

Deep UV Raman & Fluorescence Spectroscopy for In Situ Process Analysis

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Outline

- ❑ Detection goals & methods for RCV and real-time continuous manufacturing
- ❑ Advantages of deep UV Raman & fluorescence detection
- ❑ Detection examples for pharma products
- ❑ Deep UV Raman & fluorescence instruments
- ❑ Chemical printer for NIST traceable chemical concentration calibration



Quality Control in Continuous Manufacturing

The goal

Provide instrumentation for real-time detection of the key ingredients during continuous flow manufacturing

The solution

A miniature deep UV Raman instrument that avoids fluorescence interference or obscuration and provides a high level of sensitivity and specificity for the ingredients



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Rapid Cleaning Verification

The goal

To augment or replace the present swab & test method for equipment cleaning verification with a faster and better controlled and documented method.

The solution

A handheld device that quantifies trace amounts of API in real time on manufacturing surfaces.

Result: Significantly reducing production down time.



Advantages of deep UV Raman & fluorescence detection



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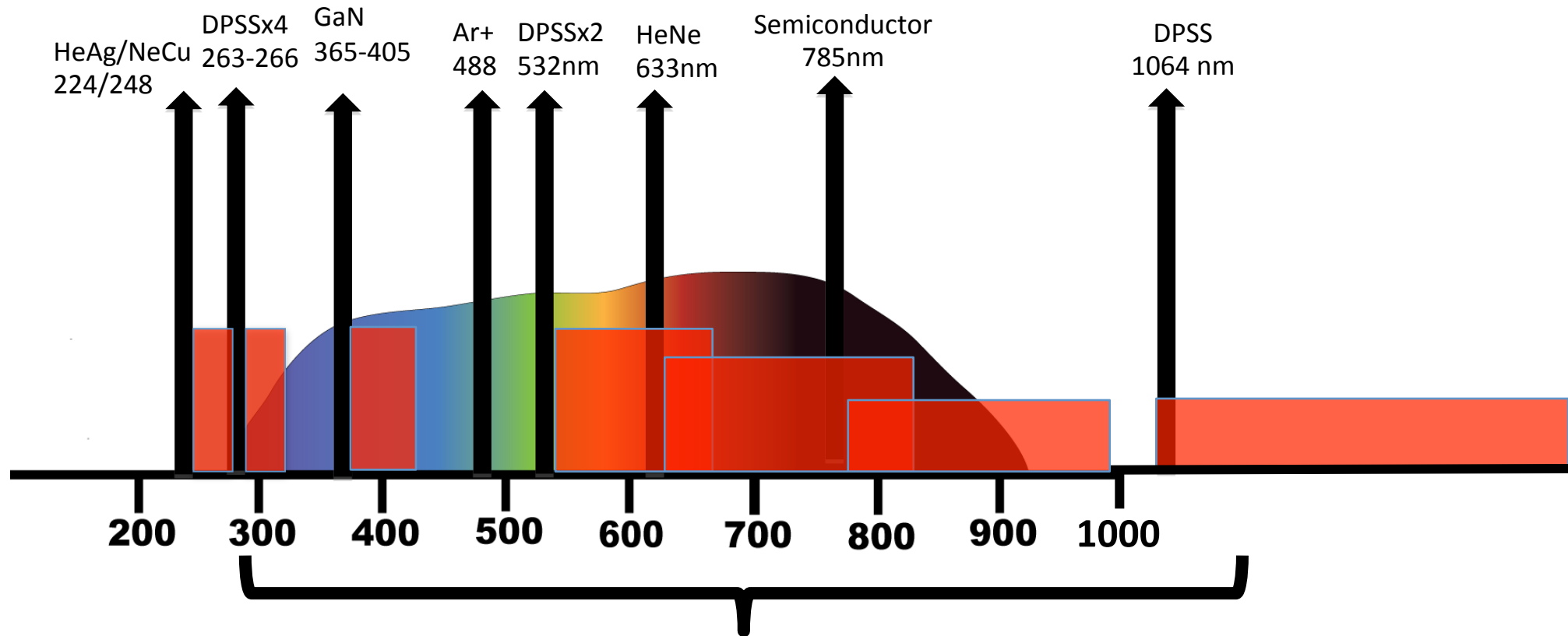
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Advantages of Deep UV Detection vs Visible or IR?

- ❑ Non-contact, reagentless, no sample handling or preparation
- ❑ Excitation below 250 nm separates Raman & fluorescence spectral regions to enable
 - ✓ Clear Raman spectra with no obscuration or alteration by native fluorescence
 - ✓ No alteration of the fluorescence spectra by major Raman bands
 - ✓ The ability to simultaneously detect Raman and native fluorescence
- ❑ Much higher Raman sensitivity due to Rayleigh law and resonance Raman enhancement effects
- ❑ Fluorescence detection alone has much higher specificity when excitation is below 250 nm
- ❑ Detection of concentration of pharma materials in the low ng/cm² has been demonstrated
- ❑ Detection is solar blind, enabling detection in full daylight without interferences

Why Deep UV below 250nm?

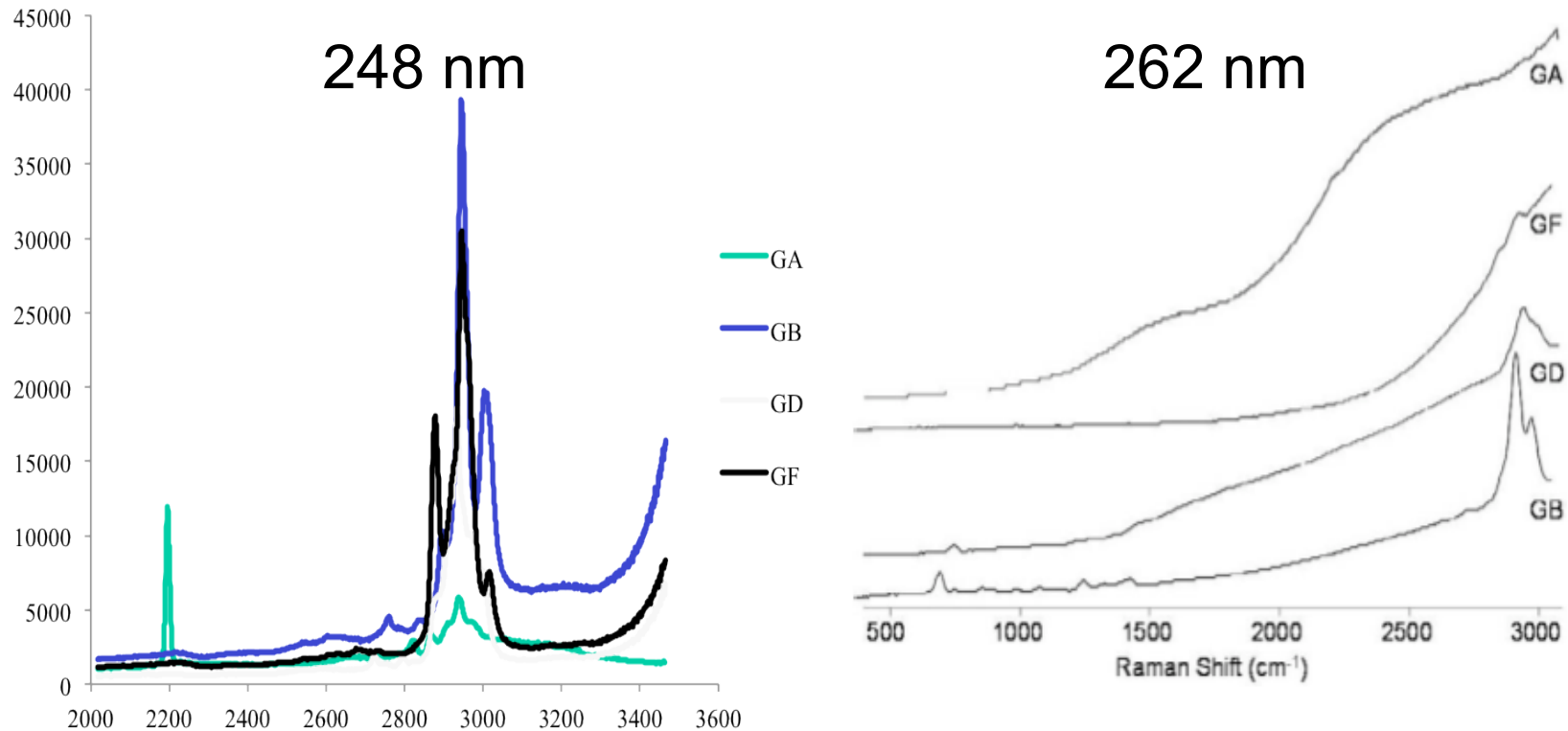
When excitation < 250nm Raman and fluorescence spectral regions are separated



Sensitivity to Excitation Wavelength

Raman Spectra with Excitation at 248 nm versus 262 nm

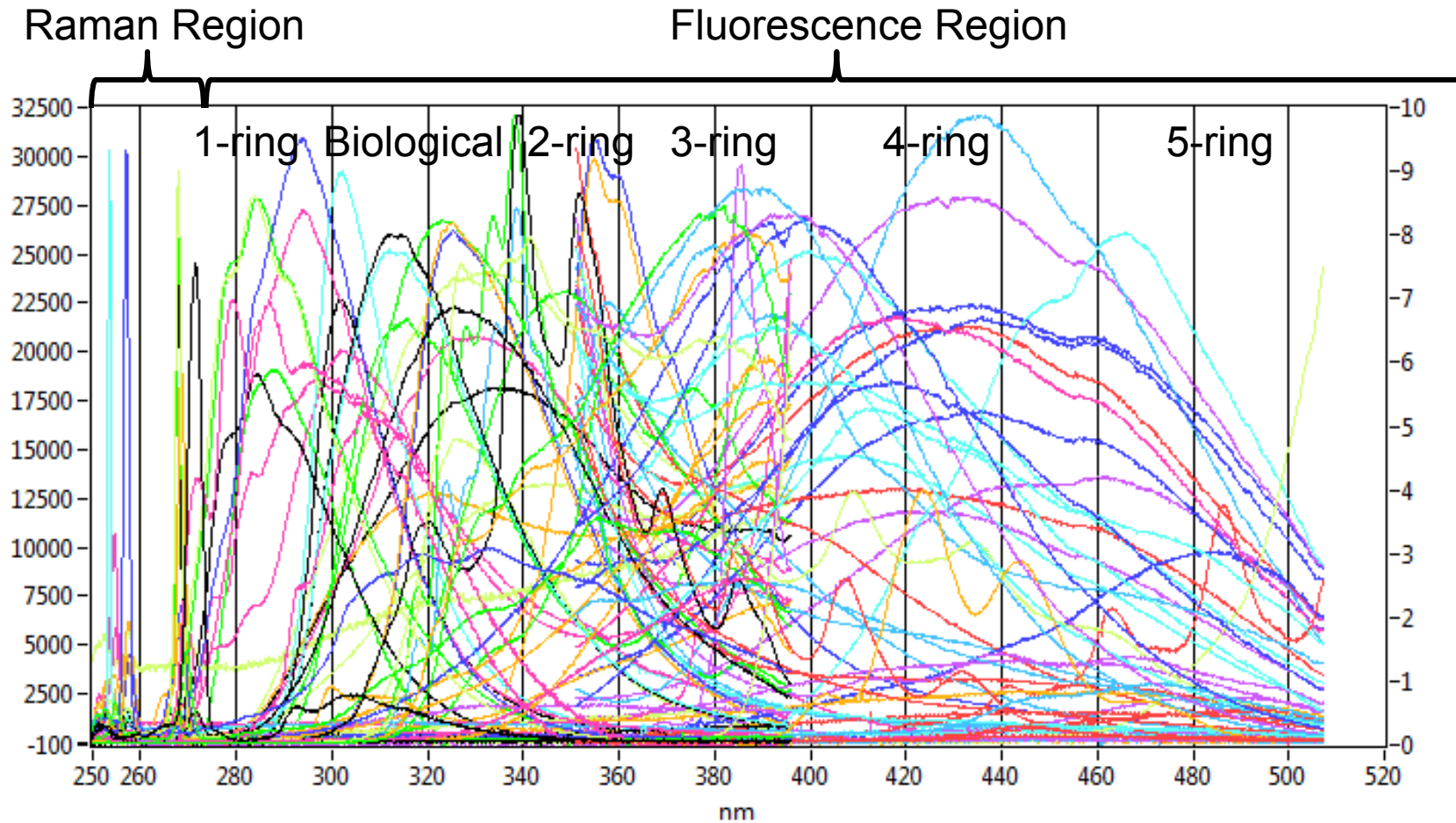
(Example is G Agents)



Adapted from Christesen, SD et al. *Appl Spec.* 2008 Oct; 62(10):1078-83

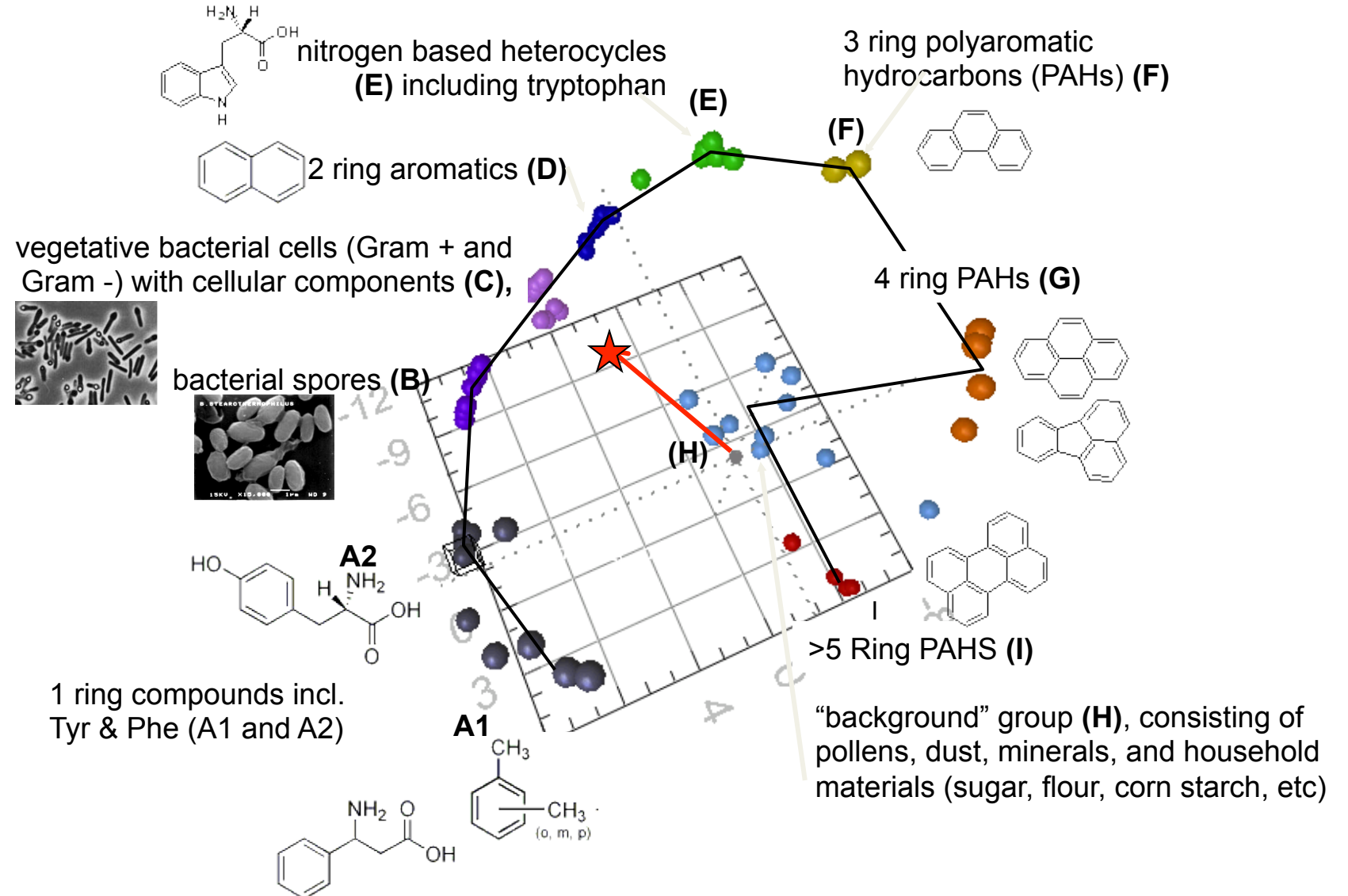
Deep UV Fluorescence Spectra of 52 Compounds

with no baseline subtraction or compensation, Ex=248 nm



Chemical Differentiability Using Deep UV Excited Fluorescence Alone

A single deep UV laser pulse determines the location of an unknown substance in this chemometric space



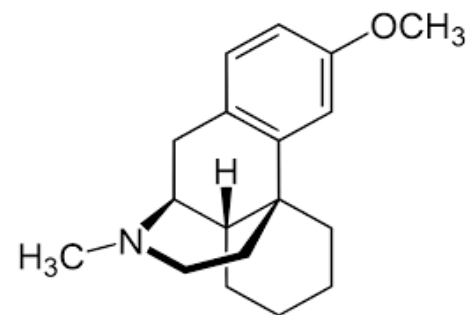
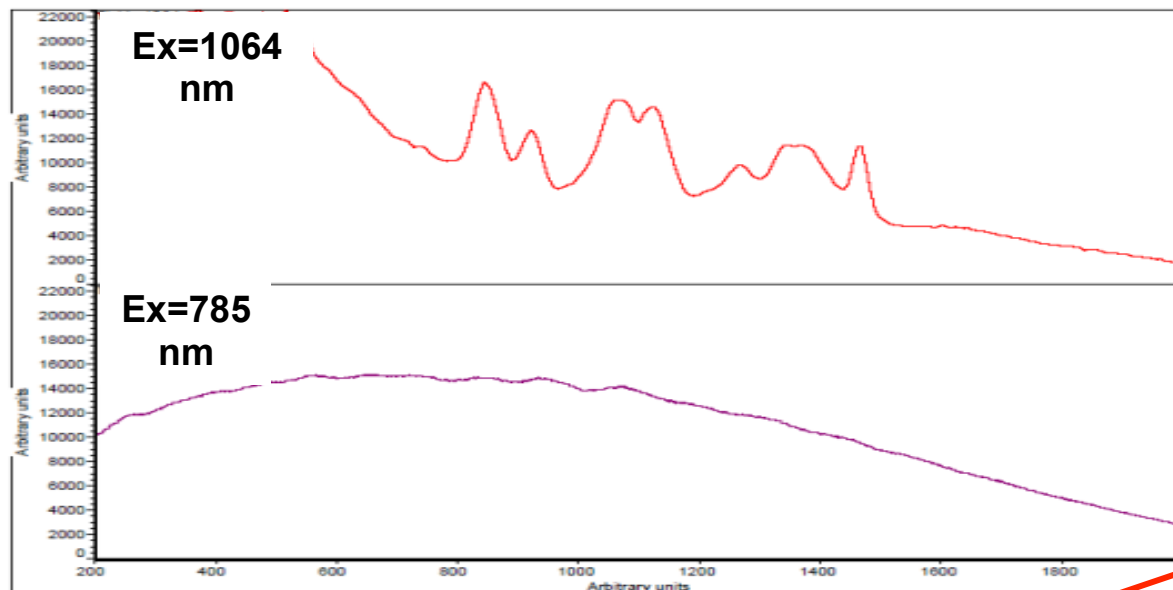
Combining the Sensitivity of Fluorescence & specificity of Raman

- Fluorescence is the most sensitive method of detection, over 10^6 to 10^8 times more sensitive than Raman, providing longer standoff distances and/or detection at lower concentrations
- Raman provides information about chemical bonds and functional groups, including those that do not fluoresce (aliphatics and simple compounds)
- Fluorescence data provides information about the overall electronic structure of target & substrate components (aromatics, ketones, aldehydes)

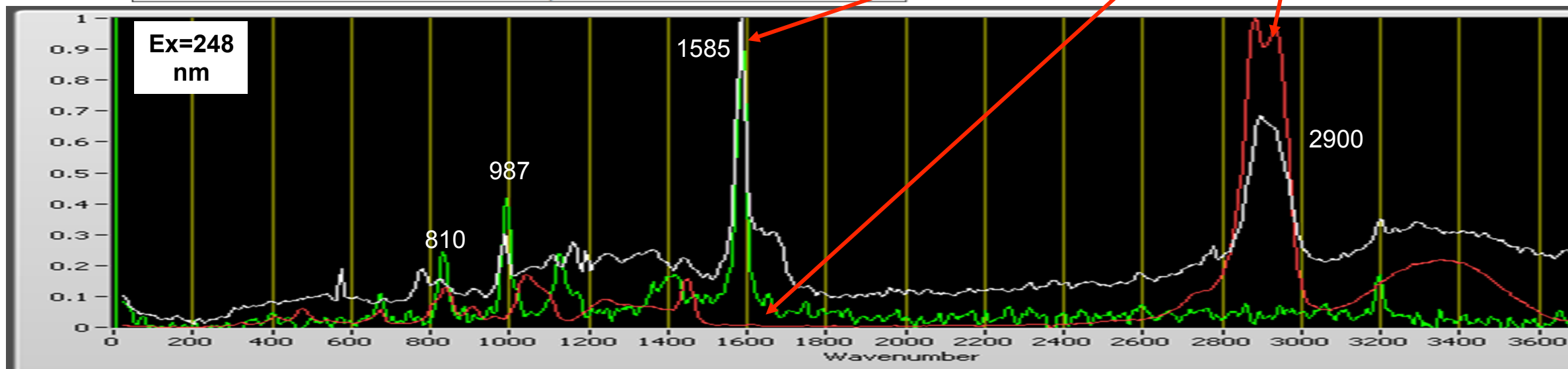
Raman Active		Weak Fluorescence		Strong Fluorescence	
Water	HMX	TDG	DMMP	C4	Microbes
Amino Acids	PETN	DIMP	TEPO	Semtex	Toxins/Proteins
Alcohols	RDX	Ammonia Nitrate		ANFOs	Narcotics
Aliphatics		Urea Nitrate			
DNA/RNA	TNT	Nitroglycerin		Aromatic Amino Acids	
Lipids	Perchlorates	Ketones/Aldehydes		PETN	VOCs

Detection Examples for Pharm Products

OTC Benylin: dextromethorphan hydrobromide



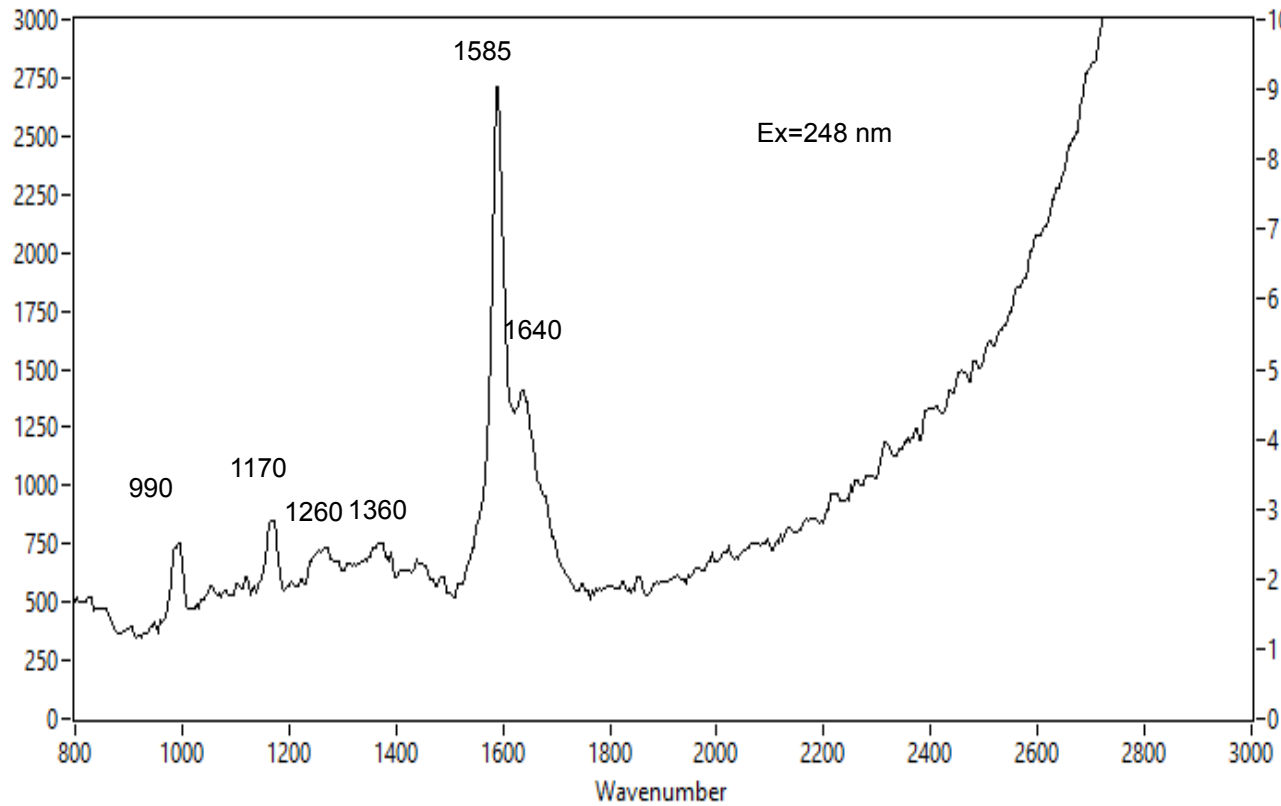
Benylin (white)
Sodium benzoate (green)
Glycerol (red)



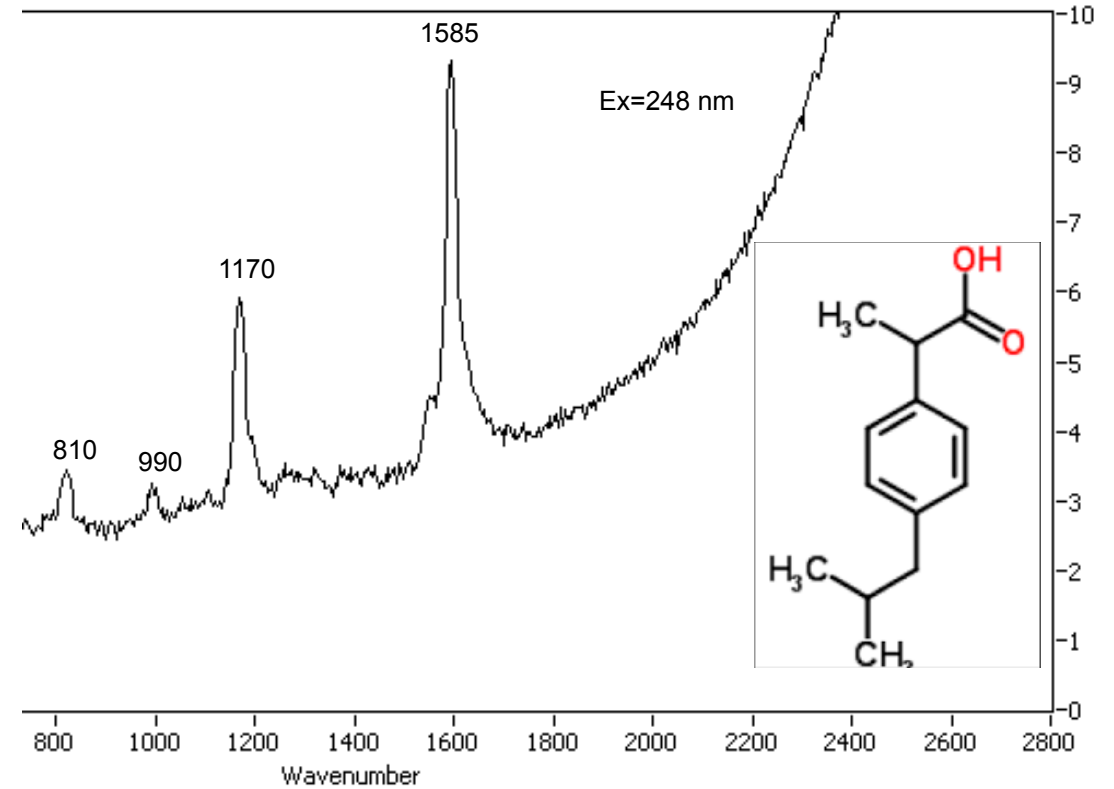
OTC Children's Motrin (ibuprofen)–Bubblegum Flavor

Ex = 248 nm

Children's Motrin-Bubblegum flavor

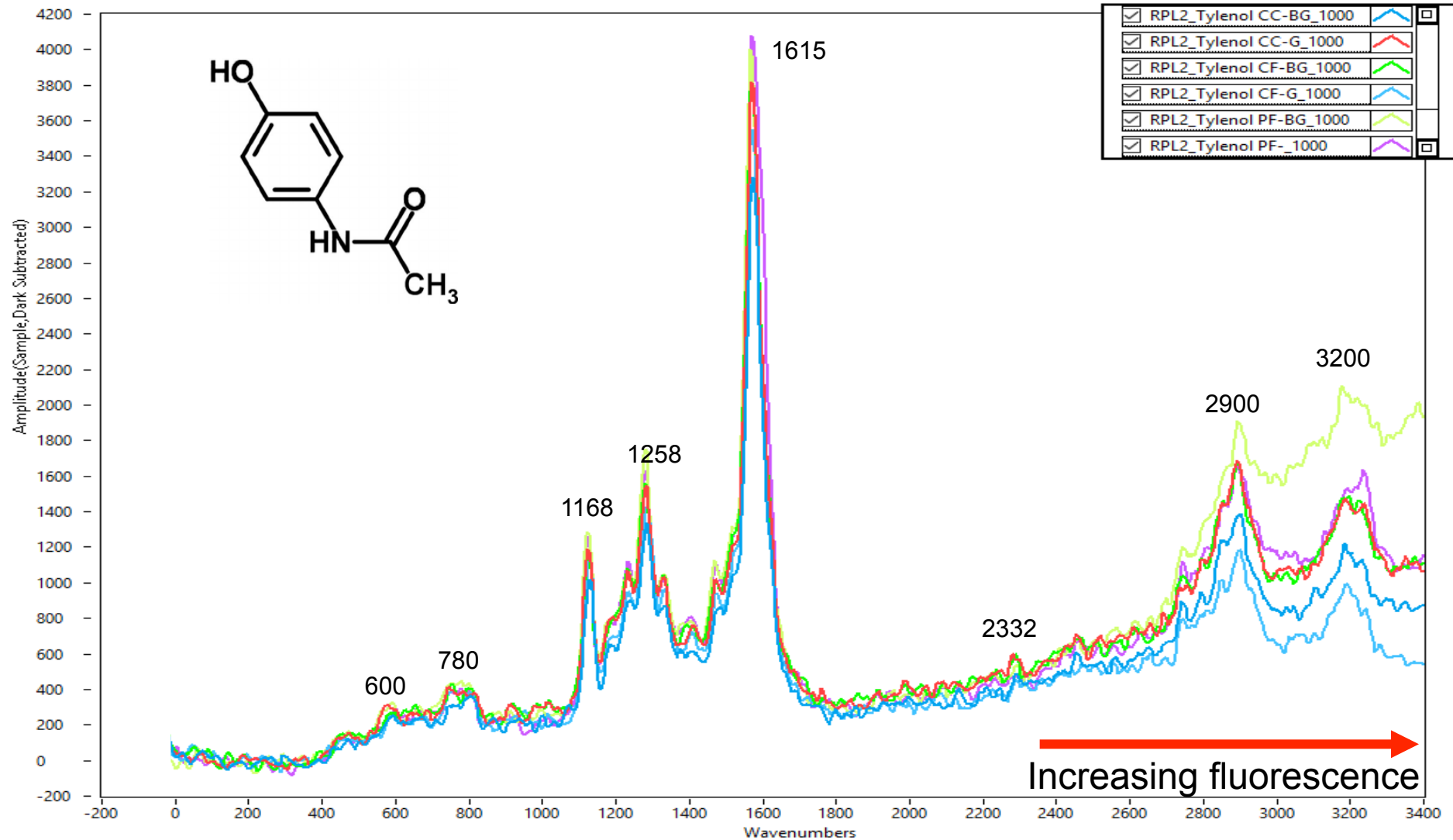


Pure Ibuprofen



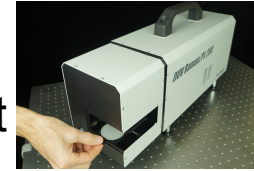
OTC Children's Tylenol (acetaminophen) w Various Flavors

Ex = 248.6 nm Raw results. No baseline compensation.



Deep UV Raman & Fluorescence Instruments

- ❑ **Raman PL 200:** Fully self-contained deep UV Raman & fluorescence instrument



- ❑ **TraC:** Handheld trace surface contamination detector for RCV



- ❑ **STANDOFF 200:** Fully self contained, handheld standoff chemical & biological sensor

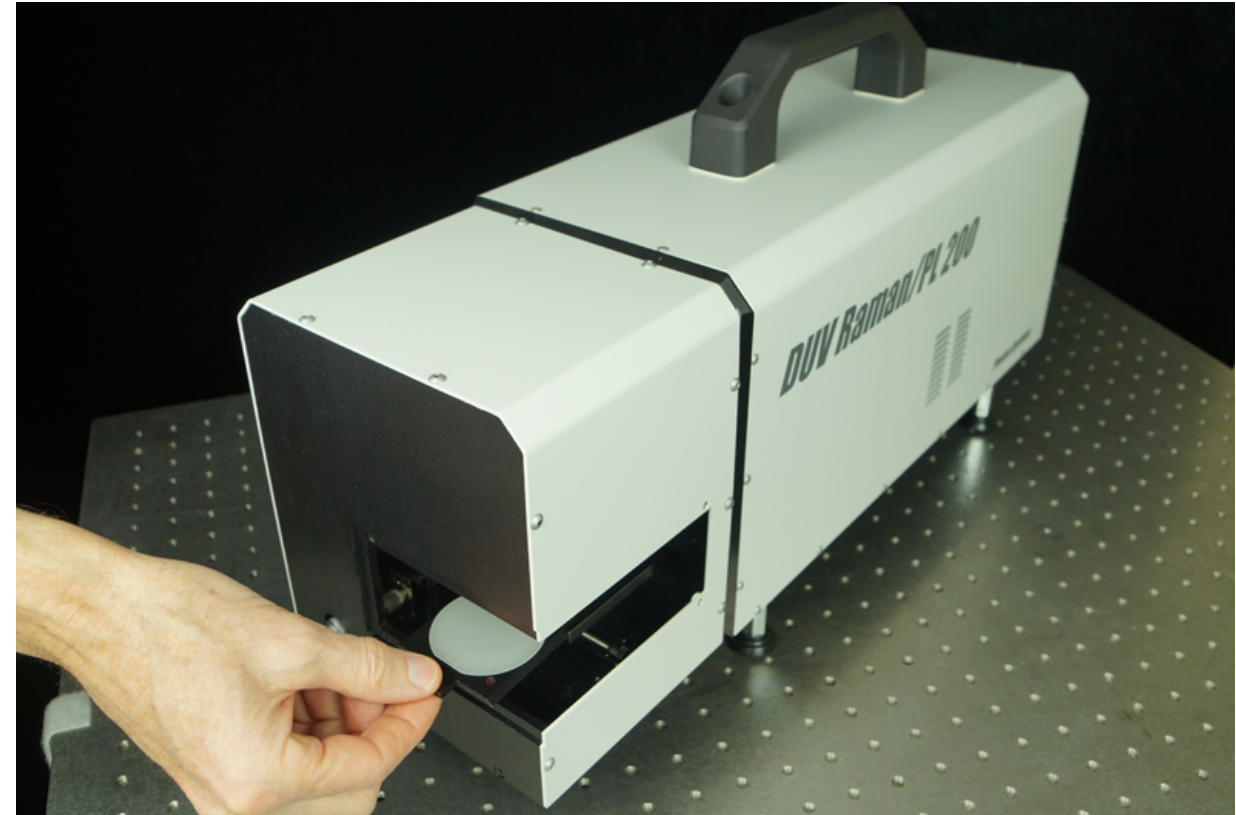
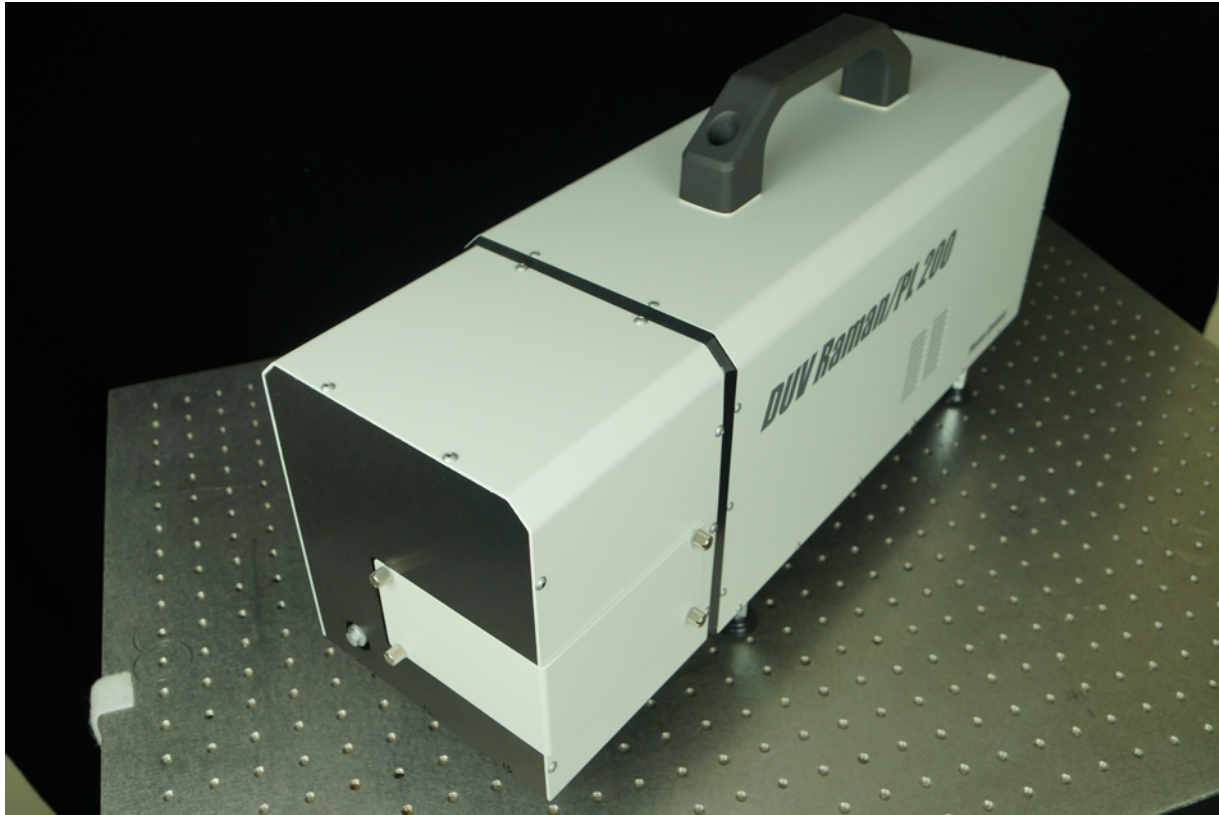


- ❑ **ChemCal:** NIST traceable chemical printer & calibration instrument for surface detectors



Deep UV Raman PL 200

with manual or computer-controlled stage or liquid flow cell



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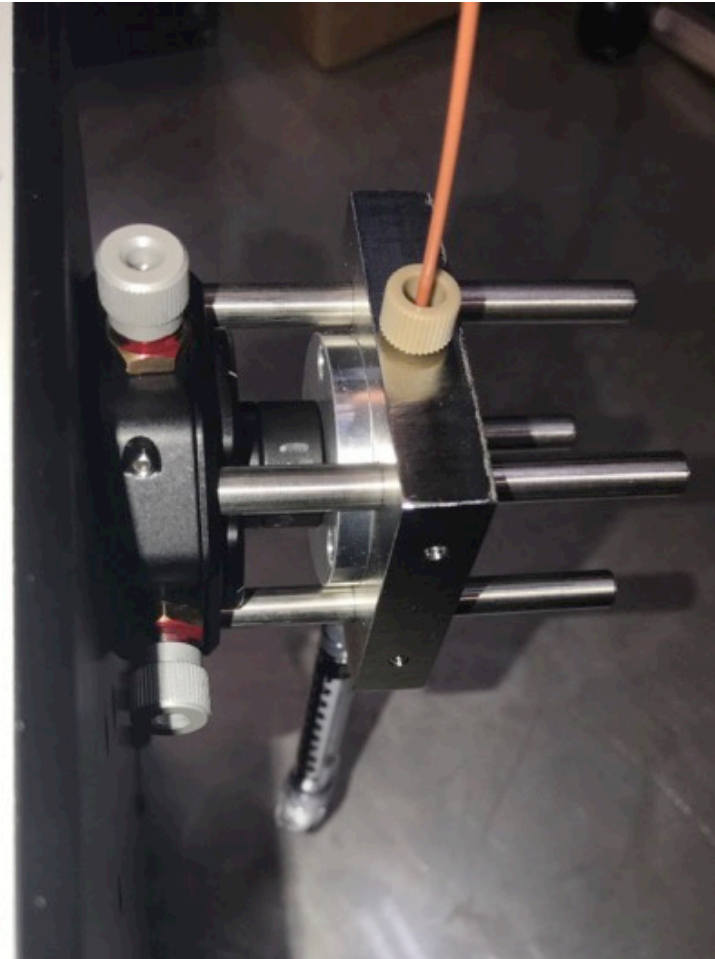
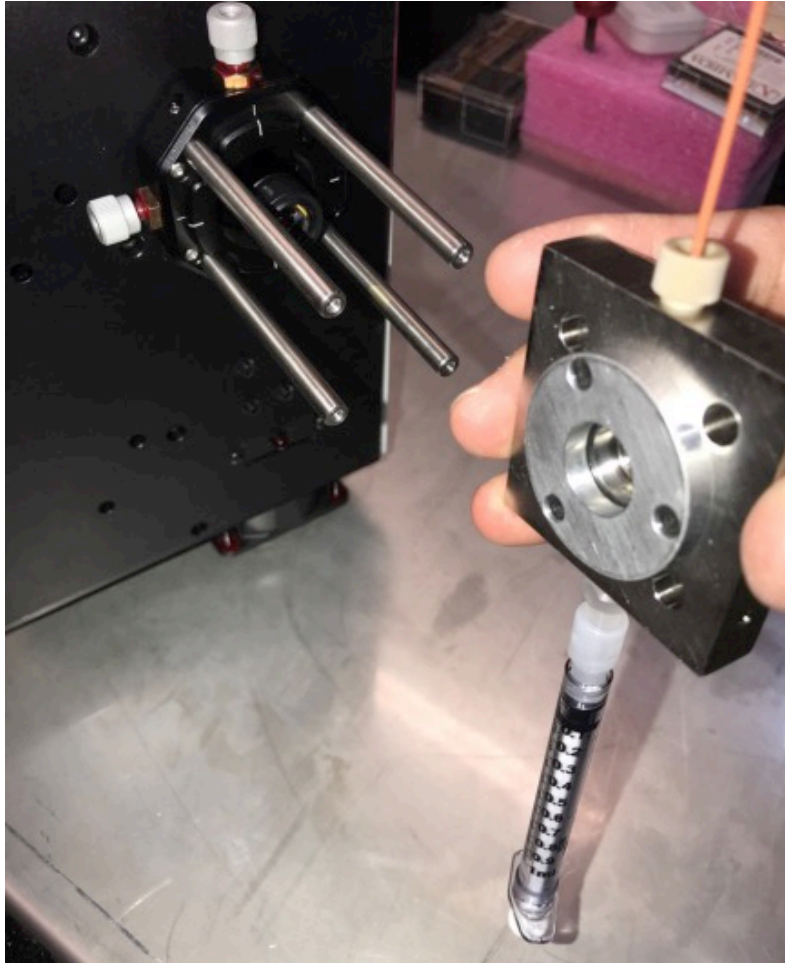
Features of the Deep UV Raman PL 200

- ❑ A deep UV Raman and fluorescence spectrometer
- ❑ With either computer-controlled stage for mapping or liquid flow cell for continuous manufacturing quality control
- ❑ Intended for OEM applications with dramatically smaller SWAP/C than other deep UV instruments on the market
- ❑ Avoids fluorescence interference or obscuration of Raman spectra
- ❑ Enables detection and quantification of Raman bands for a wide range of pharma ingredients not possible with 785 nm or 1064 nm Raman systems due to fluorescence
- ❑ SWAP: 18 x 20 x 42 cm, 10 kg, 60 W max (100-260VAC)



Raman PL 200

with various types of flow cells or cuvette holders



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Deep UV Trace Chemical (TraC) Sensor

LODs < 1 $\mu\text{g}/\text{cm}^2$ Wt. 1.5 lbs



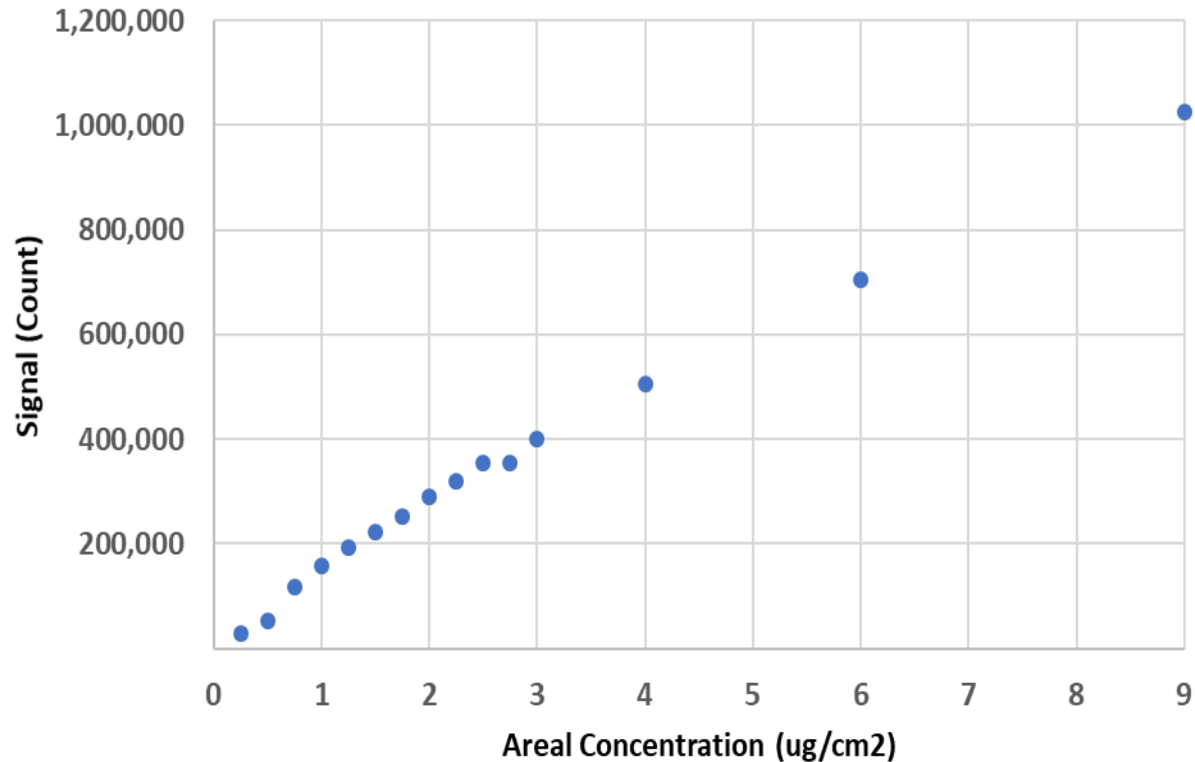
Features of Deep UV TraC RCV Sensor

- ❑ Fully self-contained RCV sensor with embedded microprocessor for instrument control, data processing, real-time data storage, and display
- ❑ Able to measure trace concentrations on curved surfaces, corners, crevices, screens, grates
- ❑ Sample rate > 10 samples/s with time-stamped real-time recording
- ❑ Hi sensitivity: able to detect concentrations of APIs < 1 $\mu\text{g}/\text{cm}^2$
- ❑ Large working distance: 0 to 2 cm
- ❑ Sampling area: 0.25 cm^2
- ❑ Non-contact sensing with large working distance (0 to 2 cm)
- ❑ Hand-Held: < 0.7 kg (1.5 lbs)
- ❑ Small: 7.6 x 8.9 x 19 cm
- ❑ Long battery lifetime: > 40 hours full power; > 120 hours standby
- ❑ Startup time < 10 s
- ❑ GMP & Intrinsically safe

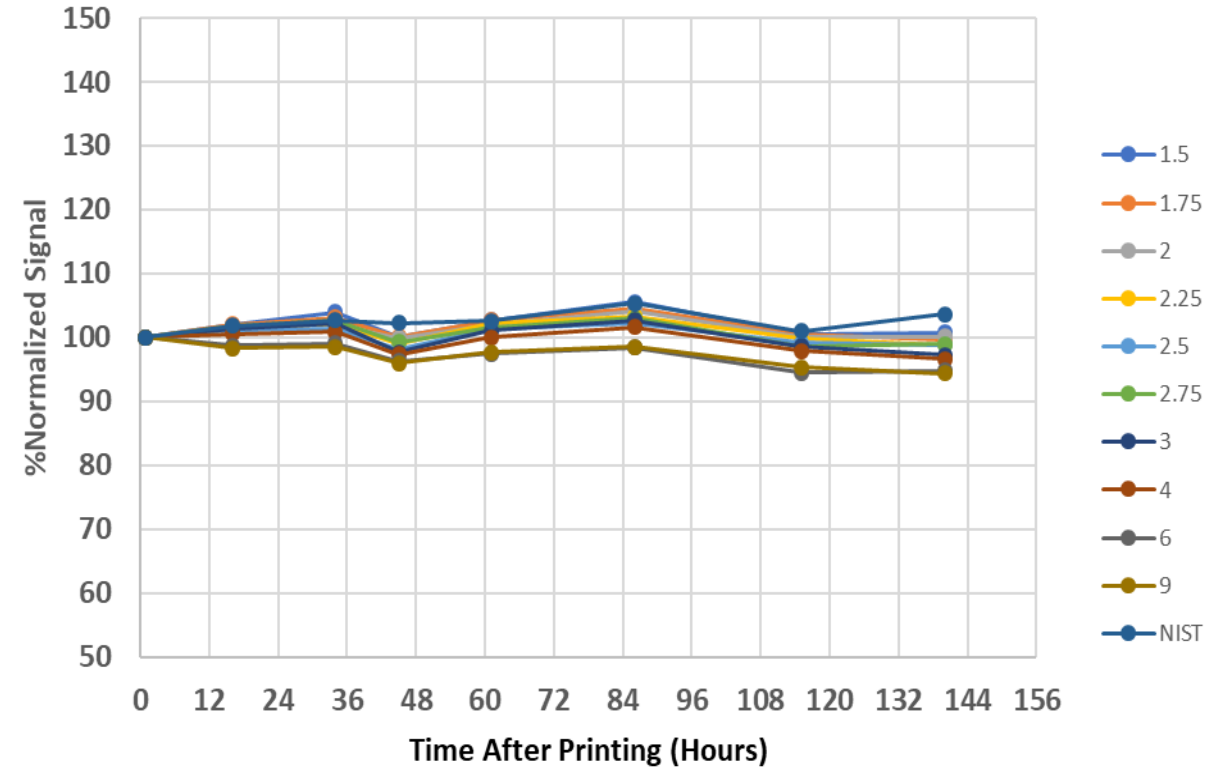


Typical Concentration Calibration Curve & Time Stability

Ibuprofen Chemical Concentration Calibration



Ibuprofen Signal Time Study



STANDOFF 200 CB Surface Analyzer



Features

Fully integrated deep UV Raman & fluorescence surface detection analyzer

Single handed operation: 4-button plus trigger control

Warm-up: < 10s from cold start, 3 s from standby mode

Built-in-test: full functional test of all components on startup

Spectral Calibration: Auto-calibrated on analyzer startup

Two Coaxial Context Cameras: 75° wide angle image, 20mm micro image around laser spot

Autofocused Standoff: 0.6 m to 5+ m

Materials Detected: Chemical and Biological

CBE Libraries: Built in unclassified library +SD card libraries

Standoff Distance: 0.5 m to 5+ m in full daylight conditions

Spectral Range: **Raman:** 250 cm^{-1} to 3500 cm^{-1}

Fluorescence: 270nm to 320nm

Context Info with Spectral Data: Date/time stamps, GPS, azimuth, distance and two contextual photos

Power Supply: User replaceable 24 V LiPO battery pack (UN/DOT 38.3 rated) or 24 V wall adapter

Communication: WiFi plus Wired USB 3.0

Weight: 12 pounds

Dimensions: 7" W x 11" H x 16" L

Ingress Protection: IP67

Robot compatible: ¼ -20 camera thread or dove-tail mount



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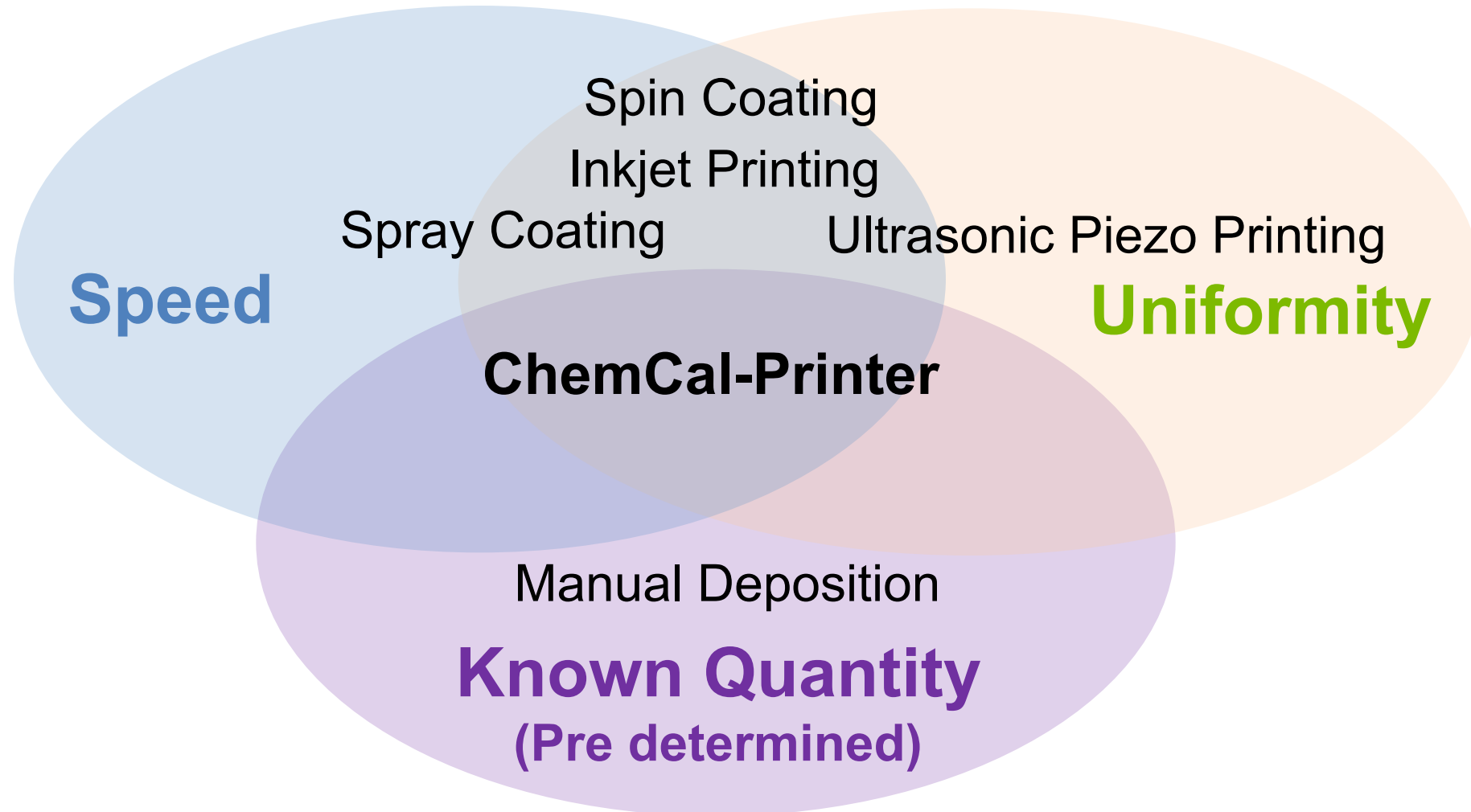
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Why do you need a chemical printer?

- ❑ Test/calibrate/validate future RCV tools using NIST traceable method
- ❑ Test/calibrate/validate CURRENT cleaning tools & methods
 - ✓ Create concentration curves for swabbing.
 - ✓ Test/train swabbing personnel with accurate areal concentrations.
 - ✓ Test recovery from various surfaces/topologies with different swabbing media.
- ❑ Create coupons for visual /hotspot detection of API.
 - ✓ Hotspot detection.
 - ✓ Train personnel on visual inspection limits.
- ❑ Perform all of these with single or multiple chemicals on a single coupon or coupons.
 - ✓ Detergent + API.
 - ✓ Excipient + API.
 - ✓ Detergent + API + Excipient.



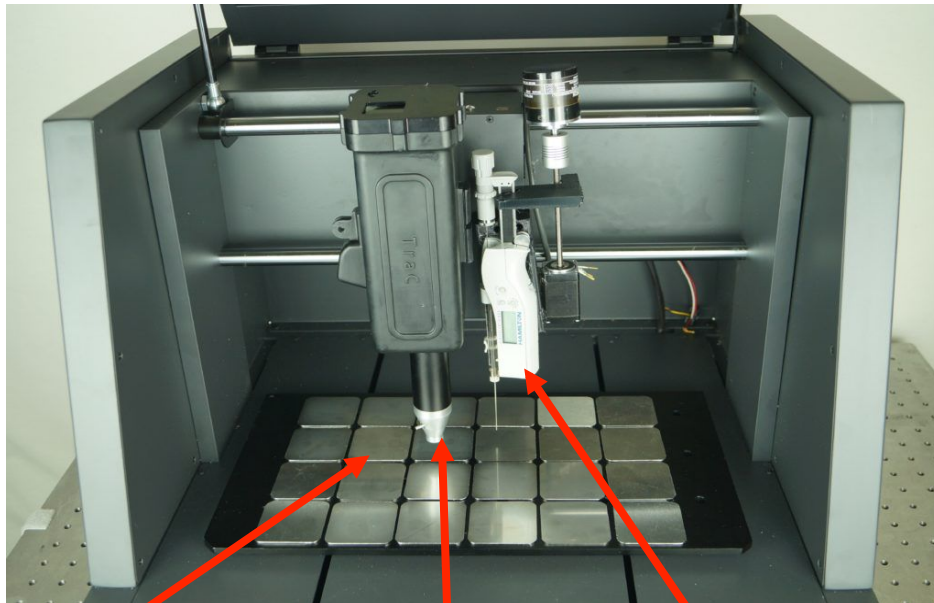
Chemical Calibration Printing



NIST Traceable Chemical Concentration Calibration

ChemCal: A chemical printer, mapper, & calibrator

- Creates up to 16 coupons with *a priori* known, NIST traceable, concentrations of many different chemicals, including APIs, detergents, excipients, etc. on Pharma-type surfaces or quartz crystal microbalance elements for the purpose of performing calibration of hand-held trace chemical sensors for rapid cleaning validation.
- Prints and detects on curved or flat surfaces, corners, grates, screens, etc.



Coupons

TraC sensor

ChemPrint head



Operational Scenario:

- ✓ Load APIs, etc in Eppendorf rack. Up to 21.
- ✓ Load coupons onto tray.
- ✓ Press Start.
- ✓ The system prints, scans, & outputs a full calibration curve in under 3 hours. (Prints and scans 16 coupons.)

Summary

- ❑ Several opportunities exist for pharma and other chemical manufacturing RCV and continuous flow manufacturing instrumentation using deep UV excitation below 250 nm.
- ❑ Excitation below 250 nm provides fluorescence-free Raman and Raman-free fluorescence detection simultaneously, enabling both modes of detection to provide more accurate information about a trace substance on a surface or in a liquid.
- ❑ Combined Raman & fluorescence detection method enhance both sensitivity and specificity in identifying unknown targets
- ❑ Detection of Raman & fluorescence in the deep UV can be accomplished using low energy lasers without major alteration or damage/ignition of targets.
- ❑ Surface detectors need a method of accurate chemical concentration calibration, common to all methods of surface detection. We call this instrument is called **ChemCal**.



Questions ?



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