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Good Medicinal Cannabis Cultivation Practice

A white paper promoting novel standards for the cultivation of pharmaceutical-quality cannabis for medicinal and scientific use.

Abstract

The recent exclusion of the cultivation process from the scope of Good Manufacturing Practice (GMP) certification in The Netherlands means that GMP compliant cultivation processes now must conform to a lower standard (i.e. GACP).

Compliance with Good Agriculture and Collection Practice (GACP), when applied to the production of certain cannabis products (i.e. cannabis flower for pulmonary administration), will have an unfavourable impact on the quality, efficacy and safety of the end-product.

To ensure pharmaceutical-quality cannabis for medicinal and scientific use and to encourage continuous product improvement requires a new set of requirements for the cultivation to be established.

Good Medicinal Cannabis Cultivation Practice (GMCCP) adopts many of the GMP principles and also accounts for the complexity of cultivating the cannabis plant for medicinal and scientific use.

This paper explains the basic GMCCP framework.

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Glossary of terms

Term	Definition
Acceptance criteria	Numerical limits, ranges, or other suitable measures for acceptance of the results of analytical procedures.
Active Ingredient	The therapeutically active component in a medicine's final formulation that is responsible for its physiological action.
Active Pharmaceutical Ingredient	Any substance or mixture of substances intended to be used in the manufacture of a medicine and that, when used in the production of a medicine, becomes an active ingredient of that medicine. These substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.
Administration (mode of drug use)	Describes the way in which a drug is taken or used, includes for example inhalation (vaporisation), ingestion or taking orally, and the injecting of a drug substance.
Adverse reaction	A response to a medicinal product which is noxious and unintended
API starting material	A raw material, or intermediate that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API.
Batch	A quantity of a product that is (i) uniform in composition, method of manufacture and probability of chemical or microbial contamination; and (ii) made in one cycle of manufacture and, if required, sterilised or freeze dried in one cycle.
Batch number	A group of letters, numbers, or symbols, or any combination thereof, from which the history of the manufacturing, packaging, labelling, or holding of a product or derived product can be determined.
Bioburden	The level and type (e.g. objectionable or not) of micro-organisms that can be present in raw materials, API starting materials, intermediates or APIs. Bioburden should not be considered contamination unless the levels have been exceeded or defined objectionable organisms have been detected.
Bulk product	Any product which has completed all processing stages up to, but not including, final packaging.
Cannabinoids	Naturally occurring or synthetic chemicals that act on the cannabinoid receptors.
Cannabis	The cannabis plant, in particular, the cannabis inflorescence consisting of the whole or fragmented, fully developed female flowers of Cannabis sativa L. (Cannabaceae).
Cannabis flos	The whole dried flower (inflorescence) of the cannabis plant (Latin: Cannabis sativae flos siccus).
Certificate of analysis	A document of quality assurance that confirms that a product meets its specifications, and results of quality control test on the individual batch of a product.
Contamination	The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a raw

	material, intermediate, or API during production, sampling, packaging or repackaging, storage or transport.
Contract manufacturer	A manufacturer performing some aspect of manufacturing on behalf of the original manufacturer.
Critical Process Parameters (CPP)	A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality (ICH Q8).
Critical quality attribute (CQA)	A physical, chemical, biological or microbiological property or characteristic that should be within an approved limit, range or distribution to ensure the desired product quality (ICH Q8).
Cultivation	Planting, tending, improving and harvesting of crops.
Deviation	Departure from an approved instruction or established standard.
Disinfectant	A physical or chemical agent or process that destroys pathogenic or potentially pathogenic microorganisms on inanimate surfaces or objects.
Dosage form	The pharmaceutical form in which a product is presented for therapeutic administration, e.g. tablet, cream.
Efficacy	The proven performance of a product established under defined conditions.
Finished product	A medicinal product which has undergone all stages of production, including packaging in its final container.
Good Agricultural and Collection Practice (GACP)	A set of standards for the collection, cultivation, harvest and primary processing of plant materials for use in herbal medicines.
Good manufacturing practice (GMP):	The acronym GMP is used internationally to describe a set of principles and procedures for the manufacturer of medicines; it helps ensure that the products manufactured are of a certain quality.
Herbal substance	The term herbal substance is synonymous with the term herbal drug used in European Pharmacopoeia. All mainly whole, fragmented or cut plants, plant parts, algae, fungi, lichen in an unprocessed, usually dried form but sometimes fresh. Certain exudates that have not been subjected to a specific treatment are also considered to be herbal substances. Herbal substances are precisely defined by the plant part used and the botanical name according to the binomial system (genus, species, variety and author).
Herbal preparations	Herbal preparations are obtained by subjecting herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation. These include comminuted or powdered herbal substances, tinctures, extracts, essential oils, expressed juices and processed exudates.
In-process controls	Checks performed during production in order to monitor and if necessary to adjust the process to ensure that the product conforms to its specification. The control of the environment or equipment may also be regarded as a part of in-process control.
Medicinal cannabis	Cannabis that is intended for therapeutic use. Is prescribed by a trained medical professional, for a known medical condition or a set of conditions where it has proven to be an effective treatment.

Pharmaceutical-grade herbal cannabis	Standardised, quality-controlled production of pharmaceutical-grade cannabis. Medical grade product with standardised content of the active constituents, presented as a pharmaceutical medication.
Production	Production of cannabis includes processing and packaging of the product, labelling, storage, testing or releasing for distribution (excluding cultivation).
QMS (quality management system)	A set of policies, processes and procedures required for planning and execution (production/development/service) in the core business area of an organisation.
Qualification	Action of proving that any equipment works correctly and actually leads to the expected results. The word validation is sometimes widened to incorporate the concept of qualification.
Quality Risk Management	A systematic process for the assessment, control, communication, and review of risks to the quality of the drug product across the product lifecycle.
Recall	An action taken to resolve a problem with therapeutic goods for which there are established deficiencies in quality, efficacy or safety.
Standarisation	Standardisation means adjusting the herbal substance/herbal preparation to a defined content of a constituent or a group of constituents with known therapeutic activity respectively either by adding excipients or by blending batches of the herbal substance and/or herbal preparation (e.g. standardised extracts).
Validation	A documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting pre-determined acceptance criteria.

Introduction

Bedrocan has been producing cannabis for medical and scientific use since 2003, when the medicinal cannabis programme was established in The Netherlands. The accumulation of knowledge on medicinal cannabis begun in 1992, when the company began cultivating cannabis for the purpose of producing cannabis seeds.

That experience provided valuable insight into the impact of the different factors on the qualitative and quantitative cannabinoid content in different plant varieties. Process standardisation and well-defined specifications has allowed for the cultivation of cannabis with a standardised cannabinoid content for almost 20 years.

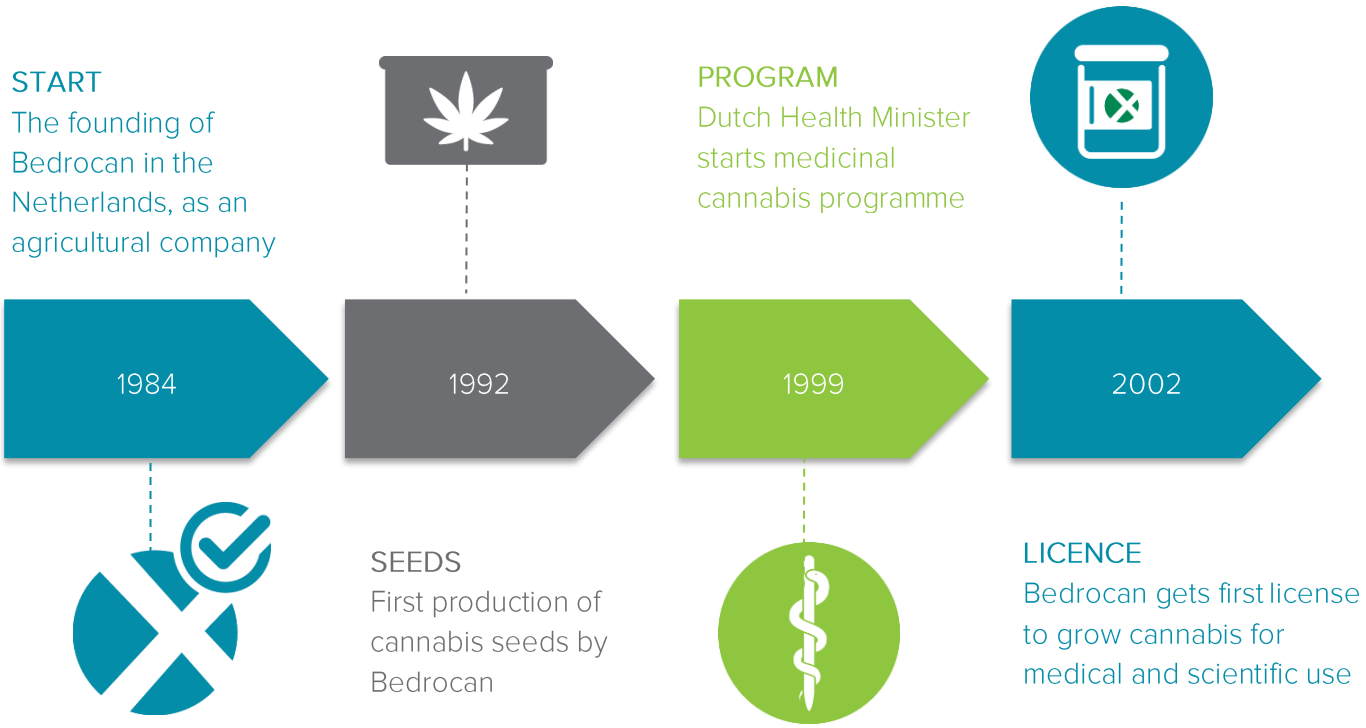

Figure 1-1. Bedrocan's history (Part 1)

Due to the increase in demand for pharmaceutical-quality cannabis outside of The Netherlands, The Office of Medicinal Cannabis (OMC) has started exporting to numerous countries worldwide. Together with a demand for larger quantities, the demand for a high-quality product increased as well. Upon opening its second production facility, Bedrocan became the first EU-GMP certified producer of pharmaceutical-quality cannabis. More importantly, Bedrocan became the first producer with a GMP certification which covered all manufacturing activities (cultivation, processing and packaging).

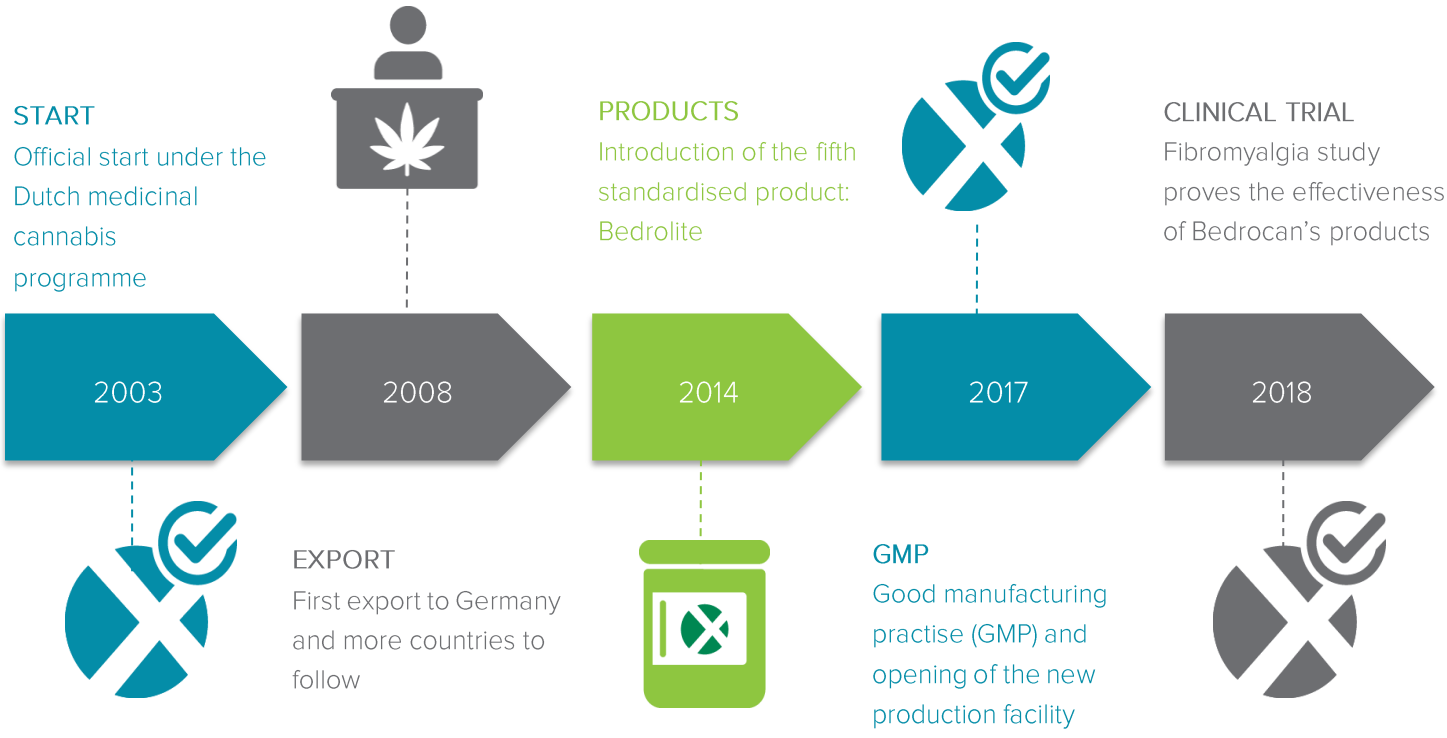

Figure 1-2. Bedrocan's history

In 2020, three years after the first GMP inspection took place, Bedrocan was audited again. This time, due to the change in the audit scope, the certificate was limited to processing and packaging of the product. The reason for this was the inapplicability of GMP requirements in the cultivation of plants. Consequently, with the lack of standards and requirements to conform with, Bedrocan now faces a challenge of demonstrating the compliance of its cannabis cultivation process.

Problem statement and background information

One of the main principles of GMP is the guaranteed control over the product and its environment. Given environmental contamination within the production facility (e.g. equipment), presents a high risk for patients health, GMP requires that potential sources of contamination are eliminated through an integrated comprehensive programme of sanitation and hygiene. To prevent contamination and improve control over the environment, GMP also requires that areas in which the production process takes place are classified according to EU-GMP cleanroom classification. The classification is based on the maximum permitted number of particles in m^3.

Keeping a controlled and clean environment for the Cannabis plant to thrive and subsequently ensure a product of consistent quality is an absolute imperative for the cultivation of pharmaceutical-quality cannabis. However, it has to be taken into account that the starting material to produce a finished product is a plant. The growing environment and the starting material (Cannabis flowers) itself is suitable for the growth of a variety of microorganisms which live in the root systems and other parts of the plant. However, ensuring a sterile environment is undesirable and would cause adverse effects on plant growth, and subsequently on the availability of the product. For that reason, controlling of the number of particles in areas where cultivation takes place is not possible. Consequently, it makes the goal of GMP classification of these areas unachievable, and presents the biggest obstacle towards the certification of medicinal cannabis cultivation under GMP.

What's the alternative?

If the cultivation of cannabis cannot be included in the scope of GMP certification, the obvious question arises; what's the alternative?

How can a company guarantee to regulatory authorities that the starting material is produced according to requirements defined within internationally recognised standards?

The alternative to the EudraLex Annex 7 (Volume 4) Good Manufacturing Practice (GMP) guidelines is the World Health Organization (WHO) Good Agricultural and Collection Practice (GACP). GACP was developed to create a single framework to ensure appropriate and consistent quality in the cultivation of medicinal plants. GACP was developed by the WHO in 2003, with the aim of improving the quality of medicinal plants being used in herbal medicines in the commercial market.

EudraLex GMP guidelines goes further and explains the applicability of GACP and GMP requirements (as shown in Figure 3). Both GACP and Part II of the GMP guidelines include cutting and drying of plants, algae, fungi, lichens and exudates. These activities are most applicable to the cultivation of pharmaceutical-quality cannabis.

The question is then; where do you draw the line between the two?

As explained in the text within Figure 2. *''For those initial steps that take place in the field, as justified in the marketing authorisation/registration, the standards applicable to Good Agricultural and Collection Practice for starting materials of herbal origin is applicable. GMP is applicable for further cutting and drying of plants.''* An important thing to highlight from the sentence above is *'...initial steps take place in the field.'* This text is important because the WHO GACP guidelines also define genetic diversity of flora and fauna, climate conditions, duration of sunlight, use of fertilisers, pesticide use, contact with soil, etc, as the consequential variabilities of in-field / field-based cultivation and collection.

The narrative around standardisation and quality within the guidelines becomes obvious. Advanced, sophisticated and high-quality cultivation does not fit within the scope of GACP.

On the contrary, for Bedrocan, whose focus is on maintaining the highest standard of cultivation, GACP certification would not meet the required defined standards applied for cultivation.

Table illustrating the application of Good Practices to the manufacture of herbal medicinal products[3].

Activity	Good Agricultural and Collection Practice (GACP)[4]	Part II of the GMP Guide[†]	Part I of the GMP Guide[†]
Cultivation, collection and harvesting of plants, algae, fungi and lichens, and collection of exudates			
Cutting, and drying of plants, algae, fungi, lichens and exudates *			
Expression from plants and distillation **			
Comminution, processing of exudates, extraction from plants, fractionation, purification, concentration or fermentation of herbal substances			
Further processing into a dosage form including packaging as a medicinal product			

[†]Explanatory Note.
The GMP classification of the herbal material is dependent upon the use made of it by the manufacturing authorisation holder. The material may be classified as an active substance, an intermediate or a finished product. It is the responsibility of the manufacturer of the medicinal product to ensure that the appropriate GMP classification is applied.

* Manufacturers should ensure that these steps are carried out in accordance with the marketing authorisation/registration. For those initial steps that take place in the field, as justified in the marketing authorisation/registration, the standards of Good Agricultural and Collection Practice for starting materials of herbal origin (GACP) is applicable. GMP is applicable to further cutting and drying steps.

Figure 2. The applicability of GACP and GMP guidelines in the manufacture of herbal medicinal products. Taken from 'Table illustrating the application of Good Practices to the manufacture of herbal medicinal products' of Annex 7 of the EudraLex (Volume 4) Good Manufacturing Practice (GMP) guidelines.

If the requirements of GACP are set as the minimum standard which companies must meet for industrial contracts or tendering processes (for production of cannabis), the bar is significantly lowered. Achieving the highest quality starting material is no longer a requirement. In the production of any medicinal product, including herbal medicinal products. The highest possible quality of the starting material should always be the scientifically objective. Aligning with the requirements of GACP only is not enough to attain that goal. For companies that strive toward developing and maintaining the highest possible quality, industry and regulatory standards for cannabis cultivation, this situation is far from desirable. In order for regulatory authorities to keep abreast with the rapid pace of industry development, there is a need for a global guideline for the cultivation of pharmaceutical-quality cannabis starting material.

Solution

The idea of a specific guideline for the cultivation of cannabis for medical and scientific use may sound exaggerated. However, cannabis is unique and unlike other medicinal plants.

To illustrate, lets oversimplify the process: the flower of the plant develops quickly after entering the generative phase, it is harvested, processed and packaged, and eventually it ends up in pharmacies ready on prescription. It is then taken by patients by pulmonary administration (Figure 3).

Similar medicinal products are rare, if not non-existent. This speaks volumes when you again consider the application of GACP guidelines in the cultivation of pharmaceutical-quality cannabis for medical and scientific use. GACP does not require the level of process and environmental control that is necessary to ensure the safety and efficacy of such a product. Nor the requirement for batch-to-batch consistency for its industrial use as a starting material.

Figure 3. (Simplified) Supply chain of cannabis for medical and scientific use

Good Medicinal Cannabis Cultivation Practice

What is Good Medicinal Cannabis Cultivation Practice (GMCCP), and which requirements would have to be met to comply with it?

Bedrocan's extensive experience in the cultivation of pharmaceutical-quality cannabis is exemplified in the consistent batch-to-batch quality of the end product through time (i.e. cannabis flower/inflorescence). The experience and insight gathered has resulted in a sophisticated and standardised cultivation process.

Bedrocan set an industry standard by achieving GMP certification for the cultivation process in 2017. While GMP was removed from the cultivation process after the inspection in 2020, Bedrocan continued to improve its cultivation process and challenge itself to improve the quality and consistency of its products. The example of Bedrocan serves as a useful foundation for establishing such good practices – the standard which would help set Good Medicinal Cannabis Cultivation Practice for the whole of industry.

Good
Medicinal
Cannabis
Cultivation
Practice

The following sections will describe a dozen aspects of Bedrocan's cultivation process which represent the main principles of the Good Medicinal Cannabis Cultivation Practice; control, standardisation, consistency and quality.

Quality Management System (QMS)

A Quality Management System (QMS) is imperative for ensuring product quality and continuous process improvement. Its versatility allows QMS to be implemented in any industry and consistently aid the organisations by improving their efficiency, helping with maintaining control over key processes, mitigating risks and deviations, enabling improvement and increasing financial performance. In the pharmaceutical industry, the manufacturing of medicines cannot take place without a compliant QMS. Each manufacturer should establish, document, and implement an effective system for managing quality. The process should involve active participation from management and appropriate manufacturing personnel. Due to the continuous process developments, an organisation is required to adapt quickly and effectively to new situations. An effective QMS helps the manufacturer to respond to changes and be ready for future developments. This should be no different in the cultivation of cannabis for medical and scientific purposes. Key systems in any QMS for medicine manufacturing are relevant to the QMS controlling the cultivation of cannabis. Several of these systems are covered in the following sections.

- **Work Instructions**

In Bedrocan, the QMS has been developed to ensure that all manufacturing operations (including cultivation) are performed in a correct and consistent manner. Contrary to popular belief, in the cultivation of cannabis, numerous processes take place which must be performed successfully to achieve a product of consistent high quality. For that reason, work instructions are written for every part of the production process, outlining the required materials, responsibilities, expected outcomes and actions to be taken in case any discrepancies are observed. The work instructions and logbooks make the bulk of the QMS. Processes such as cleaning and maintenance, which do not directly influence the development of the plants, are described in detail to provide necessary information for personnel executing the task. To ensure every task is performed according to the established instructions, all personnel is trained and their training is registered in personnel training records.

- **Batch Records**

Each significant tasks in the batch production are recorded in the Batch Record. Batch records are prepared for every production batch and include complete information relating to their production and control. These records are numbered with a unique batch or identification number, dated and signed when issued. They follow the particular batch throughout the whole production process, starting with cultivation. Upon completion of every major part of the production process (e.g. cultivation), batch records concerning that particular activity are reviewed by the Quality Assurance department. A 'Batch record review' is performed to identify any deviations which may have occurred. The batch is not released if deviations are not thoroughly investigated and closed. The Batch Records play an important role in the cultivation of cannabis for medical and scientific use because they act as proof that batches were made according to the established work instructions and checked by quality assurance personnel. Ultimately, this ensures uniformity in the end product.

- **Good Documentation Practice**

The golden rule of the manufacture of all types of medicines is 'If it is not written down, it did not happen'. Thus, registering information in the batch record and filling in other relevant QMS documentation must be undertaken according to certain principles. The principles, of Good Documentation Practice (GDP) ensure documented information and data is accurate, complete, consistent and reliable throughout their entire period of usefulness – that is, throughout the data life cycle. According to these practices, every QMS user must follow the GDP principles to assure recorded data is attributable, legible, contemporaneously recorded, original and accurate. The integrity of batch related data plays an important role when it comes to batch review, batch release and investigations of product or process-related deviations.

- **Deviation, CAPA and Change Control**

Deviations are measured differences between an observed value and expected or normal value for a process or product condition. In the cultivation of cannabis, deviations can occur in different segments of the production process. The occurrence of every deviation can be attributed to human error, equipment, system or material malfunction.

Regardless of the significance, each deviation is well documented. This allows for an investigation to take place to assess the deviation impact and to find the root cause. Eliminating the root cause aims to prevent future deviations occurring which may be related to the same issue. In essence, deviation management is a valuable system for continuous improvement and for ensuring that the end product consistently meets the established specifications. Some deviations may be more complex than others and require further assessment to find and eliminate the root cause. In such situations, the Corrective Action Preventive Action (CAPA) procedure is used. The CAPA procedure helps with identifying and evaluating the validity of the deviation issue, through evaluating all relevant available information and appraising the potential impact. This allows the manufacturer to fix the issue and to improve the production process to ensure the deviation does not happen again.

Like Deviation management, the CAPA procedure is a valuable tool for continues improvement and for ensuring consistency in the production process and product quality. Changes are common for any type of production process. At Bedrocan, for example, the cultivation of cannabis is approached with a 'pharma mind-set'; the Change Control procedure plays an important role in day-to-day operations. A change can be an addition, deletion, modification to facilities, utilities, processes, materials, products, procedures or equipment, all of which may impact product quality or regulatory compliance. Regardless of what the nature of the change is, it must be well documented and assessed before implementation. This ensures that no additions, deletions or modifications are made which could negatively impact on the production process or quality of the product.

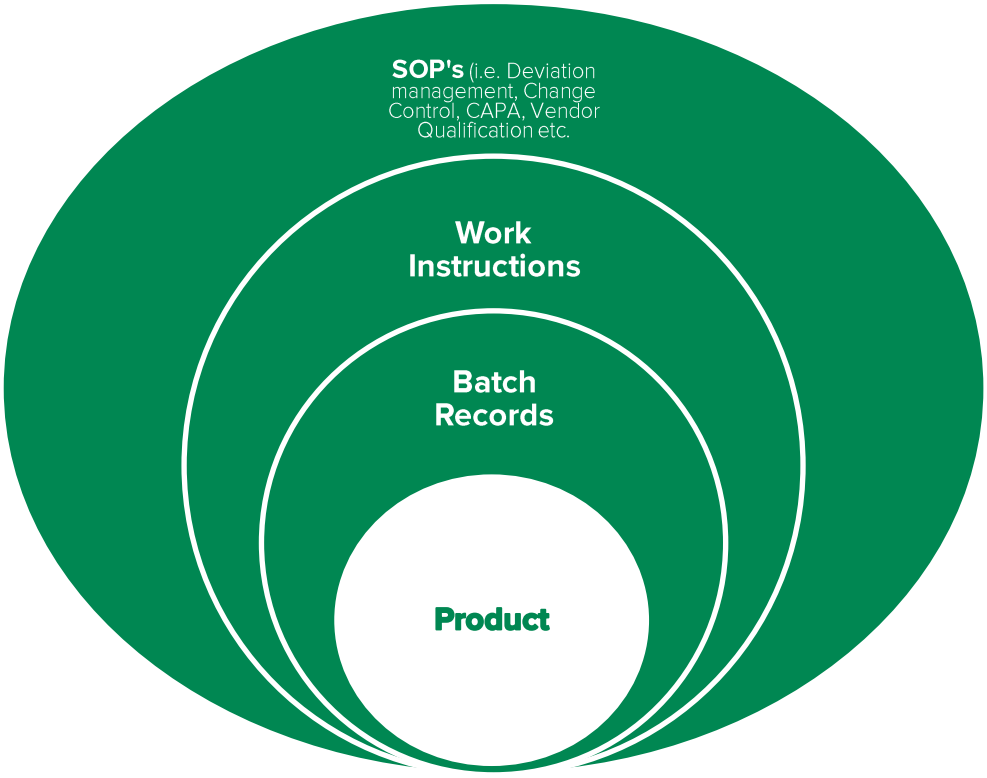

Figure 4. Structure of the QMS in the cultivation of Cannabis for medical and scientific use

- **Vendor and Material Qualification**

To ensure consistent availability and quality of the product, the production process must run smoothly. In the cultivation of pharmaceutical-quality cannabis, where batch production is planned months ahead, every stoppage of the production process has a negative impact on the availability of the product to industrial partners or directly in the pharmacies. To minimise the possibility of such scenarios, all the vendors which supply Bedrocan with materials, equipment or services are qualified according to the Vendor Qualification procedure. The process of qualification consists of three methods, and the extent of each depends on the risk classification of their products/services. A product or service can be a material that comes in direct contact with the cultivated cannabis product or maybe an extraneous maintenance services. Depending on the impact of the material, service or equipment on the cultivated product, the vendor can be audited by Bedrocan. Audits can vary from assessments via a qualification questionnaire or qualified based on the vendor's compliance with the industry standards. After being qualified, the vendor's performance is monitored continuously and depending on the results, the vendor might be disqualified or placed on the "blacklist". In the cultivation of cannabis, a number of different materials are required. To ensure that the particular material does not have a negative impact on the development of the plant and consequently on the quality or availability of the cultivated product, the material has to be assessed and qualified. The level of qualification is based on the contact the material has with the product (direct/in-direct/none). After a material has been qualified, it can be used in the production process, after which is continuously checked by the QA department upon delivery to the cultivation facilities.

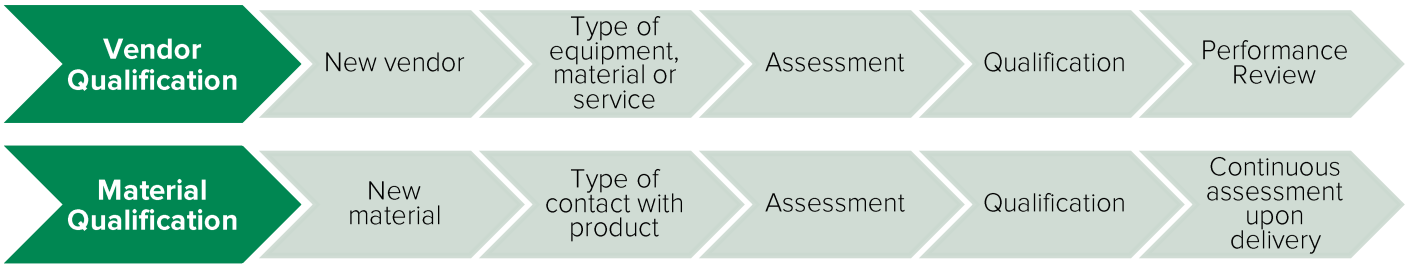

Figure 5. Process diagram of Vendor and Material Qualification

Risk Management

Risk Management has been recognised in the pharmaceutical industry as a valuable part of an effective Quality System. The manufacture of pharmaceuticals inevitably involves different types of risks with different impacts, but the ones which are the most critical concern the product quality and safety. Thus, the management of risks in medicine production is of utmost importance due to the impact these may have on patients' health. Like in the production of all starting materials, quality has to be maintained throughout the whole production process, through to the completed finished product. In the case of cannabis, this includes cultivation. Attributes that are important for the quality of the end product must not be affected by potential risks which may arise during the development of plants. For that reason, the systematic approach of risk management is included in each step and sub-step of the cultivation and production process. This also applies to the systems, utilities and equipment used to facilitate the process. For example, being aware of the risks which a single piece of equipment might pose in certain scenarios facilitates more informed decision making and ultimately control and mitigation of such risks. Therefore, a risk assessment of the complete production process is an extremely valuable exercise that points out the areas where risks might occur and how they could impact the production process and consequently the product quality. Performing the Process Risk Assessment provides a proactive means for identifying and controlling potential quality issues during cultivation and automatically enables the recognition of potential improvements. Risk management is the back-bone of Bedrocan's QMS. Classification of deviations, change controls, vendors, materials, equipment and systems is based on risk management principles.

Validation

In any type of production, it's important to have the assurance that the process and accompanying systems and equipment do what they're supposed to do. When producing starting materials, API or finished products, that assurance has to be documented. To achieve that, a series of tests have to be performed, checking if the process, system and equipment comply with the pre-determined specifications or outcomes. In the process of executing these tests, all the findings, results and observations have to be documented. That is the proof that the process and accompanying systems and equipment produce a consistent and reproducible result. Since the product is made the same way every time, it is a reasonable assumption that the medicine made tomorrow, a month, or 12 months from now, is also safe for patients to use. This process is called Validation and is an essential part of the Good Manufacturing Practice (GMP). In the cultivation of cannabis for medical and scientific use, validation is not easy to do; after all, you're trying to validate the natural process of plant growth. Thus, the scope of validation activities has to be adjusted. If you can't prove that the process will always end in the same results, then you can ensure that everything surrounding the process, like systems, utilities and equipment are successfully validated. In Bedrocan, every system and piece of equipment used in the process directly or indirectly is fully qualified. This means that a series of tests are performed to check if they are operating and performing as they should to maintain consistency in the process. Without this assurance, it is difficult to guarantee that products will always be uniform in quality. Most importantly, it's difficult to guarantee the safety of product because of the lack of control over the process. For that reason, validation, even though it is difficult to apply in cannabis cultivation, plays an important role in achieving consistency in both the process and product quality.

Cleaning and Hygiene

Cleaning, sanitation of premises, and the hygiene of personnel are vital for the prevention of product contamination and cross-contamination. Detailed instructions must be established to provide information on how to perform cleaning, when to perform it, and where to record it. Maintaining the cleaning status of the facility and accompanying systems and equipment is one of the GMP aspects which must be integrated in the cultivation of cannabis for medical and scientific use. As previously stated, since the product (cannabis flower) is already being developed during the cultivation phase, upholding the hygiene level of both the environment and personnel involved in the process is critical for the quality and safety of the end product. For that reason, Bedrocan has integrated strict cleaning regimes, hygiene and gowning procedures for its personnel. The use of chemicals in the process of cleaning is eliminated, so no residues might affect the quality and safety of the product. Recording the time and person conducting the cleaning is part of the batch records as well as a logbook for each area in which the production process takes place. The cleaning status of each area in the facility is closely monitored and ensured whenever a particular area will be accommodating the product. All premises were designed and constructed to facilitate cleaning and to eliminate the risk of a build-up of dust, dirt and batch-related residues. Given cleaning validation is difficult to successfully execute for the cultivation of cannabis for medical and scientific use due to the plants complex growing environment, samples of the surfaces and equipment used in the process are taken regularly to identify 'microbiological fingerprints' of different areas in the facility. This further improves the knowledge-base about the plants environment and how it can be optimised with the purpose of preserving the product quality and upkeep of the overall cleanliness of the facility.

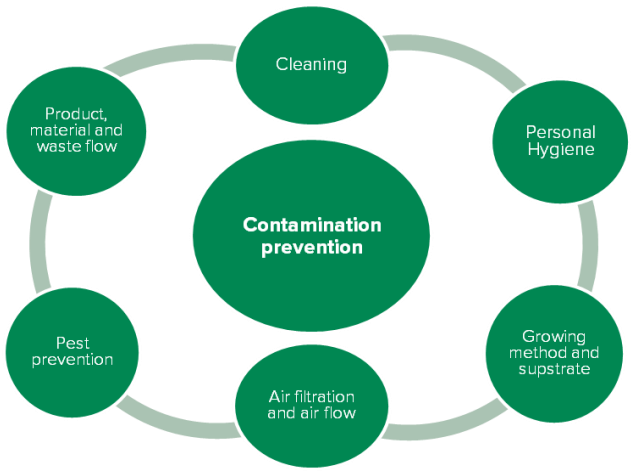

Figure 7. Scheme of contamination prevention in Bedrocan

Contamination prevention

Cleaning and hygiene play a huge role in the prevention of contamination. However, that is not enough to completely ensure the quality and safety of the end product. To minimise the risk of contamination, different systems or mechanisms have to be integrated throughout the production process. These start with the growing method and growing substrate, and include systems for pest prevention, air filtration, airflow and product separation, and material and waste flow. With regard to contamination prevention, the overall system is only as strong as the weakest link. Therefore, it is important that every mentioned mechanism is fully integrated and continuously monitored.

Process standardisation and control

Standardisation of the production process is a prerequisite for achieving uniformity of active ingredients in the end product (i.e. starting material). Without uniformity, no pharmaceutical material or product can be released to the market. The same applies to cannabis for medical or scientific use. To ensure continuous production of products of the same specification, standardisation has to be deeply integrated into every aspect of cultivation and production. Everything that facilitates cultivation and production, and has a direct or indirect impact on the product, must be included in the scope of 'standardisation'. In reality, this means that the consistency of the process can only be achieved through the standardisation of procedures and instructions of the Quality Management System (QMS), process parameters, growing methods, selection of plant material, system and equipment settings, and the use of materials. Every one of these aspects has to be consistent to develop a production process that provides reproducible results. Thus, QMS systems like Change Control play an important role in maintaining this status. This is because every change could potentially impact the consistency of the process and its outcome. Therefore, changes have to be assessed before their implementation. A simple tweak in certain process parameters could result in a higher or lower percentage of cannabinoids in the cannabis starting material - this exemplifies the importance of process control and how the lack of it can be detrimental to product quality and safety.

The difference between GMP, GACP and GMCCP

So far in this white paper, we talked about the principles of and the main differences between GMP, GACP and the GMCCP standard and how they apply to the cultivation of cannabis for medical and scientific use. The requirements of each Good Practice are presented in Table 1, from which it is fairly easy to spot the similarity between GMCCP and the GMP. On the other hand, GMCCP doesn't share much with the GACP. The reason, as previously explained, is that the GACP was developed for common starting materials used in the production of herbal medicinal products. Cannabis flower intended for medical and scientific use does not fit in that category, and the requirements of GACP are not up to the necessary level.

It is important to note that all three guidelines cross over, but the level of complexity differs considerably. A good example is cleaning and sanitation, contamination control and upkeep of documentation. These aspects are covered in each mentioned guideline, however, for GMP, cleaning and sanitation must be recorded, validated, performed according to established procedures and cleaning schedules. The acceptance criteria for residues and the choice of cleaning procedures and cleaning agents also must be defined and justified for GMP. For GMCCP, it is very similar, with the exception of additionally performing a cleaning validation. For GACP on the other hand, the requirements for cleaning only require that the equipment and building are cleaned and that machine parts in direct contact with the harvested plant material/herbal substance must be cleaned after use to ensure that remaining residue does not result in subsequent cross-contamination.

Since GMCCP has not yet been written in a format of an official guideline, but rather has been partially covered in this White Paper, it is not possible to refer to exact sections of the guidelines to describe specific requirements. However, the topics discussed in this White Paper, in addition to the example of Bedrocan's cultivation process, are enough to make the comparison between GMCCP with GMP and GACP. Also, the requirements weren't mentioned in their entirety, primarily because each requirement is described exhaustively within the applicable guideline. For that reason, the references are added to the tables below.

Table 1-1. Differences between the requirements for GMP, GACP and GMCCP standard

Subjects	Requirements		
	GMP	GACP	GMCCP
Quality Management	- There should be a system for managing quality. - All quality related activities have to be defined and documented. - There should be an independent unit for quality assurance and quality control. - No materials should be released before the satisfactory evaluation by the quality unit. - Any deviation from established procedures should be documented and explained. *Reference: 2.11, 2.12, 2.13, 2.16, 2.17*	- All processes and procedures that could affect the quality of the product must be documented. *Reference: 7.1*	- There should be a system for managing quality. - All quality related activities have to be defined and well documented - There should be an independent unit for quality assurance. - Any deviation from established procedures should be documented and explained.
Personnel	- Personnel involved in manufacture has to be qualified and trained and their responsibilities have to be documented. - Training has to be conducted regularly and results have to be recorded. - There should be an adequate number of personnel qualified by appropriate education, training and/or experience to perform and supervise the manufacture of intermediates and APIs. *Reference: 3.1*	- Personnel must be protected from contact with toxic or potentially allergenic medicinal plants/herbal drugs by means of adequate protective clothes. - Personnel should receive adequate botanical training before performing tasks that require this knowledge. - The welfare of all staff involved in growing and processing should be ensured. *Reference: 4.2, 4.3, 4.6*	- Personnel involved in cultivation has to be qualified and trained and their responsibilities have to be documented. - Training has to be conducted regularly and results have to be recorded. - There has to be an adequate number of personnel in order to execute the tasks in a timely fashion without jeopardizing the quality of the product.
Personal Hygiene	- Personnel should wear clean clothing suitable for the manufacturing activity with which they are involved and this clothing should be changed when appropriate. - Personnel should avoid direct contact with intermediates or APIs. - Smoking, eating, drinking, chewing and the storage of food should be restricted to certain designated areas separate from the manufacturing areas. - Personnel suffering from an infectious disease or having open lesions on the exposed surface of the body should not engage in activities that could result in compromising the quality of APIs. *Reference: 3.2*	- Persons suffering from known infectious diseases transmittable via food or being transmitters of such diseases, must be suspended from areas where they are in contact with medicinal plants/herbal drugs, according to regional and/or national regulations. - Persons with open wounds, inflammations and skin-infections should be suspended from areas where the plant processing takes place or should have to wear appropriate protective clothing/gloves until their complete recuperation. *Reference: 4.4, 4.5*	- Personnel should wear clean clothing suitable for all cultivation activities with which they are involved and this clothing should be changed when appropriate. - Smoking, eating, drinking, chewing and the storage of food should be restricted to certain designated areas separate from the manufacturing areas. - Personnel suffering from an infectious disease or having open lesions on the exposed surface of the body should not engage in activities that could result in compromising the product quality.

Table 1-2. Differences between the requirements of the GMP, GACP and GMCCP standard

Subjects	Requirements		
	GMP[1]	GACP[2,3]	GMCCP
Buildings and Facilities	- Buildings and facilities used in the manufacture of intermediates and APIs should be located, designed, and constructed to facilitate cleaning, maintenance, and operations as appropriate to the type and stage of manufacture - Facilities should also be designed to minimize potential contamination. - There should be defined areas or other control systems for each manufacturing activity. *Reference: 4.1*	- Buildings used in the processing of harvested medicinal plants/herbal drugs must be clean, as well as thoroughly aerated and must never be used for housing livestock. - Buildings must provide adequate protection for the harvested medicinal plants/herbal drugs against birds, insects, rodents and domestic animals. *Reference: 5.1, 5.2, 5.3*	- Buildings and facilities used in the cultivation of medicinal cannabis should be located, designed, and constructed to facilitate cleaning, maintenance, and operations. Facilities should also be designed to minimise potential contamination. - Buildings and facilities should have adequate space for the orderly placement of equipment and materials to prevent mix-ups and contamination. - There should be designated areas (separate from each other) for each phase of cultivation.
Documentation and records	- All documents related to the manufacture of intermediates or APIs should be prepared, reviewed, approved and distributed according to written procedures. - A procedure should be established for retaining all appropriate documents - All production, control, and distribution records should be retained for at least 1 year after the expiry date of the batch. For APIs with retest dates, records should be retained for at least 3 years after the batch is completely distributed. - Specifications should be established and documented for raw materials, intermediates where necessary, APIs, and labelling and packaging materials. - Batch production records should be prepared for each intermediate and API and should include complete information relating to the production and control of each batch. *Reference: Section 6*	- All processes and procedures that could affect the quality of the product must be Documented. - Extraordinary circumstances during the growth period that may influence the chemical composition of the medicinal plant/herbal substance such as extreme weather conditions and pests, particularly in the harvest period must be documented - The application of fumigation agents must be documented. - Appropriate labelling and batch assignment should take place as early as possible. - Collected and cultivated medicinal plant/herbal substance material should carry different batch numbers. *Reference: Section 7[2]*	- Batch production records should be prepared for each batch and should include complete information relating to the cultivation and control of each batch. - All production records should be retained for at least 1 year after the expiry date of the batch. - All documents related to the cultivation of medicinal cannabis should be prepared, reviewed, approved and distributed according to written procedures. - A procedure should be established for retaining all appropriate documents - All the specification related to the process and product should be documented . - All cleaning activities should be recorded in the batch records and appropriate logbooks. - Daily records of critical process parameters have to be kept and reviewed.

Table 1-3. Differences between the requirements of the GMP, GACP and GMCCP standard

Subjects	Requirements		
	GMP[1]	GACP[2,3]	GMCCP
Materials Management	- There should be written procedures describing the receipt, identification, quarantine, storage, handling, sampling, testing, and approval or rejection of materials. - Manufacturers of intermediates and/or APIs should have a system for evaluating the suppliers of critical materials. - Materials should be purchased against an agreed specification, from a supplier or suppliers approved by the quality unit(s). - Changing the source of supply of critical raw materials should be treated according to Section 13, Change Control. *Reference: 7.1*	Not applicable.	- There should be written procedures describing the receipt, identification, storage, handling, sampling and approval or rejection of materials. - Manufacturers of materials used in cultivation of medicinal cannabis have to be evaluated and qualified according to established procedures. - Changing the source of supply of materials should be handled through the Change Control procedure. - After every shipment of materials and before their use in cultivation, materials have to be checked and approved by the quality unit.
Cleaning and Sanitation	- Written procedures should be established for cleaning of equipment and its subsequent release for use in the manufacture of intermediates and APIs. - Equipment and utensils should be cleaned, stored, and, where appropriate, sanitized or sterilized to prevent contamination or carry-over of a material that would alter the quality of the intermediate or API beyond the official or other established specifications. - Acceptance criteria for residues and the choice of cleaning procedures and cleaning agents should be defined and justified - Written procedures should be established assigning responsibility for sanitation and describing the cleaning schedules, methods, equipment, and materials to be used in cleaning buildings and facilities. *Reference: 5.21, 5.22, 5.25, 4.71*	- Those machine parts that are in direct contact with the harvested medicinal plant/herbal substances, must be cleaned after use to ensure that remaining residue does not result in subsequent cross-contamination. - All containers used during harvesting must be clean and free of contamination from previous harvests. When containers are not in use, they must be kept in dry conditions free of pests and inaccessible to mice/rodents, livestock and domestic animals. *Reference: 6.2 , 11.7*	- Written procedures should be established for cleaning of equipment and its subsequent release for use in the cultivation of medicinal cannabis. - Equipment and utensils should be cleaned, stored, and, where appropriate, sanitized or sterilized to prevent contamination or carry-over of a material that would alter the quality of the starting material beyond the official or other established specifications. - Written procedures should be established assigning responsibility for sanitation and describing the cleaning schedules, methods, equipment, and materials to be used in cleaning buildings and facilities.

Table 1-4. Differences between the requirements of the GMP, GACP and GMCCP standard

Subjects	Requirements		
	GMP [1]	GACP [2 3]	GMCCP
Validation and process standardisation	- The company's overall policy, intentions, and approach to validation, including the validation of production processes, cleaning procedures, analytical methods, in process control test procedures, computerized systems, and persons responsible for design, review, approval and documentation of each validation phase, should be documented. - Before starting process validation activities, appropriate qualification of critical equipment and ancillary systems should be completed. *Reference: 12.10, 12.30*	Not applicable.	- The company's overall policy, intentions, and approach to validation, including the validation of production processes, cleaning procedures and persons responsible for design, review, approval and documentation of each validation phase, should be documented. - Qualification of critical equipment and ancillary systems should be completed. - All the equipment involved in the cultivation process has to be calibrated according to the established procedure and schedule. - The Critical Quality Attributes and Critical Process Parameters should be identified. - Appropriate in-process acceptance criteria and controls have to be established. - Cultivation process has to be standardised in order to ensure reproducible results.

[1] Basic requirements for active substances used as starting materials, EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines (2014)

[2] Guideline on Good Agricultural and Collection Practice (GACP) for starting materials of herbal origin, Committee on herbal med (2006)

[3] WHO guidelines on Good Agricultural and Collection Practice (GACP) for medicinal plants (2003)

Conclusion

There is a steady increase in the demand for cannabis material and products intended for medical and scientific use around the world. Higher demand has resulted in the appearance of numerous companies eager to conquer markets by swiftly increasing production capacity and delivering as much cannabis as possible, at any cost. The inappropriateness of GMP and the inadequacy of GACP guidelines created a gap in the regulatory landscape which enabled a flood of products with questionable quality on markets worldwide. This led to regular product recalls due to pesticide and other types of contamination. There is a high chance that some of these recalls can be attributed to low standards of process control during cultivation. Without requirements which encourage companies to improve different aspects of their cultivation process, and consequently improve the quality of their products, it is reasonable to expect more product recalls caused by a lack of control over the process and product environment.

The example of Bedrocan serves as a useful foundation for establishing such good practices. GMCCP would raise the bar for the industry and inspire other companies to strive for the highest possible quality in cannabis cultivation to produce material intended for medical and scientific use. Nowadays, the quality of the product cannot be only guaranteed by a conforming Certificate of Analysis, but by proving that cultivation and production is conducted according to certain principles, principles which, when adopted, ensure the product quality throughout its life-cycle, and which lead to continuous product improvement.

With the increasing globalisation of commerce and trade, and the rising number of pharmaceutical companies, the importance of standards, guidelines or norms has never been greater. For the cannabis industry, which exists for barely two decades and is facing accelerating technological change, market competition and public scrutiny, it is critical that quality standards are set fast to avoid defective products released on the market and potential adverse impact on patients' health. Such scenarios might force regulatory authorities to take measures but could significantly setback the industry and seriously harm the trust of the health sector who prescribe and use cannabis for medical and scientific purposes.

The advantages of introducing guidelines such as GMCCP are clear, as the opportunities for development, innovation and increased productivity. But for any guideline, norm or standard to be effective, it must be conceived, formulated, and implemented correctly, with a scientific and technical basis, while remaining cost-effective and wide-reaching. Hopefully, this white paper has demonstrated the essence of such a guideline and will pave the way towards developing and adopting new practices.