Proposed Regulation/Guidance Document:

Ph. Eur. Commission general chapter on Multivariate Statistical Process Control (MSPC) (5.28)

Comments from: International Society for Pharmaceutical Engineering (ISPE)

GENERAL COMMENTS ON THE DOCUMENT
ISPE thanks EDQM for providing this document in the European Pharmacopoeia and requesting comments from Industry. This is an important guidance to industry stakeholders with basic statistical skills and experience with statistical process control. The theoretical background makes it useful for statisticians as well. If industry stakeholders without statistical knowledge also are intended readers, we suggest adding illustrations and examples.
Sub-indexes are somewhat difficult to read. Enhanced visualization of these are recommended.

Specific Comments on the Text

ISPE indicates text proposed for deletion with ~~strikethrough~~ and text proposed for addition with **bold and underlining**.

Section or subsection	Current Text	Proposed Change	Rationale or Comment
Introduction line 2	In pharmaceutical manufacturing, process control is essential to develop new processes, improve existing processes and ensure consistent processes that yield products with satisfactory quality.	In pharmaceutical manufacturing, process control is essential to develop new processes, improve **the consistency of processes to yield products that meet their specifications and quality attributes**.	To add clarity
Introduction line 5	It is implemented by means of control charts.	**Sample data are graphed** by means of control charts.	To add clarity
Introduction Middle of page	Multivariate statistical process control (MSPC) can be defined as the application of multivariate statistical techniques to increase the quality and the productivity of a process.	Multivariate statistical process control (MSPC) can be defined as the application of multivariate statistical techniques **to improve** the quality and the productivity of a process.	To add clarity
Introduction	MSPC can be used to support many different activities in pharmaceutical manufacturing such as: – process development; – production; – process optimisation, lifecycle management; – troubleshooting, root cause analysis; – process understanding.	MSPC can be used to support many different activities in pharmaceutical manufacturing such as: – process development; – **monitoring regular production operations;** – process optimisation, lifecycle management; – troubleshooting, root cause analysis; – **increase** process understanding.	Additional detail
Section 2.1 Line 1	Univariate SPC uses measurements of a single variable at regular time intervals.	Univariate SPC uses measurements of a single variable at specified time intervals. **These intervals are in a time sequence and**	Data does not have to be evenly spaced, for example if

Section or subsection	Current Text	Proposed Change	Rationale or Comment
		can be equidistant. If the measurements are not performed at time points with equal distance the actual date should be used instead of just observation number.	professional statistical software is used.
Section 2.2	Averages of sufficiently large subgroups likely follow a normal distribution, which characterizes their natural variability.	Averages of sufficiently large subgroups likely follow a normal distribution, which characterises their natural variability. **It should be checked whether data in a specific setup actually follow a normal distribution – particularly when a process is developed and significantly changed. This can be done by drawing a histogram (should be bell-shaped) and a qq-plot to compare with a normal distribution (should be a straight line).**	Ensure correct analysis of data. If data significantly departs from a normal distribution, different charts and calculations should be performed
Section 2.2 Beginning	Control charts are constructed by collecting a set of samples of *n* consecutive measurements (rational subgroups).	**There are several ways to quantify statistical control of data by control charts. It is important to choose the one best suited for the data as well as the criticality of the values (e.g. the process step or equipment) to end product when the process is performed. A control chart may be constructed by collecting a set of samples of n consecutive measurements (rational subgroups).**	Additional detail