Practical Applications of Statistical Process Control

C. Markert-Hahn, K. Schifflˡ, M. Strohmeier,
Roche Diagnostics GmbH, Penzberg

Nonclinical Statistics Conference, 26.09.2012

Roche Pharma Production Penzberg

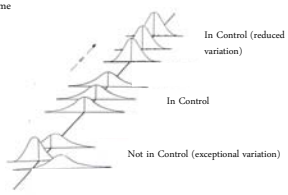
Operational Excellence

Statistics

Development	Manufacturing
• Process Development	• Trainings
• QbD	• SPC
• …	• DoE, Validation
	• Analysis of Process Data,…

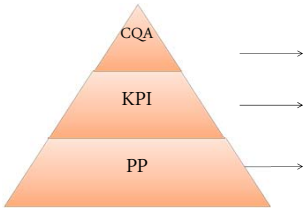
Why do we use SPC?

- Goal:
  - Detect deviations from a standard process in time
  - Reduce loss of batches
  - Communication with management
  - Actively involve project team
- How?
  - Establish appropriate control charts for process parameters.



SPC System

- Control charts are established for three different types of parameters:



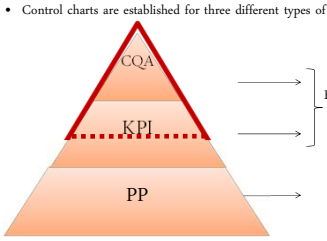
Critical Quality Attributes, #≈15

Key Performance Indicators,
≈ 30

Process Parameters (including trend data)
≈ 1000

SPC System

- Control charts are established for three different types of parameters:

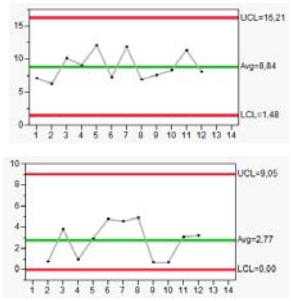


Easy interpretation, routinely monitored.

Interpretable after Statistics Training, Monitored from Process Experts, e.g. Multivariate Control Charts

5

Control Chart Example: Individual Moving Range Chart



- Example: Titer[g]* Individual Measurements and Moving Ranges.

$$MR_i = |x_i - x_{i-1}|$$

$$\overline{MR} = \frac{1}{m-1}\sum_{i=2}^{m} MR_i$$

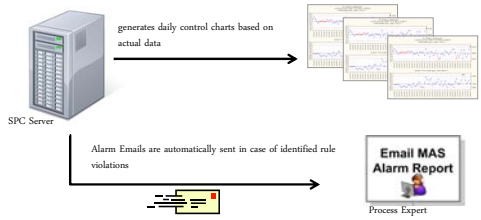
$$CL = \bar{x} \pm 3\frac{\overline{MR}}{d_{22}}$$

$$UCL = \overline{MR} + 3\frac{d_{32}\overline{MR}}{d_{22}}$$

d_{22}=Mean of
*simulated data

SPC for CQAs

- Main Work: Establish appropriate control charts and define standard process- Calculate control limits based on historical data.



7

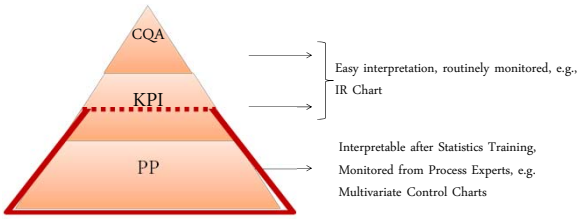
SPC for CQAs

- Control charts are accessible e.g. via web reports

8

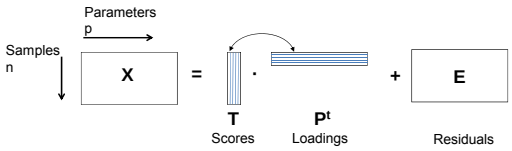
SPC System

- Control charts are established for three different types of parameters:



9

Principal Component Analysis



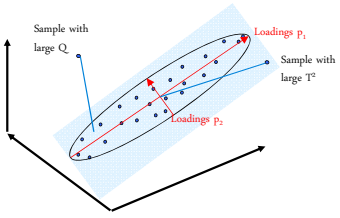
- **X:** mean centered or auto-scaled
- **Loadings:** Parameter Weights, p_i is the eigenvector of Cov(X) corresponding to the eigenvalue λ_i

$$Cov\ (X) = \frac{X'X}{n-1}$$

- **Scores:** New Coordinates, $t_i = Xp_i$

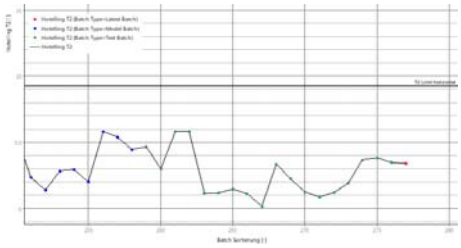
Multivariate Statistical Process Control

- Graphical Interpretation:



11

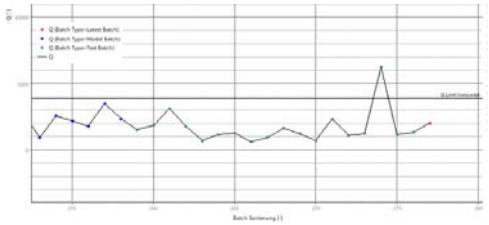
Hotelling T^2 Control Chart



- Measure of variation in each sample within the PCA model.
- $T^2_i = t_i \lambda^{-1} t_i^T$,where t_i is the i-th row of T and λ is the diagonal matrix containing all eigenvalues of X corresponding to the k principal components.

12

Lack of Fit, Q Control Chart

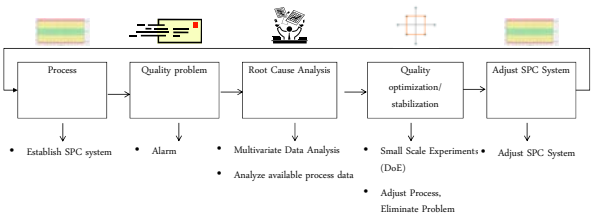


- Measure of distance between a sample and its projection into the k principal components.
- $Q_i = e_i \, e_i^T$,where e_i is the i-th row of E

Multivariate SPC for further Process Parameters

- Multivariate Control Charts:
  - Monitor the stability of a multivariate process considering many parameters at the same time
- Causes of a multivariate alarm:
  - Individual variables being outside their allowable range
  - Fouled relationship between two or more variables
- Multivariate Control Charts are analyzed by experts, no alarm emails are sent.

Process behind SPC



Innovation für die Gesundheit

Outlook

- Define historical data sets for multivariate control charts for further process steps and products.
- Apply non-standard control charts
  - Consideration of Covariates in Control Charts
  - Consideration of repeated measures

IR-Chart Constants

n	d_{2n}
2	1,128
3	1,692
4	2,058
5	2,326
6	2,532
7	2,703
8	2,849

Hartung, (2009)

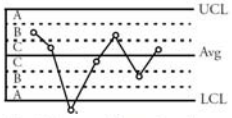
n	d_{2n}
2	0,853
3	0,888
4	0,880
5	0,864
6	0,848
7	0,833
8	0,820

Handl (1999)

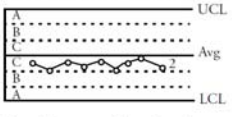
18

Western Electric Rules

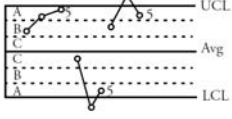
!!! **Test 1:** One point beyond Zone A



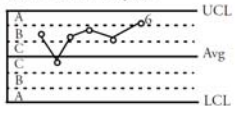
Test 2: Nine points in a row in a single (upper or lower) side of Zone C or beyond



!! **Test 5:** Two out of three points in a row in Zone A or beyond

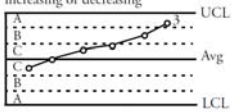


! **Test 6:** Four out of five points in a row in Zone B or beyond

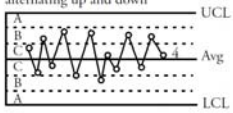


Weitere Nelson Rules

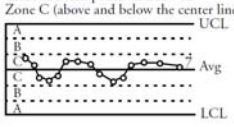
!! **Test 3:** Six points in a row steadily increasing or decreasing



Test 4: Fourteen points in a row alternating up and down



Test 7: Fifteen points in a row in Zone C (above and below the center line)



! **Test 8:** Eight points in a row on both sides of the center line with none in Zone C