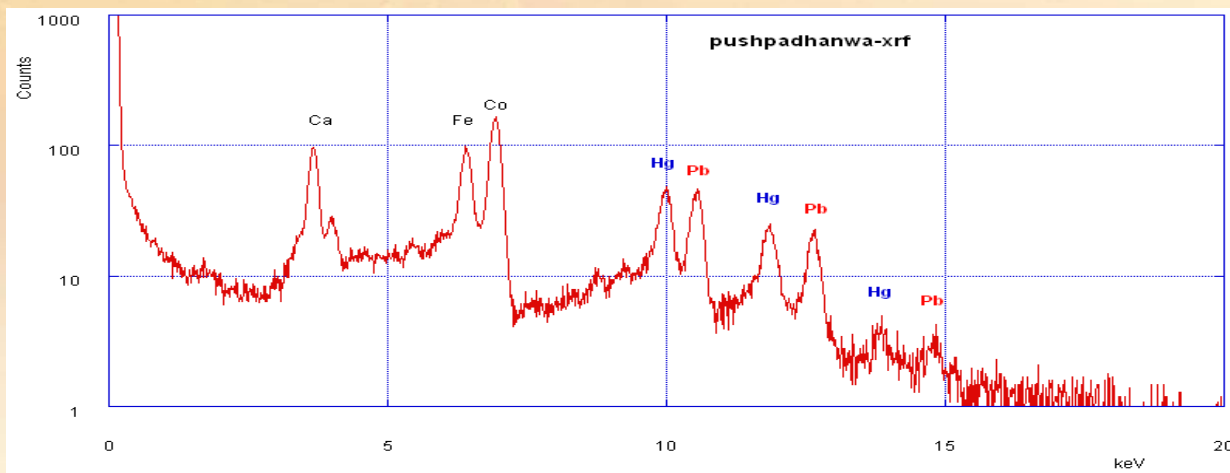
*Real viagra - contains sildenafil citrate (active ingredient, green line markers), monetite (anhydrous calcium hydrogen phosphate, blue markers) and cellulose (magenta markers). Sample provided by US Customs Laboratory, San Francisco. 15 minute acquisition.*



# Outright fraud - Indian “Fertility” Drug

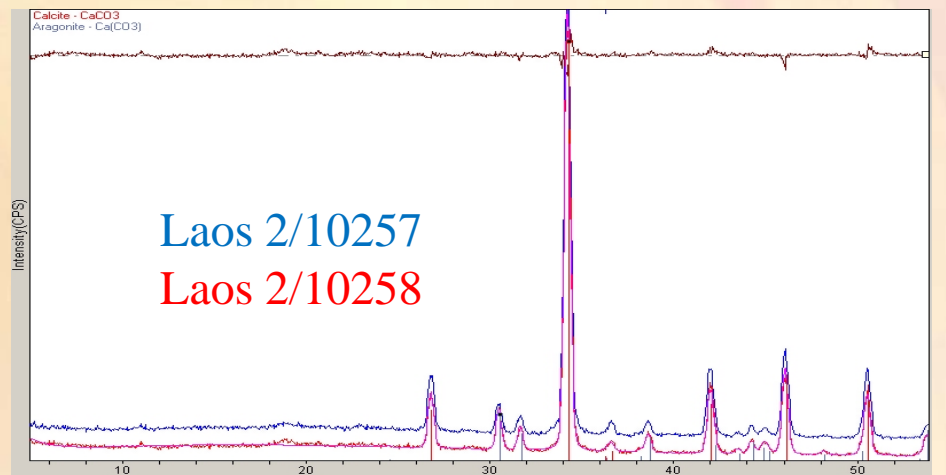
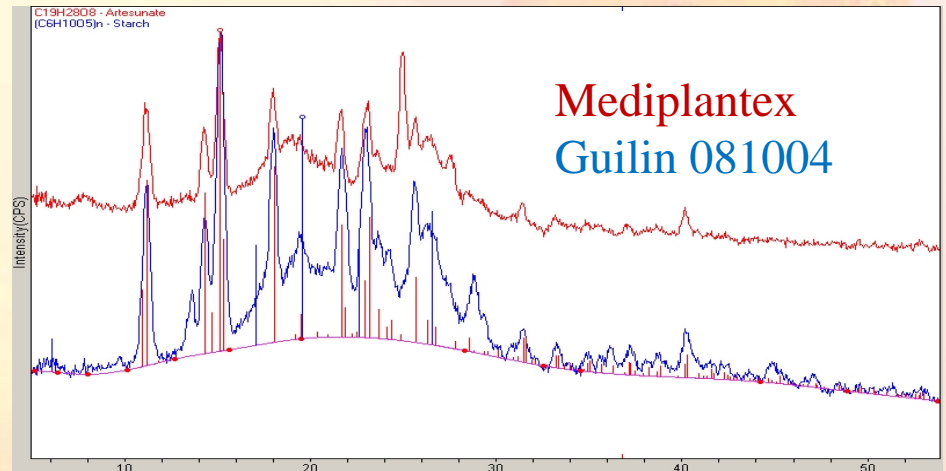
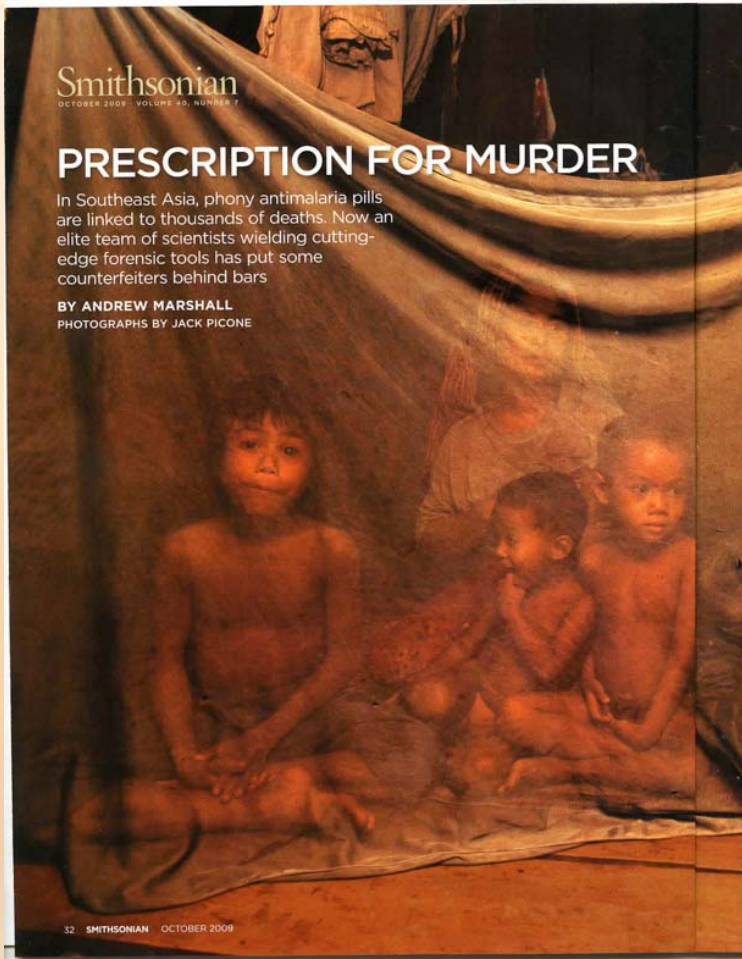


Indian “fertility drug” obtained from FDA. Consists of mercury sulfide (cinnabar), lead (phase not identified) and tin oxide (cassiterite). Upper pattern = powder XRD lower spectrum = XRF. Co (cobalt) in XRF pattern is from the X-ray source.





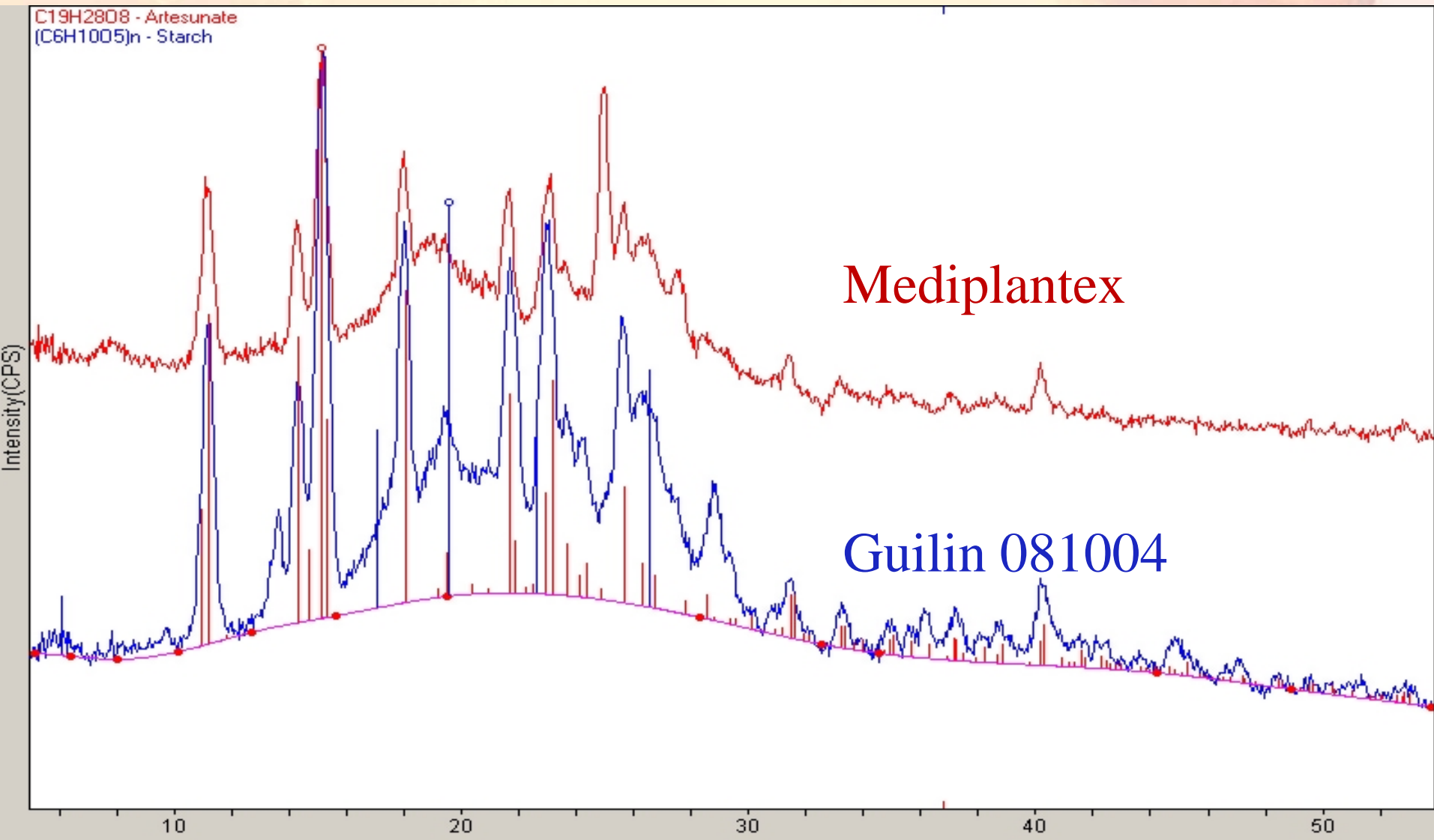
# Counterfeit Malaria Drugs



*50-90% of malaria drugs sold in SE Asia are counterfeit, causing untold death and misery, and the evolution of drug-resistant forms of the parasite.*



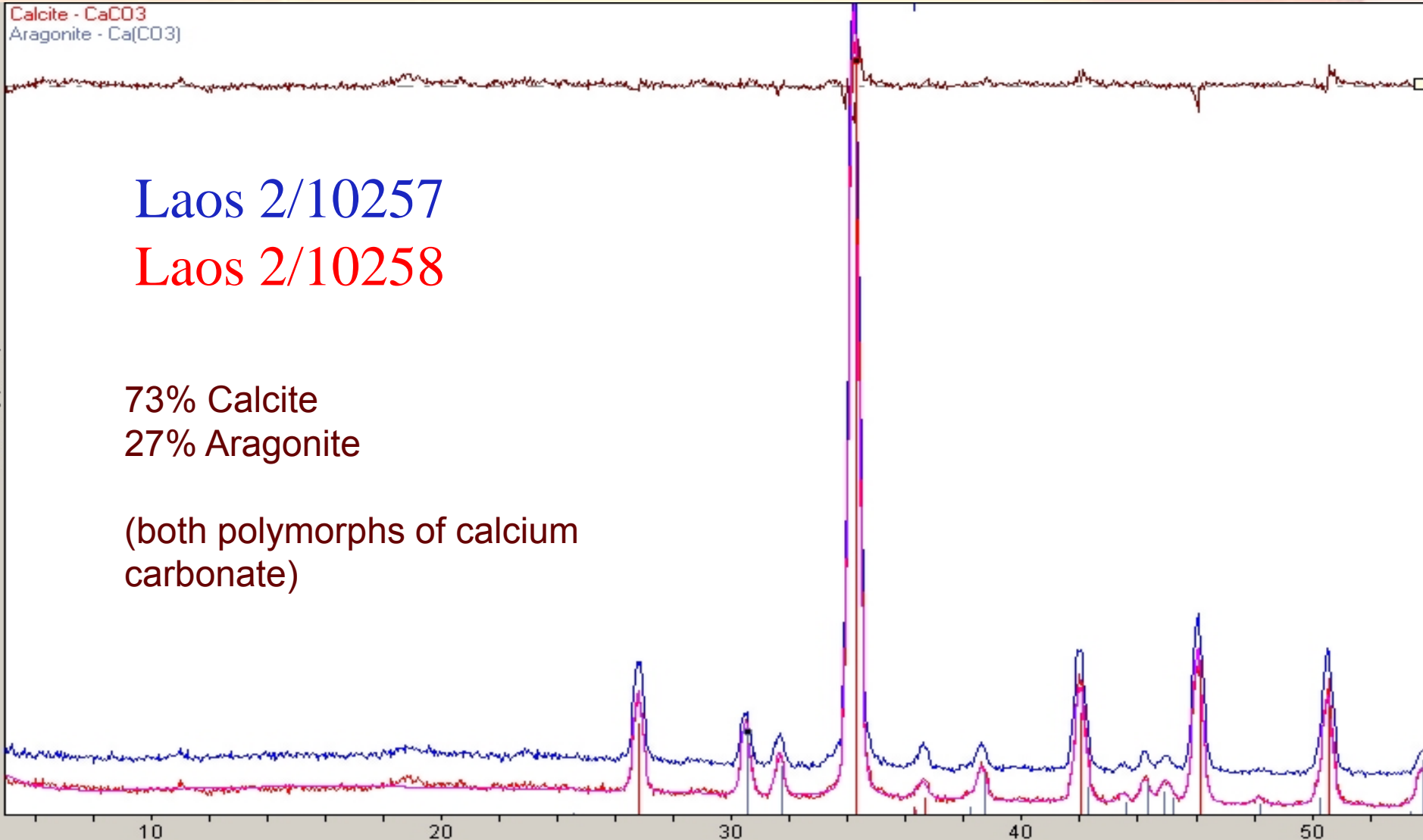
# Real artesunate drugs







# Laos counterfeit artesunate





# Vietnam counterfeit artesunate

Calcite -  $\text{CaCO}_3$   
Aragonite -  $\text{CaCO}_3$

Vietnam 2/15150

Vietnam 2/15017

Principal phases:

80% Calcite

20% Aragonite

(both polymorphs of calcium carbonate)

Balance – unidentified phases in the 5–

26 degree  $2\theta$  region

Intensity(CPS)

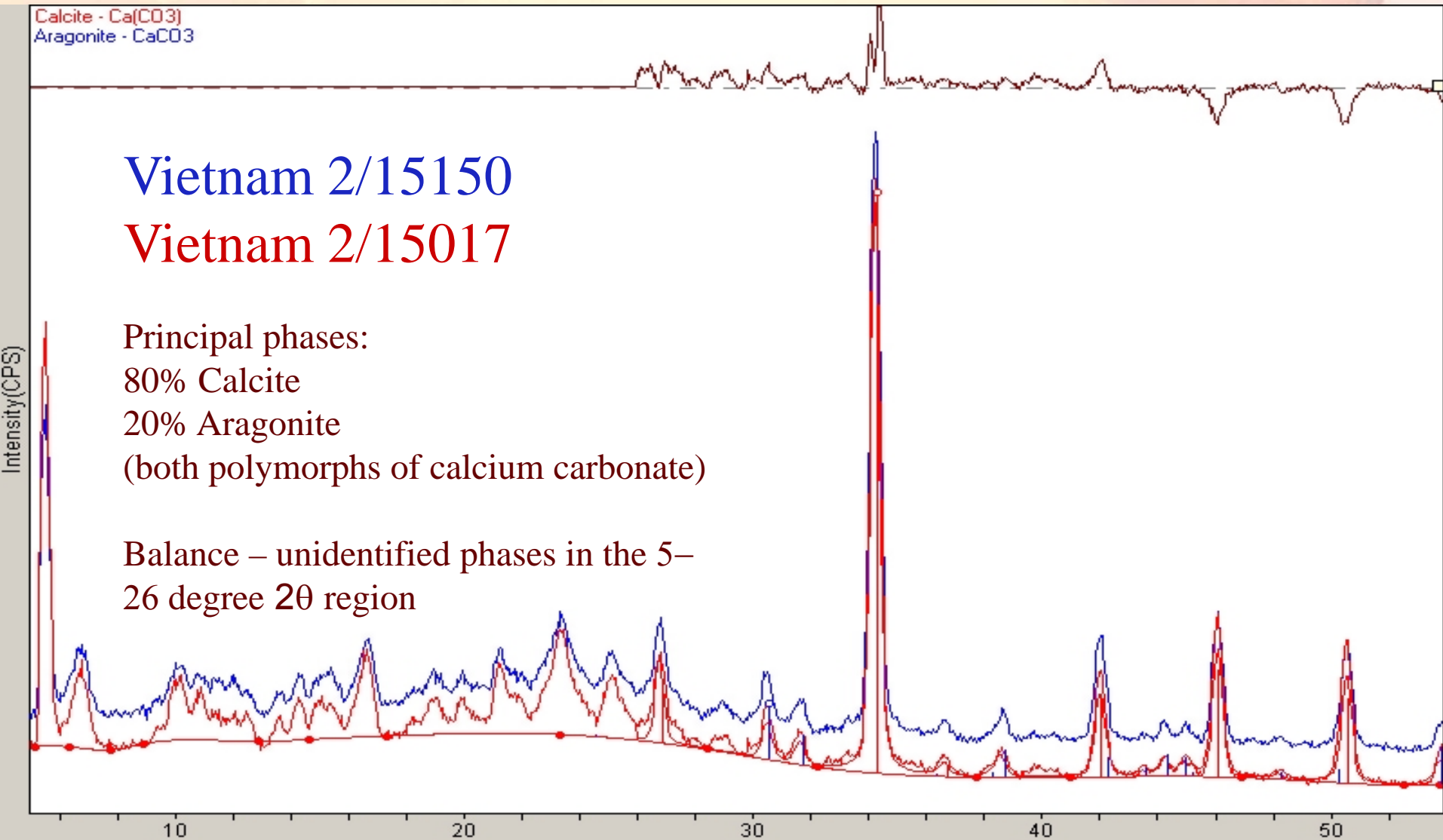
10

20

30

40

50



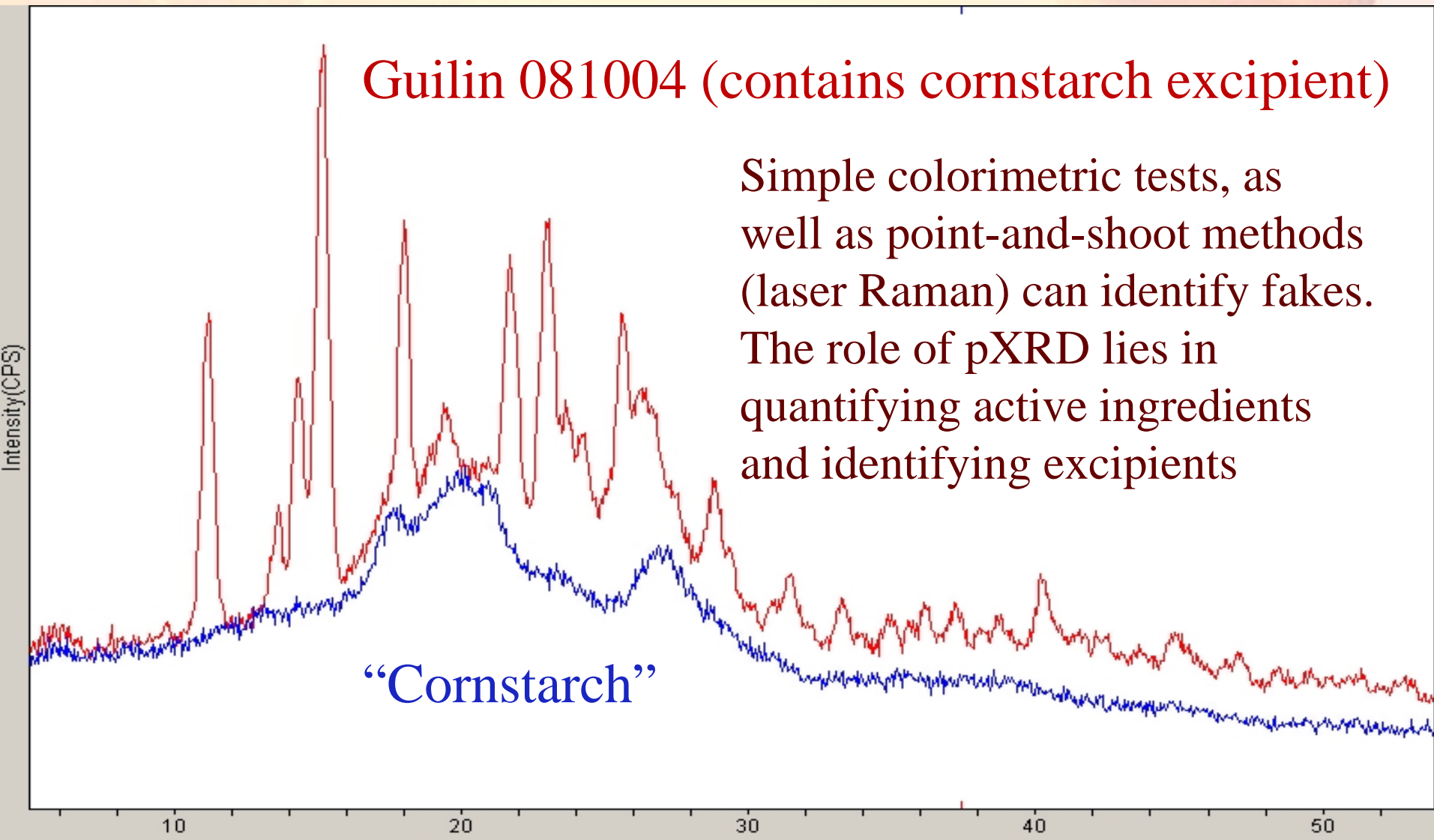


# The role of pXRD in counterfeit drug analysis

Guilin 081004 (contains cornstarch excipient)

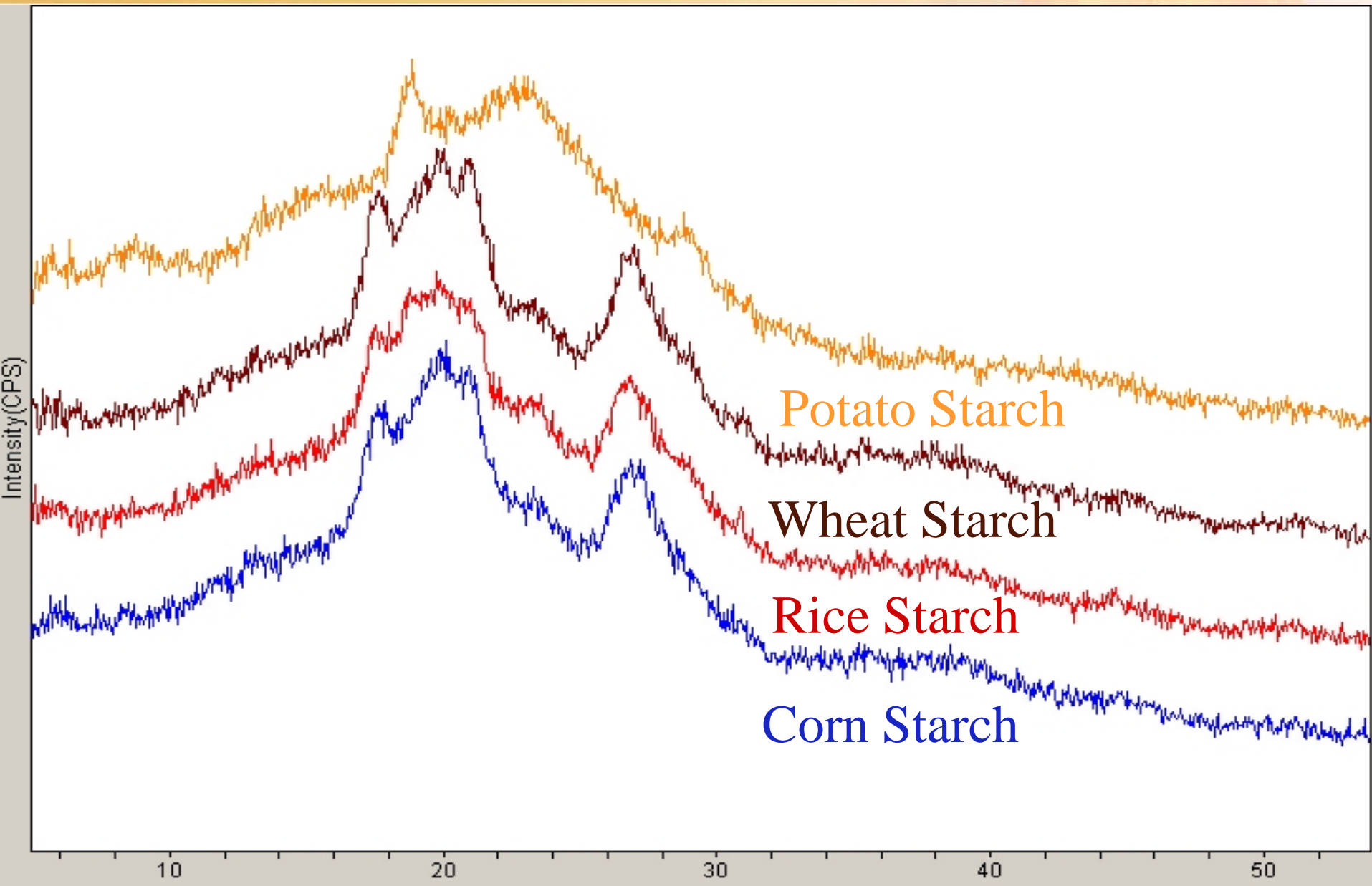
Simple colorimetric tests, as well as point-and-shoot methods (laser Raman) can identify fakes. The role of pXRD lies in quantifying active ingredients and identifying excipients

“Cornstarch”



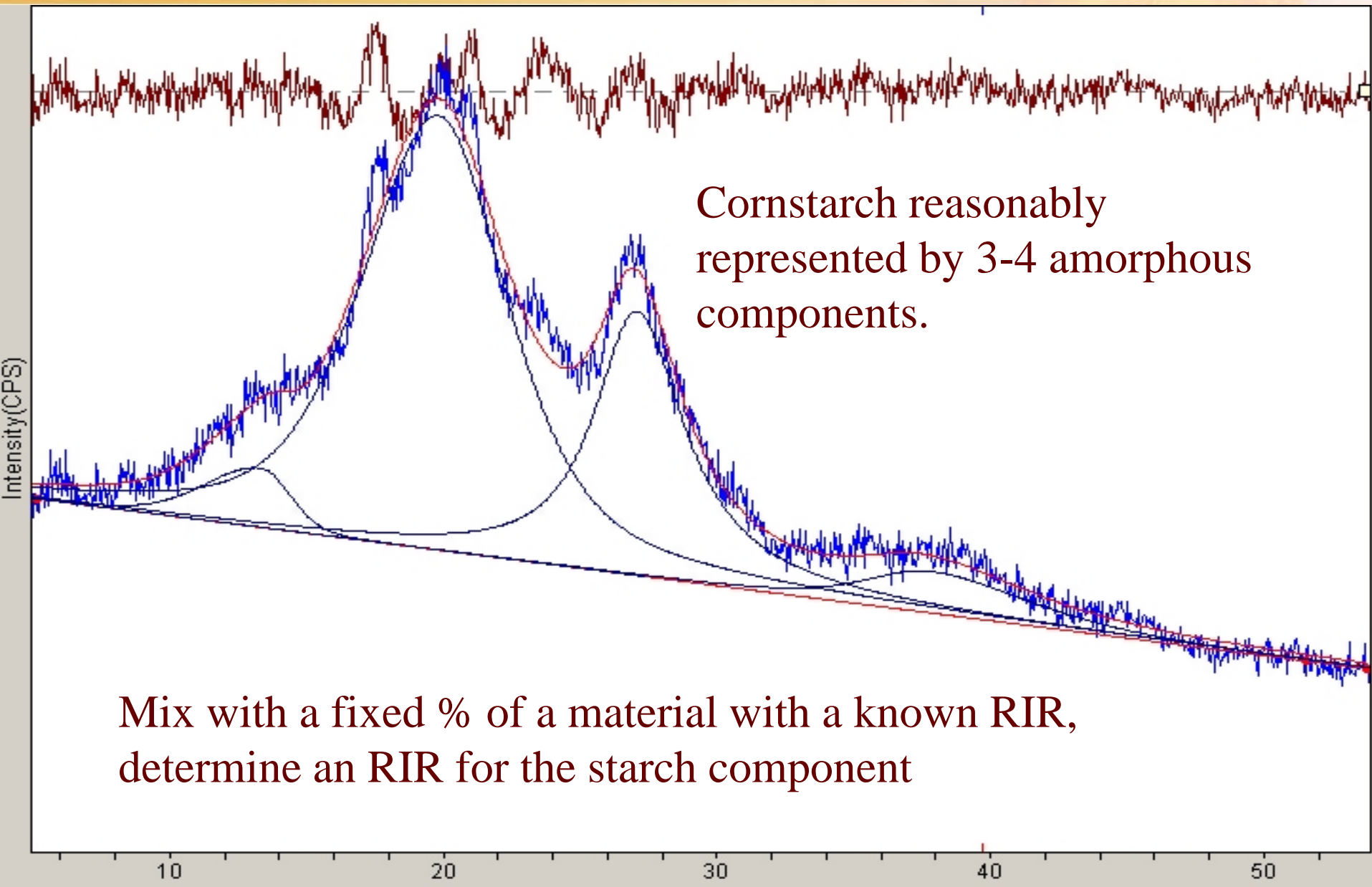


# Starch diffraction patterns



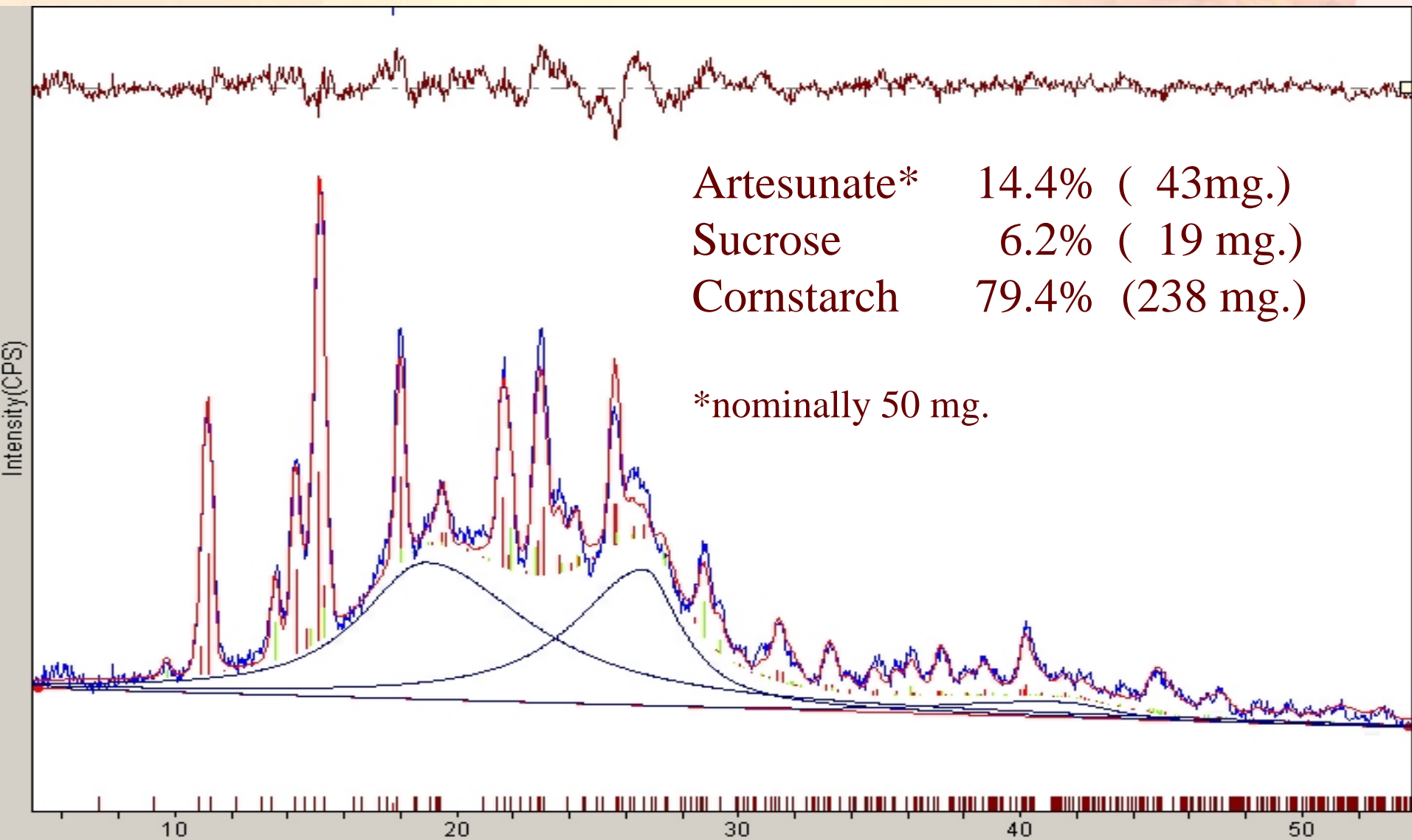


# Fitting of amorphous profiles to starch pattern





# Example quantification of Guilin tablet



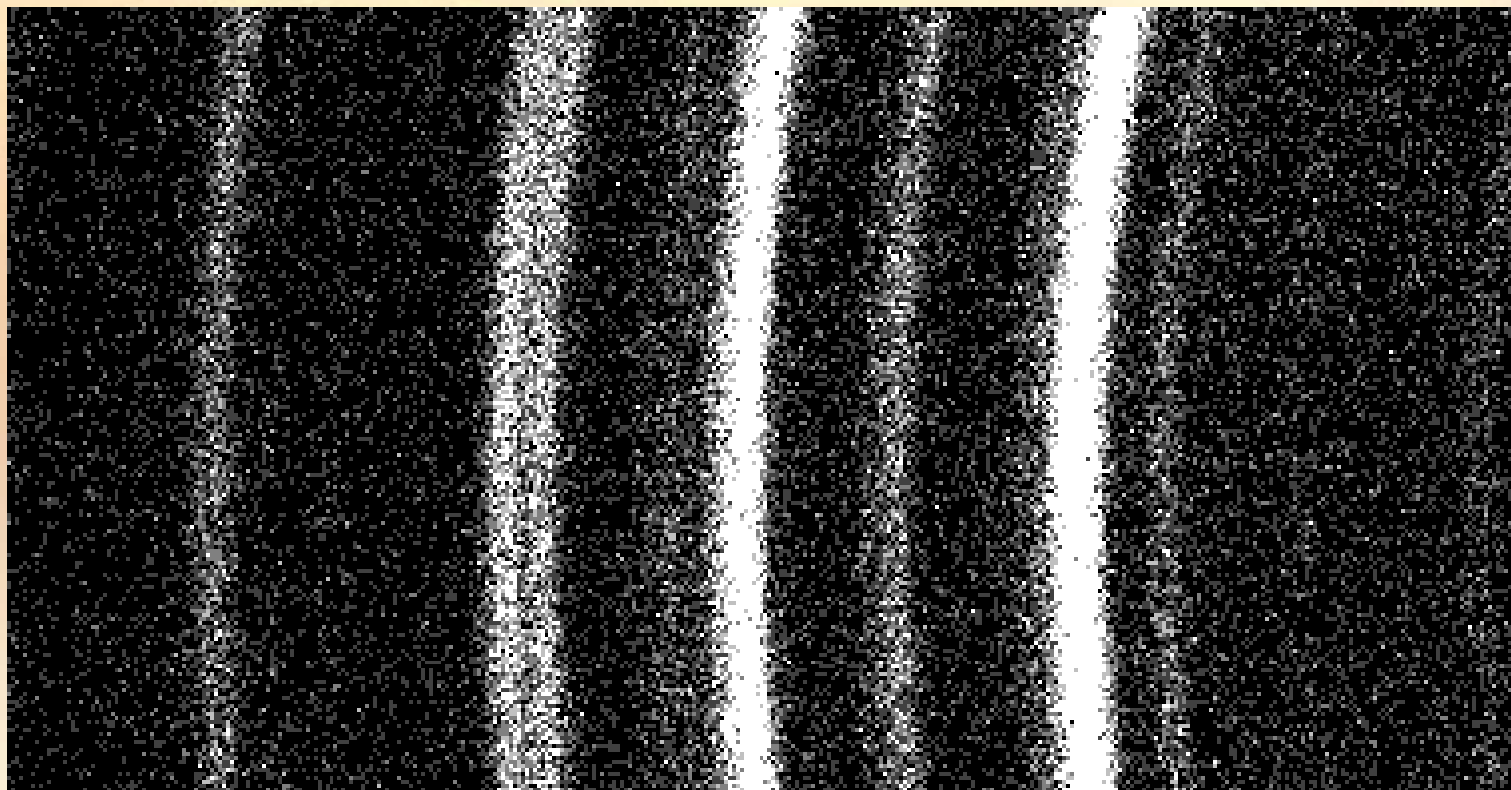
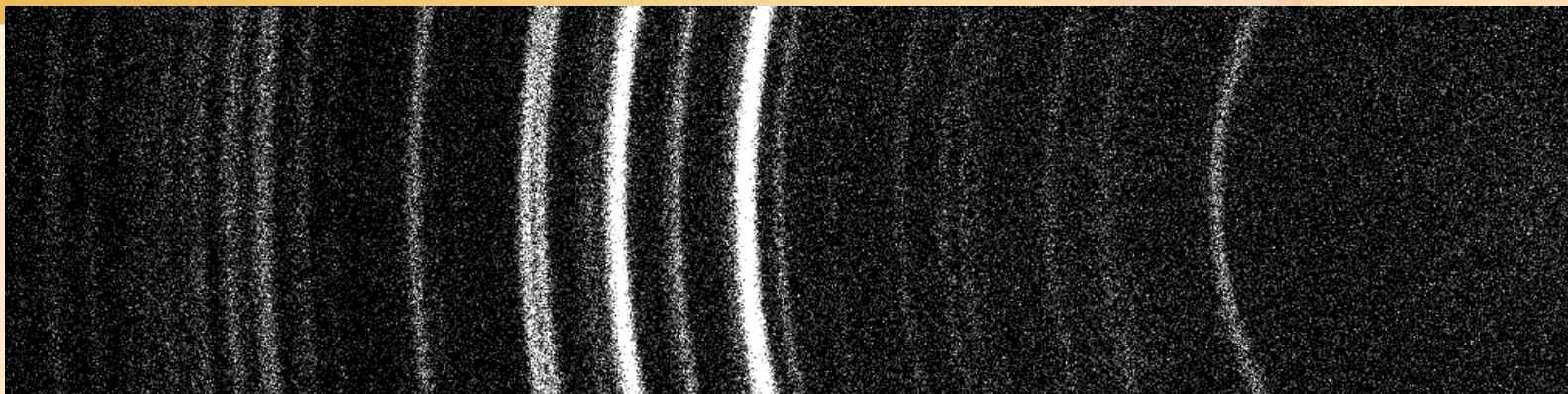
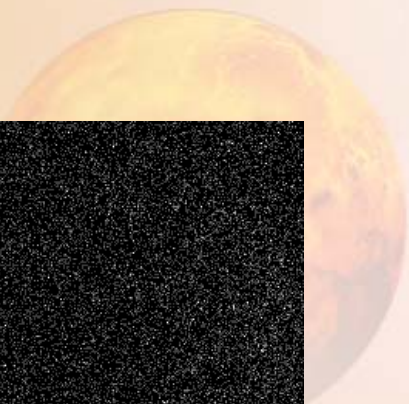


# Conclusions

*How can field-portable XRD help to stop counterfeit drugs?*

*“fingerprinting of fakes” can be done by point-and-shoot techniques (laser Raman) or simple colorimetric tests*

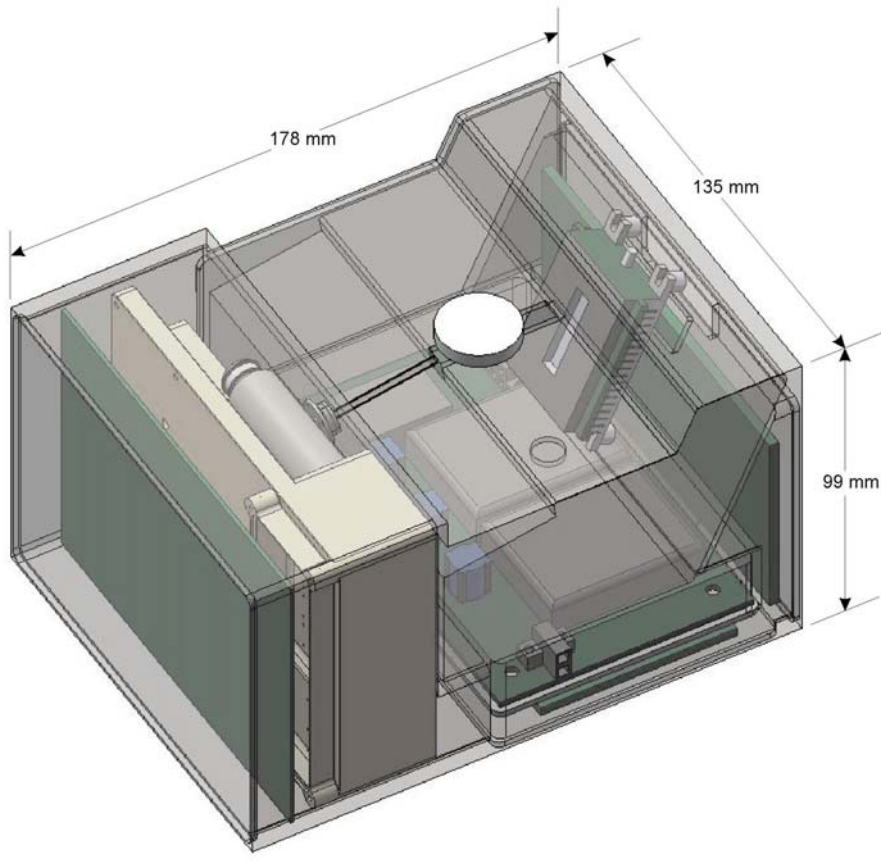
- \* **pXRD can quantify active ingredients***
- \* **pXRD can identify excipients in real and fake drugs***
- \* **Field-portable pXRD can be used to characterize fake drugs at remote locations and provide information leading to the source(s) of the fakes. These analyses can be performed by trained laypersons without the infrastructure of a normal XRD lab.***



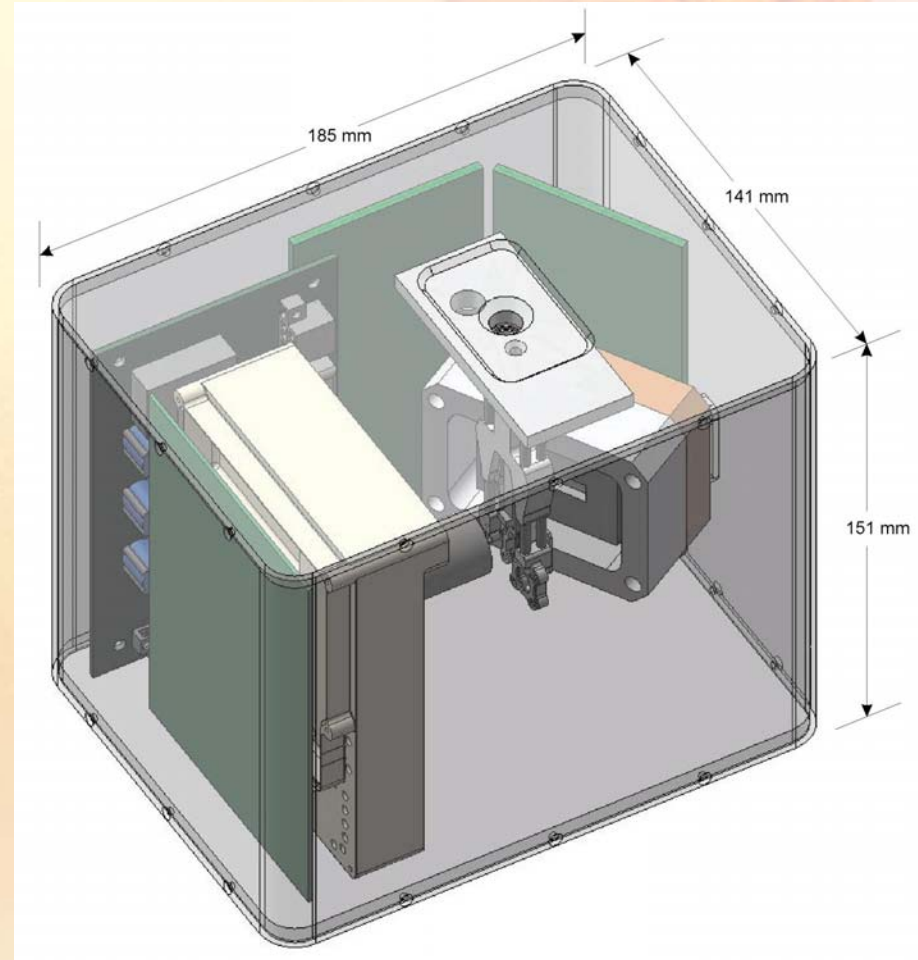




# Next-generation Lunar CheMin instrument



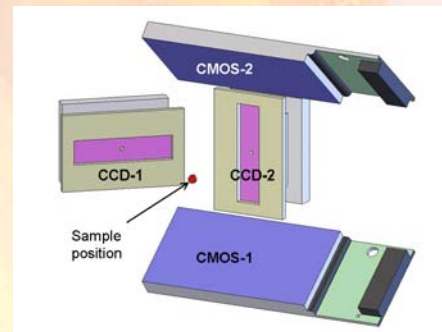
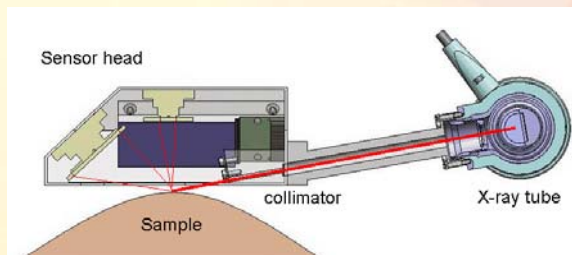
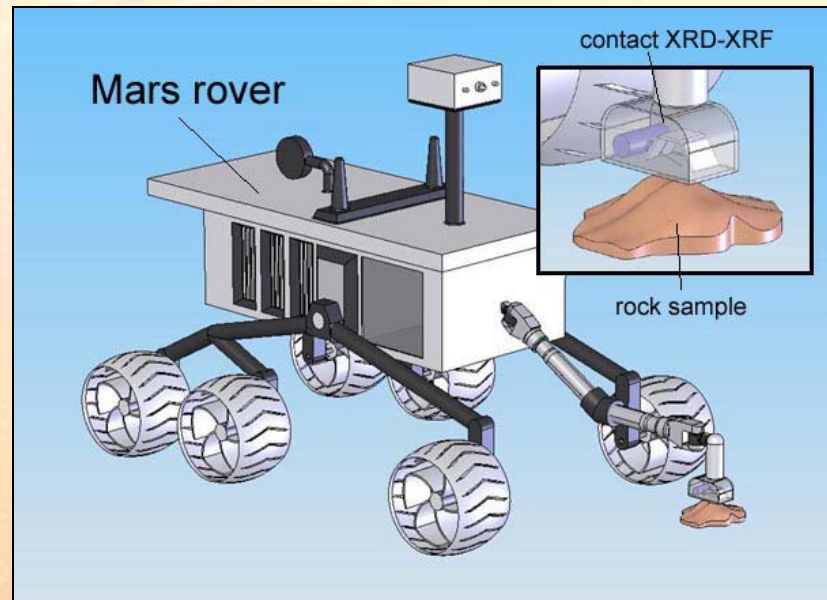
Lunar reflection geometry instrument, ~4 kg, 178 X 135 X 99 mm (7" X 5.3" X 4")



Lunar transmission geometry instrument, ~4 kg, 185 X 141 X 151 mm (7.25" X 5.5" X 6")



# Prototype Mars mid-rover instrument



## Combined pXRD single crystal Laue instrument

