THOUGHT LEADERSHIP

CBD MANUFACTURERS MUST DEVELOP GMPS EVEN ABSENT FDA INSTRUCTIONS

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Cannabidiol (CBD) is the latest “it” product. Companies across the US and internationally are eager to manufacture CBD or incorporate CBD into a variety of other products. But a mountain of uncertainty exists regarding how the US FDA and other regulatory agencies will regulate CBDs. While “wait and see” may be the answer to many CBD-related questions, there is one area where manufacturers can get a jump on future regulations: **Good Manufacturing Practices (GMPs)**.

Responsible companies seeking to enter this market need to prepare now for regulations FDA and its sister agencies may choose to apply to CBD products. And right now, there is a lot of confusion over just what those regulations will ultimately address, with little expectation of a speedy resolution from the agencies. Despite California’s enactment of GMPs in January of 2019, this regulatory framework may not turn out to align with FDA’s approach to CBD or cannabis GMPs. Reliance on California’s GMPs by companies outside of California could result in surprises down the road when FDA or other international regulators fully define their approach. Further, it appears that California took a one-size fits-all approach to CBD, hemp oil, cannabis, and related products. There are distinct differences between the use-case positioning of these product classes, and it’s unlikely that all of these product types will require the same GMP rigor.

Some FDA and industry experts speculate it could take three to five years for the FDA to come out with a comprehensive approach. If you're truly interested in tackling the CBD market, the worst thing you can do is wait three to five years for direction. **The time to act is now!**

The FDA's official position is that it is examining the science of CBD products. In a memo on its website, updated in November 2019, the agency wrote that it "recognizes the significant public interest in cannabis and cannabis-derived compounds, particularly CBD. However, there are many unanswered questions about the science, safety, and quality of products containing CBD. The agency is working on answering these questions through ongoing efforts including feedback from a recent FDA hearing and information and data gathering through a public docket." (http://fdainfo.us/cbd)

A "control framework" developed now, helps speed GMP compliance later

Without clarity in the direction of GMP requirements or expectations, one area CBD manufacturers can begin to prepare is the development of a GMP-focused "control framework." Savvy companies will benefit by the development of a framework of SOPs, risk management strategies and QA/QC programs for their CBD products. If carefully and thoroughly developed, future regulatory requirements will easily be grafted onto the existing control framework.

But there are many factors to consider, most of which will be unfamiliar to upstart CBD manufacturers. And when using growers who are more attuned to agricultural regulations aimed at food products, companies will find there is a steep learning curve for their CBD suppliers to meet more pharma-like handling, storage and transportation parameters, along with the rigorous GMP documentation requirements.

Nonetheless, companies truly interested in separating themselves from the bad actors in this emerging industry can succeed. The first steps are applying proven GMP concepts - supplier quality, risk assessment and mitigation, CAPA, quality control, product specifications and testing methods for instance - to their manufacturing processes. This needs to be done using a systemic approach, as a core principle of GMP is that foundational systems like training, procedures, specifications and testing must be established and govern the manufacture of all marketed products.

Companies need to keep in mind that the regulated product class and the marketing/labeling claims of the end product, dictate the extent of the requirements your company will need to fulfill. So, companies will need to start by determining exactly where their product will be used and work backwards from that point to determine what requirements must be met. That means that all specifications and quality standards set for production of a theoretical new CBD product - or family of products - will be based on existing standards for the end-product regulated product class.

Another key concept is that of risk management. At their heart, GMP systems are aimed at preventing, or at least mitigating, identified risks associated with manufacture of a product, regardless of whether it is a drug, a food, a supplement or some other regulated product.

Closely related to risk concepts are verification and validation, important components of any GMP system. All FDA-regulated products are subject to safety standards; in the case of medical products, efficacy requirements also apply. Any processes or procedures that are critical to ensuring safety and/or efficacy must be verified and validated. Companies eyeing CBD products will need to make sure to include well-defined and justified verification and validation activities for all critical manufacturing processes, including sourcing.

Soybeans aren't CBD: Where farm meets pharma

It's also important that companies remember that GMP - and risk management - concepts must apply at all stages of production, and this includes sourcing. In the pharma world, companies must verify the vendors that supply their raw materials, including active ingredients, and equipment, as well as those that provide transportation and storage services.

It is important to remember that the product sponsor always has the ultimate responsibility for ensuring that all quality and GMP requirements are met at every stage of production. Companies in the CBD market will need to wed these requirements with normal procedures of hemp growers and wholesalers. The question is: are hemp growers and wholesalers - who may be skilled in agricultural/food regulations - up to the standards the FDA will eventually set for CBD? **The answer is likely, no.**

Thus, guiding these growers/wholesalers into compliance – especially GMP compliance – with pharma/dietary supplement regulatory expectations may pose a significant challenge for CBD manufacturers. Manufacturers should be prepared to provide formal contractual expectations and training for everyone along the supply chain to ensure that misunderstandings about regulatory requirements do not create unexpected downstream risks.

Related processes to consider are transportation and storage. Both are core requirements of GMPs because environmental conditions - temperature, humidity, etc. - can have a significant impact on the characteristics of the raw materials, which can then affect the end product's safety or efficacy. Many CBD manufacturers are asking themselves: do we need refrigerated trucks from field to warehouse? It's a good question. The answer depends on end-product use case, claims, and characterization.

Getting into the manufacturing and quality weeds

After obtaining the raw material, the next step involves extracting the CBD from the hemp. This may well be a differentiating aspect between CBD producers, and therefore companies will need to carefully describe each step of this process, which could include extraction, separation and isolation, blending, purification and formulation steps. By creating SOPs for these steps that are sufficiently detailed, justified by science and include verification and validation processes, companies will be well-positioned to adopt any GMP requirements the FDA or other regulators will eventually develop for these products. These steps should be based on pre-established quality attributes and include QA/QC procedures aimed at guaranteeing reproducibility of all steps and consistency of the end product.

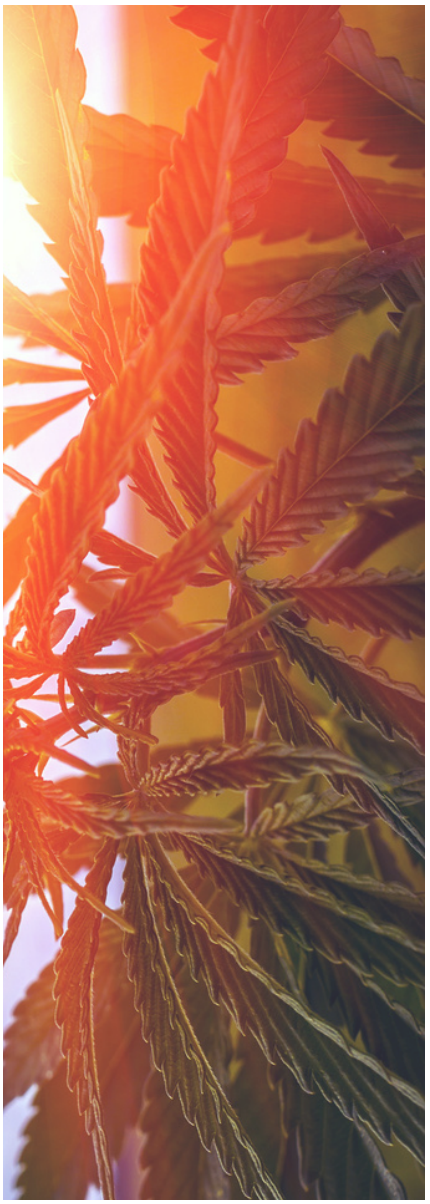
Another key part of a pre-GMP manufacturing control framework is quality control (QC) for release of product to the market, including batch testing and handling of out-of-specification (OOS) product. Companies will need to establish appropriate specifications for their CBD products, regardless of how those products are classified. It is important that manufacturers understand they cannot “test into quality.” The FDA expects accurate, reliable and timely batch testing methods and results. Laboratory practices are often a top focus of FDA inspections and failures here can lead to costly regulatory fallout.

To avoid such problems, companies need to, in advance, establish clear procedures for handling OOS test results, including measures to trace the problem to its origin and initiate corrective actions.

A solid corrective and preventive action (CAPA) program is another essential component of any GMP system. A good pre-GMP control framework will include robust CAPA requirements and procedures as part of the overall quality system. The FDA and other regulators look for well-designed CAPA systems that ensure any mistakes or quality problems are quickly investigated, root causes determined and corrected, and a corrective and preventive action plan established to ensure that the problem(s) do not recur.

And how will companies entering the CBD market manage and ensure the robustness of their GMP program? Establishing a dedicated quality unit is an important first step. This department/function should include qualified personnel whose sole focus is on quality. Experience and skills should be drawn from various technical domains, such as manufacturing quality, regulatory compliance and CBD-specific technical knowledge. Giving out titles and designating a QA/QC team as a standalone activity is not enough. In the interest of well-established control, the FDA's guiding philosophy for GMPs, the notion of quality must pervade the whole of a company's culture. Training is an important aspect of this culture.

A critical part of a fledgling CBD company's success will be the creation of and adherence to well-thought-out, easily understandable (and useful) SOPs. These should exist for all quality-related activities, as well as for all manufacturing operations, from material sourcing through final packaging and release for sale. SOPs form the foundation for GMP compliance and should be considered the cornerstone of robust GMP activities.



Well-drafted SOPs will help meet multiple business objectives. Not only will they support meeting future regulatory requirements and expectations, but they will also create efficient and reproducible business processes, resulting in consistent, cost-effective and profitable production operations.

If it isn't written down, it didn't happen

Documentation is THE cornerstone for all FDA regulated activities. In a nutshell, FDA and other regulators expect companies to document all activities accurately, thoroughly and in a timely manner. Every aspect of manufacturing must be documented to satisfy regulatory agencies, a fact that is emphasized in virtually all GMP-related guidance.

Documentation starts with SOPs. As part of every SOP, companies need to include how they will document that the procedures were followed, including identifying who has authority to sign off on that documentation. Documentation of the requirements and activities outlined in SOPs is through what are called quality records. Quality records must be well designed, easy to complete, and must serve as the record to establish what was done in the operation.

The rigor of documentation depends on the importance of the information; the importance is determined by agency expectations. For example, the importance of training records may be deemed somewhat less than product release documentation; therefore, the specificity and document control requirements for the former would be less rigorous than for the latter. Understanding the risk associated with certain activities will help companies determine how much information to include in associated documentation, and how tightly to control it with respect to access, sign-off authority, version control and other key factors.

Conclusions:

Entrance into the booming CBD market is understandably tempting for any manufacturers. But unfortunately, you can't just buy a certificate of FDA GMP approval. Nor can you just take a class and then deem yourself GMP complaint. GMPs are not a static or specifically designated "thing" - they're a precise combination of regulation, expectation, art, science and commitment. Fortunately, for companies that want to be good actors and are in it for the long haul, development of a pre-GMP control framework will give them significant advantages:

Competitive advantage - bad actors will eventually run into product quality trouble without solid control frameworks;

Certainty and predictability - preparation now will position manufacturers to quickly graft the eventual FDA requirements onto existing quality operations and be compliance-ready much faster; and

Financial success – investing in a control framework upfront will be less expensive than trying to rush to completion once FDA and other regulations are issued.

Quality, manufacturing and GMP regulatory compliance is a highly specialized area, and companies new to this area would be well-advised to seek expert guidance before making these investments. For further information or for help on how to develop a GMP framework for CBDs, please contact **Jack Garvey** at **john.garvey@compliancearchitects.com** or at **732-397-3103** or **Jeff Grizzel** at **jeff.grizzel@compliancearchitects.com** or at **703-587-8990**.