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The Road to Operational Readiness in the Cannabis Industry

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Abstract

With a rapid growth of global interest in the cannabis industry and with the push towards legalization, it is important to understand the production process of cannabis from seed to sale. Building recognition and appreciation for the complexities of the cannabis plant and associated product manufacturing will help explain the cannabis industry and the challenges it faces in its journey towards consistency and compliance.

Due to the lengthy timeframe to become operationally sustainable to supply the market leads newly legalized countries to import product from already established markets. As a result, Canada finds itself in the spotlight. Canada's legal framework for cannabis has become the industry standard in compliance, safety, and quality, and thus many countries are looking to Canadian companies to import products for the supply of medical cannabis. However, in order to enter into supply and distribution agreements, the company's level of standards need to align. The European Union countries have determined that their acceptable level of standard for cannabis production will be EU-GMP standards. Additionally, many companies throughout Canada and the United States have decided to shift towards EU-GMP standards in order to compete on the global stage. This article will provide an overview of the process and undertaking to complete a production cycle, as well as discuss the gaps and time limiting factors for companies looking to receive to EU-GMP accreditation to supply the global market.

Introduction

Considered taboo for decades, the topic of cannabis has softened considerably over the recent years and catapulted itself onto the global stage. It is everywhere, from mainstream media to casual conversations around the dinner table. The attention is undeniable. Cannabis, and the associated cannabinoids, are being studied for their potential medical benefits to patient health. Commonly referred to as an "alternative medicine", cannabis has entered the medical field and established its reputation with patients and physicians in pain management and epilepsy. One by one, countries are starting to consider the legalization of cannabis. Canada led the charge in legalizing the use of medicinal cannabis in 2001 with the Marihuana Medical Access Regulations (MMAR) (1). These regulations, under the close supervision of Health Canada, authorized cultivation of cannabis at home for those who had a valid medical prescription. In 2013 and again in 2016, the "home grow" model was expanded with new regulations authorizing commercial cultivation and distribution of cannabis for medical use (1). Fast forward to October 17, 2018, a historic date for Canada in which the most recent legislation came into force, the Cannabis Act. With this legislation, Canada became the first G7 nation to legalize cannabis for both medicinal and recreational use (1).

Many countries have begun to follow suit and legalize medical cannabis, with most of the focus seen in European countries. However, the road to operational readiness of a cannabis facility is not a simple path. Countries joining legalization rely heavily on those with already established industries for on-going supply of medical cannabis to their patients until they reach the point of self-sufficient production. Canada, due to its 18-year history of legal production of cannabis, has been regarded by many as the global leader, resulting in Canadian products being exported internationally.

Exportation of medical cannabis into the European market requires compliance to international regulations enforced by the EU and EU member states authorities. The supplier qualification process begins with understanding the regulations and standards adopted by the potential partner in the European county. The European Union has determined that the acceptable standard for importation will be to work with facilities holding EU-GMP certification (EU-GMP). EU-GMP has its own unique

requirements that vary from those imposed by the Cannabis Act in Canada, as well as other standards being implemented around the world.

Discussion

What is Cannabis?

In order to understand the life cycle of cannabis from seed to sale, it is important to understand the plant itself. Cannabis is a dioecious plant, meaning both male and female plants produce flowers. Female cannabis plants, however, are the most sought after since only they can produce buds for harvest.

The leaves and flowers of the cannabis plant contain over 500 compounds that are distributed among 18 different chemical classes, which include over 100 phytocannabinoids (10). Trichomes are glandular structures found on the epidermis of the plant leaves, flowers, and stems. They are the resin producing structures that contain cannabinoids, terpenes and flavonoids. Cannanabinoid synthesis within the trichomes begin as the plant move into the flowering stage. As flowers are produced, the trichomes form on the outer surface. During this time, cells within the gland begin to metabolize eventually becoming cannabinoids.

The most widely recognized and researched cannabinoids are delta-9-tetrahydrocannabinol (THC), which is the only compound present in the cannabis plant that produces psychoactive effects, and cannabidiol (CBD), for its many potential therapeutic uses (14). All cannabinoids present in the plant are in acidic form and require decarboxylation to transform the molecule to a non-acidic form that is absorbable by the human body.

Cannabinoids and the Body

The endocannabinoid system is a lipid signaling system found in all invertebrates. It is implicated in a vast number of physiological and pathophysiological processes in the body including nervous system development, immune function, pain, and bone development (10). The endocannabinoid system consists mainly of 2 receptors, cannabinoid 1 and cannabinoid 2 (CB1 and CB2).

CB1 and CB2 receptors are found throughout the body. CB1 receptors are found primarily in the central nervous system whereas CB2 receptors are most concentrated in peripheral tissues as well as the immune system and related organs (2). Cannabinoid receptors are G-protein coupled receptors activated by three different types of ligands, including plant cannabinoids (11). The CB1 receptor is most commonly known for its association with THC and its euphoric effects once activated by THC. CB2 receptors, although structurally similar to CB1, differ in distribution and activity. CB2 receptors act in pain modulations and have important roles in immune function and inflammation (11). As a result, CB2 receptors have received a lot of attention due to their potential therapeutic possibilities and their link to various pathologies (15).

Figure 1 has been extracted from *The Endocannabinoid System, Cannabinoids, and Pain* outlining various physiological actions that are activated by cannabinoid receptors (11).

Table 1

Physiological Actions Mediated by Activation or Inhibition of Cannabinoid Receptors.

Physiological Actions
1. Antinociception
2. Cognition and memory
3. Locomotor activity
4. Endocrine functions
5. Temperature control and heart rate
6. Nausea and vomiting
7. Intraocular pressure
8. Inflammation
9. Immune recognition and antitumor effects

Cultivation

From start to finish, the process of preparing cannabis for distribution varies significantly from all other products in the Pharmaceutical industry, where relatively short production cycles allow for products to become readily available for mass distribution. Cannabis starts from a seed. It requires time and effort to take it through its life cycle to flower and prepare it for distribution.

Figure 2 is an excerpt from *Application of GMP in the Cannabis Industry* illustrates a high-level flow of the cultivation and processing of cannabis products (16).

The most common cannabis growth cycles begin either from seeds, or from cuttings. In its infancy as a seed, development is slow and tedious rendering this the less preferred method of cultivation (2). The most commonly used method is to grow new plants from the cuttings of the “Mother plants”. Mother plants are grown for the purpose of genetic cloning (2). Cannabis mother plans are carefully chosen because they have exhibited characteristics that the cultivator deems favorable. These favorable characteristics can range depending on the desired result the cultivator is targeting to achieve (3).

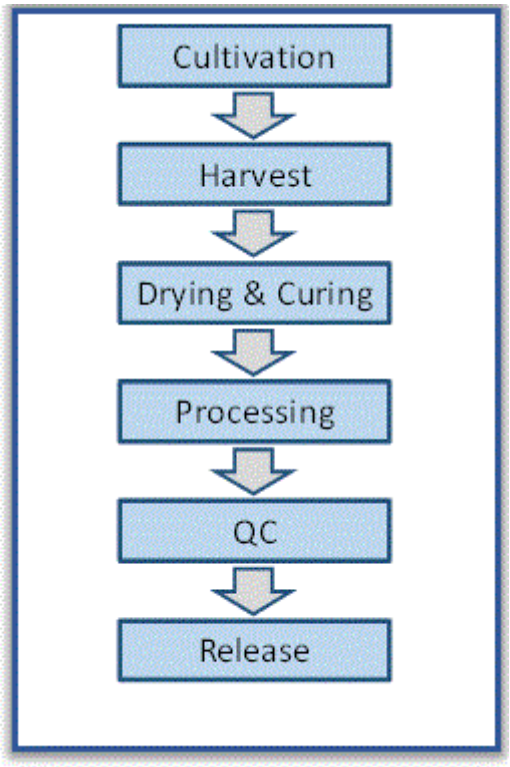

Figure 1: Cannabis Manufacturing Flow

The Mother Plants are intentionally kept in their vegetative state as their goal is not to produce flowers, but to produce cuttings for cloning (3). Clippings from the mother plant are immediately placed into water and transferred into the final rooting medium (6). After the first few days where clones do not require light, they are then subjected to 18 hours of light and roughly 6 hours of darkness. This is required for optimal growth. Most clones begin the rooting process within several days, however the process can take up to a few weeks (5). After the rooting process is complete, the clone is then transplanted.

Growth and flowering of the cannabis plant is regulated based on the number of hours of uninterrupted darkness plants are subjected to (4). Phytochrome is the hormone produced by the plant at the beginning of germination. Phytochrome is extremely sensitive to light. Even a few moments of light could be enough to destroy the chemical (4). When phytochrome builds to critical levels it will trigger the plants to begin flowering. The flowering stage can typically last anywhere from 8 to 10 weeks. During this time, a series of processes occur. At around the midpoint of the process the cannabis plant has achieved its optimal height, and the pistils, which are the female sex organs of the cannabis plant, will be almost entirely white and sticking straight out. At this point the buds will begin to form (4). As the buds continue to grow larger and more dense, the pistils will still be primarily white. During the final stage the buds will begin to flatten quickly, and the pistils will begin to mature. Maturation of the trichomes, the resin glands containing THC, CBD, and other active cannabinoids, also occur at this time. The buds are now ready for harvesting, trimming, and drying processes.

When cannabis is cultivated indoors, the cultivator can control the timing in which the plants remain in a vegetative state, and the time in which they want the plants to begin to flower. The benefit of being able to control the timing of these processes allows for the production to be staggered, giving time for the remaining steps to occur. If all the plants flower simultaneously, it would be very difficult to manage all the operations, especially those that are time sensitive (5).

Facility

A cannabis facility requires extensive and thoughtful planning prior to breaking ground for construction. There are many elements to consider when designing a facility. Whether you are retrofitting an existing structure, or building new, several factors need to be carefully assessed.

Once a company has determined its proposed cultivation and processing techniques, it can decide on the required size of the facility. The goals set for cultivation and processing will steer the design and create a unique and fully customized footprint.

An important element when designing a floor plan is assessing the flow of material and personnel. This is a critical step for those companies wishing to implement GMP. To begin, there must be a fundamental understanding of what activities and

rooms are most critical to GMP production. Rooms which are used in the seed to flower life cycle of the plant are the areas that pose the highest risk of contamination. These rooms often have soil, beneficial pests, and other materials which would typically be deemed “dirty” or non-GMP areas. In contrast trimming, drying, packaging and storage areas would be those areas which require the highest quality standards to be maintained and are consider your GMP zones.

When designing production facilities consideration needs to be given to ensure that appropriate segregation between these areas exists, while maintaining efficient product and personnel flow. Dedicated GMP vs non-GMP corridors, separate entrances, and product transfer airlocks are some of the additional considerations to be made during the design phase of a GMP facility.

Refer to Figure 3 for a high-level example of a facility and the flow of materials through it.

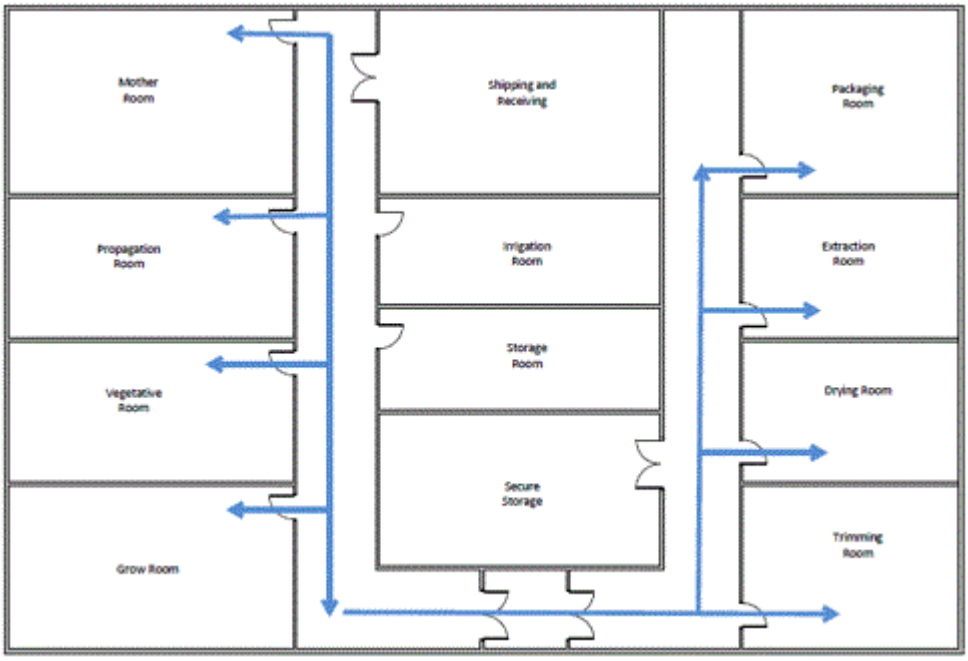

Figure 3 is a high-level diagram of the flow of materials through the facility as the cannabis moves from the Mother room to Propagation, Vegetative and Grow Rooms as the plants move through their grow cycle. Once the plants have completed their flowering phase, they continue to Trimming and Drying phases. If the intended end product is an oil, the plants would then proceed to the Extraction Room, and if not, the dried cannabis would then move to final packaging.

Equally important to the design of the facility are the materials selected to construct it. Many elements need to be properly accessed to achieve necessary design standards for GMP compliance. Among those necessary elements, wall materials are required to be non-porous, easily cleanable surfaces. Furthermore, the design of air filtration system requires extensive planning to ensure it is adequate for the facility.

Regulations and Validation

Canada established a set of regulations referred to as GPP (Good Production Practices). These are the accepted set of standards for all cannabis facilities within the country. Key focus areas of GPP are cleanliness of a facility and its equipment, analytical testing, pesticide use, and standard operating procedures. It is also intended to regulate the quality of the cannabis by ensuring the process is monitored and product is released by a Quality Assurance Person (QAP) that has appropriate training and expertise to approve the products prior to making them available for sale (9).

Other countries, such as the Unites States, have opted for a non-standardized approach. Currently, there is no legal framework on the federal level. Each State that has adopted legalization is responsible for determining its own regulations and standards, creating significant variability across the country.

With the Canadian standardized system of GPP, and with the varying standards established in other countries, the biggest hurdle in moving towards a universally accepted standard of EU-GMP, is validation. It is the largest gap seen throughout the various systems and an essential component for those choosing to implement EU-GMP standards (16).

Validation requires a proven procedure that will consistently produce outcomes and products according to set specifications.

Indeed, not all aspects of the cannabis process are consistently reproducible due to variability associated with plant production. It is not difficult to imagine the inconsistencies that one would expect to see from one crop cycle to the next. Living things that grow are unlikely to follow the exact same process during each of their growth and flowering stages. They are susceptible to many factors, such as temperature, pests, and humidity, and even vulnerable to “illness” introduced by an individual that comes into contact with the plants. For example, someone with a cold can potentially “infect” the plants and alter the course of their vegetation and flowering stages. Slight differences in exposure to light, perhaps even by error, can significantly affect the phytochrome levels in the plants. With all the potential for variability, validation of cannabis typically begins further downstream in the process.

Validation is a very laborious process. It will certainly be the one of the longest processes for cannabis companies choosing to move to EU-GMP. There are several types of equipment essential to the process, including trimmers, balances, and extractors, and all associated equipment will need to undergo equipment validation as the facility moves to EU-GMP. All production activities, whether the intended outcome is dried product, or and extracted oil, will require full method and process validation to comply with EU-GMP regulations.

Another vital step in the process is to determine product stability. This will be one of the critical steps required for companies processing the final product and packaging, and essential for those establishing product expiry dates (12). In order to ensure product quality, companies will want to validate their processes to determine appropriate shelf life and expiry dates. This is a continuing process. An on-going stability program should be established to monitor the products over their proposed shelf life to ensure that the products remain, and will continue to remain, within the given specifications under recommended storage conditions (13).

Testing

There are several tests that are required to be performed prior to releasing your final product for distribution. First, a representative sample of each batch must be tested for pesticide active ingredients. It is imperative that the laboratory validates their methods prior to use. The methods must be able to quantify pesticide active ingredients against the naturally occurring chemicals in the sample (7).

Additional to the requirements in place for pesticide testing, there are requirements for testing of solvents residues, microbial and chemical contaminants, as well as the quantity and percentage of THC, Tetrahydrocannabinolic Acid (THCA), CBD and Cannabinolic Acid (CBDA) (8). Upon completion of all testing and review of all production records, the product is now ready to be distributed.

Conclusion

The cannabis production process from seed to sale is complex, labor intensive, and time-consuming. Cannabis cannot be quickly synthesized, and mass produced with the click of a button. Understanding the intricacies of the system provides clarity for the need of a unified market. With the European Union predicted to be one of the largest markets as more of its countries move towards legalization, it is easy to understand the initiative for countries to move towards establishing EU-GMP compliant facilities. This will inevitably become the gold standard for the cannabis industry.

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