

Challenges and best practices in phytopharmaceutical production

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Introduction

Plant based drugs present unusual challenges in the pharmaceutical world with respect to indoor cultivation, processing, quality, and consistency [Chandra et al., 2017]. “Cannabis” refers to marijuana, plants and plant parts of plants of *Cannabis sativa* L., cannabis preparations (e.g extracts), cannabinoids as active substances and respective herbal medicinal products have been available to patients for several years. The spectrum of respective medicinal cannabis products is as follows:

- dried and purified herbal drug: cannabis inflorescences (“medicinal cannabis”);
- various cannabis extracts (“medicinal cannabis preparations”);
- pure cannabinoids are referred as API and even they are obtained from cannabis, are not considered as herbal products because it is highly purified.

This article will describe applicable standards in cultivation, harvest/processing, manufacture of medicinal cannabis products, challenges, and solutions.

Industry standards

GACP/GMP zone concept

In order to ensure that the quality of starting materials is as consistent as possible, there are GACP guidelines, such as the “Guideline on Good Agricultural and Collection Practices for Starting Materials of Herbal Origin” (EMA/HMPC/246816/2005) of the EMA⁴. This guideline has been in force since 2006 and is binding in

Europe for the collection of herbal starting materials, as Annex 7 of the EU GMP Guide explicitly refers to them.

The activities, according to GACP, are followed by the manufacture of the herbal preparation or the herbal medicinal product, which must be carried out under quality assurance measures according to Good Manufacturing Practice (GMP). GACP manufacturing zone must be clearly separated from GMP zone. EU GMP Guideline Part II provides an overview of the application of the Guideline to the manufacture of active pharmaceutical ingredients and highlights which steps of a manufacturing type (including plant-based active pharmaceutical ingredients) are GMP and which are GACP. Cultivation, collection and harvesting are GACP processes. Cutting (trimming) and drying of plants can be held under GACP or GMP area, while further processing: extraction from plants, purification, isolation shall be held in GMP area.

Batch definition and batch homogeneity

Definition of a batch concerns control strategy, in-process controls, release testing and traceability, as well as cleaning and process validation. Definition of a batch size can be based on propagation and cultivation cycles, origin and age of clones or cultivars, defined cultivation areas or spaces, or capacity of a drying room or equipment. As the effloresces are not cut or crushed for manufacture of cannabis flowers, homogenization is not possible, and therefore certain variability of cannabinoid content must be expected. This ranges from $\pm 15\%$ for cannabis flowers with declared content of cannabinoid up to 15%. For declared content higher than 20% limit for variation is $\pm 10\%$. Batch homogeneity is only possible if the plants are grown from small number of genotypes under strict and

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tightly specified conditions: temperature, humidity, day lengths, planting densities, growth medium ingredients and harvest timings. Good industry practice is periodical monitoring of cannabinoid profile by taking samples of inflorescences from different areas of the growing room, according to previous set sampling plan. Samples are tested every second day as plants approach the maturity stage. Optimum harvest time is important to maximize secondary metabolites which are of pharmaceutical importance.

Microbiological quality

Dried cannabis inflorescences must have minimal contamination by fungi, yeasts and bacteria, as well as specific coliform bacteria and mycotoxins. Depending on the route of administration, the requirements of Ph. Eur. monographs 5.1.4 or 5.1.8 must be met. The most important pathogens affecting cannabis production indoors are *Botrytis cinerea*, *Fusarium oxysporum*, *Fusarium proliferatum*, *Fusarium solani*, *Pythium myriotylum*, *Pythium dissotocum*, *Pythium aphanidermatum*, *Golovinomyces* spp., *Penicilium* species. Where quality policy is pesticide free cultivation, microbiological quality of a product can be optimized by maintenance of stable temperature and humidity in growing area, set parameters according to limits for vapor pressure deficit, vegetative cutting should be disease free, regular removal of diseased cuttings, regular check of plants, pruning out diseased inflorescences, removal of infected plants, maintenance of good hygiene practice.

Cannabis flowers after harvest contain up to 80% of moisture content. The most critical are first 24 hours when removing as much water as possible is essential, to prevent microbial contamination. Optimal temperature and humidity in range of 15-25°C and 30-55% RH and sufficient air changes per hour leads to slow drying and preservation of low volatile terpenes.

Stability

During processing of cannabis flowers, glandular hair has to be intact, since these are accumulation structures for cannabinoids which protects them from oxidative degradation. Light and temperature exposure leads to decarboxylation or decompositions of the cannabinoid acids to neutral cannabinoids. This process is of little relevance as the pharmacological activity comes from decarboxylated cannabinoids.

The oxidative degradation of cannabinoids can be prevented or slowed by protection from atmospheric oxygen. Oxidative degradation is thermodynamically controlled and slows down at low storage temperatures. Thus, protection over oxidative degradation can be achieved by suitable packaging under protective gas or

storage under low temperatures. The latter also slow down microbiological growth and thus prevents contamination of dried cannabis flowers.

Extraction, purification and isolation

Neutral cannabinoids do not occur at significant concentrations in the plants and are usually produced by thermal transformations. Crude extract produced by supercritical CO₂ extraction contains high concentration of cannabinoids, mono and sesquiterpenes, flavonoids, alkaloids and plant matrix: pigments, phospholipids, fatty acids. Plants matrix resembles a highly viscous black gum that form inhomogeneous tar when exposed to increased temperatures [Valizadehderakhshan et al., 2021]. Lipid and waxes precipitation at freezing temperatures, subsequent filtration, solvent evaporation and molecular vacuum distillation are purification steps of crude extract to obtain highly concentrated cannabinoids extract. Since these processes are based on high temperatures, introduction of vacuum prevent exposure to oxygen at these high temperatures and prevent thermal decomposition. Attention to details and optimization of processing conditions from extraction to component isolation remain critical to maximization of yield and purity.

Conclusion

The protocols, procedures and continuous production monitoring developed by Sinceritas enables deep understanding of challenges facing cannabis industry and finding suitable solutions following high industry standards to manufacture consistent product quality.

References

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