**This book is dedicated to my wife, Patricia,
and my parents, Oswald and Hannelore**

PREFACE

As a former supervisor and mentor to Dr. Krause, I discovered he has great passion and knowledge about analytical test method validation. As such, I have encouraged him to share his knowledge through the writing of articles, working with the Parenteral Drug Association and the authoring of this book. He has been able to succinctly provide approaches about method validation in this book that will ensure both effective monitoring of your process and products and world-wide regulatory compliance.

This book contains many new practical tips, tools, and case studies that will assist validation scientists and management in making good risk-based decisions during planning, execution and post-implementation changes for all projects. This book is therefore centered on what "sufficient performance" and "suitable for use" really mean for analytical methods. You will learn what risk really means when it comes to analytical methods. You will also learn how we can measure risk and how to control this risk using well-designed validation studies. Currently, regulatory guidelines provide only basic guidance for analytical method validation. Dr. Krause's work builds on these basic regulatory guidance documents, and provides several detailed validation practices, discussions, and case studies on the best-possible strategies to assist readers in making good decisions.

After reading this book, I felt a bright light shine on many of the items I once considered hidden in a "black box". I encourage development and validation scientists, as well as quality, and regulatory managers to read this thought-provoking book to better understand how to effectively monitor your production

processes and quality of your products. It will also allow you to prepare quicker, and more robust regulatory filings.

I hope you enjoy the work in this book as much as I have.

Martin Van Trieste
Chairman of PDA's Scientific Advisory Board,
VP Quality, Commercial Operations, Amgen, Inc.

INTRODUCTION

Regulatory requirements for validation exist because we need validations to ensure we can produce a quality product. This book offers a refined way of looking at why analytical method validation is an important task that should be done well, not only because it is a requirement, but also to ensure continuous process and product quality. Validation is all about understanding and controlling risk. We need validation to limit the use of unsuitable material, equipment, facilities, processes, methods, shipping material, and personnel not supporting the production of a quality product. Validation is a regulatory requirement because the producer/seller must provide clear evidence that the risk to consumers (patients) and to the manufacturing firm itself is acceptable. We need to start connecting data and processes if we want to come closer to the goal of improved product quality and of running leaner manufacturing processes.

Many new practical tips, tools, and case studies are provided here. They will help in the making of good-risk based decisions during planning, execution, and post-implementation changes. Once we understand the relationship between the patient and firm when looking at risks, we will be in a better position to make good decisions. To understand and control the likely implications for the patient will help us in getting approval for regulatory submissions and will likely avoid audit observations. In contrast, poor validation cuts away profits for the firm. This book will therefore evaluate in detail the risks to both the patient and firm and will try to balance these by directing the focus towards risk-based strategies and acceptance criteria.

Why did I write this book?

Several reasons provided incentives. One is the lack of tools available for validation scientists to ensure the suitability of a validated test method long after its implementation. I am not sure, even now, if most validation scientists would actually consider that ensuring a validation continuum long after the initial validation was completed as an important part of validation. Although it is currently understood that the calibration of many measuring devices will not last forever and the calibration status does, therefore, expire, formal guidance on how to handle test methods does not yet exist.

Another reason for writing this book is the fact that there is still a lack of practical guidance on what to do in the so-called "grey zone", when validation results are not black and white and do not clearly indicate a valid and suitable method. What is the difference between valid and suitable? An analytical method may be valid because we passed our formal validation protocol acceptance criteria. However, this method may not be suitable if acceptance criteria are set too wide and the validation results indicate insufficient accuracy and precision. This book is therefore centered around what "sufficient performance" and "suitable for use" really mean for analytical methods. We need to understand the significance of both before we can perform meaningful validation studies. In addition, we need to understand what risks really mean when it comes to analytical methods? How can we measure risk and how can we control this risk using well designed validation studies and protocol acceptance criteria?

Currently, regulatory guidelines provide only basic guidance for analytical method validation. Several good validation practices are insufficiently covered. Detailed validation practices, discussions, and case studies on best-possible strategies will provide tools to aid good decision-making. This book provides illustrations on how to perform analytical method validation, extensions, transfers, and how to maintain a continuous state of validity and suitability to ensure compliance and process sustainability. Among many other tips, the following major deficiencies in current regulatory guidelines will be discussed and practical solutions offered.

(1) How to set acceptance criteria that directly impact product specifications, predict release-to-reject ratios, and thus impact on patient and firm.

(2) How to build risk-based validation strategies for analytical methods with respect to the recently published guidance documents.

(3) Which test method characteristics to compare and how to compare when transferring methods, extending their validation status, or replacing approved test methods.

(4) How to deal with failed validations and validation extensions.

The scope of this book is limited to analytical method validation (AMV) and post-AMV studies. Only those activities are covered in great detail. Related qualification and validation studies such as analytical instrument qualification (AIQ) and software validation (SV) are not extensively discussed. However, these activities should be completed before AMV. As the intention of this book is to focus on the dependency of pre-validation results (for example, AIQ testing) to AMV and beyond, some critical and overlapping AIQ and analytical method development (AMD) studies are discussed. The method lifecycle starts with analytical method selection and development and eventually ends with its retirement and redundancy. The sequence of chapters and the information provided in this book is organized according to the method lifecycle process starting with the initial selection and finishing with post-validation activities. Instead of using independent case studies for each chapter, I have tried to use common case studies and data sets whenever possible. This should help in understanding that processes are connected, and many activities and decisions are centered around common principles. My personal experience with regulatory audits and worldwide regulatory submissions are an integral part of this book. Whenever possible I focus on regulatory concerns and how evidence of test method suitability can be most practically and timely delivered.

I have been publishing articles around this topic for several years. Each time I have written a new article and reviewed my previous work, I have found more connections and often better ways to find more convincing evidence (validation). At some point, we all have to complete projects knowing that we could find ways to make them even better. As when buying a new car or new computer, we all know that a better model is already in the works. So this is it.

I hope you will find this book informative and helpful.

Stephan O. Krause, PhD
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