

United States Cannabis Testing: Laboratory Compliance

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Abstract

Cannabis is a new and popular industry with the potential for exponential growth. But with such growth, quality is often an afterthought. States have been left with the difficult task of regulating the industry; due to its immaturity, these regulations are changing quickly.

To assist testing facilities in navigating the complex regulatory landscape, Agilent has created this white paper to introduce Agilent's compliance recommendations for the industry. These recommendations are based on key compliance topics found in states that have legalized the use of cannabis as well as ISO 17025 accreditation requirements. Forward-thinking laboratories should anticipate stricter compliance regulations and would do well to understand the principles outlined in this paper.

As industry regulations become more standardized, laboratories will be required to operate with a greater level of compliance focus.

The following technical overview has been written as a continuation to this series: *Recommendations for Cannabis Testing: Laboratory Compliance*¹

Introduction

With the increasing legalization of Cannabis (*Cannabis sativa* L.) in most states, there is substantial demand for Cannabis quality and potency testing. As popularity increases, the regulatory landscape has become increasingly difficult to navigate in the United States. The 2018 Farm Bill effectively separates federal laws between the two articles of the Cannabis plant: cannabis and hemp.² This legislative change is forcing both state and federal regulations to evolve quickly to address public health concerns around both articles. For Cannabis testing facilities in states where cannabis has been legalized, these regulatory expectations can be difficult to navigate, and preparing for the future can seem daunting.

To help laboratories comply with both the local regulations and industry expectations, Agilent has produced two white papers to discuss and introduce Agilent's recommendations for analytical laboratory testing in the Cannabis industry. This document is one of two white papers in this series, with the other being dedicated to hemp compliance.³ Each paper addresses three fundamental compliance topics:

1. Qualification/calibration of laboratory equipment
2. Data retention and availability
3. Data integrity controls

All three topics are of critical importance for operating a cannabis testing facility, as these topics are key to ensure compliance with state regulations and to establish and maintain ISO 17025 accreditation. As the cannabis industry continues to mature, it is expected that laboratory regulations will become more stringent.

A breakdown of ISO 17025 data control and equipment qualification requirements can be found in the appendix of this document.

Cannabis quality landscape

Consumer safety and satisfaction is the key objective of state cannabis quality testing. States that have legalized the use of cannabis have been tasked with the regulation of these products to ensure their quality, but this has been difficult to achieve. Industry immaturity, business incentives, and weak regulatory action have all contributed to the discrepancies that exist between testing facilities. Growers often take advantage of these discrepancies, settling for laboratories that provide favorable results. This form of "Lab Shopping" has become prevalent in the field, incentivizing biased results over scientific accuracy. In response, states have been adapting to promote standardization among laboratories with proficiency testing and external accreditation.⁴ As the industry matures, so will its governing regulations.

Current state regulations

At first glance, state testing regulations appear diverse and discordant. This is primarily due to the inconsistencies and ambiguity in regulatory text. However, further analysis proves that state requirements are fairly consistent for the topics discussed in this paper. To demonstrate this, Table 1 provides a regulation breakdown of the top five states that have legalized recreational and/or medicinal cannabis use. States were selected and ordered based on predictions of highest cannabis selling states in 2020.⁵ Each row represents a compliance requirement with the state code of regulation found in the corresponding column.

Forward-thinking labs should anticipate future regulatory compliance stringency. The principles discussed in this paper are universal to regulated labs and should be adopted to meet current and future requirements.

Qualify/calibrate laboratory equipment

Ensuring the accuracy and precision of laboratory equipment is at the cornerstone of any quality management system and is a requirement for most, if not all, regulated labs. However, the process for achieving this can seem unclear.

Table 1. State regulations (by 2020 predicted highest cannabis selling states).⁵

	California	Colorado	Michigan	Florida	Washington
Qualify/Calibrate Laboratory Equipment	5729 (a) (5)	1 CCR 212-3-6-440 B 1 CCR 212-3-6-430	Relies on ISO 17025	64ER20-14(4)(e)4	WAC 314-55-103 22
Data Retention and Availability	5739 5037	1 CCR 212-3-3-905 1 CCR 212-3-6-415 (4, 5, &11)	Relies on ISO 17025	64ER20-4(2)	WAC 314-55-103 25 C
Data Integrity Controls	5037 5726 (g) 5729 (a)	1 CCR 212-3-6-415 (4, 7, &12) 1 CCR 212-3-3-905 B	Relies on ISO 17025	64ER20-14(4)(e)1 & 6	WAC 314-55-103 25 WAC 314-55-103 35
ISO 17025 Accredited	Article 2 5701	1 CCR 212-3-6-415	R. 420.305 Rule 5. (1)	64ER20-14(4)(a)	N/A

Words like verify, validate, calibrate, and qualify are often used interchangeably in scientific fields. This is largely due to the inconsistencies in using these terms among regulatory texts globally. There are no incorrect definitions, just what fits your laboratory best. For the sake of consistency, this paper will use the following terminology:

Calibrate – To establish a relationship between the equipment indication and a known value. This relationship is then used as a measure for equipment correction.⁶

Qualify – To prove that equipment is working correctly, and that its results are accurate.

Regardless of your terminology, your procedures should note the distinction between the two activities. Both are part of the overarching validation of the system.

Laboratories generally possess a broad spectrum of equipment reflecting different levels of complexity. For example, a high-performance liquid chromatograph's (HPLC) parameters and outputs are significantly more diverse than those of a balance. This is because a balance records only one format of data (weight), whereas a HPLC records a great deal more (response, temperature, flow, pressure, etc.). Given the complex nature of chromatography systems, it does not make sense to demonstrate their performance through calibration alone. High-risk parameters should be individually evaluated to test the entire system's functionality.

The importance of qualification is demonstrated through the United States Pharmacopeia's (USP) Data Quality Triangle (Figure 1). In this model, the data generated is supported by the activities underneath, with the data in question being at the apex. For example,

a quality control (QC) check sample is only as strong as the validated method. No matter how precise and accurate the check sample, a poorly designed/validated method contributes more to performance. The same is true with instruments. A validated method is incapable of providing sound results if the equipment is nonconformant.⁷

The USP has classified instrument qualification as a critical event for data quality. The main purpose of instrument qualification is to produce documented evidence of the operational performance of a given system and suitability to a given application. Without properly qualifying equipment using calibrated tools, test results cannot be scientifically justified. By not qualifying their equipment, laboratories risk the chance of releasing noncompliant products.

System suitability tests are a common way to demonstrate the effectiveness of equipment use. Although not a common requirement in the cannabis industry, these tests have been deemed "good practice" in Massachusetts' regulations (9.2.1).⁸ The setup for system suitability tests can be found in USP Chapter <621>.

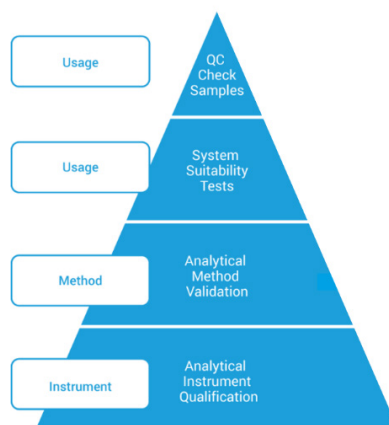


Figure 1. USP's Data Quality Triangle.

Data integrity – retention and availability

Fundamentals

The concept of data integrity is at the core of the scientific method. For conclusions to be drawn, data needs to be documented to allow for traceability and repeatability. The World Health Organization (WHO) defines data integrity as the following:

*"Data Integrity is the degree to which data are complete, consistent, accurate, trustworthy and reliable and that these characteristics of the data are maintained throughout the data lifecycle. The data should be collected and maintained in a secure manner, such that they are attributable, legible, contemporaneously recorded, original or true copy and accurate."*⁹

These principles are summarized by the acronym ALCOA+. The integrity of data can be determined by evaluating whether the data can address the following:

Attributable – Who performed the work?

Legible – Can it easily be read and traced?

Contemporaneous – When was the work performed?

Original – Is this the source data or first capture?

Accurate – Is it correct, truthful, valid, and reliable?

Complete – Is the data all there?

Consistent – Is it harmonized and chronological?

Enduring – Is it in a readable format?

Available – Can it be viewed quickly and easily?

Records/data unable to demonstrate all nine of these attributes should be considered questionable. These characteristics are necessary to reconstruct the events that produced the data in question.

Further guidance on ALCOA+ can be found in the WHO's Guidance on good data and record management practices.⁹

Metadata

Analytical data in and of itself is insufficient for laboratory use. To explain this concept further, consider the following example.

Sample A: 9.27 g MA 21SEP2020

The analytical value "9.27" is meaningless without additional information. The contextual data following the number indicates that in this instance, "9.27" refers to a sample weight measurement performed on a specific date.

Contextual data that provide information about analytical data are called metadata. This is the information that will address the individual principles of ALCOA+. The WHO defines metadata as the following:

"Metadata are data about data that provide the contextual information required to understand those data. These include structural and descriptive metadata. Such data describe the structure, data elements, interrelationships and other characteristics of data. They also permit data to be attributable to an individual. Metadata necessary to evaluate the meaning of data should be securely linked to the data and subjected to adequate review."⁹

The retention and protection of metadata is crucial to ensuring data integrity. Safeguarding the protection and retention of critical pieces of metadata is at the cornerstone of this concept.

Data life cycle

When data are generated, they typically go through a series of stages:

1. Acquisition
2. Processing
3. Reporting
4. Archiving
5. Deletion

Taken together, these stages are called the data life cycle. This process must be defined and controlled. At every stage of the data life cycle, the data must remain traceable to their previous stage.¹⁰

Acquired data (or first capture data) are the most important to protect.

Data generated in a laboratory should have a defined life cycle that specifies the retention period. Data that violate this controlled life cycle should be investigated, documented, and corrected.

For example, a power failure or an aborted run prevents the completion of a potency test. Due to the abbreviated run time, the data cannot be processed. This event should be investigated and documented to reference any of the incomplete data files.

Static versus dynamic data

As laboratories become more technologically advanced, data are being generated in electronic formats. This is significantly different from the paper and ink integrator sheets used in the past. These two forms of data have been coined *dynamic* and *static* respectively.

Static data are data that are fixed, such as a paper record or an image.¹¹

Dynamic data are any electronic file that allows for interaction by the user. An example of this would be a Microsoft Excel document or a digital acquisition file.¹¹

Due to the complex nature of dynamic data, data cannot be converted from static into dynamic. This would be the equivalent of converting a single

photo into a video. However, the reverse process of converting dynamic data to static data is possible, with the understanding that a large part of the original file is lost. This type of conversion is common practice in all laboratories, such as creating a report from a chromatography sequence file.

The conversion of data from a dynamic to a static form is a perfectly appropriate procedure, but in doing so the laboratory must ensure the following:

- The original dynamic data are retained and traceable to the report.
- All necessary metadata are included in the report to demonstrate the principle of ALCOA+.¹²

A common example where this principle is not followed is when a laboratory creates/prints a sequence report but deletes or fails to safeguard the original chromatography files after the report is generated. This destruction of source data undermines the support of the laboratory's conclusion, making the findings impossible to justify. This could be challenged by an auditor.

Data integrity – controls

Procedural versus technical controls

Strategies for maintaining data integrity have changed since the initial introduction of dynamic data, but the principles have ultimately remained the same. The integrity of paper documents is controlled in many fields with current Good Documentation Practices (cGDP). For example, most laboratories have a policy prohibiting the obliteration of data through black out or correction fluids. Historically, cGDP were established to protect paper records, but since the introduction of computerized systems cGDP has been expanded to regulate electronic files as well. Laboratories have two options available for maintaining data integrity: procedural or technical controls.

Procedural controls are enforcements that rely on individuals to follow policies.

Technical controls use software/firmware features to enforce policies. These controls must be properly designed, setup, and validated to be effective.

Consider the nonlaboratory example of sending money from your bank account. You have two options; you can write a check, or you could wire funds through your bank's website. Each of these methods requires some level of attributable control: the check requires a name and a signature, a procedural control, and the website requires a username and a password, a technical control.

Although the function of procedural and technical controls is the same, there is a clear advantage to technical controls. Technical controls are significantly better than procedural controls at enforcing policies.

To explain this further, evaluate laboratory control strategies for preventing manual integration. Because of its high risk for analyst-manipulated results, manual integration is prohibited in many laboratories around the

world.¹³ Laboratories can prevent this manipulation, either by creating a policy against manual integration or by prohibiting this functionality for the analysts in the chromatography data system (CDS). Clearly, the latter is the stronger option.

Well-designed equipment acquisition and processing software include data integrity controls. It is highly recommended that these controls are used and considered when purchasing software.

Data governance

The totality of controls to ensure the integrity of data is referred to as data governance. In addition to data integrity controls, data governance also includes the laboratory strategies for training and creating an "open" culture.

Figure 2 demonstrates the importance of data governance/integrity as the foundation of all laboratory activities. Each step in the data quality triangle is dependent upon the integrity of generated data. The primary focus of a laboratory should be on its data governance programs, which is beyond the scope of this white paper.

State regulation examples

The following are examples of direct state regulatory text pertaining to laboratory compliance. Due to the sheer quantity of regulations in the United States, this white paper can only share a few examples.

Washington: "a.) The laboratory shall establish and maintain procedures for identification, collection, indexing, access, filing, storage, maintenance and disposal of quality and technical records. b.) All records shall be legible and shall be stored and retained in such a way that they are readily retrievable in facilities that provide a suitable environment to prevent damage or deterioration and to prevent loss. c.) Records must be retained for a period of three years. d.) All records shall be held secure and in confidence. e.) The laboratory shall have procedures to protect and back-up records stored electronically and to prevent unauthorized access to or amendment of these records." WAC 314-55-103 25¹⁴

Massachusetts: "Data Integrity Requirements: The laboratory is to be committed to ensuring the integrity of data, incorporating the highest appropriate standard of quality in all analytical programs." 6.1.1⁸

California: "The laboratory shall develop and implement a LQA [Laboratory Quality Assurance] program to assure the reliability and validity of the analytical data produced by the laboratory. The LQA program shall, at minimum, include a written LQA manual that addresses the following: (1) Quality control procedures; (2) Laboratory organization and employee training and responsibilities, including good laboratory practice (GLP); (3) LQA objectives for measurement data; (4) Traceability of data and analytical results; (5) Instrument maintenance, calibration procedures, and frequency; (6) Performance and system audits; [...] (9) Record retention and document control." 5729(a)¹⁵

Examples of additional state codes can be found in Table 1.

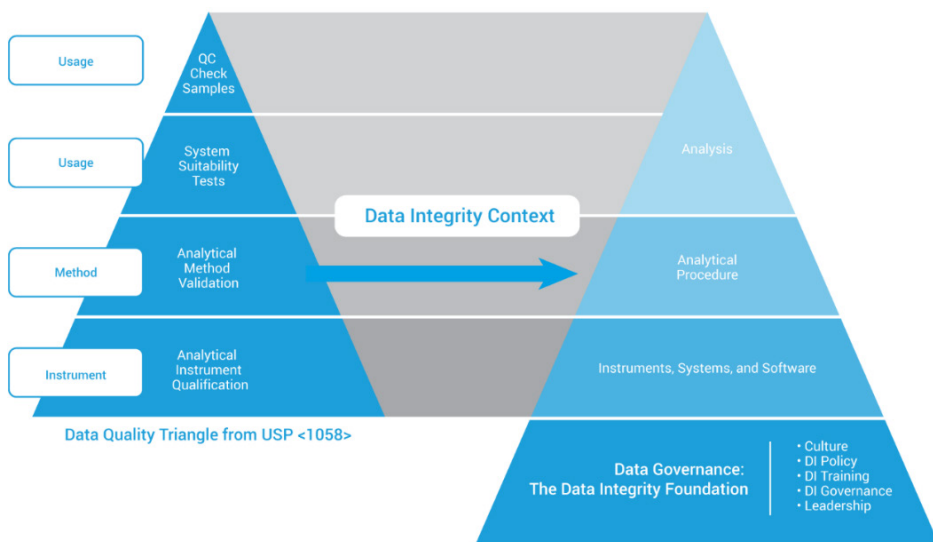


Figure 2. The Data Integrity Model.

ISO 17025 accreditation

ISO (International Organization for Standardization) accreditation is a popular demonstration of testing competence and calibration. Its requirements are outlined in ISO 17025.¹⁶ This chapter covers a range of topics such as personnel, equipment, method validation, data management, and quality requirements.

Due to its global popularity, many states that have legalized cannabis made ISO accreditation the backbone of their cannabis laboratory compliance requirements. (See Table 1 for examples.) The exception to this is the state of Washington, which asserts the chapter is too generalized in comparison to its current state cannabis regulations. Further evaluation is being discussed.¹⁷

ISO 17025 outlines strict requirements for equipment qualification/calibration and data management. These requirements are listed in Table 2 in the appendix.

Agilent recommendations for laboratory compliance in the cannabis industry

The principles discussed above are at the core of current Good Manufacturing Practices (cGMP), a common term used in many regulated industries. Although these topics can seem overwhelming, many different vendor products and solutions exist to meet these requirements. To assist the industry, Agilent has prepared the following technical overview to give laboratories meaningful guidance on meeting current and future regulatory requirements:

*Recommendations for Cannabis Testing: Laboratory Compliance*¹

Conclusion

Legalization of cannabis at the state level is relatively new, and regulations are still maturing. States around the country are requiring laboratories to develop and demonstrate a data governance plan for the safeguarding of analytical data. This requirement is satisfied through equipment qualifications/calibrations and data integrity controls protecting data throughout its life cycle. Laboratories in this industry will find regulatory expectations changing quickly, regardless of their location. Partner with Agilent to stay updated and compliant with current cannabis regulations.

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Appendix

Table 2. ISO 17025 requirements with respect to laboratory compliance.¹⁶

	ISO 17025 Requirements
Qualify/Calibrate Laboratory Equipment	<p>6.4.4 "The laboratory shall verify that equipment conforms to specified requirements before being placed or returned into service."</p> <p>6.4.6 "Measuring equipment shall be calibrated when: – the measurement accuracy or measurement uncertainty affects the validity of the reported results, and/or – calibration of the equipment is required to establish the metrological traceability of the reported results."</p> <p>6.4.10 "When intermediate checks are necessary to maintain confidence in the performance of the equipment, these checks shall be carried out according to a procedure."</p> <p>7.7.1 "The laboratory shall have a procedure for monitoring the validity of results. The resulting data shall be recorded in such a way that trends are detectable and, where practicable, statistical techniques shall be applied to review the results. This monitoring shall be planned and reviewed and shall include, where appropriate, but not be limited to: c) functional check(s) of measuring and testing equipment"</p>
Data Retention and Availability	<p>7.1.8 "Records of reviews, including any significant changes, shall be retained. Records shall also be retained of pertinent discussions with a customer relating to the customer's requirements or the results of the laboratory activities."</p> <p>7.2.2.4 "The laboratory shall retain the following records of validation: a) the validation procedure used; b) specification of the requirements; c) determination of the performance characteristics of the method; d) results obtained; e) a statement on the validity of the method, detailing its fitness for the intended use."</p> <p>7.3.3 "The laboratory shall retain records of sampling data that forms part of the testing or calibration that is undertaken. These records shall include, where relevant: a) reference to the sampling method used; b) date and time of sampling; c) data to identify and describe the sample (e.g. number, amount, name); d) identification of the personnel performing sampling; e) identification of the equipment used; f) environmental or transport conditions; g) diagrams or other equivalent means to identify the sampling location, when appropriate; h) deviations, additions to or exclusions from the sampling method and sampling plan."</p>
Data Integrity Controls	<p>6.4.12 "The laboratory shall take practicable measures to prevent unintended adjustments of equipment from invalidating results."</p> <p>7.5.1 "The laboratory shall ensure that technical records for each laboratory activity contain the results, report and sufficient information to facilitate, if possible, identification of factors affecting the measurement result and its associated measurement uncertainty and enable the repetition of the laboratory activity under conditions as close as possible to the original. The technical records shall include the date and the identity of personnel responsible for each laboratory activity and for checking data and results. Original observations, data and calculations shall be recorded at the time they are made and shall be identifiable with the specific task."</p> <p>7.5.2 "The laboratory shall ensure that amendments to technical records can be tracked to previous versions or to original observations. Both the original and amended data and files shall be retained, including the date of alteration, an indication of the altered aspects and the personnel responsible for the alterations."</p> <p>7.8.7.1 "When opinions and interpretations are expressed, the laboratory shall ensure that only personnel authorized for the expression of opinions and interpretations release the respective statement. The laboratory shall document the basis upon which the opinions and interpretations have been made."</p> <p>7.8.8.3 "When it is necessary to issue a complete new report, this shall be uniquely identified and shall contain a reference to the original that it replaces."</p> <p>7.11.2 "The laboratory information management system(s) used for the collection, processing, recording, reporting, storage or retrieval of data shall be validated for functionality, including the proper functioning of interfaces within the laboratory information management system(s) by the laboratory before introduction. Whenever there are any changes, including laboratory software configuration or modifications to commercial off-the-shelf software, they shall be authorized, documented and validated before implementation."</p> <p>7.11.6 "Calculations and data transfers shall be checked in an appropriate and systematic manner."</p> <p>7.11.3 "The laboratory information management system(s) shall: a) be protected from unauthorized access; b) be safeguarded against tampering and loss; c) be operated in an environment that complies with provider or laboratory specifications or, in the case of non-computerized systems, provides conditions which safeguard the accuracy of manual recording and transcription; d) be maintained in a manner that ensures the integrity of the data and information; e) include recording system failures and the appropriate immediate and corrective actions."</p> <p>8.4.2 "The laboratory shall implement the controls needed for the identification, storage, protection, back-up, archive, retrieval, retention time, and disposal of its records. The laboratory shall retain records for a period consistent with its contractual obligations. Access to these records shall be consistent with the confidentiality commitments, and records shall be readily available."</p>

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