PAT taking the Lab online

Imagining online Methods

PAT Session

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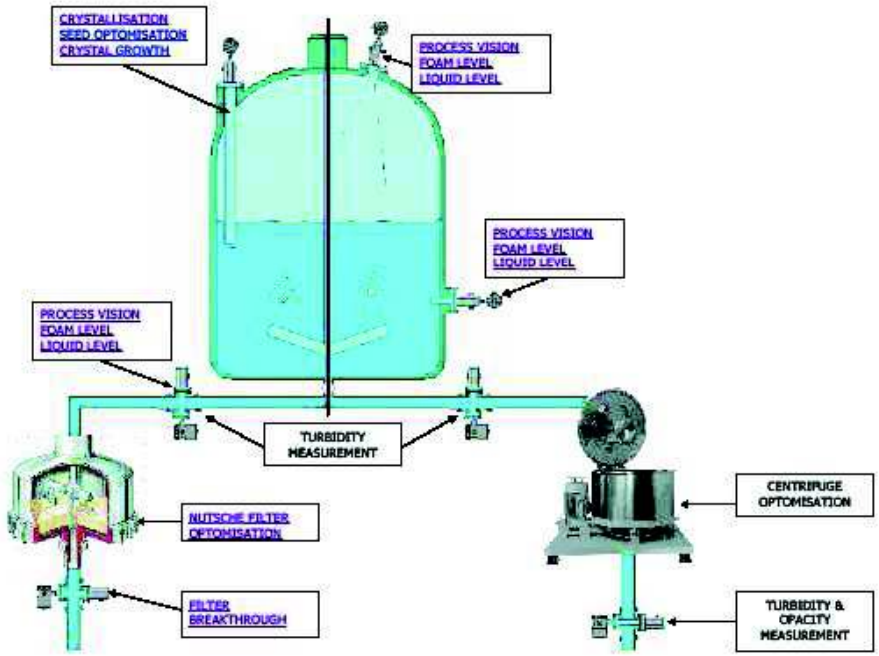
CANTY
PROCESS TECHNOLOGY

PHARMACEUTICAL



DATASHEET NEXT PROCESS CONTINUED ON DRYING

Standards PAT Equipment

- ASTM E55 (PAT and Pharma)
- ASTM E29 (particle sizing)
- ASTM E12 (Color analysis)
- ASTM D19 (turbidity)

- ASME BPE (manufacturing standard)

ASTM E55

- ASTM E55.01 and E55.02
- The 2 standards are currently being developed to deal with Risk assessment. of implementing PAT and with online measurements specific to PAT while citing and referencing existing standards
- www.astm.org

E55

- Online instruments (measurement ,accuracy and calibration methods and standards)
- Sampling methods and verification
- Risk Analysis
- Multivariable analysis and data analysis

ASME BPE

- American Society of Mechanical Engineers Bioprocessing Equipment standard
- www.asme.org

ASME BPE Active Subcommittees

- Dimensions and Tolerances
- General Requirements
- Material Joining
- Metallic Materials of Construction
- Polymers and Elastomers
- Seals
- Surface Finish
- Working group on Instrumentation

Risk Assessment and Validation

- In selecting PAT application the risk vs. reward analysis must be reviewed. The risk involved must also evaluate the time line to accomplish the goal.
- As in any evaluation the longer the time line the higher the risk and increase in uncertainty.

PAT –where to begin

- In implementing a new PAT program or bringing a PAT application to a new group or plant short term success should be the key goal.
- Look for an application which has a product yield increase as opposed to trying to go for a Validated PAT application which is much more challenging, longer time frame and higher risk

PAT does not mean validation

- The FDA initiative in PAT was a major step forward for the industry since it addressed the key need to improve productivity without the handcuffs of validation. The intent is to learn more about the process to make improvements to provide a better more cost effective product to the market

Lab = PAT

- Make sure both methods are identical not similar
- Same data
- Same Sensor
- Same Optics

Common PAT errors

- Sampling
- Location variability
- Instrument methods variance
- Lab condition (Temp ,Pressure ,etc.)
- Instrument compassion to process variables

Sampling

- Taking a sample automatically provides a different representation of the process product. Pilot testing of the sampling device will tell whether this representation will be an issue.

Liquid Sampling

- Liquid sampling is the easiest and has the lowest risk involved in homogenous solution (properly mixed suspensions). Testing of sample location and method will easily verify suitability .

Solids/Powder Sampling

- Powder sampling probes can draw a sample from the end ,the side or via mechanical pushing. This variability along with the shape and location difference to the actual PAT probe make powder/solids a very difficult operation.

2 ways to proceed with solids sampling variability

- 1st run a complete correlation test on the process to make sure the sample and probe don't effect the reading . The reading can be effect by disrupting the powder movement causing segregation. The equipment must be testing to assure this isn't the case.

Fluid Bed example

- In a fluid bed dryer or coater the powder is driven into the air to create a bed of powder. This bed will by its very nature be stratified ,smaller particles will have a higher acceleration and move higher in the bed. This means a probe will very its reading with acceleration or rotary speed . This doesn't lend itself to inline probes.

2nd option for powders At line measurement

- To totally take the sampling out of the equation you can use an at line method . The sampling system in this case feeds the analyzer to continually take the measurement of the PAT application. Sampling methods can be designed to acquire material from a larger area or confined remote space

Instrument type error

- A good example of this is the comparison between Laser particle sizing and image based measurement.
- Laser to Laser particle sizing doesn't match up (Ref PERC/DuPont report)
- In addition if online imaging is used then a lab comparison must be done prior to the start.

Location error

- We request that a sample out of our solid sizer be used in the lab for verification not a sample down or up stream which can stratify
- Verify the method 1st then check the location 2nd

Look for an easy start to PAT

- Quick success
- Easy to understand
- Good payback
- This 1st choice is critical to building a team of partners who will invest their time and resources to support you

Imaging PAT applications

- Easy to implement
- LAB=ONLINE
- Major increases in product yield
- Visual verification lets production be involved

How to proceed with online Particle imaging

- Crystallization
- Fluid Bed
- Milling
- Coating and agglomeration
- Centrifuge or Nuestch filter Cent rate
- Biotech cell filtration

Lab and online Imaging

- Microscopy is a segment of online imaging
- Imaging is 2 or 3 dimensional
- Size range .7 micron through 6 inch
- In larger sizes above .25 inch 3 dimensional becomes important.
- Correlates to Sieves

Comparison to other methods

- Sieve matches within 1 % to a particle sieve set (sieves vary by 3% in themselves) ASTM E29
- Laser 1 Dimensional (equivalent sphere) and not recommended for large aspect ratio. Tend not to correlate to each other or when suspension fluid change

Product Comparison

Canty Vision-Based Particle Sizing vs. Laser-Based Sizing

Canty Feature	Laser Feature
Visual verification both of set-up and measurement run, allows particle shape to be identified	No visual verification at any time
Direct measure of Particle Area – a two dimensional measurement	No Area measurement, only 'characteristic diameter' -- a one dimensional measurement provided
Direct measure of Particle Perimeter – a two dimensional measurement	No Perimeter measurement, only 'characteristic diameter' -- a one dimensional measurement provided
Direct measure of Major axis and Minor axis – a two dimensional measurement	No, only 'characteristic diameter' -- a one dimensional measurement provided
Able to thin measurement data using: •Minimum particle size •Maximum particle size •Particle aspect ratio	No, only 'characteristic diameter' -- a one dimensional measurement provided

PAT Failures

- Lab is light duty…not explosion proof

- Dilute sample
- Sample location
- Sample size limited
- Sample is “cut” down

- Online unit is purged…this creates a cold end which builds up
- Full Concentration
- Online not at sample point
- Not limited by size
- Not limited by location

Pilot test…test…test

- There is no substitution for good pilot testing at temperature ,pressure and flow to duplicate production conditions

IMAGE ANALYSIS SYSTEM

On-Line Particle Sizing

On Line Microscopy using fused glass and microscopic high speed camera to analyze particles on line for size shape and color.

IMAGE ANALYSIS SYSTEM - Introduction

Vision based approach for on-line particle size measurement from 0.7micron sized particles with no upper limit.

IMAGE ANALYSIS SYSTEM - Concepts

- Human Eye (Imaging Camera)
- Lighting (Key Component)
- Digitizing Image
- Image Filters
- 2D True Size and Shape Analysis
- Output Signal / Data Storage

IMAGE ANALYSIS SYSTEM Particle Sizing and Shape

- Human Eye-Live view
- Recorded Digitizing Image
- 2D True Size and Shape Analysis
- Variable outputs for control specific to application

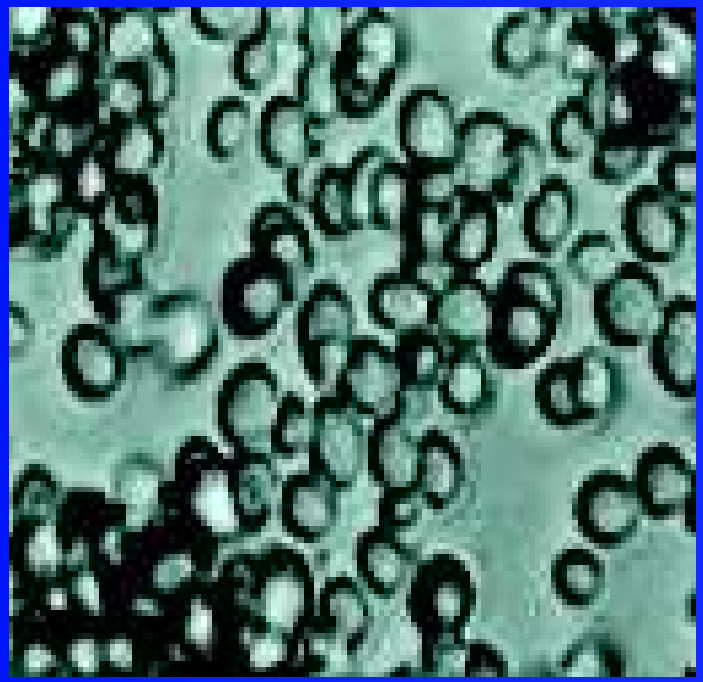


IMAGE ANALYSIS SYSTEM - System Overview

- Light source
- Viewing window
- Cleaning (Optional)
- Image processor
- Image analysis
- Outputs

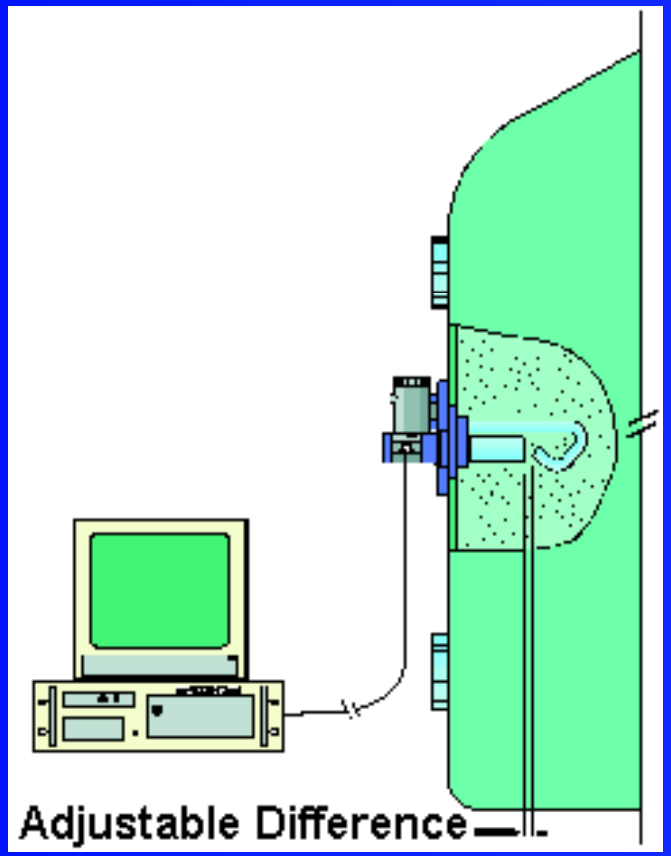


IMAGE ANALYSIS SYSTEM - Light Source…Fusedglass

- Flexible Bundle Option
- IR FILTERED
- Cold Light, NO “Bake-on”
- Explosion Proof /Weatherproof
- Fused Glass (Standard)
- No fouling

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IMAGE ANALYSIS SYSTEM - Spray Ring

- Any Fluid
- Vortex Cleaning Action
- Insertion or Flush Mount
- Standard to 2500 PSI
- Various Materials
- Various Mounting Connections

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PROCESS TECHNOLOGY

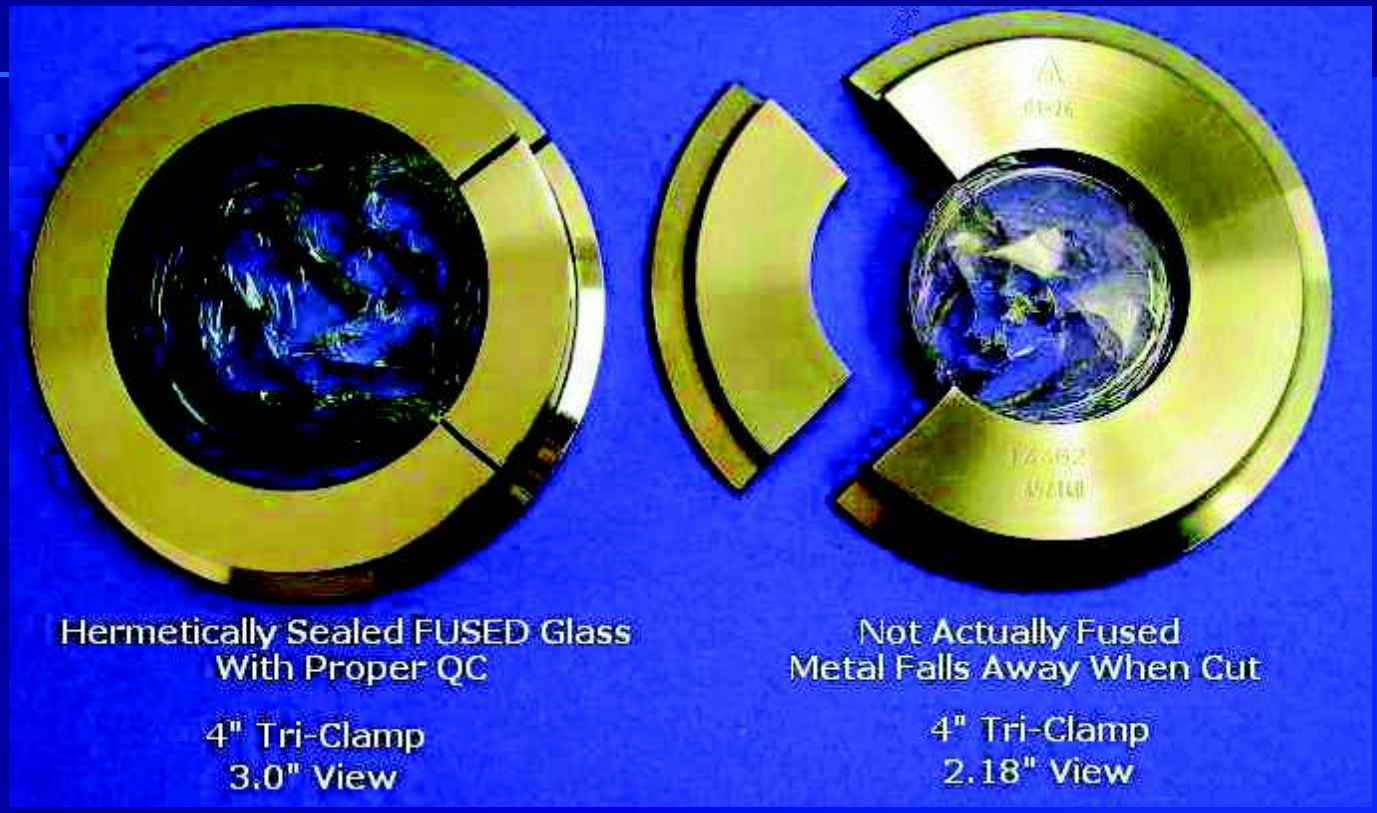
Hermetically Sealed FUSED Glass
With Proper QC
4" Tri-Clamp
3.0" View
Not Actually Fused
Metal Falls Away When Cut
4" Tri-Clamp
2.18" View

IMAGE ANALYSIS SYSTEM - Process Camera

- Colour or Black & White
- Fused Glass (Standard)
- Back or Front Lighting
- Adjustable gap
- EXP/FP or Weather Proof
- Micro Zoom Lens (1 micron)
- One Mounting Connection
- Spray Tube Option

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IMAGE ANALYSIS SYSTEM -Processor

- Ethernet Connection Windows OS™
- Industrial Chassis
- Multiple Inputs
- Multiple Outputs
- Standard 4-20mA
- Wireless and network Support

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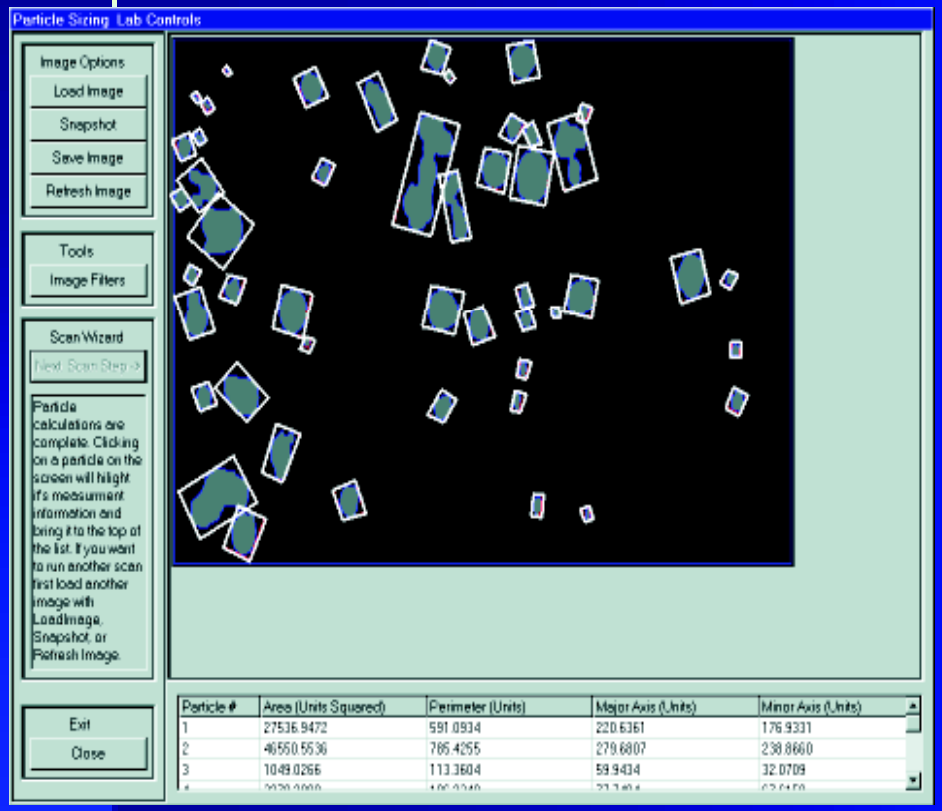
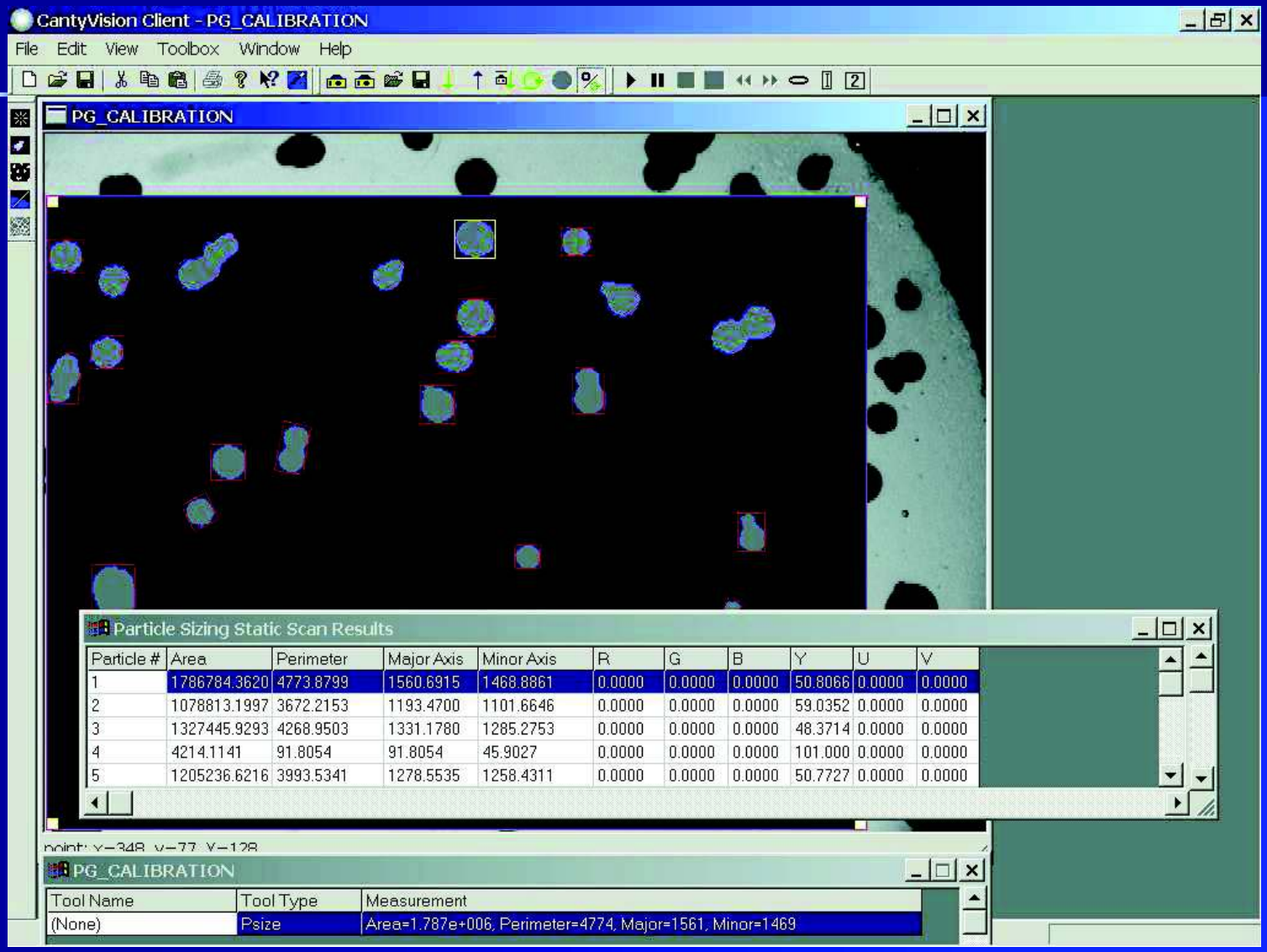
IMAGE ANALYSIS SYSTEM - Analysis



- Particle Presentation is the key Online and LAB
- Visual Verification in the software
- Output OPC server and 4-20ma ,etc

PARTICLE SIZING



PARTICLE SHAPE

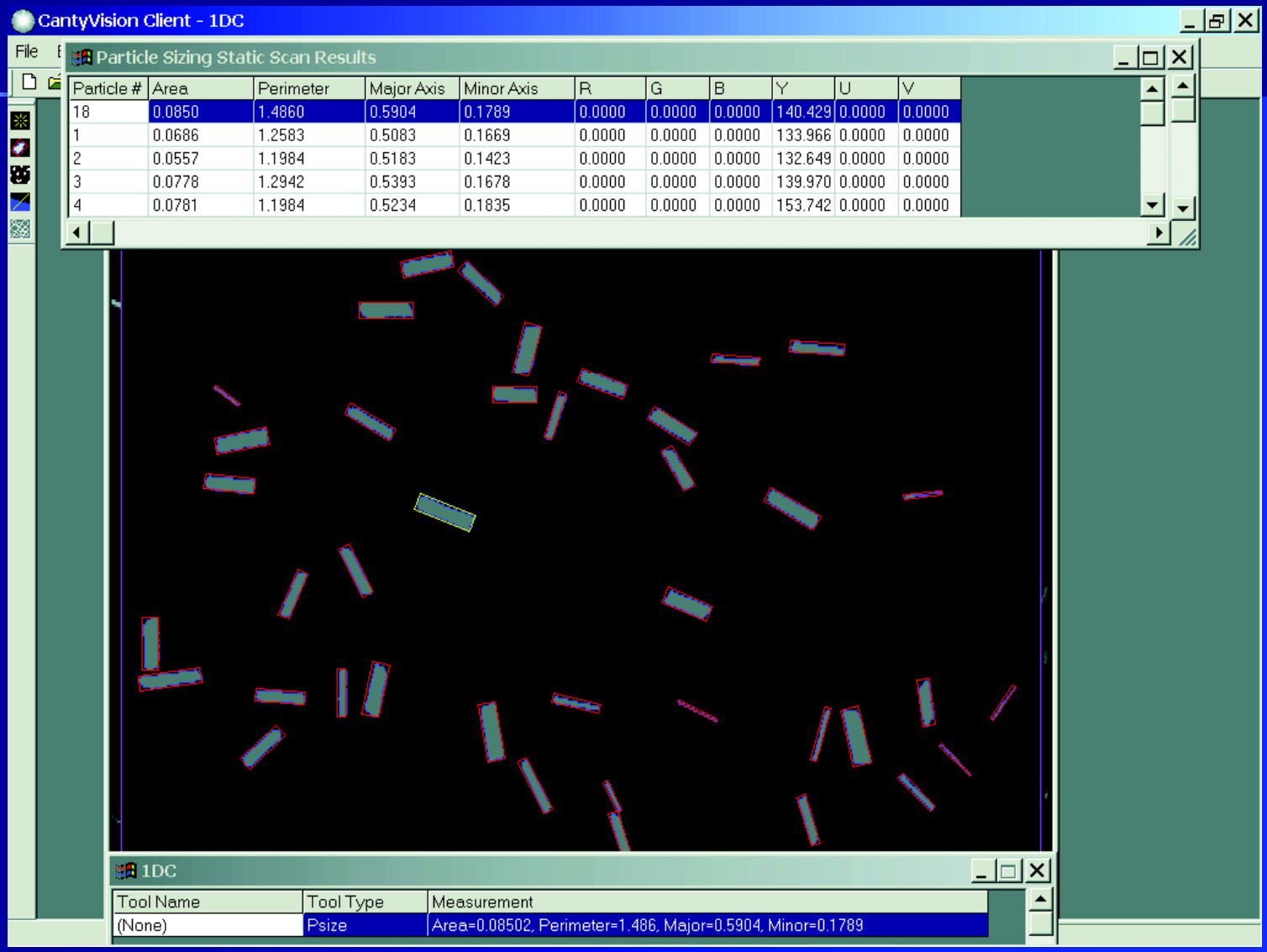


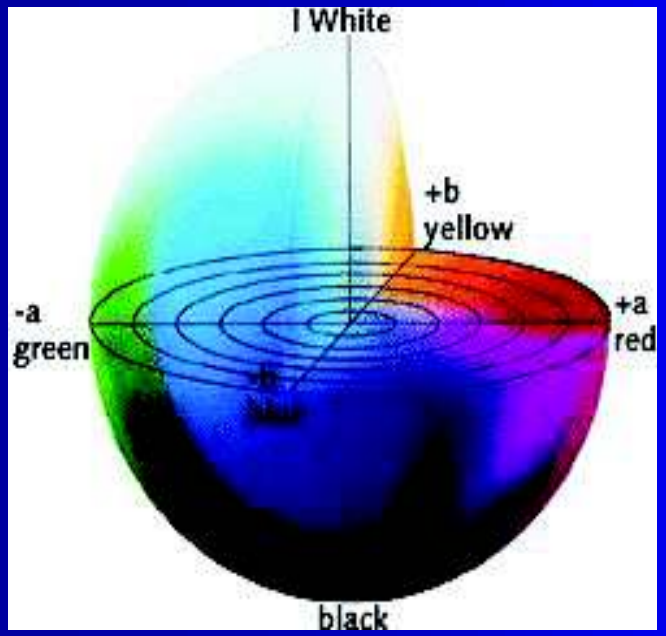
IMAGE ANALYSIS SYSTEM - Applications

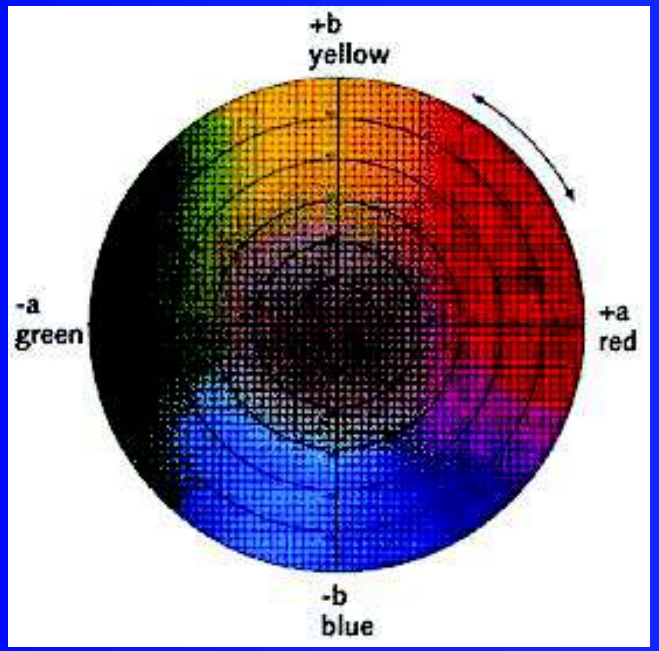
Applications:

- Colour: Liquid & Solid
- Colour Speck
- Turbidity, % Solids & Interface
- Particle Shape
- Particle Size

IMAGE ANALYSIS SYSTEM - Colour

- Colour output to any colour standard (I.E LAB, RGB, YUV, ETC)
- Suitable for solids or liquids





Particle Color

- Particle Color data along with size and shape data is used to monitor sensitive drying
- Allows research into coating in fluid beds and tablet coating
- Contamination in Bioreactors /fermentation

IMAGE ANALYSIS SYSTEM - Colour Speck

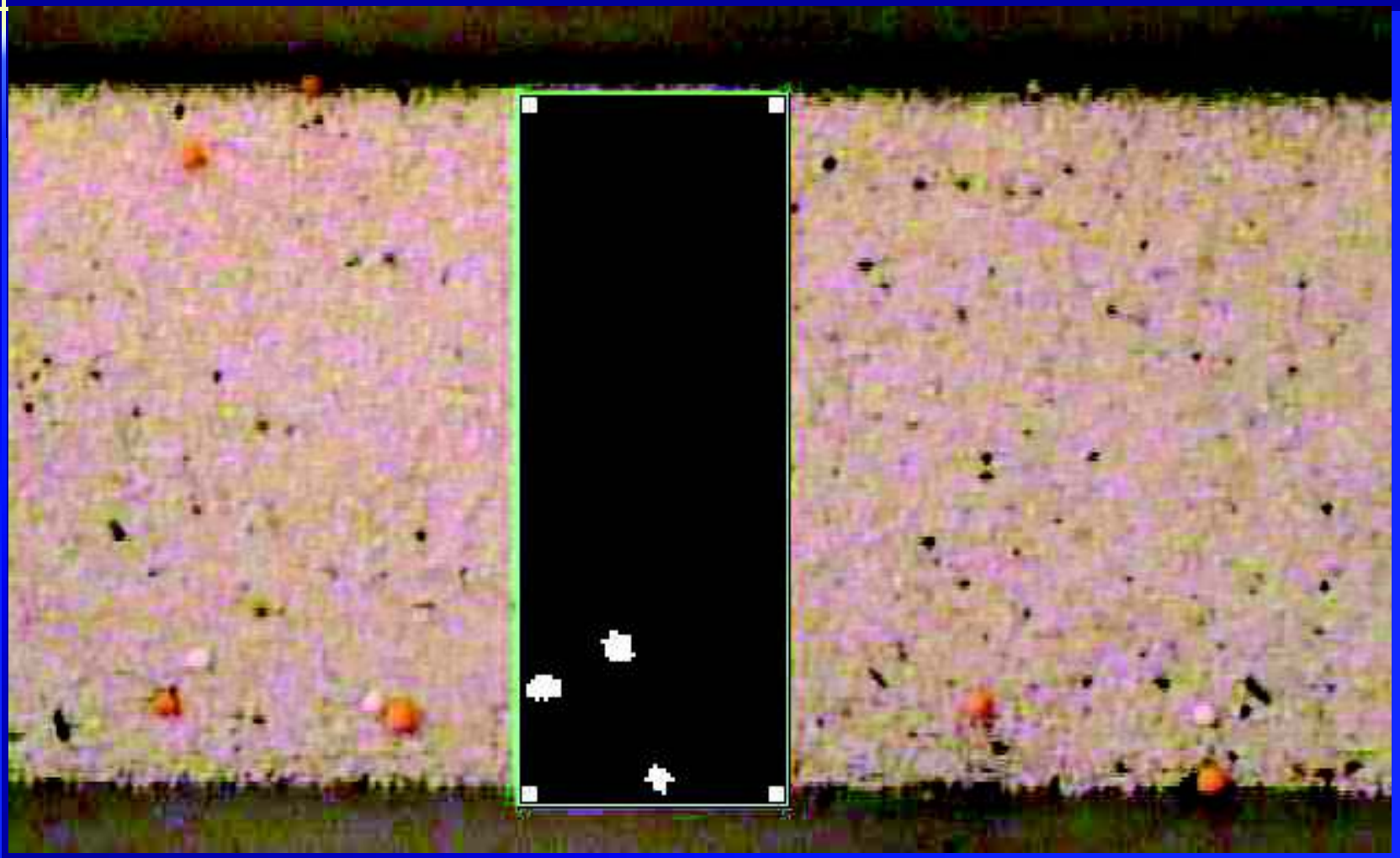


IMAGE ANALYSIS SYSTEM - Particle Size and Shape

- Solids
- Slurries

Pilot AND RESEARCH Milling PSM systems

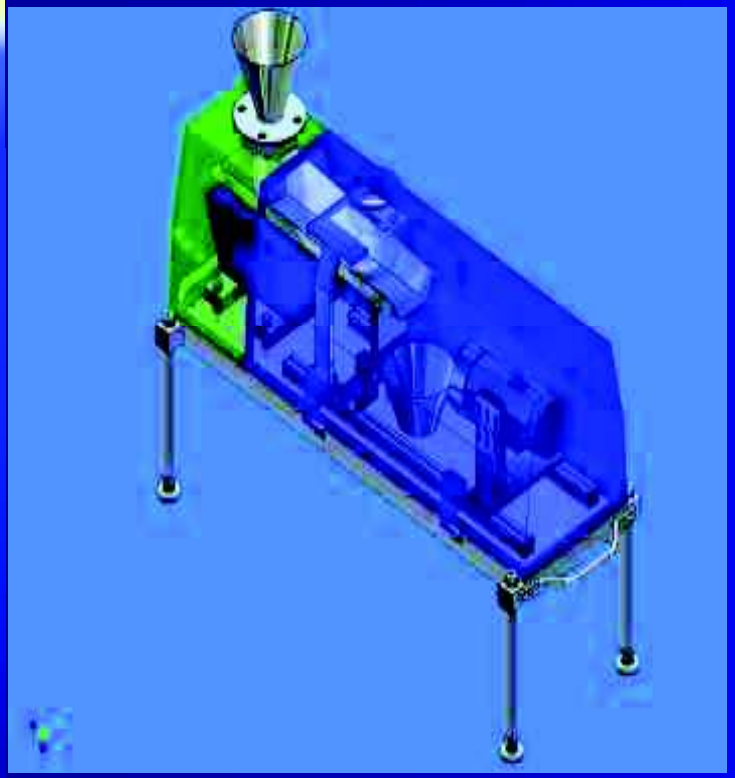
- Complete batch run of Mill is fed thorough the system . The analysis is run on the initial startup usual a tiny burst of material. This allows reliable adjustment of the Mill questionable or erroneous sample . The entire run is analyzed or randomly checked as it moves through the system.

IMAGE ANALYSIS SYSTEM - Solids Particle Sizing

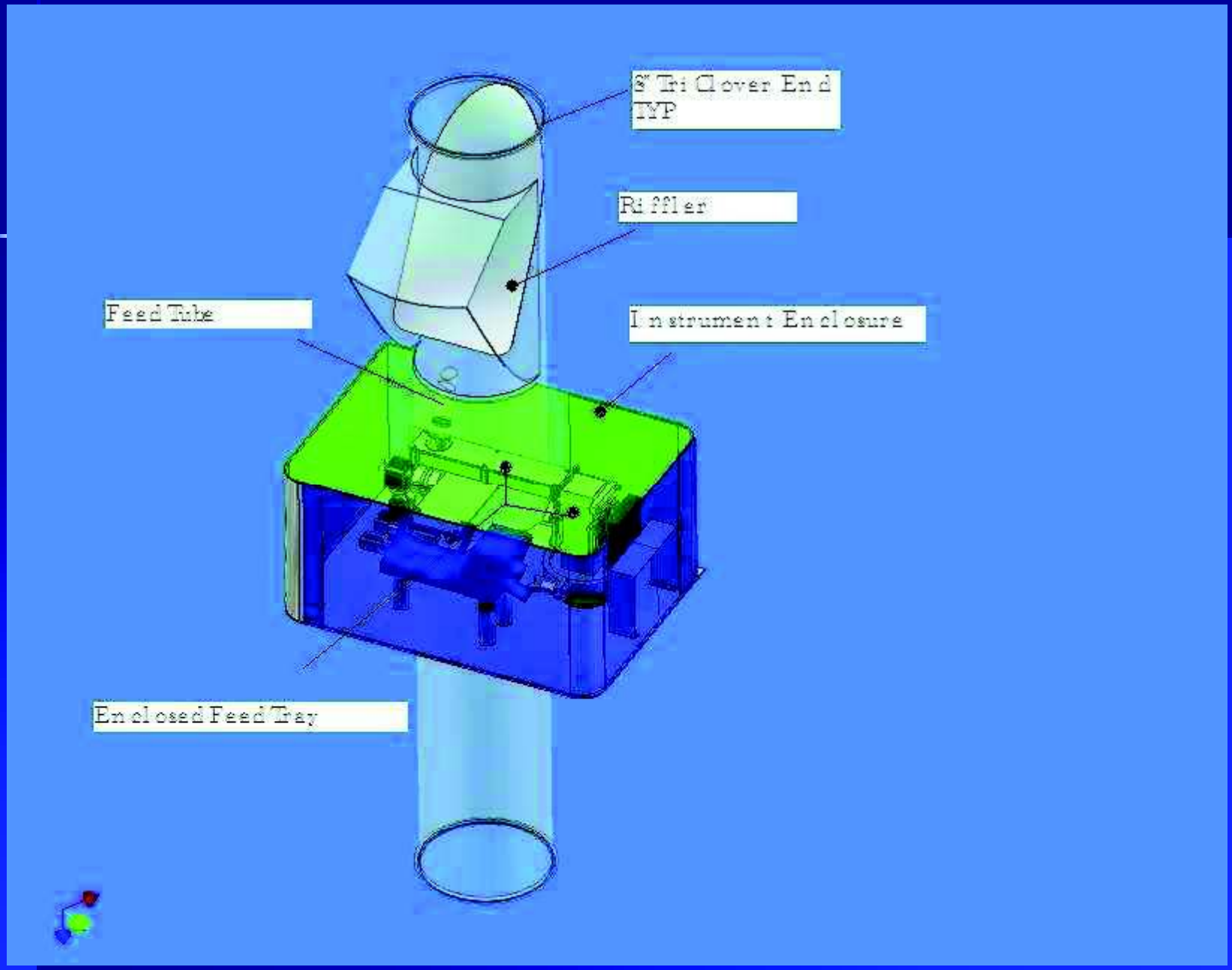
- Agglomerations
- Classifiers
- Screening
- Crushing
- Grinding / Milling

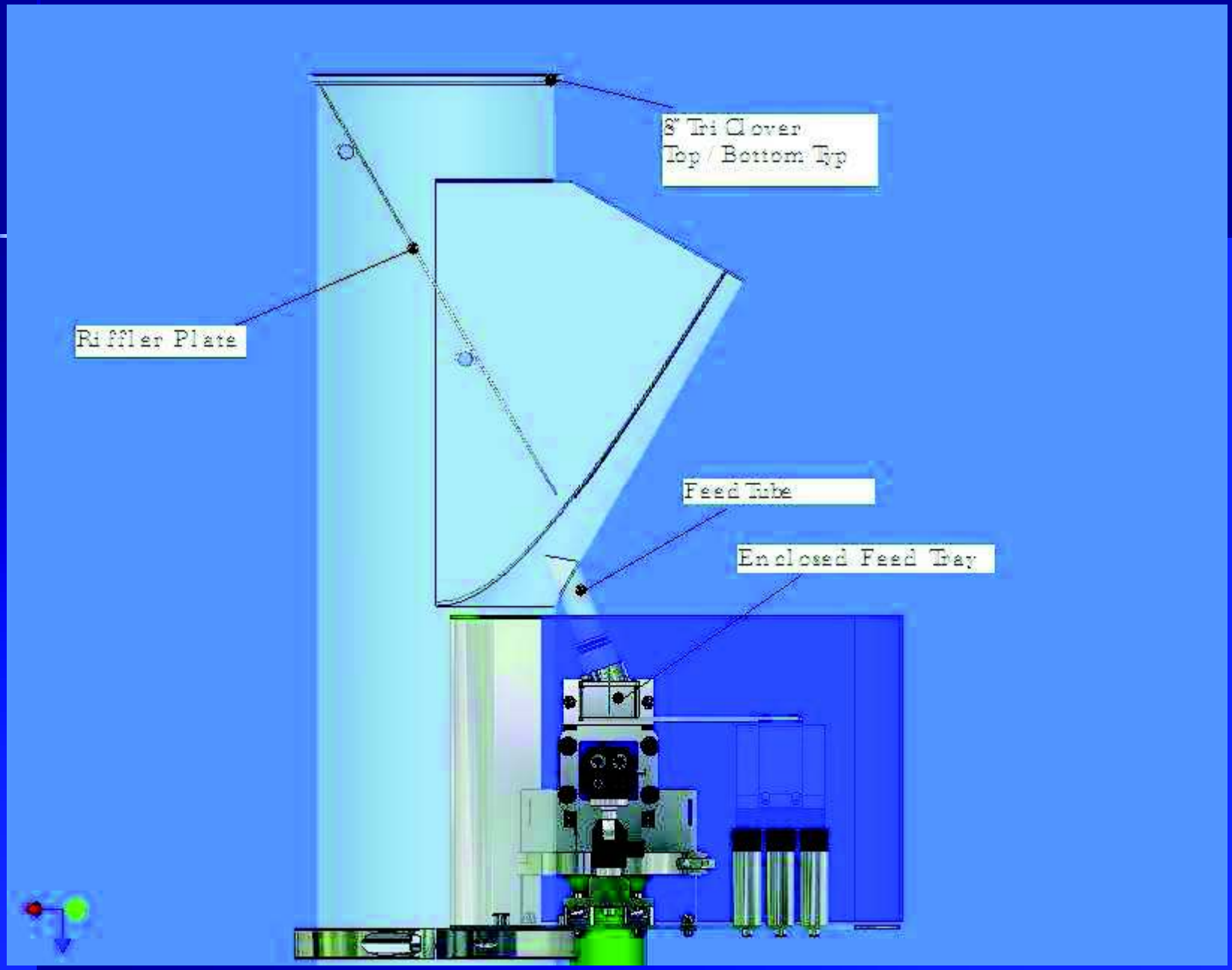
CANTY
PROCESS TECHNOLOGY

IMAGE ANALYSIS SYSTEM - On-line Solid Sizer



- On-Line at line
- Stainless Steel Construction
- EXP/FP or Weather Proof
- 1 through 6000 microns
- Sampling cross section of flow of particles
- Various Inlet / Outlet Ports


3" Tri Clover End TYP
Riffler
Feed Tube
Instrument Enclosure
Enclosed Feed Tray


8" Tri Clover
Top / Bottom Typ
Riffler Plate
Feed Tube
Enclosed Feed Tray

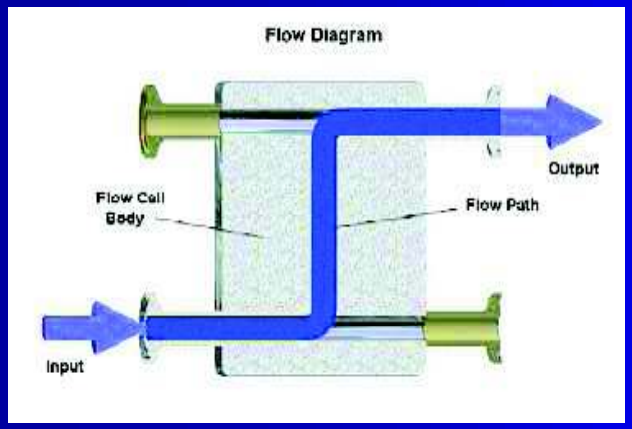
Crystallization

- Imaging online and pilot units allow detection and monitoring of seed point
- Polymorph control via size, shape and color
- Nucleation can be viewed and measured down to 1 micron
- Size and count is output
- Count monitors for Fines and Agglomerations
- Size distribution and % solids continually through crystallization
- ONLINE VIEW… You can make sense of the data

Hardware

- Key is Lighting ,Lighting, Lighting
- Constant fiber optic light avoids the variable and field problems of Strobe lights
- CCD GIGA byte Ethernet Cameras take care of speed and freezing particles for sizing (1/100,000 second)

IMAGE ANALYSIS SYSTEM - Liquid Particle Sizing



- Fused Glass
- Adjustable Gap
- Laminar Flow Path
- On-line or lab
- 6000 psi @ 800°F available
- Pressurised Sample pots
- On-Line Dilution
- Instantaneous Mixing
- Regulated Temperature
- Bypass Loop

IMAGE ANALYSIS SYSTEM - Crystallization

- Inline Microscope system
- Fiber optic lighting (cold light).
- Fused sight glass
- Sealed Camera/Lens
- Variable Insertion length
- Micro zoom lens (fixed / adjustable)

IMAGE ANALYSIS SYSTEM - Vessel Camera Calibration

- Sealed Camera/Lens unit retracted from insertion tube.
- Camera/Lens placed on Bench and recalibrated by adjusting Zoom and Focus.
- Optical Calibration against standard grid
- Unit replaced into insertion.
- Images focused on Wetted side of Fused glass.

Imaging Detection and monitoring of seed point

- You can view down to .7 micron with front or back lighting
- The software will detect and count number of particles (particle image density)
- The software will monitor size growth to avoid unwanted polymorphs , agglomerations or fines

Why Seed/Nucleation control

- The control of seeding is the most fundamental core control aspect of crystallization. Every other parameter tries to correct for improper seeding
- It is getting the train on the tracks to run and go in the right direction

Over Seeding

- Over seeding causes to many nucleation sites and creates small particles (too many fines) but a high yield. The problem becomes at filtration the product will plug and become unusable or impossible to wash

Under seeding

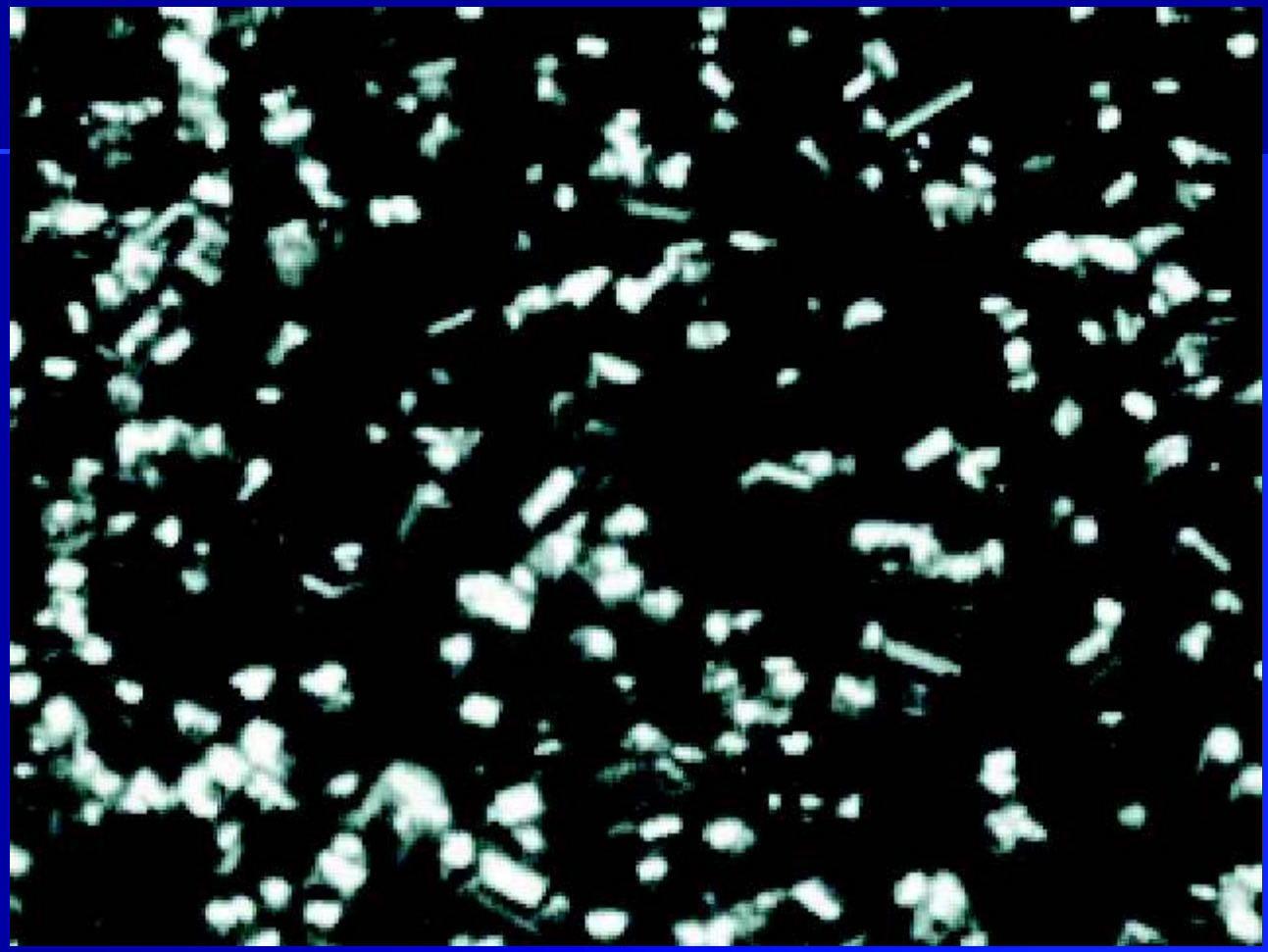
- Under seeding reduces the nucleation sites creating a lower yield in addition the liquid reaming can supper saturation and create secondary fines causing filtration problems.

Pay Back

- Controlling seeding controls yield
- Mentoring crystal growth lets you detect secondary nucleation and agglomeration
- Any problem in the early stages can be corrected by remelting the crystals and restarting the seeding process.

POLYMORPHS

- Imaging Online is the Key to PAT for Polymorphs
- Size measurement is 2 dimensional
- Shape is determined (everything is not a sphere)
- Color is given at various points in the particle (center or edge)



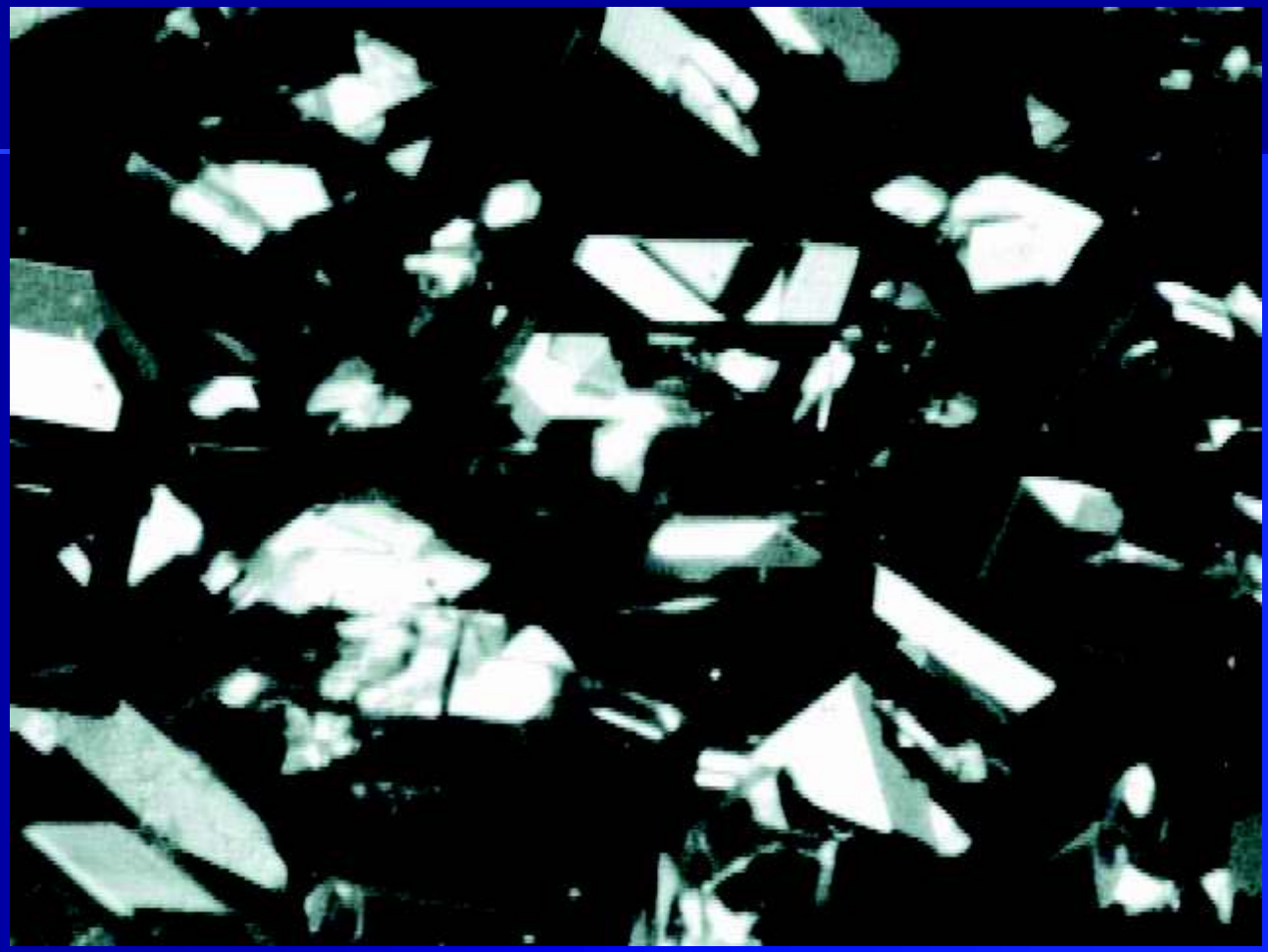
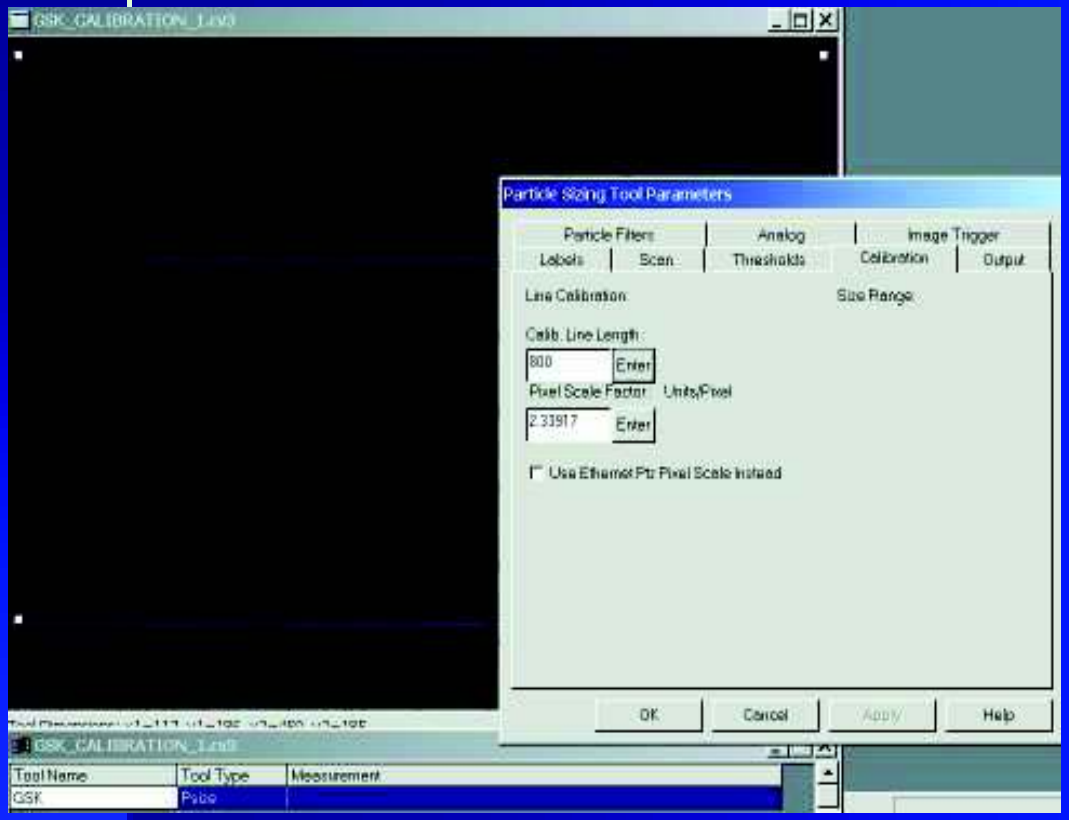
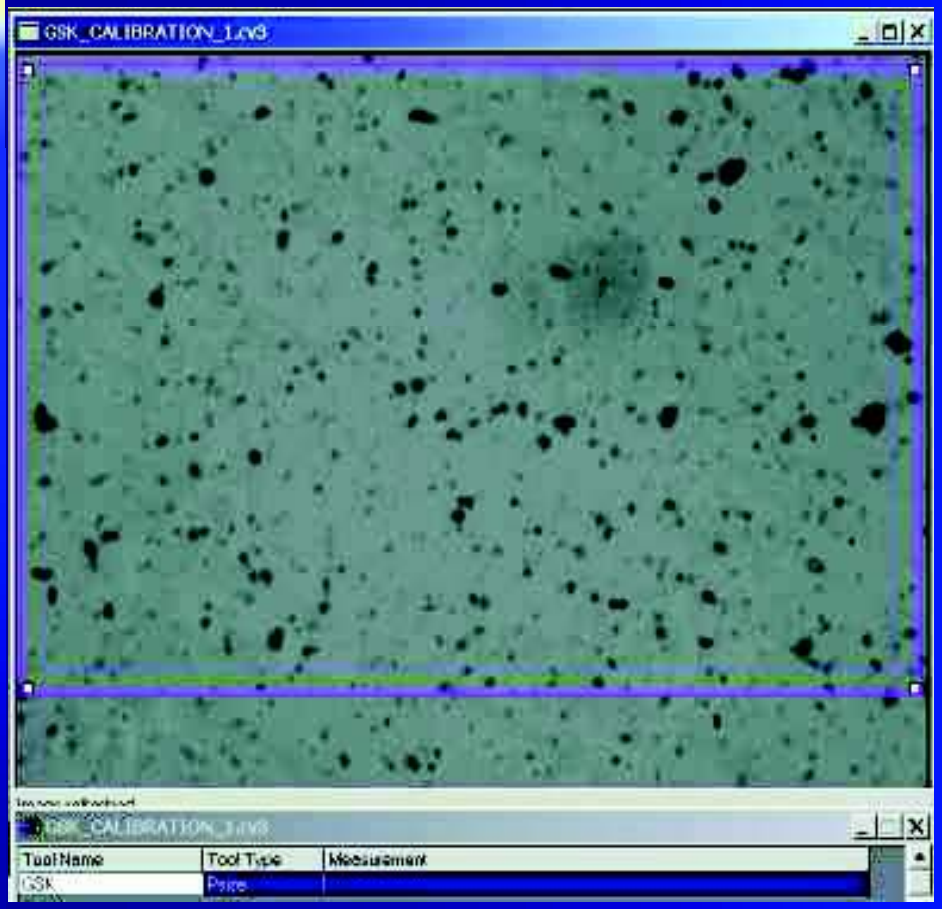


IMAGE ANALYSIS SYSTEM - Image Processing Calibration



- Still Image of Calibration scale
- System Calibrated by use of reticule grid standard
- Line drawn
- Length entered
- Micron/Pixel calculated automatically

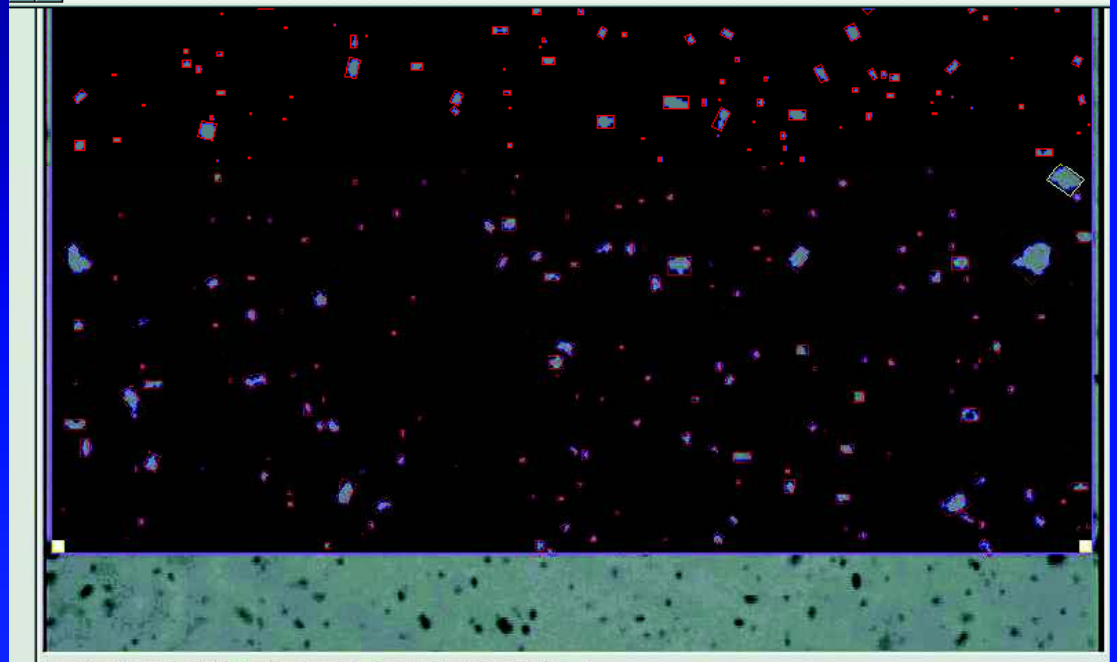
IMAGE ANALYSIS SYSTEM - Image Processing Grab



- Image of particle taken.
- Sharp image of Small fast moving particles
- Frame rate: 25 frames per second
- Shutter speed: up to 1/100,000second

IMAGE ANALYSIS SYSTEM - Calculating Size

Particle #	Area	Perimeter	Major Axis	Minor Axis	R	G	B	Y	U	V
96	55.3073	21.1658	9.4070	7.0553	101.6000	100.800	100.800	101.039	-0.1168	0.4936
97	22.1229	9.4070	4.7035	4.7035	109.0000	109.000	109.000	109.000	0.0000	-0.0000
98	143.7989	39.9798	16.0319	13.9365	99.0769	101.153	102.000	100.629	0.6705	-1.3661
99	165.9219	44.6833	16.4623	14.1105	98.6000	98.7333	98.6000	98.6783	-0.0384	-0.0689



GSK_CALIBRATION_1.cv3

Tool Name	Tool Type	Measurement
GSK	Psize	Area=1471, Perimeter=155.2, Major=52.65, Minor=39.07

- Image Digitised
- Each particle sized
  - Area
  - Perimeter
  - Length
  - Width
  - Colour Information
  - Particle Count
- Data outputted to file and Excel spreadsheet
- User Defined Output data sample size

IMAGE ANALYSIS SYSTEM - Output Data/Process Control

- Displays
  - Graphs
  - Bin Analysis
  - Tables
- Output Signals
  - 4-20mA
  - Digital
- ...ETHERNET

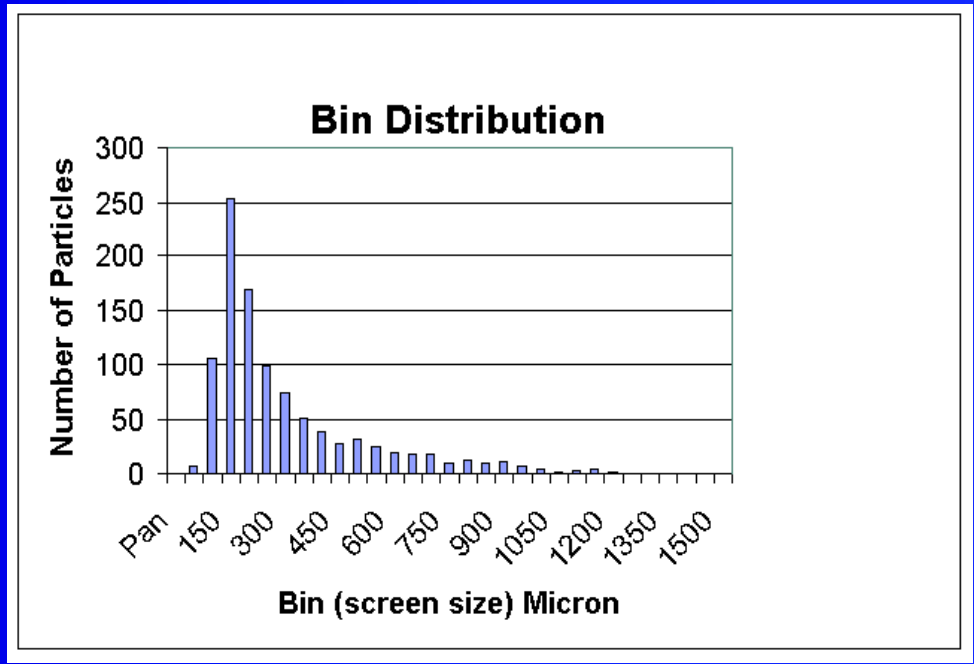
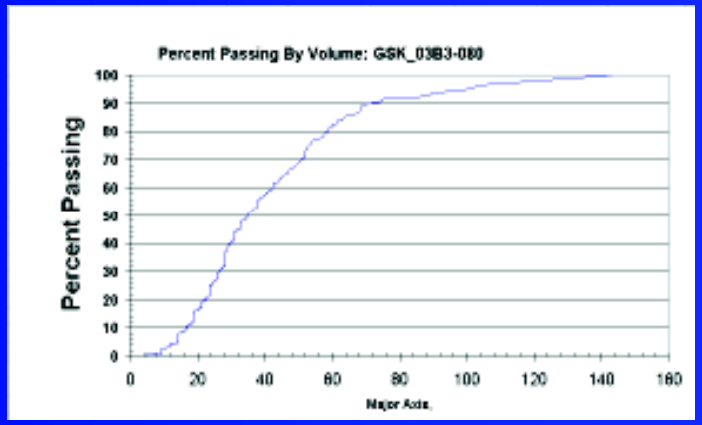
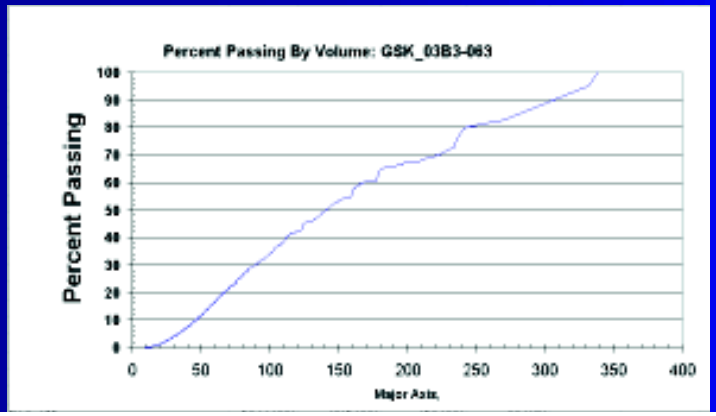


IMAGE ANALYSIS SYSTEM - Output Data: Excel Graphs

- Graphs: Automatically generated.
- Attached graphs calculated automatically with Percent passing be Volume.
- Volume calculated using Length-Width dimensions and Cylinder model.
- Various shape models possible (Sphere, Cube etc)





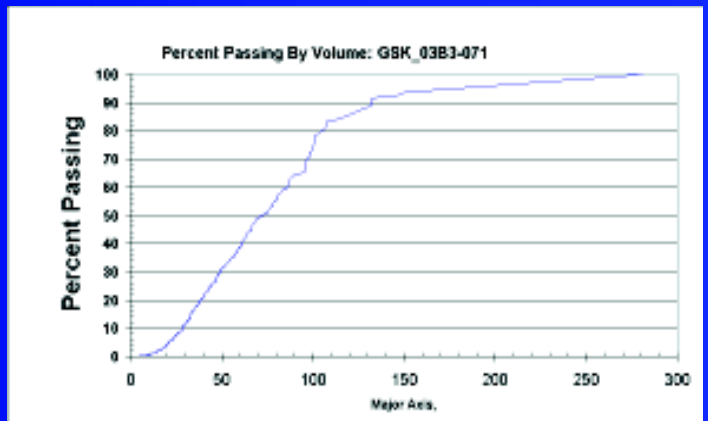
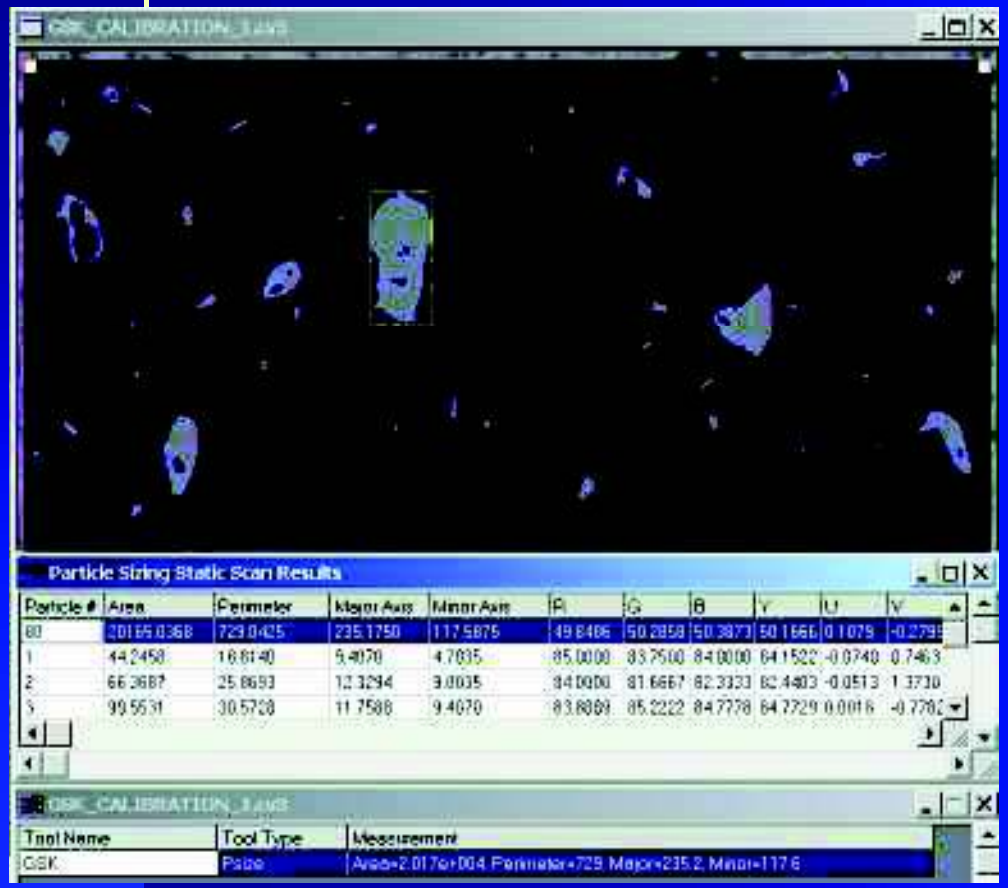


IMAGE ANALYSIS SYSTEM - Visual Verification



- Key Advantage
  - Operators View Process in Real Time
  - Suspect data can be verified by viewing images
- R & D
  - Recording Files (AVI & MPEG4)
  - Images (BMP)
  - Data (.TXT .CSV .XLS)
  - All data has File name and time stamp

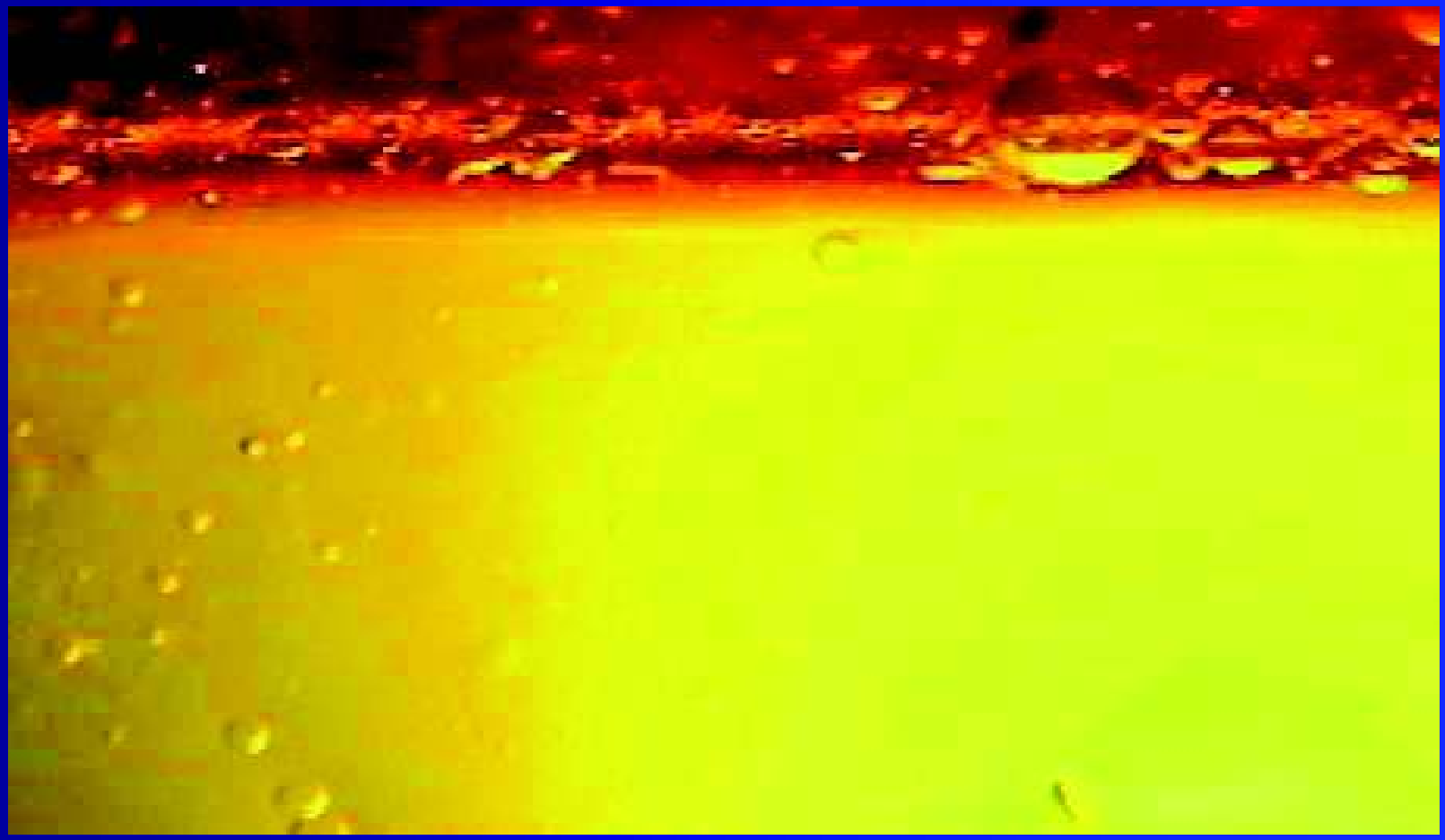
IMAGE ANALYSIS SYSTEM - On-Line Measurement

- Reduce Lab Samples
- Repeatable/Accurate
- Improve Quality
- Response Time
- Learn Process

Payback

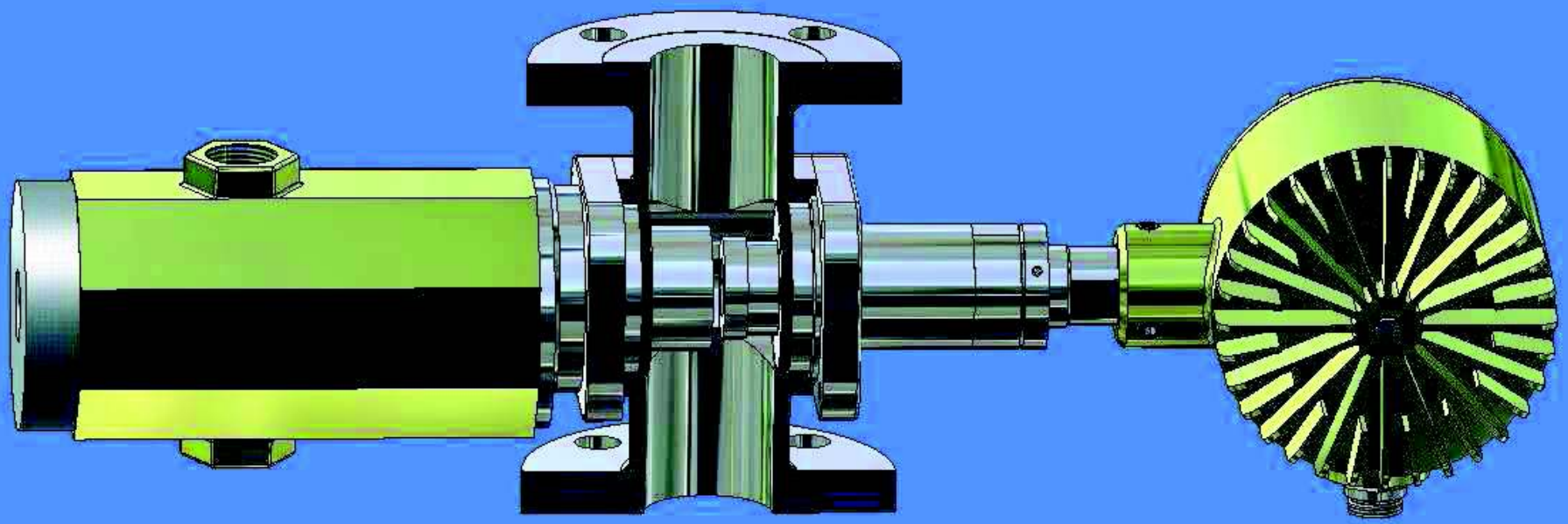
- Online Crystallization determined that the agitation in production was damaging Crystals. Reduced
- Cake detection in Nuestch filter increased product yield by 3 %
- Interface detection determined organic product loss due to gels earlier resulting in increased recovery.

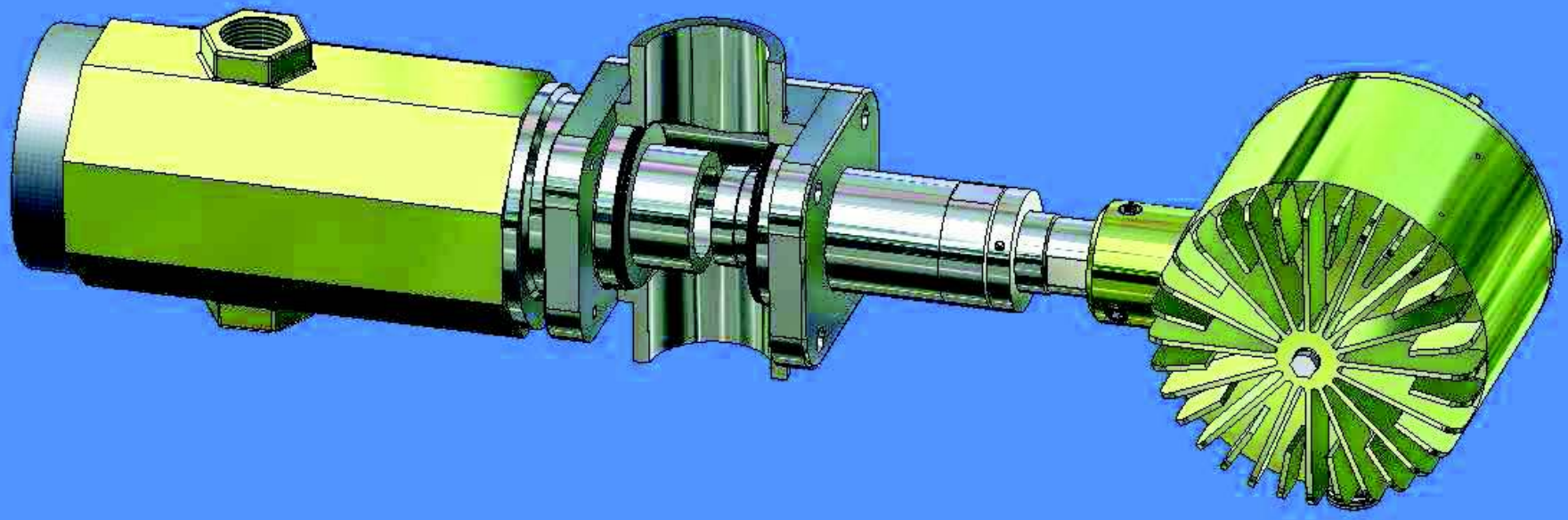
IMAGE ANALYSIS SYSTEM - Turbidity, % Solid and Interface Control



Filter Breakthrough Biotech

- Centrifuge Control
- Ultra filtration in Biotech





OPC

- OPC is a data communications protocol used to communicate between instruments and PC based systems
- Ref www.isa.org for more OPC info

Summary

- LAB,PILOT and PRODUCTION use same methodology and identical equipment
- R & D needs to accommodate the size issues.
- PAT can be research,developemnt or production orientated