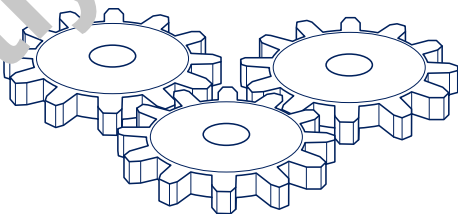


Technical Report No. 59

Utilization of Statistical Methods for Production Monitoring

PCMO
Paradigm Change in
Manufacturing OperationsSM



2012



PDA Utilization of Statistical Methods for Production Monitoring Task Force Members

Authors

Greg Flexman, Grifols (Chair)

Michael Husovich, Amgen

Jason J. Orloff, PharmStat

Jayesh Patel, F. Hoffmann-La Roche Inc.

Stephan Rönninger, F. Hoffmann-La Roche Ltd.

Mark A. Skoog, Genentech

Lynn D. Torbeck, PharmStat

Dan Weese, Amgen

This technical report was developed as a part of PDA's Paradigm Change in Manufacturing Operation (PCMO) project. The content and views expressed in this Technical Report are the result of a consensus achieved by the authorizing Task Force and are not necessarily views of the organizations they represent.

Utilization of Statistical Methods for Production Monitoring

Technical Report No. 59

ISPN 18-0-939459-44-5

© 2012 Parenteral Drug Association, Inc.

All rights reserved.



Paradigm Change in Manufacturing Operations (PCMOSM)

PDA launched the project activities related to the PCMO program in December 2008 to help implement the scientific application of the ICH Q8, Q9 and Q10 series. The PDA Board of Directors approved this program in cooperation with the Regulatory Affairs and Quality Advisory Board, and the Biotechnology Advisory Board and Science Advisory Board of PDA.

Although there are a number of acceptable pathways to address this concept, the PCMO program follows and covers the drug product lifecycle, employing the strategic theme of process robustness within the framework of the manufacturing operations. This project focuses on Pharmaceutical Quality Systems as an enabler of Quality Risk Management and Knowledge Management.

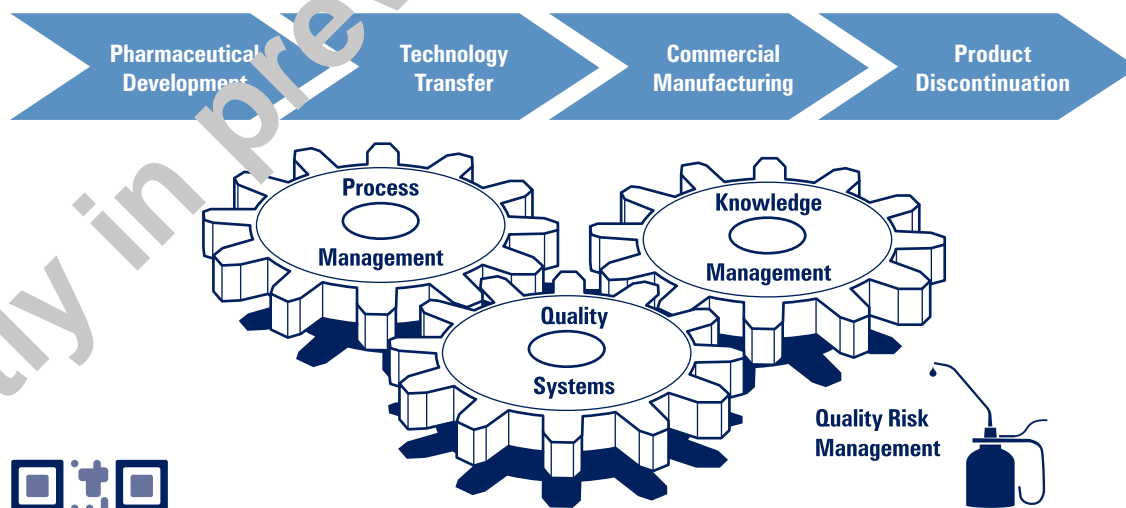
Using the Parenteral Drug Association's (PDA) membership expertise, the goal of the Paradigm Change in Manufacturing Operations Project is to drive the establishment of 'best practice' documents and /or training events in order to assist pharmaceutical manufacturers of Investigational Medicinal Products (IMPs) and commercial products in implementing the ICH guidelines on Pharmaceutical Development (ICH Q8, Q11), Quality Risk Management (ICH Q9) and Pharmaceutical Quality Systems (ICH Q10).

The PCMO program facilitates communication among the experts from industry, university and regulators as well as experts from the respective ICH Expert Working Groups and Implementation Working Group. PCMO task force members also contribute to PDA conferences and workshops on the subject.

PCMO follows the product lifecycle concept and has the following strategic intent:

- Enable an innovative environment for continual improvement of products and systems
- Integrate science and technology into manufacturing practice
- Enhance manufacturing process robustness, risk based decision making and knowledge management
- Foster communication among industry and regulatory authorities

The Product Life Cycle



For more information, including the PCMO Dossi.e., and to get involved, go to www.pda.org/pcmo

Table of Contents

1.0 Introduction.....	1	4.0 Acceptance Sampling	24
1.1 Purpose and Scope.....	1	4.1 Typical Applications.....	24
1.2 Implementation to Support Decision Making...	1	4.2 Key Terms.....	24
2.0 Glossary of Terms	2	4.2.1 Acceptable Quality Limit (AQL).....	24
3.0 Statistical Process Control Tools.....	8	4.2.2 Rejectable Quality Level (RQL).....	24
3.0.1 Prerequisites for Data Analysis.....	8	4.3 Types of Sampling	25
3.1 Run Charts.....	11	4.3.1 Attributes Sampling.....	25
3.1.1 Typical Applications.....	12	4.3.2 Variable Sampling	25
3.1.2 Pros	12	4.4 Types of Acceptance Plans.....	25
3.1.3 Cons	12	4.4.1 Single Sampling Plans	25
3.2 Control Charts: Individuals.....	12	4.4.2 Double Sampling Plans	25
3.2.1 Attribute Control Charts.....	12	4.4.3 Individual Sampling Plan.....	25
3.2.2 Typical Applications.....	13	4.4.4 Sampling Scheme.....	25
3.2.3 Pros	13	4.5 Pros and Cons	25
3.2.4 Cons	13	5.0 Appendices: Technical Details and Examples ..	27
3.3 Moving Range Control Charts.....	13	5.1 Run Charts.....	27
3.3.1 Typical Applications.....	13	5.1.1 Technical Details.....	27
3.3.2 Pros	14	5.1.2 Example.....	27
3.3.3 Cons	14	5.2 Control Charts: Individuals.....	29
3.4 Average and Variability Charts	14	5.2.1 Technical Details.....	29
3.4.1 Typical Applications.....	14	5.2.2 Example.....	30
3.4.2 Pros	14	5.3 Moving Range Control Charts.....	33
3.4.3 Cons	15	5.3.1 Technical Details.....	33
3.5 Histograms.....	15	5.3.2 Example.....	34
3.5.1 Typical Application	15	5.4 Average and Variability Charts	37
3.5.2 Pros	15	5.4.1 Technical Details.....	37
3.5.3 Cons	16	5.4.2 Example.....	39
3.5.4 Distributions – Interpretation of Histograms	16	5.5 Histograms.....	47
3.5.5 Hints for Use.....	18	5.5.1 Example Case Worked in Parallel with Theory/Principles.....	47
3.6 Process Capability (C_{pk} , P_{pk}).....	18	5.6 C_{pk} , P_{pk} for Process Capability.....	48
3.6.1 Assumptions	18	5.6.1 General Procedure for Finding C_{pk} and P_{pk}	48
3.6.2 Typical Application	19	5.6.2 Example C_{pk} for a Single Group	49
3.6.3 Pros	20	5.6.3 C_{pk} for Several Groups.....	50
3.6.4 Cons	20	5.6.4 Example 3, P_{pk} for Several Groups	52
3.7 Exponentially Weighted Moving Average Charts	20	5.7 Exponentially Weighted Moving Area Charts (EWMA)	52
3.7.1 Typical Applications.....	21	5.7.1 Technical Details.....	52
3.7.2 Pros	21	5.7.2 Calculation Example	53
3.7.3 Cons	21	5.7.3 Control Limits	53
3.8 CuSum Charts	22	5.7.4 Example.....	54
3.8.1 Process Features Suitable for This Type Method.....	22	5.7.4.1 Interpretation of Example	54
3.8.2 Typical Applications.....	22	5.8 CuSum Charts	55
3.8.3 Pros	22	5.8.1 Example Calculation	56
3.8.4 Cons	23	5.8.2 Details of Principles	57
3.9 Examples of Efficient Mixture of the Statistical Toolbox	23	5.8.3 Interpretations Worked in Parallel with Theory/Principles.....	57

5.8.4	Implementation of CuSum Charts	59
5.8.5	Example: Gradual Trend	59
5.8.6	Preventative Action Before Failure Occurrence.....	60
5.8.7	Example: For Process Optimization.....	60

5.9	Sampling	61
5.9.1	Example.....	61
6.0	References	63
7.0	Additional Reading	64

FIGURES AND TABLES INDEX

Figure 2.0-1	Example of a High Capability (Low Variability) Process Capability Histogram.....	2
Figure 2.0-2	Example of a Low Capability (High Variability) Process Capability Histogram.....	3
Figure 2.0-3	Examples of a Stable Process (Statistically In Control)	4
Figure 2.0-4	Examples of an Unstable Process (Statistically Out Of Control).....	4
Figure 2.0-5	Examples of Trends (Points Beyond Control Limits).....	6
Figure 2.0-6	Examples of Trends (Points within the control limits).....	6
Table 3.0.1-1	Suggestions and Proposals on When to Use Statistical Tools	9
Table 3.0.1-2	Areas of Potential Implementation.....	10
Figure 3.1-1	Run Chart	11
Figure 3.2-1	Individual Control Chart	12
Figure 3.3-1	Moving Range Control Chart.....	13
Figure 3.4-1	Average and Range Chart.....	14
Figure 3.5-1	Example of a typical Histogram Showing Data Location In Relation To Specification Limits.....	15
Figure 3.5.4-1	Normal Distribution	16
Figure 3.5.4-2	Histogram of a Normal Distribution ...	17
Figure 3.5.4-3	Bimodal Distribution	17
Figure 3.5.4-4	Left Skewed Distribution	18
Table 3.6.1-1	Significance of Cp.....	19
Table 3.6.2-1	Interpretation of Cp Regarding Limits Taken.....	20
Figure 3.7-1	Data Plot Compared to EWMA Chart....	21
Figure 3.8-1	Run Plot Compared to CuSum Chart of the Same Data	22
Figure 3.9-1	Example of a Tool Bar for Statistical Control of a Process	23
Table 5.1.2-1	Lot Data by Manufacture date.....	27
Figure 5.1.2-1	Run Chart (Plot of Lot Data).....	28
Figure 5.1.2-2	Run Chart	28
Table 5.2.2-1	First 15 data points/ lots.....	30
Figure 5.2.2-1	Run Chart (Plot of Lot Data).....	30
Figure 5.2.2-2	Run Chart	31
Table 5.2.2-2	Moving Range	32
Figure 5.2.2-3	Run Chart (UCL and LCL shown).....	33
Table 5.3.2-1	Lot Data in Time Order.....	34
Table 5.3.2-2	Lot Data with Moving Range	35
Figure 5.3.2-1	MR Chart.....	35
Figure 5.3.2-2	Moving Range Chart (Upper & Lower Limits Shown)	36
Table 5.4.2-1	Sample Data Collection Table	40

Table 5.4.2-2	Sample Average Data Collection Table	40	Table 5.6.2-1	Example of C_{pk} for a Single Group	49
Figure 5.4.2-1	Sample \bar{X} Chart.....	41	Table 5.6.2-2	Example of 95% Confidence Interval for C_{pk}	50
Table 5.4.2-3	Sample Data Range Collection Table..	41	Table 5.6.3-1	C_{pk} for Several Groups.....	51
Figure 5.4.2-2	Sample Range Chart	42	Table 5.6.3-2	For d_2	51
Table 5.4.2-4	Sample Data Average and Range Collection Table.....	42	Table 5.7.2-1	Step-Change Example (No process noise)	53
Figure 5.4.2-3	Sample Average \bar{X} Chart.....	43	Figure 5.7.4-1	Sample Random Distribution Plots	54
Figure 5.4.2-4	Sample Range \bar{X} Chart.....	43	Figure 5.7.4.1-1	EWMA Plot (UCL & LCL)	55
Figure 5.4.2-5	Sample Grand Range \bar{X} Chart	44	Figure 5.8.1-1	Example Calculation	56
Figure 5.4.2-6	Sample \bar{X} Chart of Average Range on the Range.....	44	Figure 5.8.1-2	X-bar Chart vs. CuSum Chart.....	56
Figure 5.4.2-7	Sample UCL and the LCL on the Range Chart.....	45	Figure 5.8.1-3	CuSum Chart with V-mask.....	57
Figure 5.4.2-8	Sample UCL and the LCL on the Average Chart.....	46	Figure 5.8.3-1	CuSum Chart with Values Around 100 ...	58
Table 5.4.2-5	Sample Average and Range Data Table	46	Figure. 5.8.3-2	CuSum Chart with a Side Move at Event 50	58
Figure 5.4.2-9	Sample Average and Range \bar{X} Chart ...	46	Figure. 5.8.3-3	CuSum Chart with an Upward Shift in Mean Between Points 23 to 50	58
Figure 5.4.2-10	Sample Average and Range \bar{X} Chart (UCL & LCL)	47	Figure 5.8.3-4	Example of a CuSum Chart	59
Figure 5.5.1-1	Sample Average and Range \bar{X} Chart (UCL & LCL)	47	Figure 5.8.5-1	Gradual Trend	60
Figure 5.5.1-2	Sample Statistical Distribution of Results	48	Figure 5.8.7-1	For process optimization	60
			Table 5.9.1-1	Characteristics of Example Test Plan...	62
			Figure 5.9.1-1	OC Chart Curve	62

1.0 Introduction

As manufacturers seek to improve the quality of their goods, statistical methods have been rediscovered as vital tools for successful development and manufacturing. Industries like automotive, electronics, and consumer products grow and change partly as a result of adopting statistical methods.

The pharmaceutical and biopharmaceutical industry increasingly recognizes the importance of statistical methods to consistently create products that conform to predetermined quality characteristics. Statistical methods provide objective evidence in meeting this goal and are fundamental for understanding the process, which enables further improvement and development.

Industry and regulatory bodies are working together to provide guidance and frameworks on the use of statistical methods. The International Conference on Harmonisation, International Standards Organization and European Union have provided guidance on the use of statistical methods.

In light of the increased focus on this topic, this PDA Task Force recognized the need to provide guidance to help companies identify and use statistical methods. The primary objective of this Task Force was to convey the appropriate use of statistical methods at a level most can understand.

1.1 Purpose and Scope

The purpose of this document is to present relevant and easy-to-use statistical process control (SPC) methods that are applicable to the pharmaceutical/biopharmaceutical industry. Advanced statistical methods, such as multivariate models and Design of Experiment (DOE) will not be considered. An overview of acceptance sampling is also included in Section 4.1.

1.2 Implementation to Support Decision Making

Statistical methods are intended to improve the quality of decision-making. They are simply a means to a result. If the manufacturer does not first understand *why* it is utilizing a statistical method, problems such as failing to detect important signals or over-detecting unimportant normal variation can occur. Caution should be exercised to first establish the question to be answered and then the statistical method to aid in answering the question.

The statistical methods may be used in an ongoing program to analyze collected data. Timely evaluation of data allows the prompt detection of undesired process variation, which facilitates process understanding and may support responses to control variability.

To best aid the end-user, each statistical method is described in the following format:

- Description
- Typical Applications
- Pros and Cons
- Technical Details and Examples (see appendices)

The guidance contained in this document is not intended to establish mandatory standards for using statistical methods across a product's lifecycle.