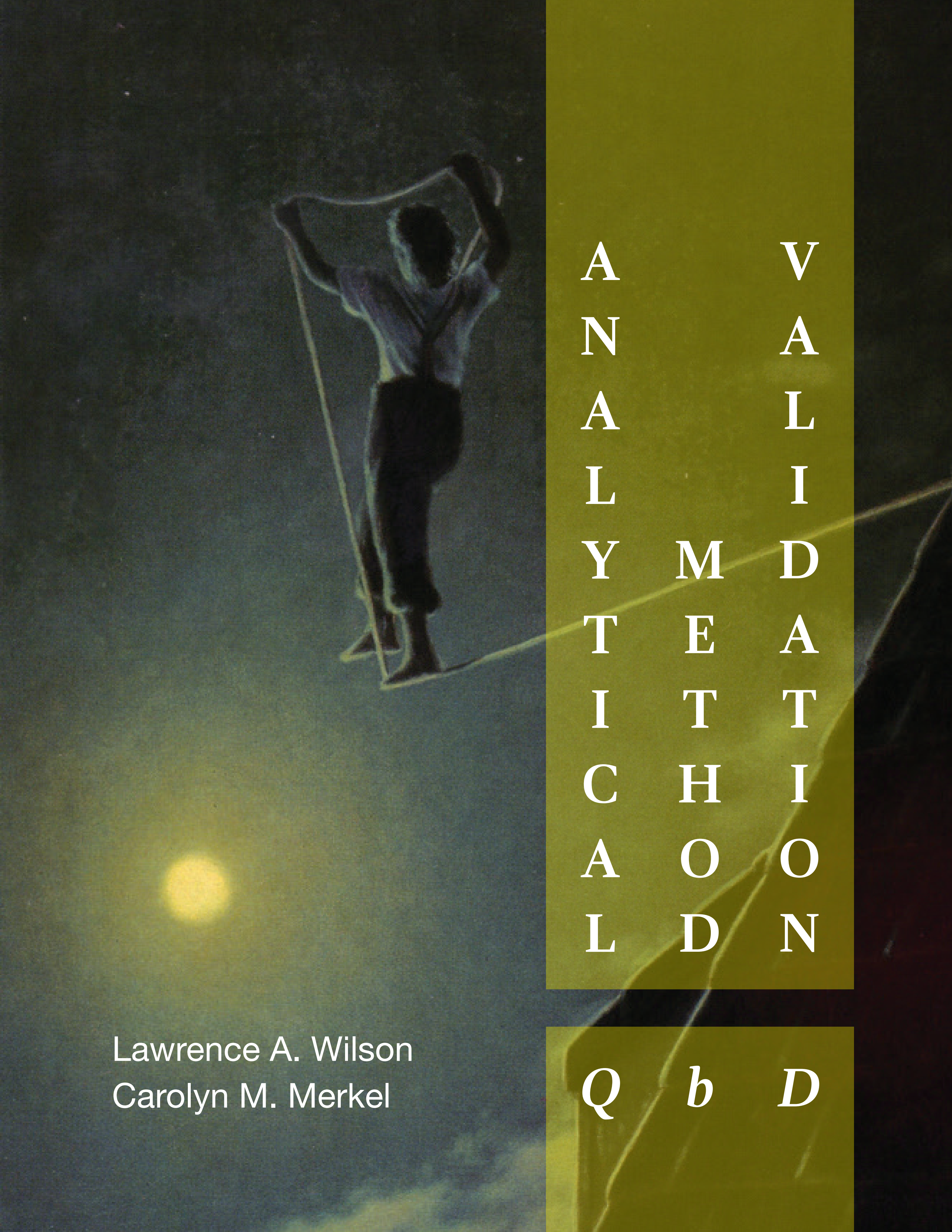


# Analytical Method Validation

## QbD


Lawrence A. Wilson
Carolyn M. Merkel

# about the authors

**LAWRENCE A. WILSON** is a Managing Partner of Mariner Analytical LLC. He received undergraduate degrees in Chemistry (BS) and Psychology (BA) from the State University of New York at Oswego, MS in Medicinal Chemistry from Stevens Institute of Technology (with Dr. Ajay K. Bose and Dr. M.S. Manhas), and MBA in Marketing and Management from Fairleigh Dickinson University (thesis: *Mathematical Tools for Decision Quality Enhancement*). He studied Applied Chemistry at the University of Texas at Arlington on the D.Sc. track and mentored doctoral candidates in a then-novel, work-study program in his research laboratory.

He has worked in diverse industries, including: fine chemical manufacturing, heavy industries [mining, building materials (cement, gypsum, roofing, glass), paper], flavors and fragrances, pharmaceuticals, pesticides, polymers (and more) at the laboratory bench, led global Teams, managed research and manufacturing facilities, contributed to multiple marketing applications for successful drugs, and advised on policy — in particular, organizational redesign to accelerate product development. Over the last two decades, he has consulted domestically and globally — chiefly within the pharmaceutical industry — at research, manufacturing/ packaging, and clinical trial sites, with a consistent focus on ensuring data integrity and data quality.

# about the authors

**CAROLYN M. MERKEL** is the Founding Partner of Mariner Analytical LLC. She earned her BS in Chemistry from Ramapo College of New Jersey; PhD at Columbia University (Inorganic Chemistry, thesis advisor Dr. Stephen J. Lippard), and an additional MS in Technology Management at New Jersey Institute of Technology. She was a Robert A. Welch Fellow at the University of Texas at Arlington (advisor Dr. Donald R. Martin).

In her business career, she focused on beverages, food, and nutritional products. After almost 20 years with global consumer product companies, she formed Mariner Analytical LLC. Mariner Analytical provides full-service technical support to a diverse roster of clients, ranging from start-ups to Fortune 50 companies. She consults domestically and internationally on projects ranging from chemical manufacturing and medical devices to dietary supplements and snack foods. She applies her passion for Quality — developed with rigorous training and excellent mentorship — to practice a multidisciplinary approach to problem-solving.

She is a Certified Food Scientist, and a member of Sigma Xi, the American Chemical Society, and the Institute of Food Technologists. She has numerous patents and publications, is an accomplished public speaker, and has received awards for teaching and research as well as community service.

She believes passionately in education, with active membership in the Ramapo College Alumni Association, currently serving as President, and is honored to be a member of the Ramapo College Board of Governors.

# about the book

## WHY BUY *THIS* BOOK?

The first chemistry book was *The Sceptical Chymist* by Sir Robert Boyle (1661), to whom was attributed: "*I should have* greater hope … if *men should make a greater distinction between that which* ***they know*** *and that which* ***they think they know***." His lament resonates with contemporary scientists' concerns for *data integrity*. This book contains essays on data integrity.

*Data integrity* is the most basic element of work in any scientific discipline. Nothing of lasting value in the hard sciences (physics, chemistry, biology, astronomy, *et al.*) lacks integrity in the data used to support the premises, the logical arguments proposed, and the conclusions drawn. ***The point of validation is, after all, to ensure that all results obtained and reported are true.***

The original premise of our book was to merge the global standard for pharmaceutical analytical methods for regulatory applications [**ICH Q2(R1**)] with contemporary thinking on ensuring data quality by thoroughly understanding a method and its intended application (**QbD**). During a preproduction meeting, an incisive question led to expanding the scope of the original five chapters: "*Can this be applied to fields other than pharmaceuticals*?" The answer was: Yes.

Three chapters were added to explore the applications of ***Quality by Design*** theory to real world problems that are bound not only by regulations, but by business constraints, professional ethics, time, resources, and technology. They may serve as case studies for classes of advanced students.

The scientific approach is rigorous, drawing on, and integrating, classical wet and modern instrumental analytical chemistry knowledge. The reasoning is detailed and well-documented. Examples are carefully explained. Two are based on historical events. The other is a problem that is not yet fully resolved despite its importance and significant risks to human health globally.

The tone throughout is conversational. It is intended to involve students — and any reader who has a vested interest in data integrity, which includes the global scientific communities from academia, industry, and government, and producers and consumers of quantitative measurements and the goods and services obtained by their use.

The objective is to impart an intuitive understanding of method validation: planning, execution, and documentation, with examples of practices and problems, and with practical strategies for addressing both.

A special feature is the inclusion of "Hints" — brief comments offering experience-based advice acquired while developing, validating, reviewing, and auditing analytical methods (and data) in a variety of industries and countries.

what you get

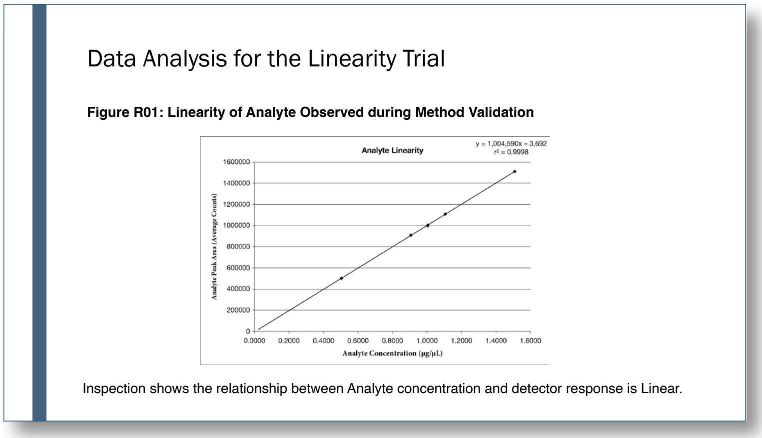
# CONTENTS



# SUPPORT MATERIALS

*Available for instructors at www.wessexlearning.com:*

- **Teaching Guide** *(for each chapter)*
- **PowerPoint** files: each set covers the main topics discussed in each chapter; includes reproductions of many of the figures and tables found in the text



# sample pages

**statistical symbols and abbreviations** — meaning of the symbols and abbreviations used throughout the textbook



### Statistical Symbols and Abbreviations

**μ**: Mean of a *population* – often referred to as the "true mean".

**$\bar{x}$**: Average of a *sample* – often referred to as the "sample mean".

**σ**: Standard deviation of a *population*.

**s**: Standard deviation of a *sample*.

**$\sigma^2$**: Variance of a *population*.

**$s^2$**: Variance of a *sample*.

**r**: correlation coefficient

**$r^2$**: coefficient of variation

**RSD**: Relative Standard Deviation

**df**: degrees of freedom

**t**: Student's *t*-statistic; used in two ways:

$t_{calculated}$: t-statistic calculated from sample data

$t_{crit}$: critical (minimum) value of the calculated t-statistic to demonstrate statistical significance

**z**: a dimensionless number allowing simple comparisons between measurements on samples presumably drawn from the same population. See z-test.

**$x_i$**: a single independent variable value

**$y_i$**: a single dependent variable value

**n**: the number of elements in a data set used in a statistical calculation

**p**: Probability value (**p** = 1 – α)

**α**: Significance level, below which a calculated inferential statistic is not significant (α = 1 – p) … in tables of distributions rather than **p**.

…tistics

… frequency dispersion of data along an axis. Distributions may be **continuous** or **dis-** …y weight yields a **continuous** distribution of prices. Letter mail priced by weight yields a …on of prices. {"Stair-step": One ounce = $1, two ounces = $2, …})

… types of distributions. Those most commonly encountered are: binomial, normal, log …ric, Poisson, t, F, Chi Square ($\chi^2$), and Weibull; there are others as well.



**Variance**

$$\sum_{i=1}^{i=n} (\bar{x} - x_i)^2/n$$

{Subtract each data point from the sample average (the *deviation*).}
{Square each deviation and sum the deviations squared.}
{Divide by the number of data points.}

**Standard Deviation** (aka Root-Mean-Square (RMS))

$$\sqrt{(\sum_{i=1}^{i=n} (\bar{x} - x_i)^2/n)}$$

{Subtract each data point from the sample average (the *deviation*).}
{Square each deviation and sum the deviations squared.}
{Divide by the number of data points.}
{Take the square root of the sum of the deviations squared (the Variance).}

**Relative Standard Deviation**

$$\%RSD = s / \bar{x} \times 100$$

{Divide the sample standard deviation by the sample average and multiply by 100.}

**Pooled Standard Deviation**

$$Sx_1x_2 = \sqrt{\frac{(n_1-1)\times s_1^2 + (n_2-1)\times s_2^2}{n_1 + n_2}}$$

{Multiply each sample standard deviation by **n-1** and add them.}
{Divide by the sum of the **n**s.}
{Take the square root of the result.}

### Inferential Statistics

**Correlation Coefficient**

$$r = \frac{\sum_{n=1}^{n}(x_i - \bar{x})(y_i - \bar{y})}{\sum_{n=1}^{n}(x_i - \bar{x})\ \sum_{n=1}^{n}(y_i - \bar{y})}$$

{Calculate the sum of the differences between the individual x-values and the average of the x-values multiplied by the difference between the corresponding y-values and the average of the y-values.} {"Sum of the x-residuals times the y-residuals."}

**equations** — equations that might be included in the ***Calculations*** section of a Method Validation Protocol or Report

# sample pages



**Inferential Statistics** draw conclusions/inferences or are used to make predictions/forecasts from sample data — usually about the population from which the sample is drawn. They include: regression analysis, correlation, confidence intervals, and estimates of the true population mean based on sample data.

**Hypothesis tests** are a subset of inferential statistics that use sample data to compare to the expected behavior of populations. They are applied to descriptive statistics, and are frequently used to determine whether a sample result is likely to belong to a specific population, or that a prediction or forecast is likely correct. Hypothesis tests include t-tests, z-tests, and ANOVA.

## Glossary

**Validation Parameters** (ICH Q2(R1))

**Selectivity/Specificity:** The ability to assess the analyte in the presence of components which may be expected to be present. Typically this might include impurities, degradants, matrix, etc. The analyst must identify all other components that may be present in the sample matrix, and then clearly demonstrate that the other components do not interfere with the analyte analysis.

**Accuracy:** The closeness of agreement between the concentration of analyte found and the verified reference standard value, or a conventionally agreed to true value.

**Precision:** The closeness of agreement of experimental values to each other. Note that values may be precise (agree closely with one another) but not accurate (agree with the true value).

**Linearity:** The linearity of an analytical procedure is its ability (within a given range) to obtain test results which are directly proportional to the concentration (amount) of analyte in the sample.

**Range:** The lowest to highest concentration of analyte that can be measured using the method.

**Limit of Detection (LOD):** The lowest concentration of analyte that can be reliably detected using the method.

**Limit of Quantitation (LOQ):** The lowest concentration of analyte that can be reliably quantitated using the method.

**Robustness:** The ability of a method to remain unaffected by small changes.

**glossary** — located in Chapter 5; lists terms and phrases used throughout the textbook



n of Intermediate Precision in the Validation of Analytical Procedures for Drugs. *pan* **2002**, *18*, 51–59.
mogorov-Smirnov Test for Goodness of Fit. *J. Am. Stat. Assoc.* **1951**, *46*, 68–78.

*good sources of regulatory information. Check for up-to-date guidance.)*
and Drug Administration (FDA): *www.fda.gov*
European Medicines Agency: *www.ema.europa.eu*
Pharmaceutical and Medical Devices Agency, Japan: *www.pmda.go.jp*
International Council on Harmonisation: *www.ich.org*

*(Private websites often change, but some have staying power and utility.)*
Wolfram Alpha: *www.wolframalpha.com* (statistical computations)
IUPAC Goldbook: *https://goldbook.iupac.org* (Extensive IUPAC [International Union of Pure and Applied Chemistry] resources for chemistry, math (including statistics), physics, and more)

## Templates

In this section, a small collection of templates used to support collection and analysis of data for a Robustness experiment is presented. The use of templates helps to reduce the opportunity for failure to record critical metadata and assists analysts executing complex and nonroutine experimental procedures with significant adverse consequences for deviations. Some templates are unique, such as the core DOE (Template One). In other cases, copies can be printed as needed for events that reoccur, such as the daily Method Condition Response Check (Template Four), the Trial Response Data Collection and Summaries (Templates Five A and B), and preparation of multiple Pareto charts (Templates Six A and B).

These templates were built in Excel and imported into Word to serve as examples. However, as Excel spreadsheets they can be used to automate repetitive tasks, such as analysis of Robustness data and preparation of graphs for inclusion in the Method Validation Report. They can be printed out with a computer-generated date-and-time stamp and, when completed, inserted in a standard laboratory notebook, or referenced, as primary data.

**Hint**

Templates may be attached to a Protocol to ensure clarity of the experimental design and the goal of laboratory activities for all reviewers and approvers. If you build your own templates, follow whatever directions are given in your organization's SOPs. Be sure to have all data and instrument settings confirmed by an independent observer.

**templates** — provided to assist in the design of the Protocol and the execution of the experiment

**hints** — brief comments offering experience-based advice from the authors

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