Digital development and production of medicinal cannabis

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PEER REVIEW

Abstract

Medicinal cannabis is being used more and more frequently as a form of therapy, which is why the demand in Germany is growing constantly. Producers are faced with the challenge not only of meeting the high demand, but also of ensuring the highest quality while complying with regulatory requirements. As in numerous economic sectors, digitalization is targeted as a solution to current and future problems by the cannabis industry. The use of new and digital technologies offers the possibility to maximize the production yield of cannabis and the quality of the products - while ensuring the highest level of product safety and traceability.

This article looks at medicinal cannabis as a form of therapy and its digitally assisted production. It shows why it is necessary to digitize existing processes and to establish modern digitization strategies. In this context, solution approaches are presented, and it is explained how the use of digital tools can have a positive influence on the manufacturing and distribution processes of medicinal cannabis.

Key Words

- Medicinal cannabis
- Digitalization
- Digital development
- Digital verification models

Introduction

There is a high demand for finished drugs and complex forms of therapy on the global market, but especially on the national German market. In particular, the demand for active ingredients from pharmaceutically adequate production processes of medicinal plants are increasing and can hardly be met so far. An outstanding example in this context is the production and use of medicinal cannabis as a basis for urgently needed therapies. Since the approval of cannabis for medicinal purposes, medicinal cannabis products have been used in an increasing number of therapies, such as cancer therapy and palliative care. To meet the great demand and at the same time the high regulatory requirements in pharmaceutical production, modern and especially digitally supported cultivation and processing strategies are necessary.

Medicinal cannabis

Probably also due to its striking appearance, the cannabis plant did not remain unknown for long. As far back as 6 000 years BC, the hemp plant was used in Asia. In recent centuries, the cannabis plant has spread to Europe and finally to the American continent. Stems and fibers offered countless applications, e.g., to produce textiles, ropes, and paper. But the use of the hemp plant for medicinal purposes also has a long tradition. Thus, medicinal cannabis was probably used as a pain-relieving medicine long before Christ. Nowadays, medicinal cannabis is available in pharmacies as prescription or finished medicines. The content of the medicines are the pharmacologically active components of the plant, the cannabinoids. The cannabis plant has up to 4 000 different components, from which 134 substances can be isolated according to the current state of science. Among the ingredients of the plant are over 100 different cannabinoids, but also various terpenes and flavonoids. The best known and most advertised ingredients are the cannabinoids Δ^9-tetrahydrocannabinol (THC), cannabidiol (CBD), cannabielson (CBE) and cannabigerol (CBG). These very ingredients have a high therapeutic potential. For example, studies show that cannabis preparations have antispasmodic, analgesic, neuroprotective, or anti-inflammatory effects. However, only THC has a psychoactive intoxicating effect.

The exact mode of action and the interaction of the individual components have not yet been fully researched and documented. The effect of cannabis products depends primarily on the composition of the ingredients. Depending on the variety of a cannabis plant and its genetics, the ingredients and their concentra-

tion can vary. Through targeted breeding, it is possible to optimize certain properties of the plant and adapt it to the intended use. By adapting the cannabis genetics to the needs, the yield of the plants can be maximized, and the production made more efficient. For example, if the goal is to produce an extract with a high CBD content, but without a psychoactive and narcotics-law-regulated THC content, it makes sense to use a cannabis plant with the appropriate genetics for production.

Production process of medicinal cannabis

The value chain of cannabis production begins with the cultivation of the plants. Classically, cannabis plants can be cultivated as seeds or seedlings. To achieve consistently good quality and harvest, it is possible to produce seedlings from a single mother plant or to multiply them via cell cultures. By using these modern methods, the heterogeneity of cannabis genetics within a production can be reduced to a minimum. The cultivation of the medicinal plants takes place under regulated conditions in a modern industrial building. There, the cannabis plants are protected from external influences and it can be ensured that each plant grows under identical and constant conditions. To optimize output and achieve consistent quality, temperature, CO_2 concentration and humidity can be adjusted according to the plants' respective growth phase. In addition, LED lamps with an appropriate light spectrum, which can also be adjusted according to the growth phase, serve as an energy source. Water and nutrients are supplied directly to the plant via irrigation systems. The irrigation system is continuously monitored so that there is no oversupply or undersupply of water and nutrients. Once the cannabis plant has reached the flowering stage, it can be harvested. The flowers are then dried and can be sold as a prescription medicine. Alternatively, the cannabinoids and terpenes can be extracted and sold as an extract.

Background/Challenges/Problems

Missing or inadequate framework conditions (regulatory, technical, and scientific), unqualified equipment and lack of qualified personnel as well as non-validated production processes mean that a consistent and comprehensive production of medicinal cannabis under GMP-compliant processes is currently not possible. As a result, there is a lack of stable and medicine-compliant cannabinoid active ingredients as well as plant material for studies. Due to these circumstances, the demand for urgently needed medicines of high-quality pharmaceutical grade medicinal cannabis for the pharmaceutical industry cannot be met.

Especially detection control is a big challenge in the production of cannabis medicinal products. Already during the cultivation and harvesting of cannabis plants and their further processing to the active ingredient and then as a medicinal product, the guidelines Good Agricultural and Collection Practice (GACP) [1] and Good Manufacturing Practice (GMP) [2] as well as other legal requirements such as the German Narcotics Law (BtMG) specify strict rules regarding traceability and the origin of a medicinal product. Close monitoring of the entire value chain is required. The genetics of origin and the manufacturing process, including storage and transport, must be fully documented. These specifications, which focus on patient protection and are generated as before with an increased documentation effort to ensure the obligation to provide proof, can be ideally implemented using digital solutions. This means that a large part of the data can be captured, linked, and used multi-dimensionally by technology systems.

Potential of the development of new finished medicinal products through digital solutions within the entire value chain

As described above, the regulatory requirements demand detailed mo-

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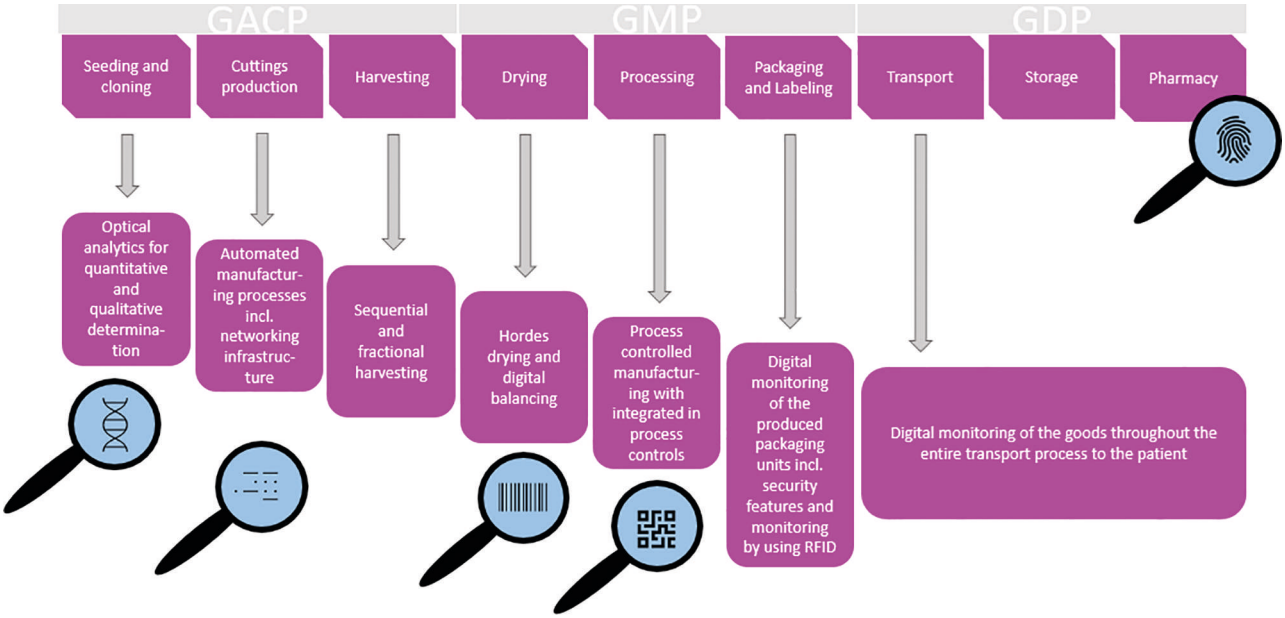

Figure 1: Value chain of manufacturing medicinal cannabis (source of all figures: J&K Consulting GmbH).

nitoring of the value chain in the manufacture of medicinal products. Manufacturers of herbal medicinal products are therefore obliged to document the origin of the plants and the processing steps in detail and to provide proof of quality. Since the quality of herbal medicines depends on many different parameters, such as genetics or cultivation or storage conditions, it is not sufficient for the highest quality standards to document only the batch or the day of harvest. Integral and central inline process solutions offer a solution for monitoring the entire value chain and the resulting complete traceability. Linked decentralized data processing systems enable high-resolution data analysis, starting with cultivation and continuing through processing to the entire logistics process. The data systems are supported by extensive data sets from plant development, plant care and process data that are continuously collected and processed from the manufacturing process using standardized process interfaces. An overview of the value chain in the production of medicinal cannabis and its digital monitoring is shown in Fig. 1.

Code systems are currently an increasingly common process solution for monitoring the value chain. Here, graphic bar or DataMatrix codes or RFID codes are attached directly to the plant, to its growing container or to the packaging. In this way, information can be firmly linked to the individual plant. The code contains, for example, data about the plant, such as its genetics, degree of maturity or growth phase, but also information about the cultivation conditions. Plant information or information about packaging and transport can also be integrally recorded. By simply scanning, the information can be displayed and edited. All information is stored in a specific database and can be retrieved at any time, schematically shown in Fig. 2. This not only allows complete tracking of the location of each plant, but also information is available on how many plants are in a production room and when the plants are ready for harvest. If, for example, a plant is to be transported from one production room to another, the code is scanned, and the change recorded in the scanner. The new location of the plant is then stored in the database. Autonomous transport solutions (such as the automated movement of plant pots by robots or on conveyor belts) are also possible here.

Growing demand requires the use of new technologies

Through the legal adjustment of the BtMG, the legislator gave the possibility for the legal prescription of cannabinoid medicines and medicinal hemp as well as cannabis extracts. Since the amendment of the BtMG on 10 Mar 2017, the demand for cannabis as a medicine has been steadily increasing. Currently, however, the demand for cannabis on the German market is mainly met by imports from abroad, e.g., from countries such as the Netherlands, Canada, Israel, or Portugal. In these countries, the cultivation of cannabis for medicinal purposes was legalized years ago. The cultivation of cannabis in Germany has only been

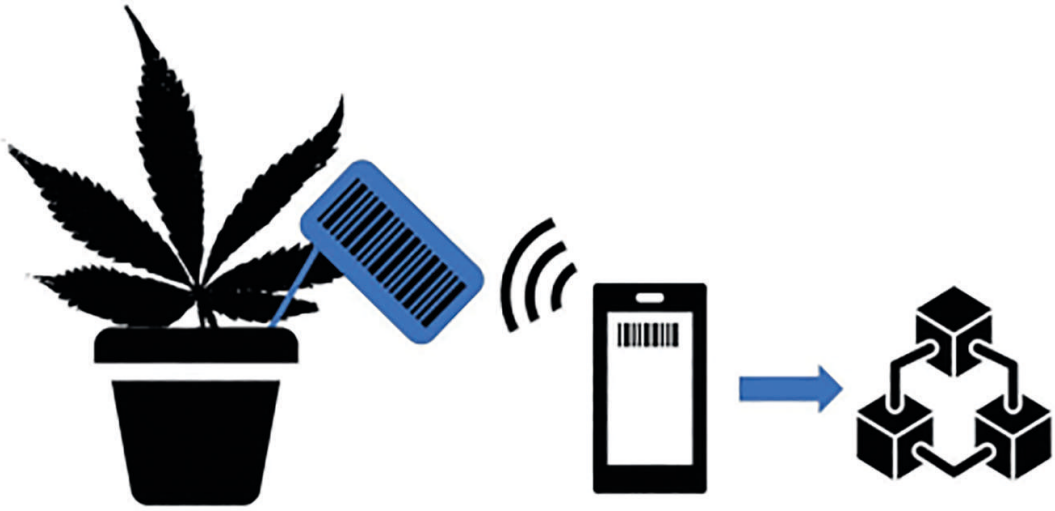

Figure 2: Track&Trace system for cannabis.

allowed since 2019 and is centrally organized and strictly regulated through the Cannabis Agency, the government agency that manages and controls the cultivation of cannabis for medicinal purposes. Currently, however, the contracted companies cannot supply the amount of cannabis required by the Cannabis Agency [3], which is why the cannabis produced in this country is already unable to meet the demand. At the same time, the demand for non-prescription cannabis products such as CBD oils, CBD supplements and CBD foods are also increasing. To meet the demand and to be able to operate independently from abroad, it is necessary to establish modular and scalable plant productions in Germany.

Process analytical specifications, e.g., in the Guidance for Industry – Process Validation: General Principles and Practices of the U.S. Food and Drug Administration (FDA) [4], were already defined in the field of pharmaceutical manufacturing in the early 2000s to develop and manufacture products and processes more integrally. Today, the specifications have been implemented in many areas of the pharmaceutical industry and are part of the standard processes.

This is not the case in medicinal cannabis production, where these processes are still in their infancy. A lack of process knowledge and information, e.g., about the biochemical processes within the plant, leads to highly heterogeneous product qualities in the production of the plant raw material. Due to technological and digital developments in recent years, the use of modern data systems and sophisticated analytics allows faster and more robust product and process information to be accumulated and thus correlated. These results generate new and essential information and thus help to optimize the manufacturing processes in such a way that the required quality including reproducibility can be achieved.

Improving growing conditions to stabilize quality or optimize certain plant traits can be supported using artificial intelligence (AI) [5]. AI is the attempt to transfer human thinking and learning to computers, and is therefore concerned with how computers analyze, interpret, and learn from data. The insights can be used to achieve development goals more efficiently through flexible adaptation and to provide maximum support to humans. These technological developments herald the next stage of digital evolution.

When using artificial intelligence, essential information is collected and evaluated from different data sources and process areas. The independent interpretation of the data and the possibility of self-learning make the information statements more precise and the evaluation approaches faster. In the field of medicinal cannabis development and production, artificial intelligence can help analyze the enormous amount of measurement and process data and evaluate it more quickly. For example, AI can be used to target genetics, manage manufacturing processes based on recognized quality attributes, and optimize digital plant twins through continuous verification processes. In the best case, it is possible to achieve an exchange of information between the digital twins and the results of the AI evaluation through digital networking.

Other links from the area of further processing of biomass or flowers, storage and transport are also conceivable. For this purpose, it makes sense to link the information using blockchain technology. Blockchain is a new technology that makes it possible to store, enrich,

process, share and manage any kind of information in a decentralized, accessible database. In a continuous list of records (called blocks), they are concatenated using cryptography. The data obtained in this way can create a unique image of the life cycle, thus making it possible to prove the authenticity of products. This technology is already used, for example, to monitor goods offered with an EU designation of origin [6] "protected geographical indication". The geographical information with the product data of the value chain is written into the blockchain so that the consumer can verify this information. The process parameters generated in the production of cannabis medicines are chained in blocks within the value chain. With interconnected data platforms and a blockchain solution, more and more complex actual states can therefore be monitored and presented in a clear overview.

The information is available to a predefined group of people. This exchange takes place according to defined procedures and cannot be manipulated. All information within a block is unique and cannot be manipulated, which promises a high level of security and data integrity.

In a classic GMP production facility, processes are managed in an analog and paper-based manner. Here, numerous folders full of paper must be collected as proof for the query as to whether a product was manufactured on a GMP-compliant system. By using digital solutions, this query can be generated cyclically and indicated by a clear traffic light display. In the process, the use of new technologies makes a large amount of data available that is related to each other through linking and inheritance processes.

In the production of medicinal plants, these solutions can be used to enable qualitative and quantitative monitoring. Qualitative monitoring of plants within plant production can be done by optical analytics implemented in a drone. The captured image and spatial information are further used to show a process statement about the quantitative growth condition of the plants. The control is carried out independently by the drone inside the plant production area. Additional data obtained during monitoring of the air and wastewater systems further enhance the analytical spectrum and can be processed immediately thanks to the 5G process application [7].

5G is a further development of the existing 2G, 3G and 4G mobile communications standards. With 5G, real-time data exchange via radio is possible for the first time. This means that control loop applications can be implemented wirelessly, and it is imperative that they function reliably and safely. This applies to a drone in plant production just as much as to the sensors and actuators of a production plant. 5G opens new fields of application in industry and enables powerful process control in real time and data processing from different data formats. 5G technology enables inline systems that directly control the processes. Process adjustments can thus be made directly via the sensor. The data obtained is not exchanged with a system but is made available in a decentralized manner. The provision of this decentralized information enables all systems to use the information and in turn to use it for further interactions between the systems.

Object-based databases, which offer a high degree of flexibility through networking and the use of neural networks and cloud technology, are a clear advantage at this point and can be further developed in an agile manner. Neural networks are based on the structure of the human brain, which processes information via a network of neurons. Artificial neural networks can be described as models consisting of at least 2 main layers – an input layer and an output layer – and usually additional layers in between, the activity layers or hidden layers. The more complex the challenge to be solved by the artificial neural network, the more layers are required by the activity layers. On each activity layer of the network lies a multitude of specialized artificial neurons. If there are many of these activity layers, this relationship is also referred to as Deep Learning.

These agile and self-learning systems could also be a realistic basis for new specific forms of therapy to generate a foundation for personalized medicine. Personalized medicine involves tailored therapy approaches that incorporate the individual characteristics of patients. So-called biomarkers, i.e., the genetic, molecular, or cellular characteristics of the patient, are anallyzed in diagnostic tests. Together with the individual circumstances of the patients, such as age or gender, an optimal tailored treatment could become possible. The goal of personalized cannabis medicine is to determine the best possible therapy in the future based on diagnostics and personal conditions. The effect of the cannabis plant is based on the interplay of many ingredients, which is why it may be that certain combinations work very well in one patient but have no effect in another. Then, for example, a specific cannabis genetics could be selected for a patient or an individual mixture of extracts could be created.

Digital networking of data and multiple use of data to extract relevant information

The future of drug crop production is digital, scalable, and fully automated production according to pharmaceutical GACP and GMP regulations. Something similar exists in the production of foodstuffs in the field of "vertical farming". But how can digital transformation be achieved?

The basis for digital pharmaceutical manufacturing are the digital

twins. These can be captured and upgraded in different areas. It is important to maintain an overview in the early process design of the manufacturing plant. Accordingly, the digital design of a value chain must be served from different data fields. A rough classification could be this gradation:

- Digital product twin
- Digital process twin
- Digital plant twin incl. metadata from supporting processes

In the case of active ingredient production in plants, this means: a digital image of plant genetics and actual plant production, starting with the growth and rearing processes, through further processing, to transport. The digital twins, in combination with inline process analytics, in-process controls and final analytics, as well as the databases and processing systems already described, create a so-called superordered data hub or digital ecosystem. By linking these data fields from further data platforms, multidimensional data information can be obtained.

By means of specific linking and provision through blockchain solutions, information can be generated and evaluated from multidimensional and different data fields. In this way, the active ingredient change within the plant is just as process-technically controllable as the individual plant in an entire manufacturing process of hundreds of plants. The data generated can be used multiple times in all directions, providing short-, medium- and long-term insights through data information that can help develop plants more specifically toward a treatment field. This can be done through cultivation processes and/or by means of genetic optimization. Within the production process, this data can be used to manage production through quality attributes and to release batches in real time through continuous inline control.

Since the technologies and processes described have already been used in a wide variety of industries in recent years, complete documentation is available in most areas and can thus be integrated and validated in a GMP-compliant manner. In addition, the digital process twin represents the manufacturing steps completely digitally. This means that important data such as the concentration of nutrients, the supply of water to the plants, or the level of CO_2 in the air are constantly recorded. The different digital data sources generate a lot of complex data and provide an overview of all process details in real time. If parameters deviate from the target, the relevant plant components automatically regulate the parameter or, in case of doubt, issue an alarm so that an employee can correct the problem. Targeted control of processes is also possible in this way: for example, the nutrient content of the water can be adjusted according to the needs of the plants – depending on the growth phase in which the plant is located. The completely digital control of the plant makes it possible to isolate growth areas from the outside.

Robots and smart conveyors eliminate the need to move plants manually and can also be controlled by the digital twin. Consequently, access by personnel is no longer necessary, which drastically minimizes the risk of contamination and at the same time maximizes the cultivation area. The digital twin thus enables the establishment of scalable and autonomous processes. The digital solution should enable consistent quality and the shift to quality-by-design (QdB) models [8]. This means that product quality already comes to the fore during product and process development.

The production of drugs according to the QbD model is based on a sound understanding of the process and knowledge of critical quality characteristics. The QbD approach is a concept that includes several quality tests during the product development process. Included in this is a targeted identification of defects to reduce them efficiently. The principle is that problems that occur afterwards can be traced back to faulty planning. For this reason, the quality of the products is built in from the outset and does not have to be laboriously achieved through subsequent improvements, so that the primary objective of pharmaceutical production of drugs – patient safety – can be achieved efficiently and in a results-oriented manner. This system and the associated approach are well known, as are the time-consuming and cost-intensive hurdles in the establishment of new technologies. By establishing digital twins along the value chain, many of these known challenges and hurdles in improving product and process quality can be overcome.

Outlook

The establishment of digital solutions to produce medicinal cannabis opens opportunities to cover the growing market for high-quality raw materials and to create the basis for obtaining active pharmaceutical ingredients. Modern and digital technologies facilitate compliance with the requirements defined by legislation and guidance documents. Similarly, technology can be used to make production processes more efficient and meet the ever-increasing demand for medicinal cannabis. The application of digital process solutions creates a digital database, which in turn can be used to develop finished pharmaceutical products. The sequence of development and production processes is known but can be raised to a level of performance through the support of digital tools, which will also provide new insights for the established industry.

The establishment and use of digital twins will open many opportunities for the industry. Change processes, which today still must be planned and approached on a long-term basis, can be positioned on a new agile system. These change

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processes enable a better meaningfulness due to highly condensed information.

The linking of data platforms will generate information and insights that are not yet recognized in today's process world. The potential gained from this will create a new dynamic for further networking of data. Smart IT solutions will be developed specifically for requirements and can be deployed more quickly. The establishment of digital marketplaces in which specific standard IT applications for the industry are offered will be just as much a part of everyday life in the future as the global networking of manufacturing processes. The digital transformation is no longer in its early stages, it has already made its entry.

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