Practical Statistical Tools for Analytical Laboratories
21-22 April 2020 | Berlin, Germany

Highlights

- Participants should gain an understanding of
  - basic statistical fundamentals
  - distribution of data and its parameters
  - accuracy and precision
  - variability and precision levels
  - Reportable result
  - linear and non-linear models
  - performance requirements for analytical procedures

- Participants will be shown how to
  - apply statistical principles scientifically and pragmatically in their day-to-day business
  - use statistical simulations
  - optimise the reportable result for minimum variability
  - trend data
  - compare data and methods
  - establish reliable Reporting/Quantitation Limits

Performance Evaluation and Monitoring for compliant Analytical Procedures and Processes

\[ \lambda_i = \frac{t_{n-i,1-p}(n-i)}{\sqrt{(n-i-1+t_{n-i-1,1-p}^2)(n-i+1)}} \]

where

- \( i = 1, \ldots, r \) outliers
- \( t_{n-i,1-p} \) is the 100\( p \) percentage point of the \( t \) distribution
- with \( \nu \) degrees of freedom and \( p = 1 - \left[ \frac{\alpha}{2(n-i+1)} \right] \)

Updated Course for R&D and QC Laboratories
Statistical calculations and tools are applied extensively in pharmaceutical analysis including:

- Procedure development and validation
- Transfer of analytical procedures
- Setting or verification of specification limits
- Data evaluation, comparison and trending

The ICH Q10 Guideline "Pharmaceutical Quality System", the FDA Guidances on Process Validation and Methods Validation require monitoring of "process performance and product quality" and "Trend analysis on method performance" throughout the product lifecycle. Hence the appropriate use of statistical trending and evaluation tools has become mandatory.

Consequently, a thorough understanding of statistical fundamentals is essential in order to be able to select parameters and test methods that are 'fit for purpose'.

Do you speak statistics?
In addition, such an understanding facilitates the communication with other technical and regulatory functions applying statistical tools in order to ensure an overall consistent approach.

Background
The course will provide the participants with recommendations, tools and examples to apply scientifically and pragmatically sound statistical principles to their day-to-day business as well as to meet future challenges described above.

The relevance of such statistical tools is also increasingly recognised by the Compendia, as reflected, for example, in the USP General Information Chapter <1010> "Interpretation and treatment of analytical data" and the recently introduced <1033> "Biological assay validation" together with the proposed General Chapter <1220> on Analytical Procedure Lifecycle.

Statistical tools are needed, for example, to evaluate:

- Distribution of data and its parameters
- How to detect outliers and trends?
- How to establish the total variability of the method?
- How to identify method parameters that must be controlled?
- Method performance and specification limits
  - Which accuracy and precision is needed to achieve an acceptable risk of OOS results?
  - Scientifically based justification and optimisation of the reportable result (single or average)?
  - What are the requirements for impurity methods?
- Comparison of methods and data
- What are the requirements for calibration models?
- How to optimise the number of calibration replicates on a scientific basis?

A brief discussion of supporting software tools (e.g. Excel, Minitab, JMP) to facilitate the generation of statistical information in a consistent manner will be undertaken.

One of the main features of this new course is the balance of presentations and more than five hours of practical exercise workshops which will allow participants to gain 'hands on' practical experience in applying the statistical methods described. By means of statistical simulation tools, the participants will gain intuitive understanding of the consequences of appropriate and inappropriate performance parameters, for example the relationship between precision and OOS results.

For this reason, the course is limited to 30 participants so that individual attention and support can be given. In order to fully benefit from the workshops, attendees should preferably bring a notebook with Excel® 2007 or later.

Target Audience
This best practice oriented course is designed for analytical laboratory managers and their colleagues charged with the day to day management and evaluation of laboratory data throughout the lifecycle, i.e. in method development, validation, transfer, specification setting, batch release and stability, continuous performance verification and change control.

QA, manufacturing and regulatory affairs professionals will benefit from participation by gaining a clear understanding of the statistical fundamentals which are important to implement scientifically sound and pragmatic tools to conform to GMP and regulatory requirements for example Product Quality Review.

Programme
Analytical Procedure Lifecycle Management (USP & ICH initiatives)

- Principles of APLM
- Proposed USP <1220>
- Risk based approach
- Target Measurement Uncertainty
- Decision rules

(Normal) Distribution of Data and its Parameters

- Data shape and its importance
- Characterisation of distributions (Location and Dispersion)
- Probability considerations; all measurements are subject to error
- Populations and samples
- Confidence intervals
- What is an outlier?
- Error of the error
WORKSHOP I
Understanding the Variability (Statistical Simulations)
- Range of expected data
- Variability of standard deviations
- Number of data and reliability of calculated standard deviations

Calculation and Evaluation of Precision Levels
- System precision, repeatability, intermediate precision, reproducibility
- ANOVA: Identification of relevant variance components from injection, measurement, sample preparation, intermediate conditions
- Total variability: precision of the reportable result and its optimisation
- Optimisation of single-point calibration
- Relationship between precision and probability of OOS results
- Practically relevant acceptance criteria for precision

WORKSHOP II
Optimisation of Variability
- Statistically based format of the reportable result (single or average)
- Number of determinations for various levels
- Probability of results outside established limits

Trending of Data
- Why trend?
- Evaluation; do we expect a trend or not?
- Statistical Process Control principles
- Types of Control charts and their application
- Application to stability testing

WORKSHOP III
Control Charts & Trending
- Interactive workshop based on supplied real data sets for interpretation
- Use of Minitab for control charting
- Team working on evaluation and interpretation of trend data

Monte Carlo simulation of Analytical Procedures
- Principles of Monte Carlo simulation
- Understanding variance contributions and how they combine
- Measurement uncertainty
- Application to analytical procedures
- Examples of unit and complete procedures using Companion by Minitab

Comparison of Data & Accuracy
- Significance (F- and t-test) and equivalence tests
- Statistical significance and practical relevance
- Differences caused by random variability: observed and true bias
- Applications in transfer and cross-validation

WORKSHOP IV
Comparison of Data (Statistical Simulations)
- Significance and equivalence tests: influence of number of data and series
- Differences between means and variability

Calibration Models, Linear and non-Linear
- What is a calibration model?
- What is the difference between linear and non-linear models?
- The principle of least squares and why it is important
- Applying the principles to linear and non-linear models

WORKSHOP V
Linearity (Statistical Simulations)
- Regression range and evaluation of the intercept
- Extrapolation effects

Performance Requirements for Impurity Procedures
- Concentration dependence of precision (Horwitz relation)
- Detection and Quantitation Limits
WORKSHOP VI

Quantitation Limit
- Basics to consider for calculation from linearity
- How to determine appropriately from precision

Summary Workshop & Discussion: Appropriate Choice of Tests/Calculations
- Practical objectives and data sets are provided
- The participants will discuss and define appropriate tests and parameters to be calculated
- The participants are given the calculation results and are asked to make an evaluation
- The defined tests and results are discussed in the audience

Moderator
Dr Christopher Burgess, Burgess Analytical Consultancy Ltd., UK

Social Event
In the evening of the first day, you are cordially invited to a social event. This is an excellent opportunity to share your experiences with colleagues from other companies in a relaxed atmosphere.
Speakers

Dr Christopher Burgess
Burgess Analytical Consultancy Ltd., UK

He is a Chartered Chemist and has more than 44 years experience in the pharmaceutical industry initially with Glaxo in Quality Assurance and Analytical R&D and then 24 years in international consultancy. He is a “Qualified Person” in the European Union. He has been appointed to the United States Pharmacopoeia’s Council of Experts 2010 to 2020 and is a visiting professor of the University of Strathclyde’s School of Pharmacy and Biomedical Sciences (SIPBS). In addition, he is the chairman of the ECA Analytical Quality Control Group and a member of the Extended board of European Compliance Academy Foundation. He is also a member of the USP Expert Panel on Validation and Verification entrusted to revise General Chapters <1224>, <1225> and <1226>.

Dr Joachim Ermer
Sanofi, Frankfurt, Germany

Head of QC Lifecycle Management Chemistry, Sanofi-Aventis Deutschland GmbH, Frankfurt, Germany, and Global Reference Standards Coordinator of Sanofi. Dr Ermer studied biochemistry at University of Halle and has more than 25 years experience in pharmaceutical analytics including development products, global responsibilities as Director of Analytical Processes and Technology, and Head of Quality Control. He is member of the USP Expert Panel on Validation and Verification and of the EFPIA support team for the update/establishment of ICH Q2/Q14.
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