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# *Quantitative Analysis using the TRS100*

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*Insight from Light*



# Outline

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- Who we are
- Technology
  - Transmission Raman spectroscopy (TRS)
- Benefits of TRS
  - Case studies and examples
- TRS100 Instrument
  - Performance
  - Regulatory compliance



# Cobalt Light Systems Ltd.



- Spin-out from UK public research facility – 6 years old
- Manufacture products for pharma and security
- The USP – we measure ***through*** objects
  - Through non-transparent containers
  - Through intact opaque objects



# Raw Materials Verification

- Verify identity of raw materials through unopened containers
- 5-20 seconds per measurement
- Easy to use



**RAPID**



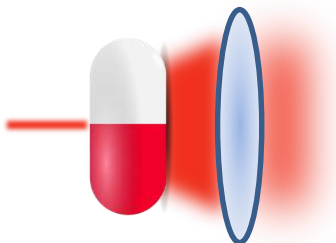
# Airport Bottle Screening

- Change in EU airport screening
  - 100ml restriction being phased out
  - Needs new screening technology
- Insight100 screens for threats in under 5 seconds



# Transmission Raman

- Transmission Raman
  - Content uniformity
  - Polymorph analysis
- Replace HPLC for routine CU
  - >10 tablets per minute
  - No sample preparation
  - Easy data modelling



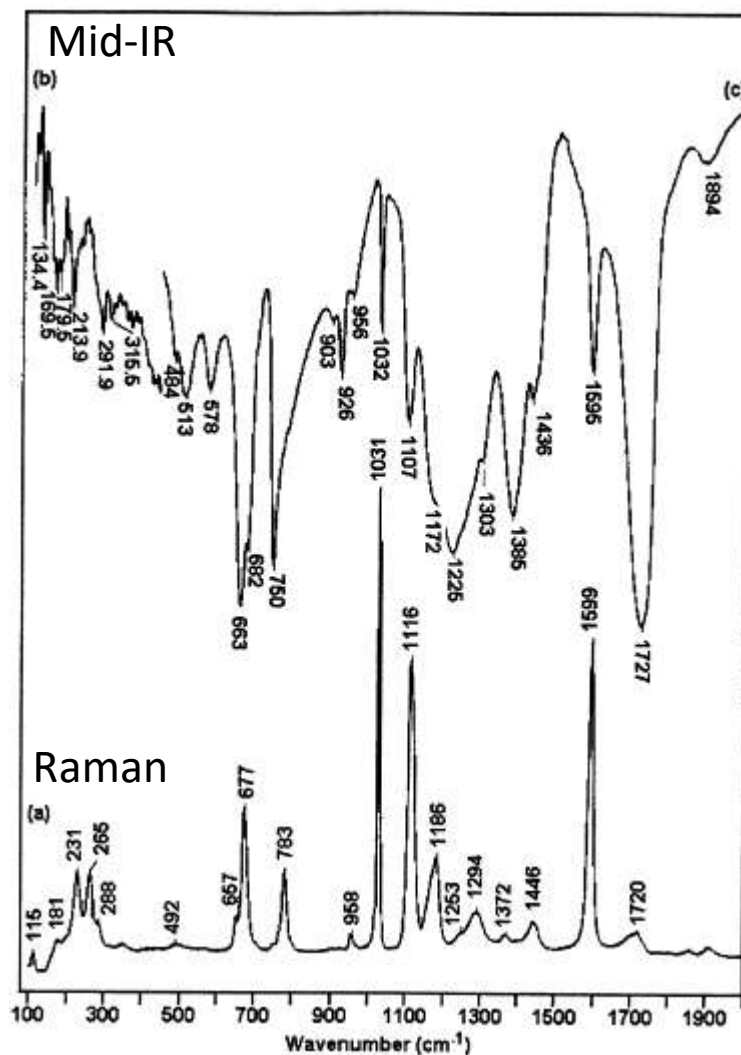
**TRS100**



- Based on Raman spectroscopy
  - High chemical specificity (>NIR, similar to mid-IR)
  - Non-destructive, non-invasive, and no sample preparation
  - BUT typically limited to surface layer (few hundred  $\mu\text{m}$ 's)
- What we do differently:
  1. Transmission Raman Spectroscopy (**TRS**)
    - Bulk averaged Raman measurements
    - Great for content uniformity, formulation development and QA/QC
  2. Spatially Offset Raman Spectroscopy (**SORS**)
    - Raman measurements through containers
    - Great for security screening, raw materials ID

# Raman Spectroscopy

- Similar information to Mid-IR (FT IR) spectroscopy
- Both techniques highly chemically specific
- Raman faster to measure and easier to use



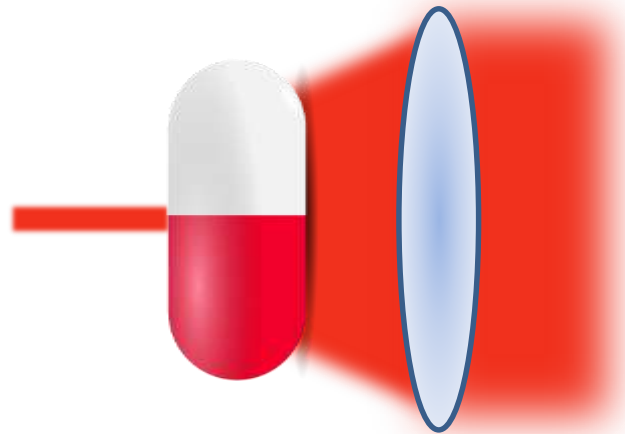
Raman and infrared spectra for *trans*-[RuCl<sub>2</sub>(dinic)<sub>4</sub>]





# Transmission Raman Spectroscopy (TRS)

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# TRS for Pharmaceutical Analysis



Transmission Raman spectroscopy ideal for:

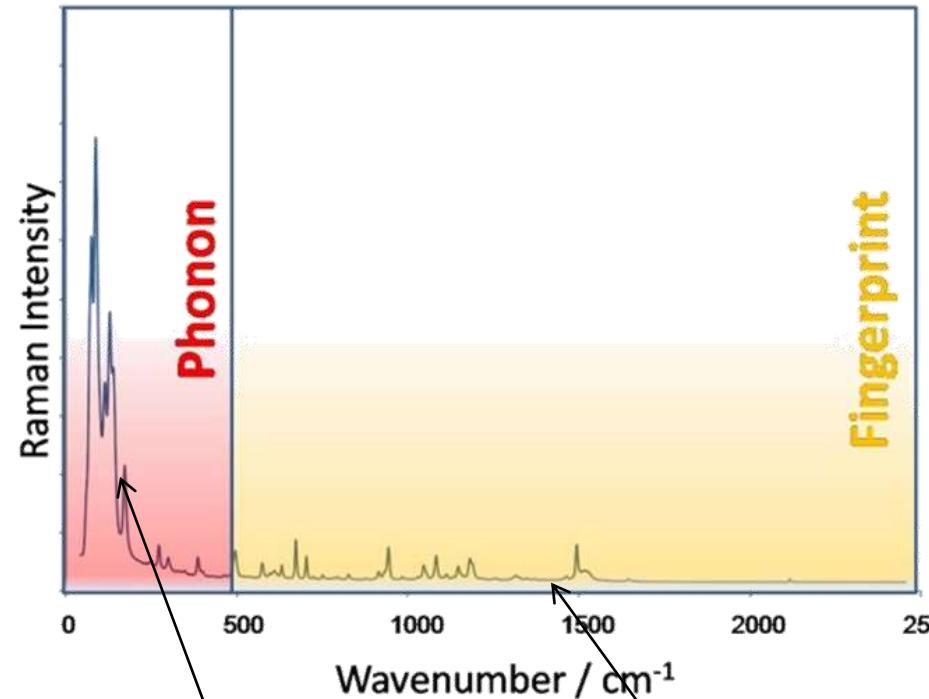
- **Content uniformity analysis**
- Polymorph detection/quantification
- Rapid sample screening, e.g., counterfeits, process variation monitoring

Benefits:

- **Speed** – full content uniformity in seconds
- **Flexibility** – tablets, capsules, powders, multi-API dose
- **No preparation** – through capsules, coatings, vials, etc.
- **Fast method development** – rapid turnaround, lean calibration sets, robust to process/supply changes

# Raman Spectroscopy

- Vibrational spectroscopy
  - Similar information to mid-IR
- Sharp, well-defined peaks
  - Chemical identity by peaks
  - Easy to analyse
  - Good for fault-finding
- Extends into phonon region
  - Polymorph quantification
  - Amorphous content

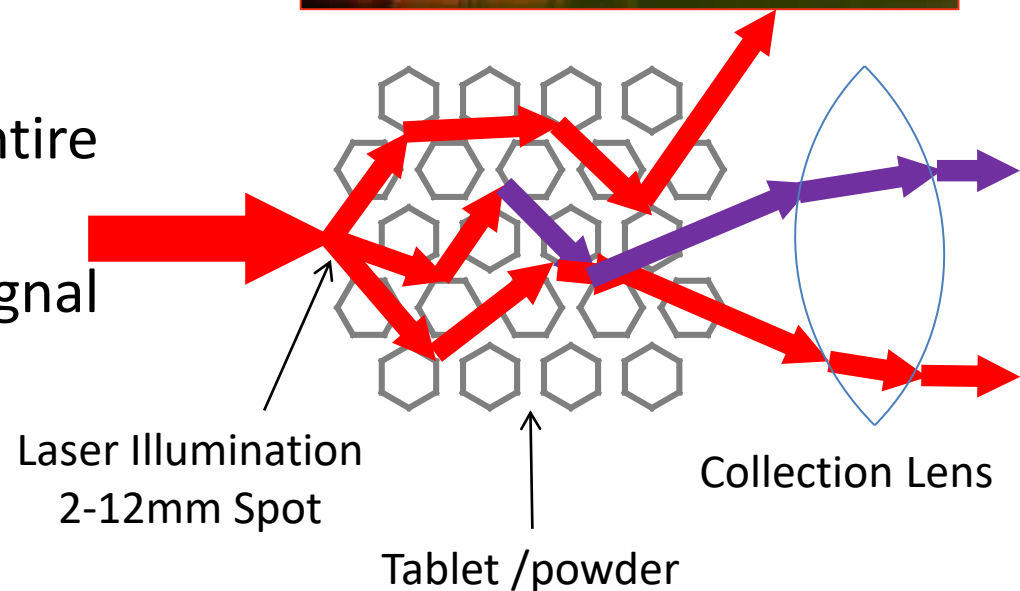


Crystal structure  
information

Chemical composition  
information

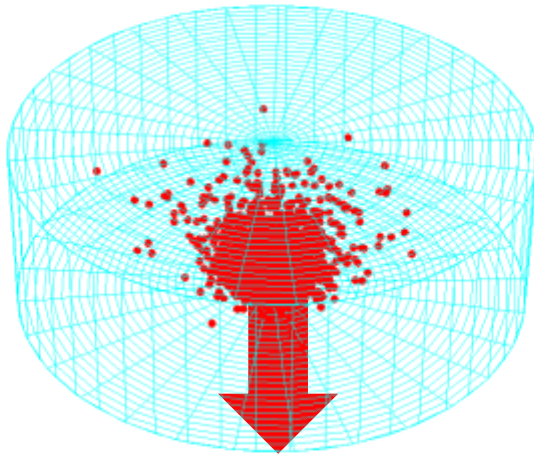
# Transmission Raman Spectroscopy

- Light scatters through object
- Raman generated throughout
- Collected on other side
- Analysis benefits
  - Representative of the entire sample
  - Good capsule/coating signal suppression



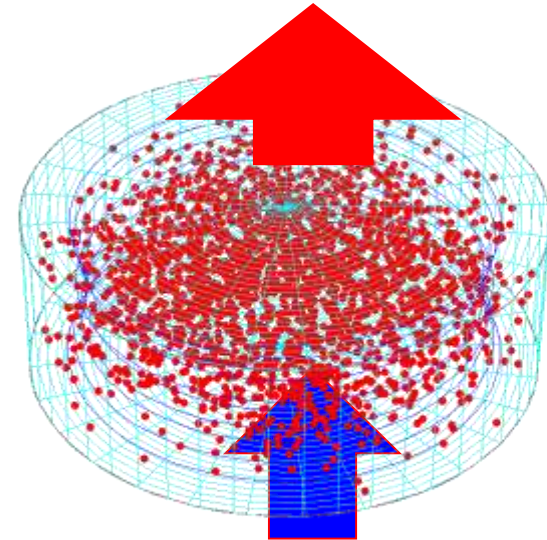
# Samples Whole Tablet

## Sub-sampling in conventional Raman/NIR and TRS

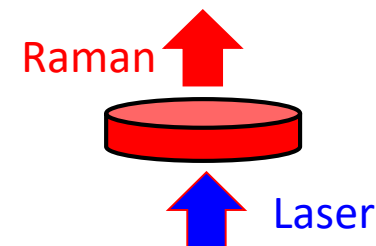
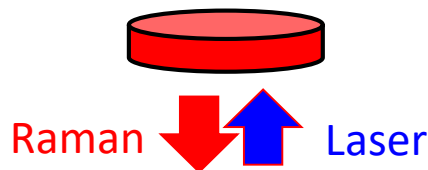


Conventional Raman  
Signal limited to excitation region

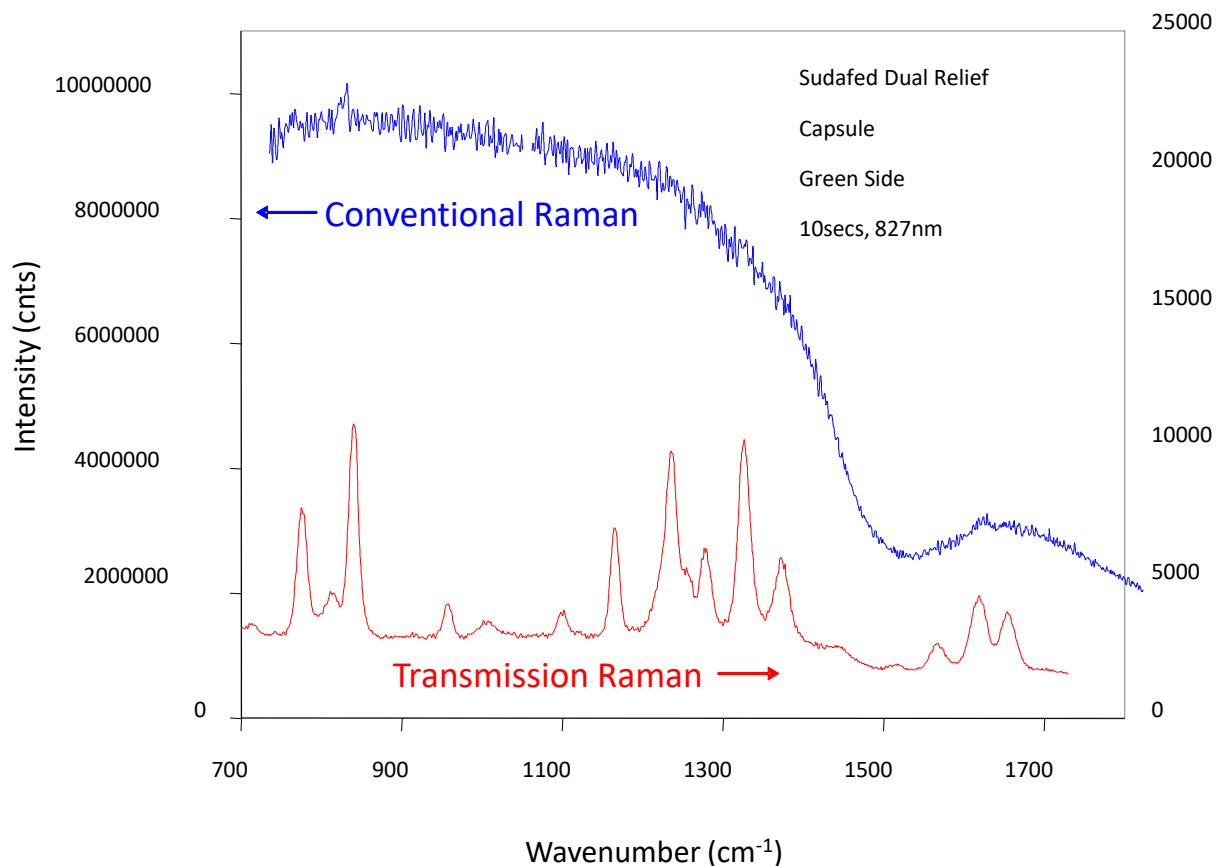
Tablet  
Sample



Transmission Raman  
Signal representative of whole volume



# Coatings and Capsules

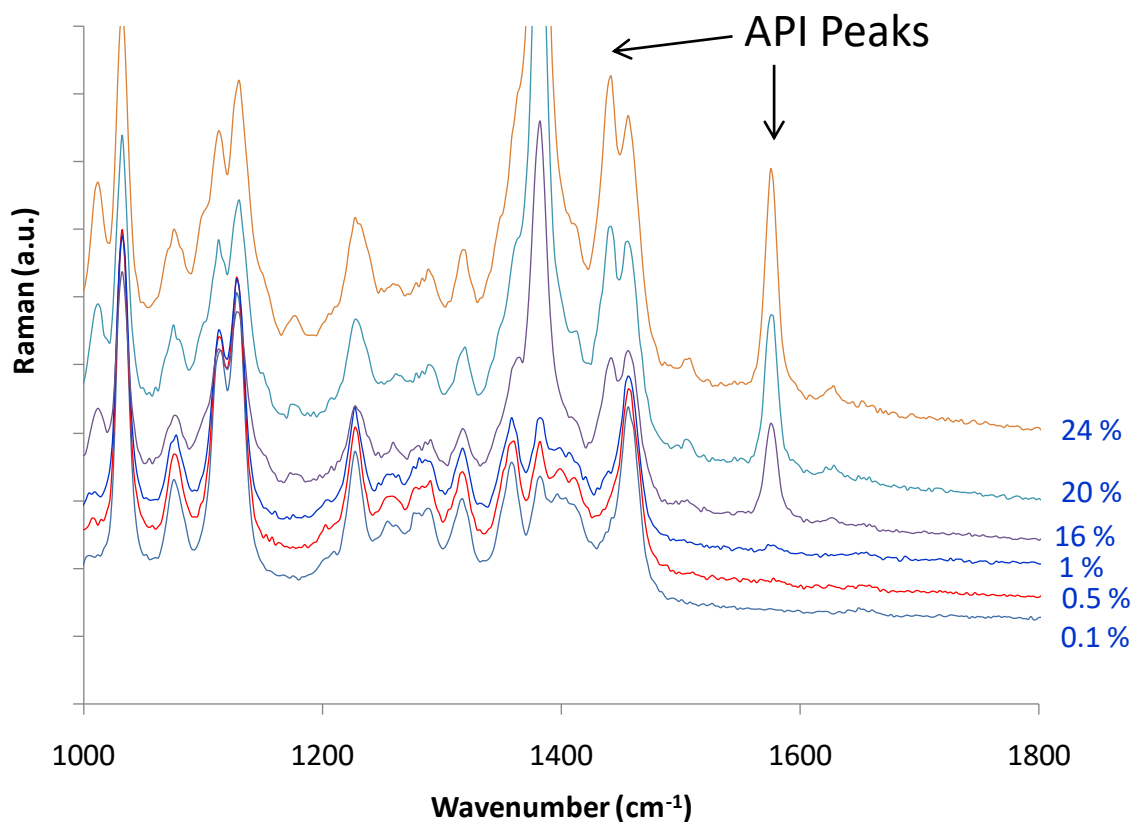


Highly fluorescent  
coloured shell

- Capsule shells and tablet coatings contribute little to the signal
- No preparation required to measure finished products

# TRS Spectral Benefits

Propranolol tablet with mannitol excipient



- Sharp, distinguished bands
- Total spectrum
  - linear sum of component spectra
- Light absorption not an issue
  - >10mm thickness
- Low sensitivity to:
  - Particle size distribution
  - Tablet compaction
  - Formulation processing

Spectra captured in **1 second** on TRS100



# TRS in Formulation Development and QA/QC

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# Content Uniformity Analysis

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- Take a calibration set of ca. 75-125% API concentration
- Measure the TRS spectra
- Use the known concentrations to build a model
- Test the model to make sure it works
- Because TRS is less sensitive to matrix effects this is often all that is needed

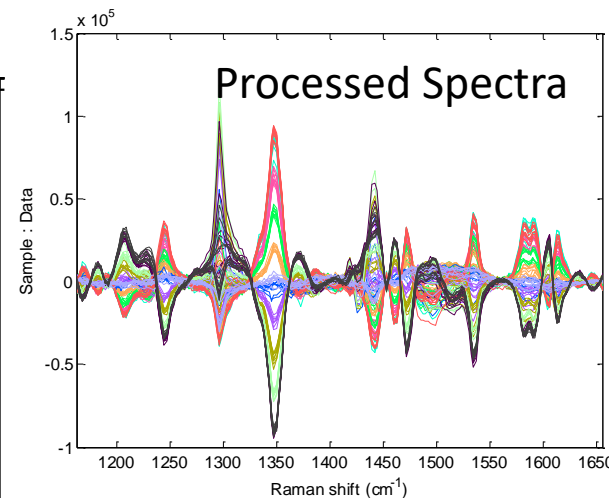
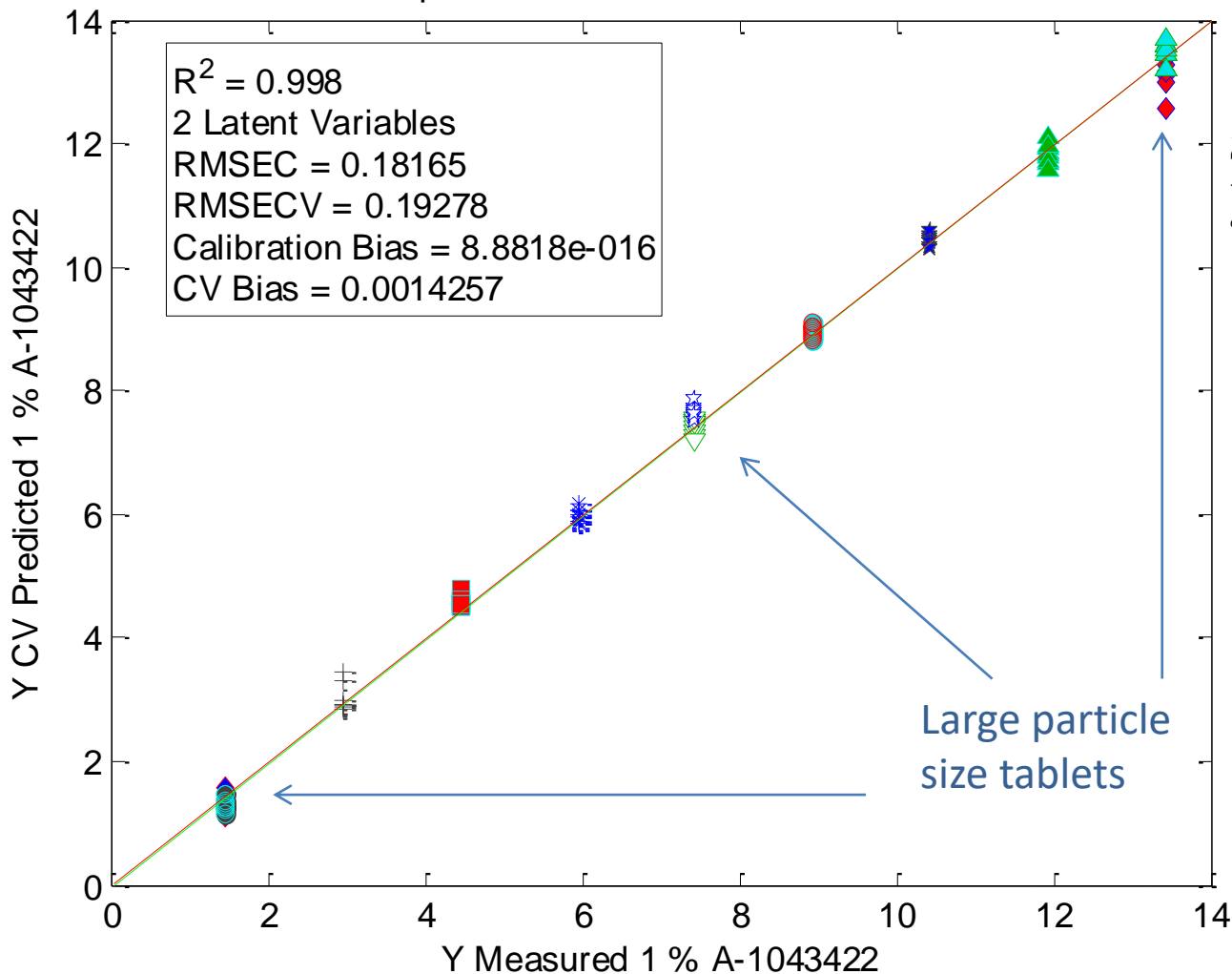
# Example

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- Two APIs in tablet
- Large (ca. 8mm thick) tablet of about 1g in weight.
- APIs at about 8% w/w in tablet
- Will also test the sensitivity to API particle size variations

# Measured versus Predicted

Samples/Scores Plot of ContentQC Data



- Both APIs predicted well
- Even when larger particle size used doesn't affect prediction



# Content Uniformity Testing

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Routine Testing Process

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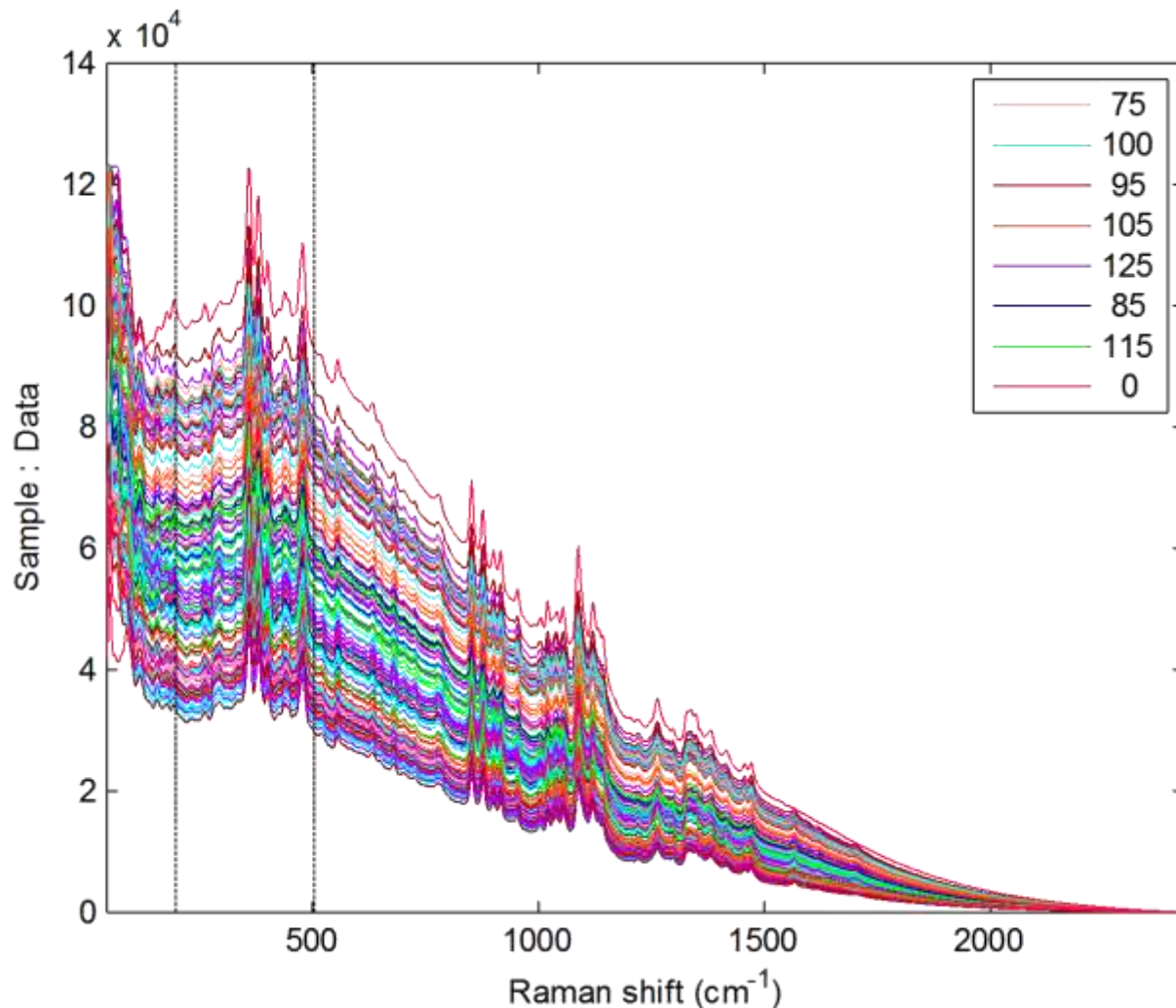


# TRS for Batch Release

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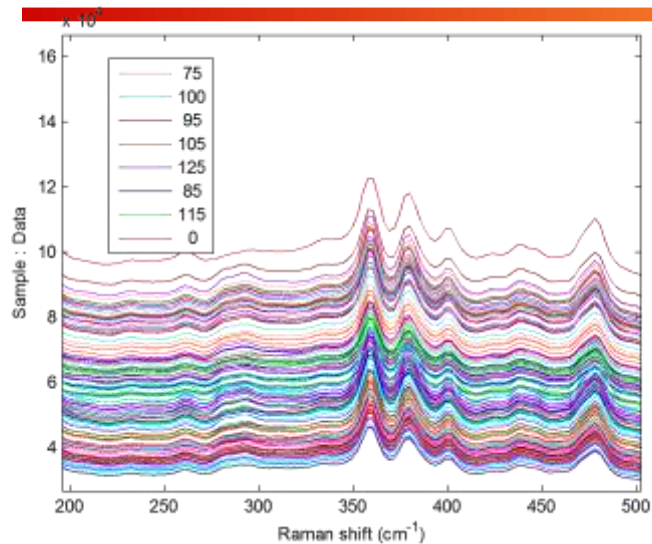
- Building a model for production batch release
  - Calibration set manufactured by hand
  - Validation set a combination of hand-made and production samples
  - Different MCC and lactose raw materials used to test sensitivity to supplier variability
  - Aged samples with known degradation loss of API included
- TRS performed first, then HPLC on individuals
  - Ca. 230 tablets in all
  - Aged samples with known degradation loss of API included

# Spectra and Selected Region

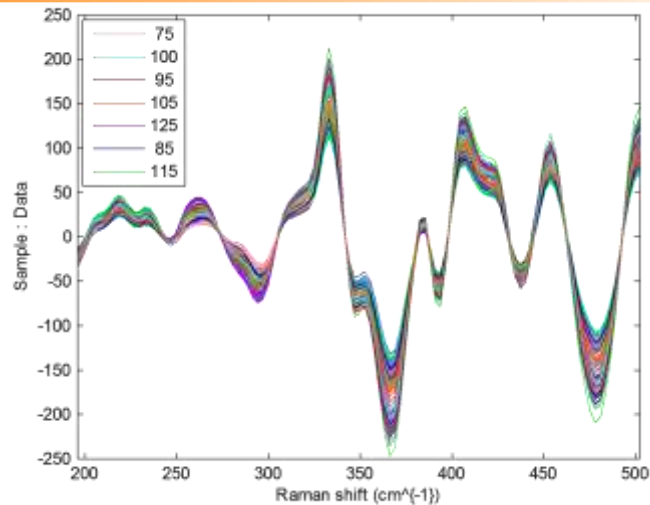


- Raw data showing all calibration samples
- Lots of spectral information available
- Best region of interest for model around  $200\text{-}500\text{cm}^{-1}$

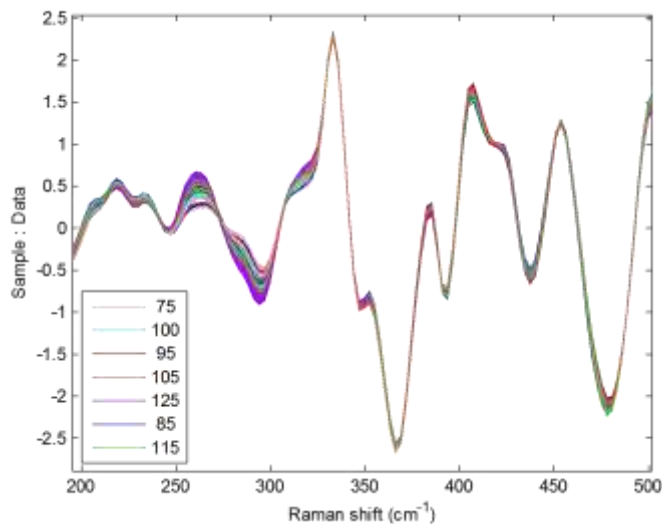
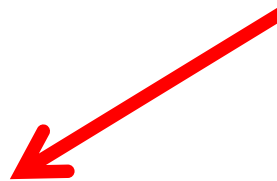
# Raw Data and Preprocessing



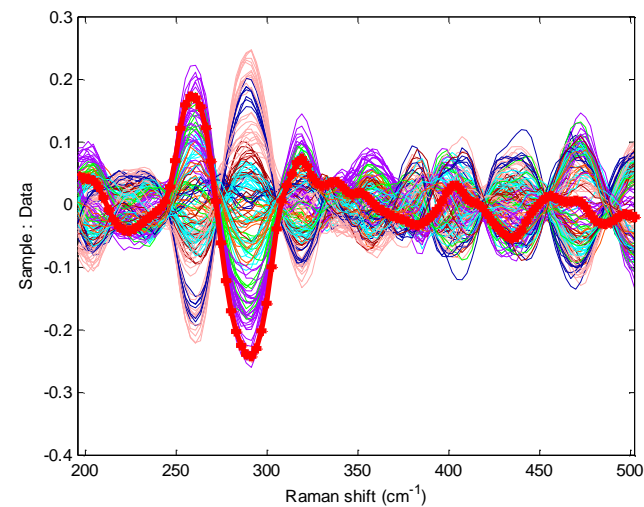
Raw Data



Derivatised

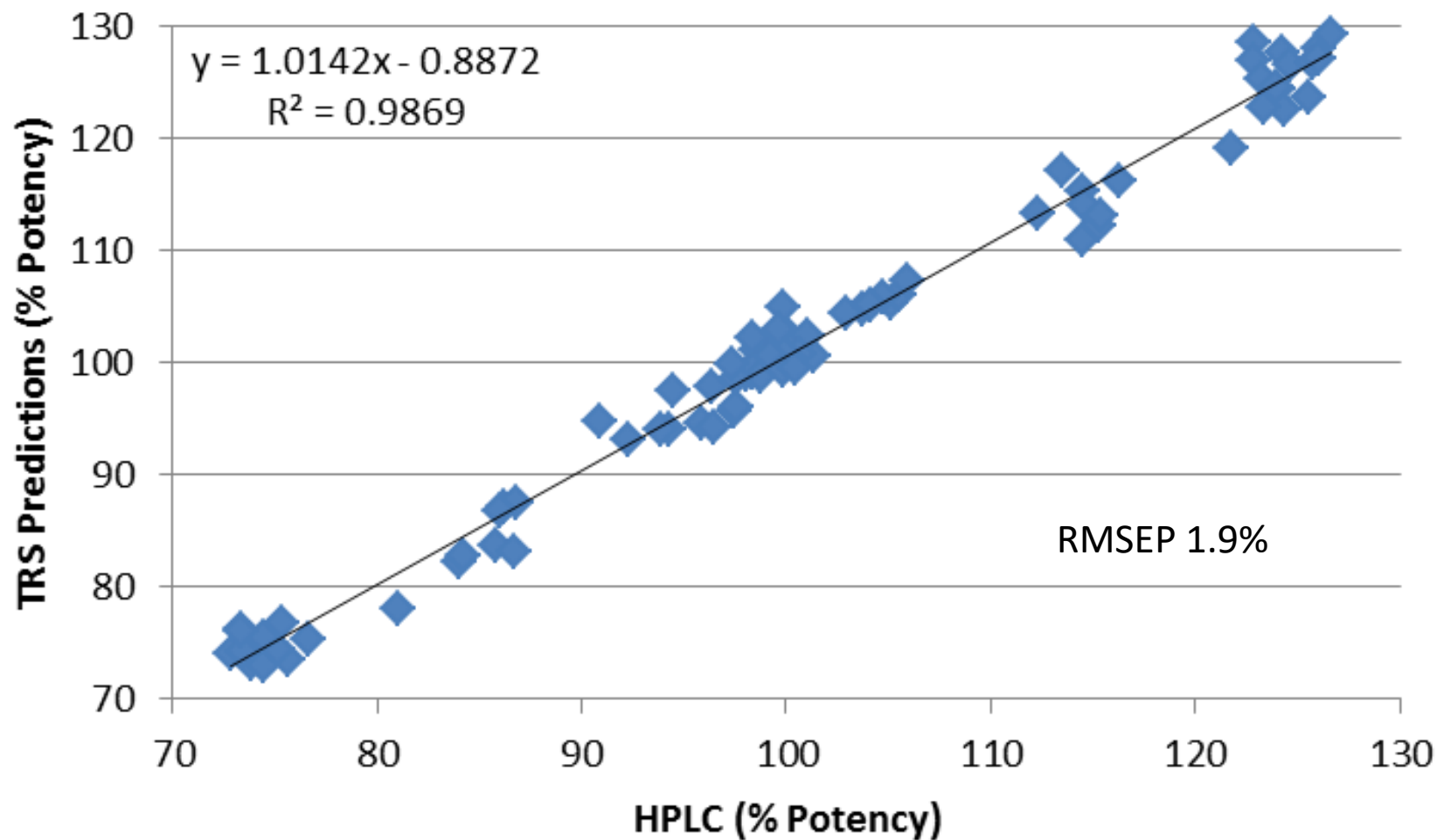


SNV Normalised



Mean Centred

# Model Fit to Data





# Equivalence with HPLC

- To file TRS alternative method, equivalency with the existing HPLC technique is required

Comparison/performance	Test	Result
Accuracy	$1.4 \times \text{RMSEC}$ (0.0836)	0.1171
“	RMSEP	0.1047
“	$1.4 \times \text{SEL}$ (0.0973)	0.1362
“	$\text{RMSEC} < 1.4 \times \text{SEL}$	Yes
“	$\text{RMSEP} < 1.4 \times \text{RMSEC}$	Yes
Bias	<0.05 @ 95% confidence	$0.0019 \pm 0.020$
Linearity	Correlation coefficient $R^2$	0.99
Specificity for API	Spectral match	Excellent match

# Summary

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- TRS method satisfies regulatory guidance questions for an alternative filing
- Time taken for method development:
  - 1 week to make tablets
  - 2.5 days to acquire TRS spectra
  - 2-5 weeks for HPLC
- Routine TRS100 analysis time for up to 100 tablets per batch, including report output
  - <30 minutes



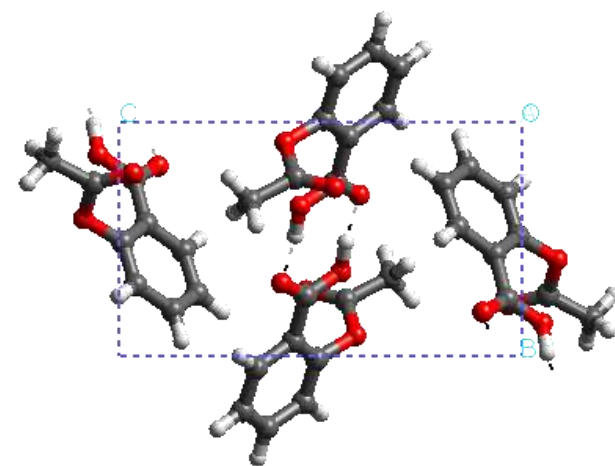
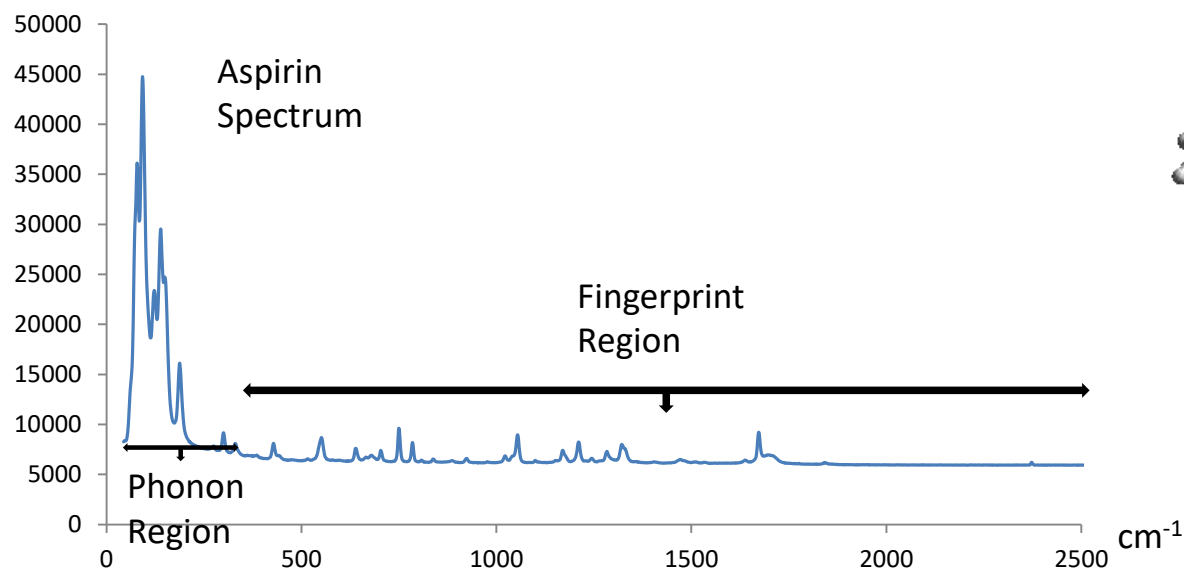
# Polymorph/Amorphous Quantitative Analysis

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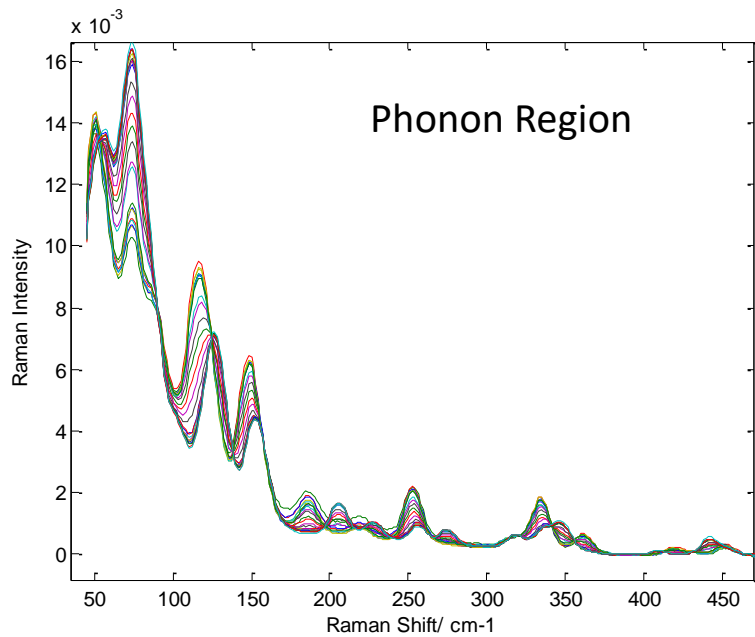


# Polymorph Analysis

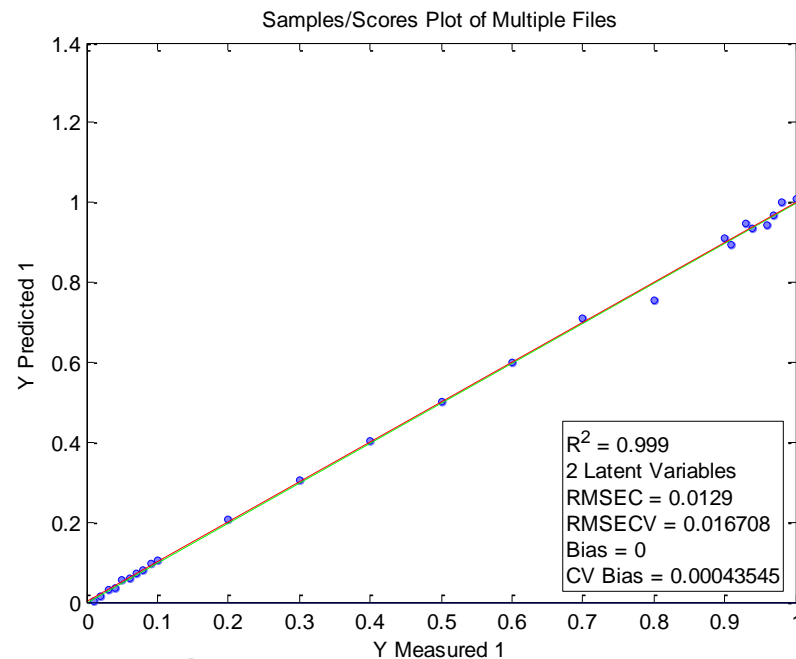


- Standard Raman usually sees ‘fingerprint’ region (200cm<sup>-1</sup> and higher)
- LiteThru engine also analyses phonon mode region
  - DIRECT crystal lattice vibrational information
  - Highly characteristic of polymorph and salt form
  - In crystalline materials usually much more intense than fingerprint region
- Combines chemical and crystal information in a single measurement

# Polymorph Quantification



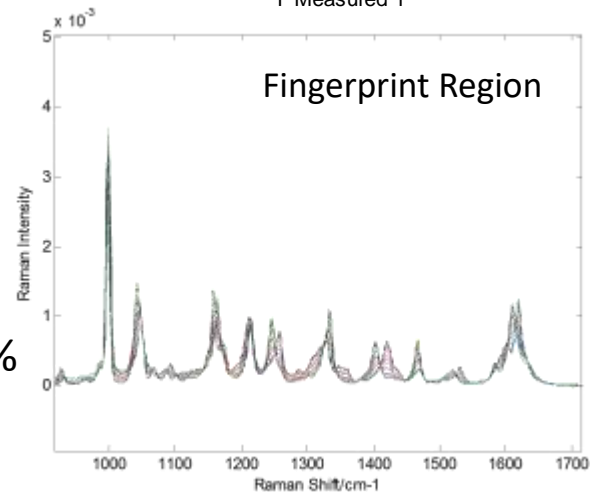
PLS  
Analysis  
→



Raman of mixtures of flufenamic acid polymorphs

Measurement time = 10 seconds

- 0-100% mixtures of flufenamic acid types I and III
- Phonon mode features change significantly
- Chemometric analysis gives concentration to  $\pm 1-2\%$





# Low Limits of Detection

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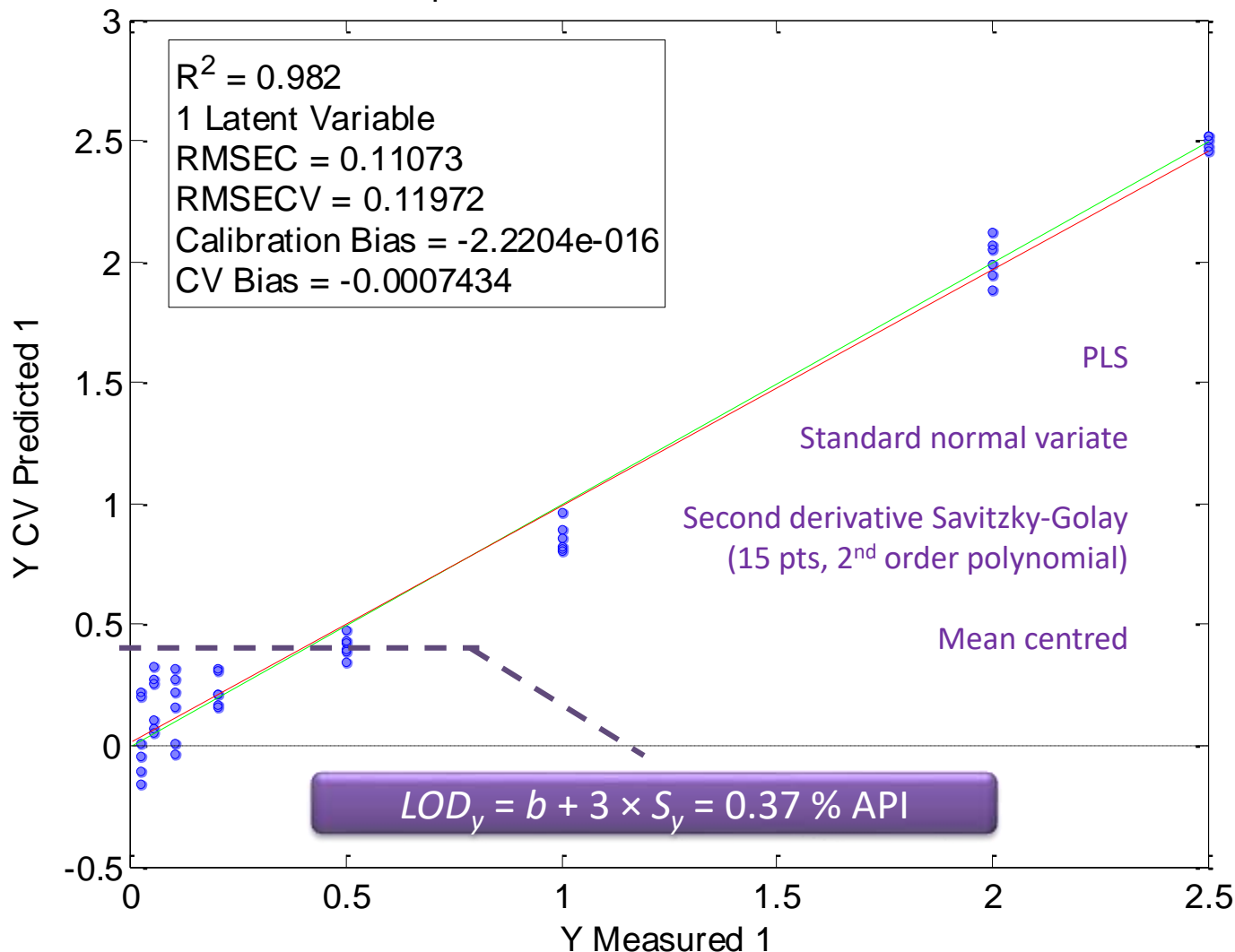
# Limit of Detection

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- Formulated tablet, ca. 7mm thick
  - API is in amorphous form
  - Compression blend is for commercial released tablet
  - Common excipients
- API can relax back to crystalline (polymorphic) form
- Looking for sensitive analysis technique for quantifying in manufactured tablet product
- Used phonon region where the maximum differences are observed

# LOD for Residual Crystallinity

Samples/Scores Plot of ContentQC Data



Using phonon region, LOD as low as 0.27% was measured



# Limits of Detection

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- TRS properties
  - Samples large volume of tablet
  - API tends to have strong Raman signal
  - Excipients tend to have weak Raman signal
  - LOD/LOQ can be 0.1% or lower of API
- NIR properties
  - Excipients tend to be more absorptive than APIs
  - LOD/LOQ around 10x higher than TRS

# Other Applications

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- Coating thickness determination
  - Quantify average coating amount in seconds
- Physical state concentration
  - Solvation/hydrated state
  - Recrystallised polymorph content from amorphous
- Rapid screening uses
  - Counterfeit analysis
  - Stability monitoring
- Process validation for manufacturing
- Online analysis (TRS technology)
- 100% tablet inspection (TRS technology)



TRS100

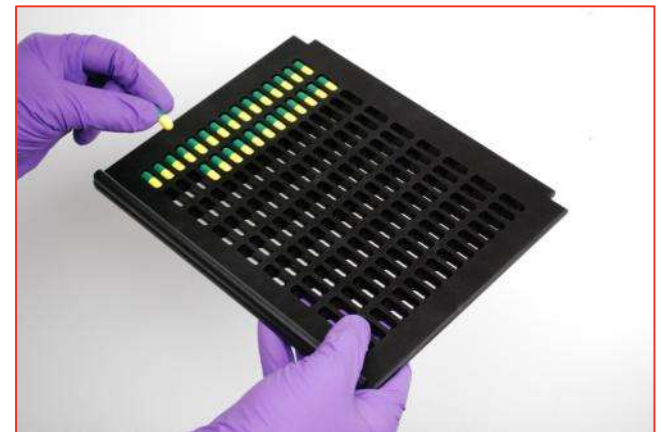
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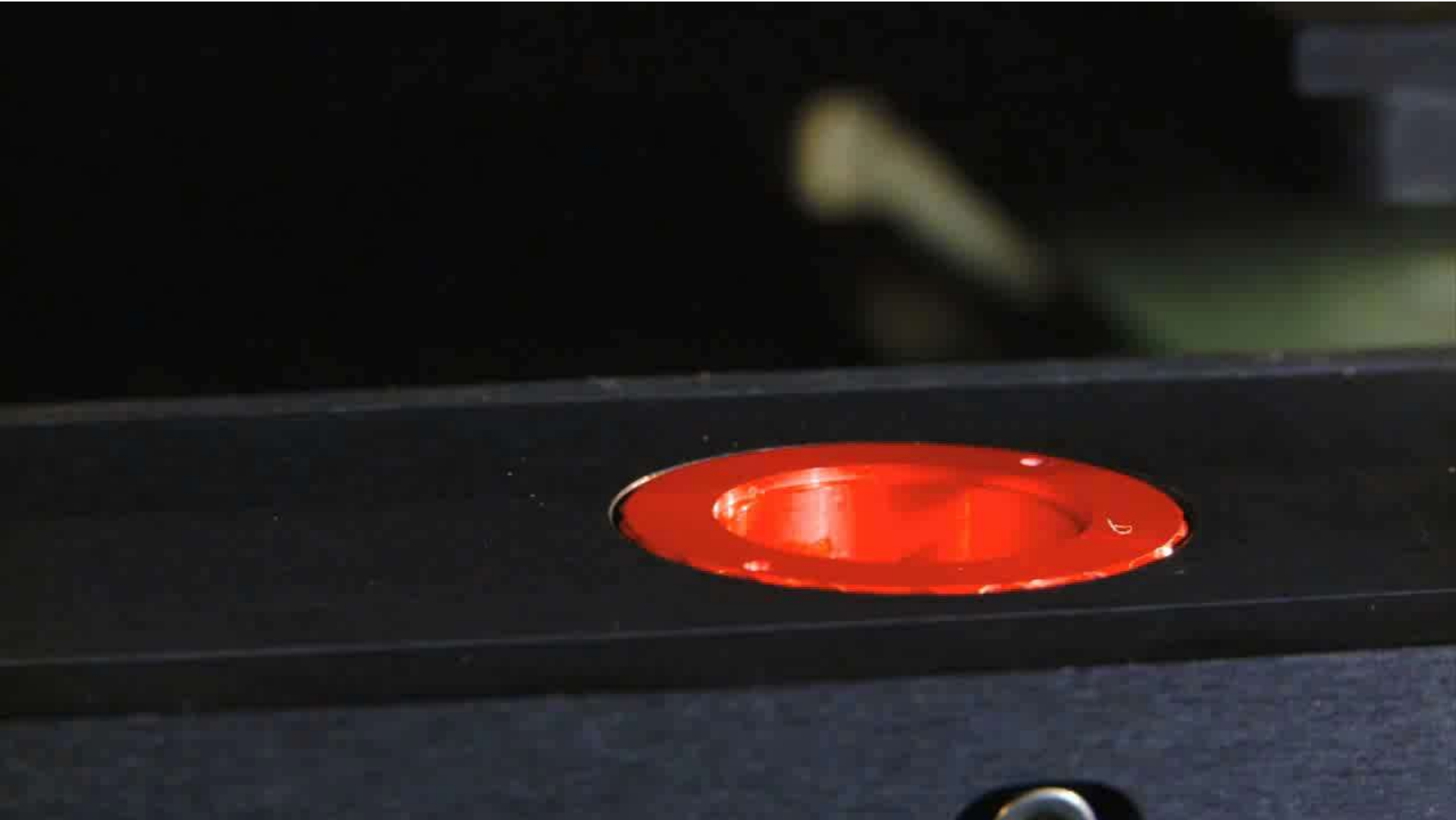
# TRS100

- TRS Instrument
  - Seconds per sample
  - Hundreds of samples in minutes
- Samples Presentation
  - capsules, tablets, vials powders, well-plates etc.
- Comes with ContentQC Software
  - 21CFR part 11 compliant

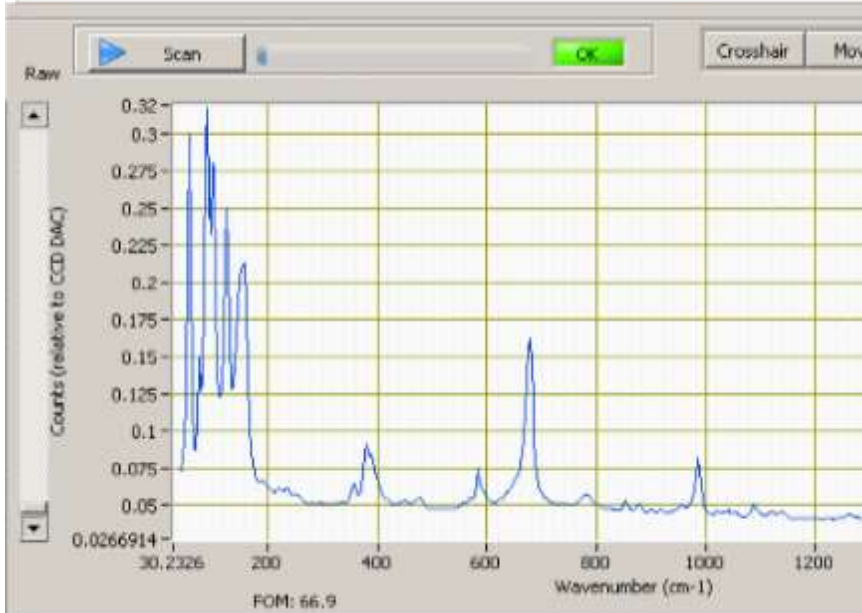


# Operation

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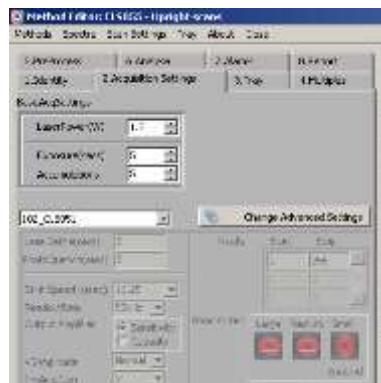


# Content QC Software



- Complete solution
  - Controls instrument
  - Built-in chemometrics
  - Database, audit & reporting
- Designed for the pharmaceutical industry
- ERES and 21CFR part 11 compliant

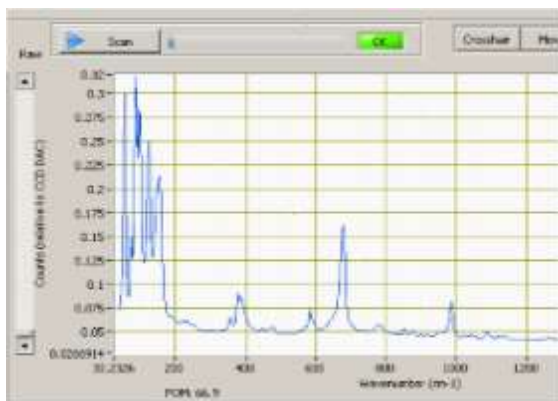
# TRS100 Model Creation



Set Instrument Parameters

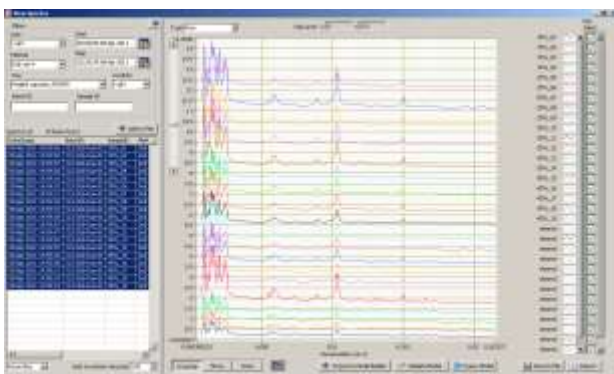


Collect Data

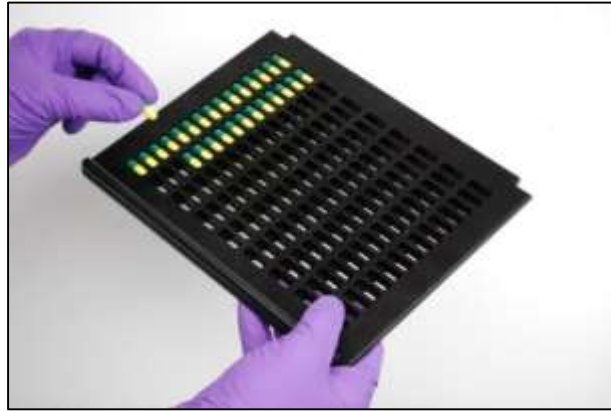


Build Model

- **Expert Mode**
  - Complete flexibility and control
  - Use to develop analysis method
  - Saved models used in production measurements



# TRS100 Process



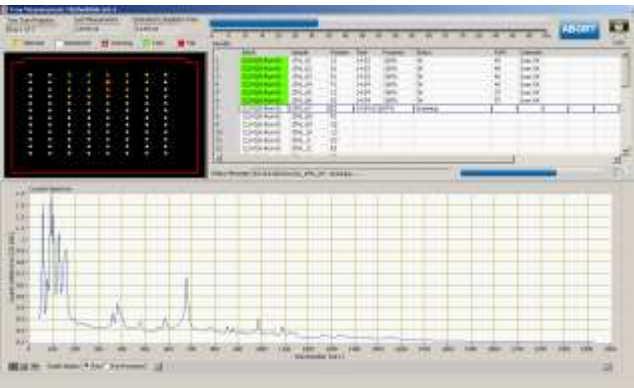
Fill/Insert  
Tray



Run  
Method



Output  
Report



- **Run Mode**

- Methods locked down by user/group
- Routine analysis with minimal training
- One-button solution



# Tray System

- 300cm<sup>2</sup> active sample area
  - >200 common tablets
  - 135 size 1 capsules
  - 2x 96-well plates
- Up to 5 cm accommodation above and 2cm below tray
  - Cuvettes, vials, etc.
- Self-locating and locking



# Regulatory Compliance

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- Hardware
  - Follows GAMP 5 guidelines
  - CE marked and designed to UL requirements
  - Class 1 laser
- ContentQC Software
  - Designed for 21CFR11 compliance
- Validation
  - Standard IQ/OQ procedures
  - No extra cost

# TRS100 Summary

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- High performance purpose-built pharmaceutical analysis system
- Designed for early stage R&D through to routine factory batch-release testing
- Complete with everything necessary for use in a validated testing environment
- Incorporates flexible sample tray system with beam enhancer technology





End

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