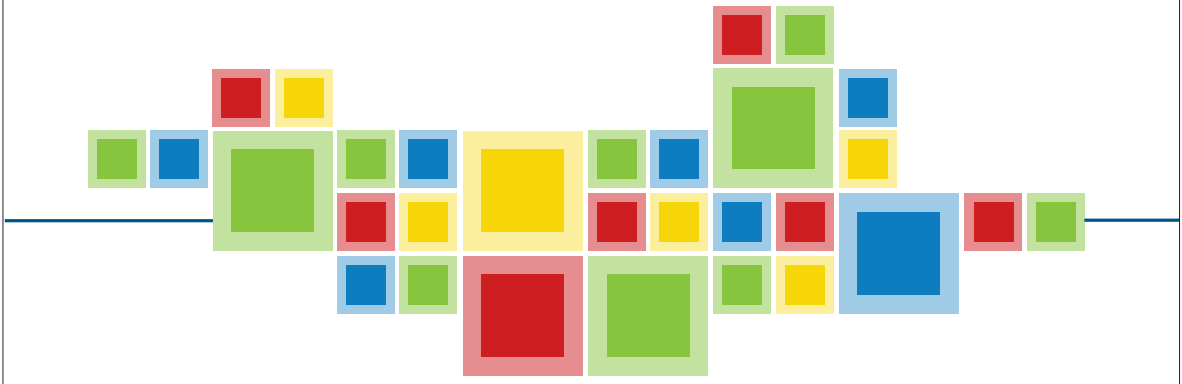
Trend and Out-of-Trend Analysis for Pharmaceutical Quality and Manufacturing Using Minitab



Lynn Torbeck

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Trend and Out-of-Trend Analysis

For Pharmaceucial and Quality Manufacturing Using Minitab®

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Bethesda, MD, USA

DHI Publishing, LLC
River Grove, IL, USA

10 9 8 7 6 5 4 3 2 1

ISBN: 1-933722-90-8

PDA®
Parenteral Drug Association

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PDA Global Headquarters
Bethesda Towers, Suite 150
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Bethesda, MD 20814
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001-301-986-0293

Davis Healthcare International Publishing, LLC
2636 West Street
River Grove
IL 60171
United States
www.DHIBooks.com

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PREFACE

This book is for pharmaceutical professionals working in product discovery, development, manufacturing, quality assurance and quality control.

The need for a trend analysis book is justified by the continued interest in presentations and discussions both public and private. Philosophies and definitions have been proposed and presented, but there is not yet a widely accepted clearly defined approach by the industry that lends itself to consistent interpretation and uniform application.

Like other topics, (i.e., assay and process validation), trend analysis is good business and good science.

Trend analysis should not be done only to meet a minimum regulatory expectation but to establish base line reference trends for key processes, products and business variables. These reference trends are then used to identify out-of-out trend data and events and initiate root cause investigations.

That the FDA is concerned about current and future industry practice for trending is obvious and can be measured by the volume of investigator's observations. See Chapter 9.

It is hoped that this book will contribute to an industry/regulatory dialog and consensus that will serve and benefit all stakeholders, especially the group for whom we serve, the patients.

LDT April 30, 2015

INTRODUCTION

The essential message of this book can be illustrated with an everyday example. My wife Joyce and I have lived in a condo for the last 15 years or so. It has an assigned parking space. Love it in the winter time. Next to our space is a neighbor's space. For as long as I can remember, he has always parked straight in and parallel to the painted strips. Unlike me, where every attempt is a unique heart pounding event.

He had never varied, was always perfectly parallel, until one day he wasn't. I was startled to say the least. This had never happened before. Now of course, this is not a big deal in the grand scheme of life, but it did raise questions in my mind. Was he ill and someone else parked the car? Was he in a big hurry because of an emergency and he didn't take the usual time to straighten out?

Why was I surprised? Because it was a change from his typical expected and established pattern. He departed from his historical baseline. Something changed for that parking event and my curiosity was raised. What changed to be out of the expected and established norm? I didn't ask, but wanted to.

Another classic is the mother with eyes in the back of her head so to speak. She knows her house and her children so well that the smallest noise or object out of place sets off alarm bells in her head. Something is atypical or out-of-typical (OOT), from the expected norm. "Get out of the candy jar."

Let's now define an established expected pattern of data or events as the trend. Then my neighbor's established trend that I expect to see was that he was always perfectly parallel to the strips. His one nonparallel event was out of my expectation of his established trend.

Thus in this book, a trend is a series of events or data collected, generally over time, that has an established and expected pattern that repeats. It is the typical pattern or baseline. The trend can be observed, historical, or it can be based on theoretical models. Any departure from the trend is then an unexpected OOT event. It is atypical and begs for investigation.

Analysis can be as simple as a line plot over time to identify the trend, or as complicated as necessary to gain understanding. If a trend can't be established then an out-of-trend event or data doesn't exist either. To summarize:

- Trend is the data or events we expect to see.
- Out-of-Trend is the events or data we did not expect to see.

Chapter 7 presents trend and OOT definitions with discussions and example graphics. Readers with some statistical background can proceed to that chapter.

Chapters 1–6 present a basic introduction to data and simple graphical analysis for those new to the topic or who wish a brief review.

Chapter 8 proposes terminology to clarify the use of the word "control" in the context of OOT, out-of-specification (OOS), and out-of-statistical control (OOSC).

Chapter 9 reproduces outtakes from Food and Drug Administration (FDA) warning letters, plant audits and investigations for trend and OOT. These are very helpful in understanding the scope of the topic from the agency's viewpoint.

Chapter 10 details the references in the text material.

Finally, there are two appendices.

Appendix A provides a brief overview of statistical control charts as a place to start for more in-depth self study.

Appendix B presents an example of setting alert limits for trend data with statistical tolerance intervals. An example table is included for six values of population percentages and for 99% confidence. The table is for two-sided intervals when the standard deviation is unknown and estimated from the data. This is the most common situation, but the references lead to other conditions.