ENGINEERING PHARMACEUTICAL INNOVATION

Use of Statistical Quality Control to Improve the Productivity and Quality of a Biopharmaceutical Process

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UNIVARIATE and After the Fact Statistical Process Control

- Simplest: Looks at one variable at a time
- Purpose is to detect changes in process which occur over time. Learn from the changes
  - Individual Batches which are outliers
  - Shifts in the mean
  - Shifts in the amount of variation
- Both Negative and Positive changes are important and both can lead to improvements in quality or productivity

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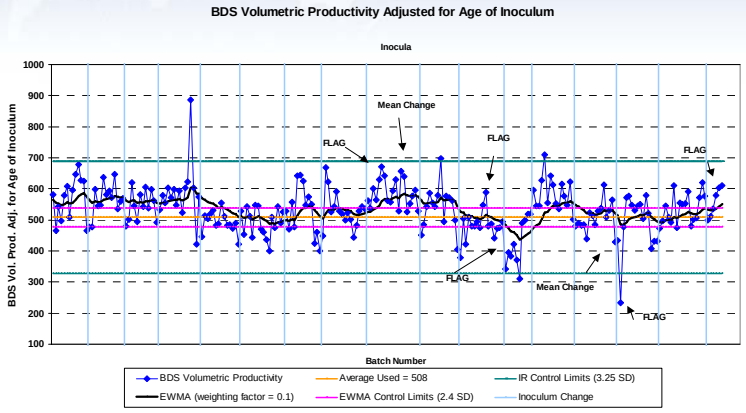
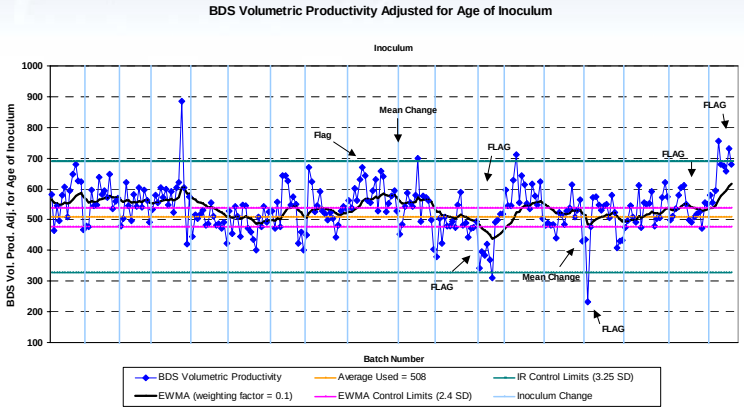
EXAMPLE SPC CHART

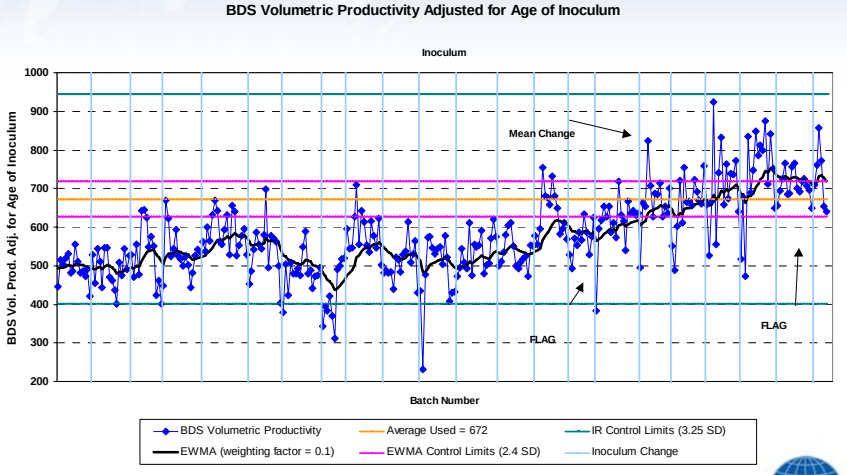


The Next Month



ONE YEAR LATER

MAKE TODAYS BEST TOMORROWS AVERAGE



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UNIVARIATE Statistical Process Control

- **Keep the number of variables tracked per process to a minimum.**
  - More variables will generate excessive false alarms and not shed anymore light on what is happening in the process.
  - The most important part of the program is the careful in depth evaluation of the alarm. Too many alarms, especially if false, quickly start to reduce the quality of the evaluations.

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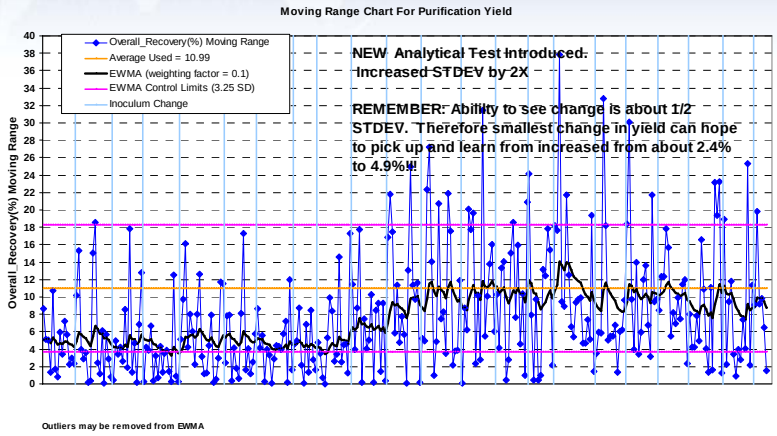
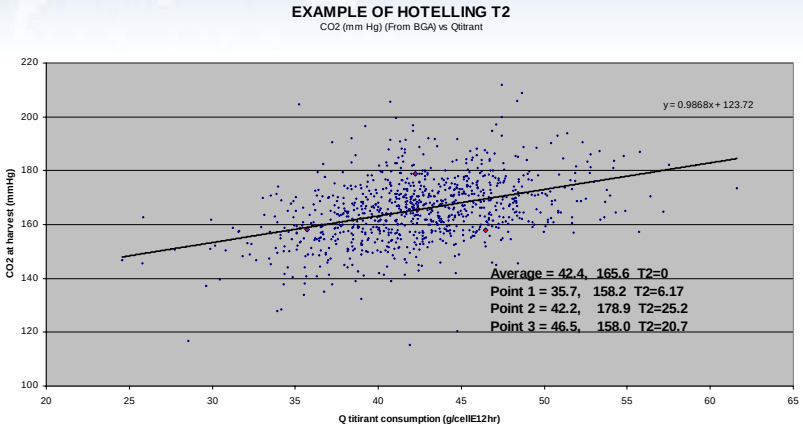
EXAMPLE OF MOVING RANGE CHART



MULTIVARIATE SPC

- Sometimes Treating Variables as a Group has Advantages
  - Information in the covariance between the variables is accessed
  - Multiple small indications from several variables can add up to significant indication
  - Can track many variables at once and not have the issue of creating a lot of false flags

Statistical Distance

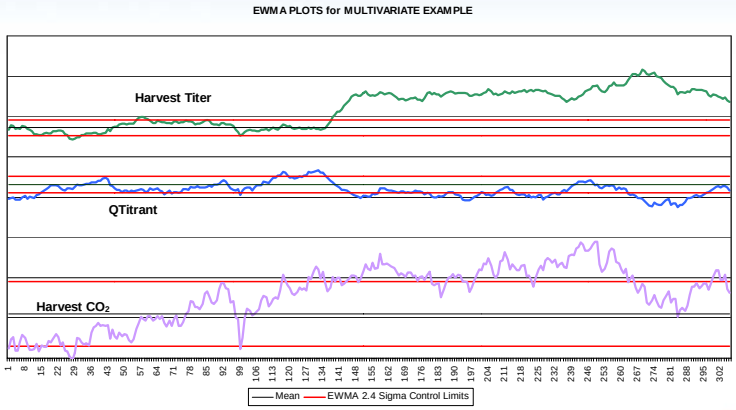


Multivariate SPC (MSPC)

Calculates the Statistical Distance from the data point (or the EWMA) and a chosen average.

- Statistical Distance is the squared distance from average divided by the appropriate variance/covariance.
- The result is always positive and represents statistical distance, in an unknown direction, by all or some of the variables used.

Multivariate Example



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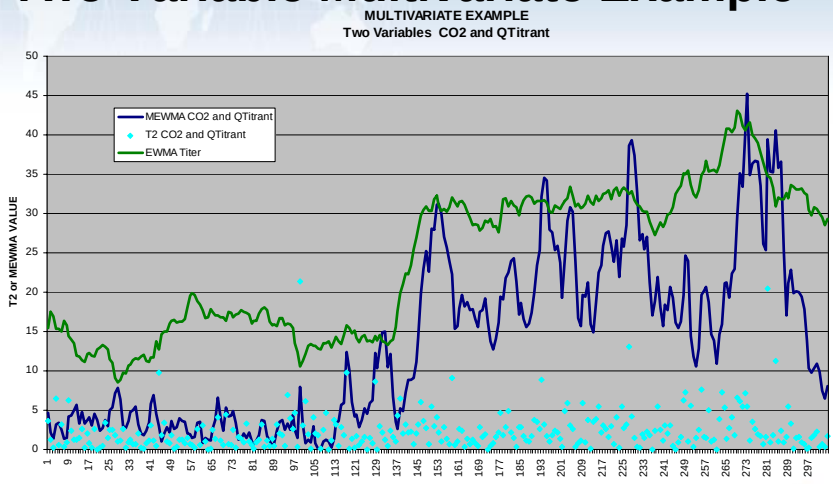
Two Variable Multivariate Example



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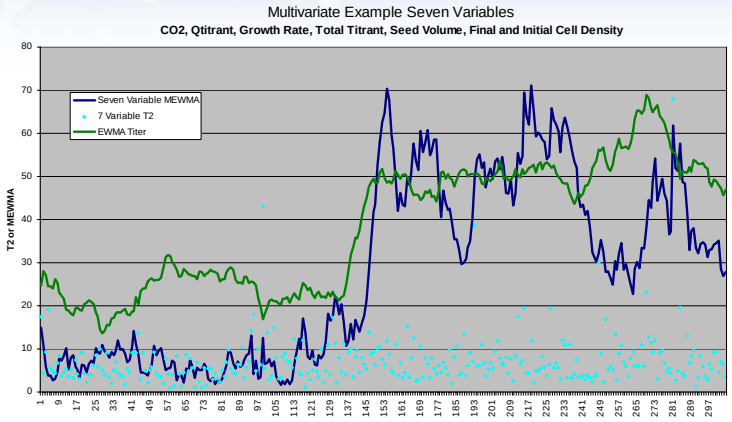
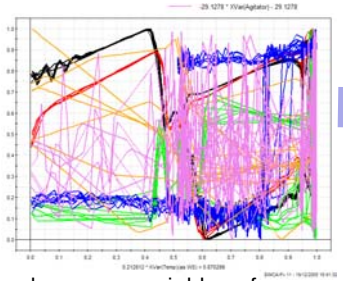
EXPAND TO SEVEN VARIABLE MULTIVARIATE



Monitoring During A Process Multivariately

- The process variables measured during the evolution of historical batches is summarized into a few new variables (the scores)
- Creates a “finger print” of how a good batch should evolve
- Few plots to look at instead of many -> easier overview

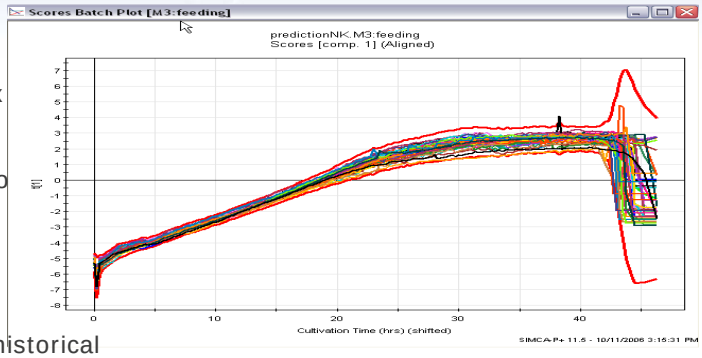


Several process variables of historical batches

All historical Batch plotted as a score (t1)

Control chart of historical good batches

Process summary index that takes all process parameters into account



Model of historical batches creates a "fingerprint" for how a good batch should evolve over time

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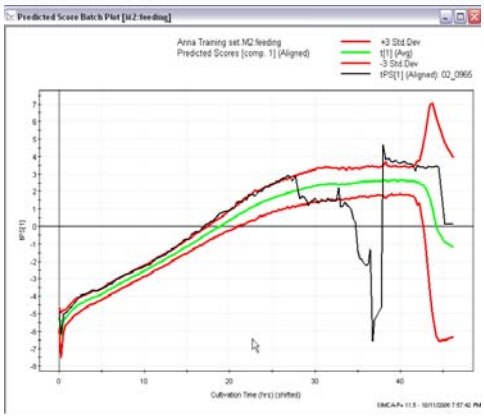
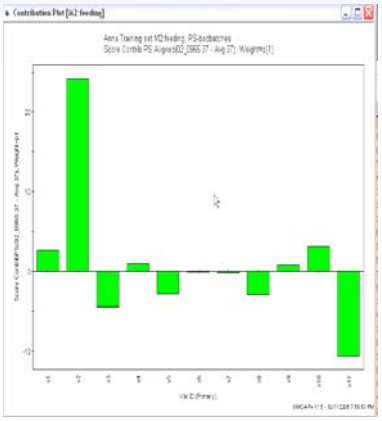
Testing problem batch on model and root cause analysis





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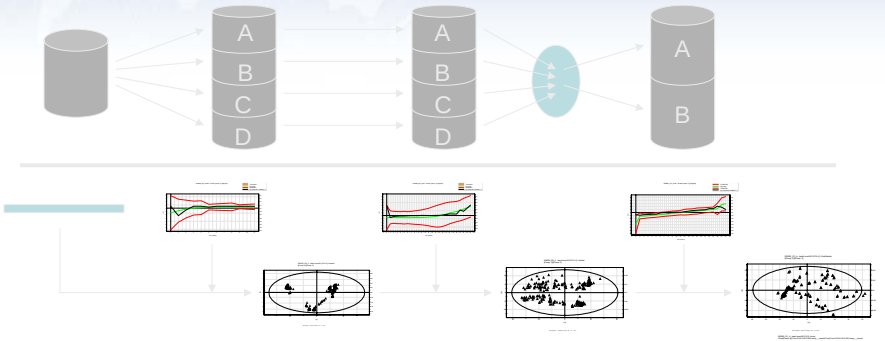
Manufacturing Train

Raw Materials Granulator Dryer Coater



Hierarchical structure of batch models allows for integrated modeling of production trains

- Separate modeling / analysis of each unit operation
- Integrated model of the complete process to final product

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Build your Skids and Equipment to Measure/Record Many Variables

FOR EXAMPLE A CENTRIFUGE

- Power
- Temperature (s)
- Feed Vessel Level Temperature and Pressure
- Feed Line Pressure
- Solids Discharge Pressure
- Collection Vessel Pressure and Level
- RPM
- Vibration
- Flow Rate
- Volume Processed
- Opacity/Turbidity In
- Opacity/Turbidity Out

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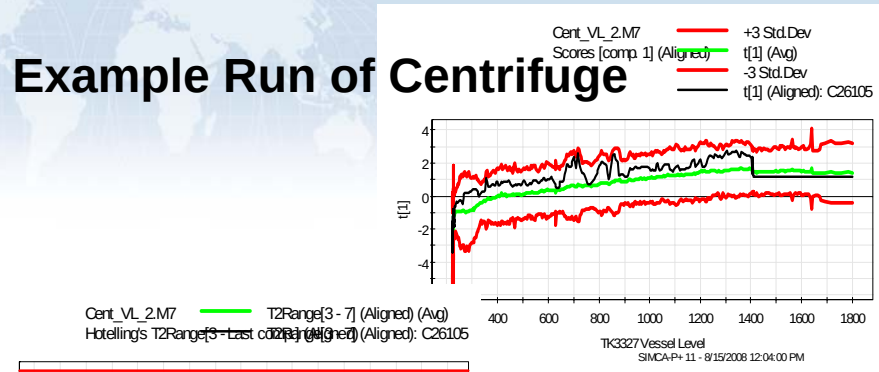
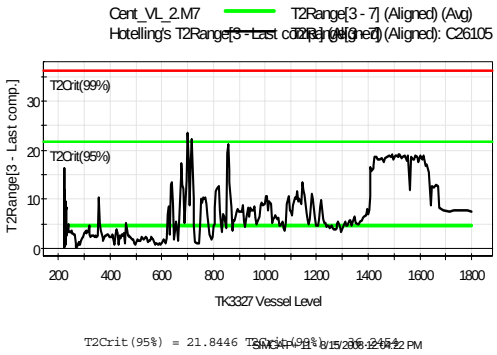
Example Run of Centrifuge





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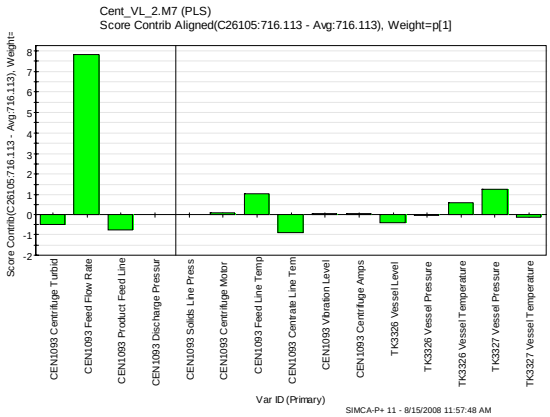
Drill Down: This is a quick way to follow many variables Univariately vs many Screens



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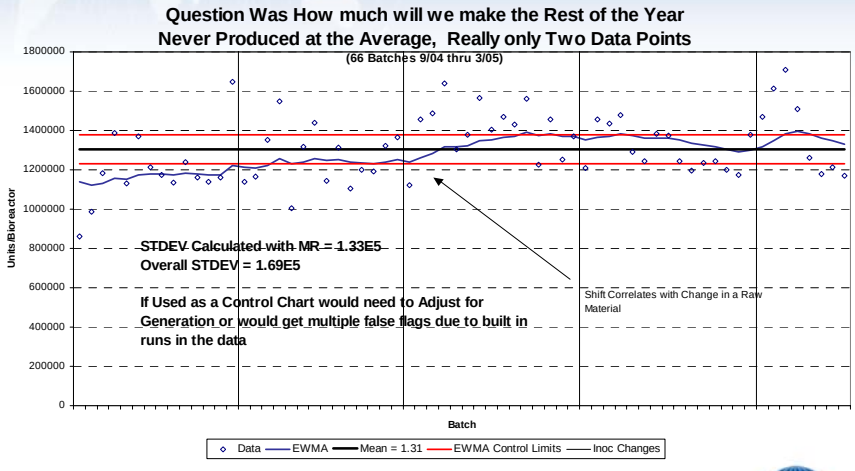
Evaluating the Alert

- If you set up a SPC program you will see lots of Alerts
- The most important and difficult part of any SPC program is evaluating the alert and taking steps based on the analysis
- The fact that almost all measurements have significant error in them makes analysis “challenging”
- One good DOE with 10 data points is better than thousands of points from SPC, but ….

Mean Shifts and Underlying Data Runs



Nothing is more Basic than determining when the change Occurred

- THE FOLLOWING IS MANUFACTURED DATA
  - The standard deviation is 10%
  - The shift is 10% or ONE STANDARD DEVIATION
  - The Shift is from 1 to 1.1
    - We know for sure starting average is 1.0, which is more than you will have in real data
  - The step change occurred when?

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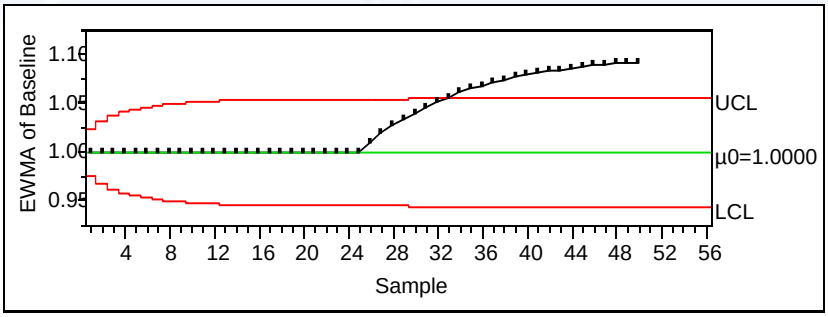
What Moving Average Ideally would look like



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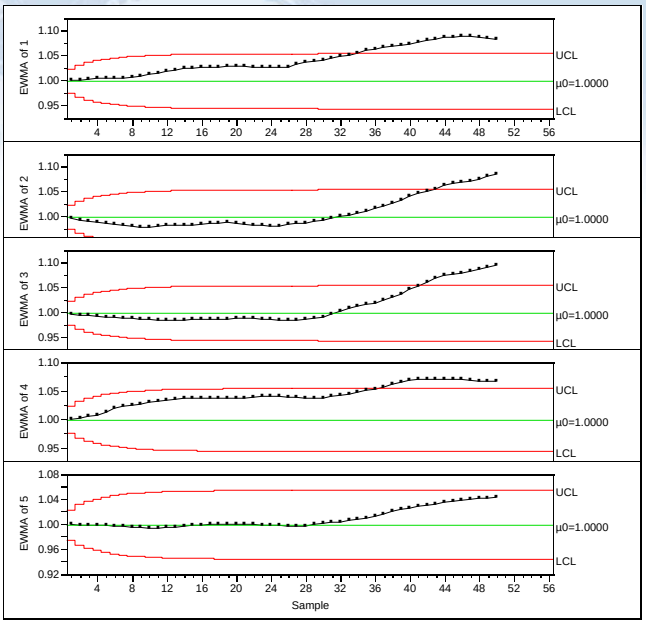

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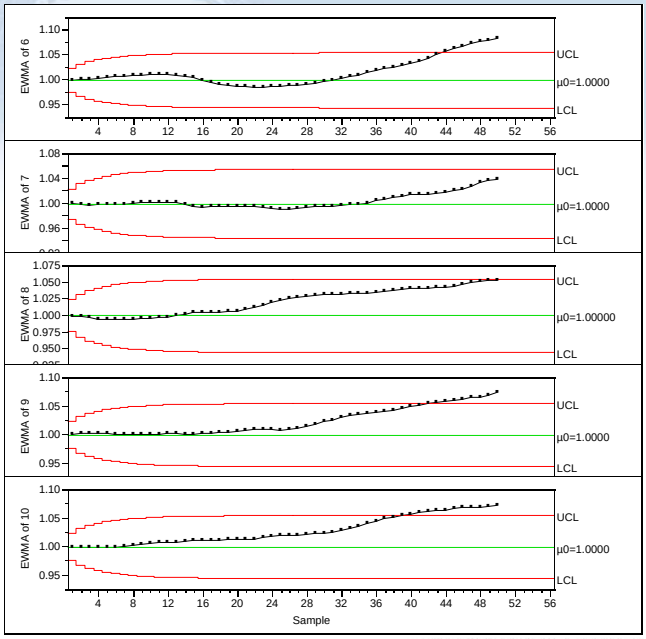

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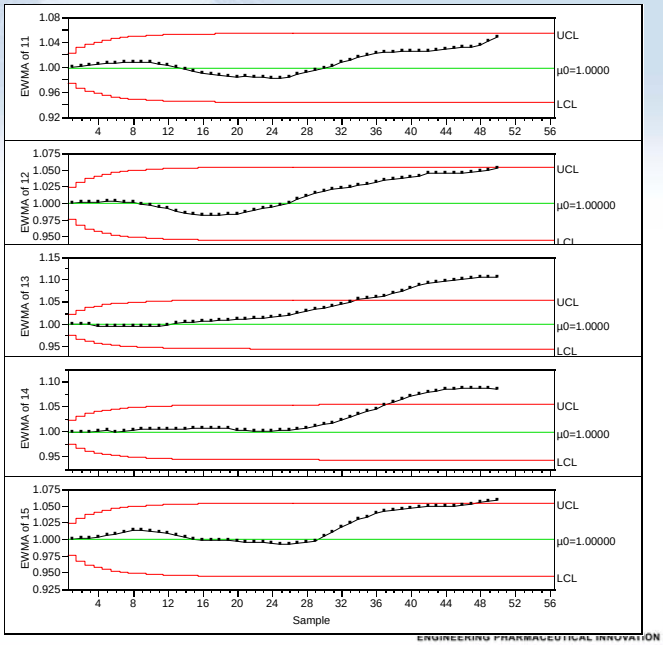
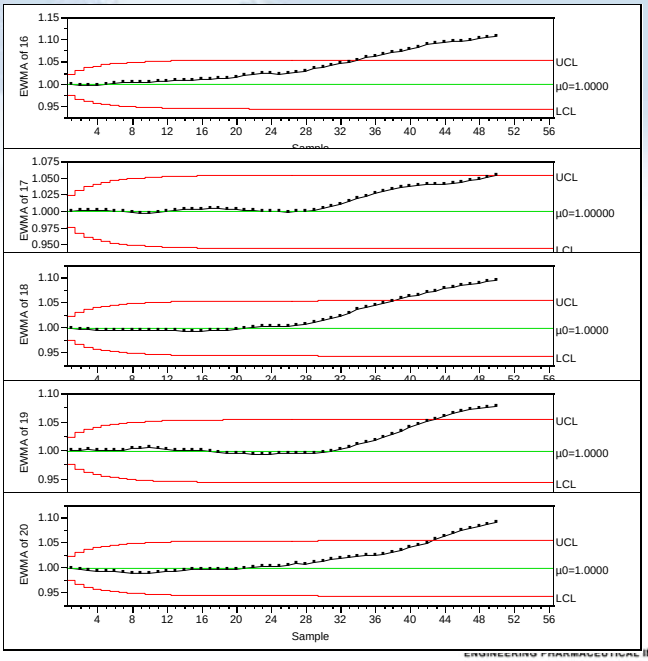

EWMA of 11
EWMA of 12
EWMA of 13
EWMA of 14
EWMA of 15
UCL
μ0=1.0000
μ0=1.00000
LCL
Sample


EWMA of 16
EWMA of 17
EWMA of 18
EWMA of 19
EWMA of 20
UCL
μ0=1.0000
μ0=1.00000
LCL
Sample

Evaluating the Flag: Other Difficulties

- Happenstance Data with Lurking Variables
- Probably full of False Correlations
- Limited real movement relative to error in Data leads to
  - Low Signal to Noise Ratio. (low r^2)
  - Reduction of regressed slope of correlations
- One GOOD DOE or Controlled Experiment can be worth more than Thousands of Manufacturing Data Points

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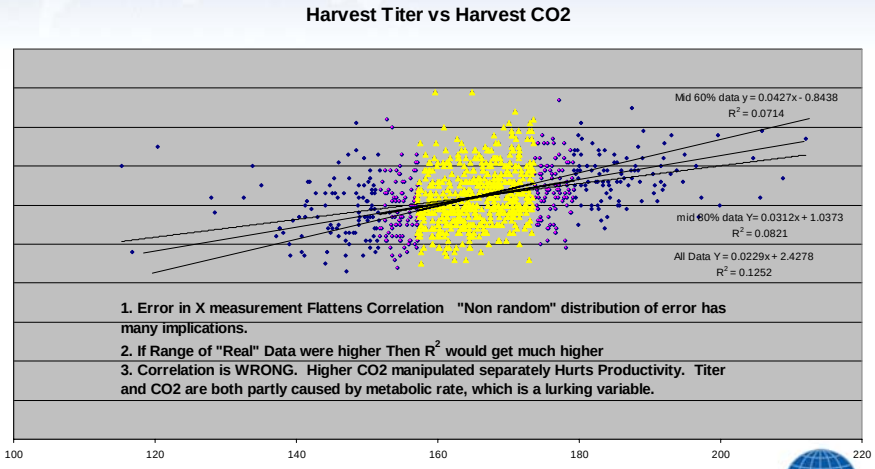
Example of Some problems with Production Data



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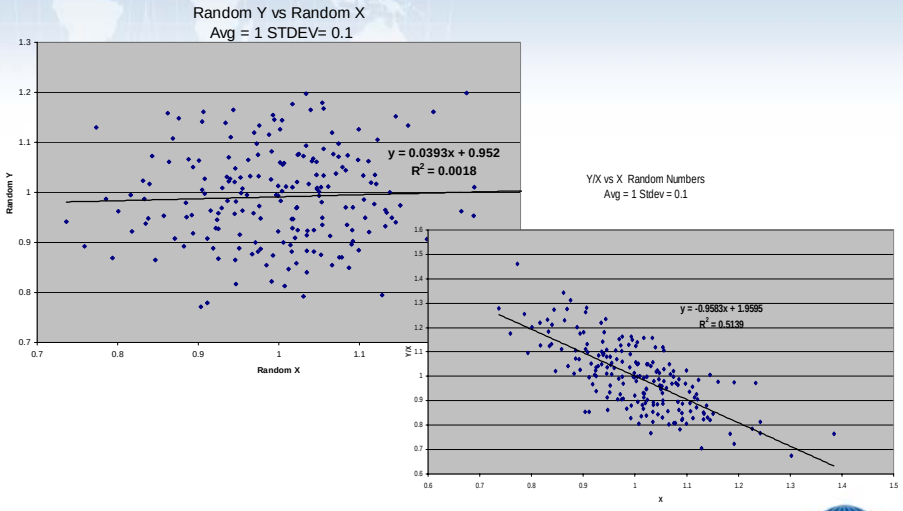
Example of How Errors can Mislead



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RAW MATERIAL CHANGES

- Since most of our processes are well controlled a major source of our flags are raw material changes.
- Multiple raw materials could be changing within the time frame that the shift could have occurred. WHICH ONE???
  - Knowledge of Chemistry and Process First Resort
  - Run experiments
  - If need to make a guess Fratio maximum test

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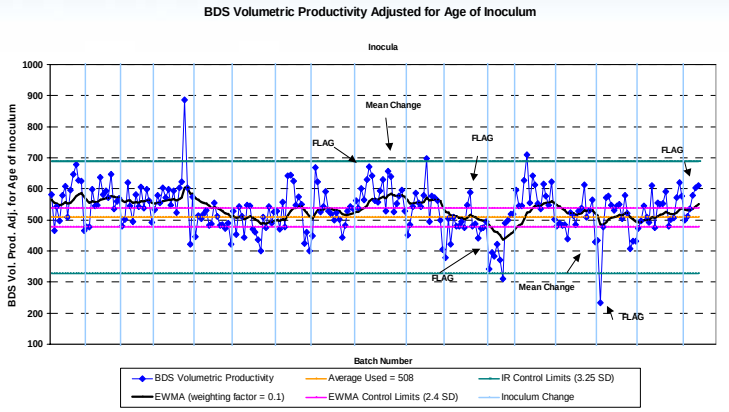
EXAMPLE SPC CHART



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Fratio Test

- One way Analysis of Variance of Raw Material Changes (vendor lot in most cases) vs Parameter of Interest
- Shift Data Vendor Lot Change Relative to Parameter and recalculate Fratio from Analysis of Variance test for each shifted Column.
- If Maximum Fratio occurs at or near 0 shift is an indication changes in this raw material historically correlates with parameter.

EXAMPLE of VENDOR LOT SHIFTS						
		RAW MATERIAL LOTS				
Index	Variable of Inte	Shifted -2	Shifted -1	Real Order	Shifted +1	Shifted +2
1	1.00984526	A	A	A	B	B
2	1.011714535	A	A	A	A	B
3	1.028384275	A	A	A	A	A
4	1.011746539	B	A	A	A	A
5	1.004302761	B	B	A	A	A
6	1.009036869	B	B	B	A	A
7	1.017030541	B	B	B	B	A
8	1.031073023	B	B	B	B	B
9	1.042191764	A	B	B	B	B
10	1.04767269	A	A	B	B	B

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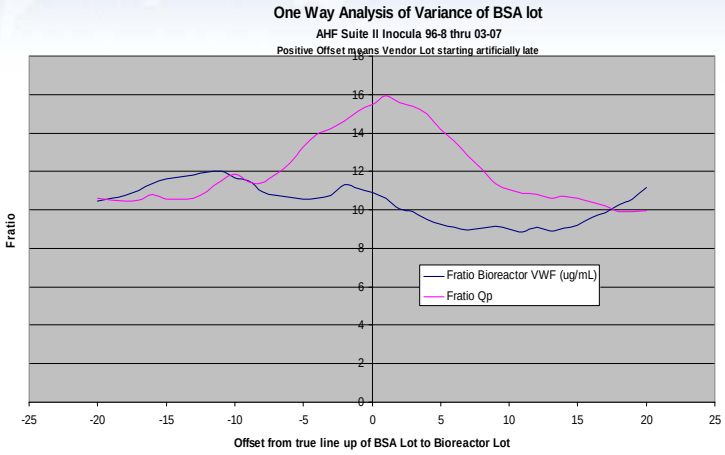
Fratio Method Raw Materials



SUMMARY

- Monitoring your Manufacturing Process using SPC Tools can yield significant knowledge that can be used to improve your process
- Simple Univariate monitoring first (KISS)
- Multivariate monitoring may allow detection of changes not possible with Univariate monitoring
- In Process Mulivariate is also a “simple” way to set up and monitor many individual variables at once. Condenses the number of variables to follow