Case Study in implementation of RCV tool.

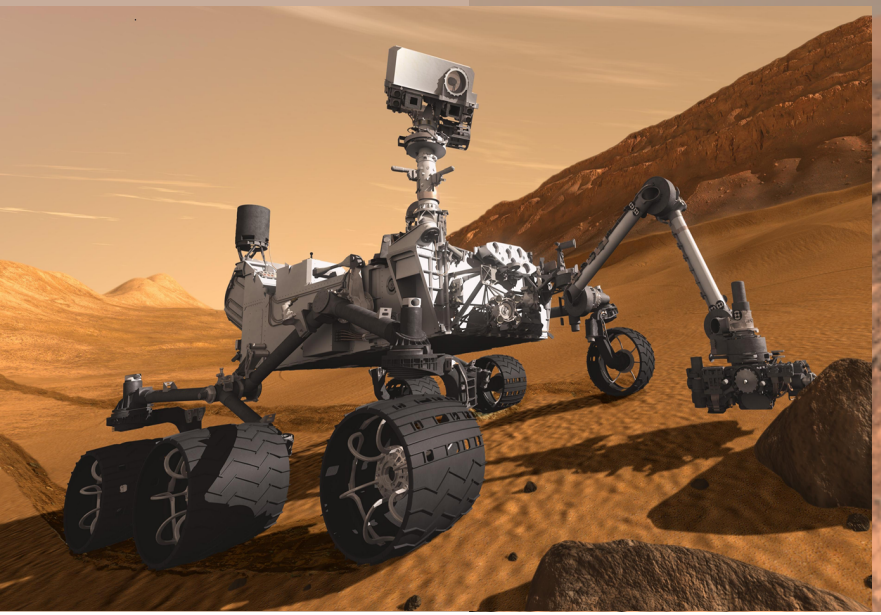
Ray Reid from Photon Systems

Rapid Cleaning Verification

The fast track to swab results

Who is Photon Systems:

Photon Systems and JPL have been working for over 20 years to develop deep UV Raman and spectroscopic methods for detection of organic compounds of biological origin materials on Earth, Mars and beyond.



Rapid Cleaning Verification/Validation

Problem:

Cleanliness must be verified between batches. The current process uses time consuming and error prone technologies (i.e. swabbing).

The goal

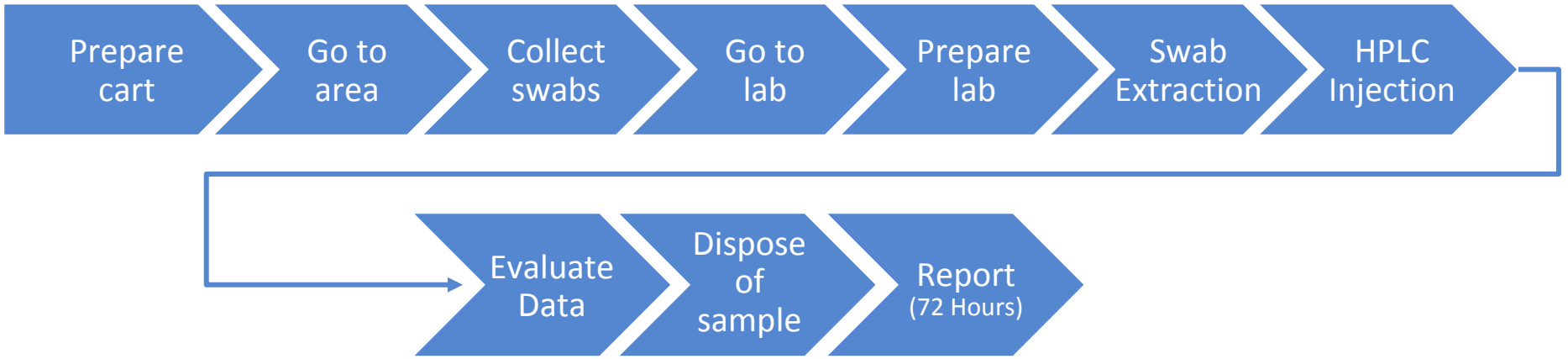
To augment or replace the present swab & test method for equipment cleaning verification with a faster and better controlled and documented method.

The solution

A handheld device that quantifies trace amounts of API in real time on manufacturing surfaces.
Result: Significantly reducing production down time.

Cleaning Verification Methods

Steps in today's traditional swab & test methods



Steps for today's TraC sensor surface detector

The Drivers for Rapid Cleaning Verification Methods

Quality

- Reduction of human errors
- Reduction of the “art” of sample acquisition and testing
- Decreased risk to production

Safety

- Decreasing the number of operations
- Improving knowledge
- Reducing/improving cleaning cycles

Cycle Time

- Processing samples on the “shop floor”
- Enabling business decisions at the point of process
- Decreased wait time

The Tools of Rapid Cleaning Verification: Surface Detectors

TraC Chemical Detector

A disruptive new hand-held rapid measurement system to verify surface cleanliness of pharma equipment.

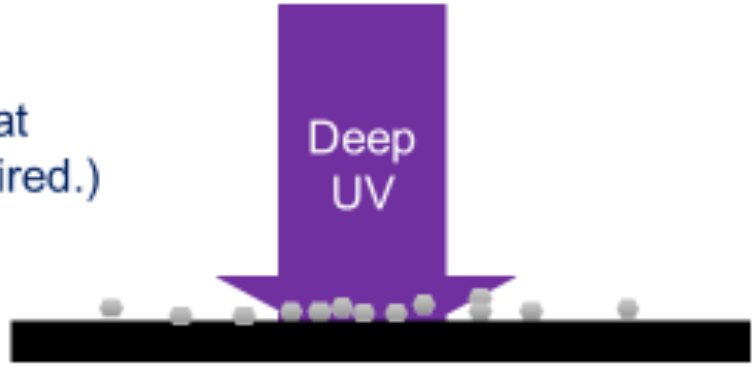
ChemCal-

A precision chemical printer enabling API deposition for calibration of cleaning validation methodologies such as TraC.

How the Surface Detection Tool (TraC) Functions

FOR EACH SPOT/AREA ANALYZED:

Step 1: Deep-UV source illuminates surface that may contain residual API. (No preparation required.)



Step 2. Deep UV interaction with sample causes native fluorescence emission, returning back to the instrument, without the need for reagents.

Step 3. Collected light is collected in 180 degree backscatter and is separated and detected with a multichannel detector.

Step 4. Multichannel spectral data is processed & stored with site, API, and position information.

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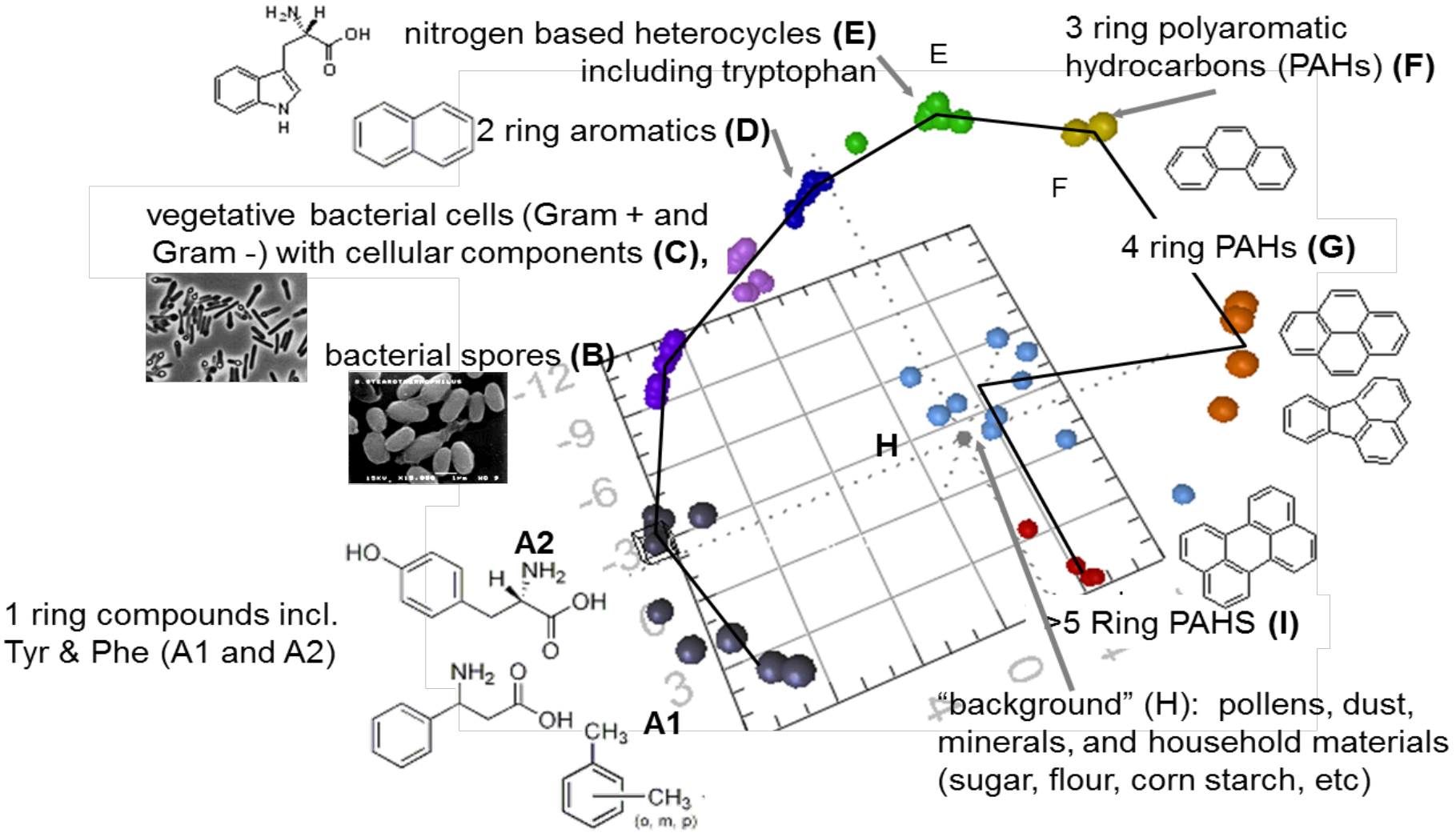
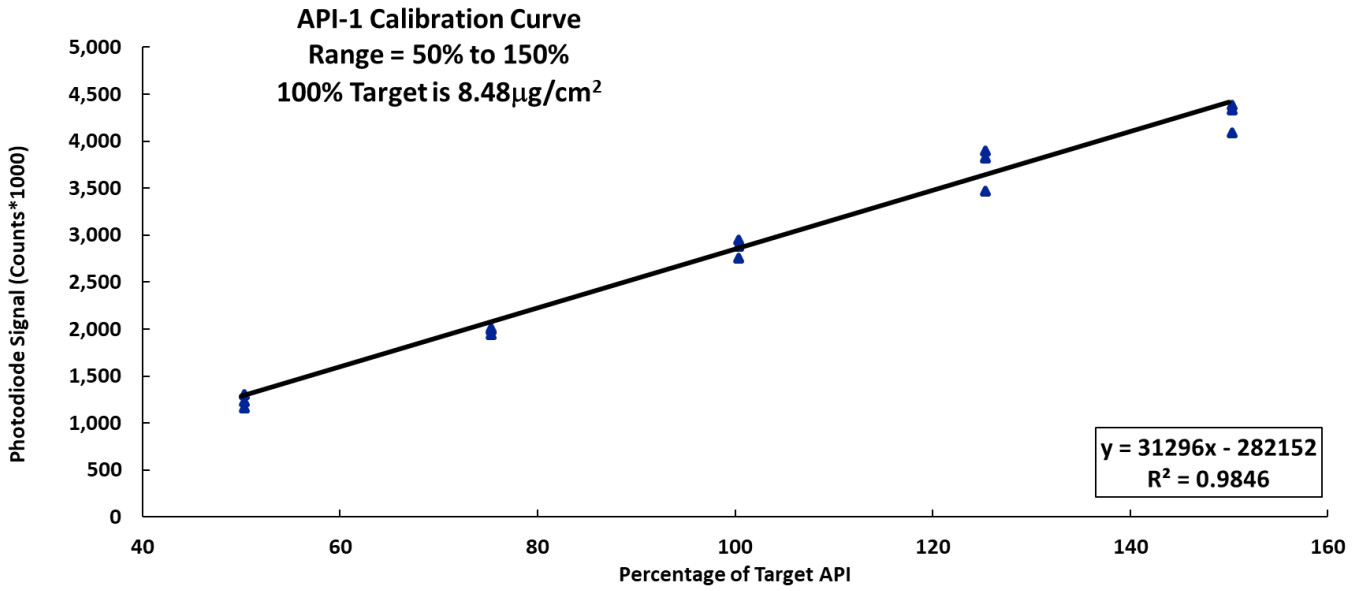
UV Fluorescence Detection of Organic Compounds

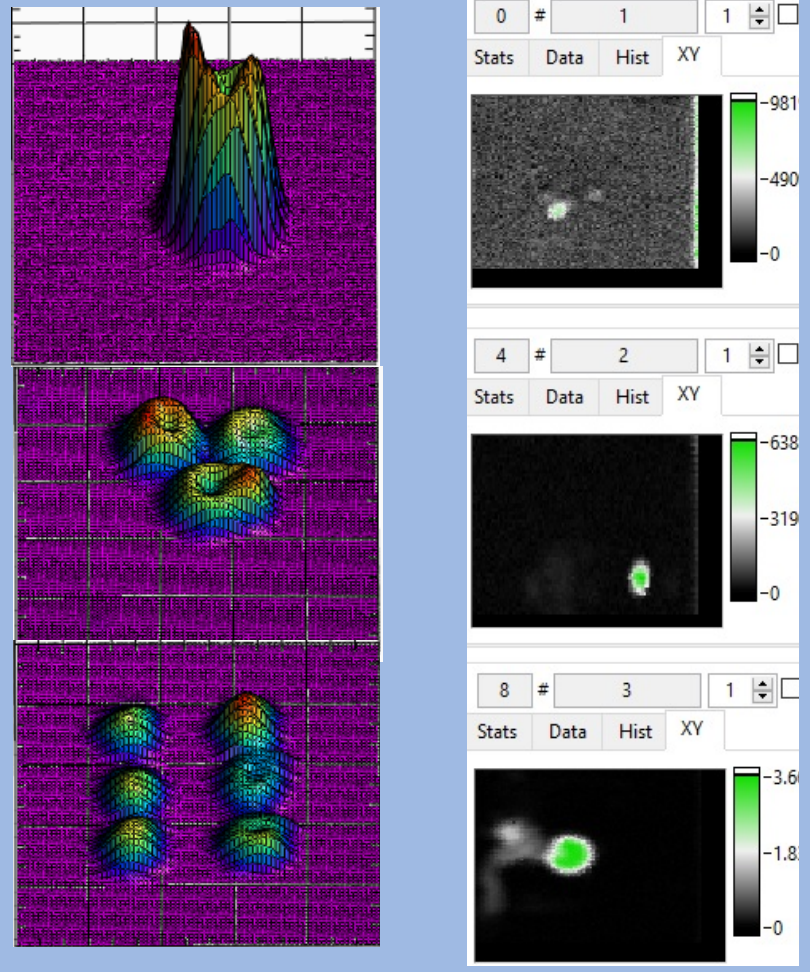


Fully Automated Scanning Functionality and Calibration Curves:

Scan Mode – XYZ scanning adds autonomously generated calibration curves and high resolution heat maps of API. :



Heat Mapping



Generation of Samples for Surface Detection:

Ultrasonic Piezo Printing

Spin Coating

Spray Coating

Inkjet Printing

Speed

Uniformity

ChemCal
Depositor

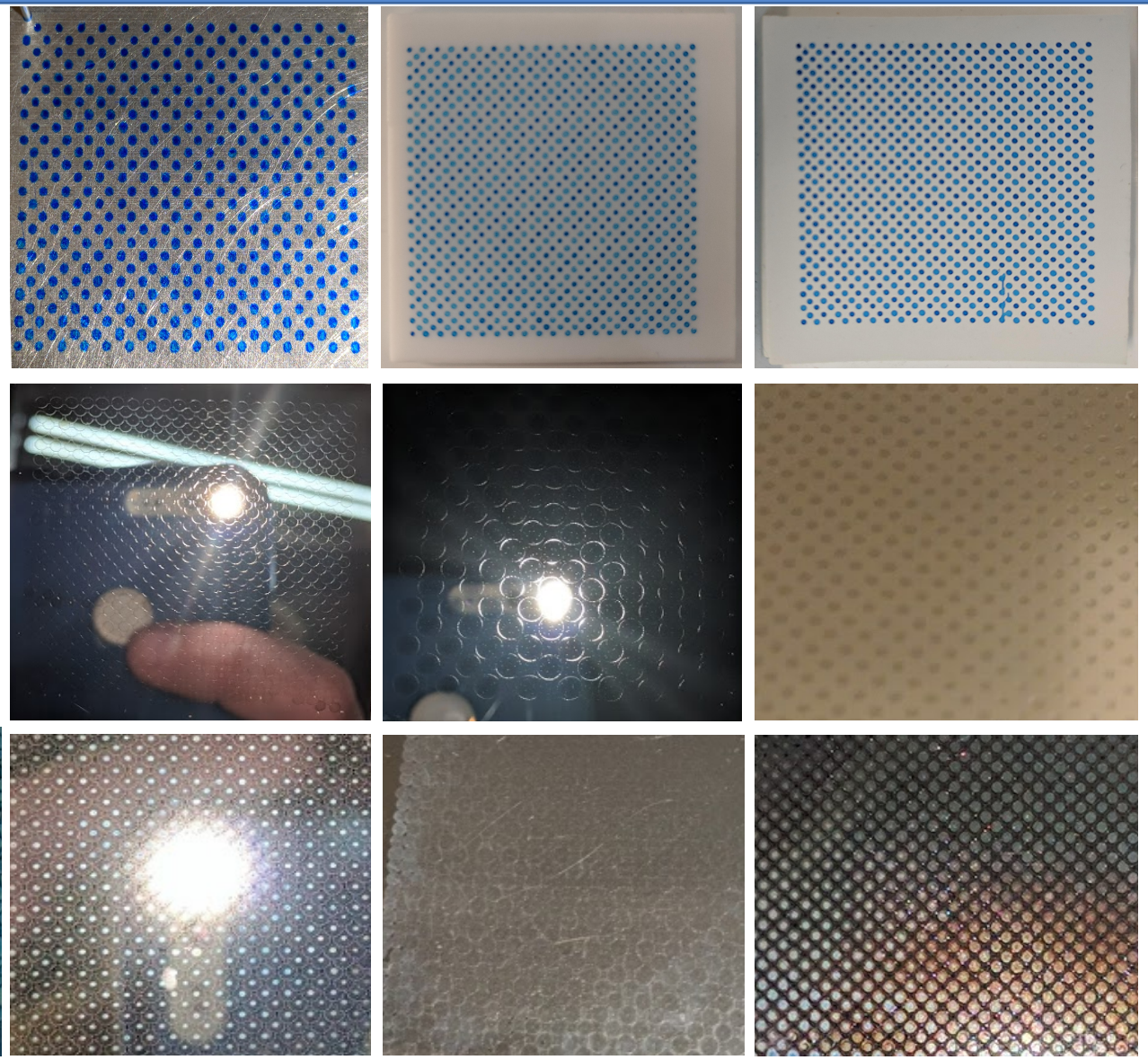
Manual Deposition

Known Quantity

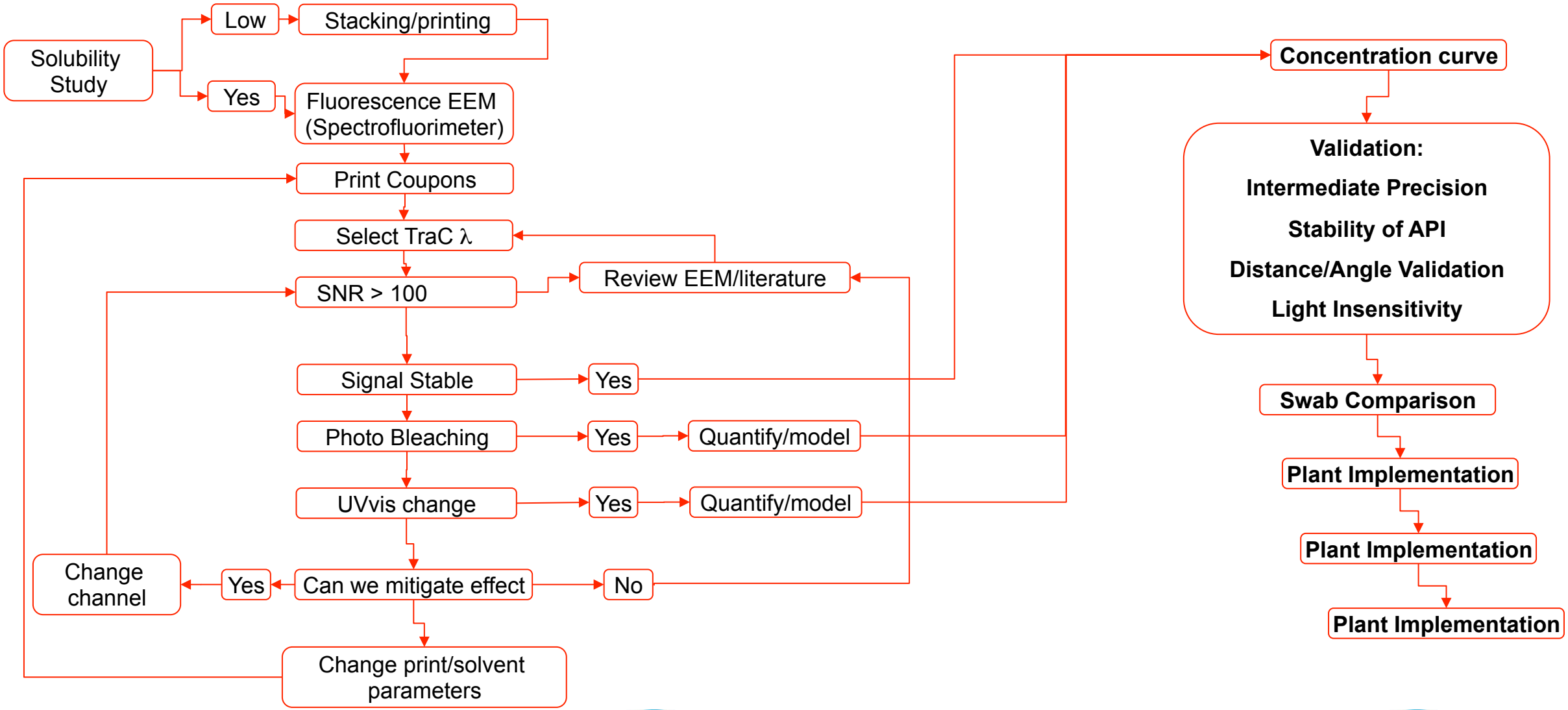
Sample Types for Surface Detection

Surfaces and Solvent/Solute Compatibility:
Hydrophobic (Hexane, oils like petroleum oil, etc.), Hydrophilic, Acids , Bases, High Viscosity (Glycerol and elixirs), Low Viscosity (Dichloromethane, R-OH) and ALL others.

Successful Deposited Materials:
stainless steels (304, 316, [#8,#7,#4])
Teflon, aluminum, Brass, copper, titanium, EPDM, paper, quartz, Polycarbonate, glass, PVC, acrylic , rubber, silicone, food products, Many more..



Pathway to Adopt TraC RCV



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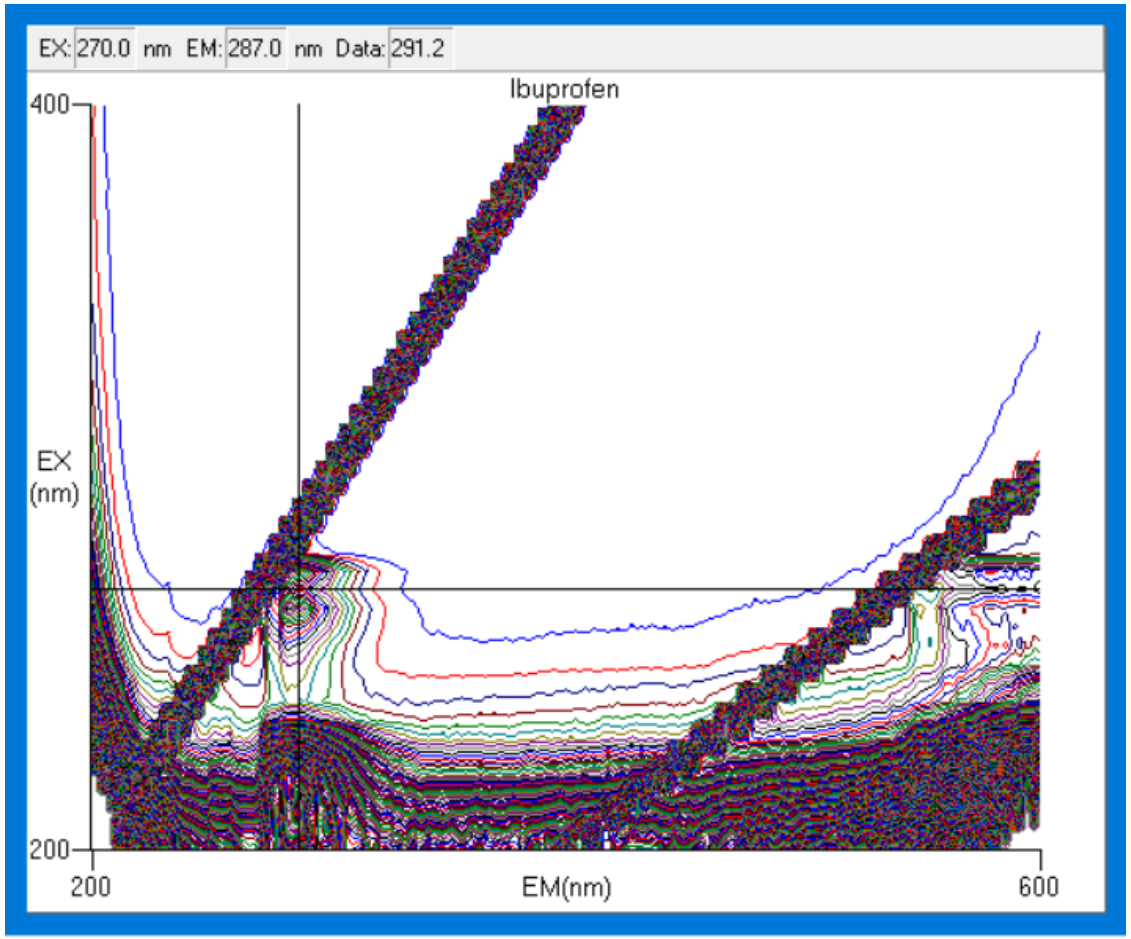
Ibuprofen Fluorescence Profile Using 3d Scan:

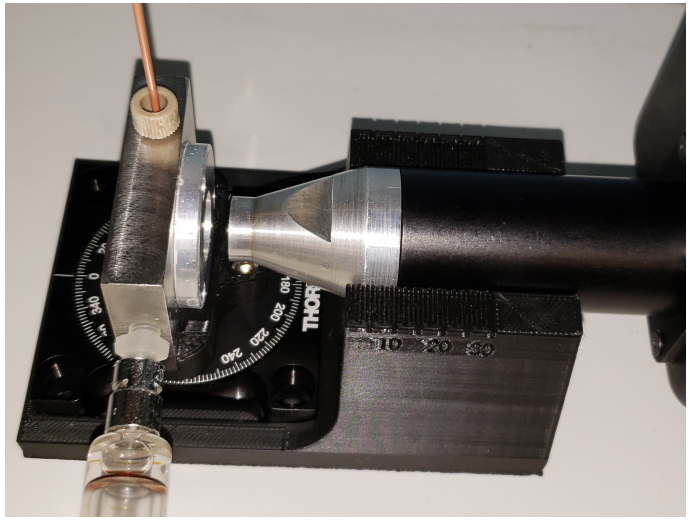
Hitachi Fluorimeter Scan of Ibuprofen Sodium

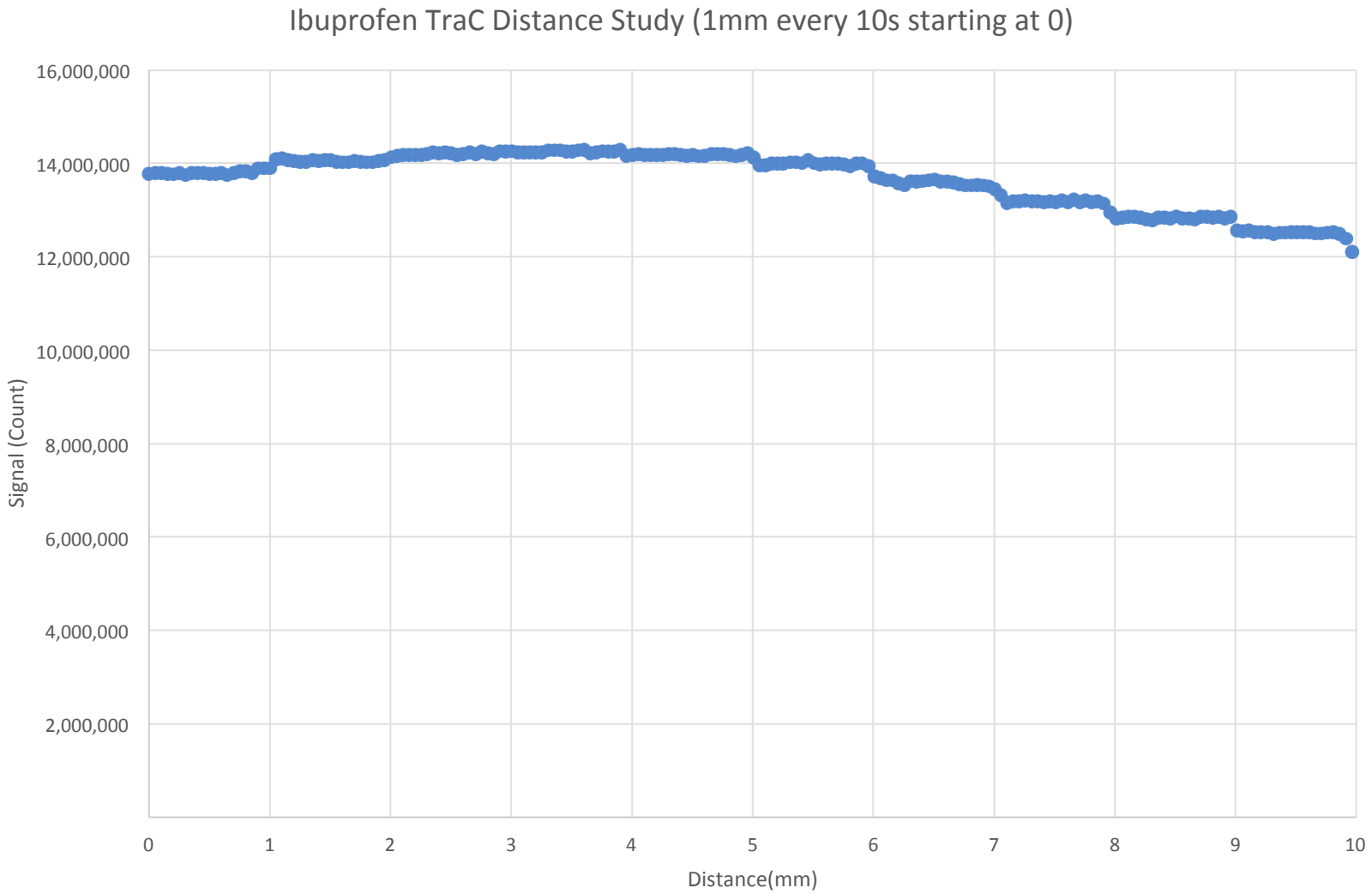


Integral to choosing optimal emission and excitation is understanding the fluorescence profile at every emission wavelength.

Standoff Distance measurement:

- Distance study is performed on the TraC with a flow cell containing 10mg/mL Ibuprofen stock standard solution
- Every 10 second interval is a 1mm increase in distance from the sapphire window of the flow cell starting at contact.
- The angle is set to 0° for the entire experiment





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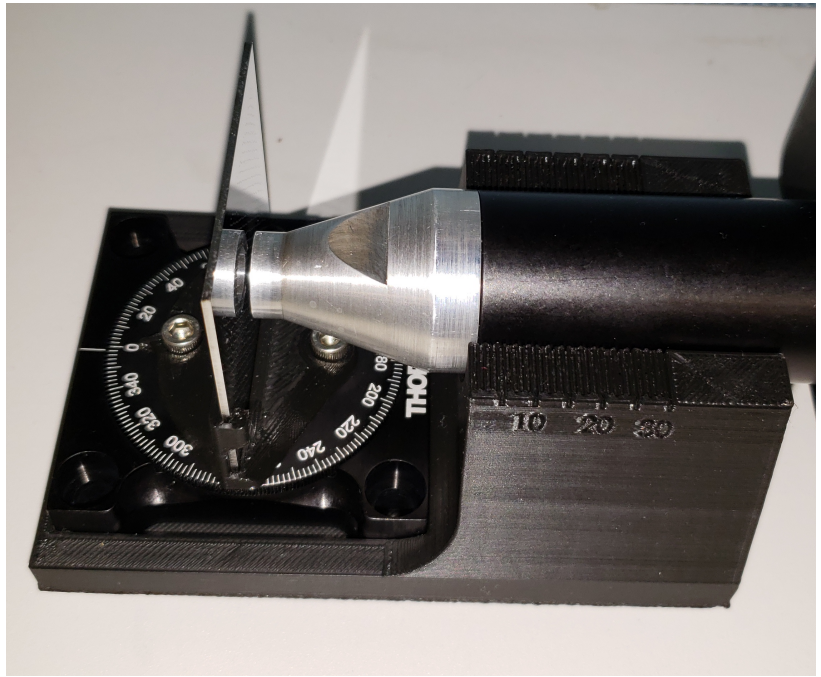
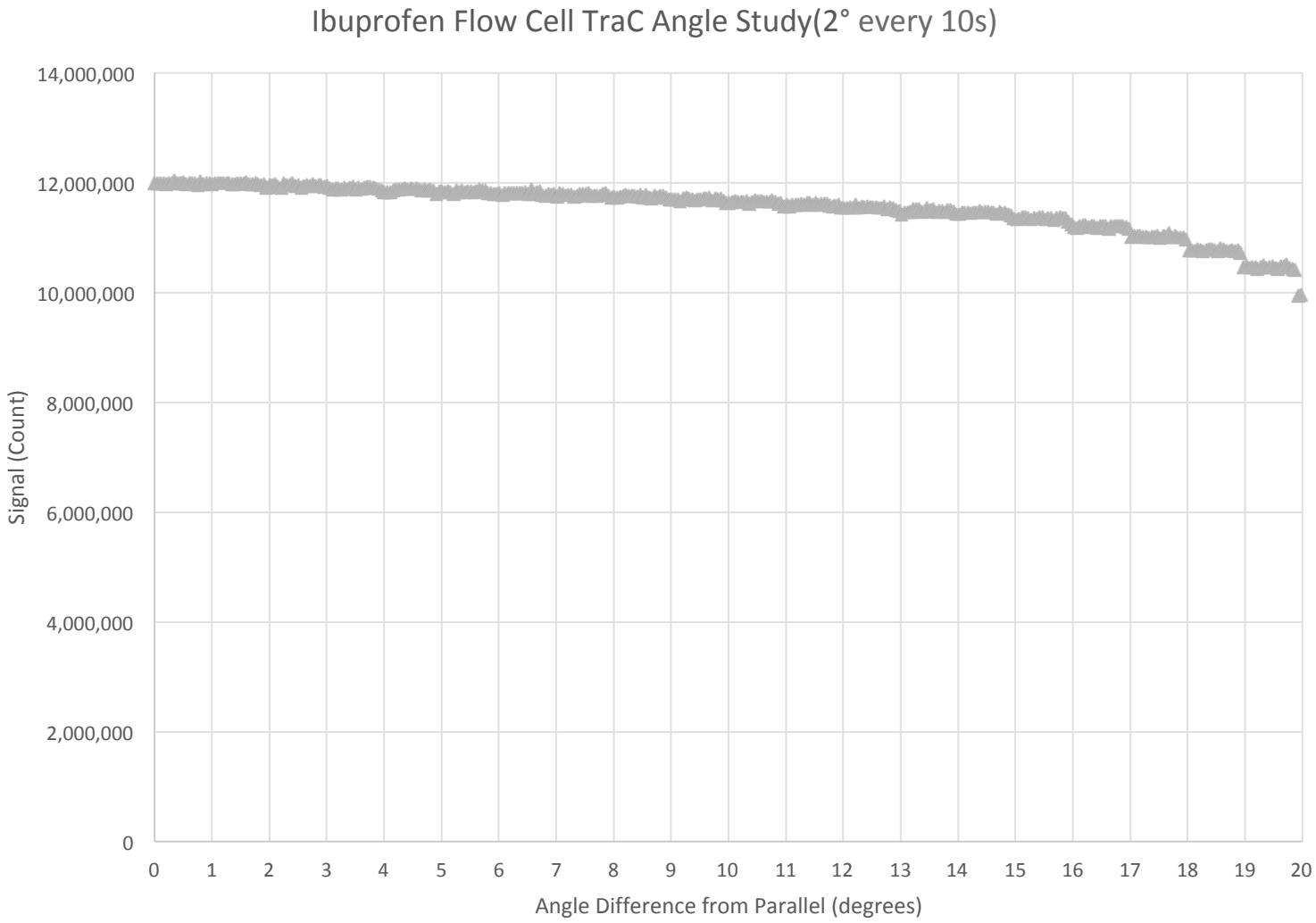
Ibuprofen TraC Angle Study:

- Angle study is performed on the TraC with a flow cell containing 10mg/mL Ibuprofen stock standard solution
- experiment began at 0° and increased by 2° every 10 seconds





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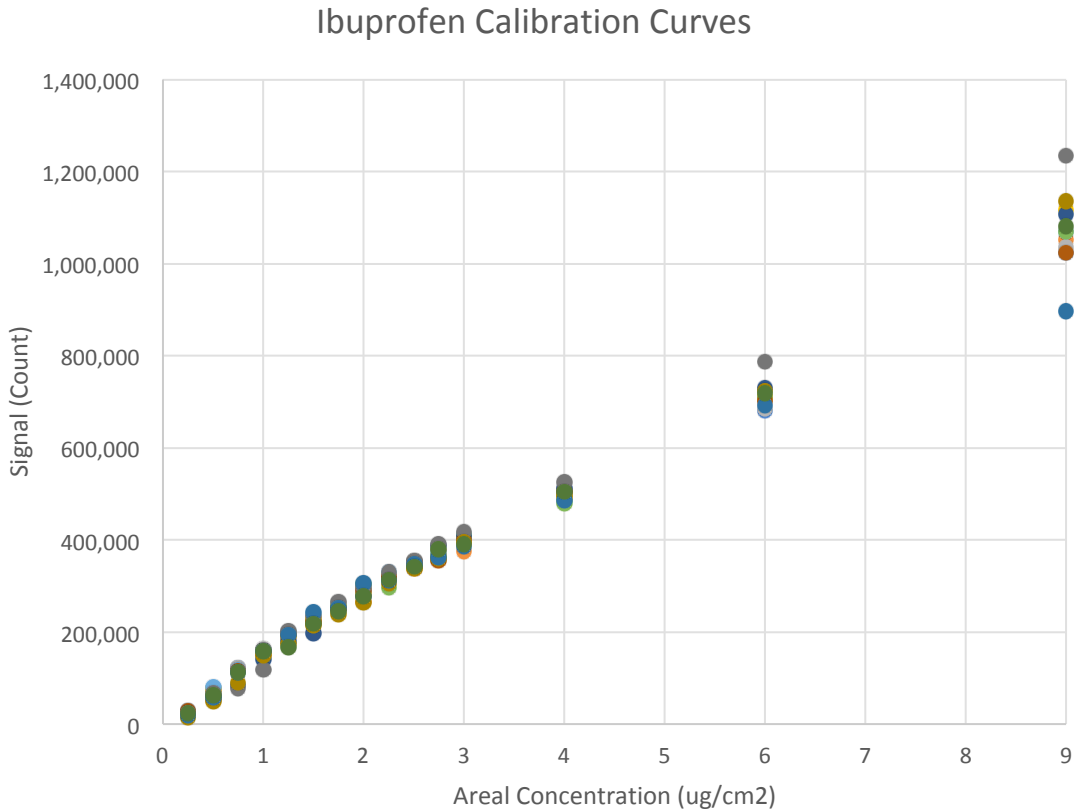
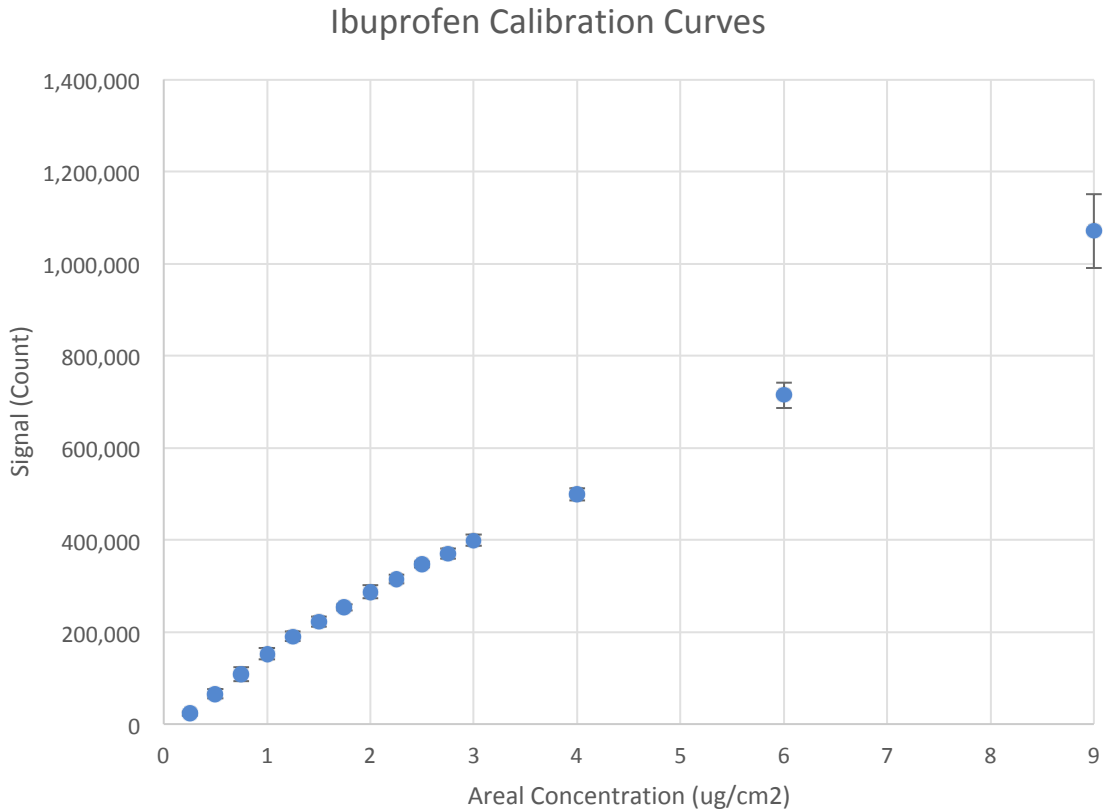
Ibuprofen – TraC Calibration Curve

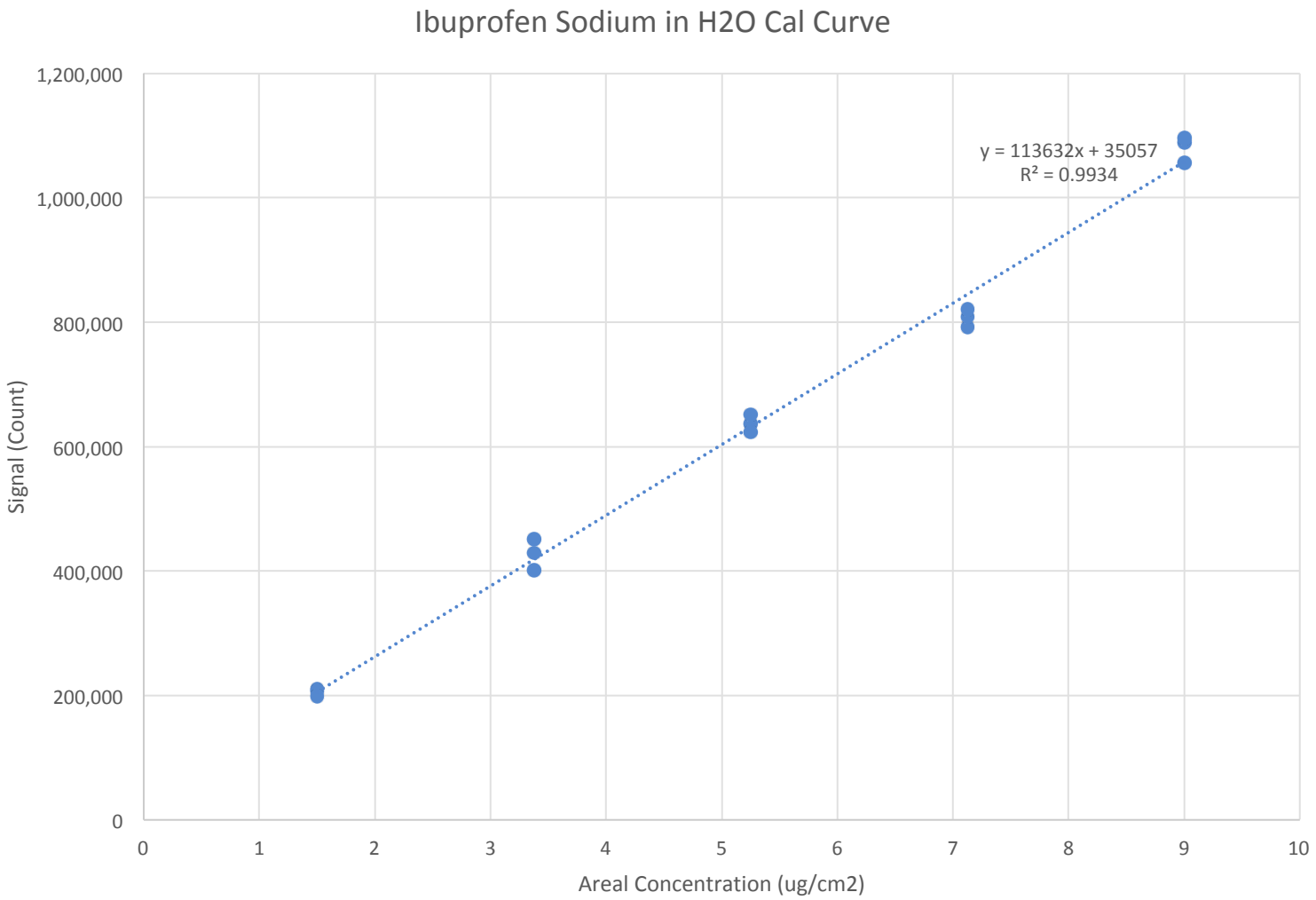




- High resolution calibration curves: The graph on the left shows all of the data points at the first scan ranging from 1-16 hours. The graph on the right shows the mean of all data points at each concentration with error bars depicting the standard deviations

Ibuprofen – TraC Validation

- Calibration Curve :
- The Time 0 scan is 1 hour after printing completed.



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Ibuprofen – TraC Validation

[conc]	Background	Signal @ 0H		Signal @ 48H	
		Raw	Background Sub	Raw	Background Sub
1.6	75382.694	274258.694	198876	277208.528	201825.834
1.6	74872.528	289874.056	215001.528	289325.361	214452.833
5	76149.778	639073.139	562923.361	634218.056	558068.278
5	76416.444	668840.667	592424.223	658307.889	581891.445
8.5	75929.111	1085908.167	1009979.056	1043740.444	967811.333
8.5	74434.694	1186550.222	1112115.528	1123929.028	1049494.334

Regression Model

Finally, the linear regression is done:

Shown below is the printout for the model.

- SurfaceDensity = -0.4769 + 7.977172210^{-6}*Counts
- R-sq = 0.9851
- RMSE = 0.3771

- Table above shows Areal concentrations were chosen to be within the 1.5-9µg/cm^2 range and 10% from the low, mid and high points
- RMSE is calculated through RStudio to be 0.4 –
- Slope was taken from the 0H and 48H of calibration curve

Ibuprofen – TraC Validation 3:

Ibuprofen – TraC Validation

PASS/No Pass

- √ CRITERIA: For each plate / scan, the %RSD should be <10%
- √ CRITERIA: A scatterplot of mean Surface density v Counts with best-fit line should be linear and have no clear outliers or non-linearity.
  - √ This plot should have a number of points equal to (number of plates * number of time scans) on it
- √ CRITERIA: A linear regression of mean surface density v counts should give:
  - √ $R^2 > 0.95$
  - √ Residuals for the model should have no weird patterns
- √ CRITERIA: The lowest sample's signal should be > Quantification limit
- √ CRITERIA: A time-series plot of each plate scanned over time should show no significant signal drop or any strange patterns
- √ CRITERIA: For each plate over the time scans, the %RSD of the calculated means should be calculated and be <%10
  CRITERIA: Each predicted concentration should be +/- 15%
- √ CRITERIA: The predicted error should not be unidirectional, e.g. All of the predicted values shouldn't be under-predicting. This would be a clear case of bias in the model and be bad.
- √ CRITERIA: The RMSEP can be calculated and should be low.

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TraC Plant Trials at Guayama

Goal of the Guayama study

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- To evaluate the performance of the TraC to quantify ibuprofen *in situ* (side by side study with swabs)

- To determine which surface / equipment could be difficult or impossible to analyze with the TraC

Methodology

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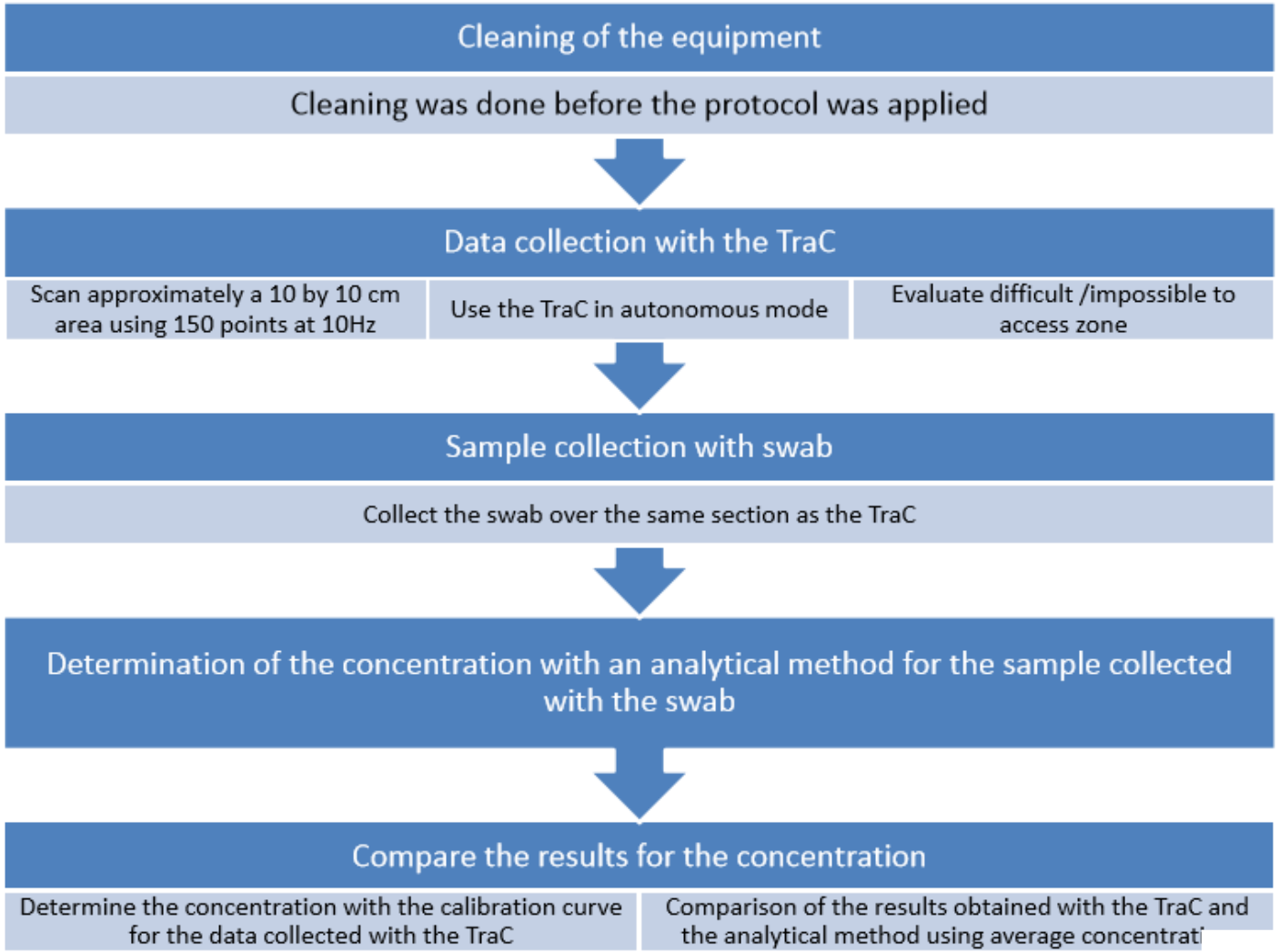

Why This is Important:

Results
Type of equipment & area analyzed

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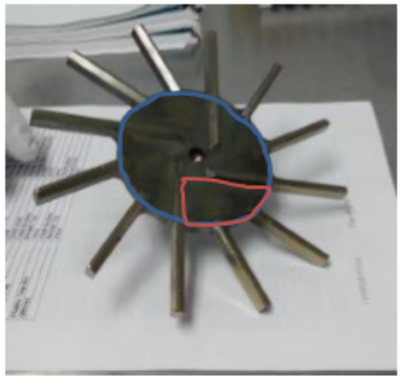
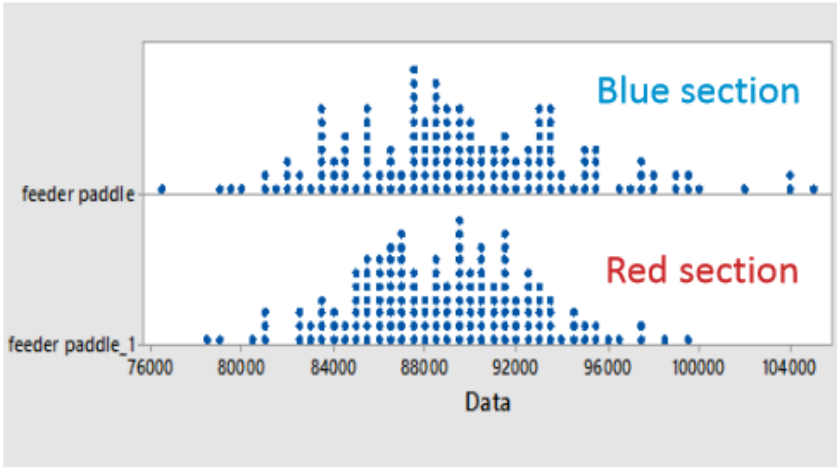
Holding bar
- Limit: 6µg/cm^2
- TraC result is higher than the swab result (positive bias)
- **TraC: Pass**
- **Swab: Pass**



Brass feeder paddle
- Limit: 6µg/cm^2
- There is apparently no impact caused by bumps on the signal
- **TraC: Pass**
- **Swab: Pass**

Side of bowl
- Limit: 3µg/cm^2
- TraC result gives a concentration between 0 and 3.47µg/cm^2
- **TraC: ?**
- **Swab: Pass**



Results
Type of equipment & area analyzed

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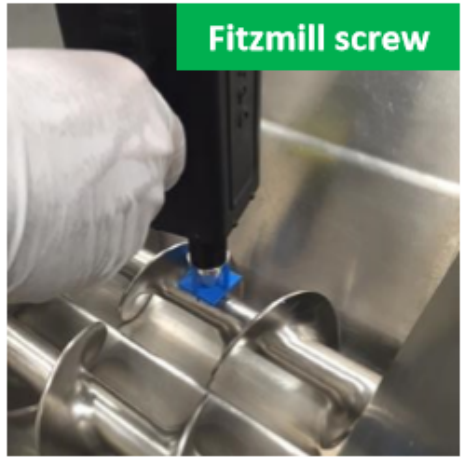
Disassembled parts

Equipment

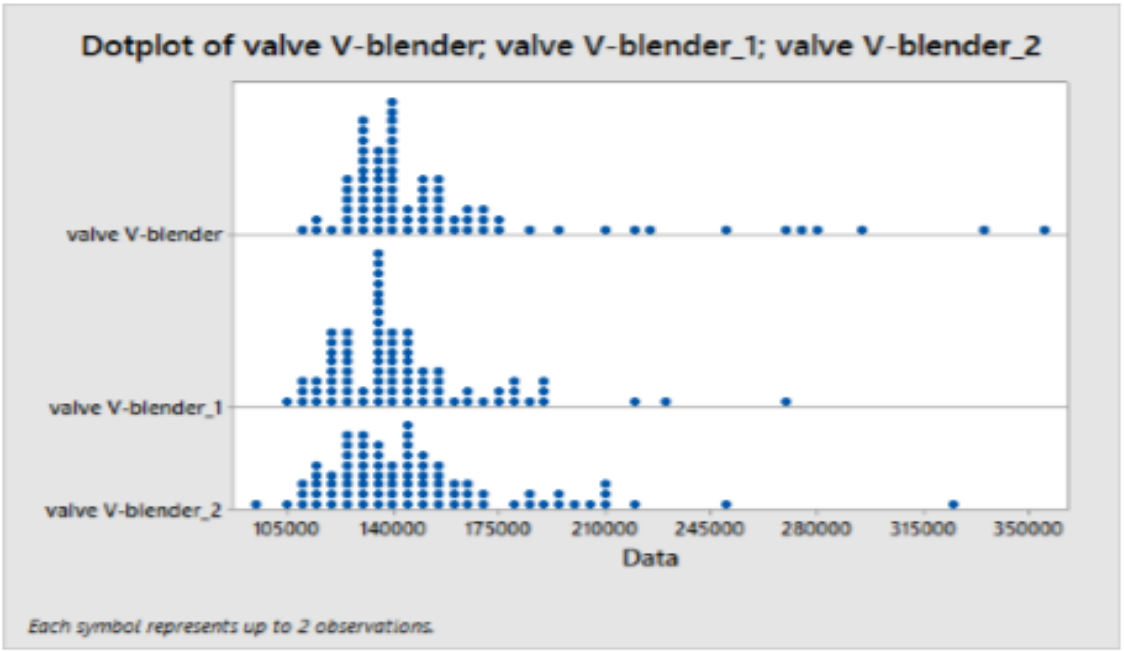


Results
Impact of different operators

User 1

User 2

User 3



- TraC training: scanning the valve of a V-blender
- Good reproducibility between the results collected by three different operators

Comparison of Cleaning Techniques

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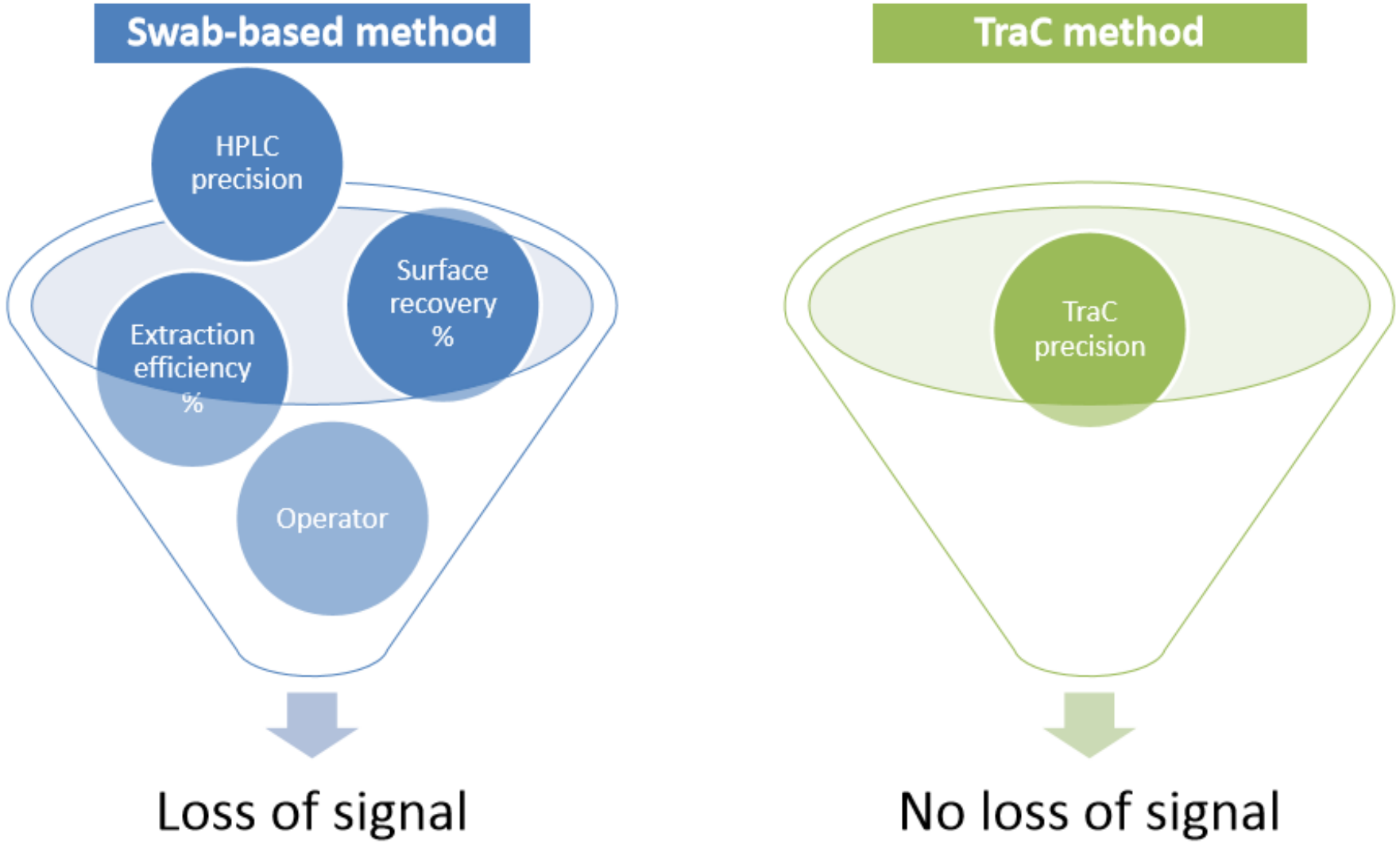
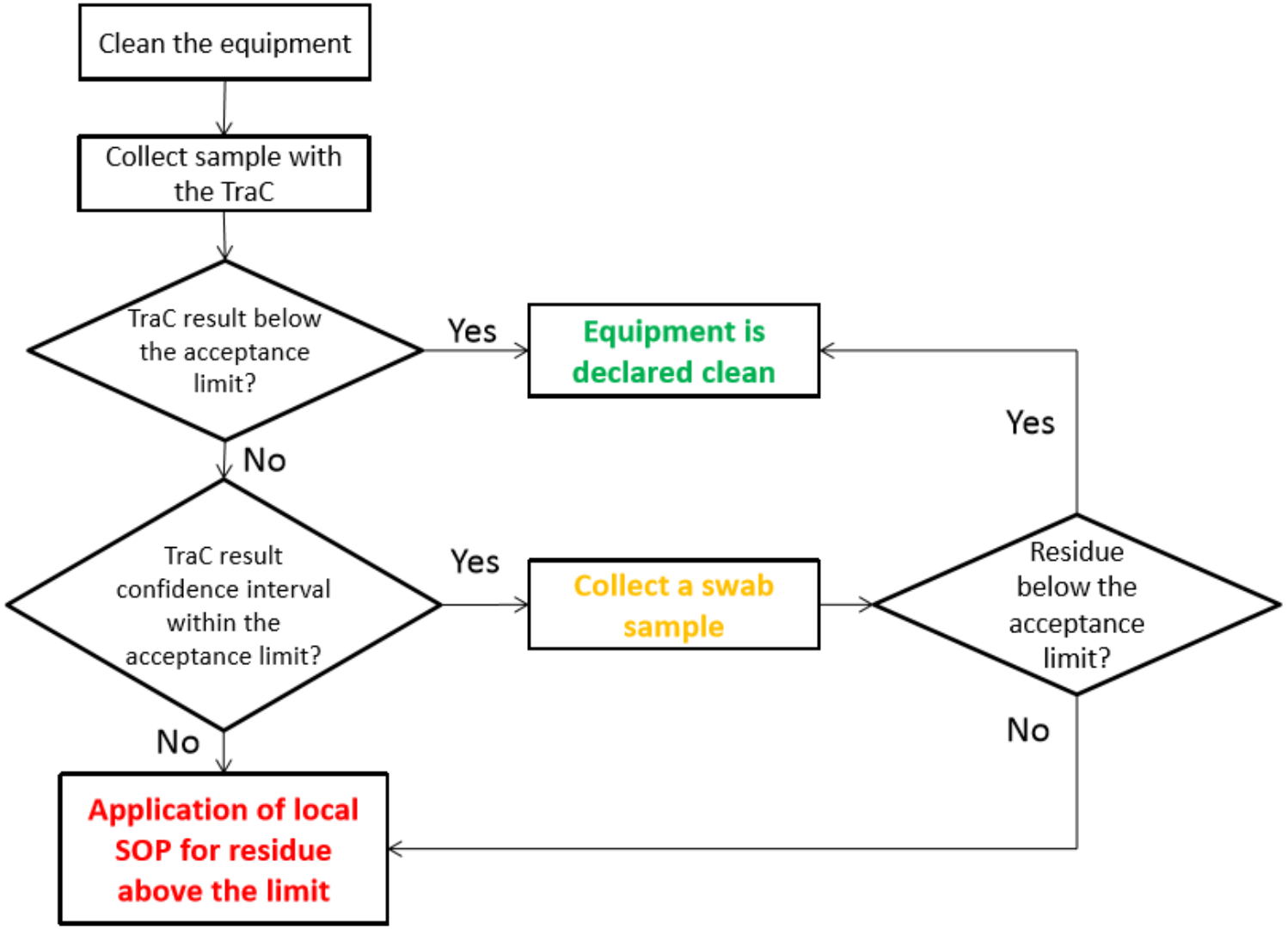


Proposed workflow of future use



Potential applications

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- Routine cleaning verification
- Support in cleaning revalidation
- Support in cleaning validation for new equipment or new cleaning methods
- Support in investigations

Potential applications

Pfizer GLOBAL SUPPLY

Impact on future methods and compliance:

Fully self-contained sensor enables go/no-go certification of results.

Printer provides standard coupons for verification of current methodologies.

Provides dramatic savings in cost and speed for certification of machine cleanliness compliance.

Other applications:

Hot Spot cleaning detection.

Trace contamination non production areas (i.e. shipping and receiving).

Rapid cleaning procedure development: due to instant feedback of surface cleanliness.

Training New Swabbing personnel and protocols.

Acknowledgements:

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