Rapid Cleaning Verification & Quality Control Instrumentation for Pharma

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PMCT Knowledge Day
Advanced Technology Solutions in Pharmaceutical Manufacturing
Kemmy Business School
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August 29, 2019

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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

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.

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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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Advantages of deep UV
Raman & fluorescence detection

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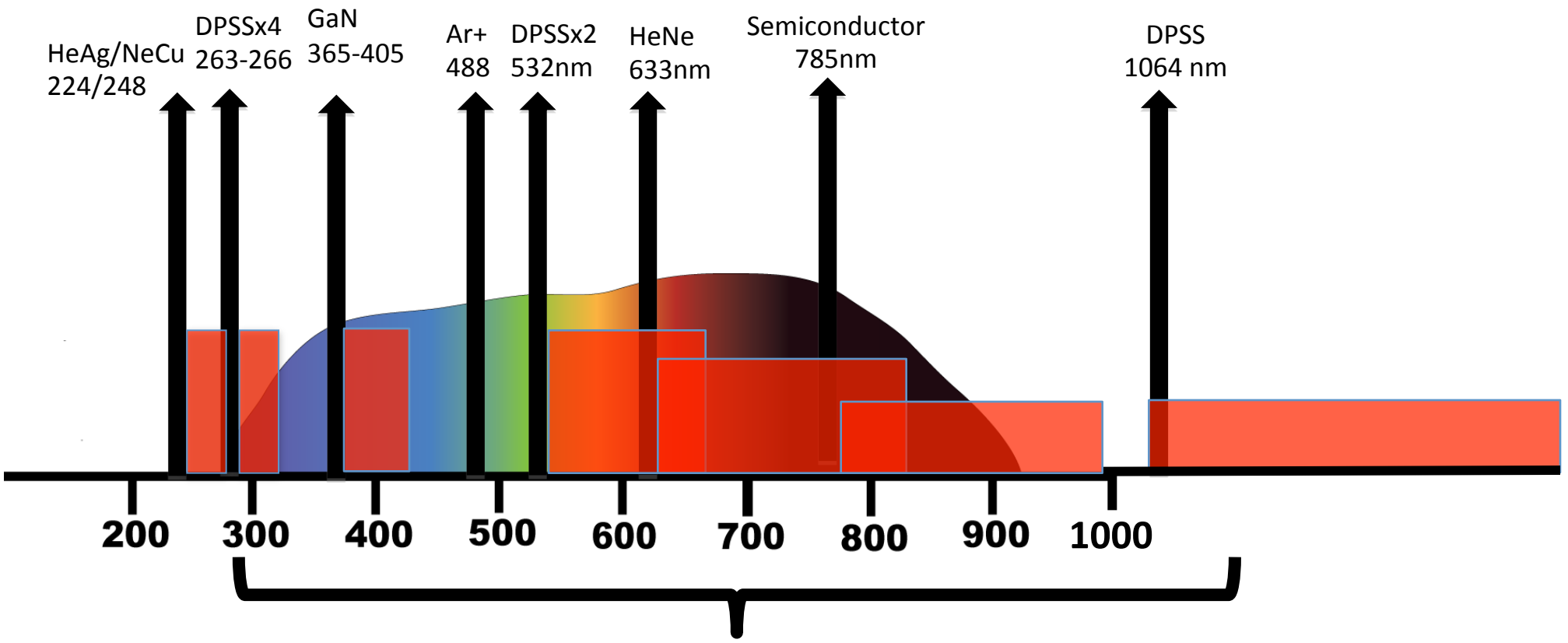
Advantages of Deep UV Detection vs Visible or IR?

- 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?

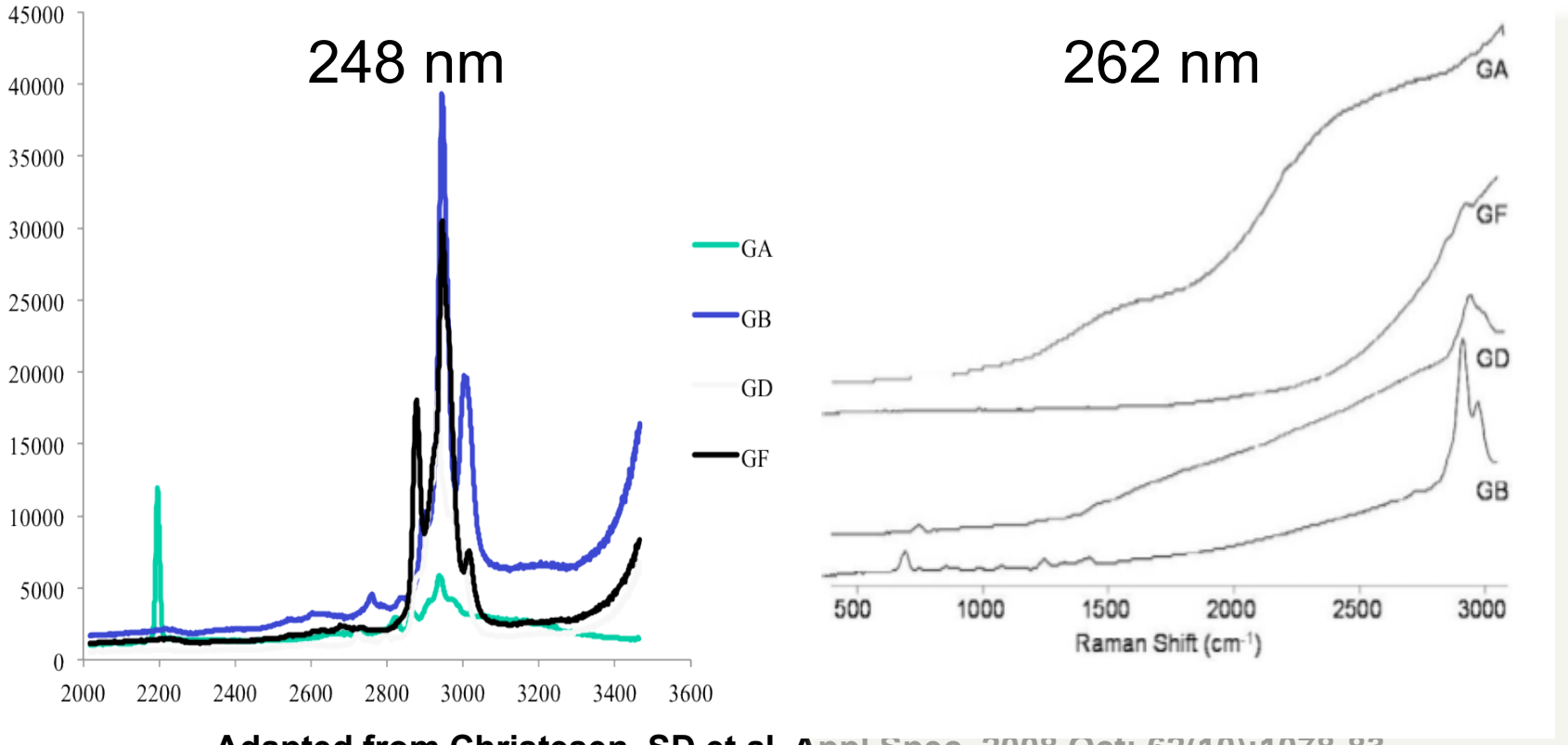
When excitation <250nm Raman and fluorescence spectral regions are separated



Sensitivity to Excitation Wavelength

Raman Spectra with Excitation at 248 nm versus 262 nm

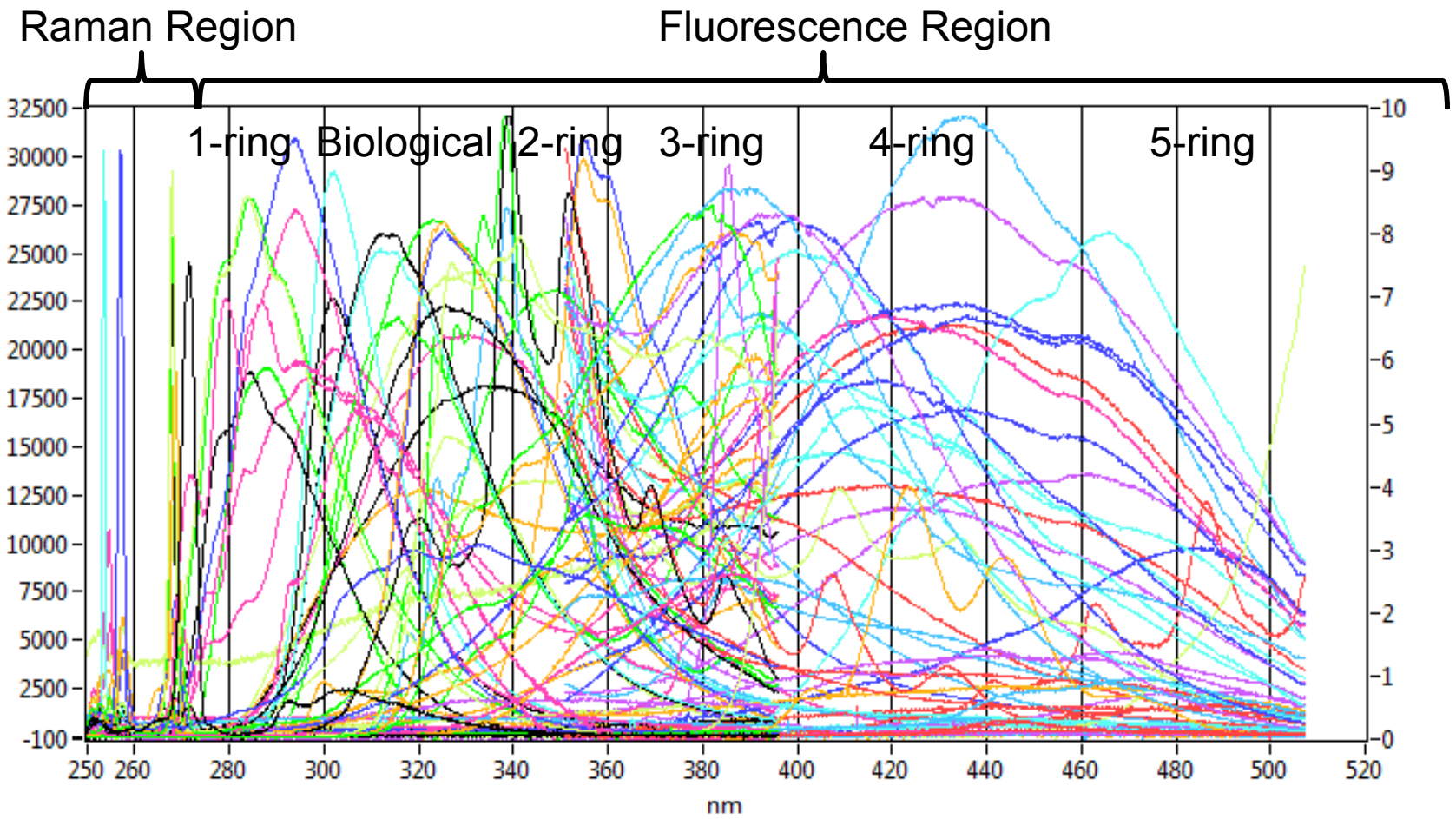
(Example is G Agents)



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

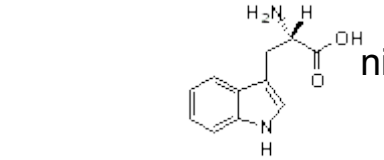
Deep UV Fluorescence Spectra of 52 Compounds

with no baseline subtraction or compensation, Ex=248 nm



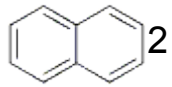
Chemical Differentiability Using Deep UV Excited Fluorescence Alone

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



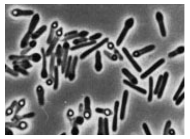
nitrogen based heterocycles **(E)** including tryptophan

3 ring polyaromatic hydrocarbons (PAHs) **(F)**



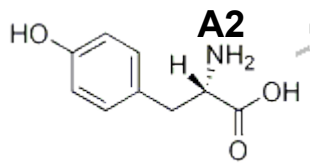
2 ring aromatics **(D)**

vegetative bacterial cells (Gram + and Gram -) with cellular components **(C),**



bacterial spores **(B)**

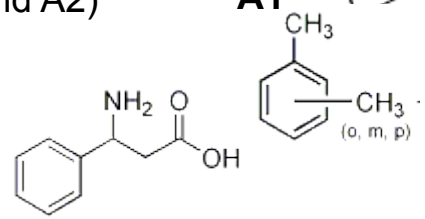
4 ring PAHs **(G)**



A2

1 ring compounds incl. Tyr & Phe (A1 and A2)

A1



(H)

>5 Ring PAHS **(I)**

"background" group **(H)**, consisting of pollens, dust, minerals, and household materials (sugar, flour, corn starch, etc)

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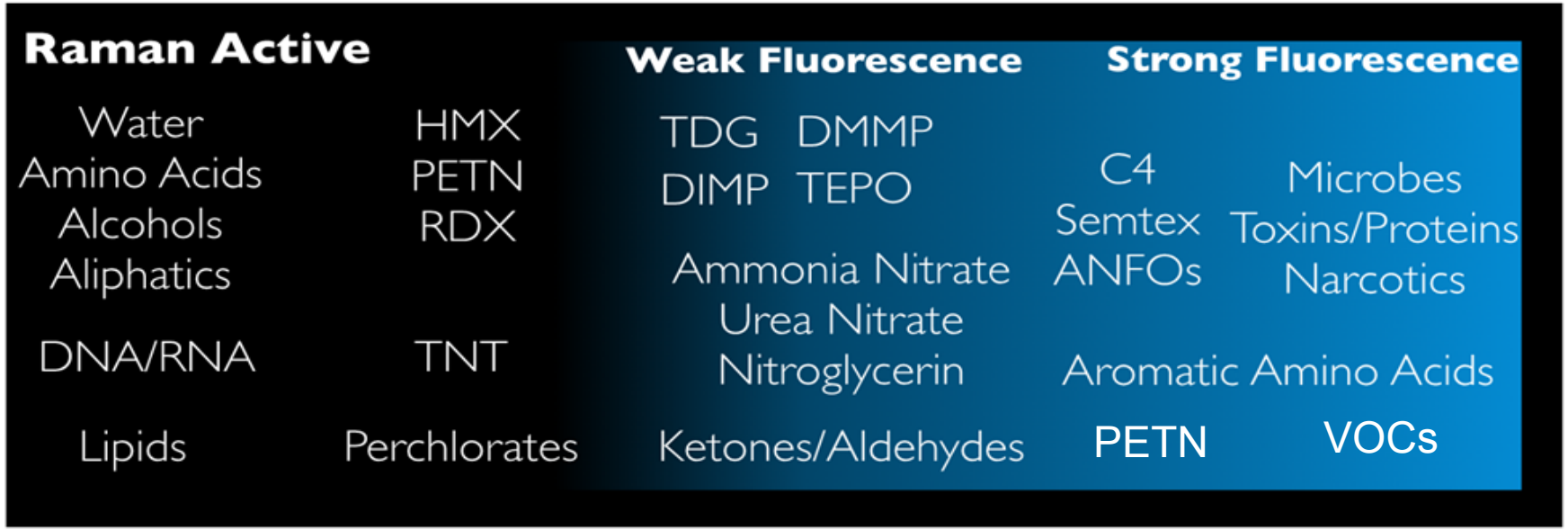
Combining the Sensitivity of Fluorescence & specificity of Raman

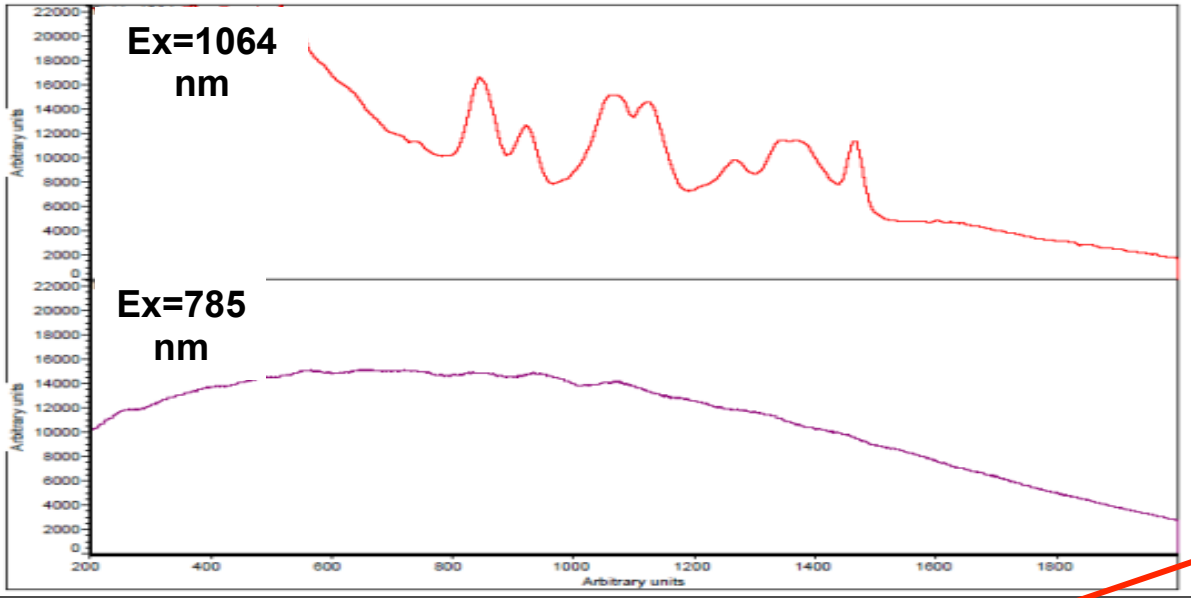


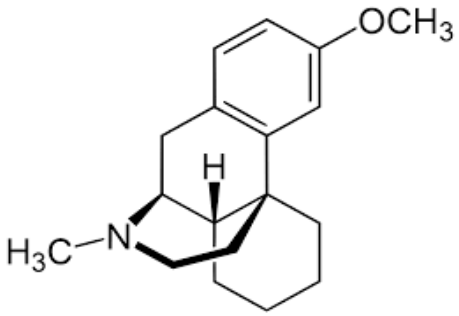
- Fluorescence is the most sensitive method of detection, over 10^6 to 10^8 times more sensitive than Raman, providing longer standoff distances and/or detection at lower concentrations
- Raman provides information about chemical bonds and functional groups, including those that do not fluoresce (aliphatics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

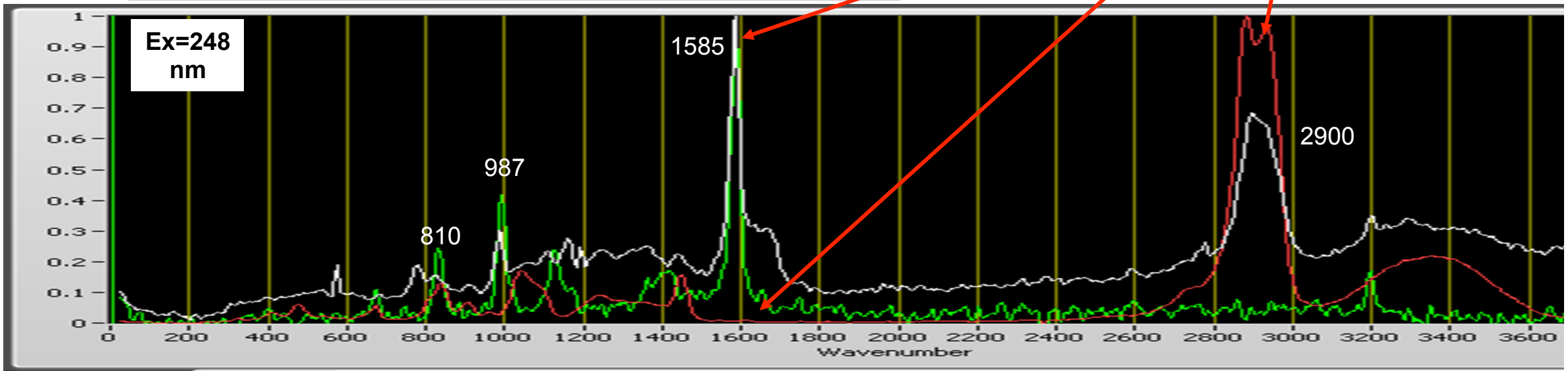
Detection Examples for Pharm Products

OTC Benylin: dextromethorphan hydrobromide

$C_{18}H_{28}BrNO_2$



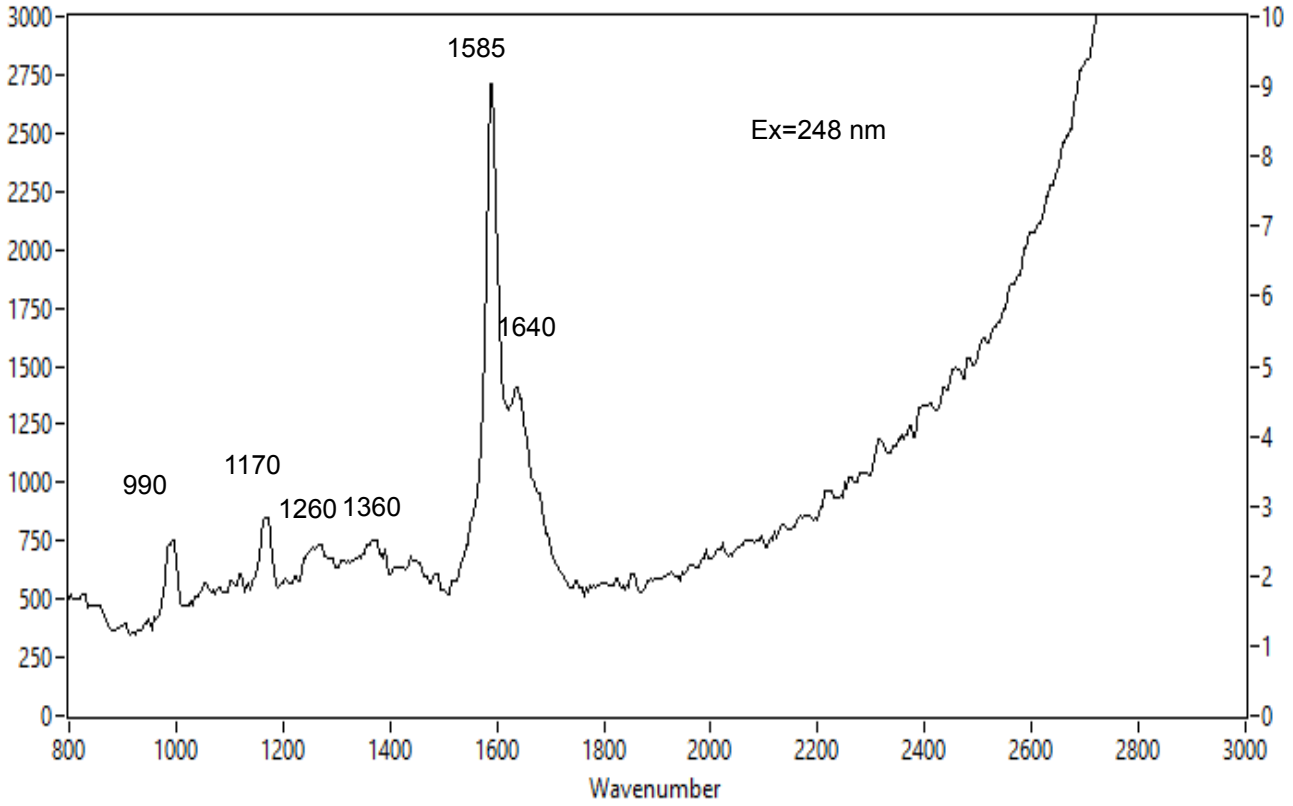




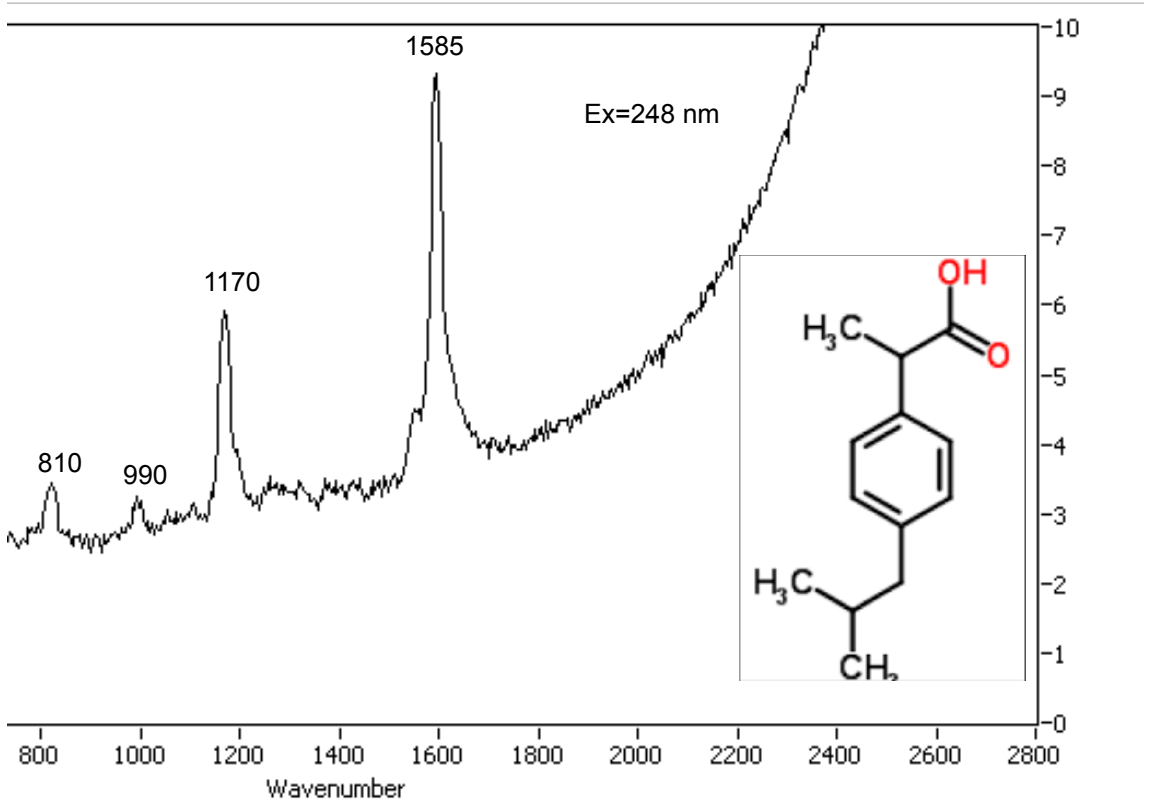
OTC Children's Motrin (ibuprofen)–Bubblegum Flavor

Ex = 248 nm

Children's Motrin-Bubblegum flavor

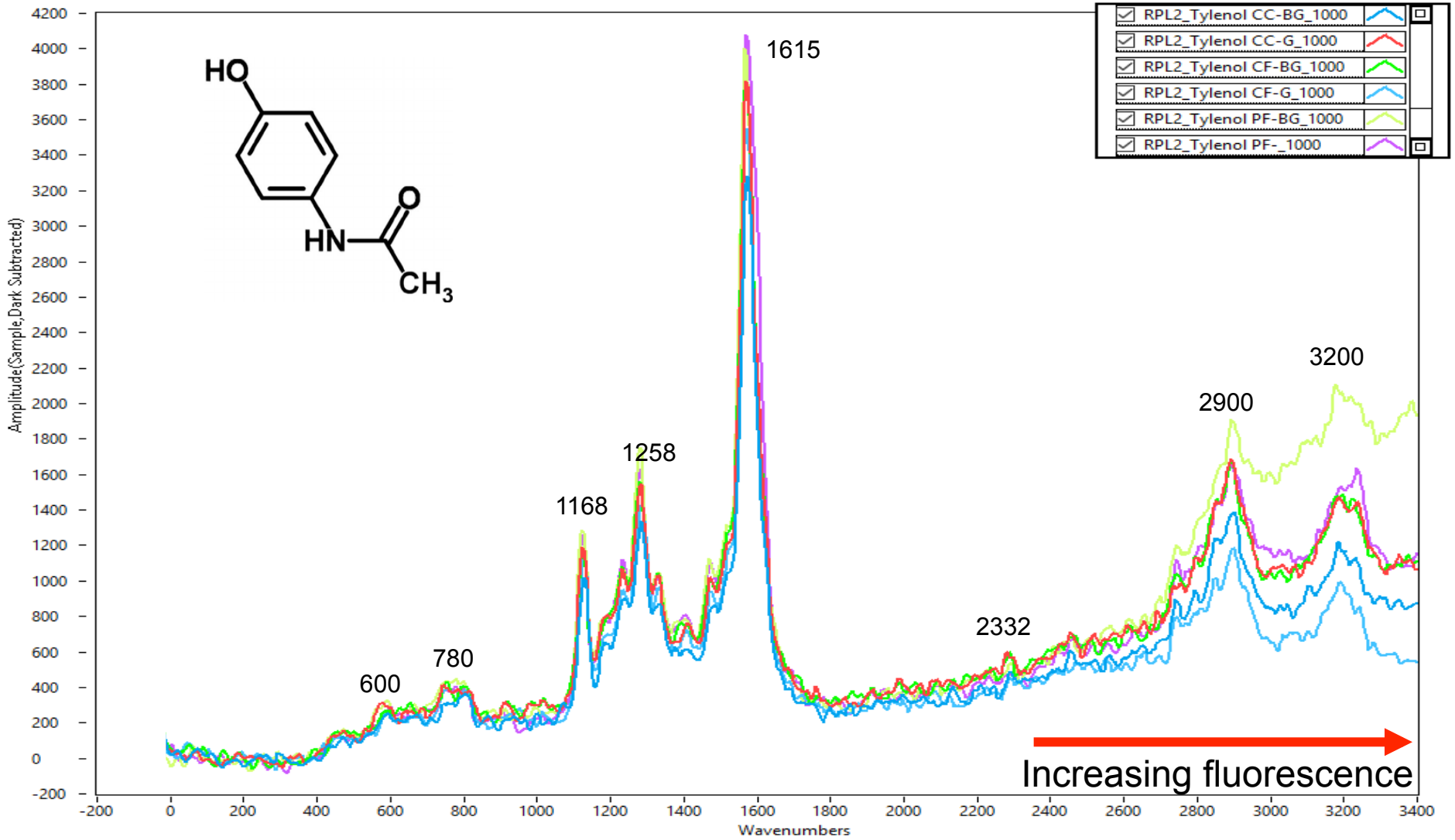


Pure Ibuprofen



OTC Children's Tylenol (acetaminophen) w Various Flavors

Ex = 248.6 nm Raw results. No baseline compensation.



Deep UV Raman & Fluorescence Instruments

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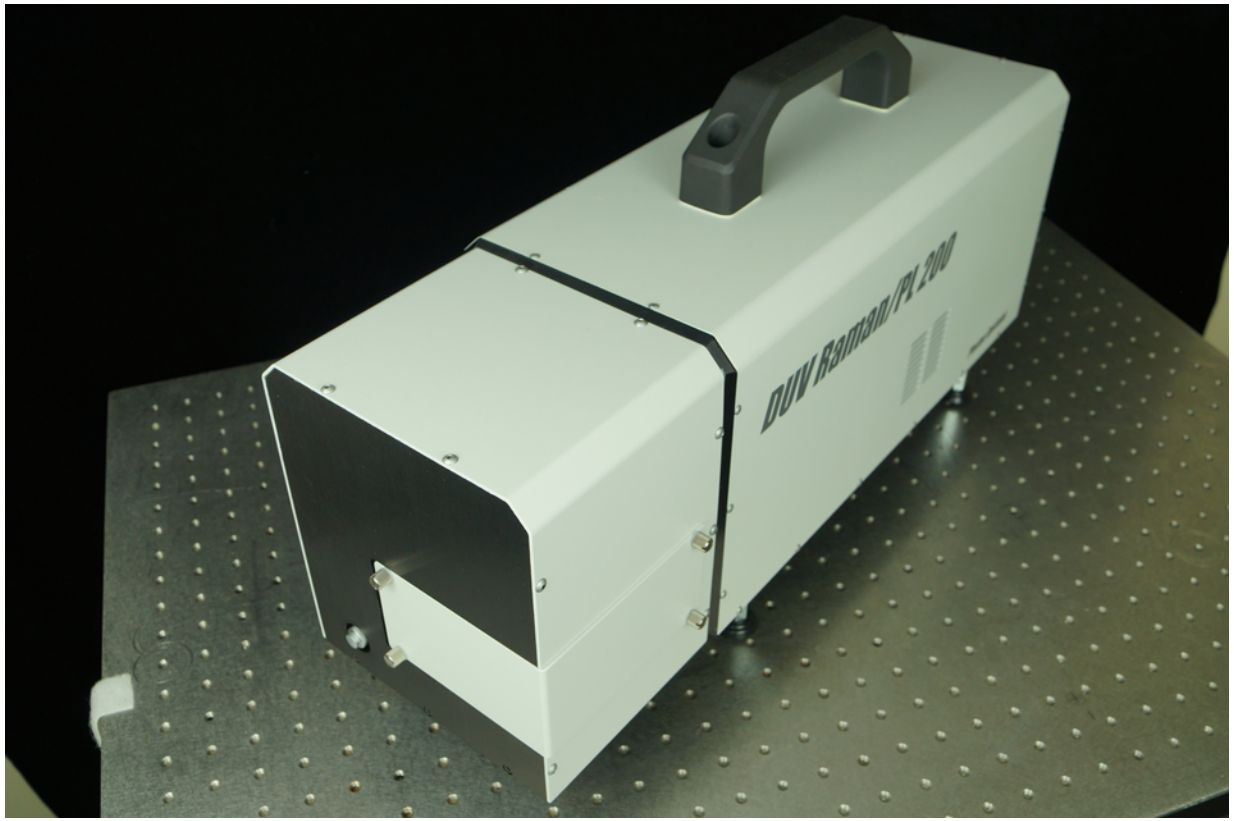
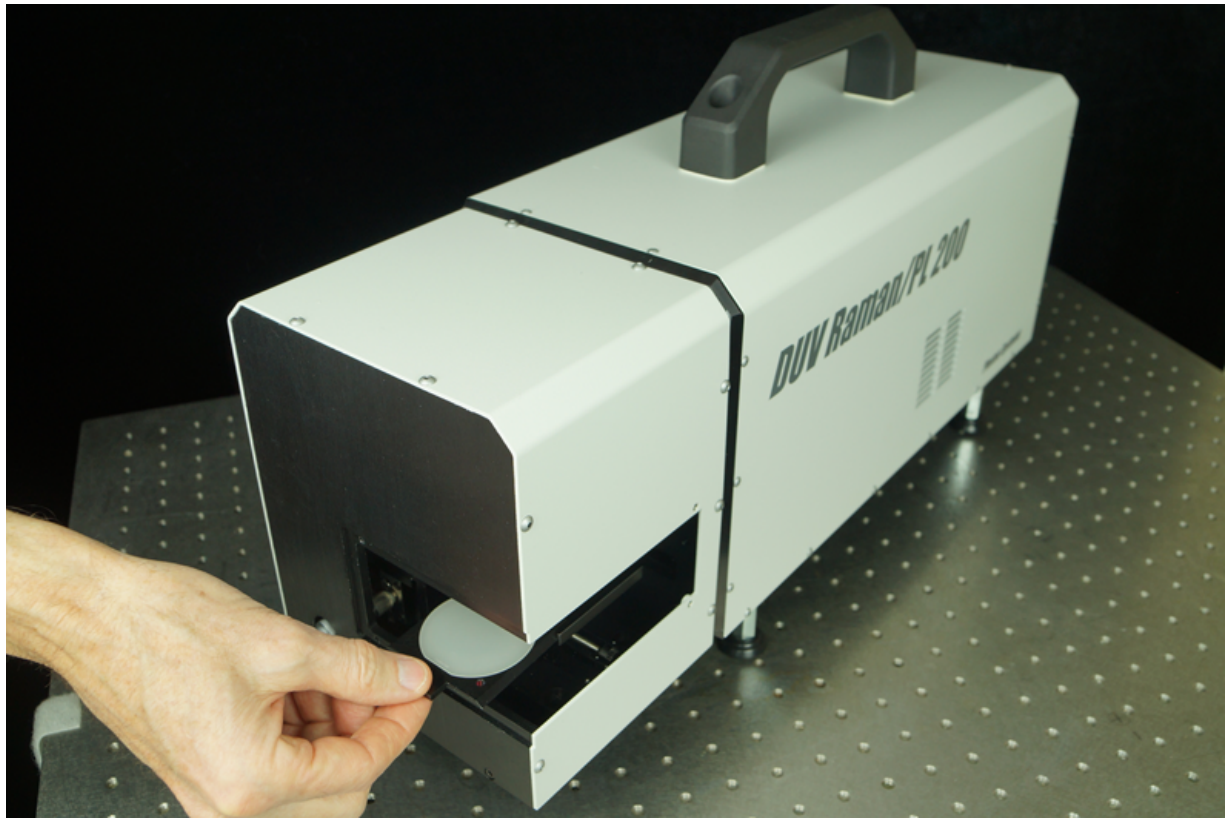
Deep UV Raman PL 200

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)

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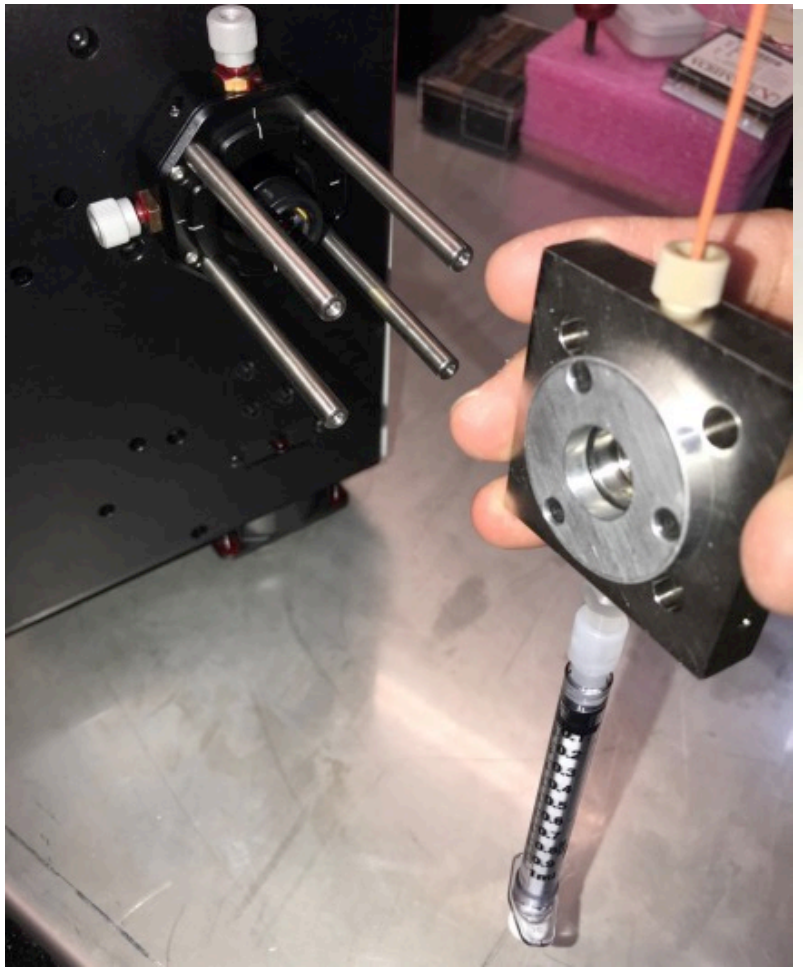
Raman PL 200

with various types of flow cells or cuvette holders



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Deep UV Trace Chemical (TraC) Sensor

LODs < 1 µg/cm^2 Wt. 1.5 lbs

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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 µg/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

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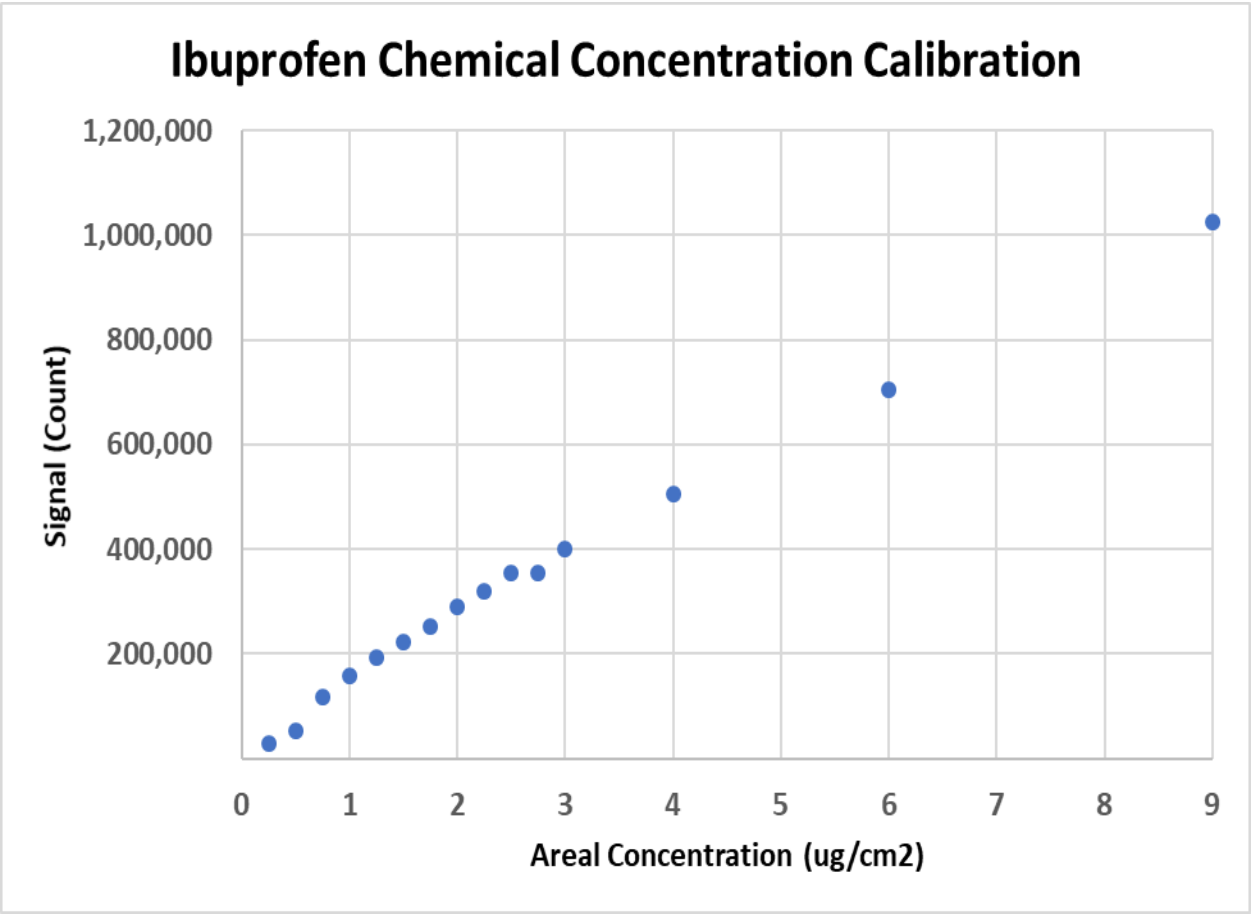
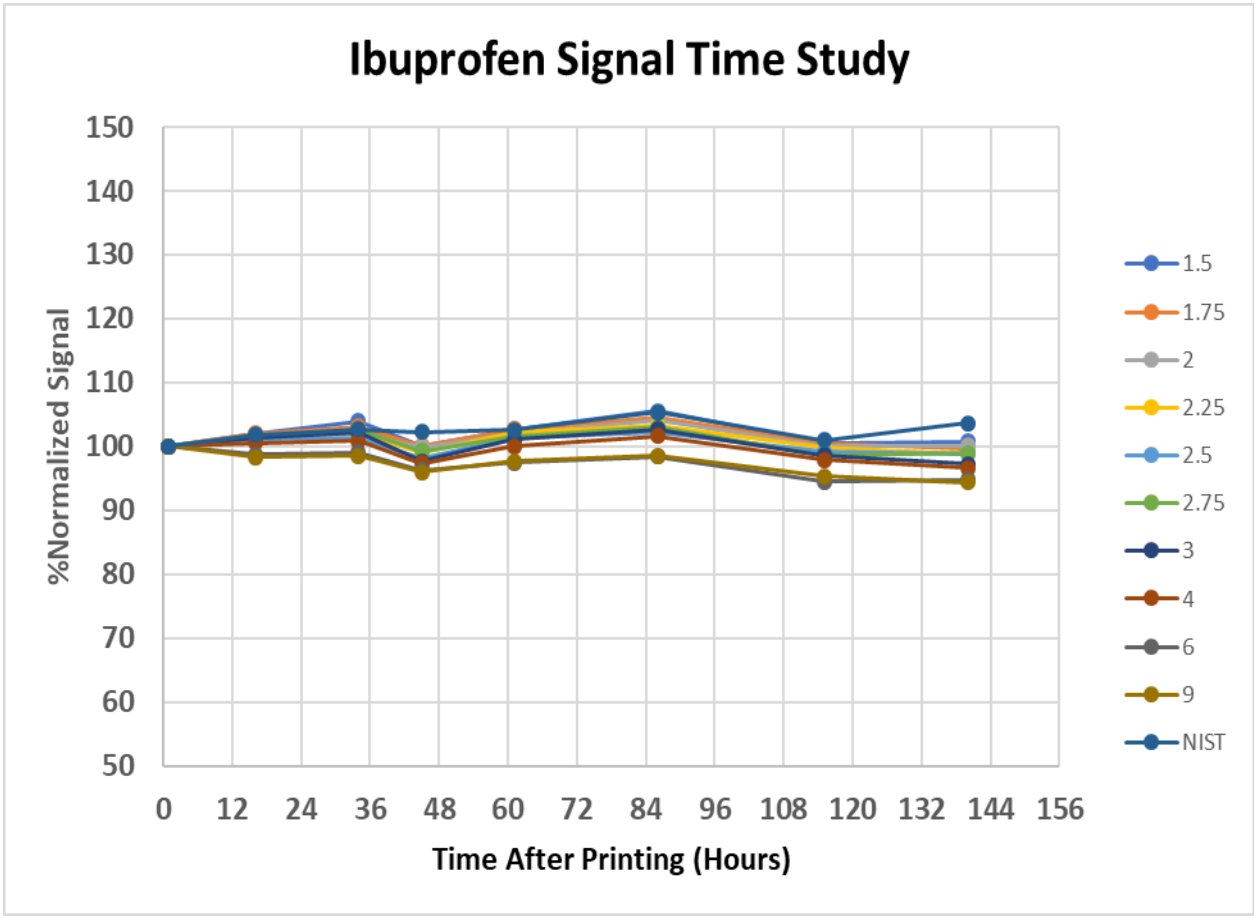
Typical Concentration Calibration Curve & Time Stability





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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 3500cm^{-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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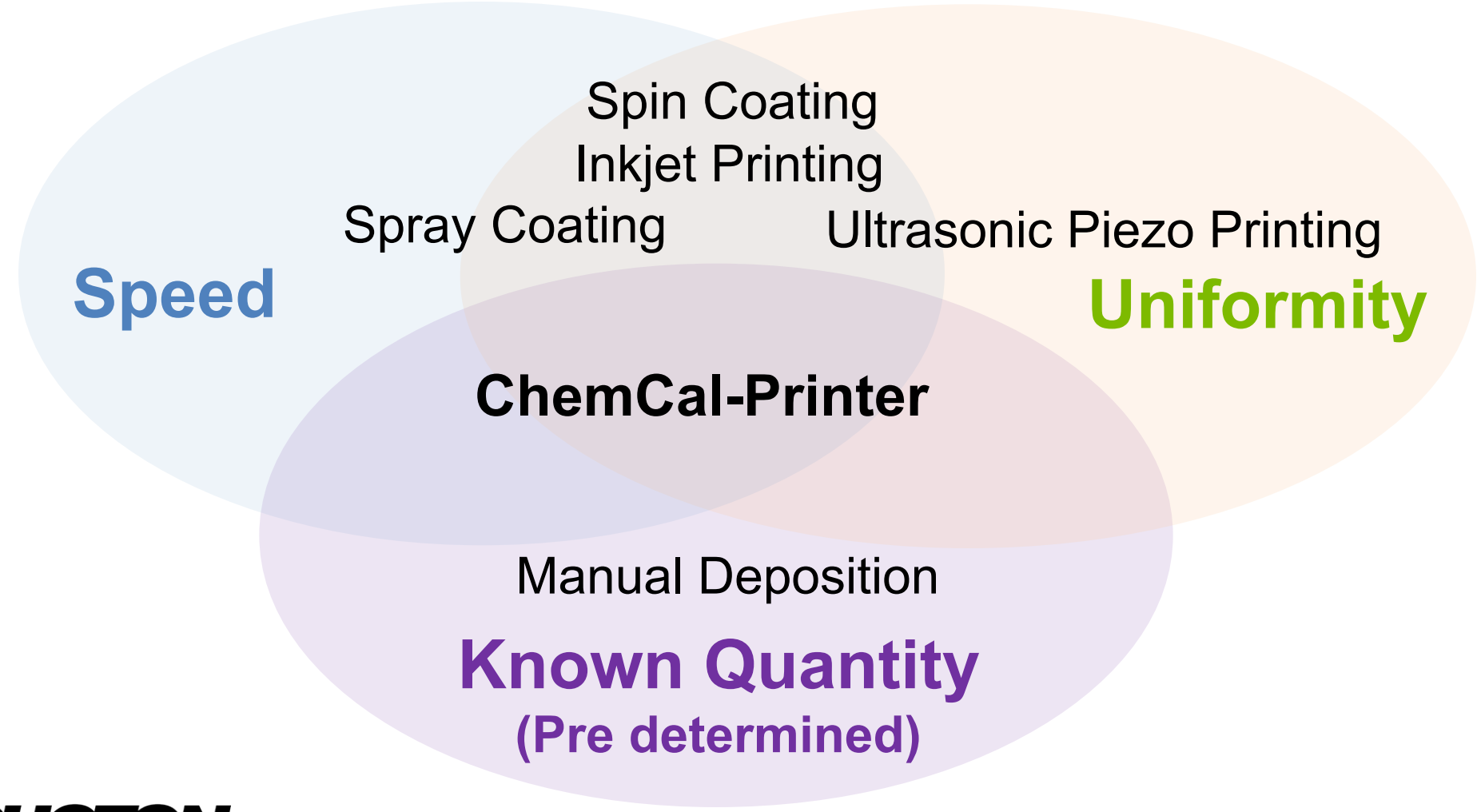
Why do you need a chemical printer?

- 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



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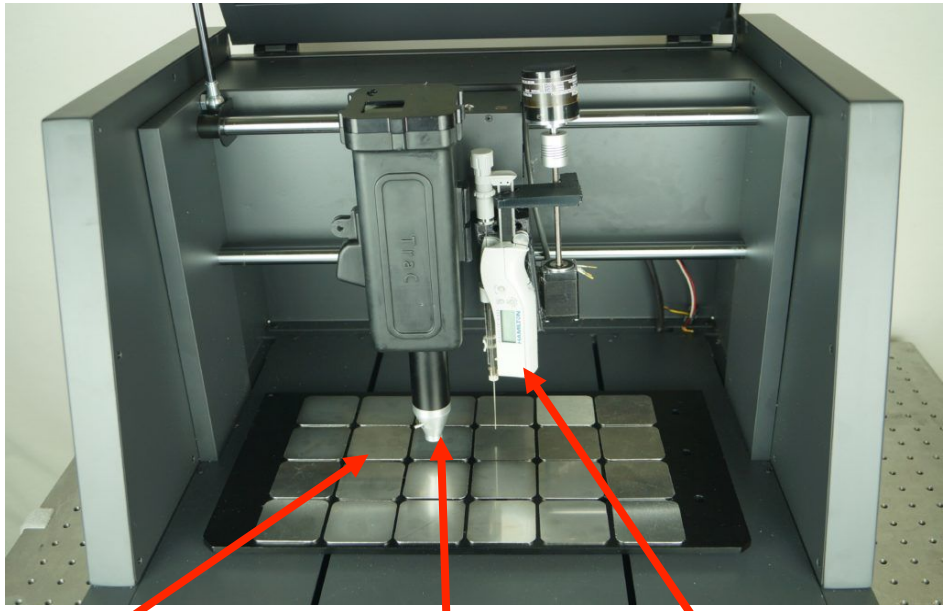
NIST Traceable Chemical Concentration Calibration

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.



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.)**

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Summary

- Several opportunities exist for pharma RCV and QC 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 ?