PREFACE

In our cost conscious world, most people believe that it is still essential to provide patients with medicines of consistent, reproducible quality that meet their needs and expectations. To achieve this requires good teams of people working in a focused, systematic, disciplined and cost effective manner including continually striving to improve and ensure that quality is built into products throughout their lifecycle. However, even with the best of systems and people, one of the biggest challenges to achieving consistent quality and compliance is the variation that exists in all of the processes employed in the research, development, manufacture and distribution of pharmaceuticals. Since variation exists in all processes, the understanding of and the ability to reduce and control such variation appropriately are critical success factors as has been widely known and understood by the Industry and its Regulators for many years whether striving for compliance with Regulatory Requirements including Good Manufacturing Practice or efficiency, effectiveness and reduced costs.

However, the concept of understanding and managing variability has taken on a new and added importance following the introduction of the initiative "*GMPs for the Twenty-first Century*" and related projects by the US FDA and the development of the three guidelines in ICH, Q8 Pharmaceutical Development, Q9 Quality Risk Management and Q10 Quality Systems. These initiatives place increased emphasis on understanding processes and products and hence consistently controlling variability so that risk of significant threat to product and therefore patients are minimized.

Consequently I believe the timing of the publication of this book is excellent and its content highly topical and relevant addressing as it does, a wide variety of the major sources of variability which impact on the development, manufacture and supply of pharmaceuticals. The book provides a fine blend of chapters on areas where variability is traditionally recognized such as Manufacturing, Quality Control Laboratories, Supply Chain Management and People with some on other less frequently considered

topics such as Non-Manufacturing Functions and the GMP Codes around the world where as the Industry becomes more global, a better understanding of the variability in the Regulations and their potential impact on key activities is increasingly essential.

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INTRODUCTION

Variability is the tendency for something, an event, a process, a product, and/or a person to deviate from an established convention, state or value. The concept of controlling variability may, at first, seem counterintuitive or impossible. However, if one directly confronts variability by analyzing it in a multi-staged approach, control may actually become a viable management option. Before one can begin to determine ways to control variability, one must first seek to recognize and understand the elements of variability themselves, after which the true management of variability can surface. Recognition can be thought of to be influenced by the simple ability to detect, which is, in turn influenced by one's experience and training. Understanding variability, once recognized, is to a certain extent proportional to one's level of applied knowledge. The concept of managing variability, once understood, is affected by one's ability to measure and guide change and drive improvement. It is simply not possible to manage variability without first recognizing and understanding the root sources and resulting effects. This book is about confronting variability and should be of interest to professionals across functional boundaries in a pharmaceutical setting. Variability is more than just the 'noise in the system'. It represents an insidious threat to companies, ranging from the reliability of their product lines to the strength of their financial bottom-lines. The understanding of likely sources of variability, therefore, can provide a solid framework for risk assessment and an estimation of the impact these risks pose. This book will specifically focus on examining those elements of variability related to people, processes, manufacturing systems, non-manufacturing systems, quality systems, laboratory systems, supply chains, and GMP codes related to the pharmaceutical industry.

Generally speaking, variability has many global causes: climactic, demographic, political, economic and social. Not all countries and not all regions of countries are prepared to respond to and adapt to these global sources of instability. Variability is incessantly at work within nature and within the many fields of science. Species may mutate or new species may be discovered, leaving our taxonomists to try and make sense of it all. Drug research, drug manufacturing and drug testing processes are rife with variability. For example, patient populations that are treated in a clinical trial may

not have the same medical profile that physicians ultimately treat once a drug is approved. Variability is introduced simply with the passage of time, or if related processes are not adjusted. For example, a manufacturing process that is changed to include a nitrogen blanket to prevent oxidation of the active pharmaceutical ingredient should result in corresponding changes in the charging of vessels (e.g., apply less overage) and, possibly, in the product specifications themselves based on a statistical review of historical process performance. Changing a manufacturing process without regard to possible changes in corresponding methods and product specifications could lead to unexpected and thus unmanageable variability. Using another example, the relative variability in a process designed to coat a medical device with a drug can be the difference between a patient receiving an efficacious dose or not of a life-saving medication. The incremental variability that can occur in ethylene oxide sterilization vessels, for example, in the sustained delivery of all predefined physical parameters, can affect the validated state of a terminal sterilization process. In recognition of this phenomenon, companies typically re-validate their sterilization vessels each year. This represents a case in which the recognition of the phenomenon of variability in sterilization vessels and the understanding of the effect that minute changes in sterilization cycles can have on calculated lethality of product loads has resulted in the industry effectively taking action to institute a change that effectively manages the sources of this known manufacturing variability.

Variability is all around us. We resent the imposition of variability in our daily affairs as any person accustomed to the inefficient drag of shoveling snow or maneuvering one's car along a slippery or jammed road can attest. Climactic changes can thus have a profoundly adverse influence on ourselves and on the companies we work for. Since we started work on this book in 2004, there has been a devastating tsunami in Southeast Asia and a catastrophic hurricane (Katrina) hitting the United States. Political instability in much of the world surrounding the decades-old ideological struggle underway between the West and parts of the Islamic world has resulted in outright war and violent acts in the name of fiercely held religious or political belief systems. For example, members of the pharmaceutical community were among the victims of the attacks perpetrated on 'September 11th'. Both climactic and political change can have a major (and sometimes negative) impact on the relative stability of systems of any kind.

We also personally exhibit variability in our daily lives much as we hope this was not the case. For example, how often do we deviate from a standard practice when we are ill or debilitated? That has an effect on everyone around us to a certain degree. Variability tends to be intrinsic and random within both biological and human-controlled systems. The degree that we can adequately manage variability depends on our ability to recognize, understand and subsequently control those things that tend to change. A change, if unrecognized, non-understood or non-controlled, can have a deleterious impact on the state of control required in pharmaceutical manufacturing setting.

Variability related to people is driven by our genetic make-up. We are literally designed to be different and unique. These differences are accentuated by the cultures and traditions in which we are raised. Surmounting these differences in a regulated industrial setting is no easy or ordinary task. Depending on where you are and who you are speaking to, 'yes' may mean 'yes' or 'yes' may mean 'no'. Just ask any English-speaking GMP auditor who has circled the globe auditing companies where English is not the primary language. Understanding people through the prism of their background, and understanding what motivates people to perform in an expected manner is one critical way to begin to confront, understand and manage variability.

Variability within a Quality System is affected by all constituent quality system elements, and the myriad causes that contribute variability to each of these elements. Variability within the manufacturing arena spans personnel, production operations, facility elements, process controls, equipment design, calibration, maintenance and validation. Each element can contribute to the accumulated variability that may eventually become detectable and directly impact the final product we produce. For example, method variability can lead to the release of unsuitable product or rejection of acceptable product, thus affecting a firm's ability to make the right disposition decision and impacting supply chain management. The variability of a complicated purification scheme can cause an atypical fluctuation in a product's impurity profile with the potential to cause an unexpected adverse event. An unplanned or uncontrolled variation in the storage conditions of a temperature-sensitive product can bring about the use of an ineffective drug treatment. Variability within a Quality System can influence one of the obvious sources of variability, personnel. Well-trained people make fewer mistakes, which, in theory, should reduce variability.

Variability in the analytical laboratory involves personnel, method design and validation, equipment use, calibration, maintenance, analytical standards, and test samples. Each element can contribute to the accumulated variability that may eventually become detectable and impact the final test result and batch disposition decision. For example, variability in the preparation of an analytical reference standard may lead to the detection of an inaccurate drift in a product quality attribute that questions a material's ability to meet specifications at shelf life. This event may lead to a discussion as to whether a product recall is warranted. Variability of product sampling techniques, on the other hand, can lead to an analysis that does not truly represent the batch in question. This could result in the release of substandard material or the rejection of acceptable material, neither of which would constitute the right management decision.

Variability in Supply Chain management is experienced at all levels, from the manufacture of raw materials and components up to and including product distribution. For example, process yield variability can lead to low yields and the unavailability of critical components necessary to manufacture key drug products. A strike at a port in a foreign land could prevent a freight forwarding firm from

distributing finished goods to the intended destination in a timely manner. We need to consider both the proactive and reactive indicators of variability. Proactive indicators of variability include solicitation of customer feedback such as a customer satisfaction surveys or market analysis. Reactive indicators of variability include product complaints, adverse events and product recalls.

Variability experienced by regulatory authorities is affected by government funding, recruitment, scientific and technological progress, and the pace of change in industry. It can be safely said that capitalism, in its pure economic forces such as supply and demand and the forms it takes in the marketplace such as competing businesses and products, can be an important contributor of variability on bureaucratic institutions such as regulatory authorities, culturally disinclined to responding to change, and more accustomed to causing variability within the entities they regulate!

The key step towards effectively understanding variability is to recognize its centrality, the work that we are asked to perform, and the work environments from which we operate. The key step towards effectively managing variability is to understand why it must be measured (or how it can be measured) which can then result in controlling the systems and processes that we are responsible for. Variability is part and parcel of our genetic makeup, but it is the bane of heavily regulated work environments. We humans represent a tremendous array of variability. We richly tap that variability in free and open societies in the form of ideas, pursuits, and behavioral practices. We conversely calibrate or control that variability when free individuals work for private or publicly held institutions. Understanding our own failure tendencies and foibles helps us to understand how to better operate organizations composed of our fellow human beings.

We hope this book provides the reader with a new perspective on the meaning and relationship of variability on the work they perform and provides an insightful framework for the quality assessment of risk in the pharmaceutical industry.

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