FLUIDIZED BED SPRAY GRANULATION:

Equipment and Processing Considerations

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Topics of the Presentation

- Equipment description
- Application considerations
- Process and product variables
- Sequence of operations
- An example
- Summary

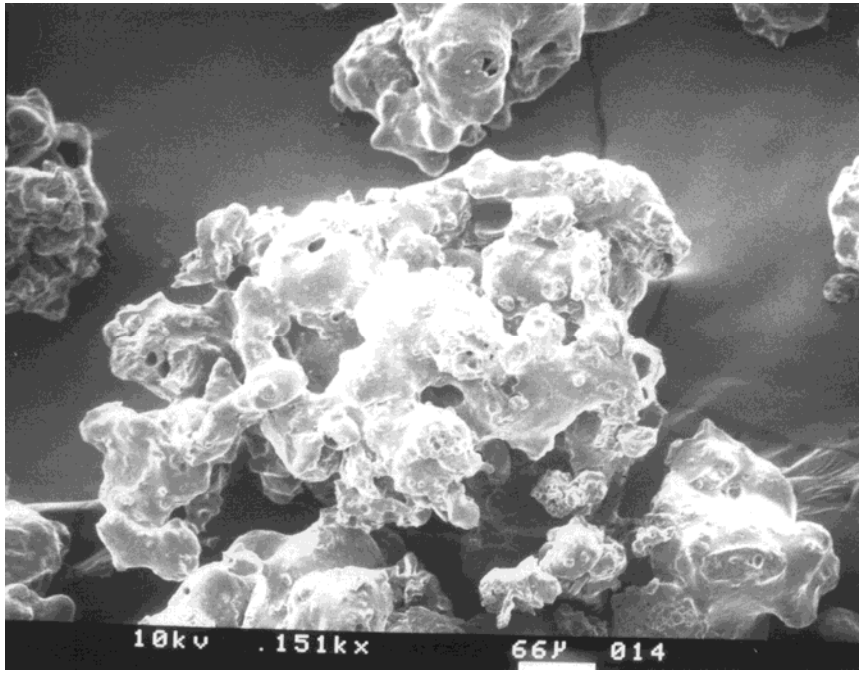
Graphics courtesy of Glatt Air Techniques, Inc., Ramsey, NJ

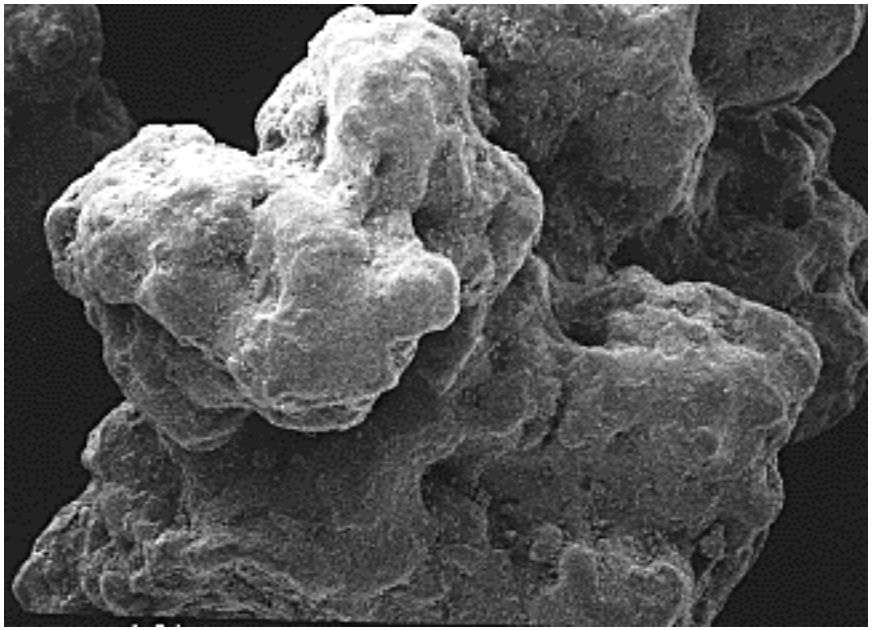
Why consider fluid bed spray granulation?

Attributes of Fluid Bed Spray Granulation

1. High rates of heat and mass transfer
   A. Quantity of liquid is immaterial
   B. Control of in-process moisture content
   C. Water or organic solvents are possible
2. Excellent mixing
   A. As a solid, added to the product container
   B. As a liquid, sprayed onto the substrate
3. Porosity of agglomerates yields high wettable surface area

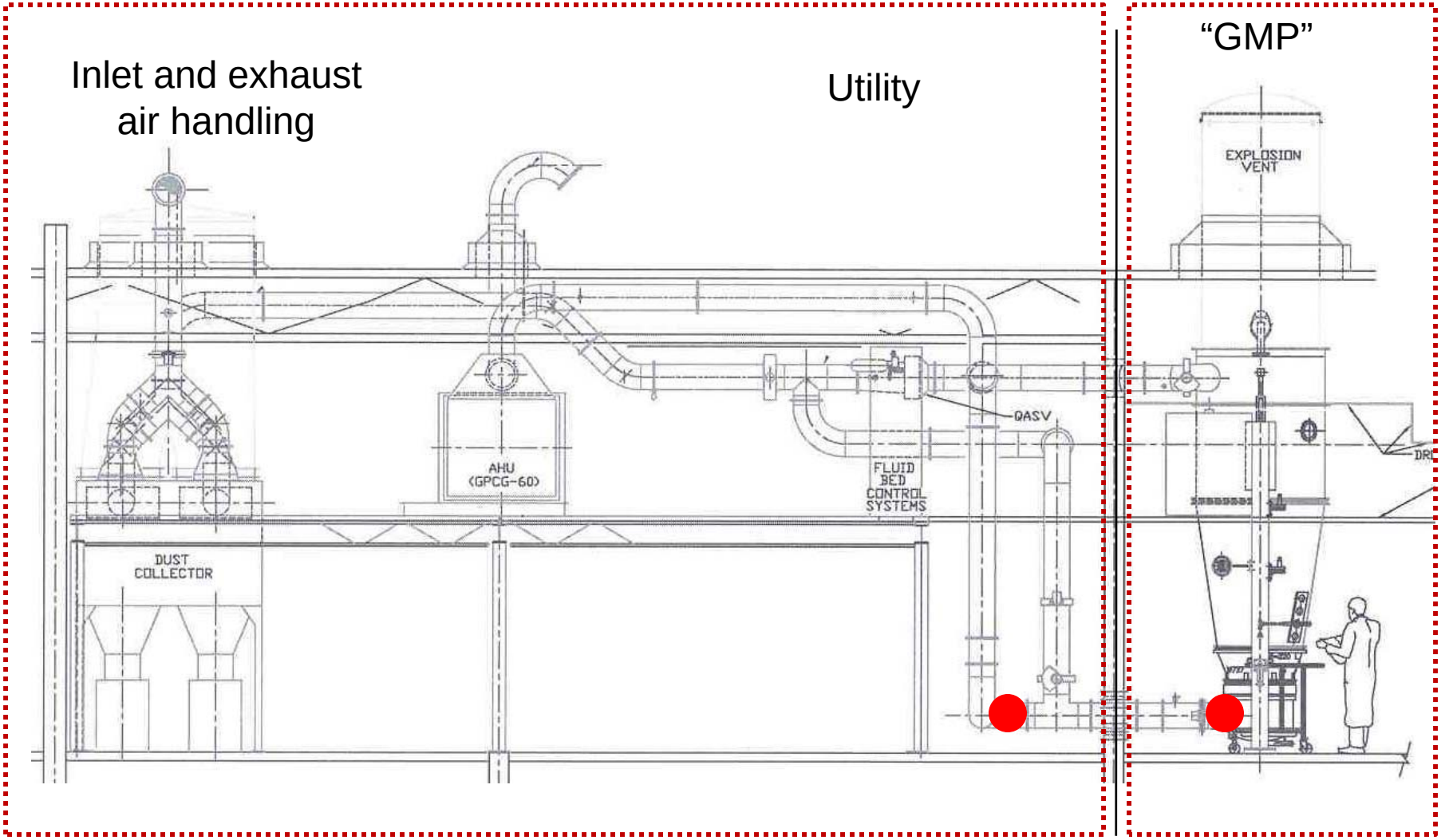
Fluid bed agglomerates





SEM's courtesy Stephen E. Abele

A Typical Fluid Bed Spray Granulator Installation



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Inlet Air Handling (AHU) and interconnect ducting

1) Older machines:
   - Filtration, heating
2) More recent machines:
   - Filtration, dehumidification, heating, face and bypass
3) “State of the Art”
   - Filtration, dehumidification, humidification, heating, face and bypass. May also include desiccant for very low dew points

1) Older machines:
   - Direct connection
2) More recent machines:
   - Preconditioning bypass
3) “State of the Art”
   - Active bypass

The Machine Tower Components

Outlet filter housing

Expansion chamber

Spray nozzle wand

Product container

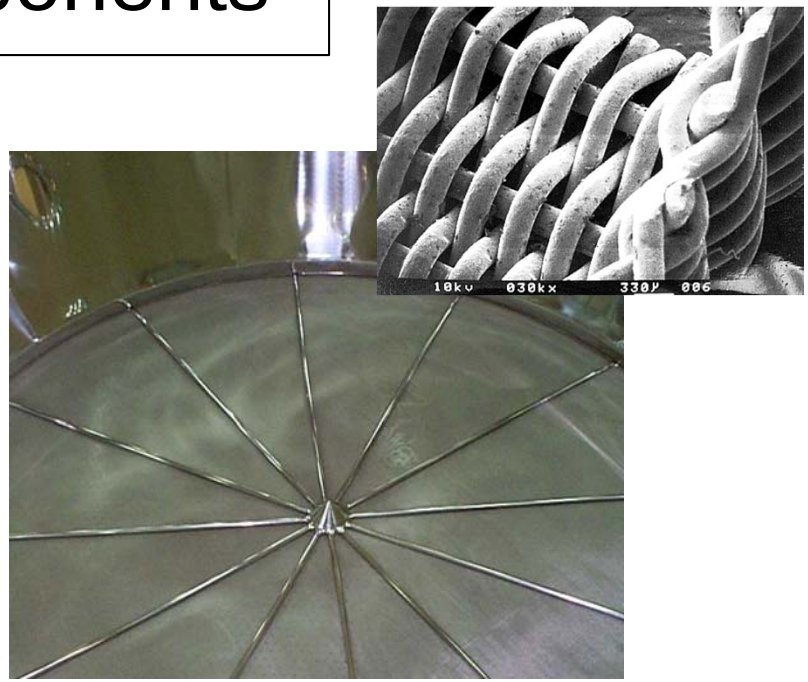
Inlet duct and lower plenum

The Machine Tower Components

Product container

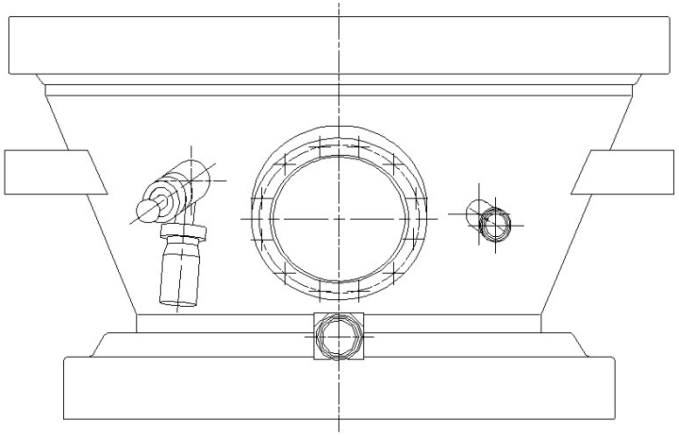
The product container may be comprised of several components

The distributor plate provides resistance to help distribute air flow across the base of the product container. It also supports the retention screen and product.



The screen retains the product, and must be strong. The rods hold the screen in place (against the strong suction of the fan).

Product Container Components



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The Machine Tower Components

Expansion chamber

The spray nozzle wand is mounted in the expansion chamber, spraying downward. Make sure that the pump has the capability of pumping the binder solution at the rate at which it is needed.

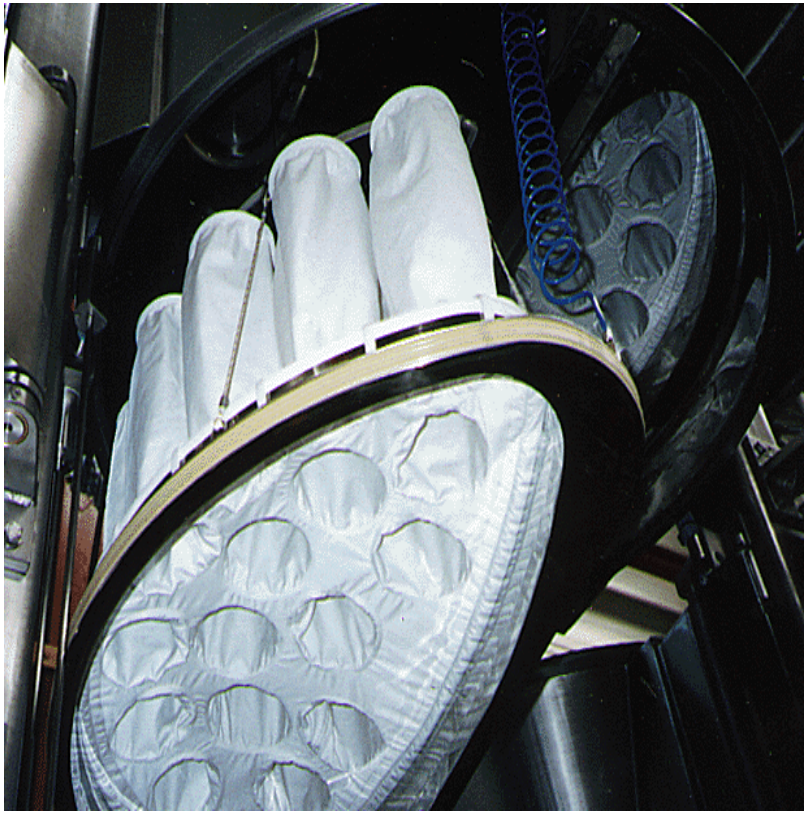
The Machine Tower Components

Outlet filter housing

The Machine Tower Components

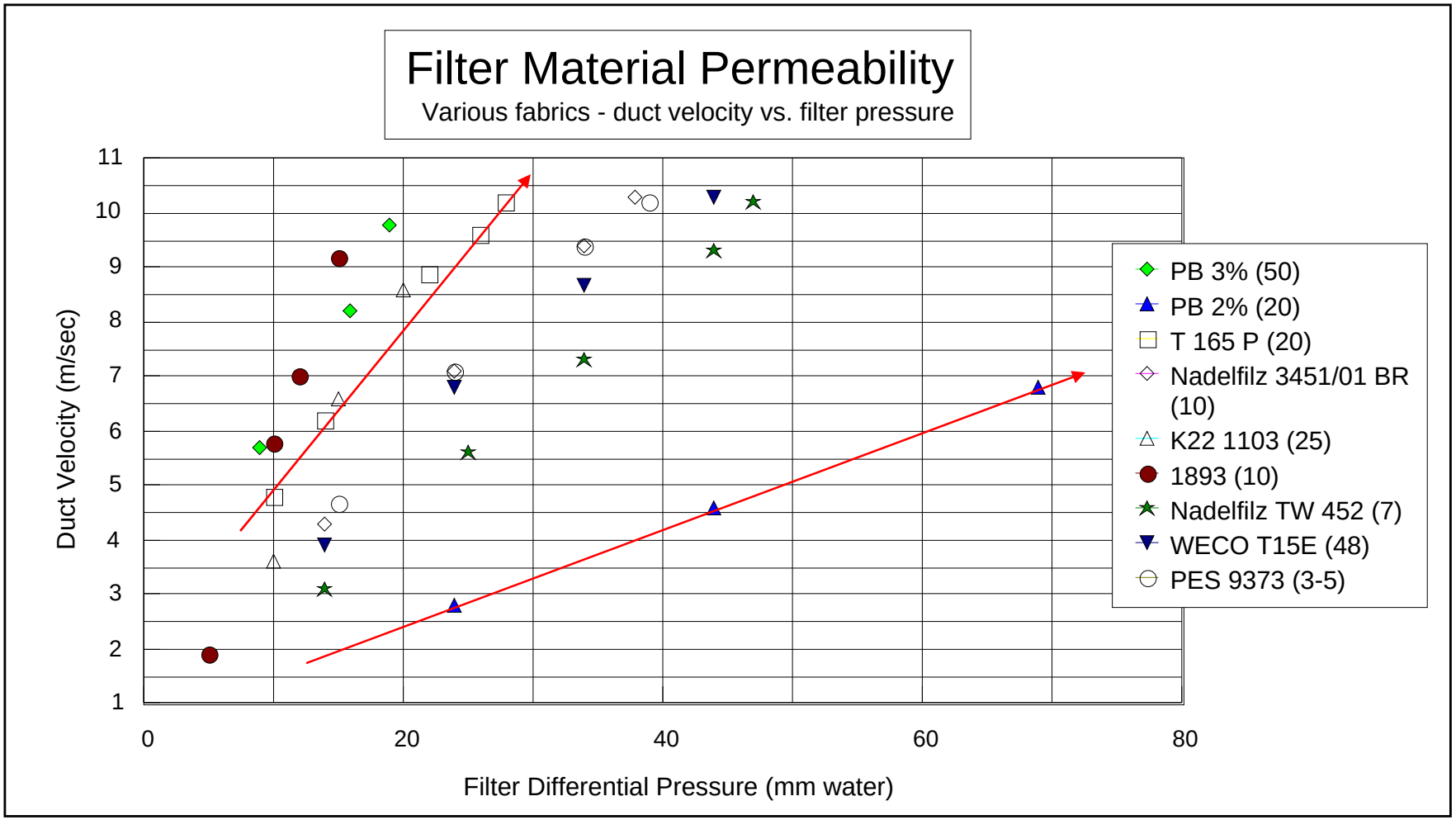
The vast majority of fluid bed systems incorporate the use of fabric filters (as shown). The two dominant considerations are:

A. Porosity (the size of the openings in the fabric)
B. Permeability (the number of openings per unit area



However: there is NO standardized test for determining this behavior, and periodically, fabrics are discontinued.

Filter Fabric - Performance



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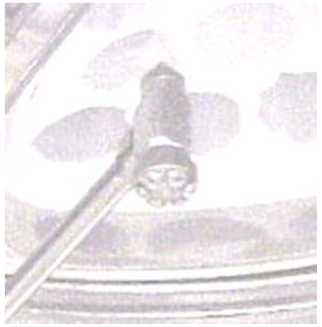
Any questions related to the equipment?

Fluidized Bed Spray Granulation:

The Unit Operations

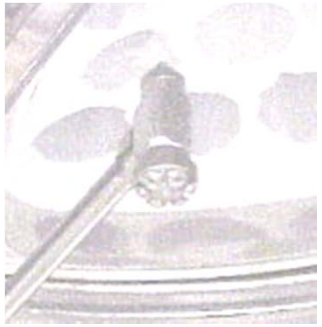
What are the Basic Principles of Operation?



1. Product is loaded into the product container (order of addition is generally not important)
2. Heated/treated air is drawn through the product container and fluidization begins
3. The materials fluidize for 1-2 minutes to begin mixing (it is NOT mixed completely)
4. Spraying commences with simultaneous accumulation of moisture and evaporation of water
5. At the completion of spraying, drying continues
6. When drying is complete, the granulation is discharged

Product – What Goes Where?

1. Product is loaded into the product container (order of addition is generally not important)



Granulation components:

API (if >1% of the mix)

Bulking agents (Product container)

Disintegrants

Spray components:

API (if <1% of the mix)

Binder (Liquid vessel)

Water

Blending components:

Lubricants (Blended externally)

Extra-granular excipients

What are the Basic Principles of Operation?

1. Product is loaded into the product container (order of addition is generally not important)
2. Heated/treated air is drawn through the product container and fluidization begins
3. The materials fluidize for 1-2 minutes to begin mixing (it is NOT mixed completely)
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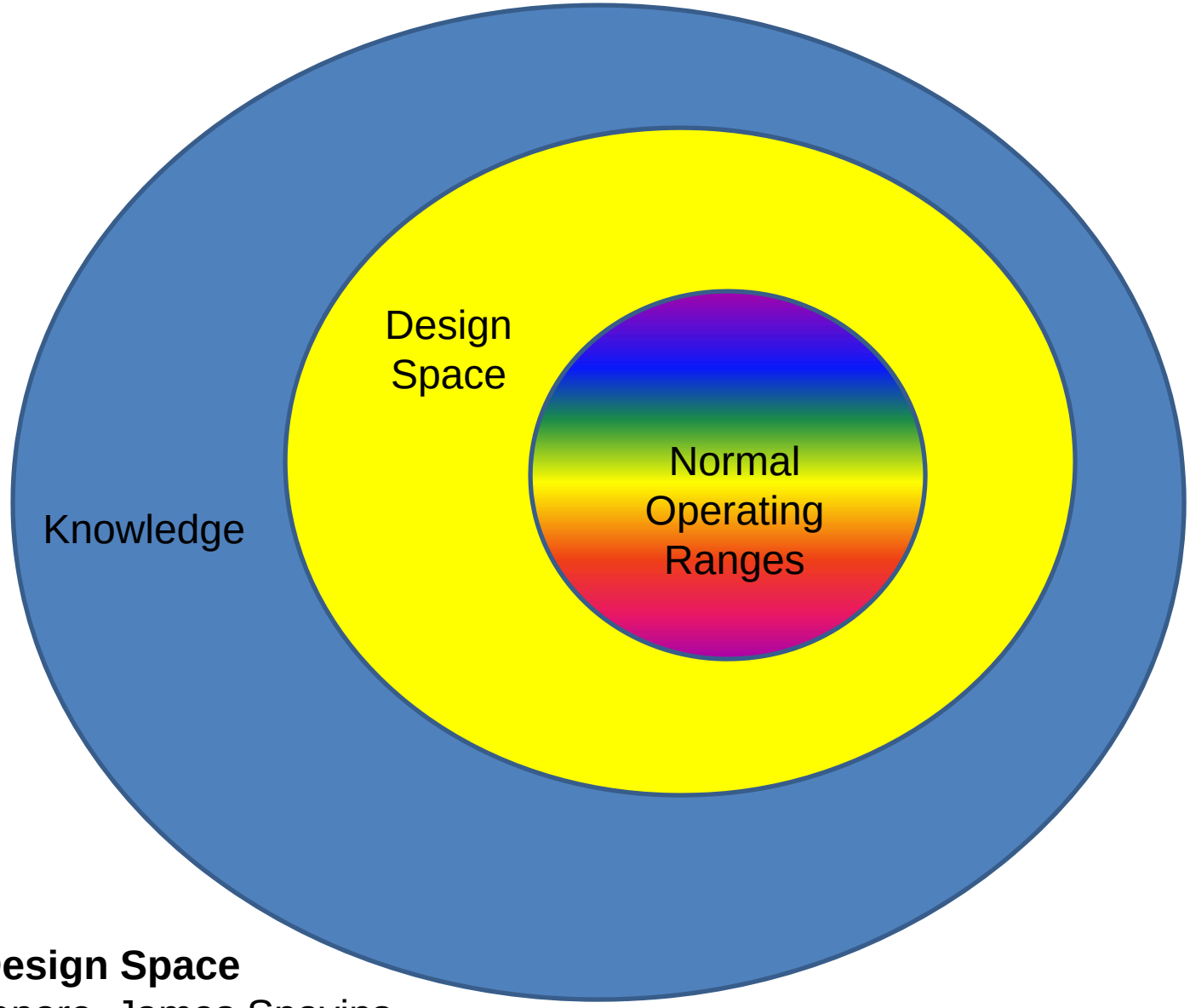
Process Parameters

Process Air	Spraying	Other
Ambient Air Dew Point	Spray rate	Bed Depth
Dehumidifier Dew Point	Atomizing Air Pressure	Batch Size
Pre-heater Temperature	Atomizing Air Volume	Outlet Filter Media
Process Air Dew Point Temperature	Liquid Line Pressure	Bowl Screen Media
Bypass Air Temperature	Liquid Viscosity	Filter Shake Interval
Process or Inlet Air Temperature	Nozzle Port Size	Filter Shake Time
Total Air Volume	Air Cap Position	Atomizing Air Dew Point
Process Air Volume	Nozzle height	dP Product
		dP Outlet Filter

Of This List, Which are the "Critical Process Parameters"?

Definition:

Critical Process Parameters (CPP) have a direct and significant influence on Critical Quality Attributes (CQA) and must therefore operate within a defined or limited operating range.



PQLI Design Space
John Lepore, James Spavins
J. Pharm. Innov. (2008) 3:79-87

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Critical Process Parameters

Note: some parameters are defined as CPP only during certain process steps – a process is comprised of heating (machine tower/ substrate), spraying, drying and cooling steps.

With this as background, which of the listed items ARE likely to be CPP? What are the direct impacts on product attributes?

Process Parameters

Process Air	Comments	Steps: H, S, D, C
Ambient Air Dew Point	It depends if the machine has dew point control	If yes: S, D, C
Dehumidifier Dew Point	No – it can vary independently of process air dew point	
Pre-heater Temperature	No – it operates independently of process air temperature	
Process Air Dew Point Temperature	Yes, unless the process air temperature is very high (>90 C)	H,S, D, C
Bypass Air Temperature	No – controlled by process air temperature PID in pre-conditioning	
Process or Inlet Air Temperature	Yes	S, D
Total Air Volume	No – accommodates process air volume	
Process Air Volume	Yes	H, S, D, C

Process Parameters

Spraying	Comments	Steps: H, S, D, C
Spray rate	Always a CPP – impacts granule structure	S
Atomizing Air Pressure	Almost always – impacts granule size via droplet size	S
Atomizing Air Volume	Linked to AAP – the REAL factor in droplet size control (sensor needed)	S
Liquid Line Pressure	No – typically just an indicator of nozzle performance (clogging)	
Liquid Viscosity	Yes – for viscose binders; no for low viscosity binders or water alone	If yes: S
Nozzle Port Size	No – accommodates liquid delivery – generally does not impact droplet size	
Air Cap Position	Machine parameter. Must be specified and documented	
Nozzle height	Machine parameter. Must be specified and documented.	

Product Temperature (CPP)

Condition	Comments	Impact to moisture profile
No dew point control	Seasonal variation in ambient dew point will cause it to rise or fall, impacting drying rate	Up or down
Process air dew point - dehumidifier only	Minimizes seasonal variation. Batches will run dryer in winter (low dew points)	Down
Process air dew point – set point control	Consistent year 'round. Best system.	None
Process air volume	At saturation there is NO impact on product temperature. Below saturation the PT will change depending on adjustment to air flow. Be careful with ramping!	Up or down
Process air temperature	Direct impact on PT. Very high temperatures mitigate seasonal dew point variation; low temperatures are strongly impacted. Beware of ramping – if it is necessary, small increments are recommended to avoid condensation impacts.	Up or down

Although product temperature is a CPP, DIRECT control is NOT recommended!

Operating Ranges

- Sensor reading range
- Calibrated range
- OQ range from installation (empty machine)
- Operating range derived experimentally

An example: Process Air Temperature

- 0 – 100°C
- 5, 50, 95°C
- 35 - 90°C
- Operating range derived experimentally

Operating Ranges

Process Air	Operating Range	Comments
Ambient Air Dew Point		
Dehumidifier Dew Point	± 2°C	Final dew point control depends to an extent on narrow upstream control.
Pre-heater Temperature	±3°C	
Process Air Dew Point Temperature	± 1°C	Water in air is exponential. If it is a CPP, it must operate in a narrow range.
Bypass Air Temperature	±2°C	Process air temperature is a CPP for all products and should be controlled in a narrow range.
Process or Inlet Air Temperature	±2°C	
Total Air Volume	± 5% of full scale	Tuning for these parameters is critical. Avoid 'competing controllers' and over-correcting. Fluidization impacts behavior.
Process Air Volume		

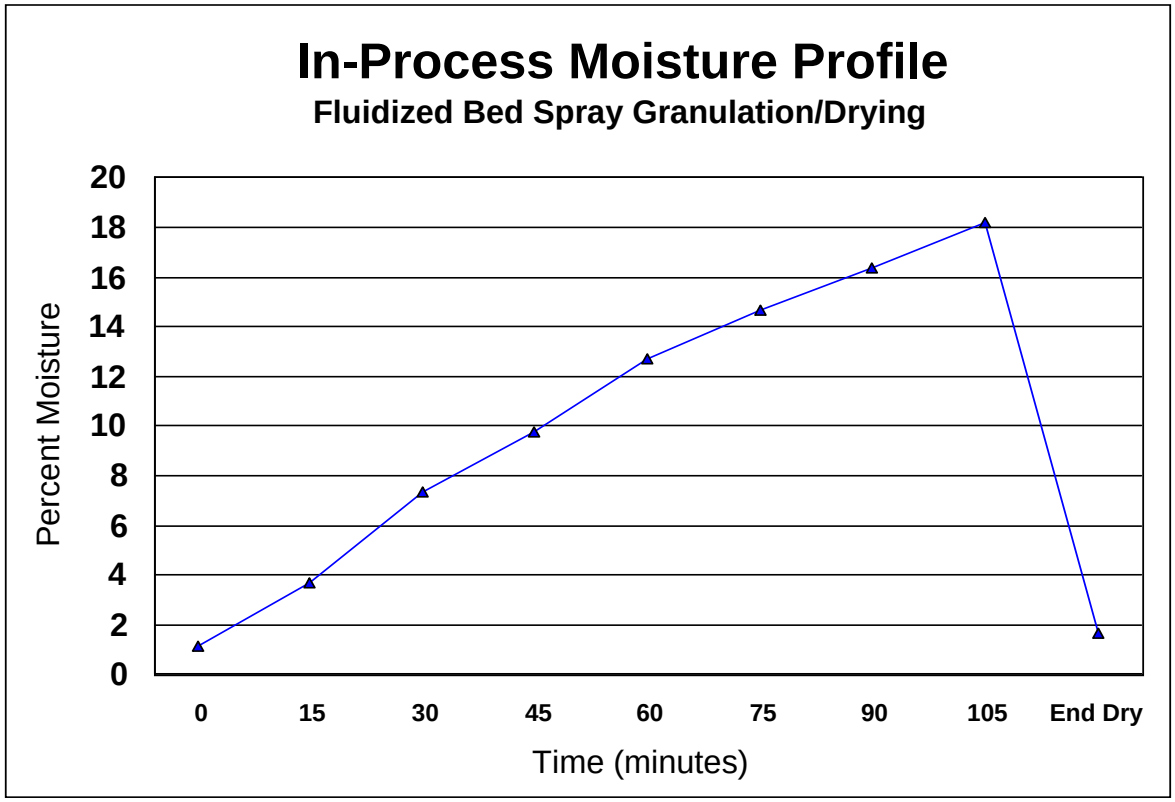
Operating Ranges

Spraying	Operating Range	Comments
Spray rate	± 20 g/min	Always a CPP, erratic variability can indicate poor nozzle performance.
Atomizing Air Pressure	± 0.1 bar	Must operate in a stable, narrow range.
Atomizing Air Volume	± 5 cfm/ nozzle	Reflects reproducibility of nozzle set-up.
Liquid Line Pressure		
Liquid Viscosity		
Nozzle Port Size		Machine parameter
Air Cap Position		Machine parameter
Nozzle height		Machine parameter

How do the parameters work together?

1. Droplet size
   a. Atomizing air pressure
   b. Spray rate
   c. Viscosity
2. Evaporation rate
   a. Process air volume
   b. Process air temperature
   c. Process air dew point temperature

A Useful Dependent Variable…

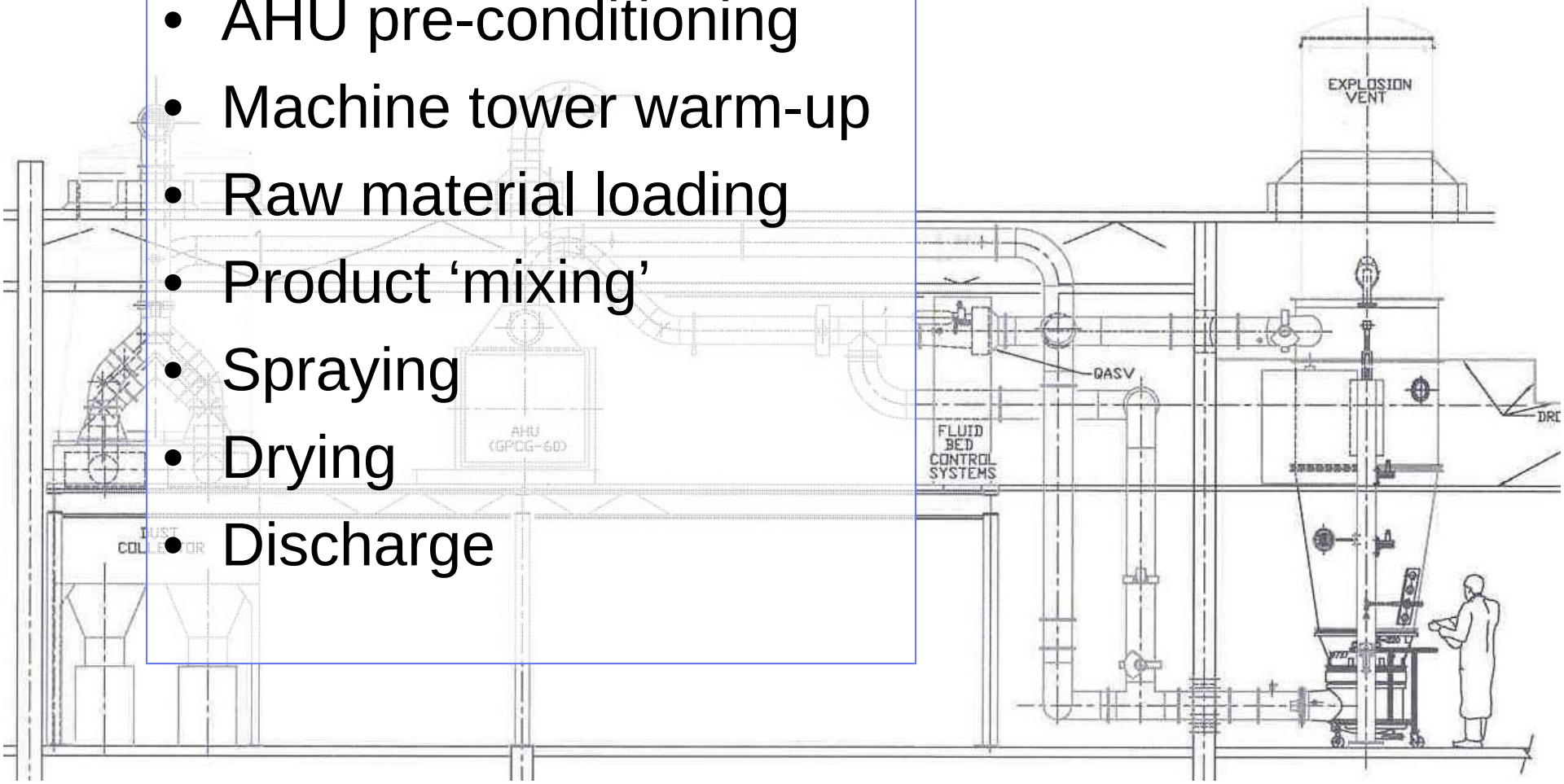


An in-process moisture profile may be followed and confirms the accuracy of several of the process variables

Process Variables as Observed During Manufacturing

Process Steps – a Recipe

- AHU pre-conditioning
- Machine tower warm-up
- Raw material loading
- Product ‘mixing’
- Spraying
- Drying
- Discharge



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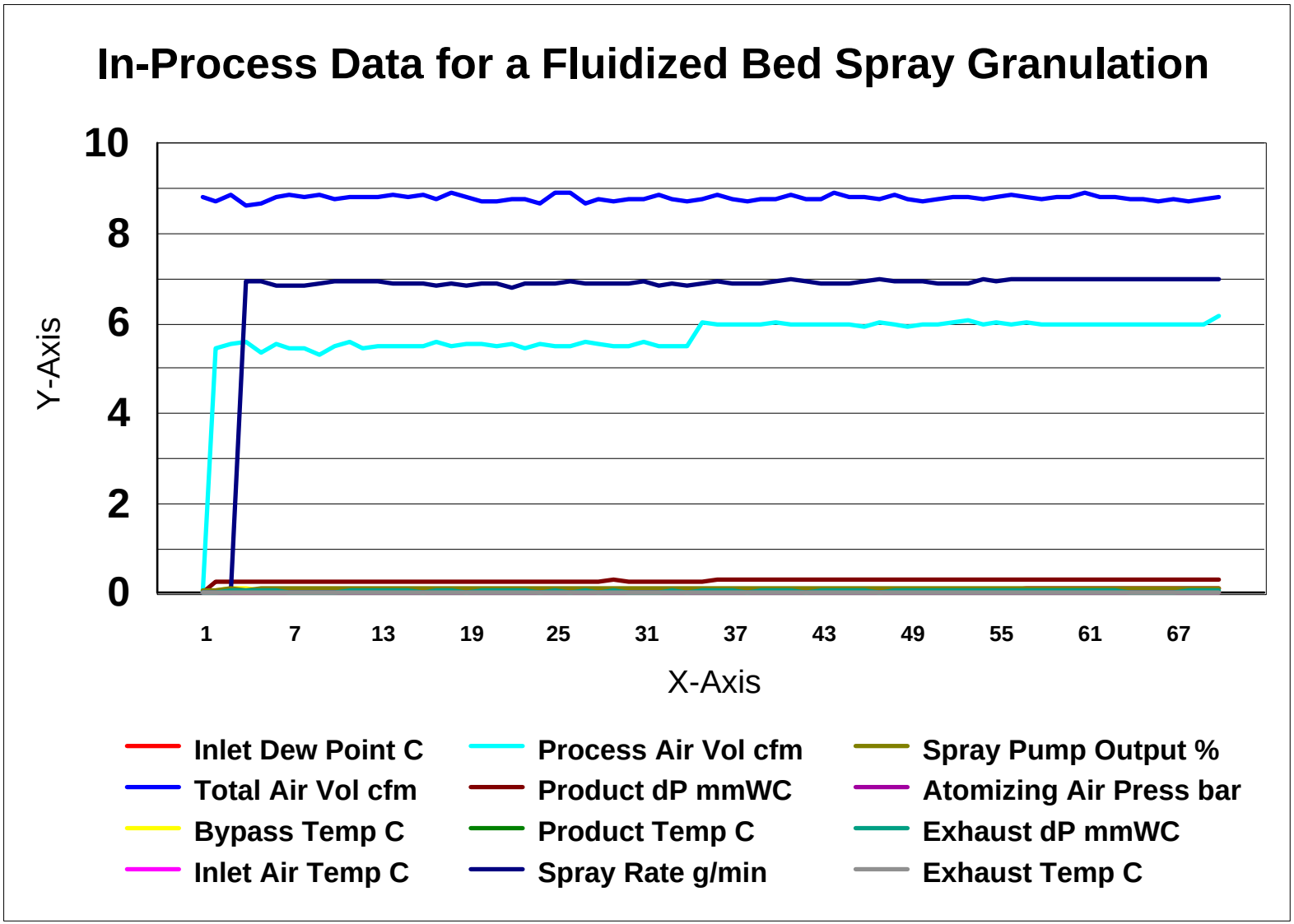

Data overview for the process variables.
"Grouping" by type is more revealing…

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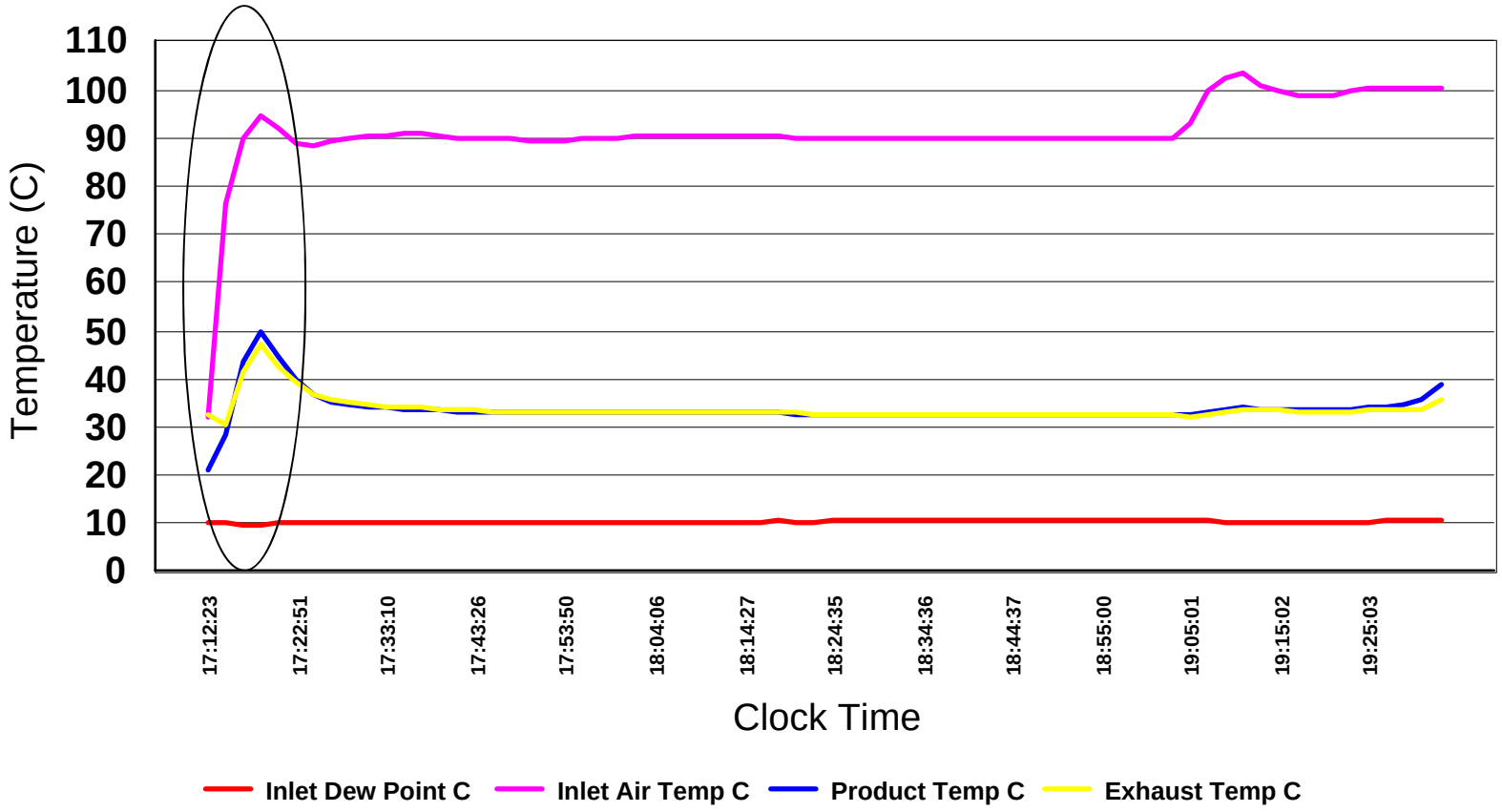
Fluidized Bed Spray Granulation

Process data - temperatures



Pre-mix: The inlet temperature approaches its set point, product and exhaust temperatures rise. Is it really mixing, or is there something else to think about?

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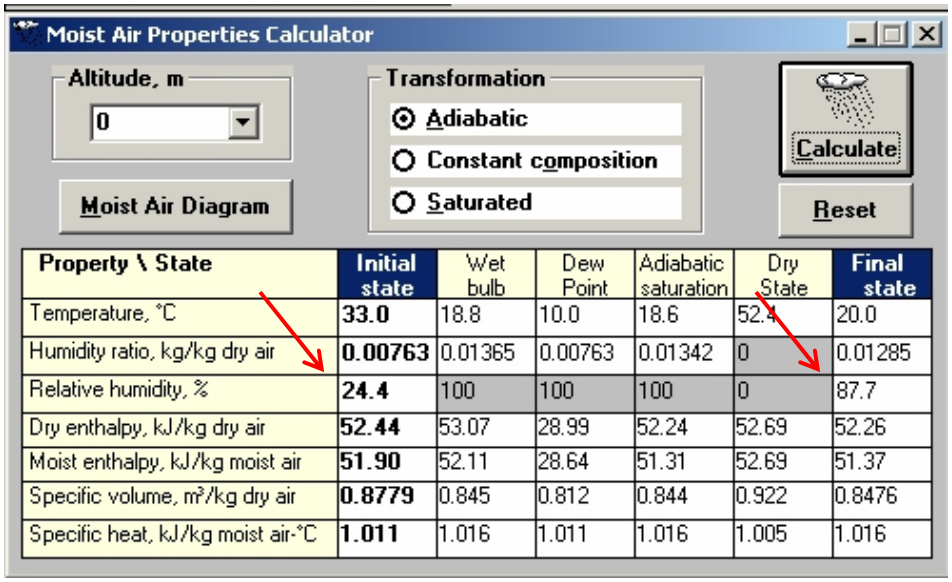
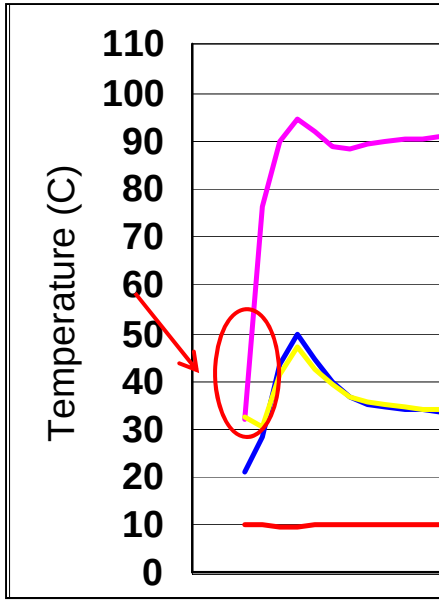
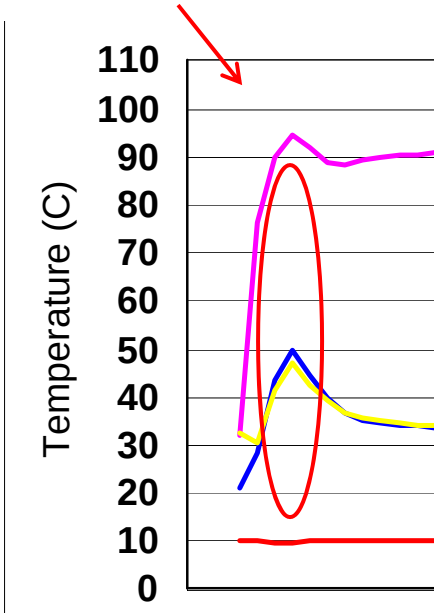


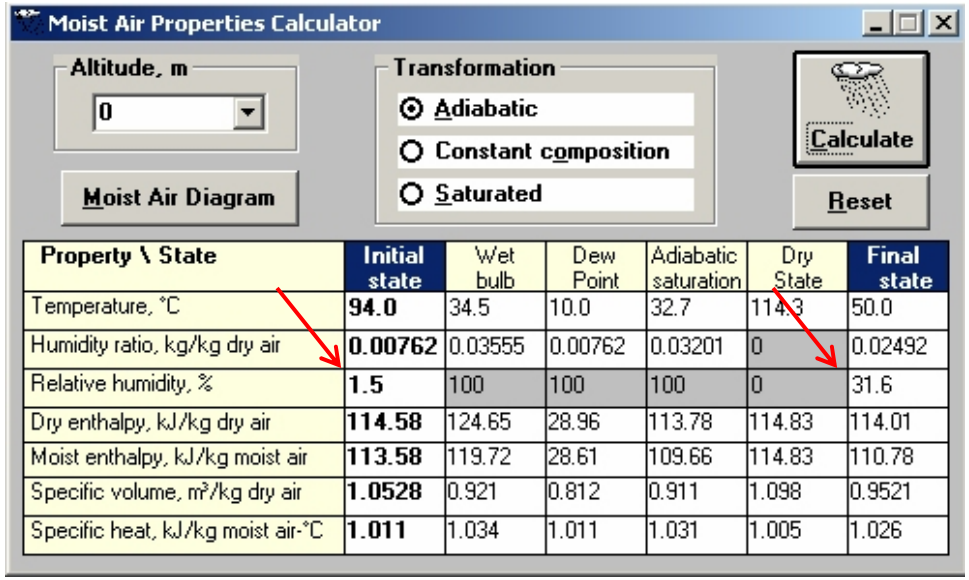
Property \ State	Initial state	Wet bulb	Dew Point	Adiabatic saturation	Dry State	Final state
Temperature, °C	**33.0**	18.8	10.0	18.6	52.4	20.0
Humidity ratio, kg/kg dry air	**0.00763**	0.01365	0.00763	0.01342	0	0.01285
Relative humidity, %	**24.4**	100	100	100	0	87.7
Dry enthalpy, kJ/kg dry air	**52.44**	53.07	28.99	52.24	52.69	52.26
Moist enthalpy, kJ/kg moist air	**51.90**	52.11	28.64	51.31	52.69	51.37
Specific volume, m³/kg dry air	**0.8779**	0.845	0.812	0.844	0.922	0.8476
Specific heat, kJ/kg moist air-°C	**1.011**	1.016	1.011	1.016	1.005	1.016

The beginning of mixing…





Only 5 minutes later, at the start of spraying…



Property \ State	Initial state	Wet bulb	Dew Point	Adiabatic saturation	Dry State	Final state
Temperature, °C	**94.0**	34.5	10.0	32.7	114.3	50.0
Humidity ratio, kg/kg dry air	**0.00762**	0.03555	0.00762	0.03201	0	0.02492
Relative humidity, %	**1.5**	100	100	100	0	31.6
Dry enthalpy, kJ/kg dry air	**114.58**	124.65	28.96	113.78	114.83	114.01
Moist enthalpy, kJ/kg moist air	**113.58**	119.72	28.61	109.66	114.83	110.78
Specific volume, m³/kg dry air	**1.0528**	0.921	0.812	0.911	1.098	0.9521
Specific heat, kJ/kg moist air-°C	**1.011**	1.034	1.011	1.031	1.005	1.026

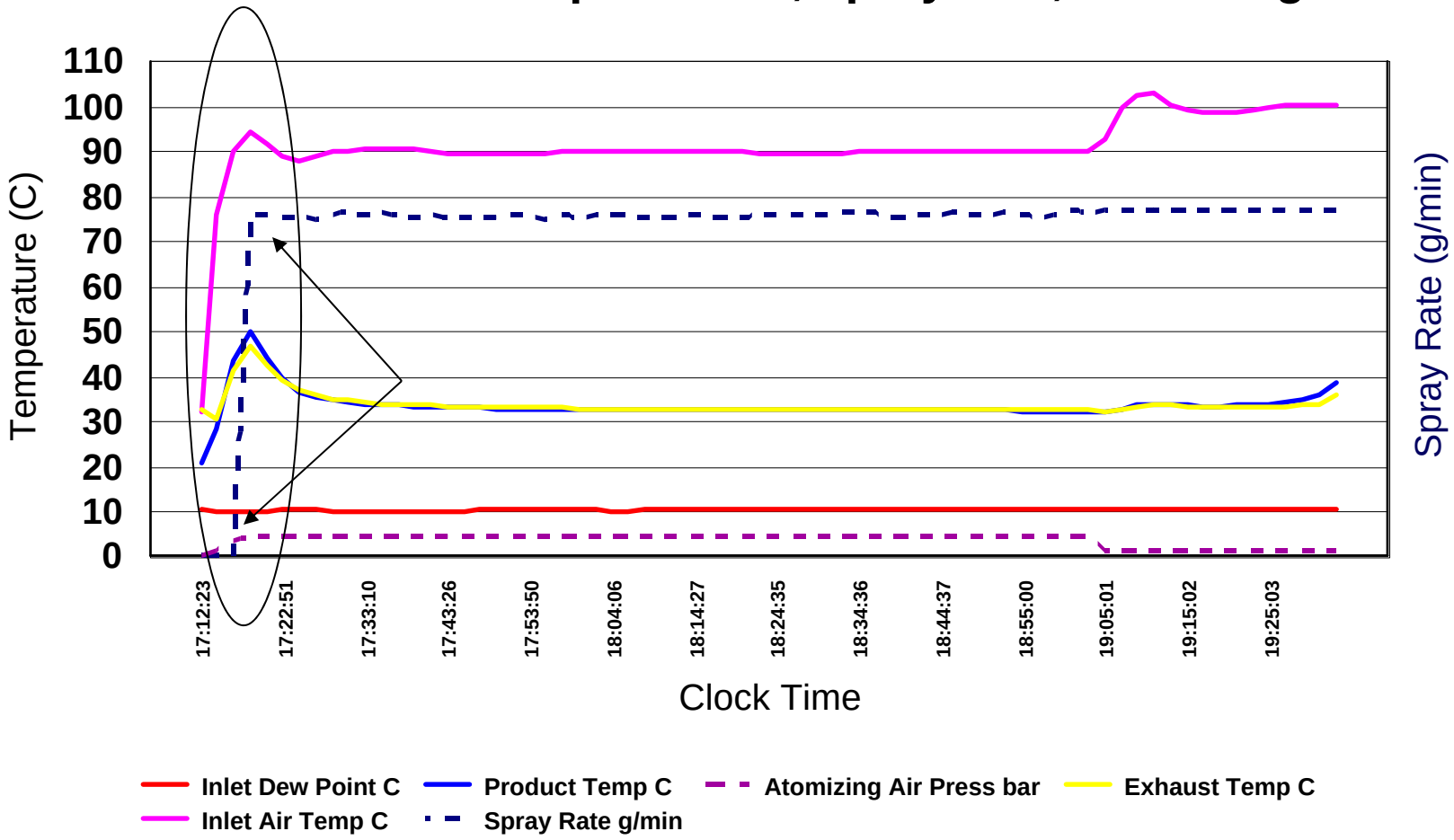
After the brief pre-mix…

Spraying is initiated at a controlled rate

- Moisture builds slowly in the bed
- Treated process air is used to evaporate some of the moisture as it is being applied
- Evaporation raises the relative humidity in the processor, helping to dispel electrostatic charge
- Droplets help to produce and build granules
- Granules are held together primarily by liquid bridges

Fluidized Bed Spray Granulation

Process data - temperatures, spray rate, atomizing air



Spraying - The pump is enabled and atomizing air increases from purge pressure to the spraying set point.

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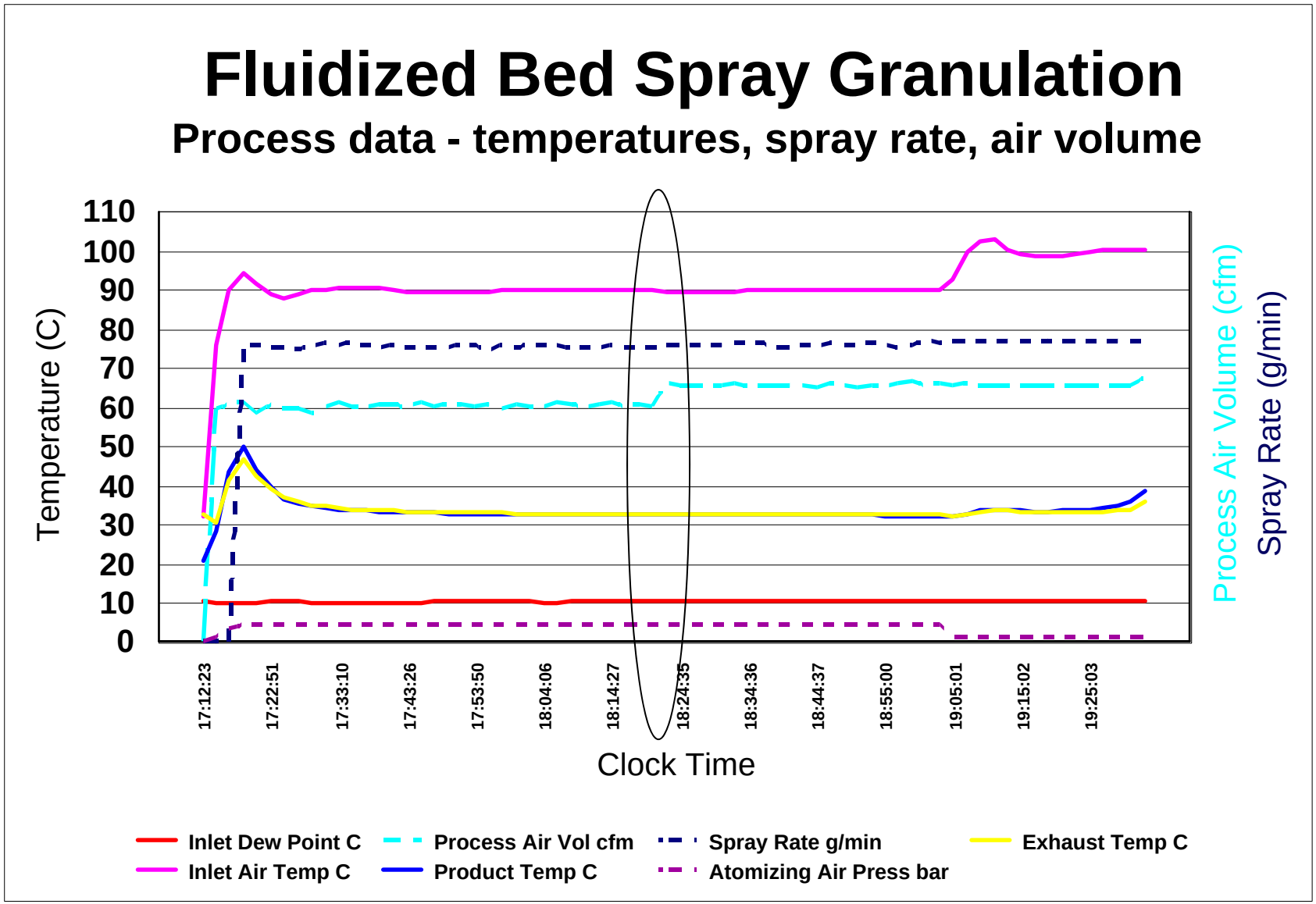
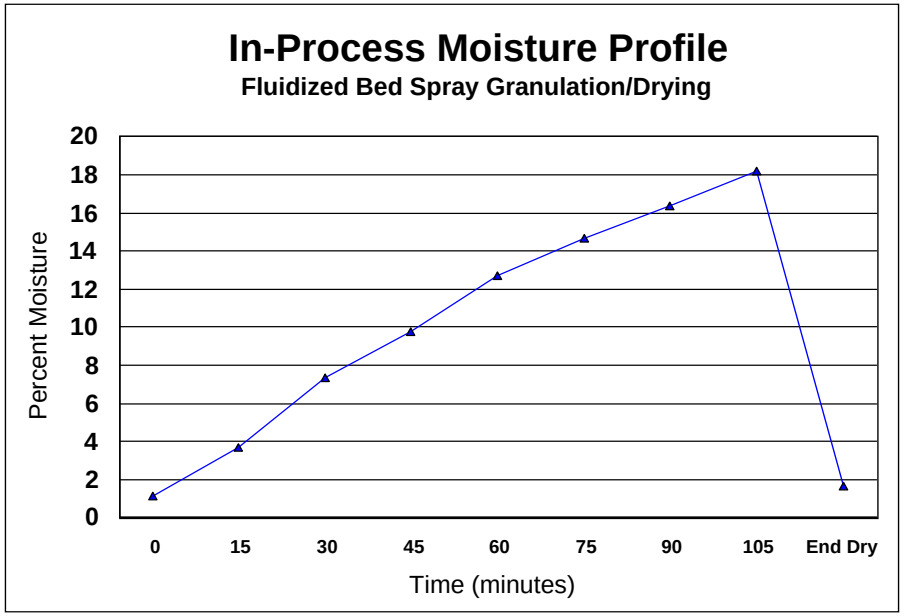
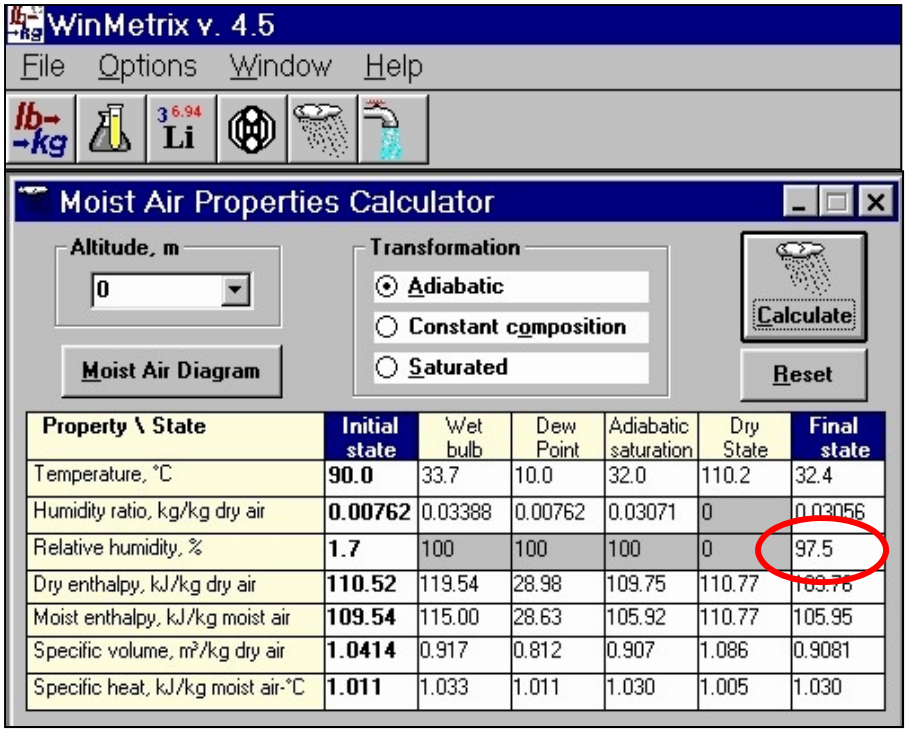


Later, air volume is increased to accommodate the increasing batch weight (to maintain a reasonable degree of fluidization).

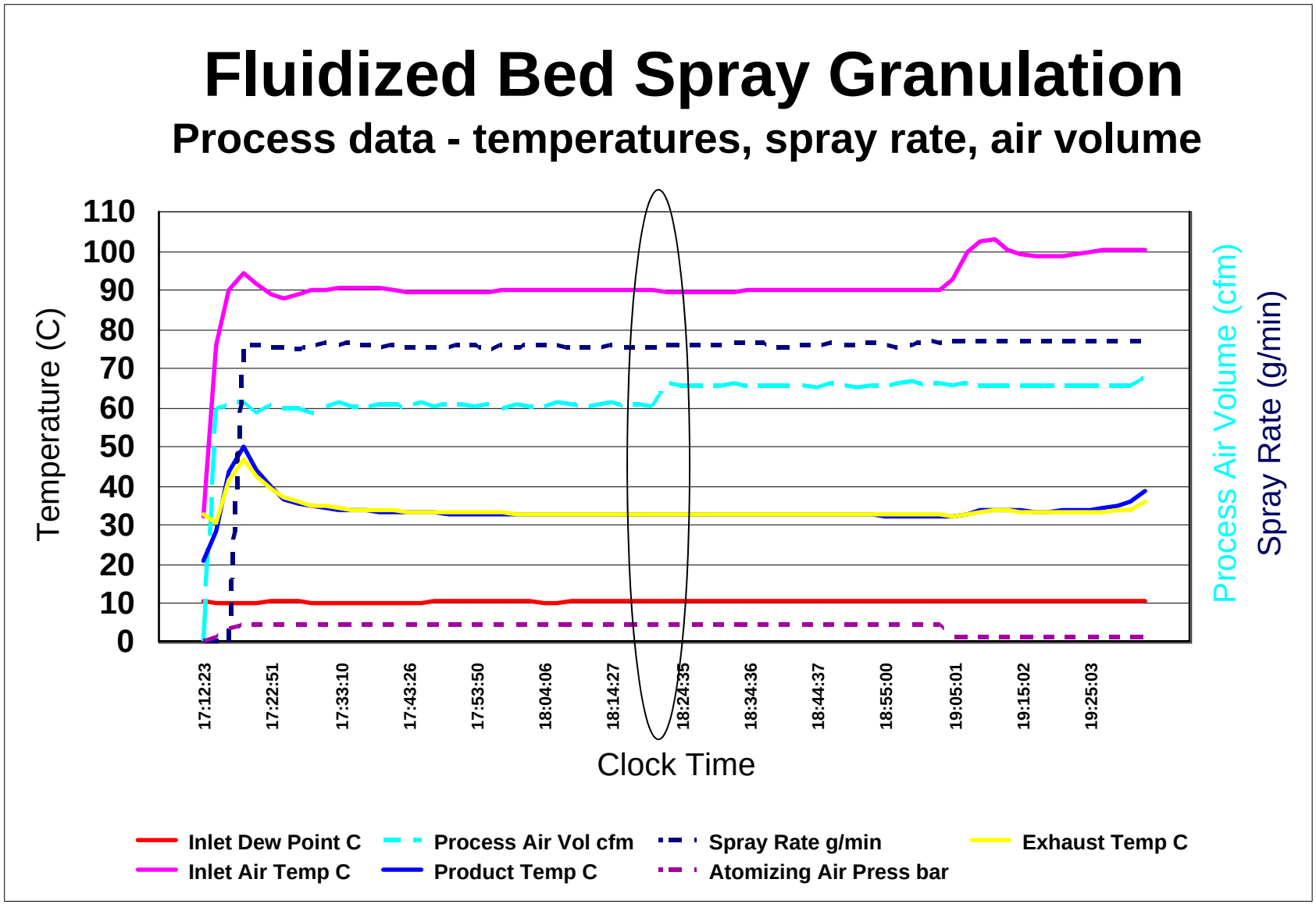


Moisture builds in the bed as the water addition rate exceeds the drying rate. Properties of the granulation may rely heavily on the moisture profile, and it should be reproduced.

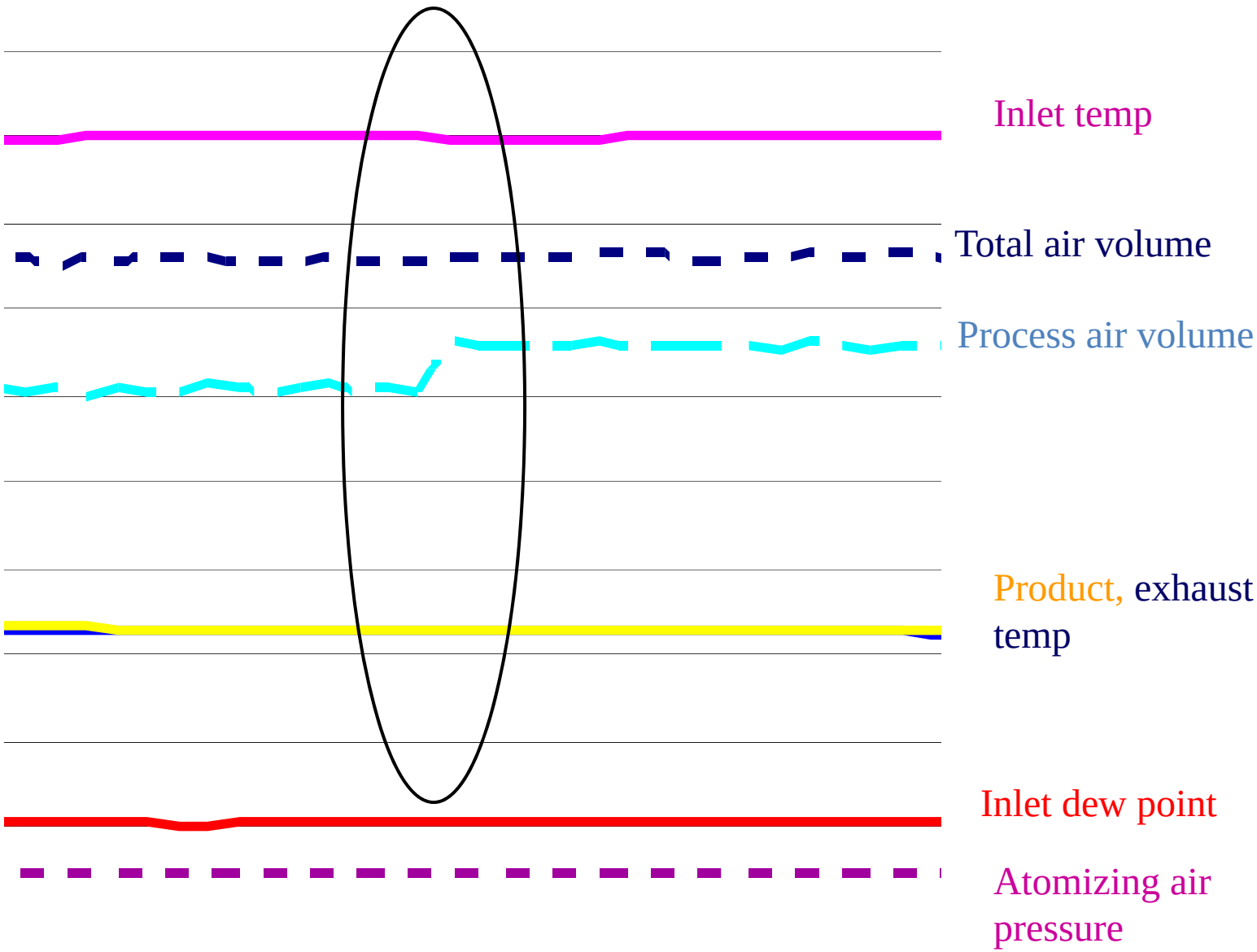
At steady state, the air leaving the machine tower is at or near saturation.



Property \ State	Initial state	Wet bulb	Dew Point	Adiabatic saturation	Dry State	Final state
Temperature, °C	**90.0**	33.7	10.0	32.0	110.2	32.4
Humidity ratio, kg/kg dry air	**0.00762**	0.03388	0.00762	0.03071	0	0.03056
Relative humidity, %	**1.7**	100	100	100	0	97.5
Dry enthalpy, kJ/kg dry air	**110.52**	119.54	28.98	109.75	110.77	109.76
Moist enthalpy, kJ/kg moist air	**109.54**	115.00	28.63	105.92	110.77	105.95
Specific volume, m³/kg dry air	**1.0414**	0.917	0.812	0.907	1.086	0.9081
Specific heat, kJ/kg moist air-°C	**1.011**	1.033	1.011	1.030	1.005	1.030



What impact does the higher air volume have on the product/exhaust temperatures? Is there any impact at all?



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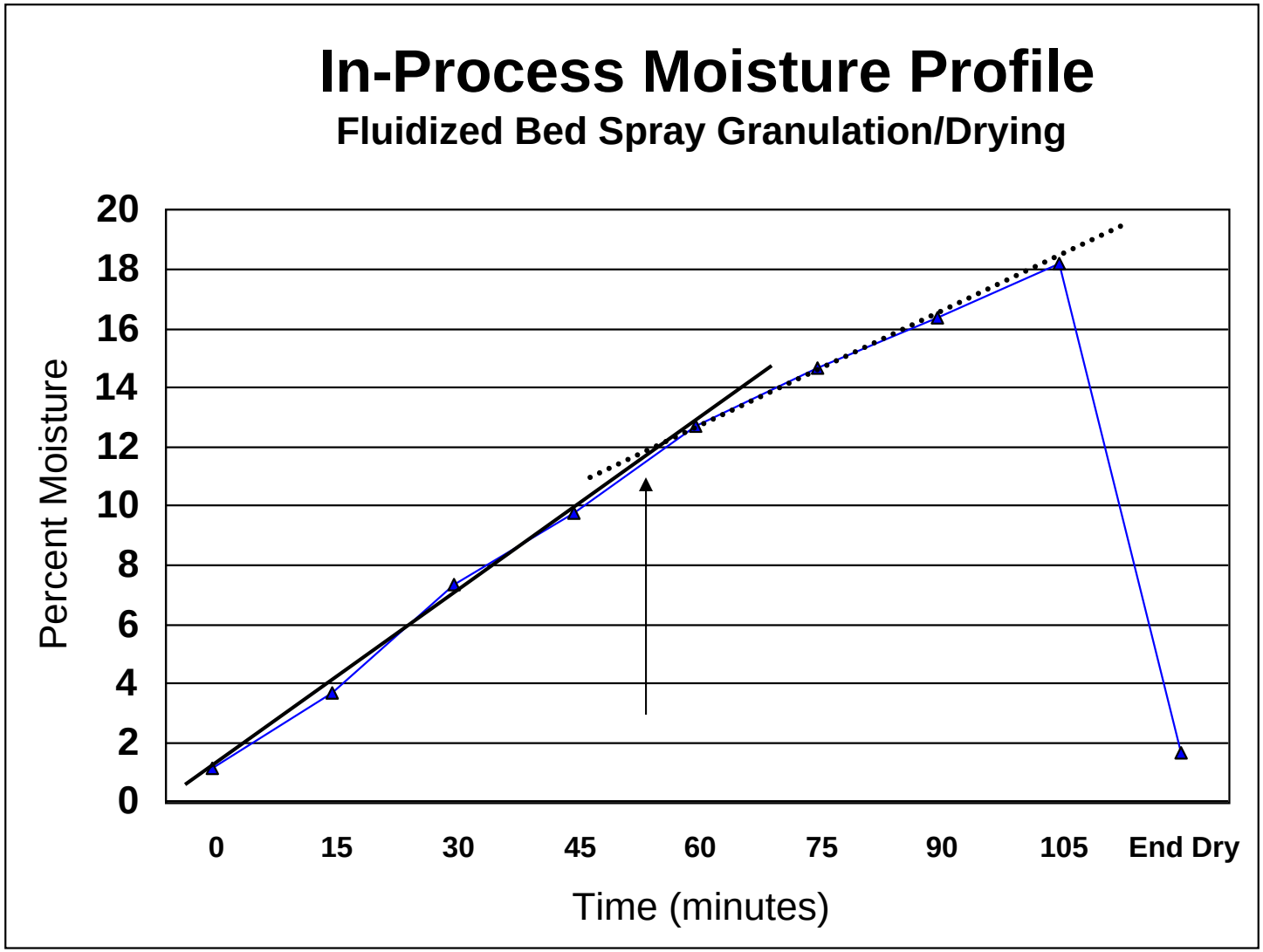


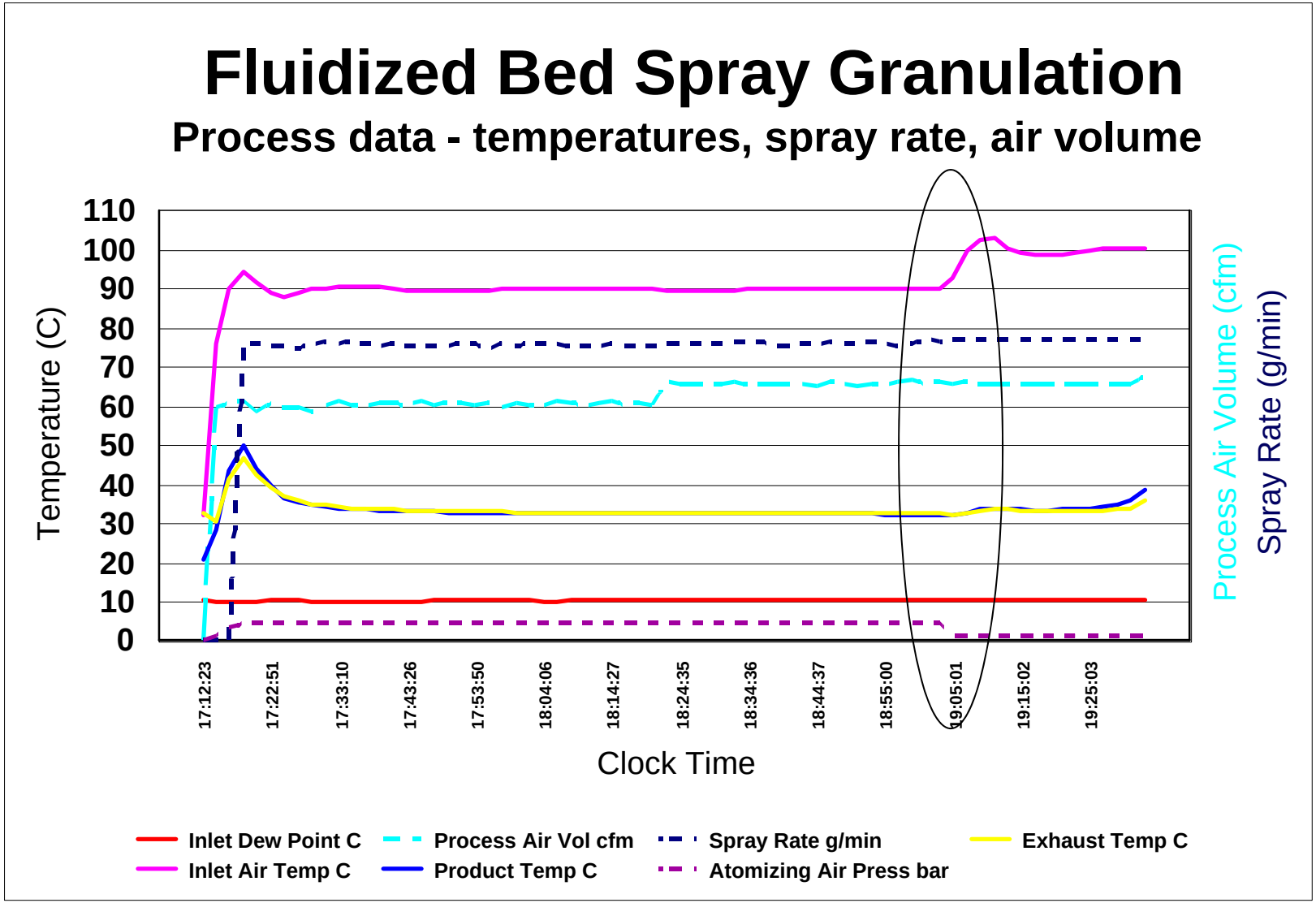
The moisture accumulation rate changes …

How Does the Process Work?

When the liquid is gone, drying continues

- Excess liquid in the batch is evaporated
- Temperature and air volume deliver the energy needed to dry the product (the inlet temperature may change)
- Drying time depends on how much moisture needs to be removed and the characteristics of the product
- As product temperature rises, the end is near

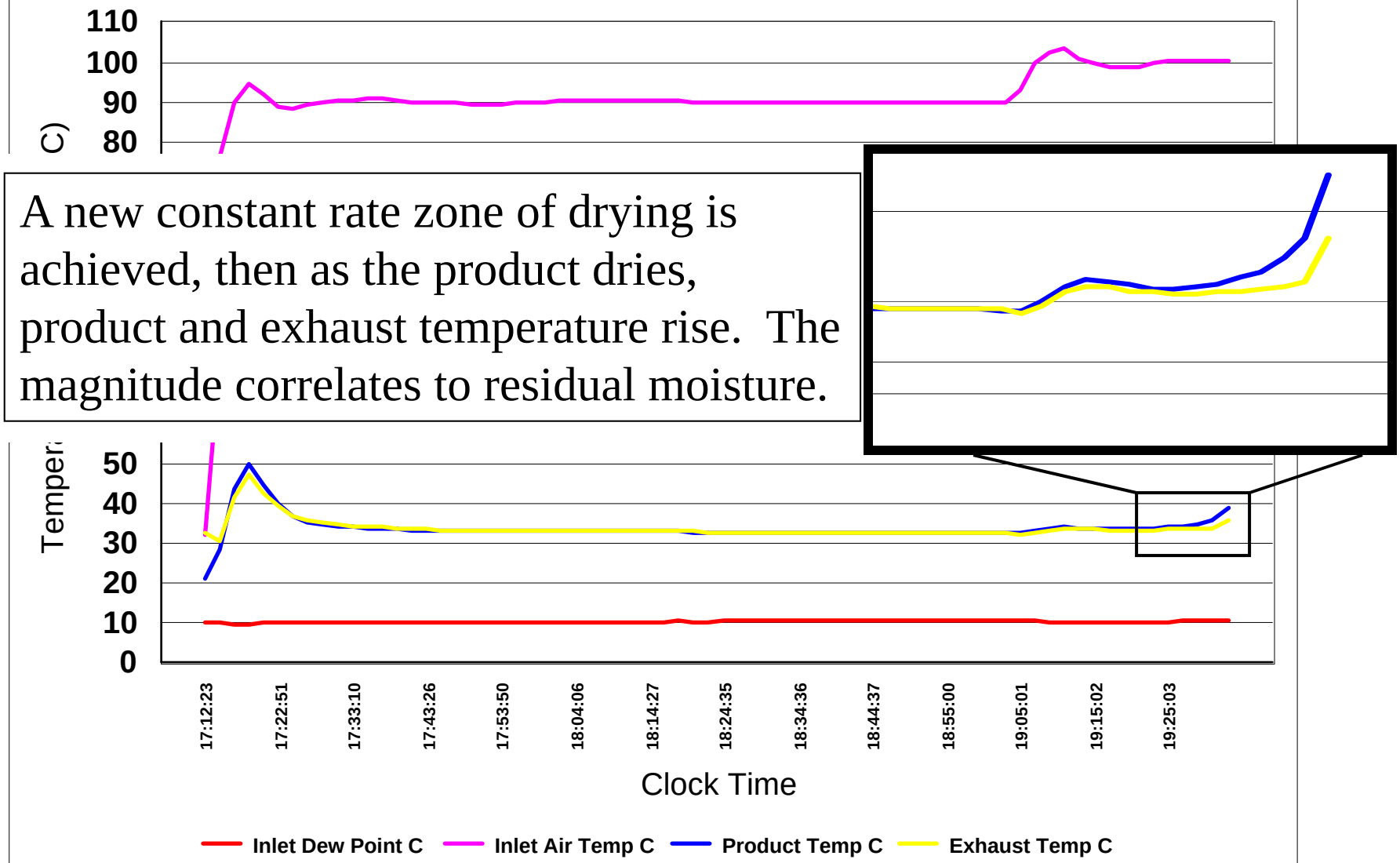
Sample for moisture, stop the process



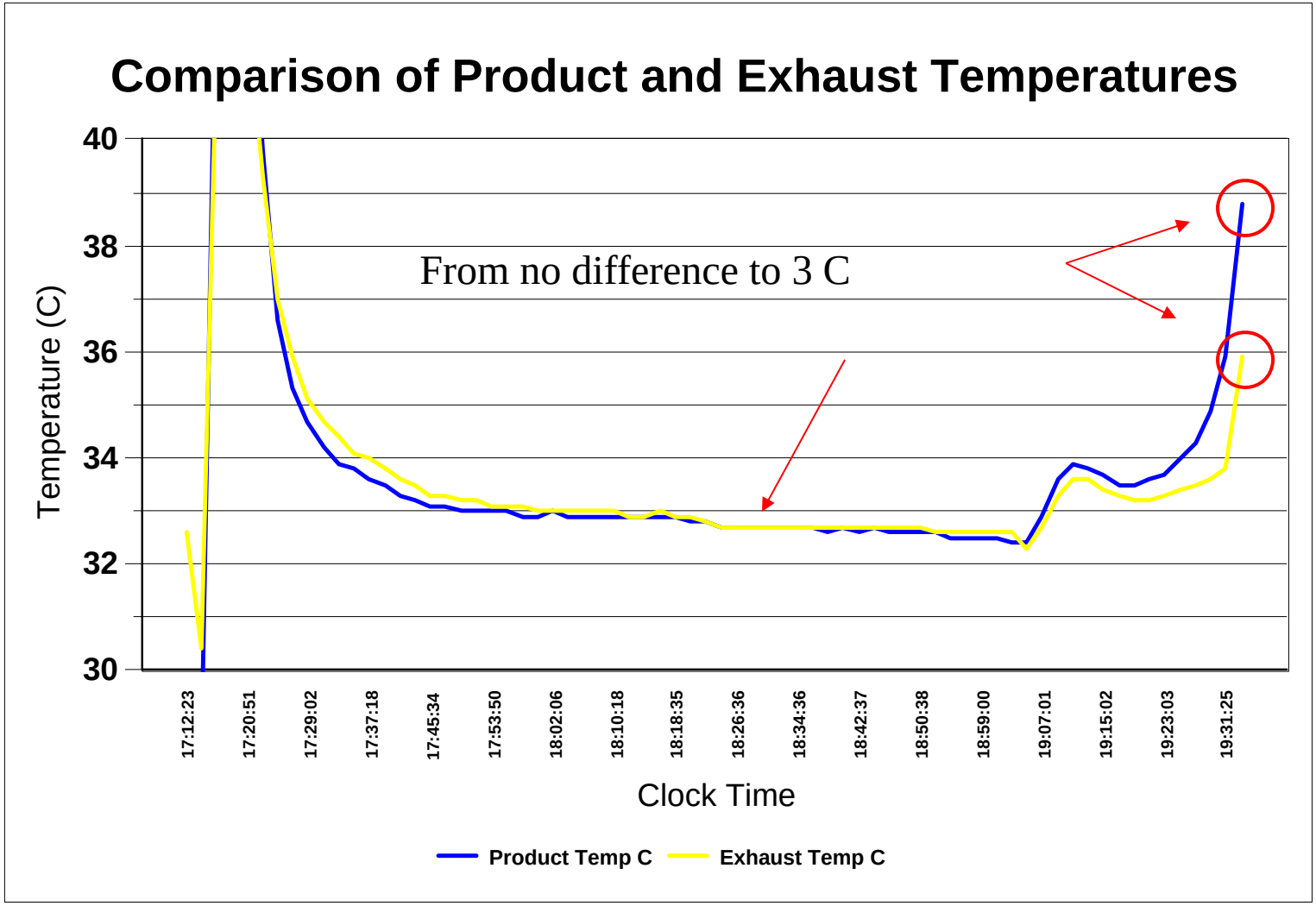
The spray liquid quantity trip point has been reached, the pump goes into recirculation, atomizing air drops to purge pressure, the inlet air temperature is raised to accelerate drying.

Fluidized Bed Spray Granulation

Process data - temperatures



A new constant rate zone of drying is achieved, then as the product dries, product and exhaust temperature rise. The magnitude correlates to residual moisture.



Why the difference in product and exhaust temperatures? Can either one be used to indicate drying endpoint? Which is better?

Summary

- The fluidized bed spray granulation process produces granules with unique properties.
- Interstitial porosity yields a high degree of wettable surface area – excellent for rapid disintegration, dissolution.
- Process variables and their impacts are well understood and reproducible.
- Scale-up is reasonably direct although mass effects must be considered, even in small scale development trials.

Any Questions?

FLUIDIZED BED SPRAY GRANULATION:
Scale-up Considerations

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Major Scale-Up Issues to Consider

- Drying capacity

  Spray rates are related to the increase in drying capacity, not the increase in batch size
- Droplet size

  Nozzle type/size, atomizing air pressure/volume, spray rate
- Mass effects

  Agglomerate/granule porosity may be impacted by the increased batch weight

Less Obvious Considerations

- Atomizing air kinetic energy (potential for attrition)
- Proximity to saturation (exit air humidity)
- Variations in ambient process humidity
- A few batches at the commercial scale may not be representative of long term success
- Productivity matters!

Common Issues in Scale-Up

- The lab trials do not effectively bracket what will be seen in scale-up
- The process used for the formulation was developed in a conservative manner
- The formulators do not have a feel for how production equipment works

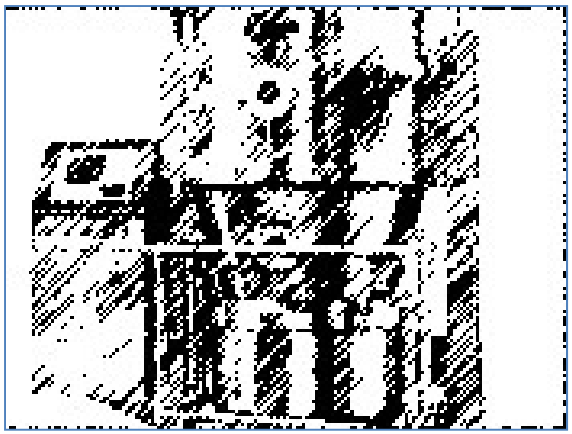
Factors to Consider…

- Batch size determination
- Spray rate
- Droplet size
- Process air volume
- Temperatures (process, product)
- Mass effects (bed depth, batch size)

Batch Size Determination

$S_{min} = V \times 0.4 \times BD$

$S_{max} = V \times 0.8 \times BD$



Where:

V = Maximum Working Capacity of the Product Container

S = Batch Size (kg)

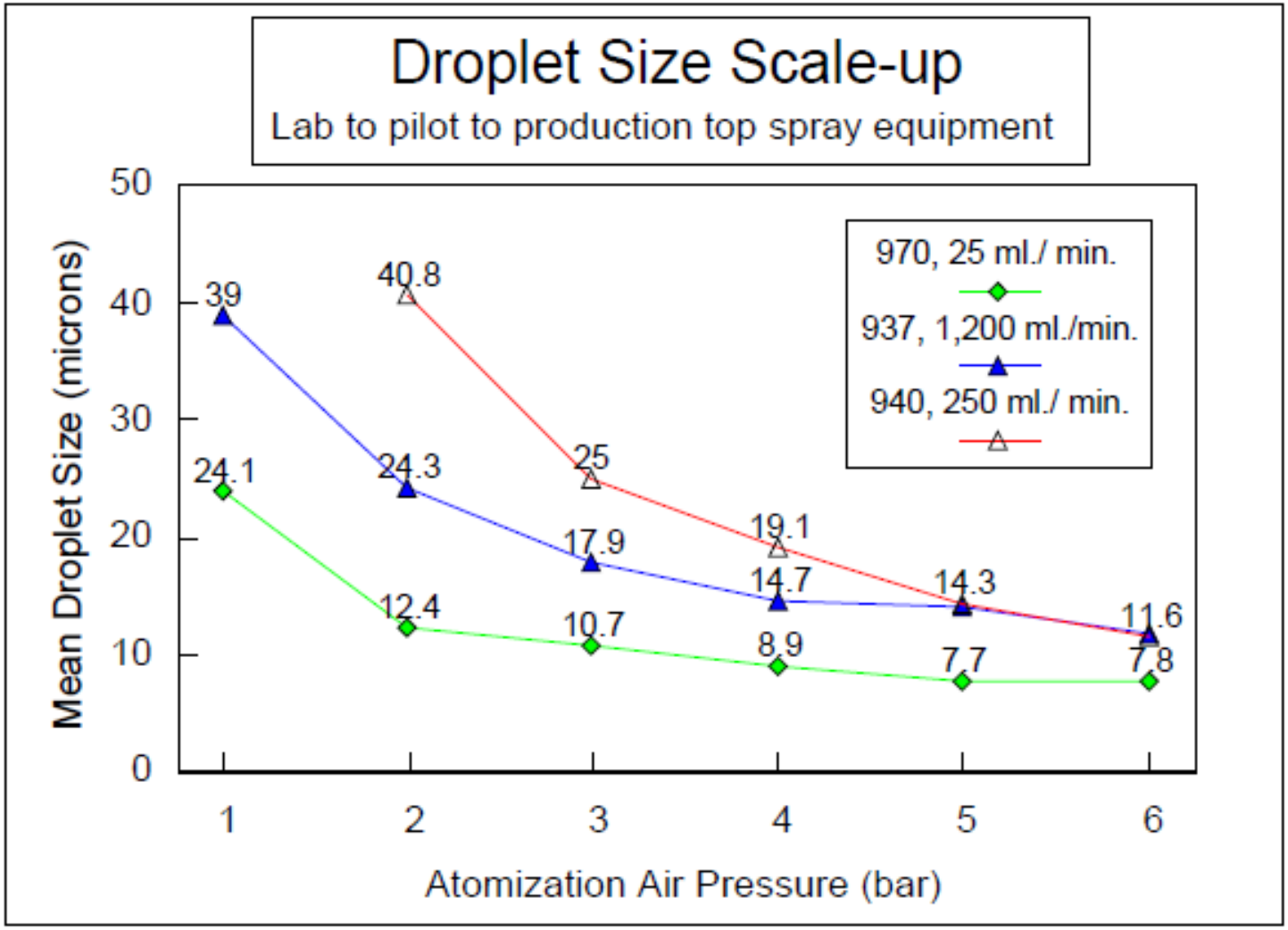
BD = Finished Product Bulk Density (kg/liter)

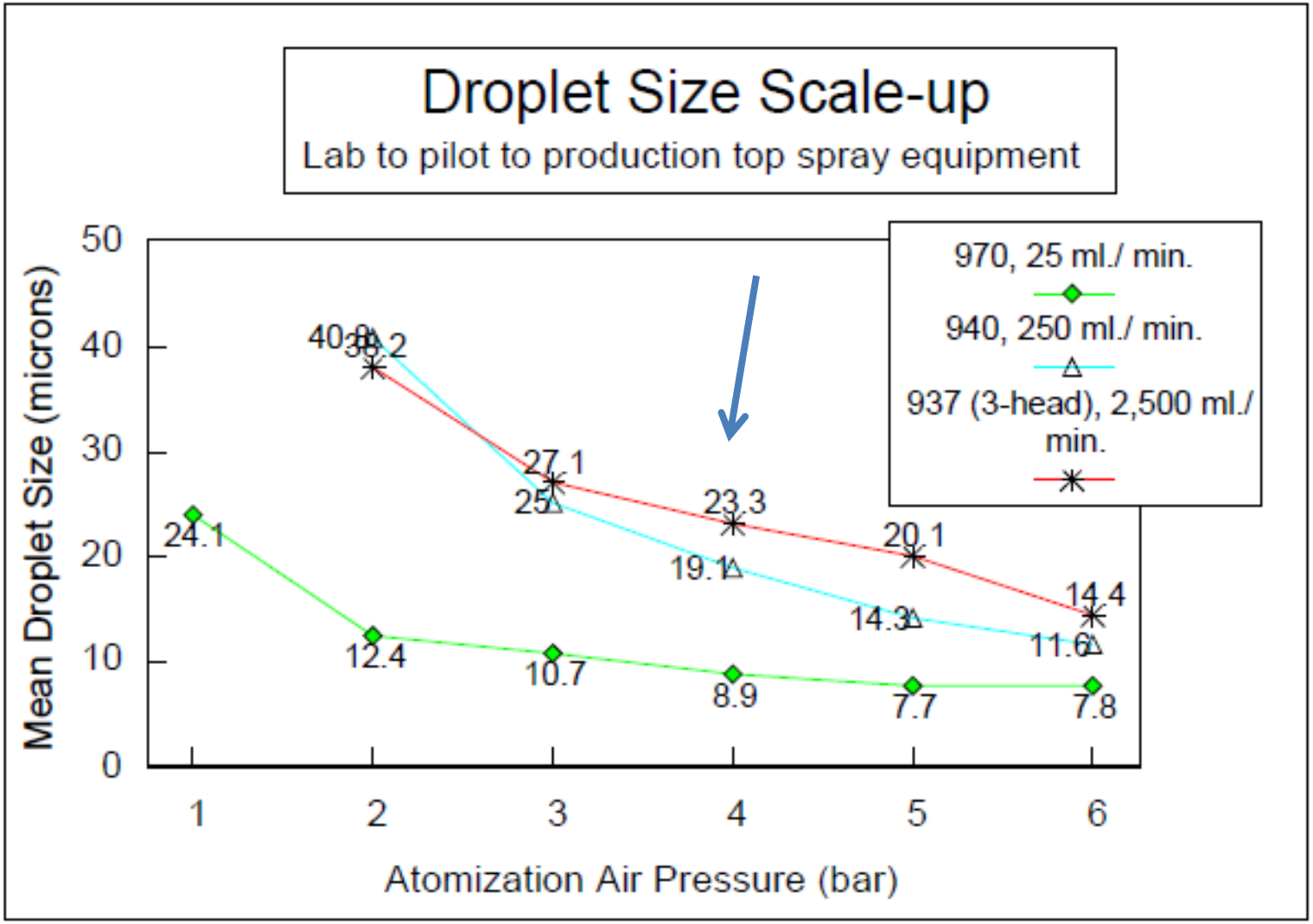
Droplet Size in Scale-up: From the lab to Pilot and Production

You must maintain the droplet size!

- Project the spray rate based on the expected increase in drying capacity (air volume) for the machine to be used.
- Make sure that the projected spray rate is within the air to liquid mass ratio capacity of the spray nozzle.
- Consider additional or multi-headed nozzles to reduce the spray rate per nozzle port.

For example:


Droplet Size Scale-up
Lab to pilot to production top spray equipment
Mean Droplet Size (microns)
Atomization Air Pressure (bar)
970, 25 ml./ min.
937, 1,200 ml./min.
940, 250 ml./ min.
0
10
20
30
40
50
1
2
3
4
5
6
39
24.1
40.8
24.3
12.4
25
17.9
10.7
19.1
14.7
8.9
14.3
7.7
11.6
7.8



Doubling the spray rate dramatically shifts the droplet size profile upwards

What Schlick nozzle are used in each size of top spray granulator?

- 970 series – up to 100 g/min
- 940 series – up to 500 g/min
- 937 series – up to 2,500 g/min (with 3 ports)
- 937 – up to 5,000 g/min (with 6 ports)
- Multiple 937 nozzles and wands can be used for spray rates exceeding 5,000 g/min

Process Air Volume

If the face velocity is kept constant at the bowl screen, the increase in air volume will be related to the increase in the bottom screen area. For example:

Machine	Bowl size	Screen cross-sectional area	Scale-up factor
GPCG-5	22 liters	0.0415 m	1
GPCG-60	220 liters	0.415 m	10
GPCG-300	1,060 liters	1.0382 m	25

If the ***measured*** air flow in the 22 liter GPCG-5 was 150 cfm, the starting point for the GPCG-60 would be 1,500 cfm and about 3,750 cfm for the production scale GPCG-300.

What About the Spray Rate?

Scale-up in spray rate is based on the increase in drying capacity, not batch size. For example:

Machine	Bowl volume (liters)	Batch size (kg)	Spray rate (g/min)
GPCG-5	22	8	100
GPCG-60	220	80	1,000
GPCG-300	1,060	400	2,500

Although the batch size in the GPCG-300 is 50 times larger than that in the GPCG-5, the drying capacity, at the same inlet temperature is only 25 times greater. Spraying at 50x will quickly over-wet the batch.

Process Air Temperature Considerations

Things to Think About

- In general, deeper beds in larger machines yield denser granules (mass effects – some of the interstitial porosity is compacted).
- Higher process air temperatures yield lower density granules, at least partially countering the mass effect.
- In some circumstances, the goal is to keep the process air and product temperature the same in scale-up (assuming the process air dew point is the same).

HOWEVER…

Process air temperature can be increased to:

- Increase the spray rate (within the performance envelope of the nozzle).
- Shorten the process time.
- Reduce the bulk density of the product (countering the consequences of the mass effect).

…as long as the consequences of the higher process air temperature are known and understood!

Case Studies

1. Spray nozzle maintenance and testing program
2. Effectiveness of DOE in lab/pilot scale
3. ‘Nuisance’ alarms (electronic controls)
4. Identifying ranges for dependent variables
5. “After calibration, everything is the same but now we are having batch failures”

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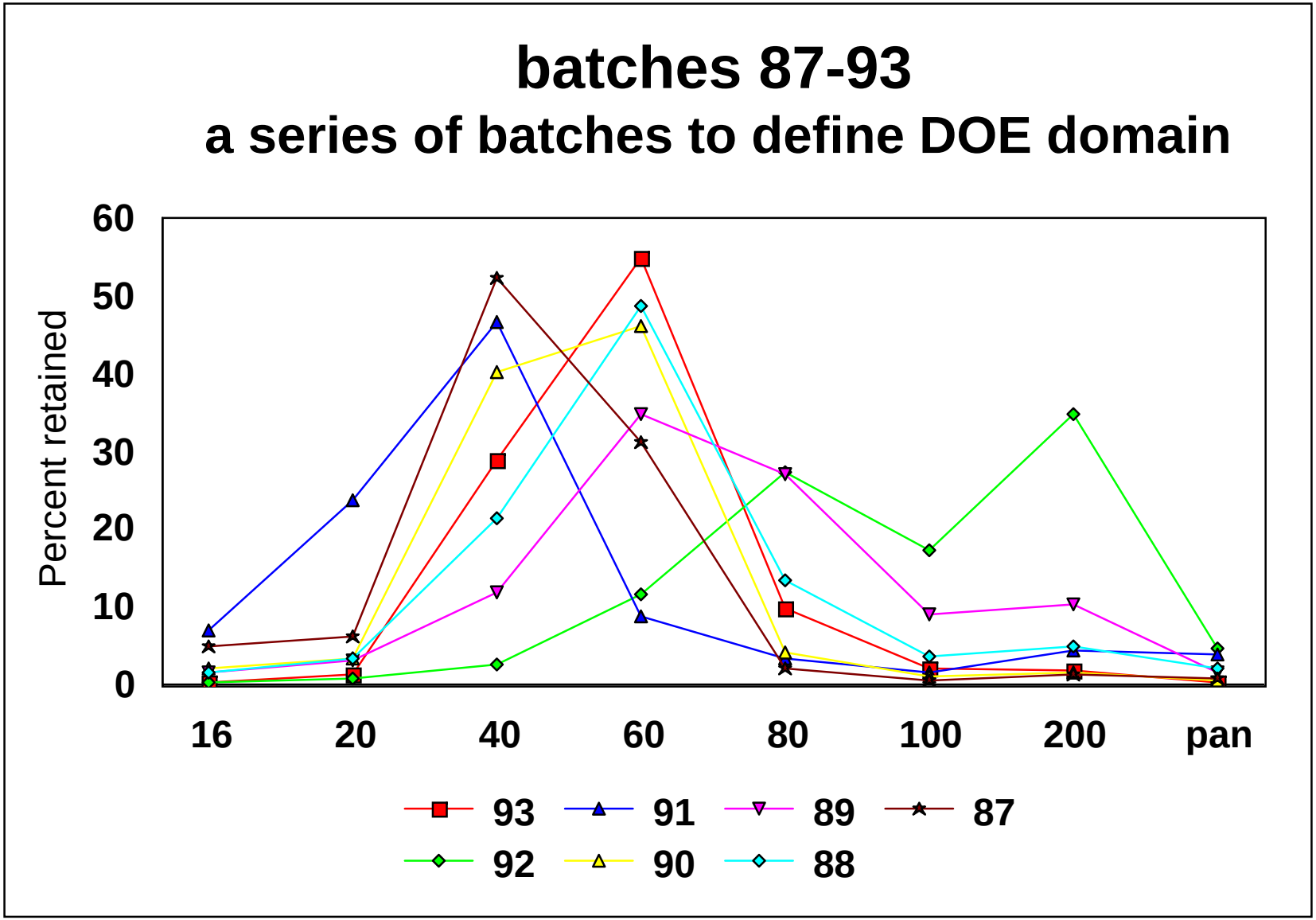
Application of DOE to pilot scale product development

A case study: Top spray fluidized bed spray granulation

A preliminary ‘range’ study to identify the domain for a 3 factor, 2 level DOE.

The factors are inlet air temperature (evaporation rate), liquid spray rate (primarily in-process moisture content) and atomizing air pressure/volume (droplet size)



Particle size and distribution respond strongly to the range of process variables selected for study.

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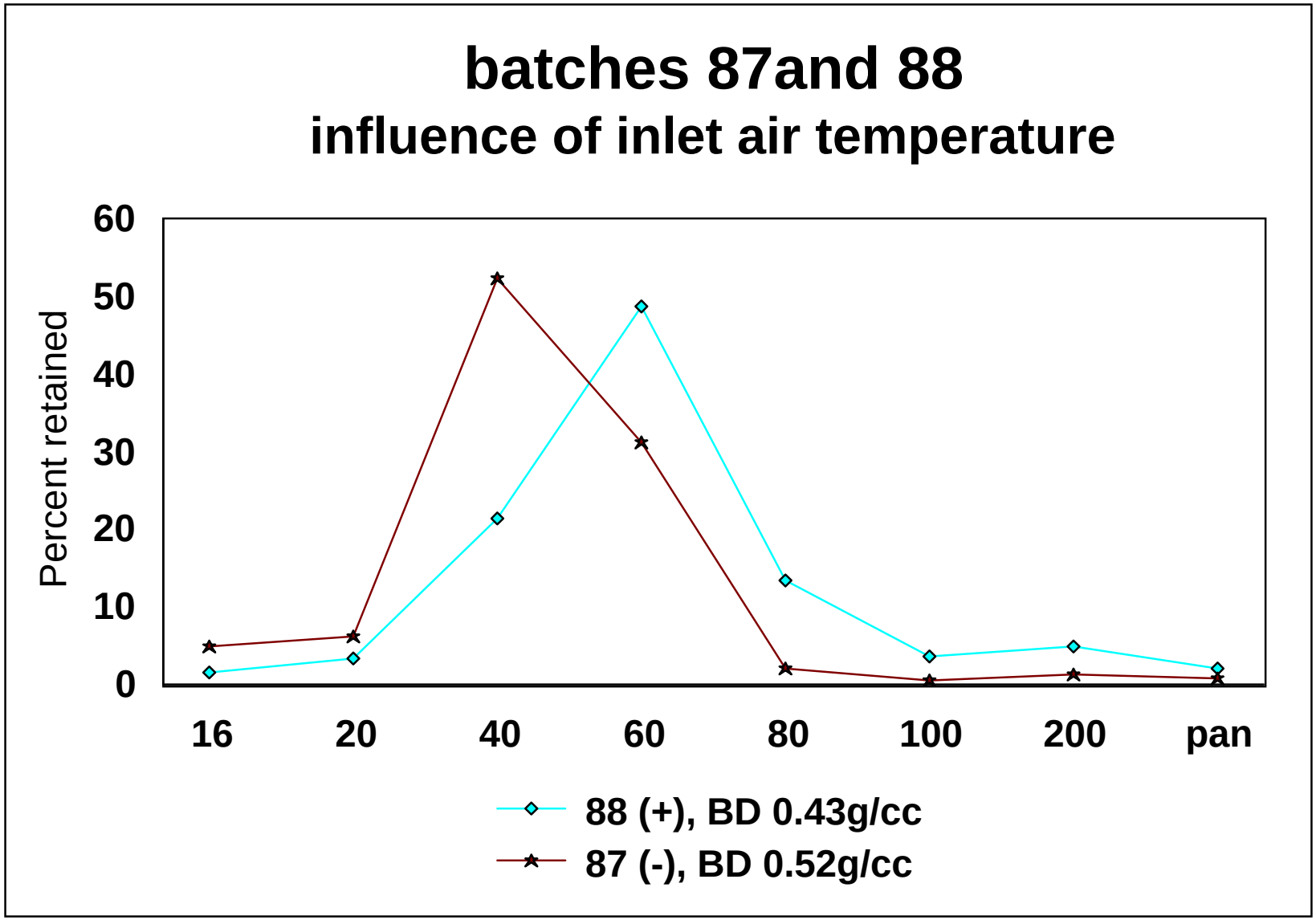
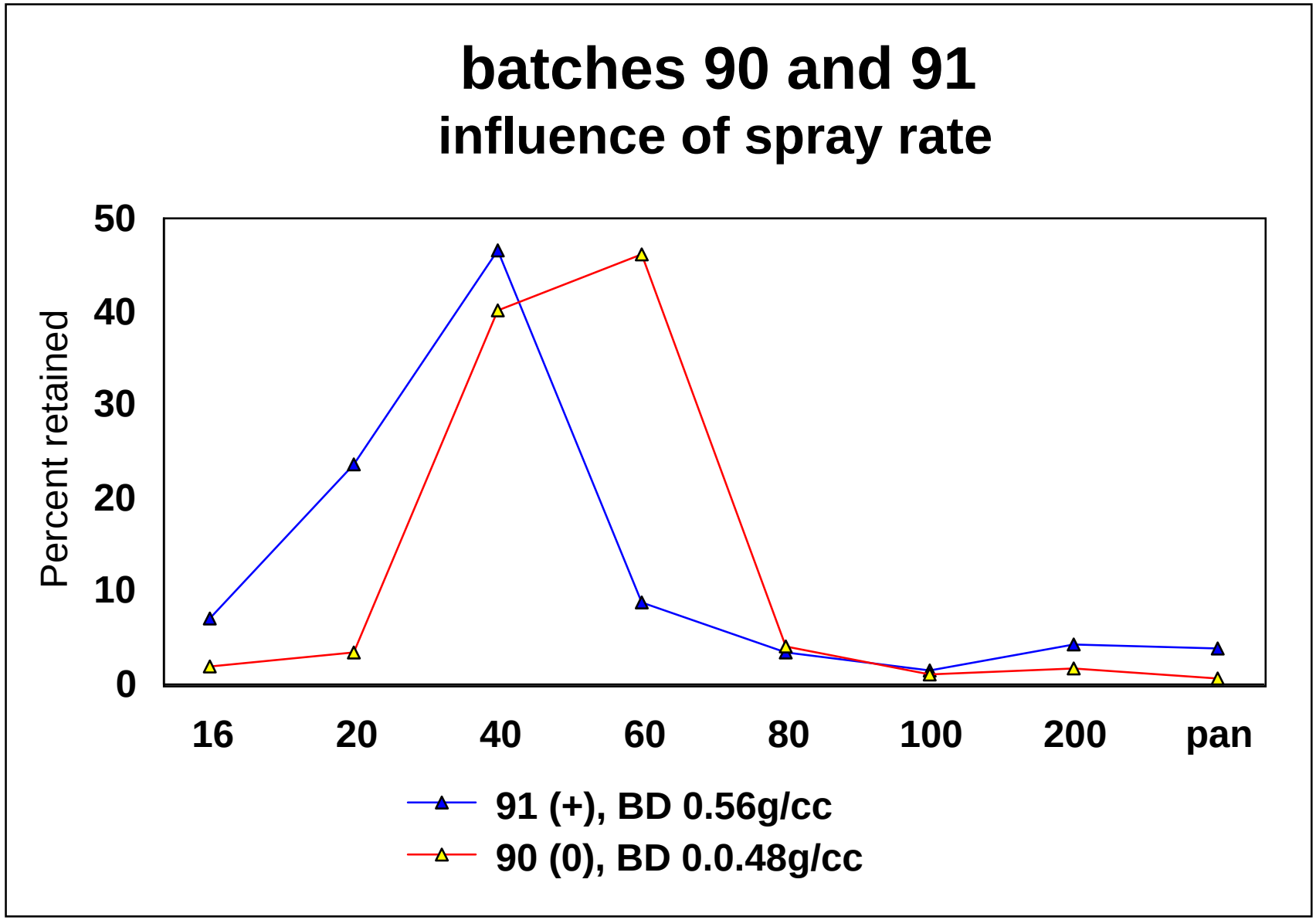
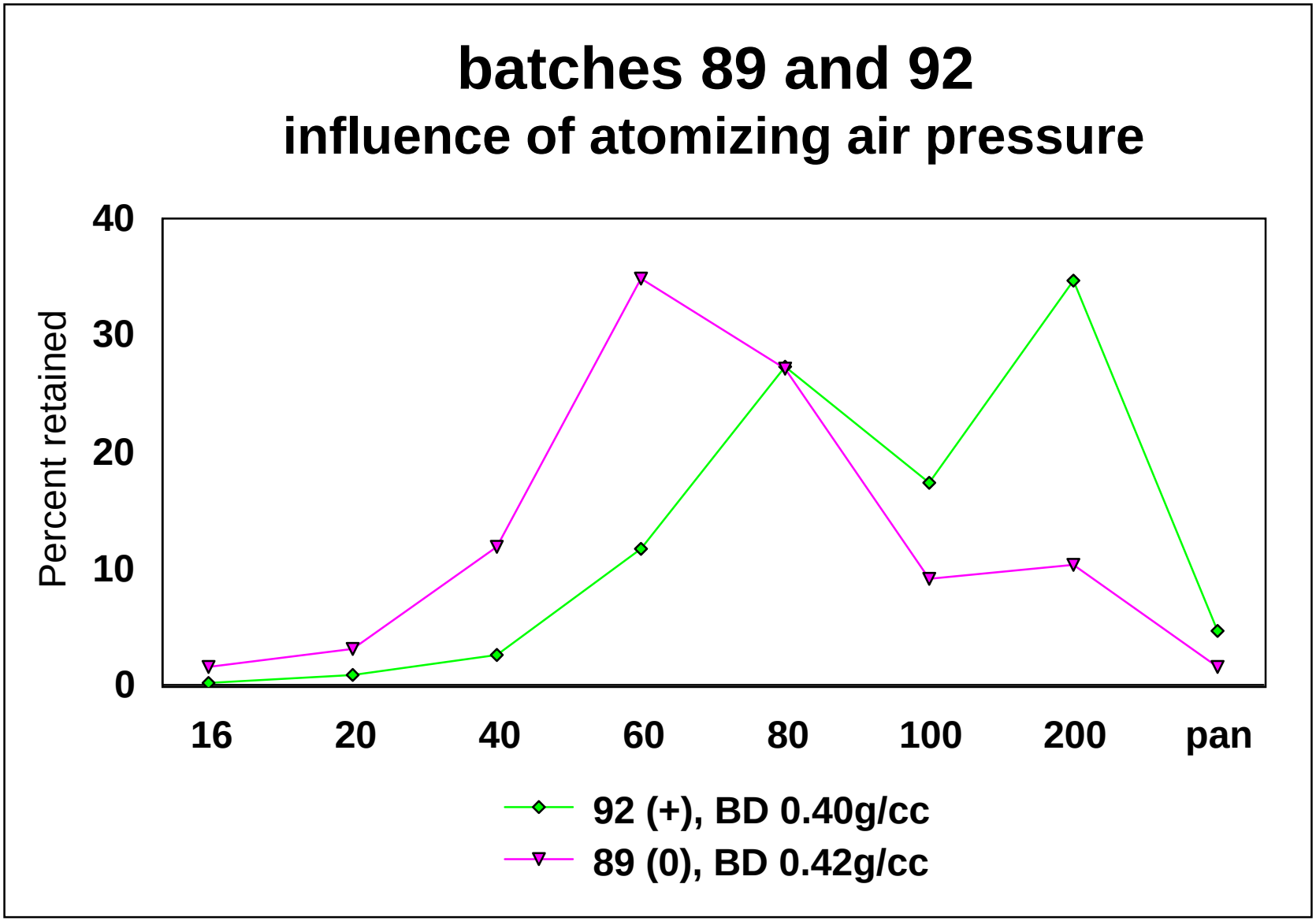


The lower inlet air temperature results in a coarser particle size and higher bulk density (principally due to higher in-process moisture content).



The increased spray rate increases particle size and bulk density. Note: this batch was the ‘worst case’ and required a revision to the domain.

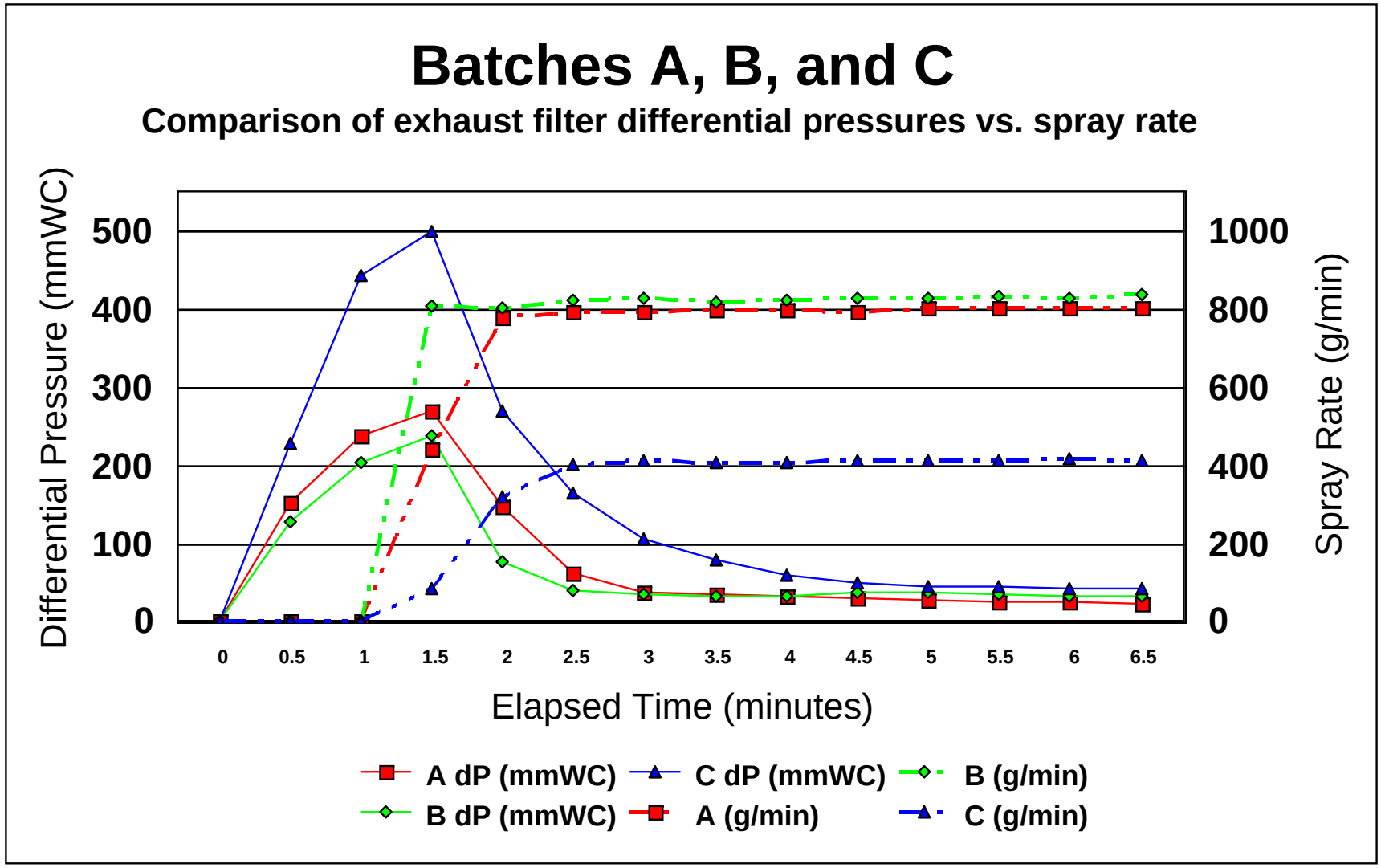


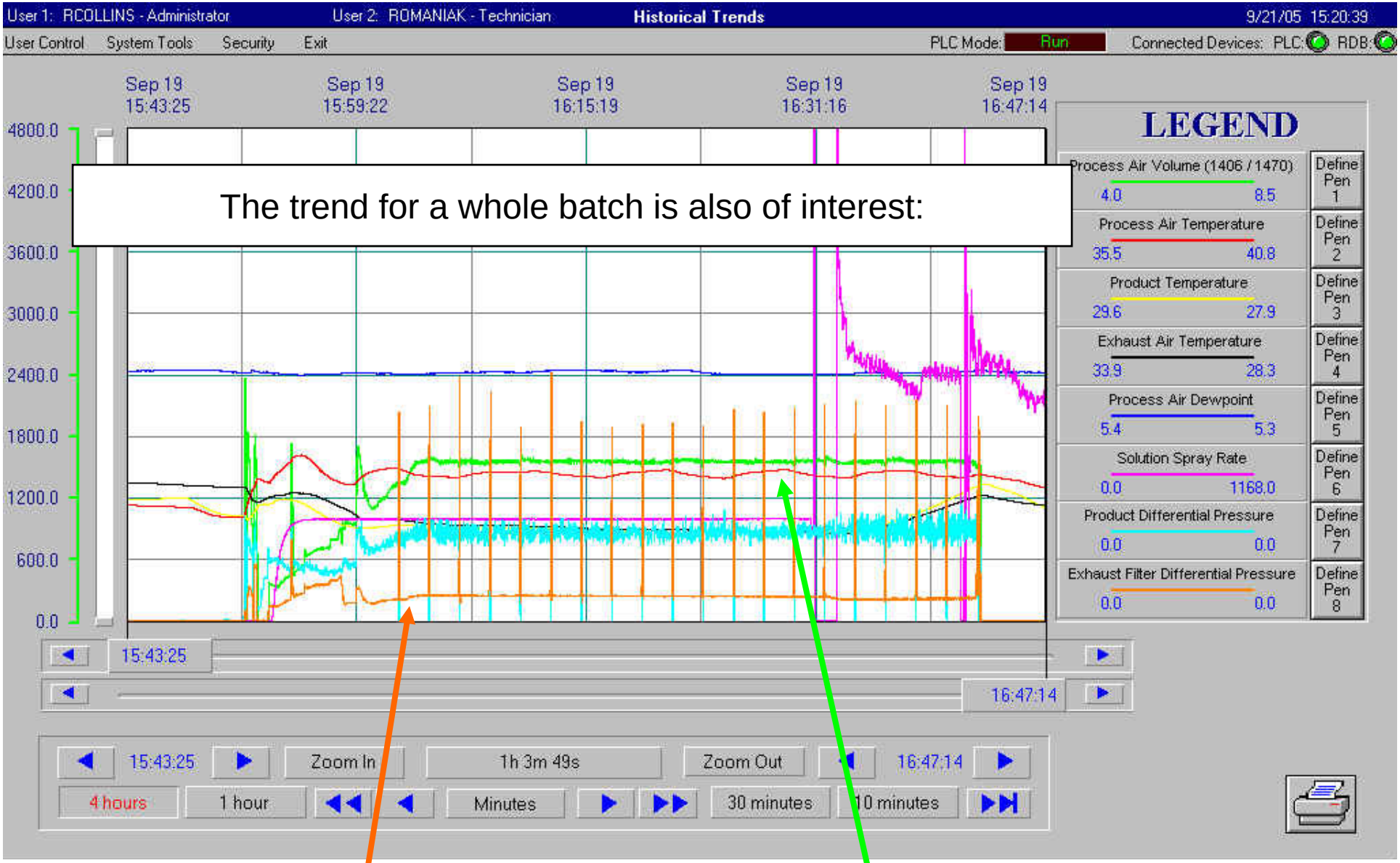
Atomizing air pressure/volume strongly affects droplet size, and ultimately particle size and distribution

Results:

- All batches tabletted successfully. Distribution uniformity, hardness, friability and disintegration time all passed the specification. A robust process? There was an interesting impact on a machine component…

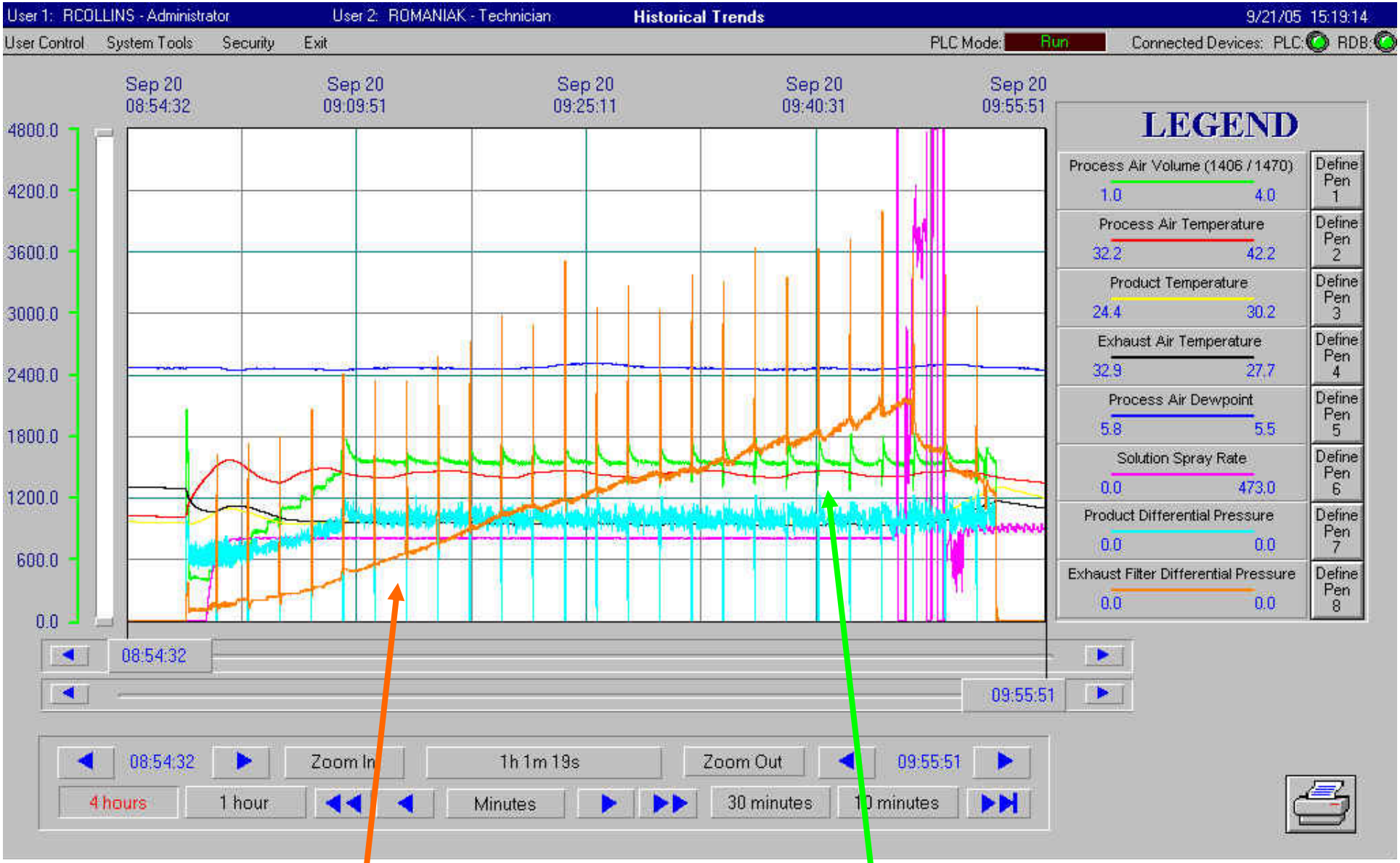
Initial behavior is interesting:



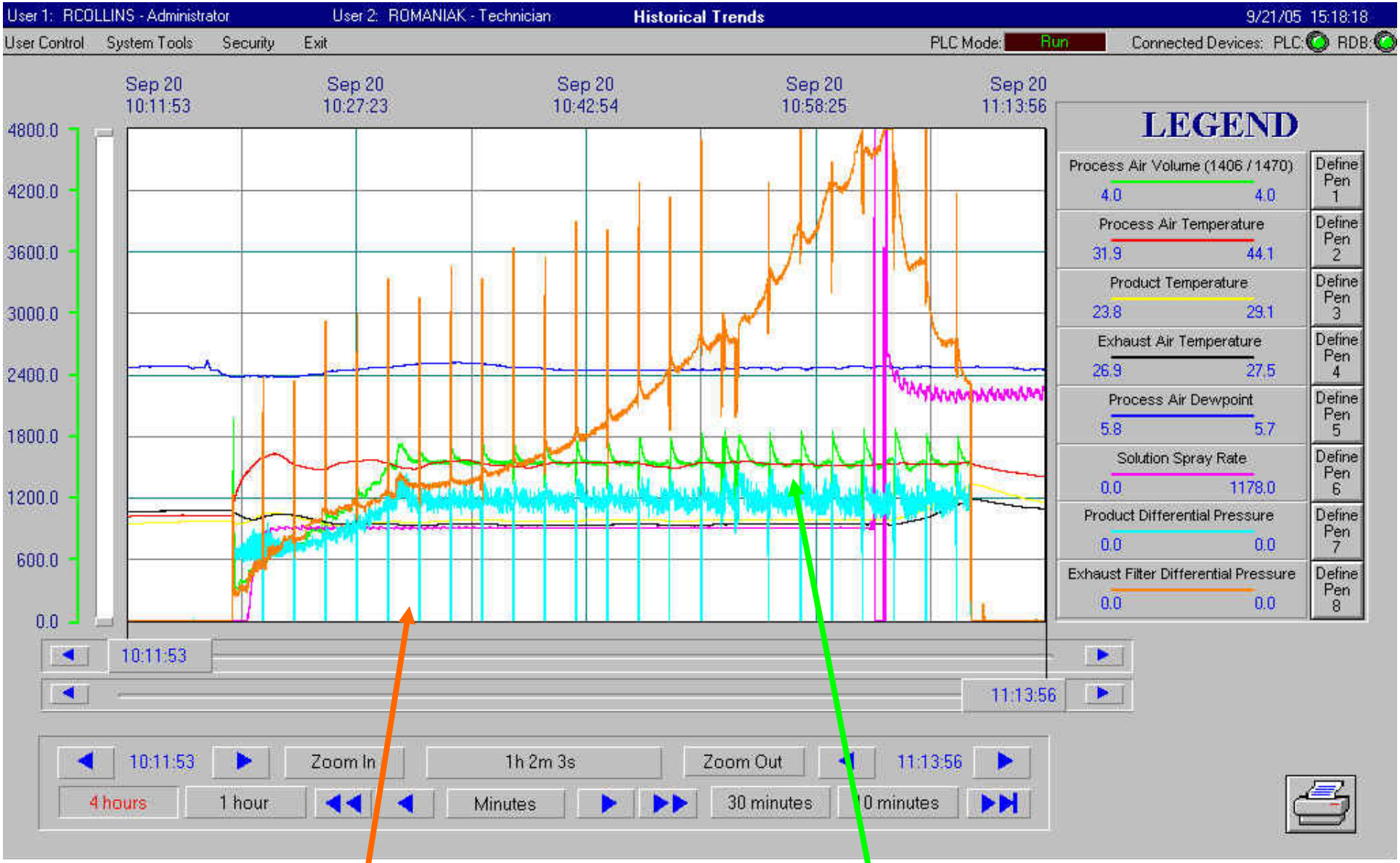


The trend for a whole batch is also of interest:

Here, the filter pressure remains low for the entire batch, and there is no appreciable variability in process air volume.



Here, the filter pressure is trending upward, but not to an alarming level. Variability in process air volume is nominal.



Here, the filter pressure reaches the display limit, and variability in process air volume is increasing.

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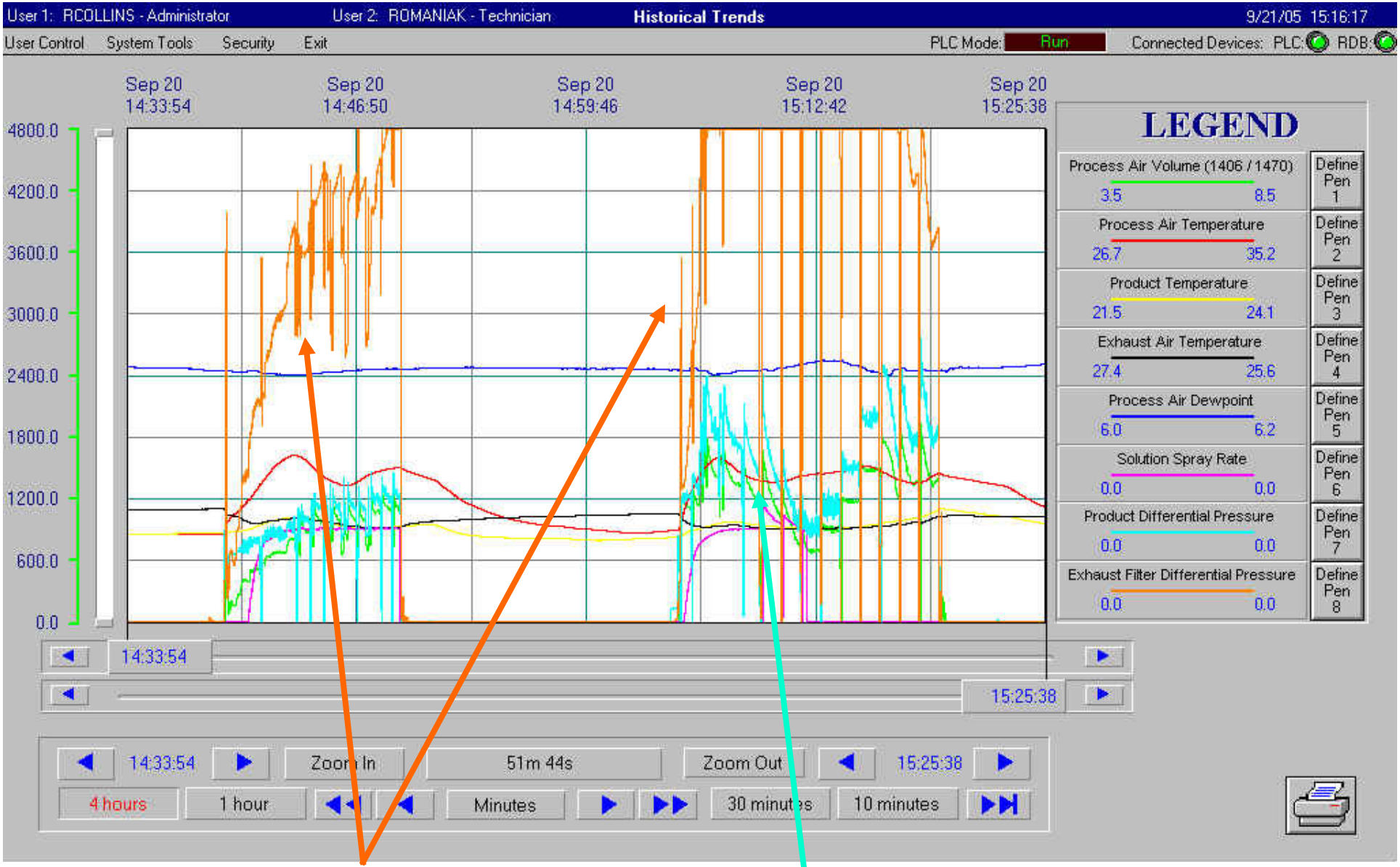
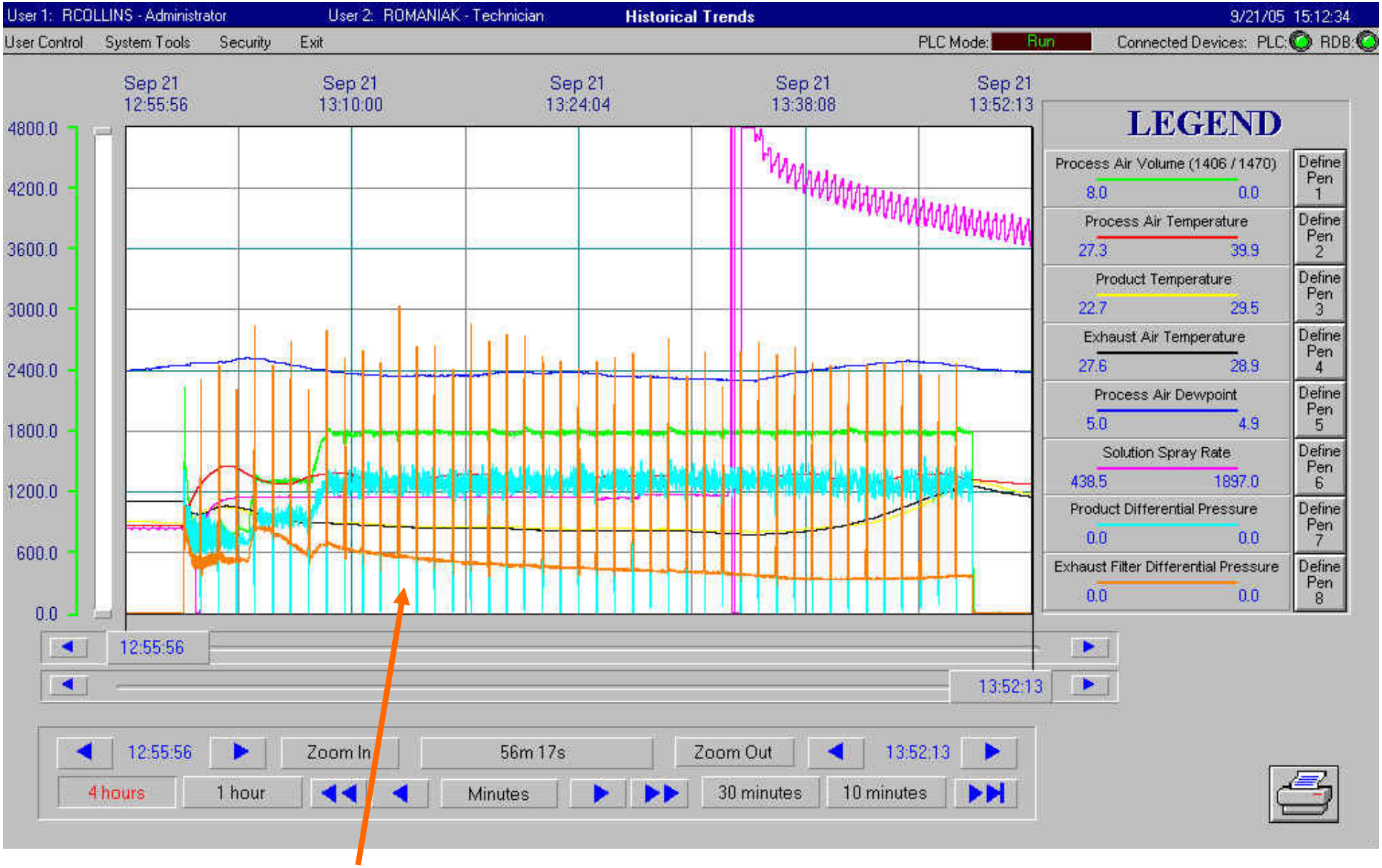


Here, the filter pressure is extreme – the batch was interrupted in an attempt to manually clean the filter. After restart, it was evident that this failed (air flow control not possible). The batch was aborted.



It was found that the filter pressure was related to in-process moisture content. Wetter batches did not tend to foul the filter. A later batch, at high spray rate, actually seemed to ‘clean’ the same filter.

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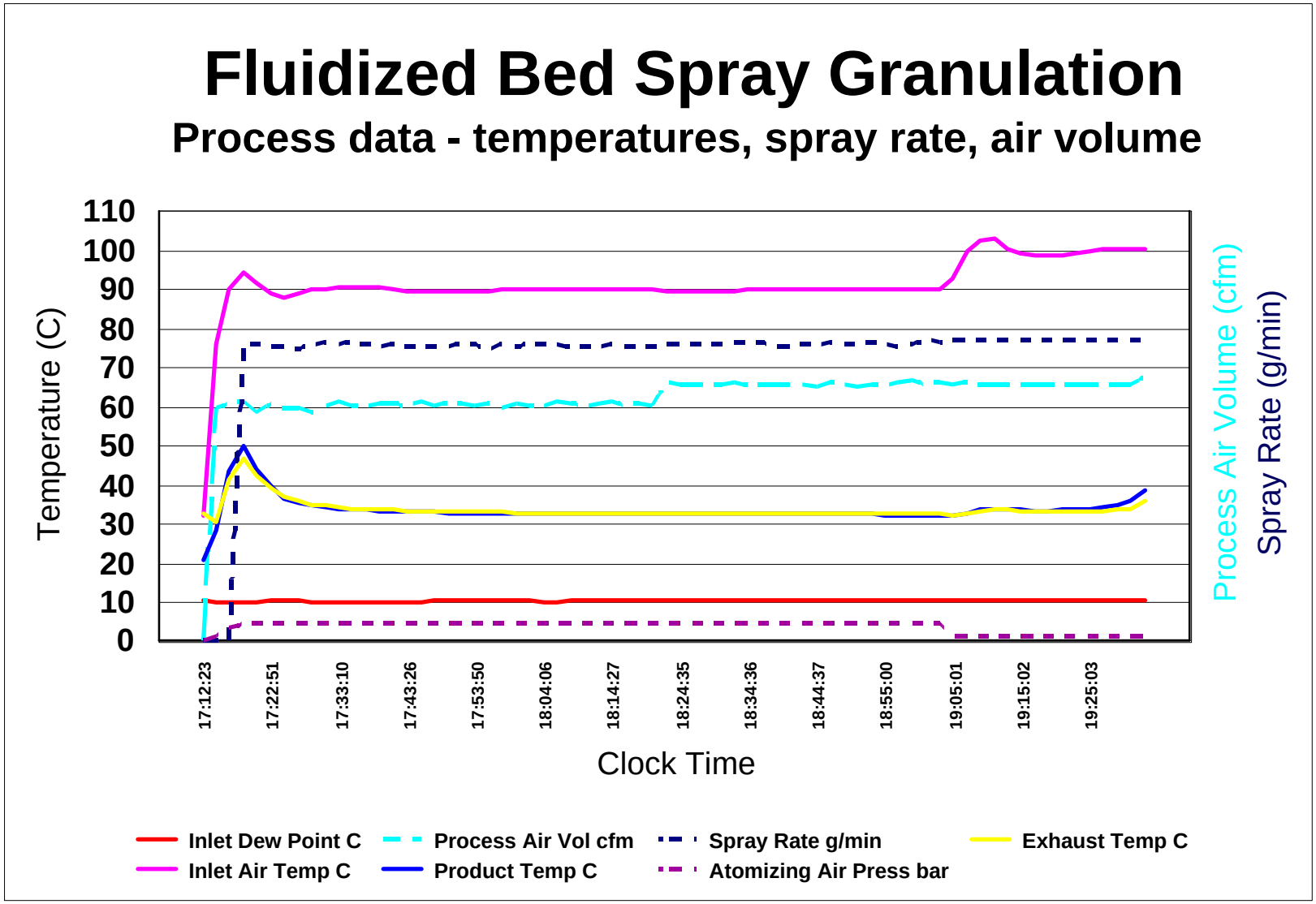
Nuisance Alarms



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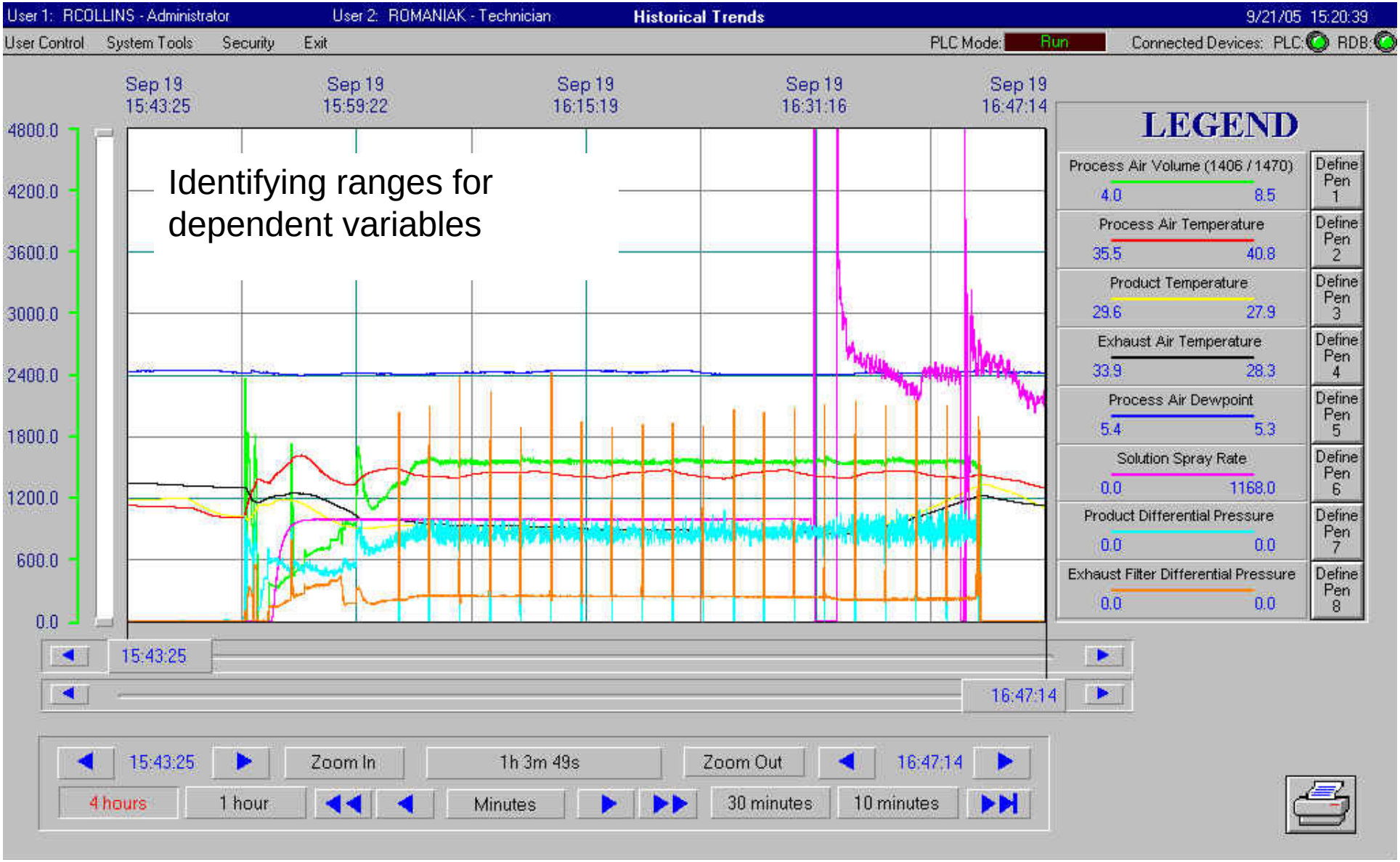
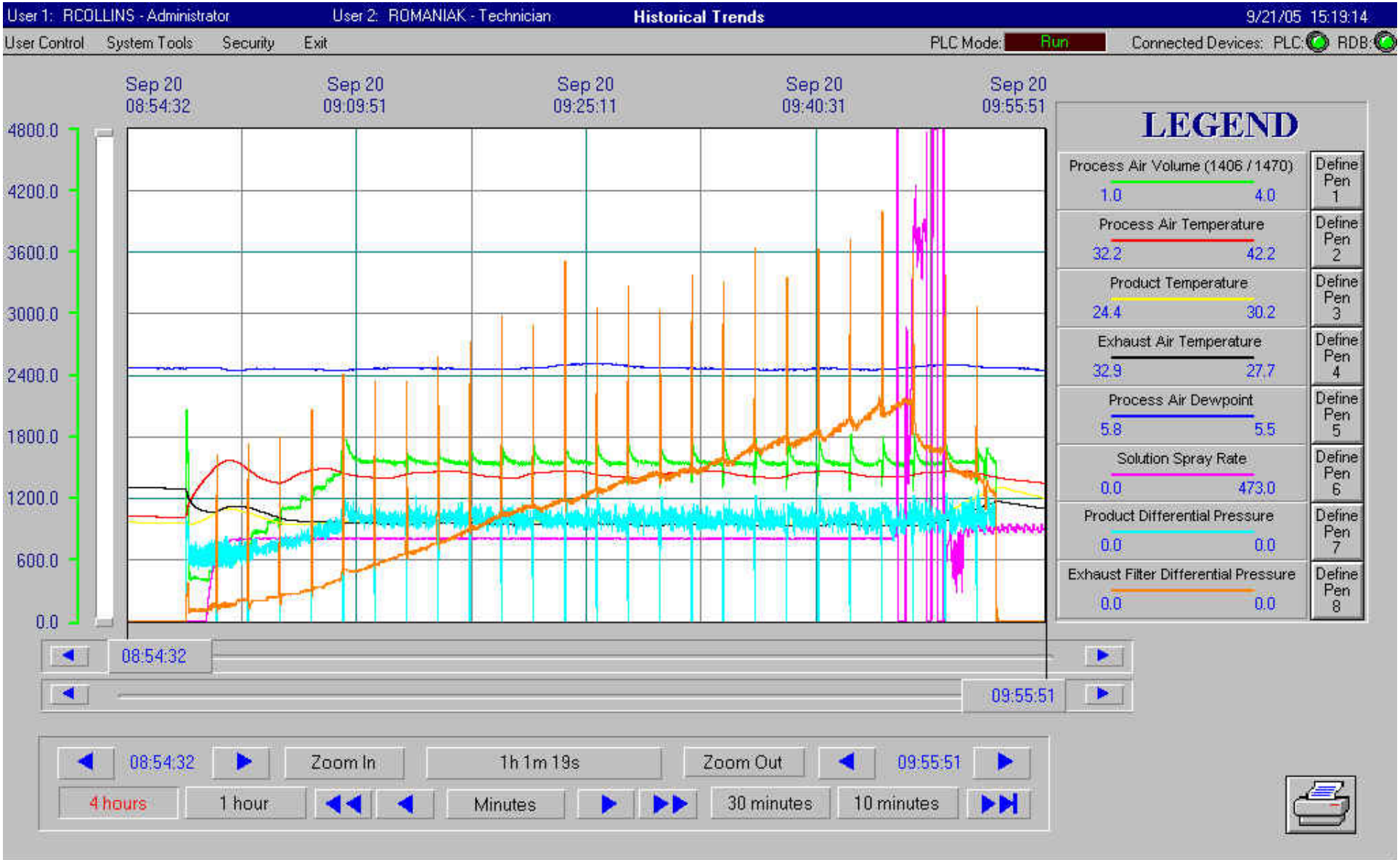
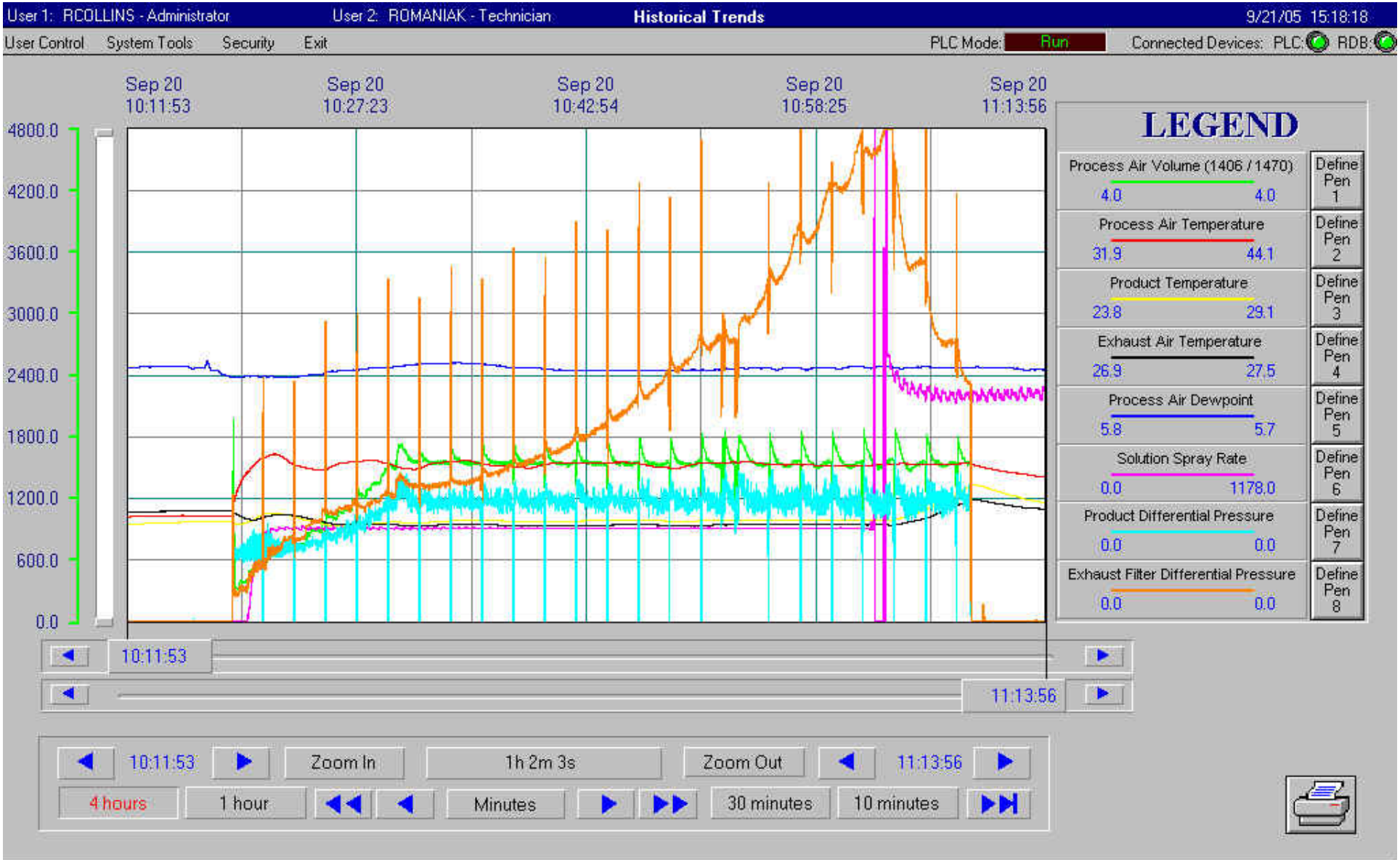


In the first example, filter pressure is very low for the duration of the batch. Process air volume is not impacted during shaking.



In the second example, filter pressure trends upwards during the batch. Process air volume fluctuates during shaking, but not to a great extent.



In the final example, filter pressure trends upwards to the maximum display value. Process air volume responds during shaking but the m/c is able to maintain the desired set point between filter shakes.

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Failure Analysis

1. Batch data was examined for ‘good’ and ‘bad’ batches
2. Calibration data was examined
3. Moisture content at the end of spray was compared
4. Drying time was examined
5. Wetter batches seized, causing batch failures
6. Process air volume accuracy became the focus of attention
7. The air volume sensor was re-calibrated

Summary

- The fluidized bed spray granulation process yields unique product attributes which are attractive for many products.
- Although most commonly conducted using conventional top spray equipment, the process may be performed using the Wurster and rotor techniques.
- Raw material attributes contribute to finished product properties – release specifications must be robust and well defined.
- Process variables are well understood and may be controlled repeatedly.

Any Questions?