White Paper

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United States Hemp Testing: Laboratory Compliance

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Abstract

Following the legalization of hemp in the 2018 Farm Bill, the number of hemp-derived products has dramatically increased. Laboratories that inspect the quality and safety of these products are now required to comply with the Food and Drug Administration (FDA) current Good Manufacturing Practices (cGMP). Even facilities that manufacture Cannabidiol (CBD) products should anticipate eventual FDA regulations. For companies new to this process, this landscape can seem difficult to navigate.

To assist testing facilities, this white paper has been created to introduce Agilent's compliance recommendations for the industry. These recommendations are based on FDA cGMP requirements for dietary supplements and Agilent expertise in this space.

As federal regulations continue to mature, more hemp-based products will require FDA cGMP adherence. Quality testing labs and manufacturers that do not comply may receive regulatory action.

The following technical overview has been written as a continuation to this series:

Recommendations for Hemp 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, 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 cannabis 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 hemp testing/manufacturing facility, as compliance in these areas is required for many hemp products. As the industry continues to mature, it is expected that laboratory regulations will become more stringent.

A list of nonconformance citations for dietary supplement manufacturing can be found in the appendix of this document.

Current hemp regulatory landscape

The products that can be made or derived from hemp are diverse and regulated within different federal requirements. This section will briefly discuss the requirements surrounding hemp products as well as testing facilities that are required to differentiate cannabis from hemp.

Cannabis potency testing

The 2018 Farm Bill legalized the commercial cultivation of hemp in the United States and defined hemp as any part of the *Cannabis sativa* L. plant that does not exceed the concentration of 0.3% Δ^9-tetrahydrocannabinol (THC) on a dry weight basis.[2] As a result of this bill, the United States Department of Agriculture (USDA) released its Final Rule dictating that all hemp production must be sampled and tested for THC concentration levels. This testing must be performed in a Drug Enforcement Administration (DEA)-approved lab, as samples are to be treated as a controlled substance.[4] The USDA does state that a laboratory's quality assurance program must ensure the validity and reliability of results (7 CFR 990.3 (3) (iii) (A)), but little direction is provided.

Conventional food

Not long after the legalization of hemp, the Food and Drug Administration (FDA) approved the use of three hemp-seed derived ingredients for food products. They have been classified as "generally recognized as safe" because of their trace concentrations of THC and Cannabidiol (CBD).[5] Manufactures of hemp seed products must comply with the FDA's current Good Manufacturing Practices (cGMP) for food products. These requirements are outlined in 21 CFR Part 117 and require minimal laboratory testing.

Dietary supplements

Under the Food, Drug, and Cosmetic Act, hemp concentrate, metabolite, constitute, extract, or combination meant for digestion can be marketed as dietary supplements. (21 U.S.C. § 321 (ff) (1)). Except for Cannabis-derived drugs, supplement manufacturing requires the strictest level of cGMP compliance and will be the primary focus of this paper. Supplement requirements are outlined in 21 CFR Part 111 and a breakdown of laboratory requirements can be found in Table 1.

Table 1. Federal manufacturing regulations for dietary supplements.

Dietary Supplements cGMP	
Qualify/Calibrate Laboratory Equipment	"Instruments or controls used in the manufacturing, packaging, labeling, or holding of a dietary supplement, and instruments or controls that you use to measure, regulate, or record temperatures, hydrogen-ion concentration (pH), water activity, or other conditions, to control or prevent the growth of microorganisms or other contamination must be: (i) Accurate and precise; (ii) Adequately maintained; and (iii) Adequate in number for their designated uses." – 21 CFR Part 111.27 (a) (6)
Data Retention and Availability	"You must keep written records required by this part for 1 year past the shelf life date, if shelf life dating is used, or 2 years beyond the date of distribution of the last batch of dietary supplements associated with those records. Records must be kept as original records, as true copies (such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records), or as electronic records." – 21 CFR Part 111.605 (a) and (b) You must have all records required under this part, or copies of such records, readily available during the retention period for inspection and copying by FDA when requested." – 21 CFR Part 111.610 (a)
Data Integrity Controls	"Persons who use closed systems to create, modify, maintain, or transmit electronic records shall employ procedures and controls designed to ensure the authenticity, integrity, and, when appropriate, the confidentiality of electronic records, and to ensure that the signer cannot readily repudiate the signed record as not genuine." – 21 CFR Part 11.10

CBD edible products

Although the 2018 Farm Bill removed hemp from the Controlled Substances Act, it is important to note that CBD products derived from hemp cannot be marketed as food or dietary supplements under the Federal Food, Drug, and Cosmetic Act.[6]

While not currently the case, over time it is anticipated that regulations for these products will be comparable to dietary supplements. Manufacturers that market or produce edible CBD products should expect cGMP similar to dietary supplements and consider the topics discussed in this paper.

Cosmetics

Generally, products designed to be applied to the skin for beauty or cleansing purposes are classified as cosmetics and do not require FDA premarket approval (with some exceptions). Certain ingredients are restricted, but this is not the case for Cannabis-derived ingredients.[7] Although cosmetics do not have their own cGMP regulations, the FDA can take regulatory action against firms that produce adulterated products. Not following generic cGMP guidance may result in the manufacturing of harmful cosmetics.[8]

Drugs

Hemp products intended for the diagnosis, cure, mitigation, treatment, or prevention of any diseases are considered drugs. These products cannot be sold without FDA approval and require strict adherence to cGMP, among other things.[9] These requirements are outlined in 21 CFR Part 210 and 211, and require significant laboratory testing.

Laboratory compliance

The types of products derived from hemp are varied, and each has different manufacturing requirements. Forward-thinking labs should anticipate future regulatory compliance stringency, especially around CBD edible products.

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.

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.[10]

Qualify – To prove that equipment is working correctly, and that its results are accurate.[10]

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.[11]

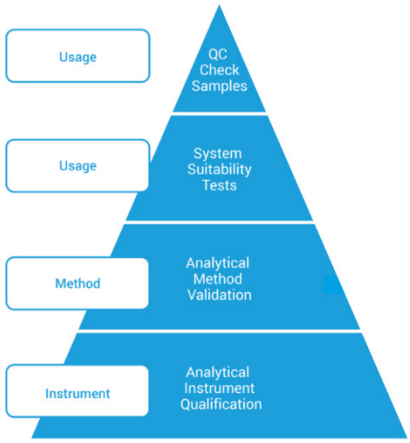

Figure 1. USP's Data Quality Triangle.

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.

The FDA's requirements for instrument calibration/qualifications are purposely ambiguous (Table 1) and provide little in meaningful direction to assist laboratories. USP Chapter <1058> addresses this gap and is the only regulatory chapter dedicated to instrument qualifications. Regulated laboratories should follow this chapter to ensure the validity of their equipment.

More information on this chapter can be found in Bob McDowall and Paul Smith's four USP <1058> white papers.[12]

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." [13]

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.[13]

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." [13]

The retention and protection of metadata are crucial to ensuring data integrity. Safeguarding the protection and retention of critical pieces of metadata are 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.[14] 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 is fixed, such as a paper record or an image.[15]

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.[15]

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+.[16]

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, set up, 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.[17] 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.

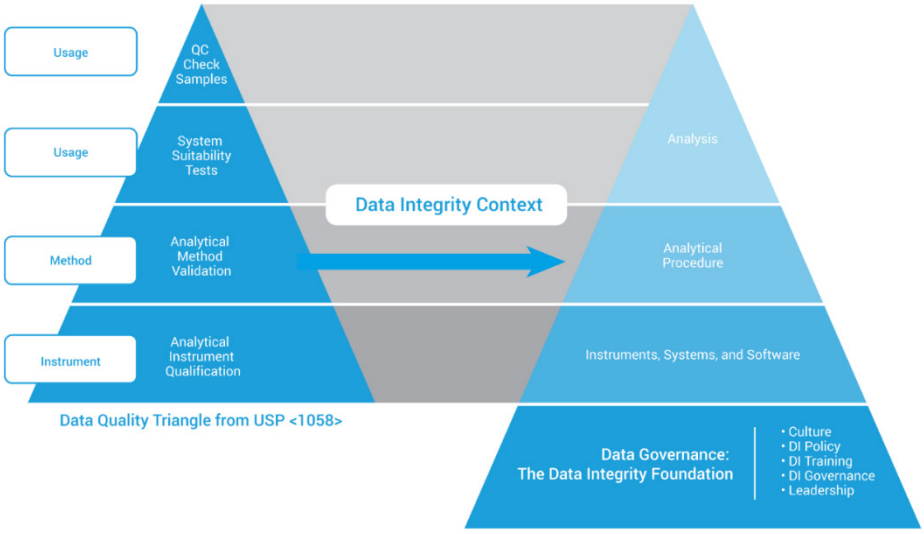

Figure 2. The Data Integrity Model.

Agilent recommendations for laboratory compliance in the hemp industry

The principles discussed previously are at the core of cGMP for dietary supplements and drug manufacturing. 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 Hemp Testing: Laboratory Compliance[1]

Conclusion

The legalization of hemp is relatively new, and regulations are still maturing. The manufacturing of hemp-derived food, dietary supplements, and drugs is required to adhere to cGMP to ensure the quality and safety of these products. Although edible CBD products cannot be marketed as a food or dietary supplements, forward-thinking labs should anticipate possible FDA oversight and requirements to develop and demonstrate a data governance plan for the safeguarding of analytical data. These requirements are satisfied through equipment qualifications/calibrations and data integrity controls protecting the source/raw data that is captured. Laboratories in this industry will find regulatory expectations changing quickly. Partner with Agilent to stay updated and compliant with current hemp regulations.

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Appendix

Table 2. Examples of non-conformance citations for dietary supplement manufacturing.

No.	Example Dietary Supplement cGMP Citations	Observation	Reference
1	"…you had no records showing the date that the review, approval, or rejection was performed or the signature of the person performing the review, approval, or rejection…"	Data not retained	FDA Warning Letter Reference: 606640
2	"You did not qualify a supplier of a component by establishing the reliability of the supplier's certificate of analysis through confirmation of the results of their tests or examinations."	Supplier's quality program not qualified for use	FDA Audit Citation FEI: 3010539352
3	"You did not calibrate instruments or controls used in manufacturing or testing a component or dietary supplement before the first use to ensure the accuracy and precision of the instruments or controls."	Calibration/Qualification not performed	FDA Audit Citation FEI: 3002767376
4	"Your quality control operations did not include periodically reviewing all records for calibration of instruments and controls."	No periodic review of records	FDA Audit Citation FEI: 3004693308
5	"You did not establish appropriate controls to ensure that your automated, mechanical, or electronic equipment functions in accordance with its intended use."	Calibration/Qualification not aligned with intended use	FDA Audit Citation FEI: 3010312584
6	"You failed to calibrate instruments and controls you use in manufacturing or testing a component or dietary supplement…"	Calibration/Qualification not performed	FDA Warning Letter Reference: 585324
7	"Your calibration documentation did not provide the calibration reading or readings found."	Missing source data	FDA Audit Citation FEI: 3009152755
8	"You failed to include complete information relating to the production and control of each batch in your batch production record (BPR)"	Missing metadata	FDA Warning Letter Reference: 583992
9	"Electronic records are used, but they do not meet audit trail requirements to ensure that they are trustworthy, reliable and generally equivalent to paper records."	Data integrity issues with electronic records	FDA Audit Citation FEI: 3006481857
10	"You did not keep original records, true copies, or electronic records."	Data not retained	FDA Audit Citation FEI: 3009487794
11	"Your electronic records for your laboratory operations do not comply with the electronic records requirements."	Data integrity issues with electronic records	FDA Audit Citation FEI: 3009748303
12	"You did not make and keep backup files of outdated software necessary to retrieve records from the computer systems that you use to manufacture, package, label, or hold dietary supplements."	Electronic data unreadable	FDA Audit Citation FEI: 3005570707
13	"Electronic signatures based on identification codes/passwords are used, but they do not meet the id/password issuance control requirements of 21 CFR Part 11."	Data integrity issues with electronic records	FDA Audit Citation FEI: 3002315216
14	"You did not have required records, or copies of such records, readily available during the retention period for inspection and copying by FDA when requested."	Data not readily available for an auditor	FDA Audit Citation FEI: 3002315216
15	"You use (b)(4) to conduct identity testing on all of your components but you have not qualified your (b)(4) spectrometer for this purpose."	Calibration/Qualification not performed	FDA 483 Report FEI: 3006481857

FEI = FDA Establishment Identifier

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