



INTELLIGENT DATA ASSIMILATION

WLTR — A SOFTWARE
PLATFORM ENABLING
USERS TO EVALUATE DATA
THROUGH A PRODIGIOUS
DATA VISUALIZATION DECK
(DVD)



INTRODUCTION

Imagine driving down the highway with binoculars strapped to your head; nervously adjusting lens settings, and continuously zooming in and out while trying to dodge traffic and not destroy the vehicle! That is the mind-set of most instrument chromatographers as they navigate the construction of initial calibrations while judiciously trying to cross all the regulatory T's and dot the I's without a meltdown.

The International Union of Pure and Applied Chemistry (IUPAC) states that “In general, calibration is an operation that relates an output quantity to an input quantity for a measuring system under given conditions”. In the *International Vocabulary of Basic and General Terms in Metrology (VIM)*, calibration is defined as an “Operation establishing the relationship between quantity values provided by measurement standards and the corresponding indications of a measuring system, carried out under specified conditions and including evaluation of measurement uncertainty”.

Laboratories that conduct chromatographic or spectrophotometric sample analysis, calibrate instruments to predict a target analyte concentration from the measured instrument response, and to transform the instrument response into an analytical result requires an initial calibration model. Thus, the initial calibration is used to ensure accuracy, precision and repeatability and is the cornerstone to all laboratory analysis. Therefore, the root foundation for the success of an analytical laboratory hinges on the decisions made during the construction of the initial calibration. Conversely, the biggest challenge and least favorite job in the laboratory is the process of conducting and building an initial calibration.



ANALYTICAL INSTRUMENTS

Analytical instruments provide important scientific data regarding anthropogenic and natural products as it relates to environmental or regulatory requirements. These data results are used to investigate and understand sites that may have been polluted or to test for naturally occurring analytes. Analytical instruments also provide important scientific data regarding manufactured products that serves to ensure these products meet a product specification. Analytical data used in this context helps to ensure confidence that products being produced by the manufacturer are both safe and efficacious for public consumption.

Analytical instruments run the gamut from a simple UV/VIS spectrophotometer to sophisticated chromatographic systems that combine an analytical instrument function with software control. Laboratories operating in regulated environments are typically required to conduct instrument validation tests to produce documented evidence that instruments are fit for their intended use and operate in a controlled manner to produce accurate data results.

Because of their potential for impacting environmental stewardship or product quality, laboratory instruments are key targets for laboratory audits and governmental inspections. During an on-site inspection, the auditors will expect to see definitive evidence that instruments have been properly calibrated which directly affects reported data results. The lack of or insufficiently documented initial calibrations are in fact frequently cited audit citations.

CHROMATOGRAPHY DATA SYSTEM (CDS) SOFTWARE

The pharmaceutical industry is a critical national security market sector and accordingly, it is one of the most heavily regulated industries that rely on analytical instruments for data analysis. The USP General Chapter 1058 Analytical Instrument Qualification is often cited in laboratories functioning in this market arena and is used in this discussion, however, other analytical laboratory markets, (e.g., environmental use similar approaches to instrument, software and method validation studies).



The USP classifies instruments into three categories to manage risk in the instrument qualification process, and for the sake of this discussion, we are interested in Group C: computerized laboratory systems that typically consist of an analytical instrument that is controlled by a separate workstation running instrument control and data acquisition, and process software. Group C instruments require in-depth calibration protocols and software validation, to ensure proper functioning.

The software in these instruments can be classified into three categories:

- a) non-configurable software that cannot be modified to change the business process,
- b) configurable software that includes tools from the vendor to modify the business process,
- c) configurable software with customization options, (i.e., custom software or macros to automate the business process).

In these cases, the software is needed to qualify the instrument and the instrument operation is necessary when validating the software, i.e., a symbiotic relationship. As a result, the software validation and analytical instrument qualification are generally integrated into a single activity to avoid duplication. There are several steps that are critical to properly qualify and documenting an analytical procedure as follows:

1) Analytical Instrument Qualification (AIQ) — This step is not an isolated one-time event, but instead consists of interconnected activities that occur over the lifetime of the instrument. This initial step involves the creation of user requirements, i.e., SOPs, which effectively specify the operational and functional requirements that the instrument is expected to fulfill for product testing. This SOP defines the analytical instrument protocols relating to product safety, identity, strength, purity, and quality of the product.

2) Design Qualification (DQ) — The DQ is a step that seeks to demonstrate the selected instrument has all the capabilities necessary to satisfy the product testing requirements. As such, the DQ will document the requirements, along with all decisions made in selecting an instrument vendor. This information is formulated to help the



purchaser ensure the selected instrument can perform and meet the specified product testing criteria. Instrument manufacturers produce white papers and method development papers to take this burden off the purchasers. Most often, verification that instrument specifications meet the desired requirements may be sufficient for commercial off the shelf (COTS) instruments.

3) Installation Qualification (IQ) — The IQ documents the activities necessary to establish the instrument was received as designed and specified, is installed in the correct environment, and the environment is suitable for the proper use of the instrument. Depending on the results of a risk assessment, IQ may apply to any new instrument, used instrument, onsite instrument that has not been previously qualified, or a qualified instrument that is being moved to another location.

4) Operational Qualification (OQ) — The OQ documents those activities necessary to verify the instrument functions according to the operational specifications designated in the user environment. OQ activities are designed to simulate actual testing conditions, including worst-case scenarios, and be repeated enough times to assure reliable testing results. Some of the more important OQ testing activities include:

- i. Software Functions – OQ testing typically includes the critical elements of the CDS software to demonstrate the instrument works as intended. Such critical elements would include data acquisition, analysis, security and reporting, along with access control and audit trails.
- ii. Software configuration and/or customization – This OQ element is designed to document the configuration and/or customization of instrument software is adequate.
- iii. Secure Data Storage, Backup, and Archiving – Laboratories must demonstrate data is being properly secured, stored, backed-up and archived and is a critical OQ testing element.
- iv. Instrument Function Tests – This OQ testing activity is to confirm the instrument is operating as the manufacturer intended.

5) Performance Qualification (PQ) — Also described as user acceptance testing (UAT), PQ testing activities are designed to demonstrate an



instrument consistently performs according to specifications appropriate for its intended use.

6) Preventative Maintenance, Periodic Reviews and Change

Control — Preventative maintenance which includes initial calibration or re-calibration, data and procedural reviews, repairs and other changes are typically documented as part of instrument qualification requirements. When an instrument malfunctions, the cause is investigated and documented. Once maintenance activities, changes, upgrades, moves or repairs are complete, relevant IQ, OQ and PQ tests are typically reevaluated to verify the instrument is operating satisfactorily.

Analytical instruments can provide a high level of confidence in the quality of finished product through scientific data if they are qualified properly. Instrument qualification is an important part of compliance for laboratories in regulated industries and is important to ensure product quality and safety in any industry. Failure to qualify instruments properly can lead to serious consequences for an organization because of compliance violations and poor product quality.

While a commitment to quality requires an enormous amount of effort and focus, industry leading organizations understand that good quality practices and culture leads to a more efficient work environment, improved employee satisfaction, and ultimately increased profitability.

THE CONUNDRUM

Chromatography software developed by instrument manufacturers are designed as a turnkey utilitarian CDS software tool integrating functions such as:

- instrument control.
- sample management,
- data acquisition,
- data management, and
- laboratory workflow management.



Chromatography software engineers continue to make software upgrades by combining preventative maintenance tools and other artificial intelligence (AI) functions aimed at helping the analyst make better informed operational decisions. However, these software upgrades are not targeted at helping aid the analyst to better understand and produce higher quality initial calibrations which in-turn produces higher quality analytical data!

The calibration of analytical test equipment is the key component to ensure the quality of reported data. It should be obvious laboratories face a daunting task ensuring they are compliant with initial calibration criteria. Thus, laboratories need a program that will take the labor-intensive process of initial calibration construction, review, verification and validation and automate it without mistake; a true mathematically based calibration validation and documentation program that helps take analyst error out of this process.

EXAMINING THE ISSUES

Analyst Issues — As an analyst the software shortcomings are related to a) making bad or inappropriate calibration construction decisions that are not readily caught at the bench, and b) the time required to construct and review the initial calibration, not to mention the secondary review process.

QA Officer Issues — QA Officer have the general responsibility for ensuring the quality system is implemented and always followed, including the review and oversight of initial calibrations.

Secondly, QA Officers are tasked to write procedural method and ancillary SOPs to arm the analyst and general laboratory staff with the process knowledge to perform initial calibrations and their review. Thirdly, QA Officers are often tasked to help train staff members analytical methods, techniques, bench chemistry, and instrument procedures with the goal of minimizing random and systemic errors. Therefore,

QA Officers also recognize the need for a software tool to help train analyst regarding initial calibration construction as well as train the analyst the review and validation of initial calibrations. A software tool



that allows the analyst to make quick and efficient calibration decisions and a software tool the reviewer can use to ensure those calibration construction decisions are mistake free would be invaluable to the QA Officer.

Technical Director Issues — The Technical Director requires both a science and technical background to examine and understand current technology when considering instrument and ancillary equipment purchases. These purchasing decisions typically center around instrument robustness, down-time, ease of use, instrument manufacturer's production cycles, hardware and software technology platforms, all in the hope of advising laboratory management the best return on investment (ROI). Technical Directors also have an unwritten mandated goal: to **Buy, Build, Bestow** knowledge and **Bridge** information and technology gaps to staff, and management.

Corporate Ownership Issues — All business owners and entrepreneurs understand the bottom line is the prized possession of business success. The hunt to improve upon the bottom line never ends; it entails a continuum of activities and exercises which include a conscious stream of ideas, suggestions and actions to increase corporate profits. The question and issues are always the same: how to improve the bottom line while maintaining quality while decreasing exposure to potential litigation. Owners understand the key to solving this issue centers around finding a mechanism, a tool, a procedure, or new technology to increase production efficiency. Therefore, if owners could find a technology that would increase production efficiency while minimizing liability exposure; it would be a fiduciary responsibility to their shareholders to purchase that product.

CDS Data Display Issues — The analytical chemist constructing an initial calibration must proceed through a complicated decision tree while evaluating and constructing the initial calibration. This process is predicated on the method and/or program criteria which drives the bench chemist decisions making process. The issues with current CDS software structures is as follows:



- CDS software employs a myopic data visualization approach requiring the analyst to review and evaluate a single target analyte against a single mathematical calibration model one at-a-time.
- The CDS format is clumsy, inefficient, and does not allow the analyst to form a conscious intellectual data stream in a way to effectively assimilate data as information. Therefore, the chemist constructing the initial calibration has a very limited understanding of the behavior of the captured data used for the initial calibration.
- The larger the target analyte list, the larger the number of data points decisions and hence potential analyst mistakes.
- In addition, the larger the target analyte list, the more inefficient this process becomes while using on-boarded CDS software.

Initial calibrations are constructed, reviewed and evaluated for a multitude of calibration parameters to ensure the chosen calibration model will pass the calibration criteria. The analyst typically reviews the initial calibration parameters for the following functions:

- Standard Deviation (SD),
- Relative Standard Deviation (RSD),
- Correlation Coefficient (r) and / or coefficient of determination (r^2),
- Calibration Check Compound (CCCs), or minimum RSD
- System Performance Check Compounds (SPCCs) or minimum response factors,
- Relative Standard Error (RSE),
- Percent Error (PE),
- Linear Dynamic Range (LDR),
- Limit of Quantitation or Reporting Limit (LOQ/RL), and
- Minimum number of calibration points.

Current CDS software does not produce some of these initial calibration metrics, nor does the software have the capability of reviewing and validating these calibration metrics, ensuring they have been achieved.



RE-IMAGINING THE ASSIMILATION OF INITIAL CALIBRATION DATA USING A DATA VISUALIZATION DECK (DVD)

WLTR was designed, incorporating a novel architectural software data concept, empowering users to assimilate data through an intuitive data visualization deck (DVD). This architectural software design approach allows the user to objectively review, select, evaluate and verify initial calibration mathematical functions, while producing true data validation; technically defined as the confirmation by examination and provisions of objective evidence that the requirements for a specific intended use are fulfilled.

WLTR was conceived to address the following CDS software issues:

- to help aid the bench chemist make better informed initial calibration model decisions,
- to take the guess work out of initial calibration construction, review, verification, validation and scientific prudence,
- to help the analytical bench chemist as well as the laboratory increase data production by increasing efficiency,
- to independently validate initial calibration mathematics while also acting as a data auditing tool, ensuring the analytical data would pass scientific and legal scrutiny, and
- as an insurance policy, protecting the laboratory, the auditor, the auditing agency, and the consumer from both poor decision and analyst mistakes.

WLTR — DATA VISUALIZATION DECK (DVD) PROVIDES COMPLETE DATA VISIBILITY

WLTR was designed and developed to provide instrument users a mathematically based platform to compute, construct, display, review, select and evaluate initial calibrations using a novel data visualization deck (DVD), summarizing the data in an initial calibration summary table.



WLTR was written and coded to mathematically calculate the nine (9) most common calibration models used in CDS software and display each target analyte for all calibration models on the data visualization deck (DVD) using either internal or external calibration techniques.

WLTR was designed to digitally upload and accommodate the mathematical construction of an initial calibration containing up to twenty (20) discrete calibration points and to display that data on the DVD as real-time calculated concentration values, for each concentration point, for each target analyte and for all nine (9) mathematical models.

WLTR was designed to allow the chromatographer to delete any calibration point and/or manipulate calibration construction in any conceivable fashion and to display all construction manipulations on the DVD including updating calculated concentration values in real-time.

WLTR was designed to display the graphical depiction of five (5) of the nine (9) calibration curves for each target analyte as an unfettered view on the DVD.

WLTR uses the DVD architectural design concept to display the graphical depiction of the calibration curves along with the RF, RSE, r , r^2 , equation coefficients, etc. allowing the chromatographer to assimilate actionable information, through direct data comparison, i.e., the cause-effect relationship resulting from calibration construction manipulation.

WLTR was designed to calculate and evaluate the LOQ/RL against the initial calibration and display those evaluation results on the DVD.

WLTR was designed to extrapolate and estimate concentration values for each target analyte and for each mathematical model, values corresponding to 0.75%, 0.50%, 0.25% and 0.125% of the lowest calibration point and to display that information on the DVD.

WLTR was designed to estimate the concentration value of a zero (0) area response for all nine (9) mathematical models and to display that information on the DVD.



WLTR was designed to calculate and display both curve refitting functions, e.g., RSE and PE%, for all nine (9) mathematical models and display that information on the DVD.

WLTR — PROVIDES MATHEMATICALLY BASED DATA VALIDATION

WLTR was designed to independently compute the initial calibration verification (ICV) standard, i.e., second source, concentration values for each target analyte against all possible mathematical calibration models and display the concentration values determined by WLTR as well as the on-boarded instrument software on the DVD.

WLTR was designed to mathematically compare and evaluate the ICV concentration values determined by WLTR against the concentration values determined by the on-boarded CDS software, thus reviewing, verifying and validating:

- a) the construction parameters of the initial calibration using the on-boarded CDS software is correct,
- b) the chosen mathematical model is correctly identified,
- c) the computational mathematics of the chosen initial calibration model is correct, and
- d) true mathematical calibration validation.

WLTR was designed to incorporate calibration evaluation parameters not currently programmed into on-boarded CDS instrument software.

WLTR — FRAUD PREVENTION

WLTR was designed to help aid the bench chemist, make better calibration decisions, produce better quality data, provide the analyst an evaluation tool as a Personal Data Assistant (PDA) and minimize liability exposure for corporate ownership.

WLTR is the ultimate Fraud Prevention, Data Integrity and Data Validation Assistant (DVA).



WLTR was designed to ensure data produced from the laboratory would pass scientific, legal, and auditing scrutiny.

WLTR is used by the analyst, to self-document the absence of fraud in the calibration construction while incorporating all essential data integrity elements.

WLTR is used by the QA Officer or secondary reviewer to verify and validate the initial calibration meets method and/or program specified criteria and secondarily to verify the absence of any fraud in the calibration construction.

WLTR is used by the laboratory management to verify, validate and ensure the data is digitally stored, maintaining data integrity and secondarily used to document the absence of any direct or perceived fraud while incorporating essential data integrity elements, i.e., a fiduciary fraud prevention program.

WLTR is used by an auditor or third-party data auditor as a QA evaluator, a QC evaluator, an instrument software validator, an initial calibration data validator and a calibration construction validator and secondarily used to document the absence of any direct or perceived fraud.

WLTR — THE ULTIMATE STRESS RELIEVER

WLTR uses a metadata approach to review, verify and identify best-fit initial calibration model construction, to achieve better decision outcomes by displaying those data parameters on the data visualization deck, empowering the chromatographer.

WLTR allows the chromatographer to choose the calibration model for each target analyte they wish to conduct a calibration review and evaluation audit.

WLTR summarizes the initial calibration using the method evaluation parameters and the user selected evaluation criteria, displayed on the DVD, and documented on the initial calibration evaluation table.



WLTR evaluates each initial calibration evaluation parameter for each target analyte and summarizes that data on the initial calibration evaluation table.

WLTR assigns an overall final pass / fail to each target analyte ensuring the chromatographer the chosen calibration model meets all evaluation criteria.

WLTR increases production efficiency while minimizing liability exposure bringing dollars to the bottom line. This is the mark of a true GREEN investment!

WLTR — FROM THE CORPORATE BOARD ROOM TO THE BENCH CHEMIST - WLTR GETS IT RIGHT!

WLTR upholds the Environmental, Social and Corporate (ESC) governance principles and is an Environmental Green Investing (EGI) product as well.

WLTR helps laboratories produce high-quality analytical data and is an ESC industry multiplier; **better analytical data produces better corporate decisions which produce higher corporate profits!**

WLTR is taking initial calibrations to the next frontier enabling chromatographers to visualize calibrations at a level to provide the Where, What, and When so you can understand the Why!

WLTR is GREEN SQUARED!