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# An Industry Perspective on the Potential for Emerging Process Analytical Technologies

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## Agenda

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- History of PAT and vision for the future
- Some specific, current PAT applications of interest
- Possible implementation scenarios for these and other applications - shaping the future
- Proposals to ensure that implementation proceeds as we ALL would like
  - ◆ “the win-win scenario”



## Evolution of NIR/PAT Within Pfizer

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- **Mid '80s**
  - ◆ Control of fermentations, hazardous reactions, solvents, raw materials, packaging materials, drug product process troubleshooting
- **Early '90s**
  - ◆ Dedicated group formed ('90), libraries for APIs and RMs developed, automated methods for sample presentation, some DP applications. Still largely NIR based
- **Late '90s**
  - ◆ Other techniques emerge (Raman, vision systems, acoustic, LIF etc. Increasingly used in DP processes)

# PAT Applications at DP Sites

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- RM Testing (warehouse based)
- Packaging Components
- Blending (at-line or on-line)
- Drying
- Tableting (potency and CU)
- Encapsulation (potency and CU)
- Tablet Coating (coating thickness)
- Packaged product
- Equipment cleaning (on line monitoring of CIP)
- Equipment cleaning (surface monitoring)

*Note - Less than 15% of applications at US sites*

## What Does the Future Hold?

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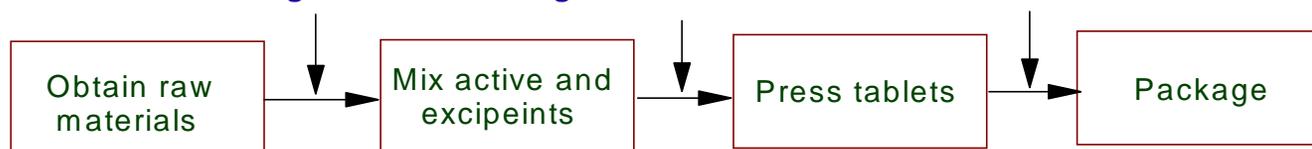
- Significant increase in number of applications
- Broadening of type of analysis e.g. mid-IR, Raman, LIF, acoustic, vision
- Availability of “off the shelf” solutions, including analyzers offered as options by equipment vendors
- Integration of applications. Used for “Continuous Quality Verification” as opposed to control of discrete unit operations

# Shift the Manufacturing Paradigm

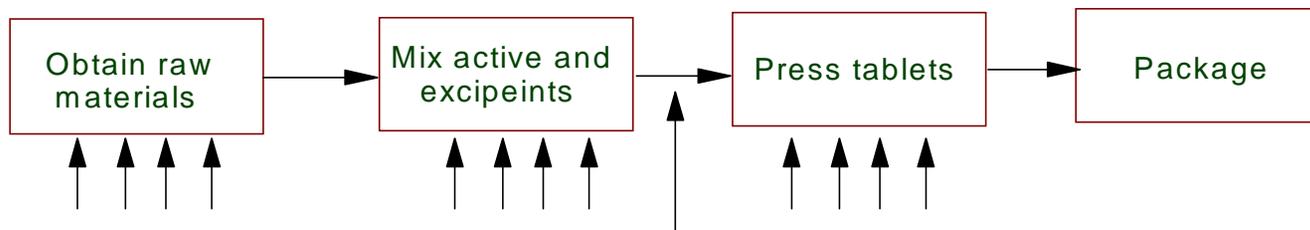
## Process Control Philosophy - Paradigm Shift

Conventional approach - lab based

End of phase testing of quality, to reduce the risk in moving to the next stage



P.A.T approach - process based, at-line or on-line



Continuously or more frequently test quality during each phase, to remove the risk in moving to the next stage

# Changing the Manufacturing Paradigm - Challenges

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## Technical

- Considerable progress in some areas
  - ◆ chemometrics, fiber optics, “industrialization” of some instruments (e.g. NIR)
- Opportunities still exist in other areas
  - ◆ smaller, faster, cheaper instruments (e.g. Raman)
  - ◆ sample interfaces

## Regulatory

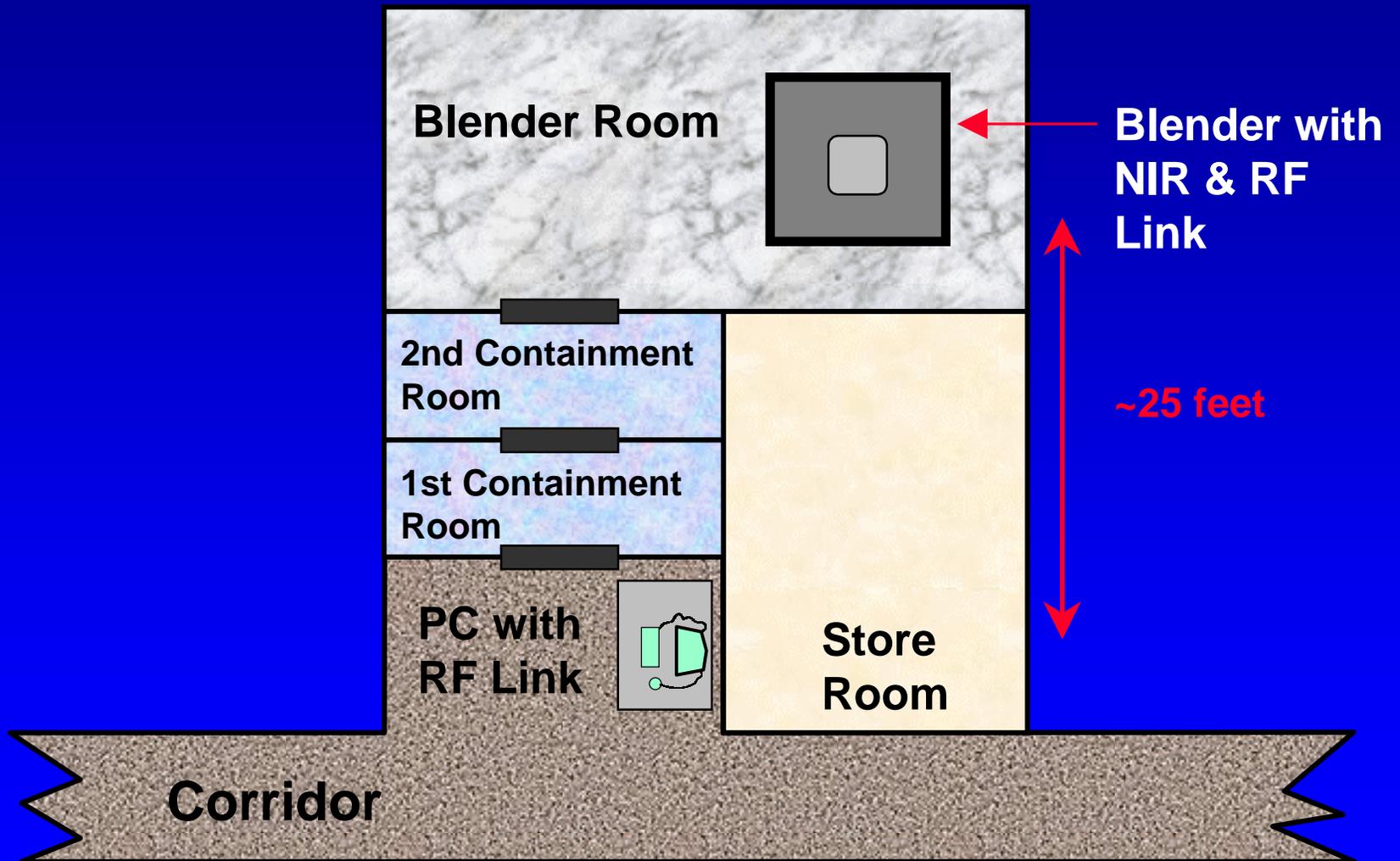
- Real or perceived regulatory hurdles may effect the way PAT is implemented

## **On-Line analysis of blending**

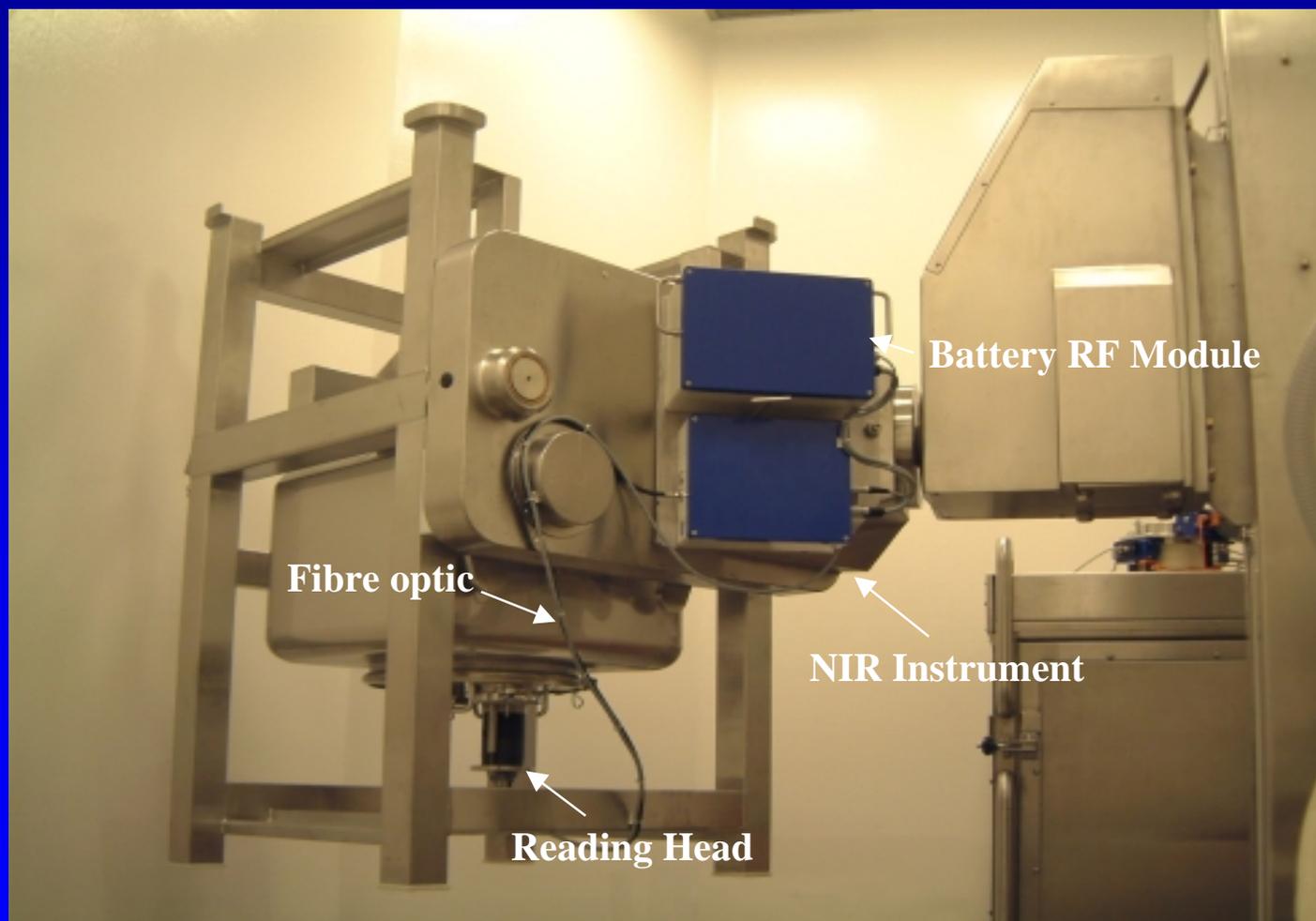
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- **Driven by safety issues with new potent API's**
- **Uses battery power and radio communication**
- **Small fast diode array instrument**
- **Mounted on the moving blender**
- **Controlled outside of containment area**
- **Results appear outside of containment area**

# Layout of Containment Blending Room



## On- line NIR bin blender



### Corona Sensor Head

Lid of blender & window

Focal Point just inside bin

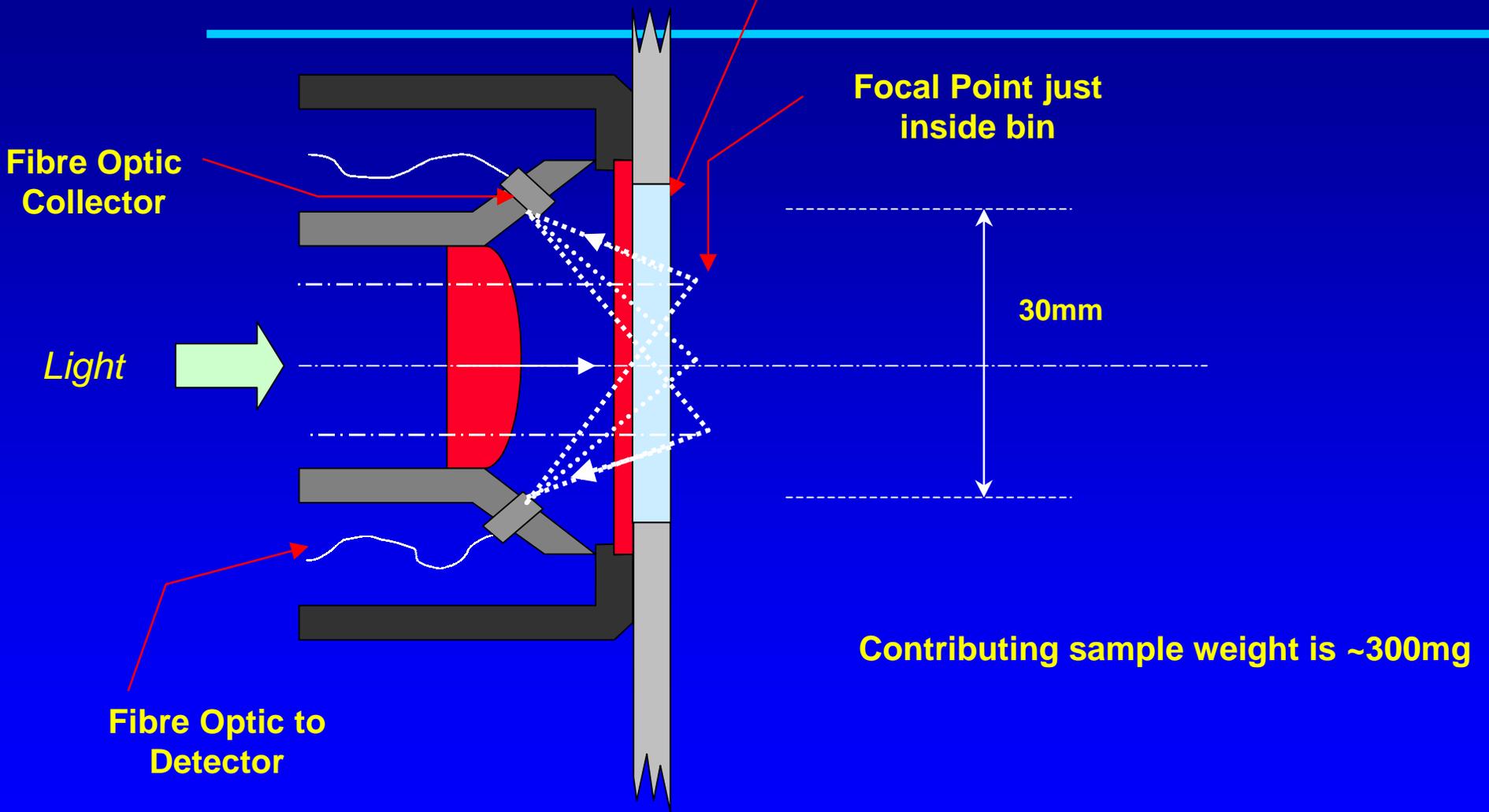
Fibre Optic Collector

30mm

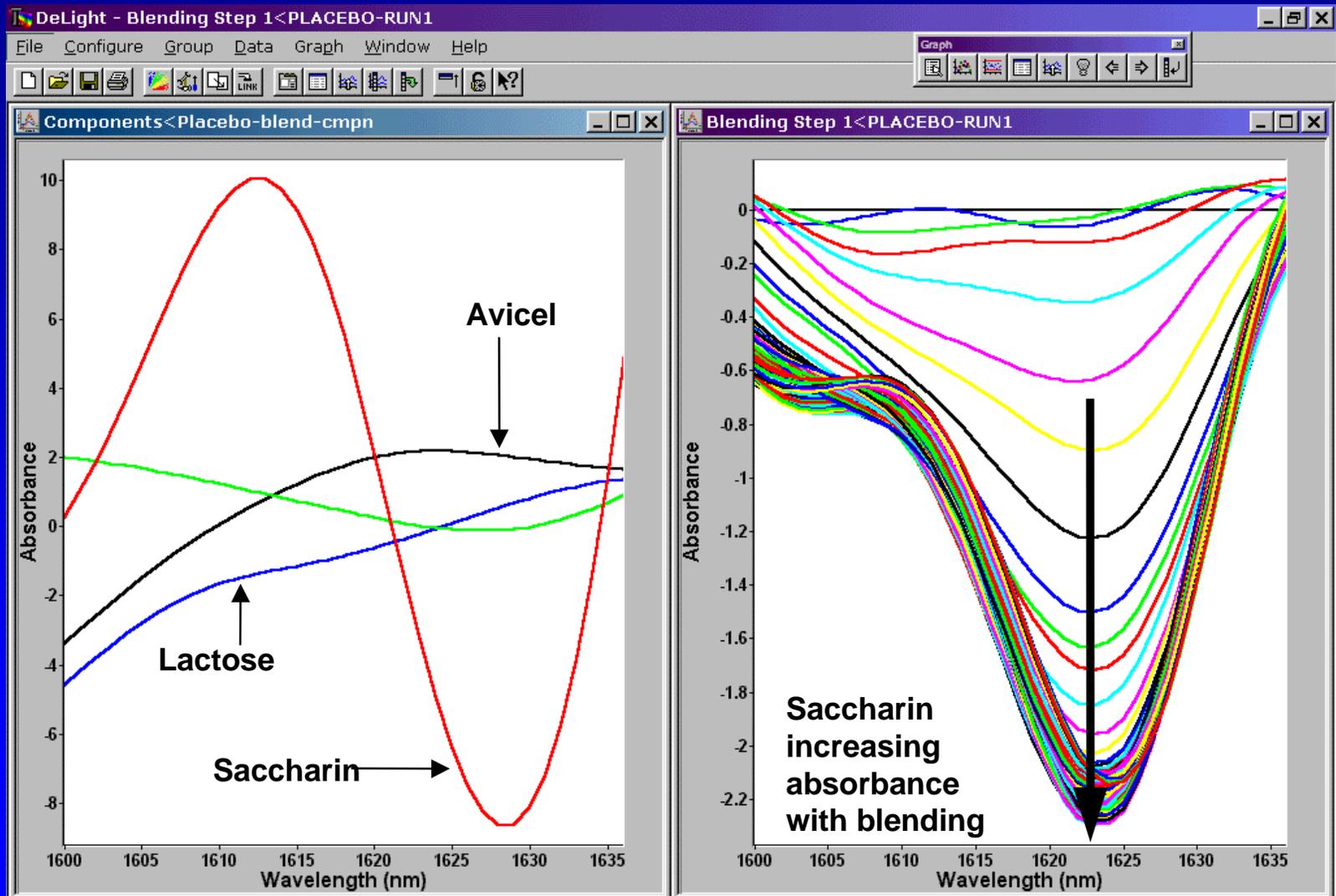
Light

Fibre Optic to Detector

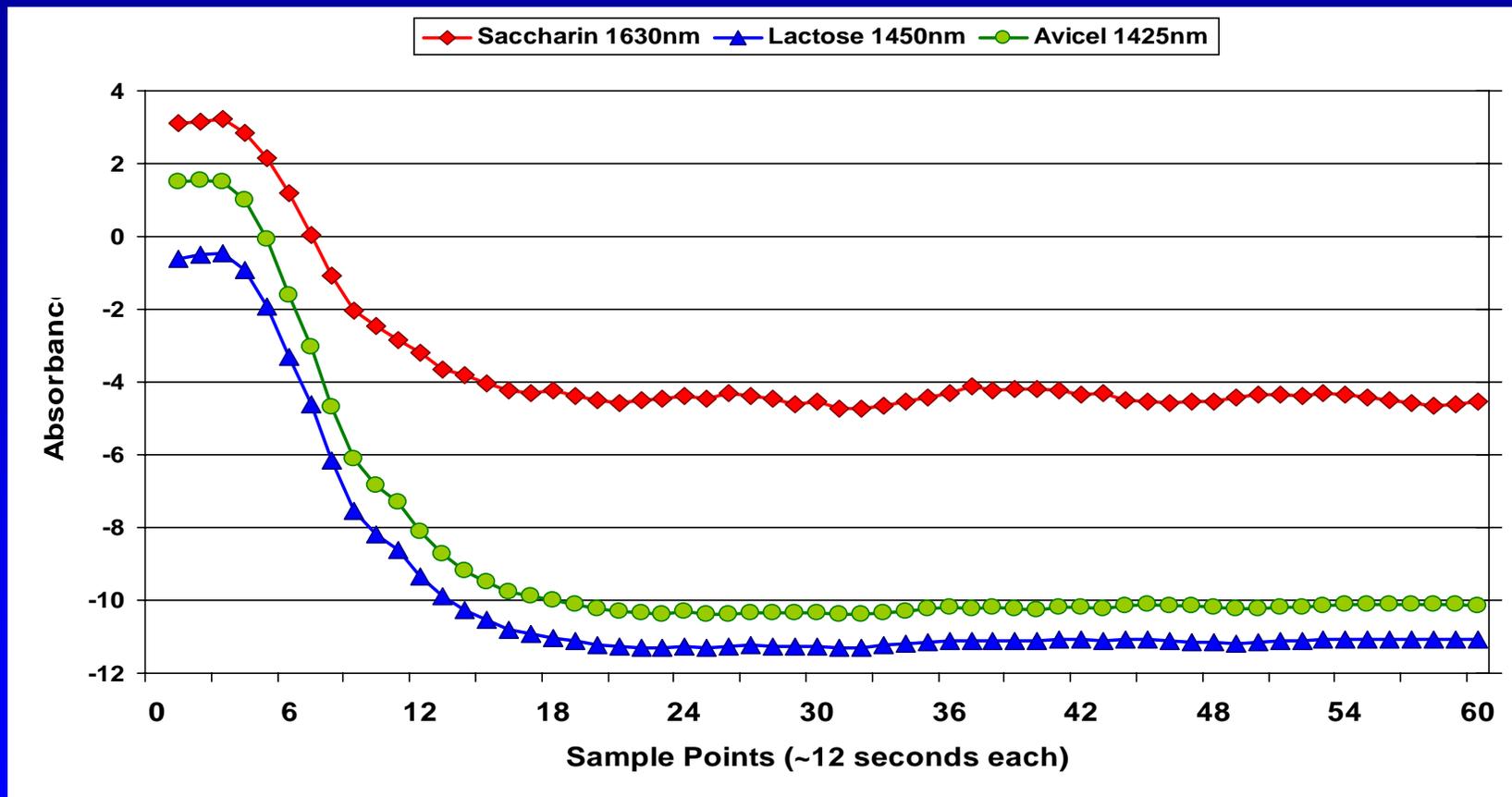
Contributing sample weight is ~300mg



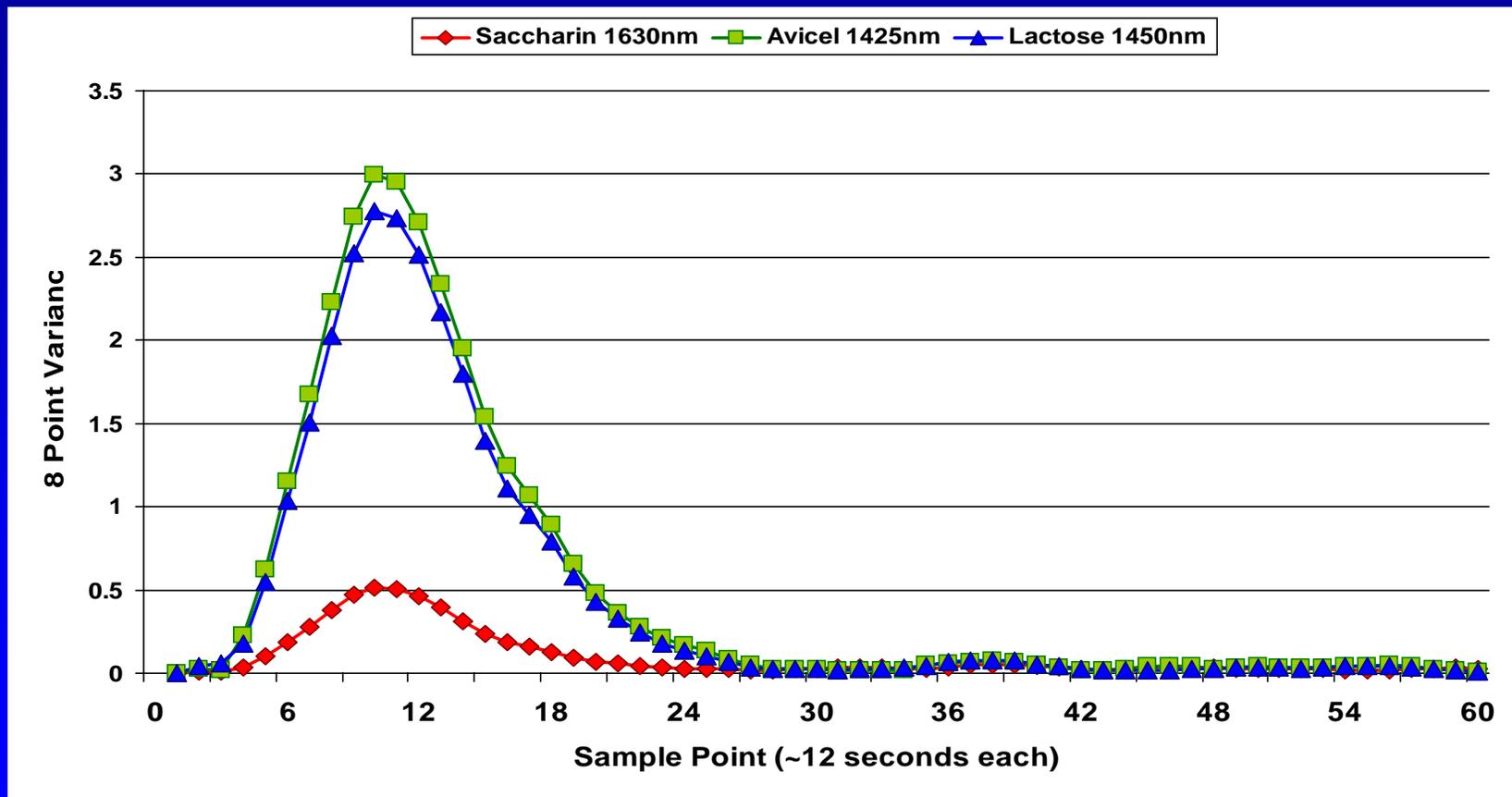
# Saccharin Specific Absorption



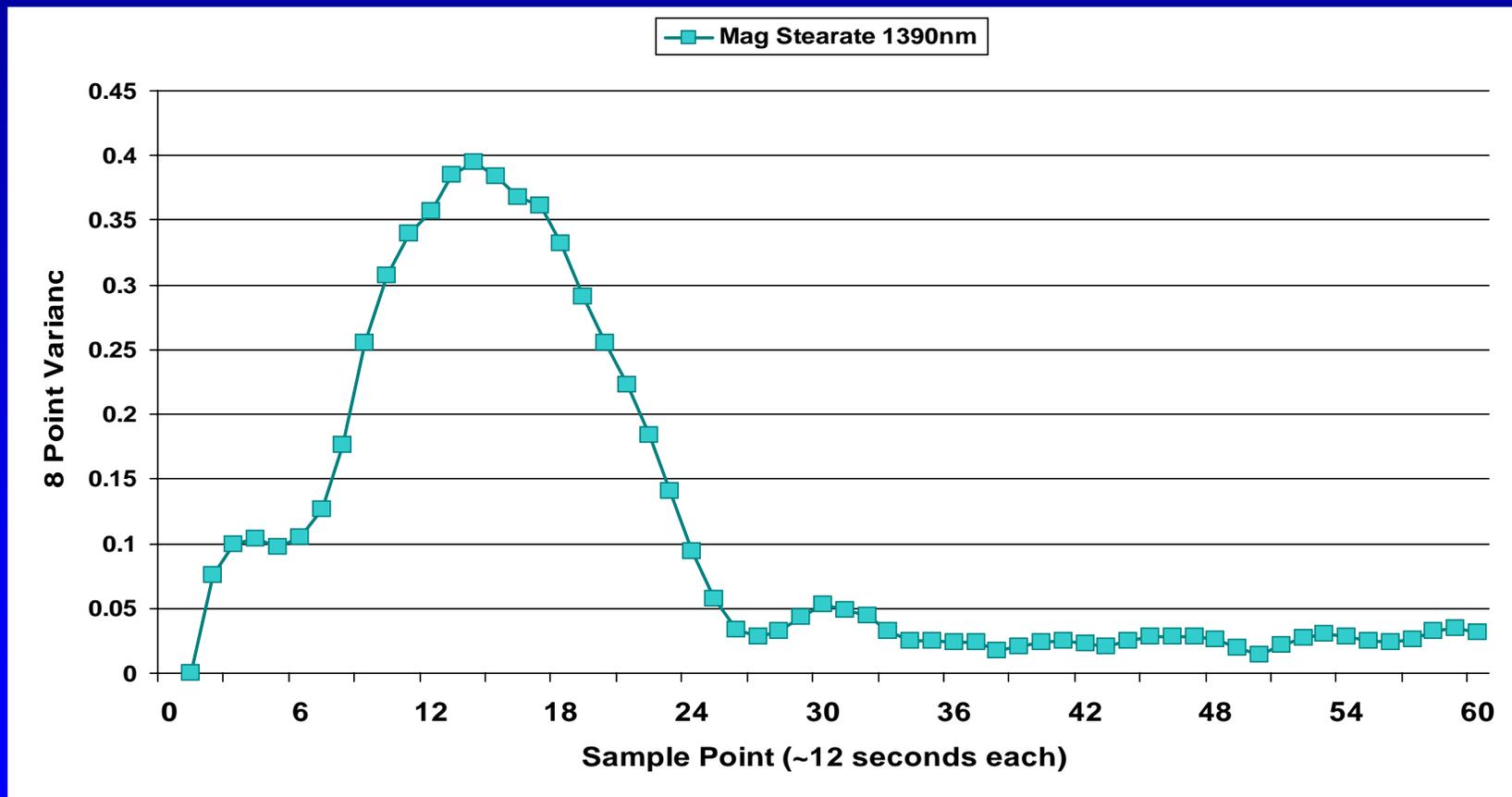
# Absorbance of Blend Components (Step 1)



# Blend Uniformity All ingredients(Step 1)



# Magnesium Stearate Uniformity (Step 2)



## **On-line blending - benefits**

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- **No operator contact**
- **No sampling errors - no thief**
- **real-time information**
- **Multi-ingredient uniformity**
- **Process understanding**
- **Process finger- printing for scale up**
- **Right first time**
- **Fast release of the blend - reduced cycle times**

## **Tablet analysis by NIR transmission**

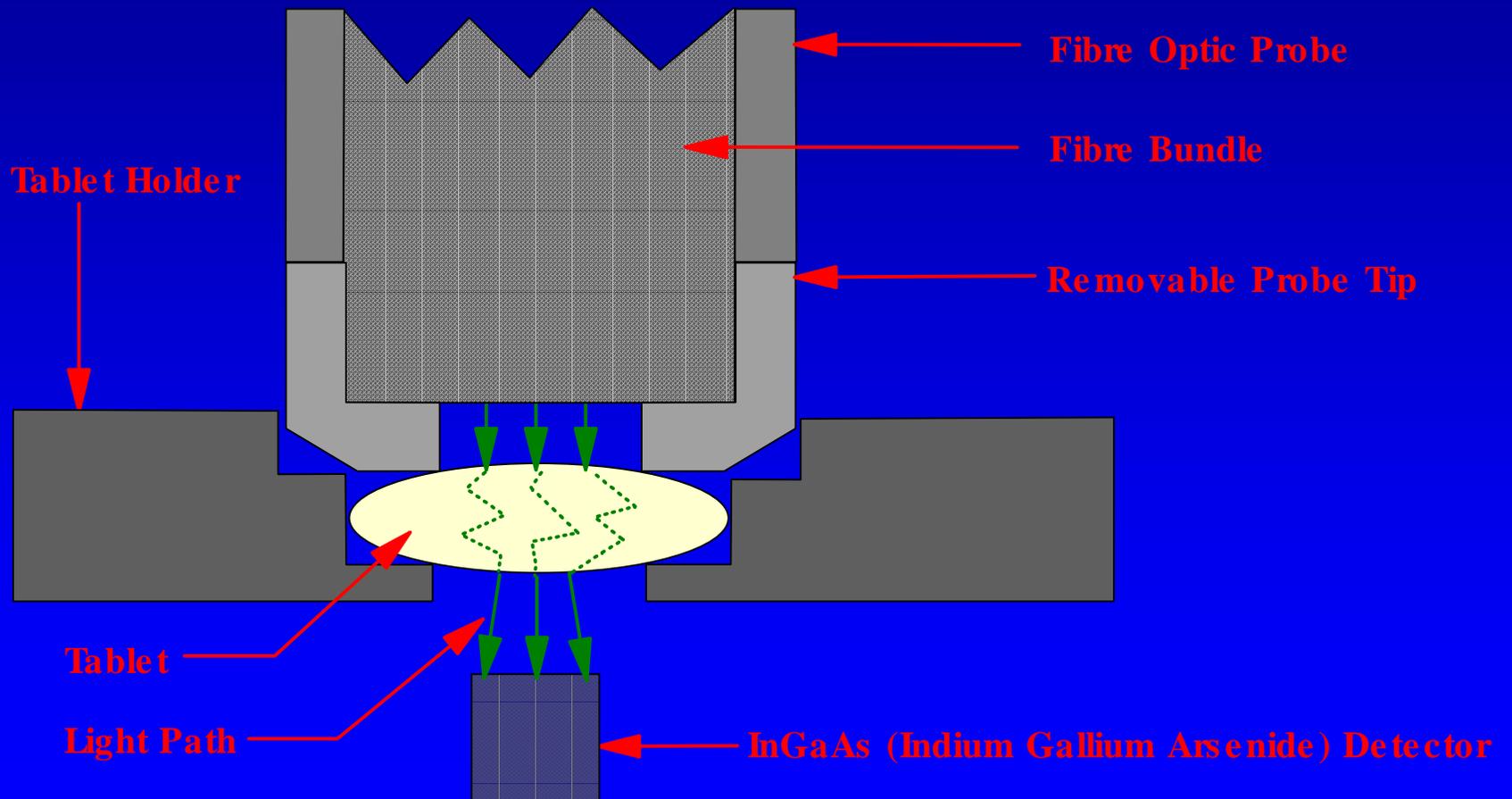
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- **Started at-line with plant operators analysing 200 - 400 cores per lot**
- **With containment issues needs to be non attended**
- **Development of a fully automated test station sited at the press**
- **NIR chemical analysis - weight thickness hardness by normal module**
- **Integrated into one unit.**

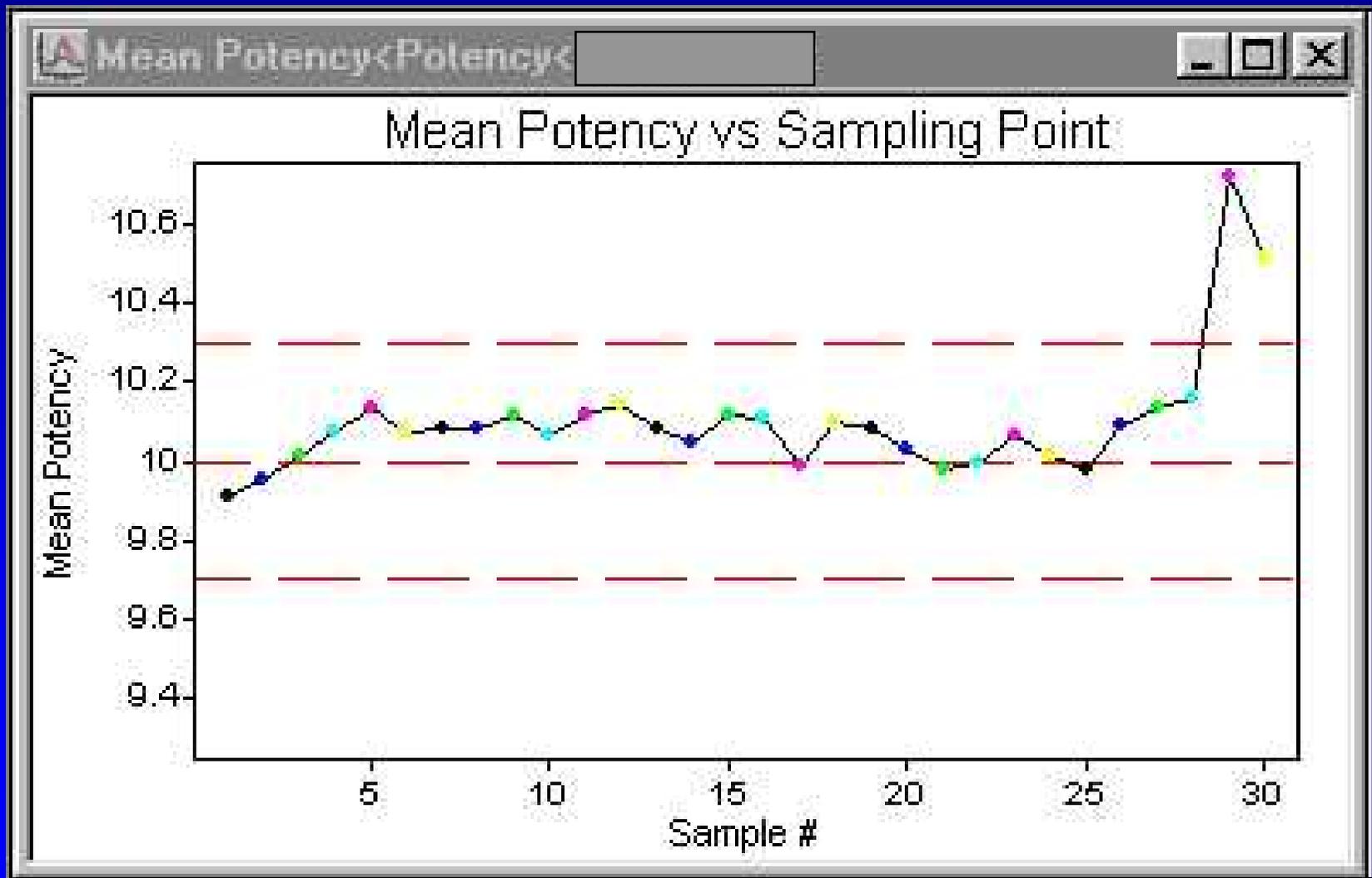
# NIR in Production



# NIR Tablet Transmission Device

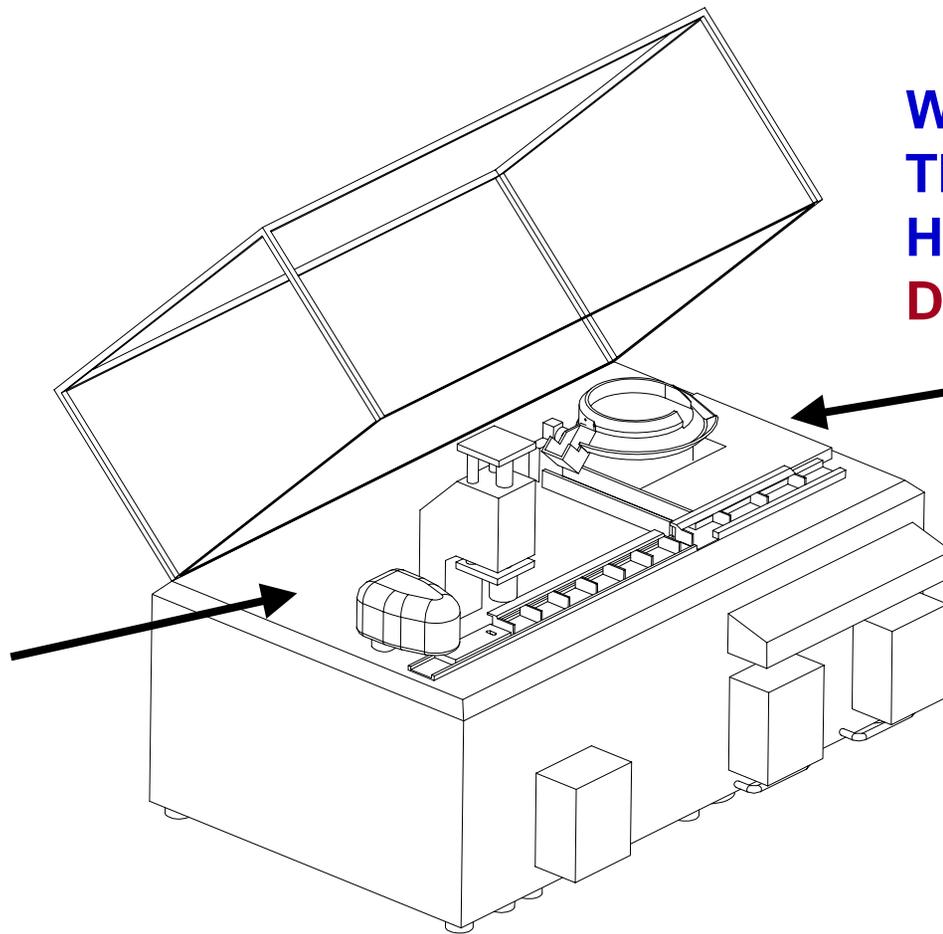


## Tablet core potency - blend segregation in the bin



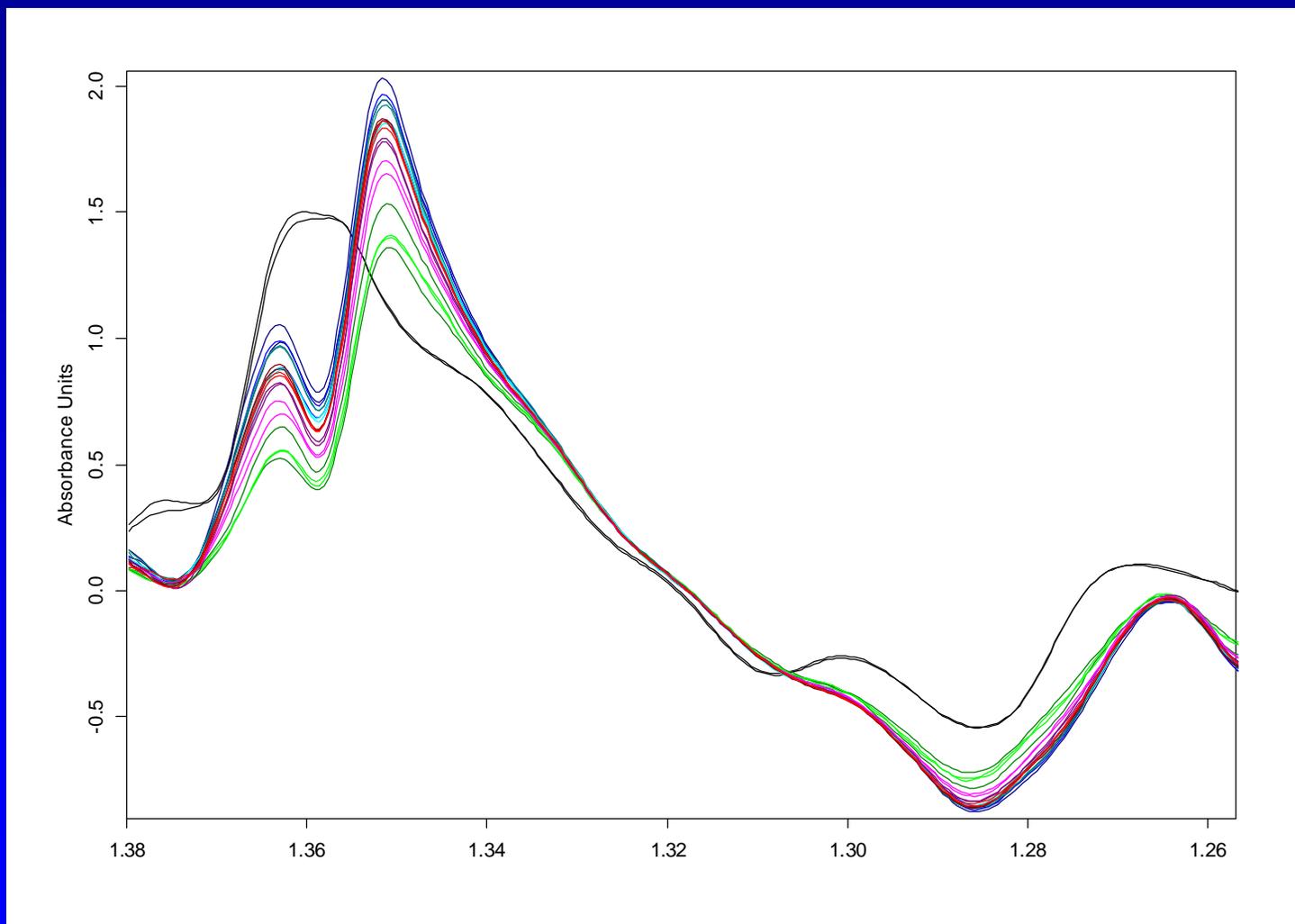
# Automated tablet analysis

NIR  
Identity  
Potency  
Uniformity  
Bruker

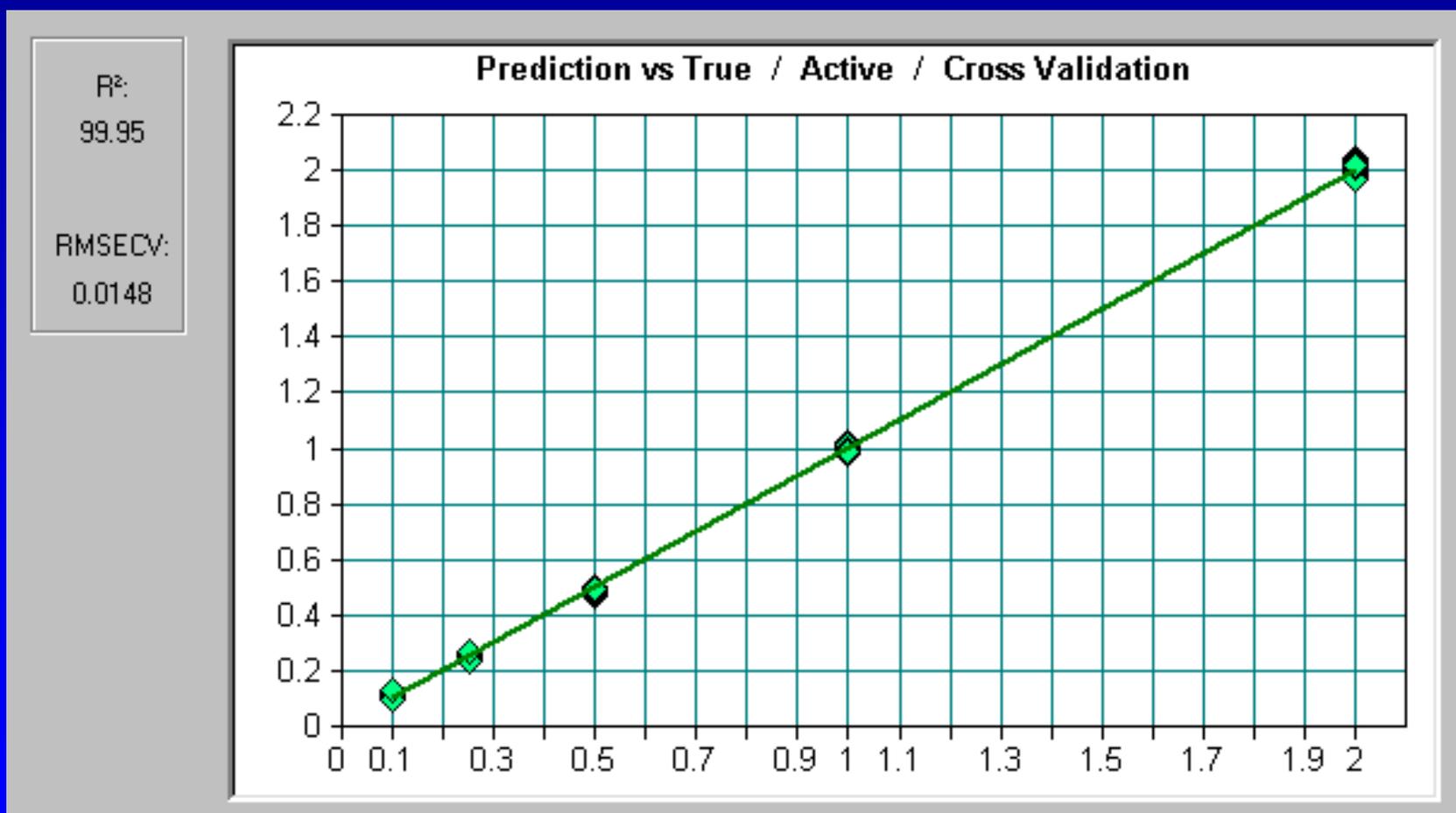


Weight  
Thickness  
Hardness  
Dr S Pharmatron

# Absorbance of active tablets Vs placebos



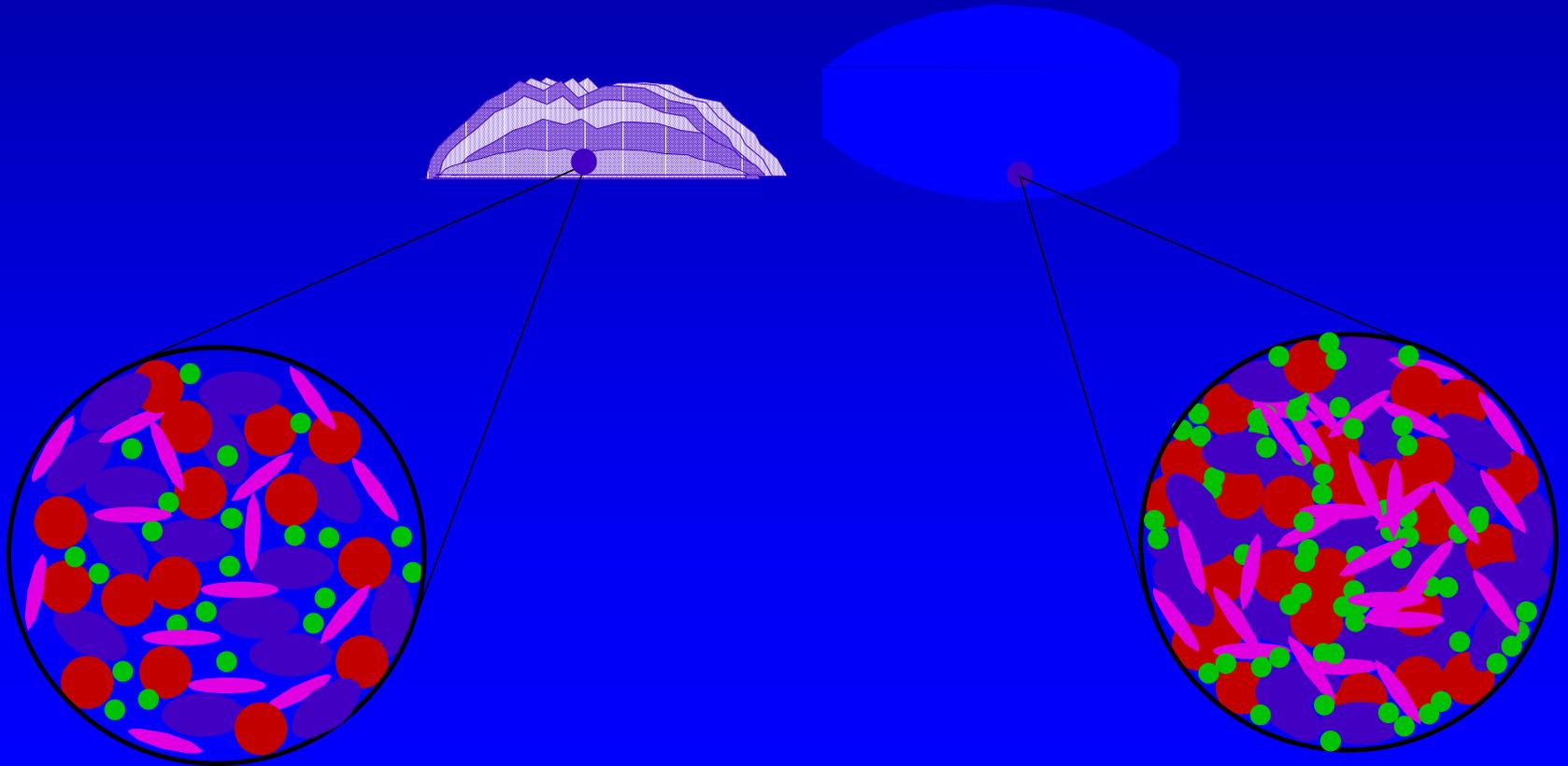
## NIR transmission Vs conc in tablets 0.1% - 2.0%



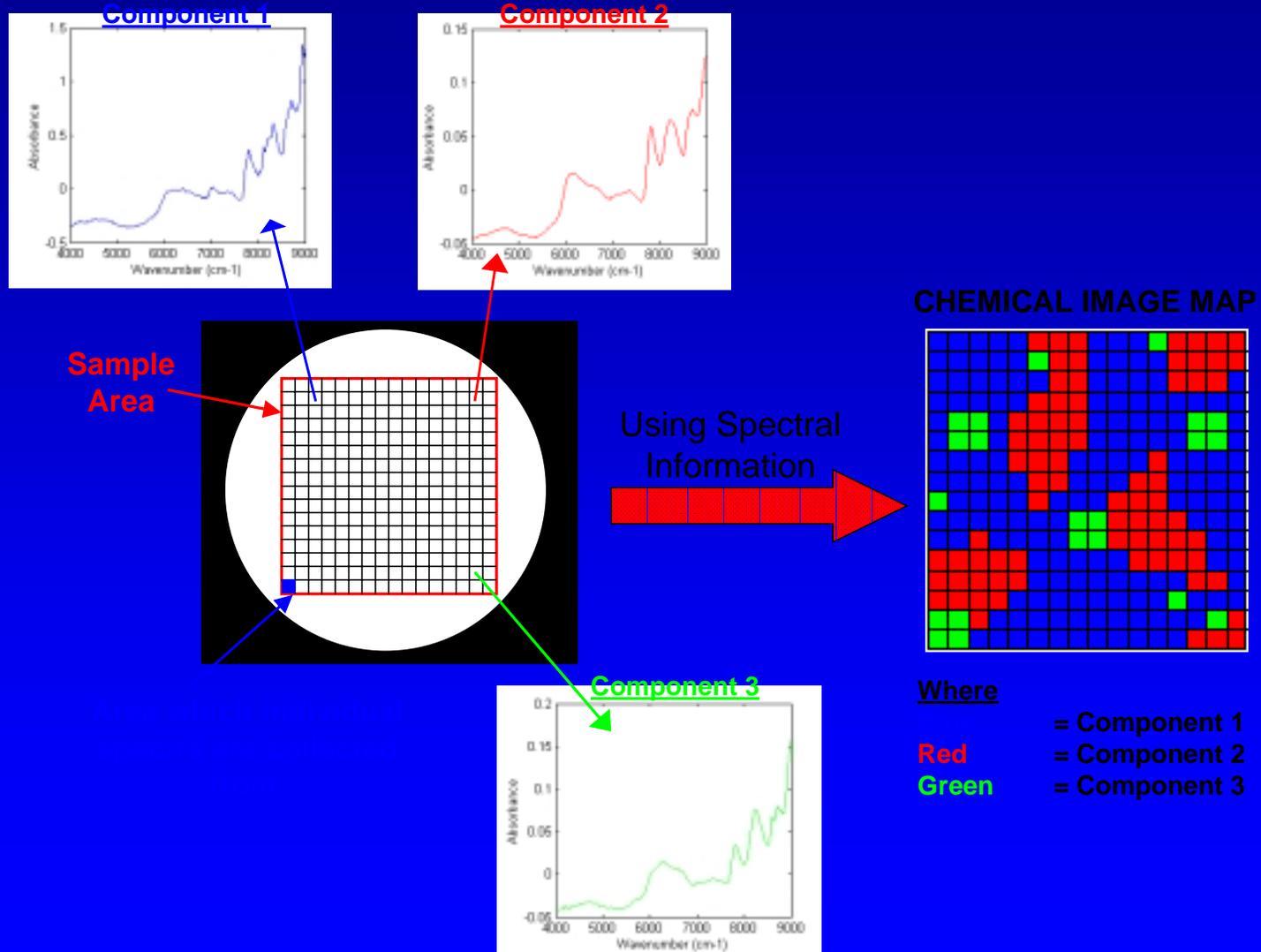
# Microscopic View of Dosage Form

Blend

Tablet

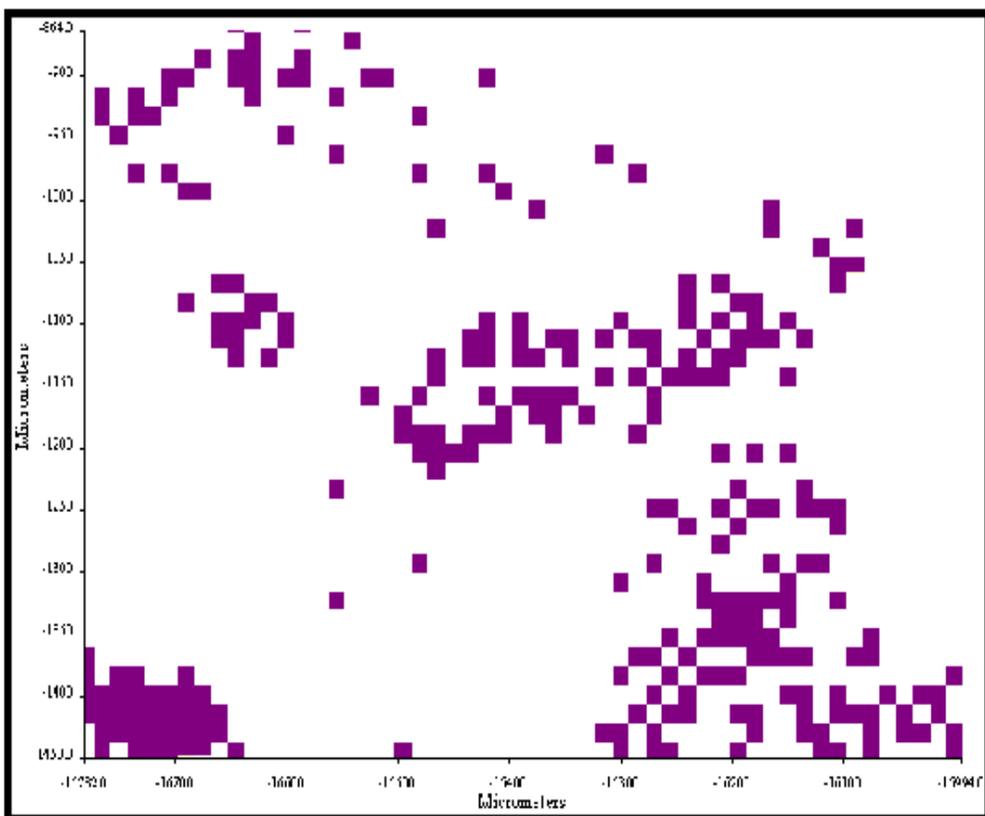


# NIR Microscopy mapping process

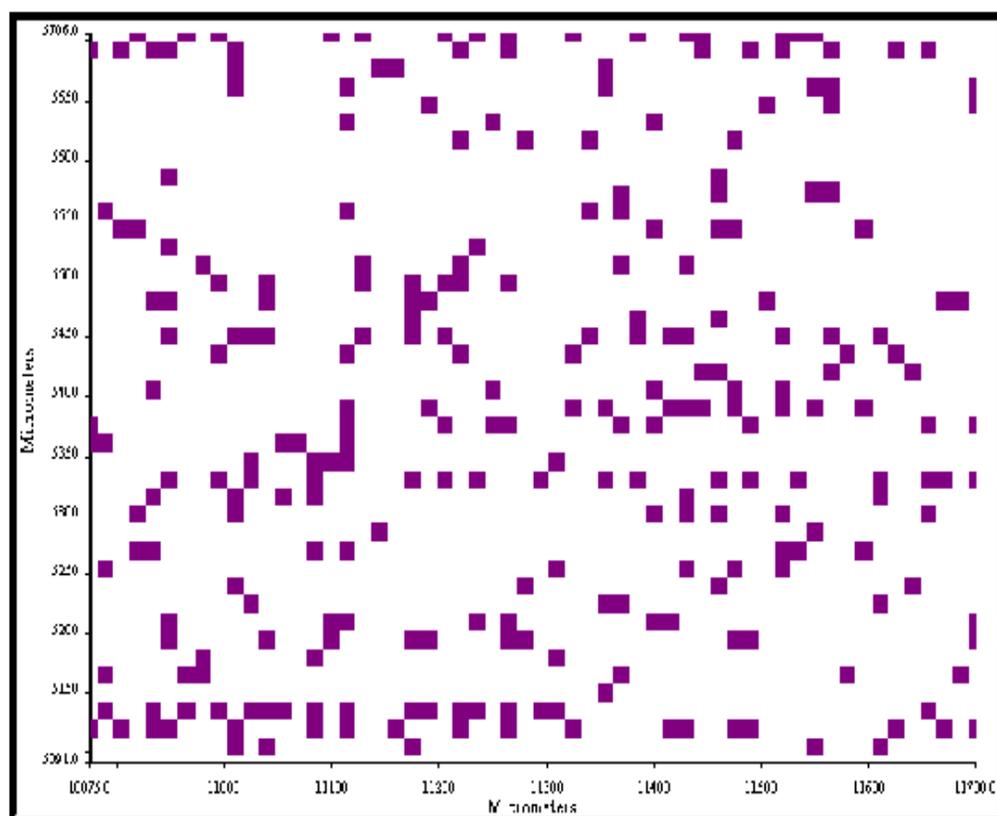


# Distribution of Lubricant in Blend

Spectra obtained every 15 $\mu$ m, 0.6mm X 0.6mm area



**Bad Flow Blend**



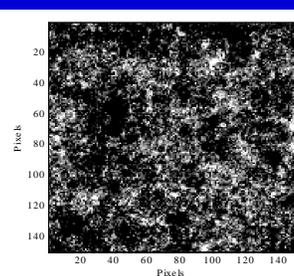
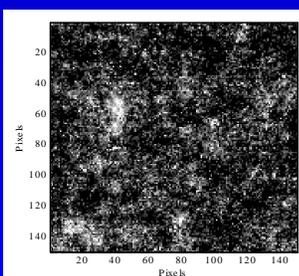
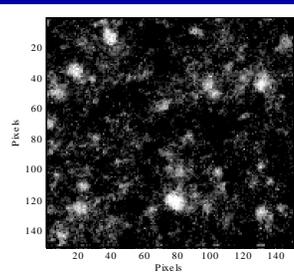
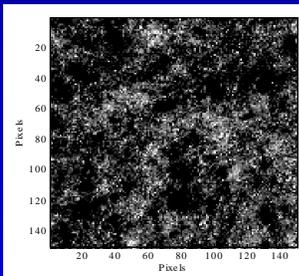
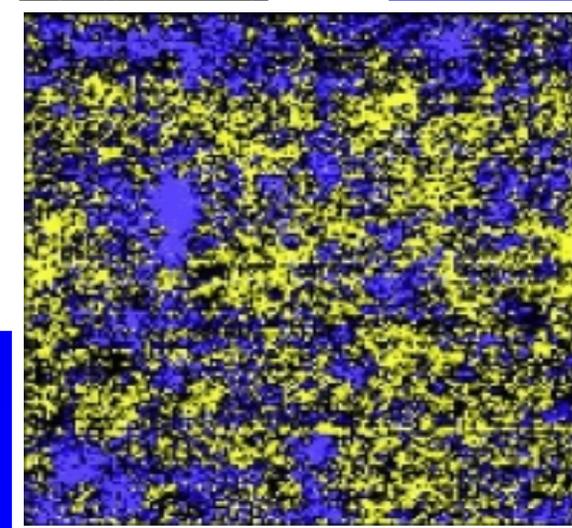
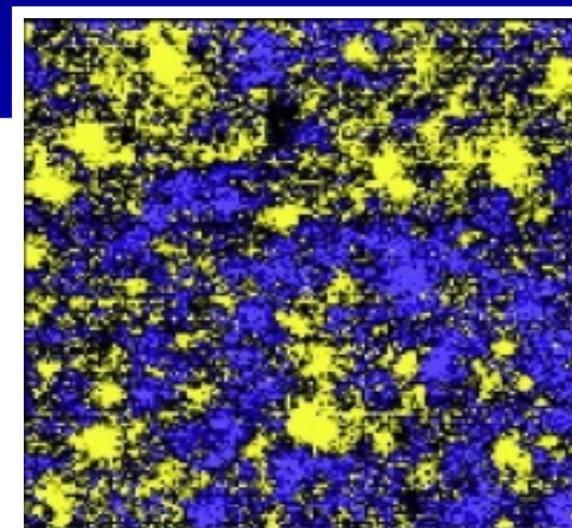
**Good Flow Blend**

# Maps of sticking and non-sticking tablets

Diluent

Binder

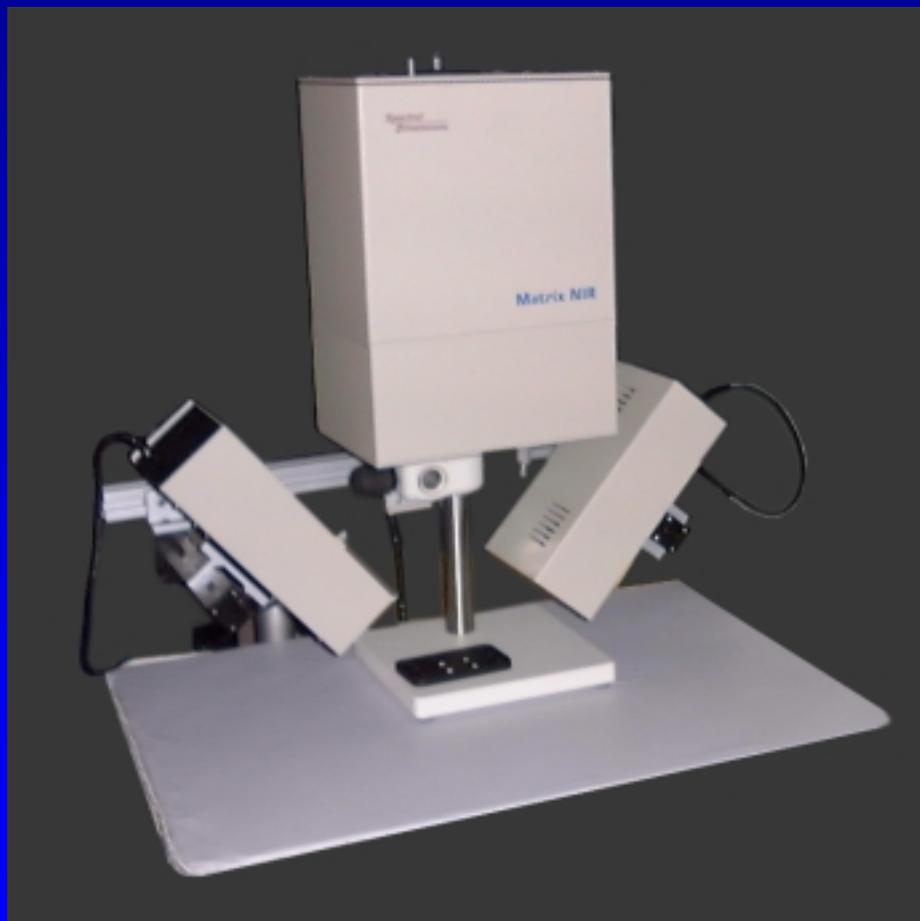
Non sticking



Sticking

# MatrixNIR - Spectral Dimensions

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## Regulatory

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## The “Don’t Use” Scenario

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- **What:**

- ◆ Modern PAT methods not used/developed during product development so not used for routine process control

- **Why:**

- ◆ Fear of regulatory delays
- ◆ Wasteful of resources to duplicate method development - “current methods work OK”
- ◆ Concern of “raising the bar” unnecessarily: information generated for one process may be expected from all

- **Issues:**

- ◆ Loss of benefit of PAT - improved process information and control
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## Example of “Don’t Use” - Antifungal Polymorph Conformation

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### Method A

- Powder XRD
- Established technique
- Not common in IPC/QO labs
- Did not exist at site of manufacture
- Samples sent to another site 3,500 miles away for release (LT 1 week plus)

### Method B

- NIR
- New technique (for polymorph)
- Common in IPC/QO labs
- Existed at site of manufacture
- All assays could be done on site (LT minutes if necessary)

## The “Don’t Tell” Scenario

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- **What:**

- ◆ PAT methods not registered but used in parallel with registered (conventional) methods to gain greater process insight and control

- **Why:**

- ◆ Concern over delays in regulatory approval
- ◆ Concern that data may be interpreted inappropriately by regulators. More data will lead to more deviations from “norms” - need to be able to determine which are relevant and which are not

- **Issues:**

- ◆ Duplication, inefficiency, environment of “mistrust”
- 

# Control of Antibiotic Fermentation

<u>Parameter</u>	<u>Registered method</u>	<u>Advanced</u>	<u>Benefit</u>
Antibiotic concentration	HPLC after extraction. time to result 2 hours	NIR time to result 15 mins	Efficient analysis provides resource for more data points Kinetic production curves
Cell growth	Differential centrifugation time to result 12 hours	NIR time to result 15 mins	Kinetic growth curves linked to other measurement i.e. production rates - process understanding
Residual Fat	Solvent extraction time to result 4 hours	At-line NIR time to result 15 mins On-line NIR continuous	x4 more data points, and almost "real time" values improves computer trending thus control of residual level
Respiration rate		Mass spec. of off-gas time to result continuous	Allows computer control by real time trending Allows balancing of residual nutrient levels to cell state and activity
Dissolved oxygen		Redox probe time to result continuous	Allows computer control by real time trending Allows balancing of residual nutrient levels to cell state and activity

## Benefits of Improved Control

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- Conventional methods give product which is fit for intended use, but...
- Advanced control gives
  - ◆ better batch to batch consistency
  - ◆ better quality (less impurities)
  - ◆ fewer reworks/rejects
  - ◆ better productivity
  - ◆ lower cost
  - ◆ improved process understanding
  - ◆ faster response times

## The “Win - Win” Scenario

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- **What:**

- ◆ Modern PAT methods used to gain greater understanding of processes during development, are registered and used as in-process control (and release?) methods
- ◆ PAT methods accepted as alternatives to traditional lab based methods - but not required

- **Why:**

- ◆ Methodology understood and accepted by regulators and industry alike

- **Issues:**

- ◆ This is where we should all want to get to. Making progress, but we are not there yet.....

## How can we create a “Win-Win” Environment?

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*Dealing with the real or perceived regulatory hurdles:*

- Sponsor joint forums to promote discussion and enhance understanding of the issues and opportunities offered by PAT
- Develop an effective process for the evaluation of new PATs
- Develop appropriate guidelines for the development, validation and implementation of new PATs
  - ◆ lab based extraction/chromatography rules don't apply
  - ◆ participate in “dummy run” submissions
- Ensure consistent approach to PAT by Review and Inspection