Next Generation Sensors for Pharmaceutical 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

Advantages of deep UV
Raman & fluorescence detection

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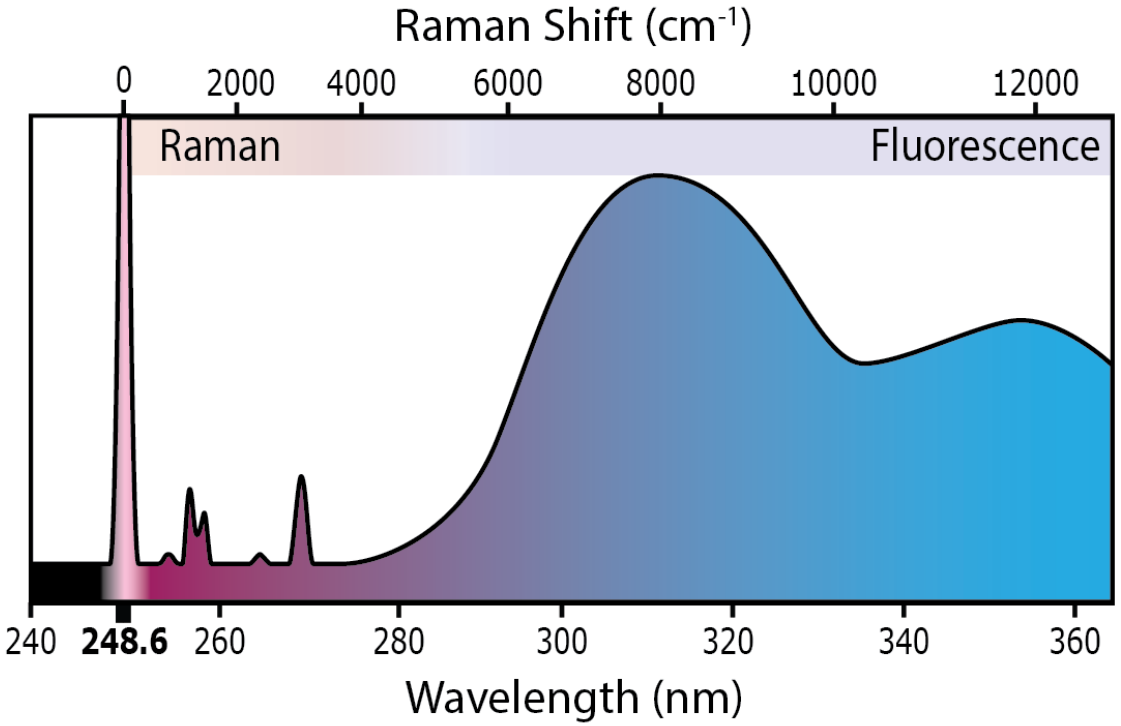
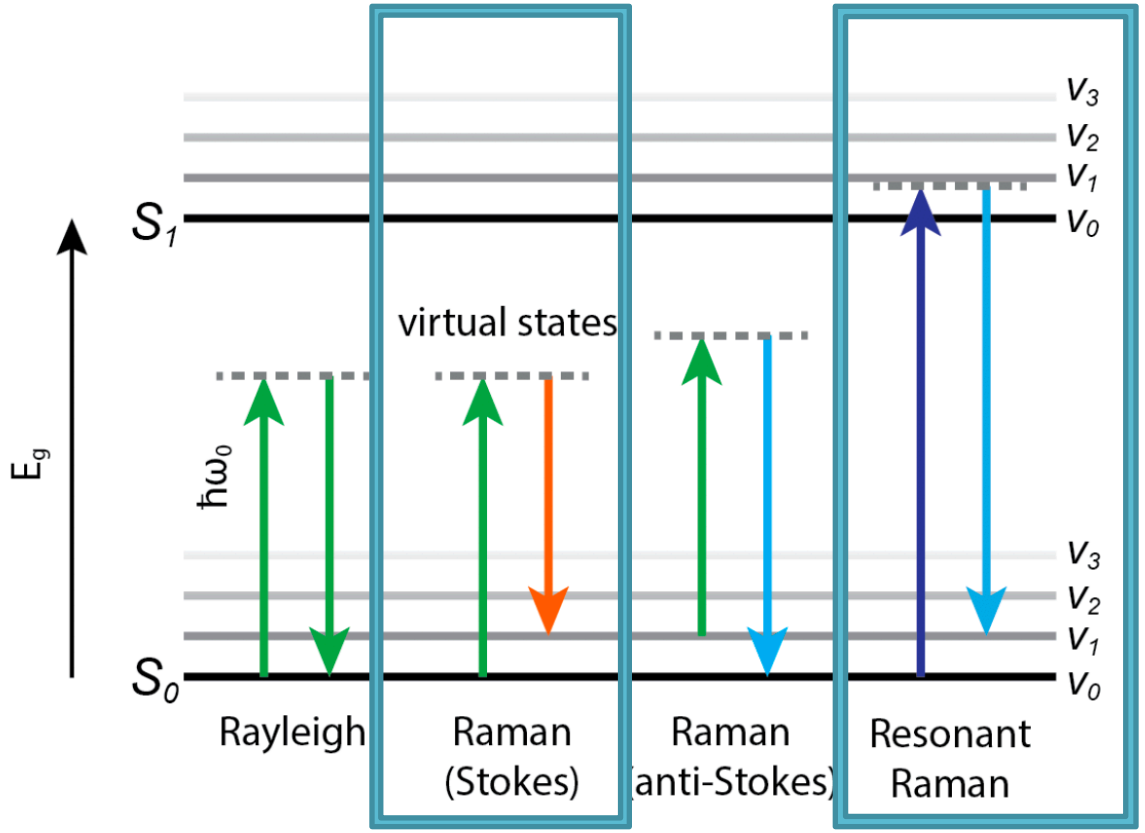
Advantages of Deep UV Detection vs Visible or IR?

- 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

Deep UV Raman Advantages

Primary advantages

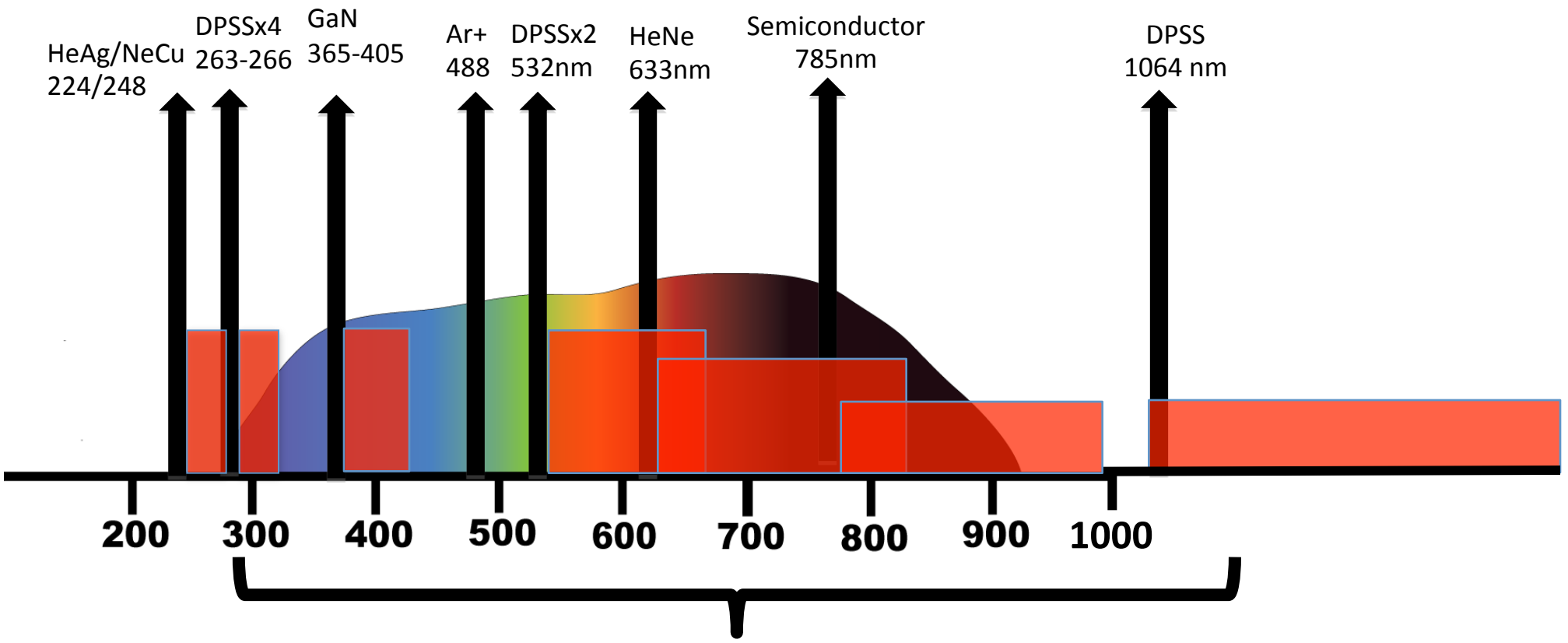




- Spectral separation of Raman and fluorescence
- Increased sensitivity to UV-absorbing compounds (primarily aromatics, but others exhibit pre-resonance)
- Simplification of Raman spectra

Why Deep UV below 250nm?

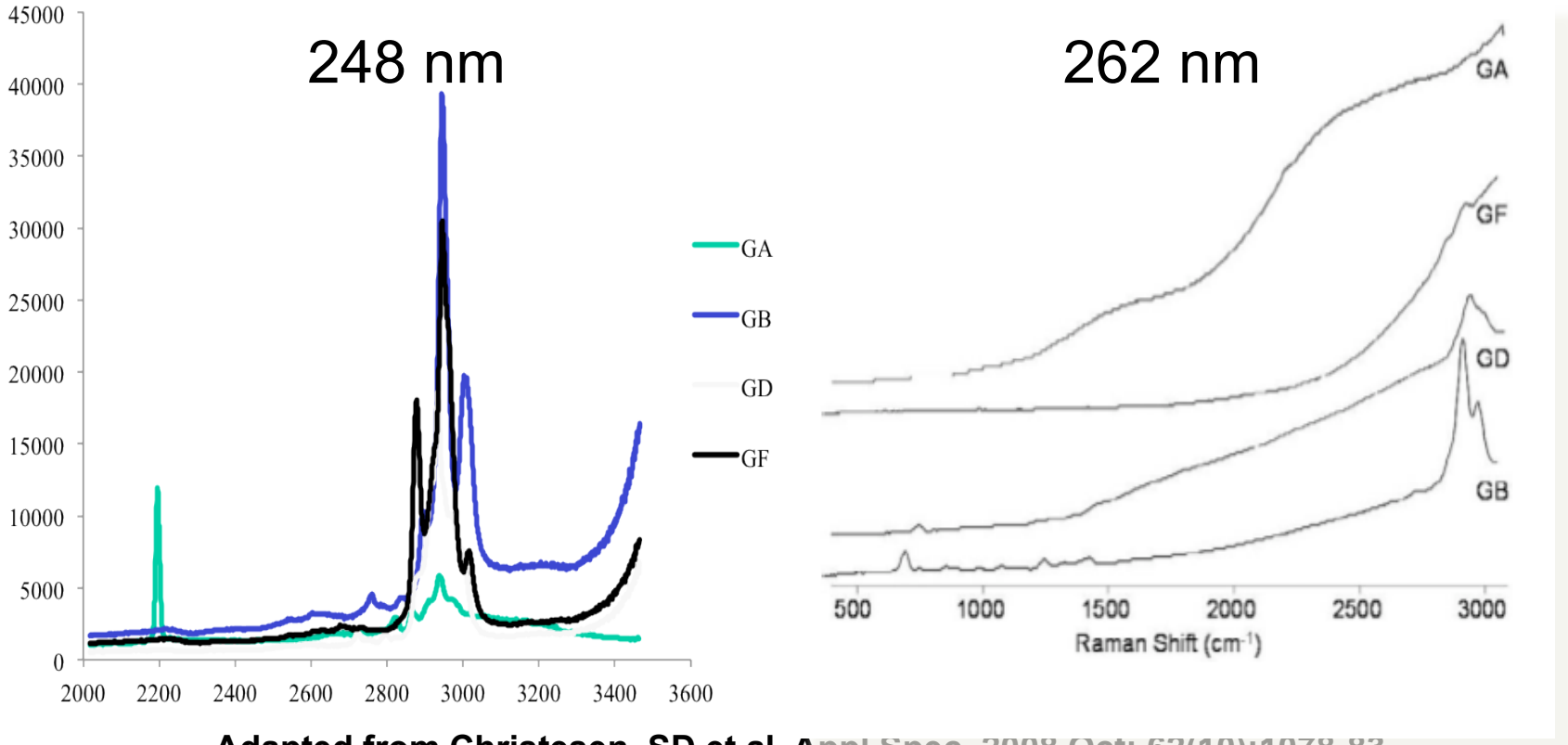
When excitation < 250nm Raman and fluorescence spectral regions are separated



Sensitivity to Excitation Wavelength

Raman Spectra with Excitation at 248 nm versus 262 nm

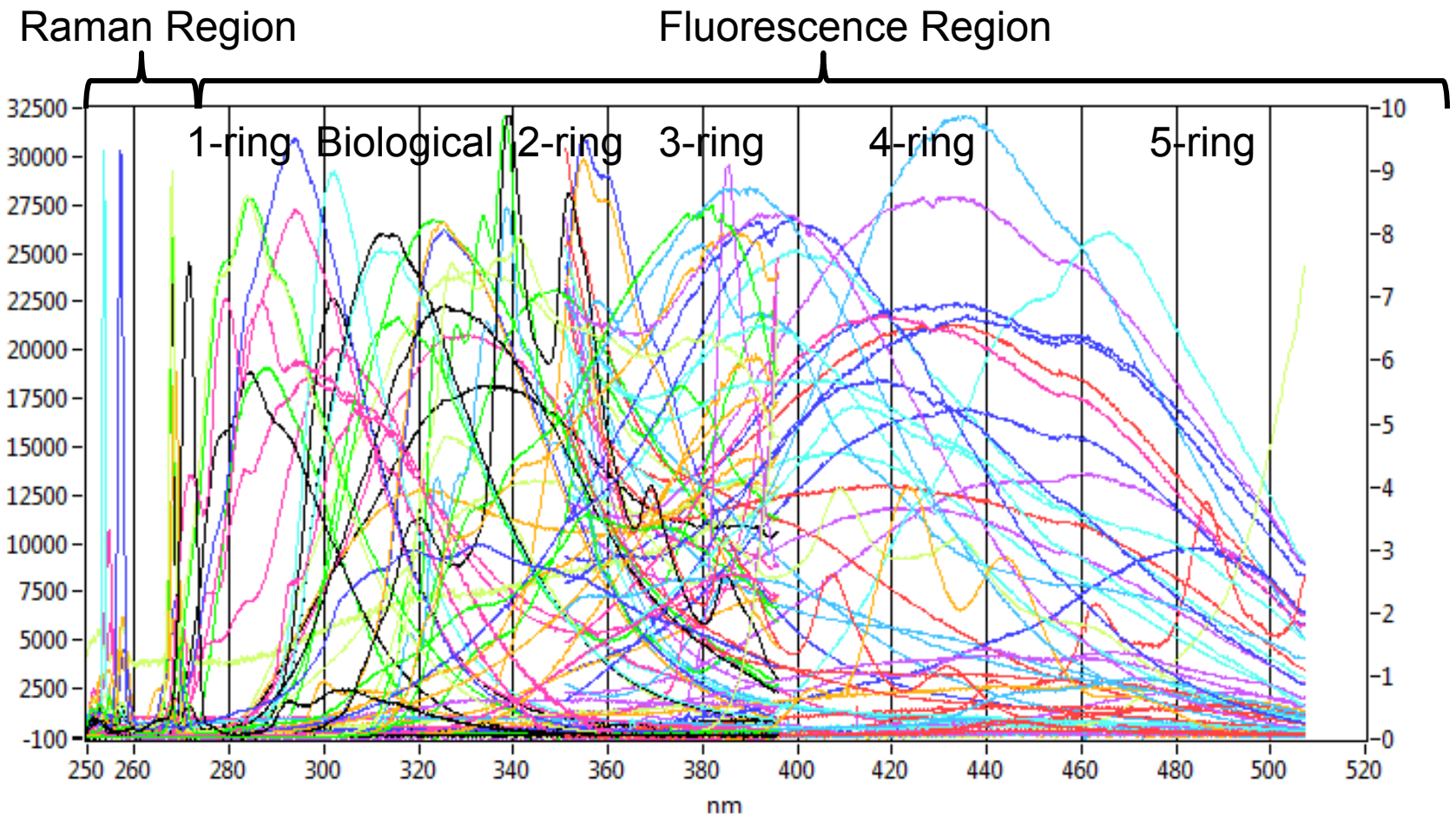
(Example is G Agents)



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

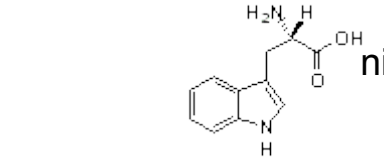
Deep UV Fluorescence Spectra of 52 Compounds

with no baseline subtraction or compensation, Ex=248 nm



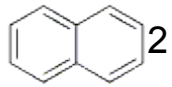
Chemical Differentiability Using Deep UV Excited Fluorescence Alone

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



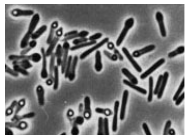
nitrogen based heterocycles **(E)** including tryptophan

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



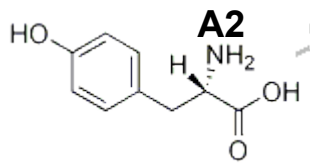
2 ring aromatics **(D)**

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



bacterial spores **(B)**

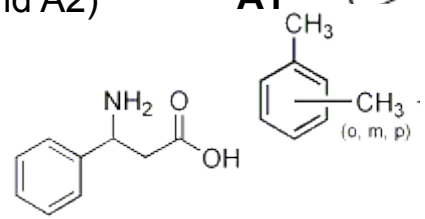
4 ring PAHs **(G)**



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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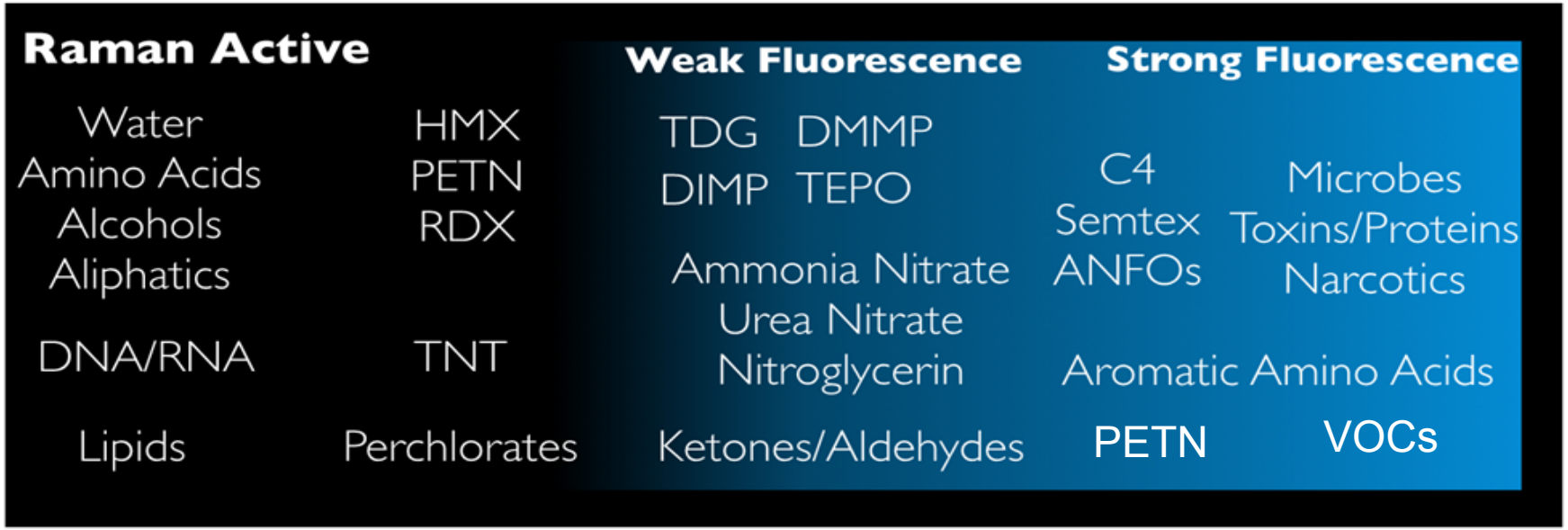
Combining the Sensitivity of Fluorescence & specificity of Raman

- 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)

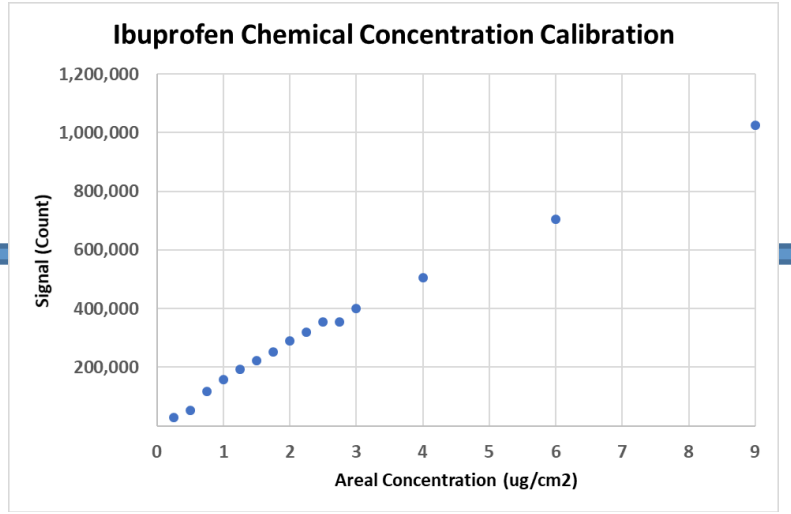


Detection Examples for Pharm Products

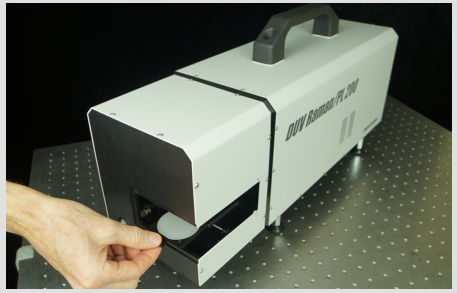
Pharma Applications and Products

TraC: Small Deep UV multi-channel fluorescence with high sensitivity

- Rapid Cleaning Verification RCV tool
- Feed Frame detector: low API concentrations high potency drug mixtures (in development)

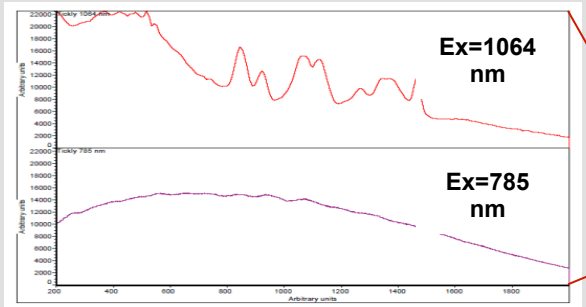


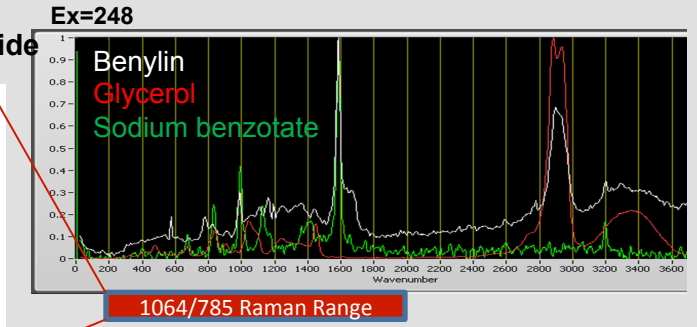
RPL 200: Portable Deep UV high resolution Raman and fluorescence spectral analysis



- Enables Raman without fluorescence obscuration.
- Enables detection not possible with 785 or 1064 systems
- Microbial detection

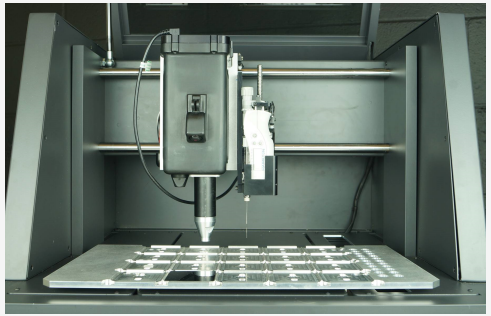
Benylin: dextromethorphan hydrobromide



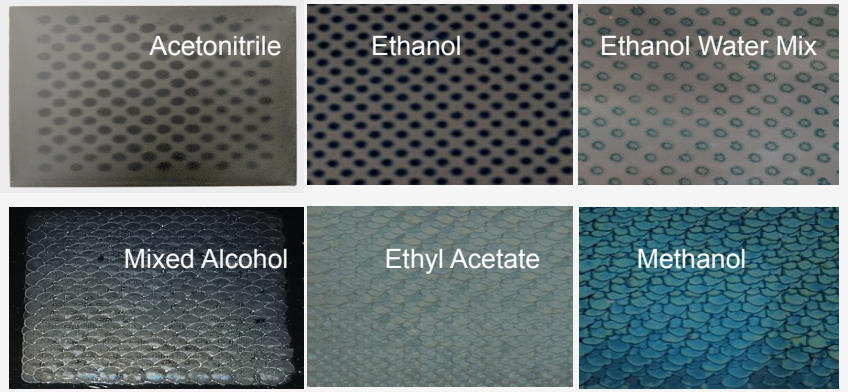


248.6 nm data: Raw, unprocessed data: No Fluorescenc

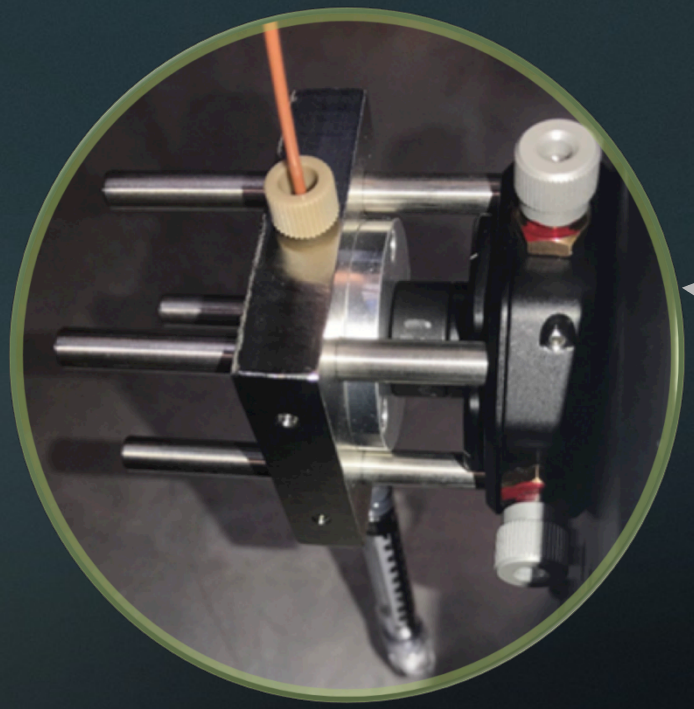
ChemCal: NIST Traceable chemical printer



- Enables printing of a priori concentrations of Pharma materials.
- Enables direct concentration calibration of many RCV tools
- Training and evaluation of Swabbing techniques.

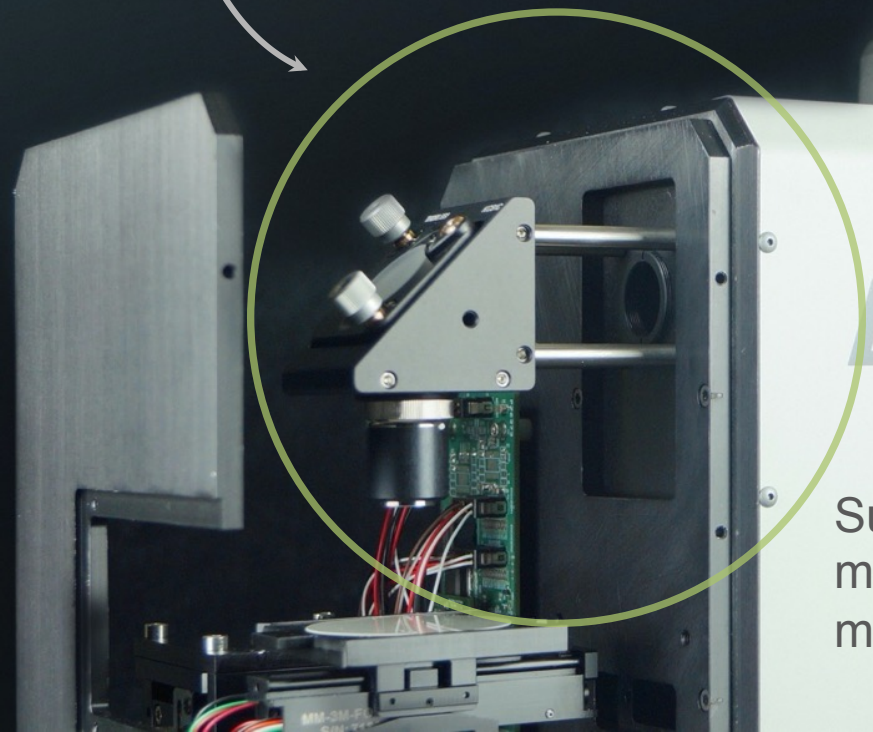


Raman/PL 200 Flow Cell Module



Modular front-end design to fit a variety of applications

Flow cell module currently being used for in-line waste water analysis (NO3, Organics, etc.)



Surface analysis module being used for microbial detection

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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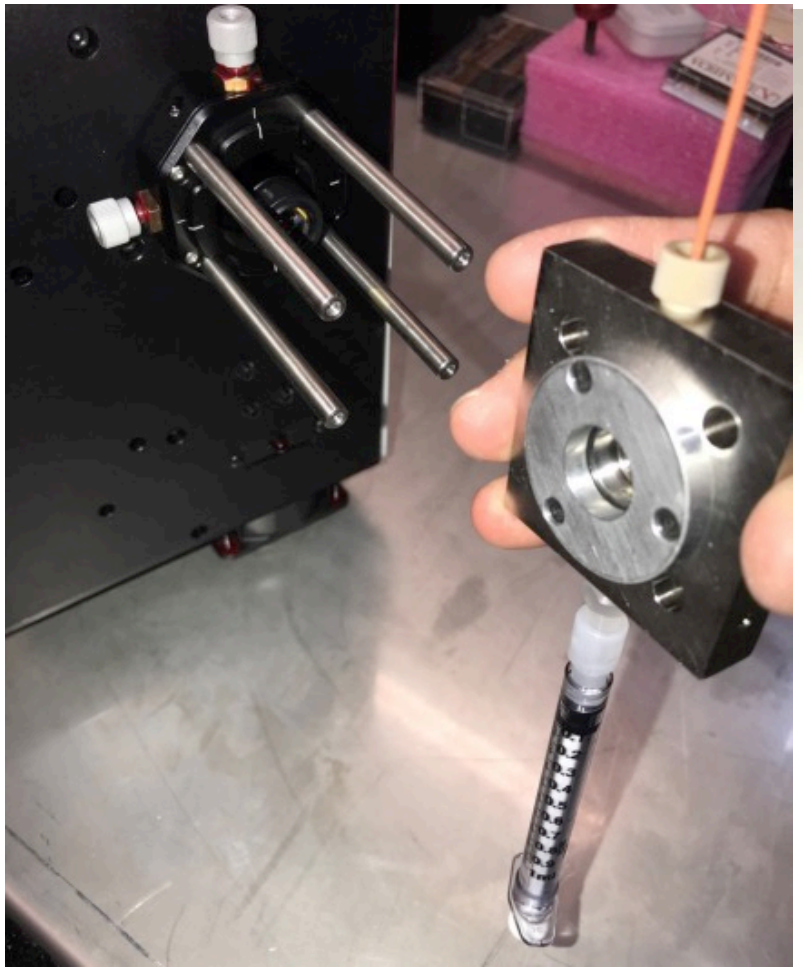
Raman PL 200

with various types of flow cells or cuvette holders



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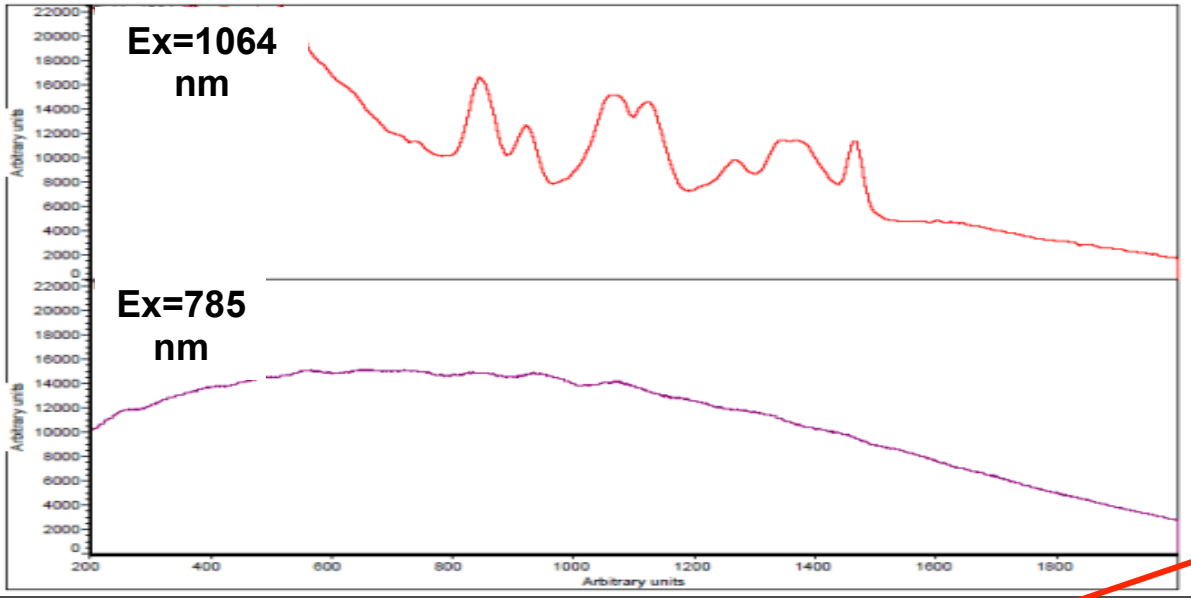
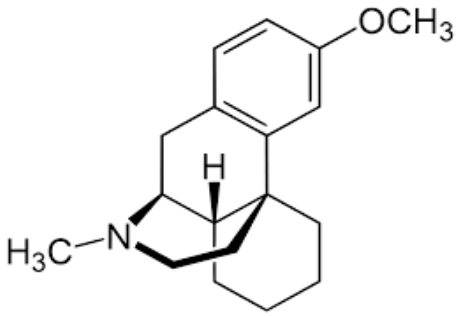
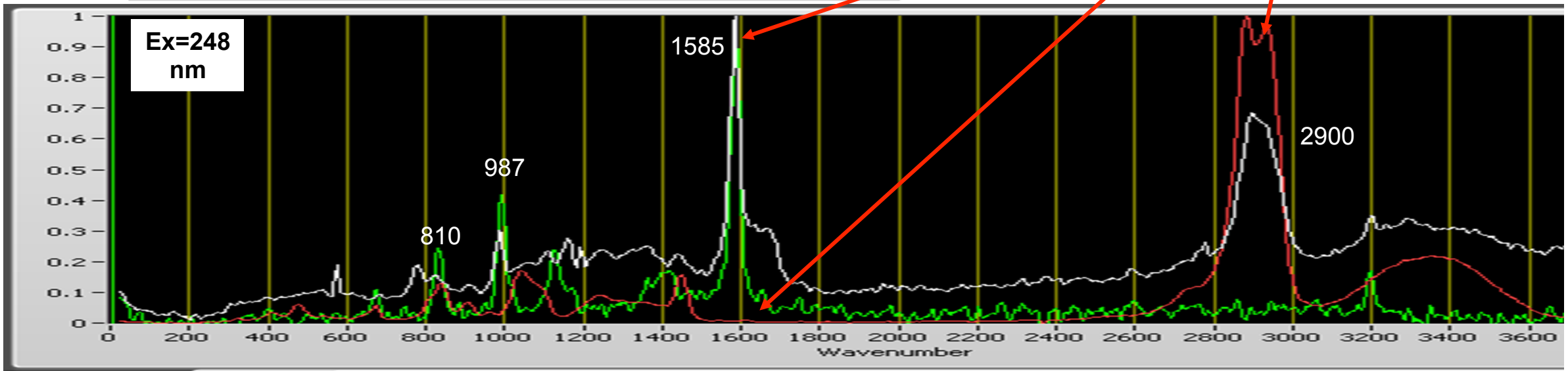
OTC Benylin: dextromethorphan hydrobromide $C_{18}H_{28}BrNO_2$





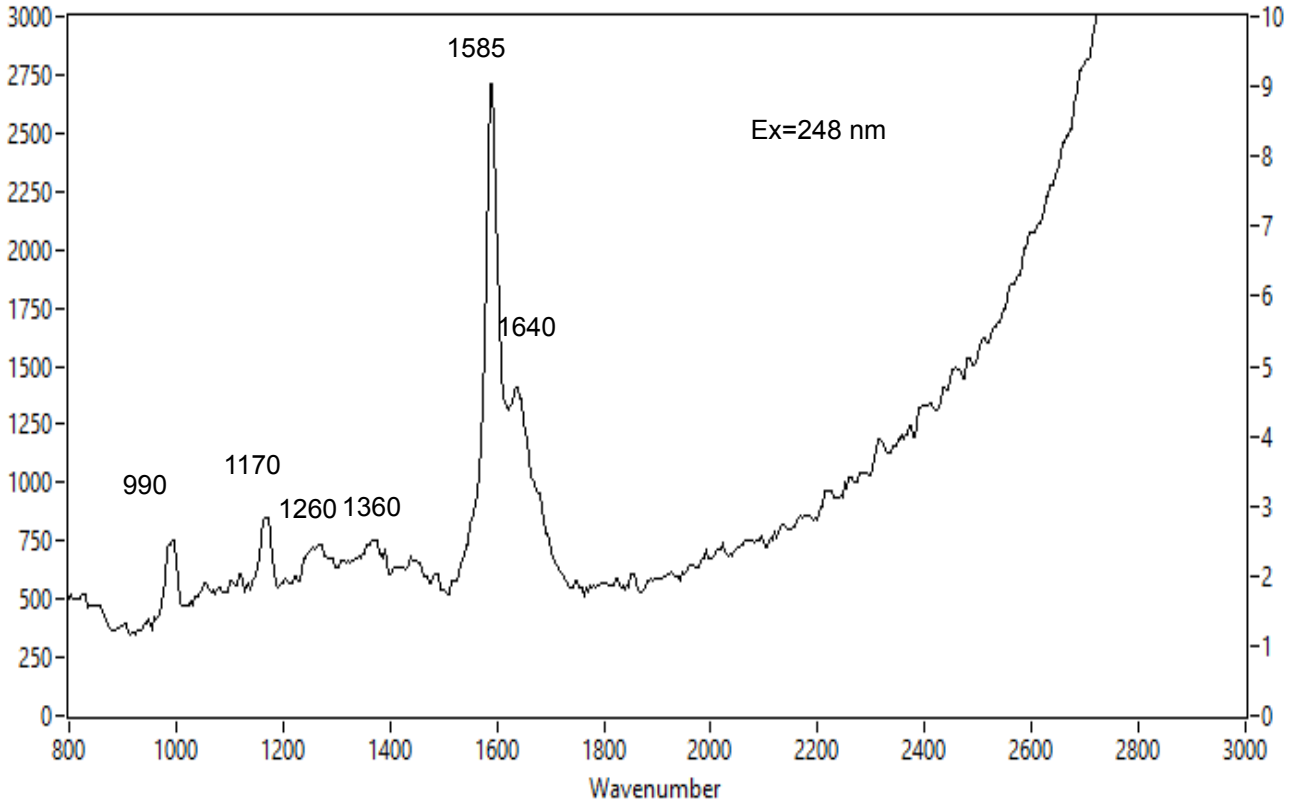
Benylin (white)
Sodium benzoate (green)
Glycerol (red)



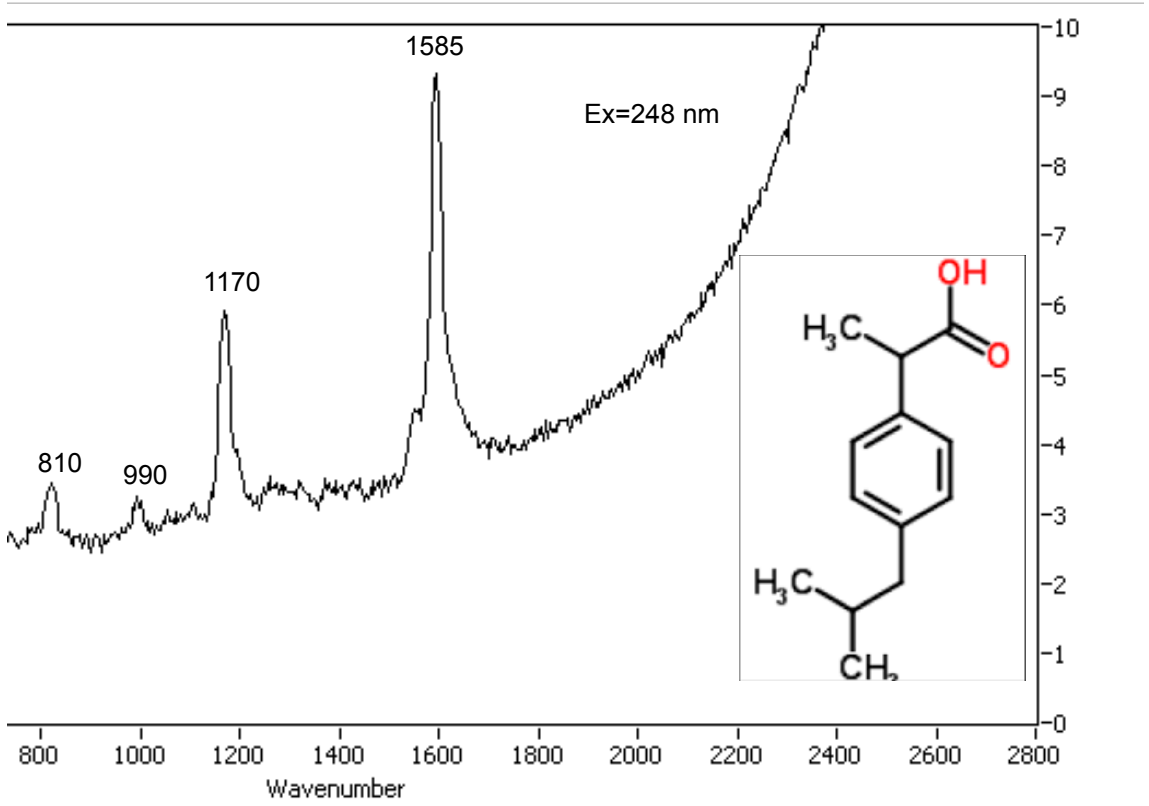
OTC Children's Motrin (ibuprofen)–Bubblegum Flavor

Ex = 248 nm

Children's Motrin-Bubblegum flavor

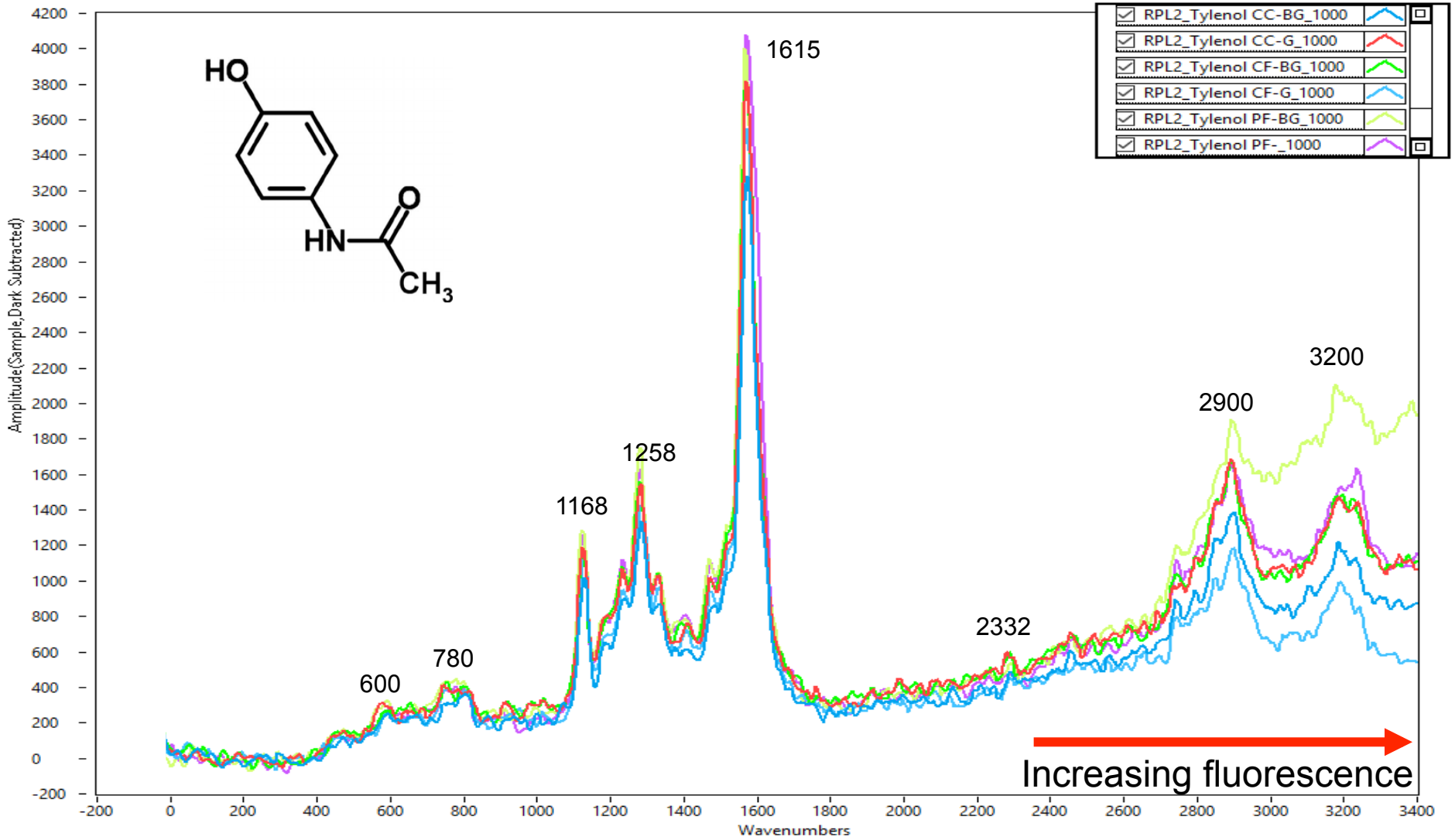


Pure Ibuprofen



OTC Children's Tylenol (acetaminophen) w Various Flavors

Ex = 248.6 nm Raw results. No baseline compensation.



Deep UV 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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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 instrument that enables quantification of API extending the current NRI levels of ~2% volume to well below .1% mixture. Feed Frame

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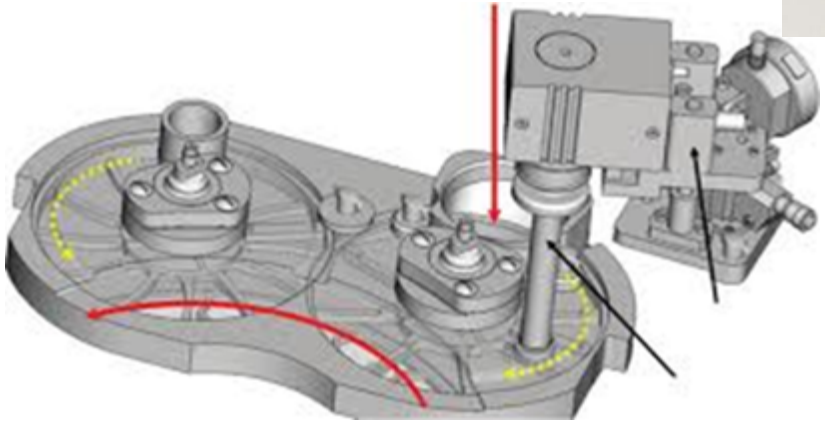
Detector Choices for Moving Powder

Deep UV application Feed Frame

- **Problem**:
  - NIR and FITR techniques are limited in most powder mixtures to > 2% bulk ratios. Absorption techniques and excipient interferents limits dynamic range.
- **Goal**:
  - Explore other techniques focused in Deep UV spectroscopy (fluorescence and Raman) to extend in process control of high potency drugs to better than 0.1% bulk ratios.
- **Solution**:
  - A handheld size, deep UV Raman/Fluorescence instrument, that avoids spectral obscuration enabling the advantage of both spectroscopic techniques.

Fluorescence

- High sensitivity with API
- Typically, 6 order magnitude more sensitivity than Raman
- Easy to configure fluorescence detection to optimize sensitivity and specificity
- Meets GMP requirements



Feed Frame instrument under development

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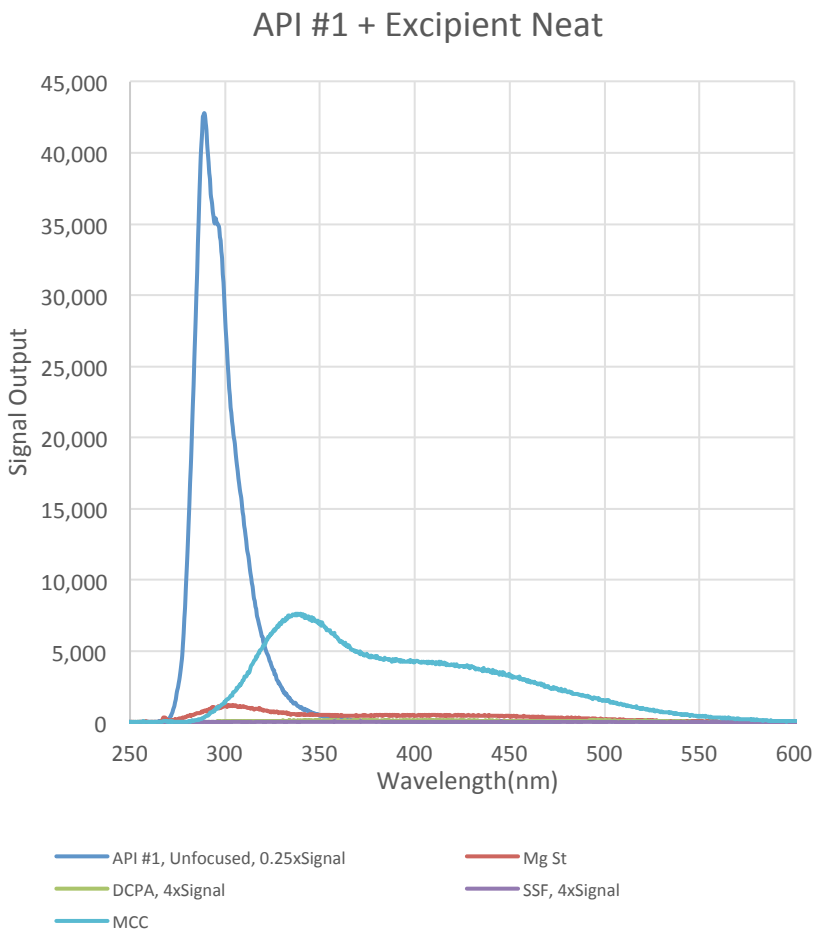
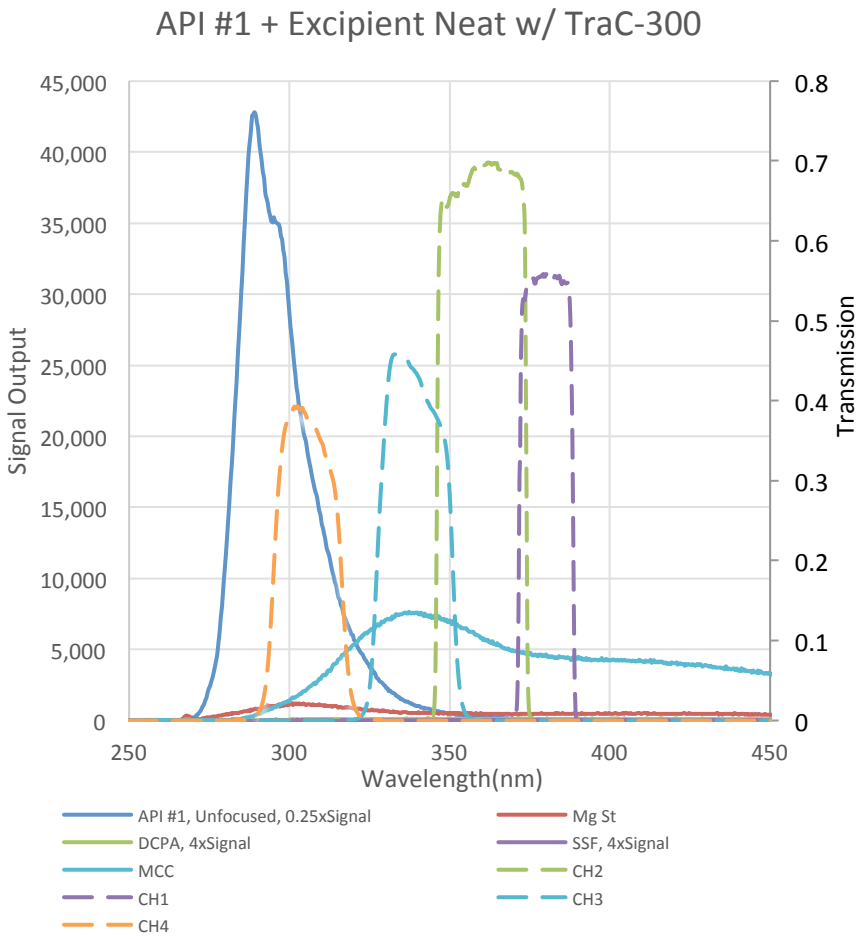
API #1 Fluorescence

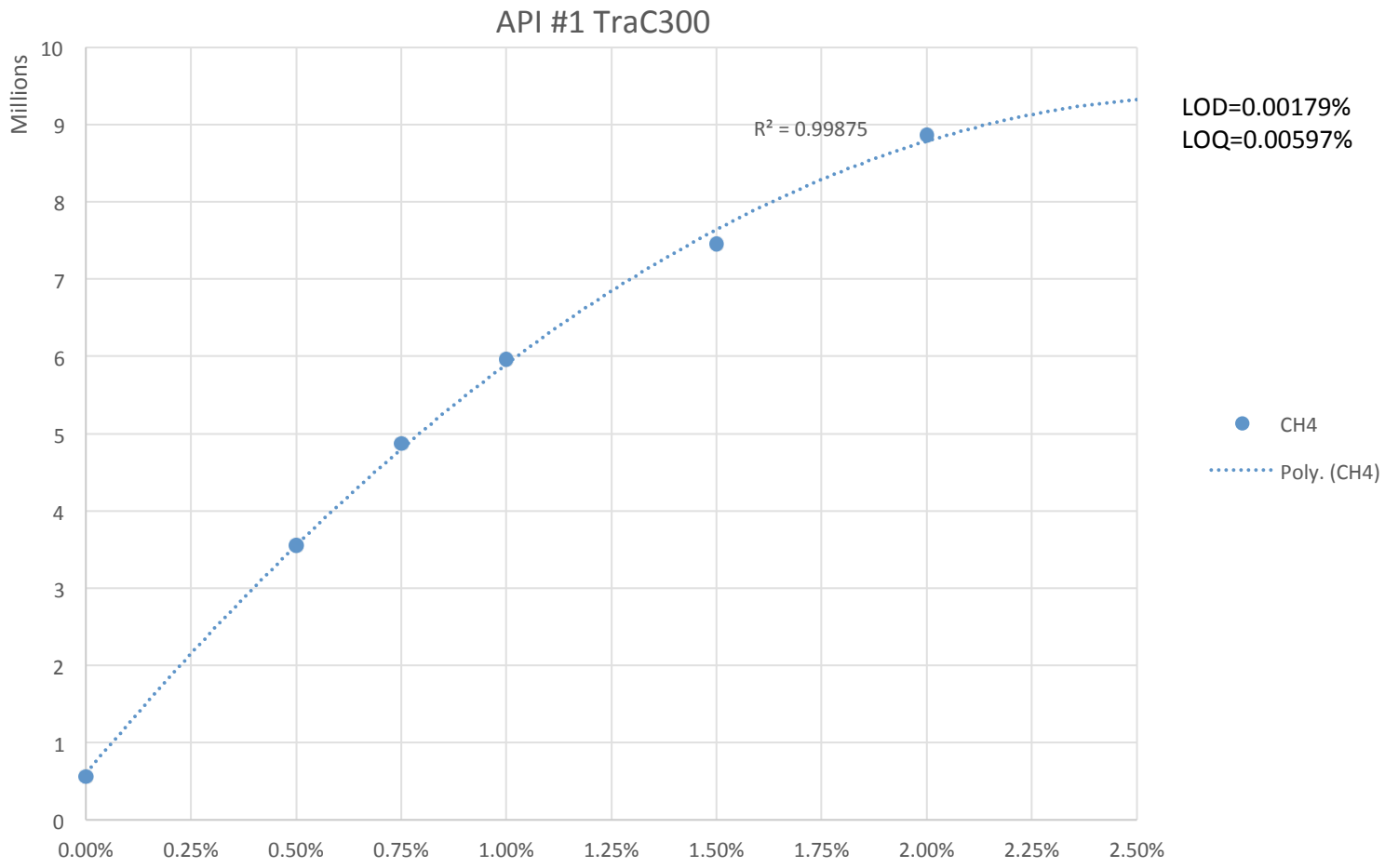




API #1

LOD calculation is 3*stdev signal to background 0%API
LOQ is 10*stdev signal to background 0%API
Note stdev for channel 4 is quite small resulting in very low LOD/LOQ

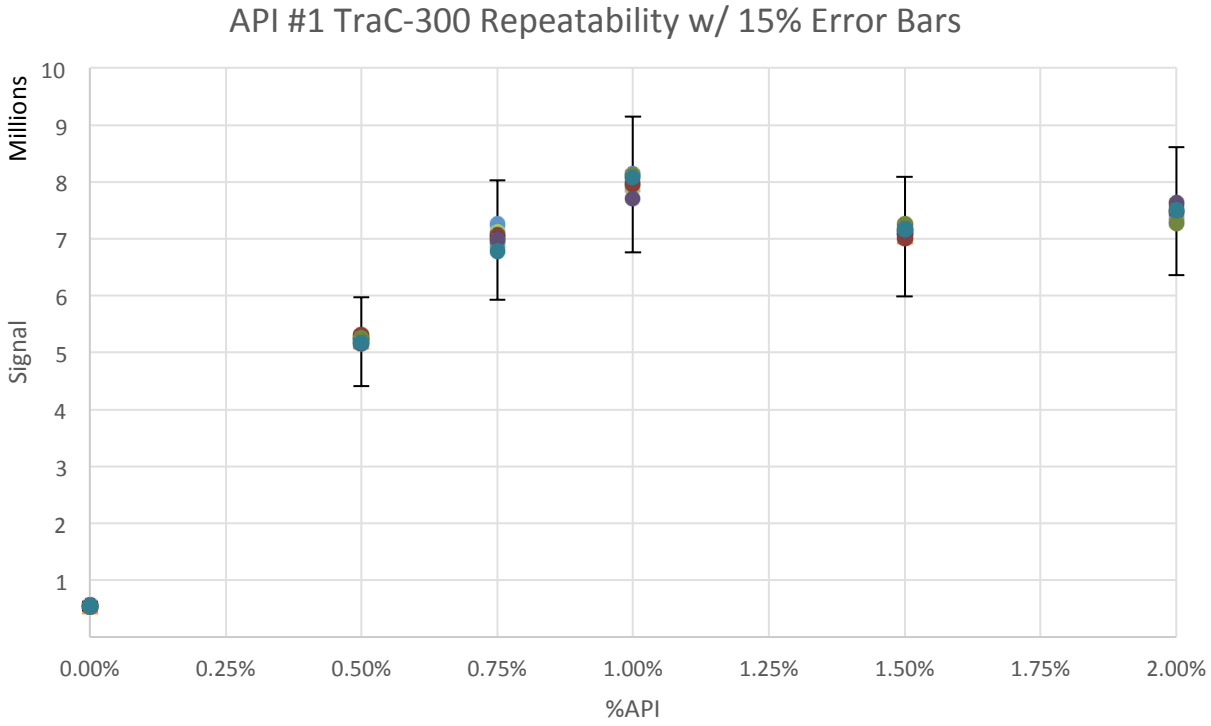
API #1	(Placebo)	TraC300		
Pulse #	CH1	CH2	CH3	CH4
1	1158016	4330302	15426030	562882
2	1158790	4324586	15414404	563500
3	1154584	4324712	15407616	566510
4	1158775	4313648	15405742	563924
5	1150324	4314752	15389699	555454
6	1162153	4310587	15384947	557960
7	1150843	4305384	15379319	558977
8	1153033	4306050	15377898	562912
9	1153379	4299269	15359867	567778
10	1151667	4301042	15346608	559587
avg	1155156	4313033	15389213	561948
stdev	4022	10635	24772	3879
stdev*3	12065	31905	74315	11636
stdev*10	40216	106349	247716	38786
graph equation				graph equation
x^2				-12049151022
x				650129212.8
c				600259.64
LOD in % using -				5.393853%
LOQ in % using -				5.389671%
LOD in % using +				0.001790%
LOQ in % using +				0.005973%

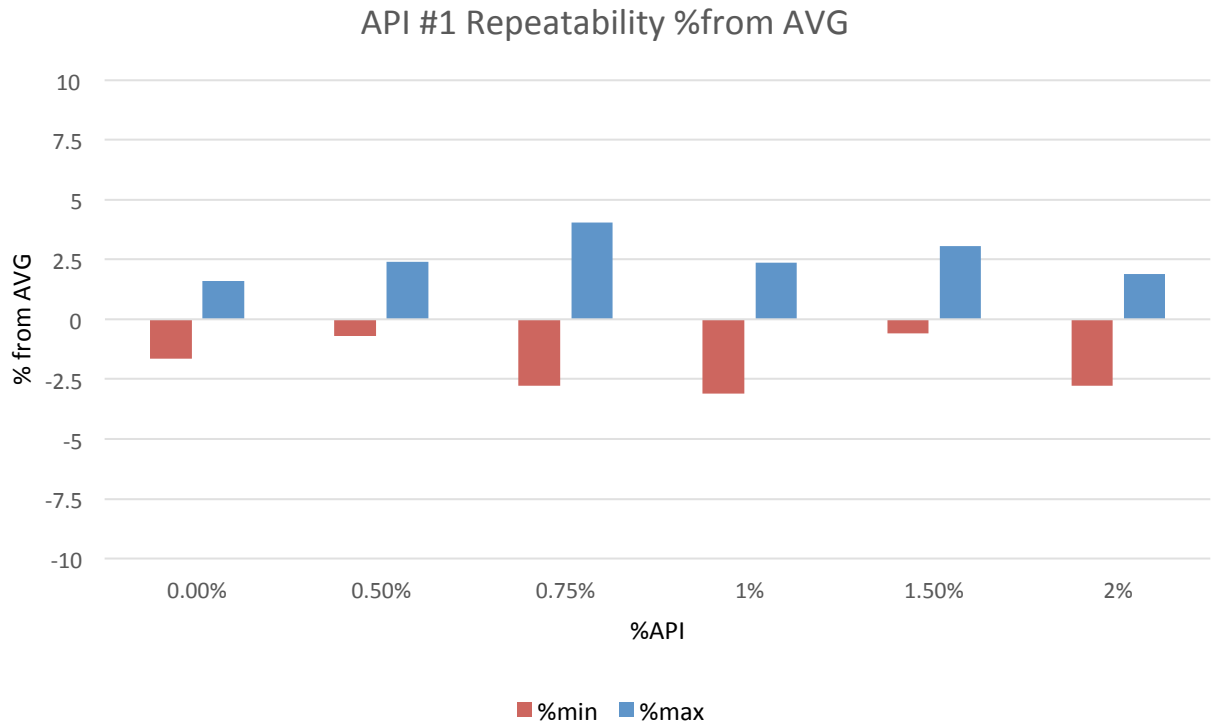


LOD=0.00179%
LOQ=0.00597%

API #1

TraC300 Repeatability on API #1 samples





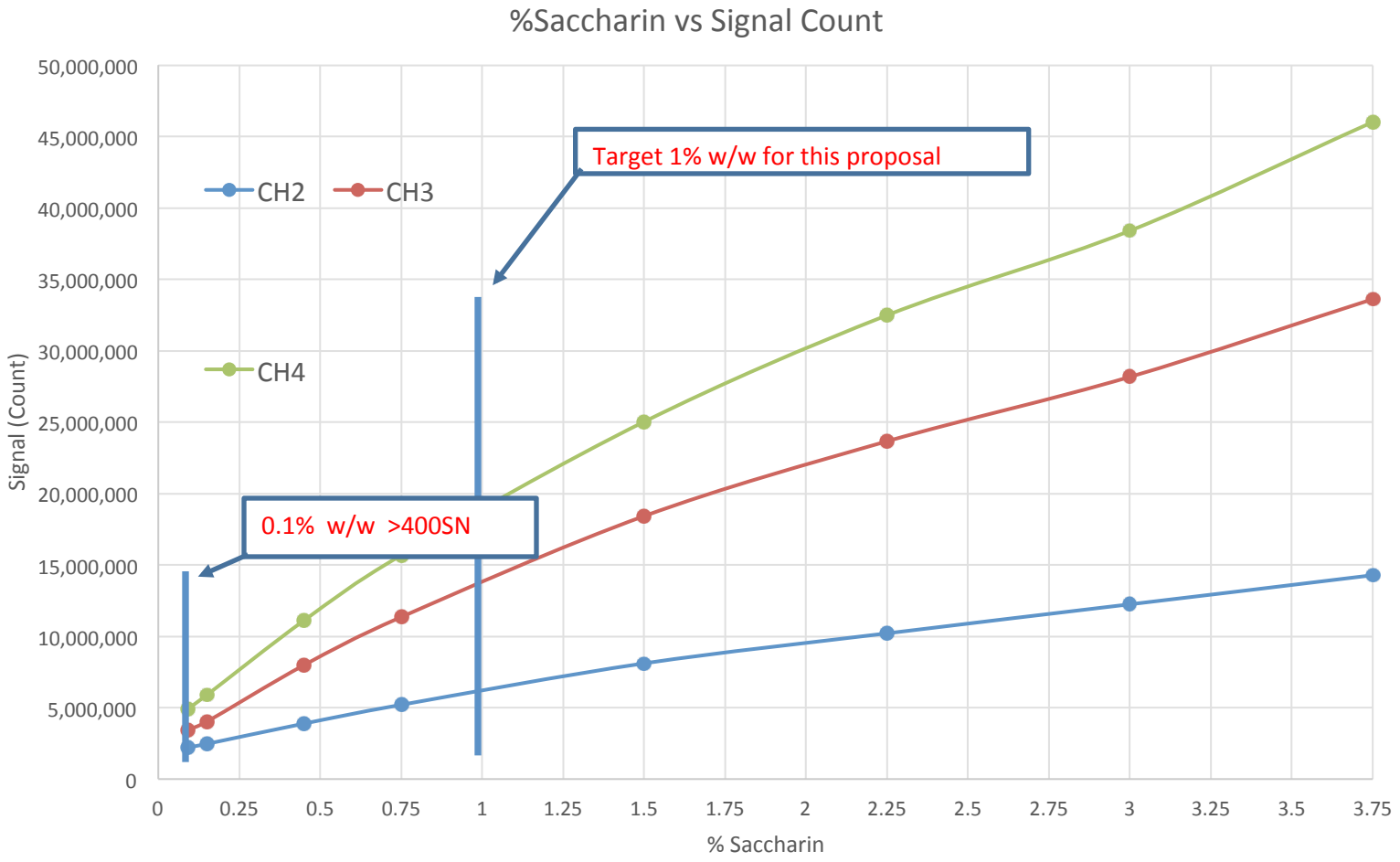
- TraC set stationary on the ChemCal and the samples were manually moved underneath the TraC nose.
- Repeatability of the various concentrations range from 3.0% to 6.7%, which are well within the ±15% repeatability limits previously set for API TraC development.

TraC: Saccharin concentration curves

Fluorescence response Feed Frame application

TraC

- 3.00% saccharin in 5 standard excipients is 100% mixture
- Dilution from 125% (3.75w/w) to 3% (0.1%w/w)
- We would estimate the LOD with SN of 3 to be ~0.04% W/w Saccharin.
- Roughly 20 times more sensitive than NIR techniques currently used.
- Currently under study with ETC (Emerging Technology Consortium) a Global Pharma group



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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.

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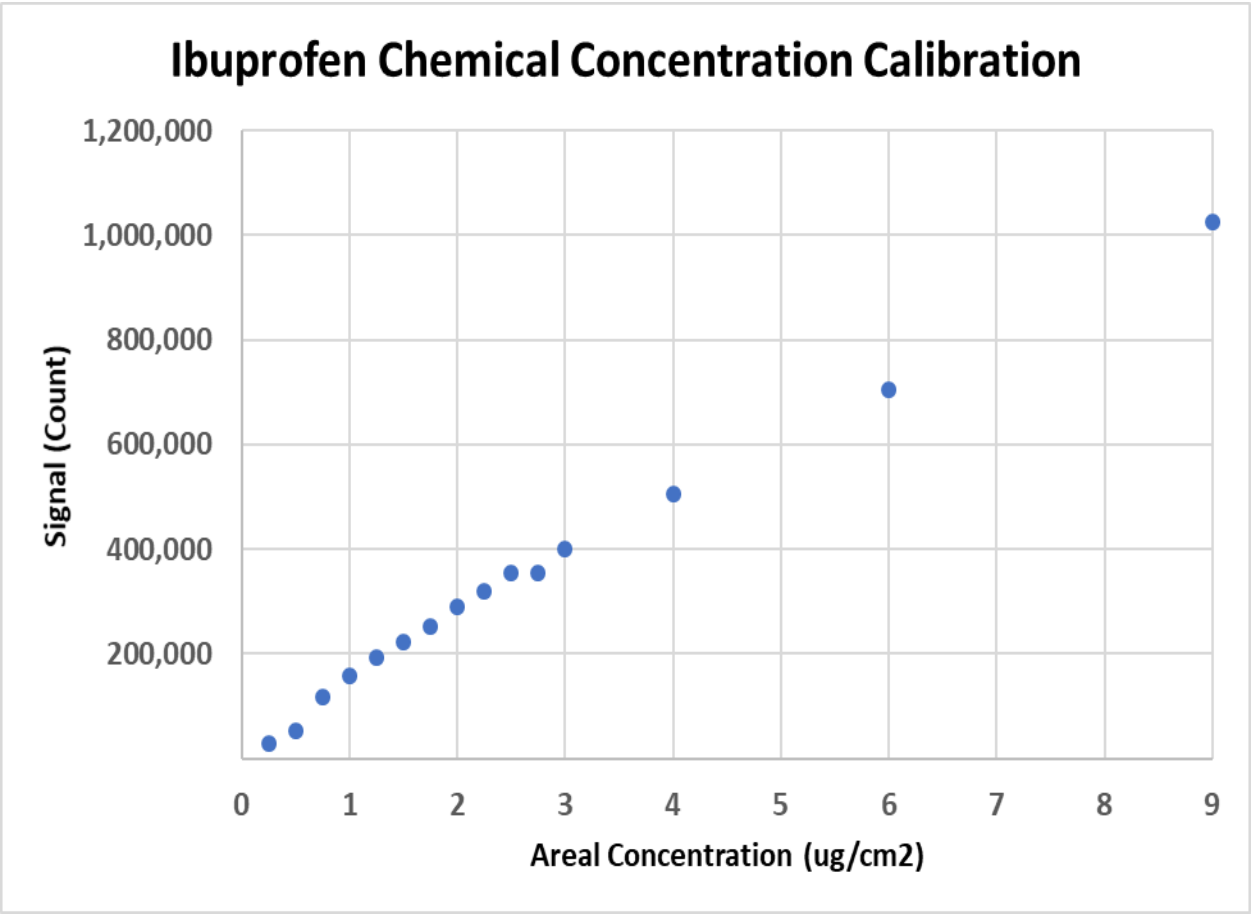
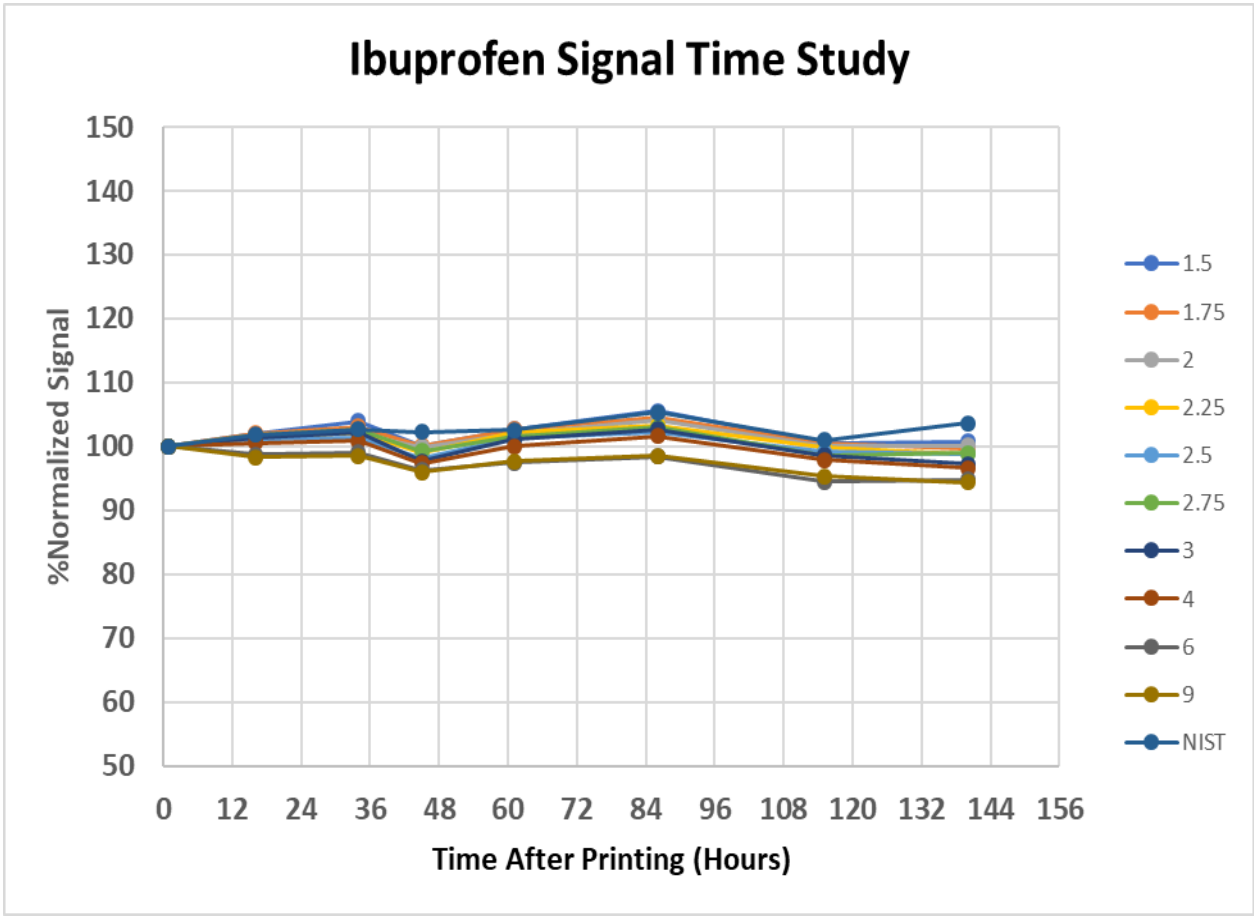
Typical Concentration Calibration Curve & Time Stability





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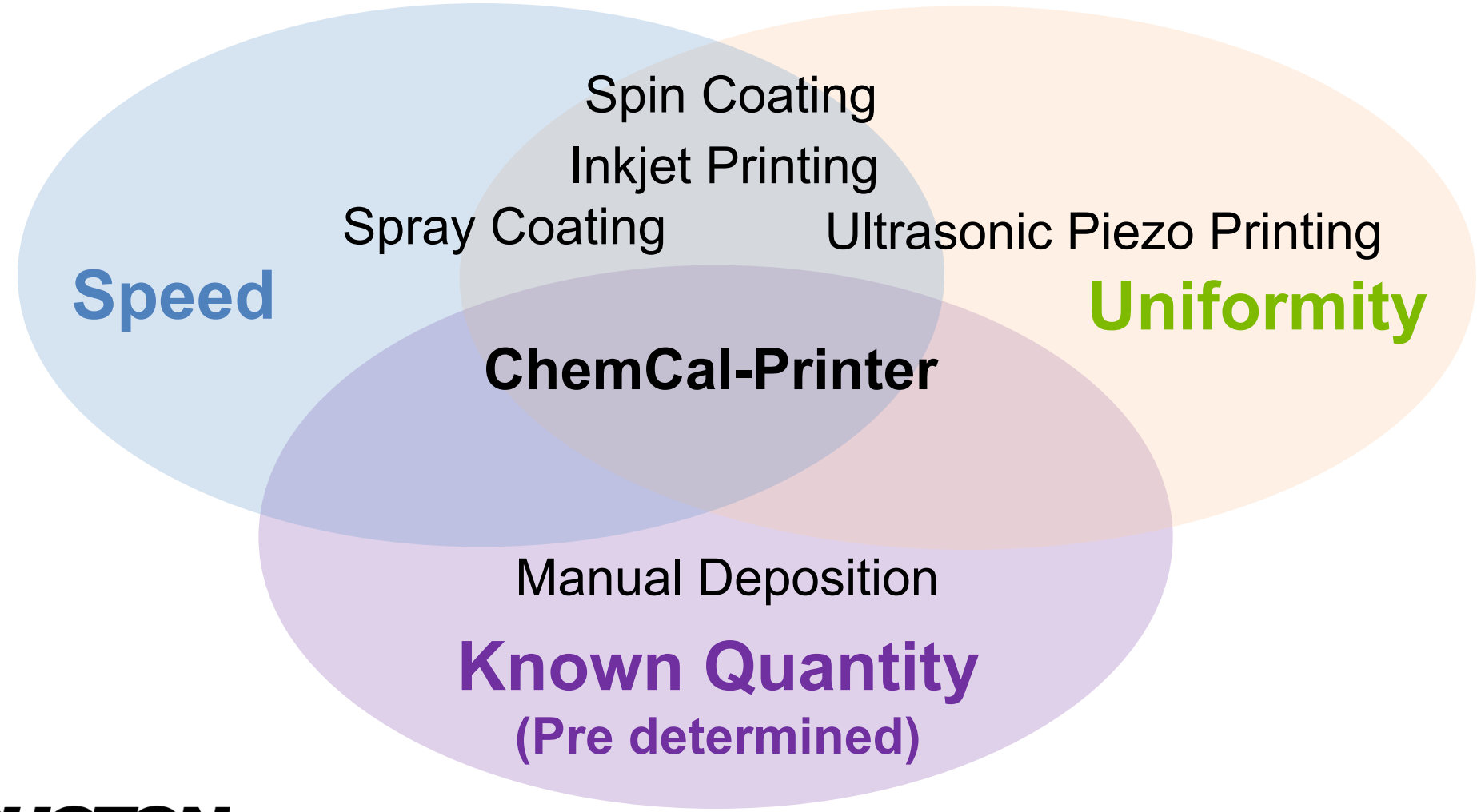
Why do you need a chemical printer?

- 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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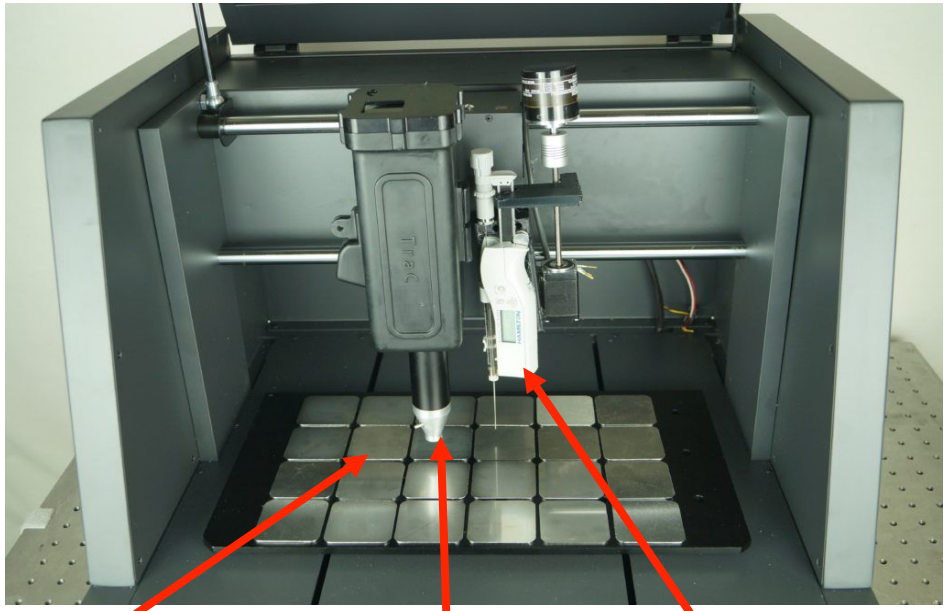
NIST Traceable Chemical Concentration Calibration

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.)**

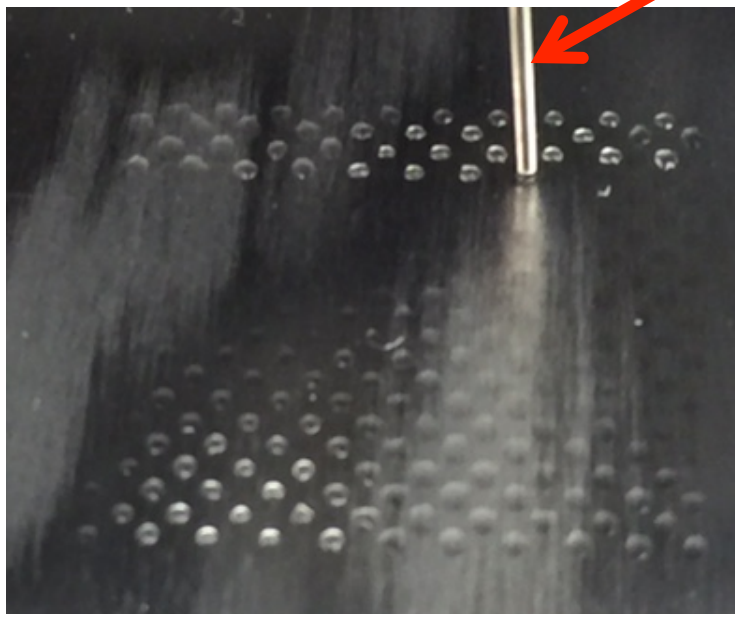
PHOTON SYSTEMS

1512 Industrial Park St., Covina, CA 91722 T: 626 967-6431 F: 626 967-5813 www.photonsystems.com

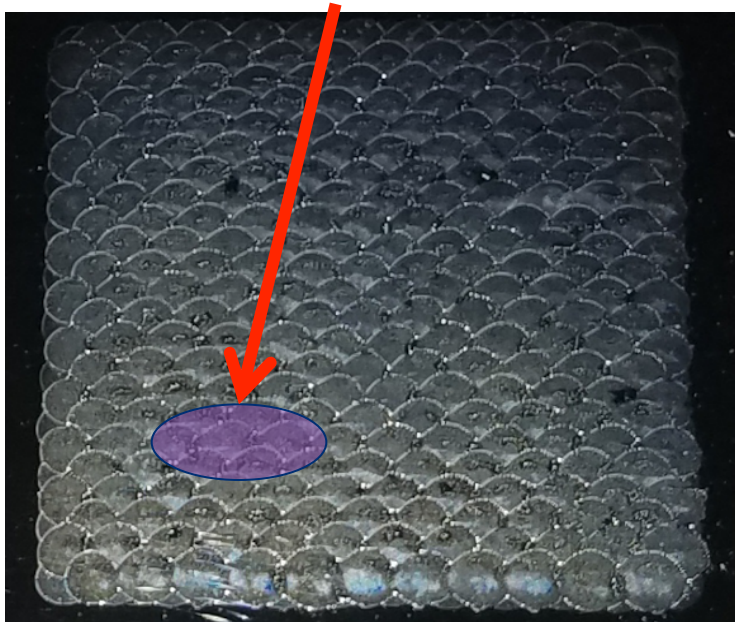
Printing

Up to 5x5 cm grid

NIST Tracible Syringe



TraC Beam Diameter



High surface tension solvent. Individual drops.

Low surface tension solvent “Fish Scale Pattern” Overlapping drops

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 **ChemCal.**

Questions ?