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Quality Requirements for Medicinal Cannabis and Respective Products in the European Union – Status Quo#

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ABSTRACT

Medicinal cannabis and respective products have been available in EU member states as single-patient prescriptions without regular marketing authorizations for a couple of years. The Netherlands was the first member state to realize this; in the meantime other member states have followed. Today, aside from the Netherlands, Germany is the most important market for such products. The regulatory framework for the approval of medicinal cannabis and its distribution to patients in the EU member states is, however, not harmonized at all, and there are distinct national regulations. Regarding the quality of such products, the general requirements for herbal medicinal products as defined in the European Pharmacopoeia, national pharmacopoeias, and the EMA guidance documents in place beside GMP requirements in the EU are applicable. However, for a couple of aspects, every EU member state follows its own interpretation of these requirements. To facilitate free distribution of such products between EU member states in future and to harmonize requirements for quality and GMP, an EU-wide approach is needed. As a first step, this should be realized by implementing monographs for cannabis medicinal products in the European Pharmacopoeia.

Introduction

"Cannabis" refers to marijuana, plants, and plant parts of plants of *Cannabis sativa* L. Cannabis, cannabis preparations (e.g., extracts), cannabinoids as active substances and respective herbal medicinal products have been available to patients in Europe for several years. The spectrum of respective medicinal cannabis products in the EU member states is as follows:

- dried and purified herbal drug: cannabis inflorescences ("medicinal cannabis")
- various cannabis extracts ("medicinal cannabis preparations")
- one authorized finished medicinal product (Sativex®).

Medicinal products with synthetic pure cannabinoids, such as dronabinol, which is used as the active ingredient in the authorized product Canemes®, strictly speaking do not belong to the "cannabis medicinal products", as they are not necessarily obtained from cannabis. Also, the authorized product Epidyolex® is not subsumed under "medicinal cannabis", even though its API cannabidiol (CBD) is obtained from cannabis, but not considered a herbal product as it is highly purified.

The species *Cannabis sativa* L. has undergone major domestication and breeding, which results today in numerous cultivars with different growth and sex forms, which can also differ cytologically [1]. These cultivars are called "strains", for which names are given arbitrarily. These names are unordered and are not to be confused with protected breed varieties. A broad spectrum of constituents is accumulated in *Cannabis sativa* L. More than 550 different structures have been identified in the meantime [2]. With about 120 representatives, the cannabinoids are probably the most in-

Dedicated to Professor Dr. Gerhard Franz on the occasion of his 85th birthday.

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ABBREVIATIONS

DAB	"Deutsches Arzneibuch" (German Pharmacopeia)
EMA	European Medicines Agency
EU	European Union
GACP	Guideline on Good Agricultural and Collection Practices for Starting Materials of Herbal Origin
GDP	Good Distribution Practice
GMP	Good Manufacturing Practice
HMP	Herbal Medicinal Product
HMPC	Committee on Herbal Medicinal Products
HPLC	high-performance liquid chromatography
HPTLC	High performance thin-layer chromatography
Ph. Eur.	Pharmacopeia Europaea/European Pharmacopoeia
Ph. Helv.	Pharmacopeia Helvetica (Swiss Pharmacopeia)
TLC	thin-layer chromatography

teresting group of active substances of cannabis. The cannabinoids are accumulated in high concentrations in glandular hairs, which occur particularly densely on the underside of the bracts of female flowers along the leaf veins and the leaves in the inflorescence area [3]. Genuinely, cannabinoids are accumulated as carboxylated compounds, these compounds are therefore called cannabinoid acids; to make this clear, an A for "acid" is then added to their abbreviation (▶ **Fig. 1**). These terpene phenols can be psychoactive. (−)-Δ9-trans-tetrahydrocannabinol (THC) is the most psychoactive cannabinoid; others like cannabinol (CBN) show weaker psychoactivity. With other cannabinoids, such as cannabidiol (CBD), psychoactive effects are completely absent [4]. In addition to these activities, which are mediated via the human endocannabinoid system, numerous other pharmacological activities are now known, including the modulation of various receptors and the influencing of ion channels as well as influences on enzymes and their gene regulation [5]. The main cannabinoids are accumulated in the plant as pharmacologically non-active carboxylic **acids** (e.g., THC**A** and CBD**A**) that have to be decarboxylated before they become pharmacologically active (▶ **Fig. 1**). The content of the two main cannabinoids THC and CBD in the inflorescences varies enormously between cultivars. There are genotypes that are almost free of THC, while others contain up to 2% THC. The same applies to the CBD content.

Medicinal Cannabis and Medicinal Cannabis Products

Different products based on cannabis flowers and cannabis extracts are marketed in the EU member states as herbal medicinal products without regular marketing authorizations. Patient-specific prescription medicinal products manufactured in pharmacies or medicinal products are available to individual patients based on distinct national authorization or registration procedures. It is surprising that the conditions for making cannabis products available and for distributing them to patients in Europe are by no means harmonized and that there are specific regulations in each EU member state due to different frameworks for narcotics and individual prescriptions, which will not be discussed here. Neither does this article cover the aspects resulting for the status of medicinal cannabis as narcotics. This review is focused on quality aspects.

Cannabis and cannabis preparations are herbal active substances or herbal medicinal products. Therefore, the definitions of Directive 2001/83/EC, the HMPC guidelines for herbal medicinal products in Europe and the European Pharmacopoeia (Ph. Eur.) are relevant. Within the scope of these regulations and guidelines, the harvested cannabis inflorescences are to be defined as herbal drugs (starting materials), and the extracts produced from them as herbal preparations, i.e., the active ingredient. This is then turned into an extemporaneous (magistral) preparation by essential manufacturing steps in the pharmacy or into a medicinal cannabis product by industrial production (▶ **Fig. 2**). Extemporaneous preparations are defined in the European Pharmacopoeia as pharmaceutical preparations individually prepared for a specific patient or patient group, supplied after preparation; if they are prescribed regularly, they could be manufactured in pharmacies as stock preparations, which are defined as pharmaceutical preparations prepared in advance and stored until a request for supply is received. In this context, trimmed cannabis inflorescences are directly used as medicinal products ("medicinal cannabis"). Trimming is performed by removing buds, leaves, and non-flowering branches from the Cannabis inflorescence. Trimmed inflorescences or extracts obtained from cannabis are used as active ingredients for the manufacture of distinct dosage forms, e.g., tablets, capsules, liquids, and preparations for vaping ("medicinal cannabis products"). Medicinal cannabis is best compared with medicinal herbal teas, for which there are well-established concepts in Europe. If we apply these concepts to medicinal cannabis, we can define the harvested inflorescences as herbal drugs (starting materials), the trimmed flowers as the herbal preparation, i.e., the active ingredient, which is then turned into a extemporaneous preparation through essential manufacturing steps in the pharmacy, for example (▶ **Fig. 2**). Although this concept is clearly established in Europe, the EU member states follow their own concepts, in which the purified flowers or even extracts are frequently already defined as extemporaneous preparations and/or medicinal products. This has far-reaching consequences for the import into Europe, the manufacture, and the movement of goods into and within the European Union as well as the authorizations required for these activities. It is surprising that no harmonized concept is being pursued here and that the European regulatory bodies, e.g., the Herbal Medicinal Products Committee of the EMA, are not addressing this issue. As there are specific quality requirements for herbal medicinal products for the three different stages of the value chain, this also has consequences for the quality assurance and testing of medicinal cannabis and medicinal cannabis products and the related starting materials and intermediates.

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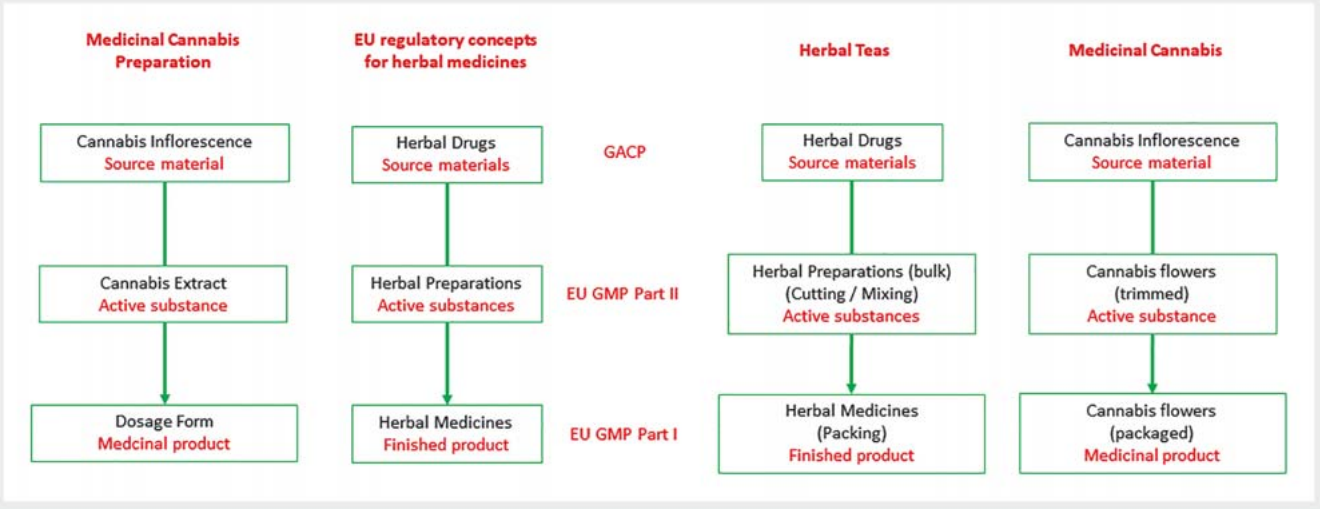
▶ **Fig. 1** Δ^9-Tetrahydrocannabinol acid THCA (**a**) and Cannabidiol acid CBDA (**b**) are the target cannabinoids in medicinal cannabis. By decarboxylation at C-2 they are inverted to the pharmacological active constituents in medicinal cannabis.



▶ **Fig. 2** Established concepts in the EU for the different stages of the manufacture of herbal medicines and GxP requirements applicable, respectively. These concepts could be easily transferred to medicinal cannabis (flowers) and medicinal cannabis preparations (extracts). Data partly from [30].

Good Agricultural and Collection Practices (GACP)

In the manufacture of herbal medicinal products, the wild collection or cultivation of plants as herbal starting material is the first step.

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" (EMEA/HMPC/246816/2005) of the EMA [6]. 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 [7]. This guideline takes into account the special features of herbal starting materials and covers the entire processing of plants used for the manufacture of medicinal products.

Annex 7 and the GACP guidelines define rules for the wild collection and cultivation of medicinal plants. This includes requirements for:

- quality assurance
- personnel involved and their qualifications, as well as necessary hygiene measures
- the buildings and premises used for drying, initial processing steps, and storage,
- equipment and devices to be used
- documentation
- the production of seeds, cuttings, and other plant material for propagation purposes
- cultivation and harvest (for medicinal plant cultivation) or collection (for wild collection)
- drying and initial processing of the plant materials
- packaging, (intermediate) storage, transport, and distribution.

Within the framework of an audit, it is the responsibility of the distributor in the European Union to verify whether the requirements of GACP are fulfilled. 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).

Good Manufacturing Practices (GMP)

The first part of the EU GMP Guideline outlines the requirements for medicinal products [8]. The second part serves as GMP guidance for the manufacture of active pharmaceutical ingredients. Part II is an internationally harmonized guidance that was origi-

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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			■

▶ **Fig. 3** Demarcation between GACP and EU GMP Part II provided as a table in Annex 7 EU GMP. Regarding the explanatory notes provided in the table (*, **, +, 4) please refer to the original guideline [31].

nally published as ICH Guideline Q7A [9] and was then implemented in the European legal framework as Part II of the EU GMP Guide [10]. Table 1 of the 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. A similar but not identical table is provided in the Annex of the EU GMP Guide (▶ **Fig. 3**). According to Annex 7 of the EU GMP Guideline, the responsibility for performing an appropriate demarcation lies with the medicinal product manufacturer. Only active ingredients that have been manufactured in accordance with the EU-GMP requirements may be used, both for production in a company or for further processing in the pharmacy. In Europe, GMP supervision of manufacturers of active pharmaceutical ingredients (EU GMP Part II) and of finished medicinal products (EU GMP Part I) is the responsibility of the national competent authorities of the EU member states. When importing active ingredients from countries outside the EU, a "written confirmation" is required from the local authorities of the country in which the production takes place. In the "written confirmation", local authorities confirm that the standards of GMP applicable to the respective manufacturing plant are at least equivalent to those laid down in the EU; the manufacturing plant is subject to regular, strict, and transparent controls, and to the effective enforcement of good manufacturing practice, including repeated and unannounced inspections. This ensures a protection of public health at least equivalent to that in the EU, and that in the event of findings relating to non-compliance, information on such findings is supplied by the exporting third country to the EU without delay. This certificate must be issued for each active substance of a manufacturing site; e.g., for each singular batch of cannabis extract to be imported. A copy of the relevant certificate is a mandatory part of the delivery documents of each consignment to the EU. These requirements only apply to those countries not included in the list published by the European Commission according to Art. 111b of Directive 2001/83/EC ("White List"). Currently listed are the USA, Canada, Japan, Brazil, Australia, Israel, Switzerland, New Zealand, and South Korea. Even for these importing countries, not all of them issue such GMP certificates for medicinal cannabis and/or medicinal cannabis products, e.g., in Canada and Israel such certificates are not issued (so far) – neither for extracts or other preparations nor for flowers as active ingredients, because their production is not subject to GMP supervision in these countries. If the competent authority of the country of origin does not issue a "written confirmation", the competent authority of an EU member state must issue a corresponding GMP certificate for the active substances to be imported. This requires an on-site GMP inspection of the active ingredient production by an EU medicines competent authority. Even the external testing laboratories, which may be responsible for quality control, in Canada, for example, must be inspected – even if they have a GMP certificate from Health Canada – as the analysis of active herbal ingredients is not subject to the agreement between the EU and Canada on the mutual recognition of GMP certificates ("White List Country").

If cannabis flowers or preparations made from them are categorized as medicinal products by an EU national competent authority, an EU import permit is required. This requires a GMP certificate from the non-European manufacturer. If this is not available, such a certificate must be issued in the EU and the competent authority of a Member State must certify that the GMP requirements are met. This also requires an inspection in the third country concerned. This is also the case for MRA countries (MRA stands for "mutual recognition agreement" and refers to agreements between the EU and third countries on the mutual recognition of GMP certificates or quality standards), such as Canada, because cannabis is not subject to local medicinal product legislation there and a certificate is therefore not issued by the local authority. In the non-European countries from which cannabis has been imported to date (e.g., Israel, Canada, Colombia, Australia, Jamaica, Lesotho, Uruguay, Uganda) or from which an import is intended (e.g., Australia, South Africa, Zimbabwe), the extraction of cannabis flowers has so far been carried out with a corresponding local manufacturing license, but not under GMP. Companies

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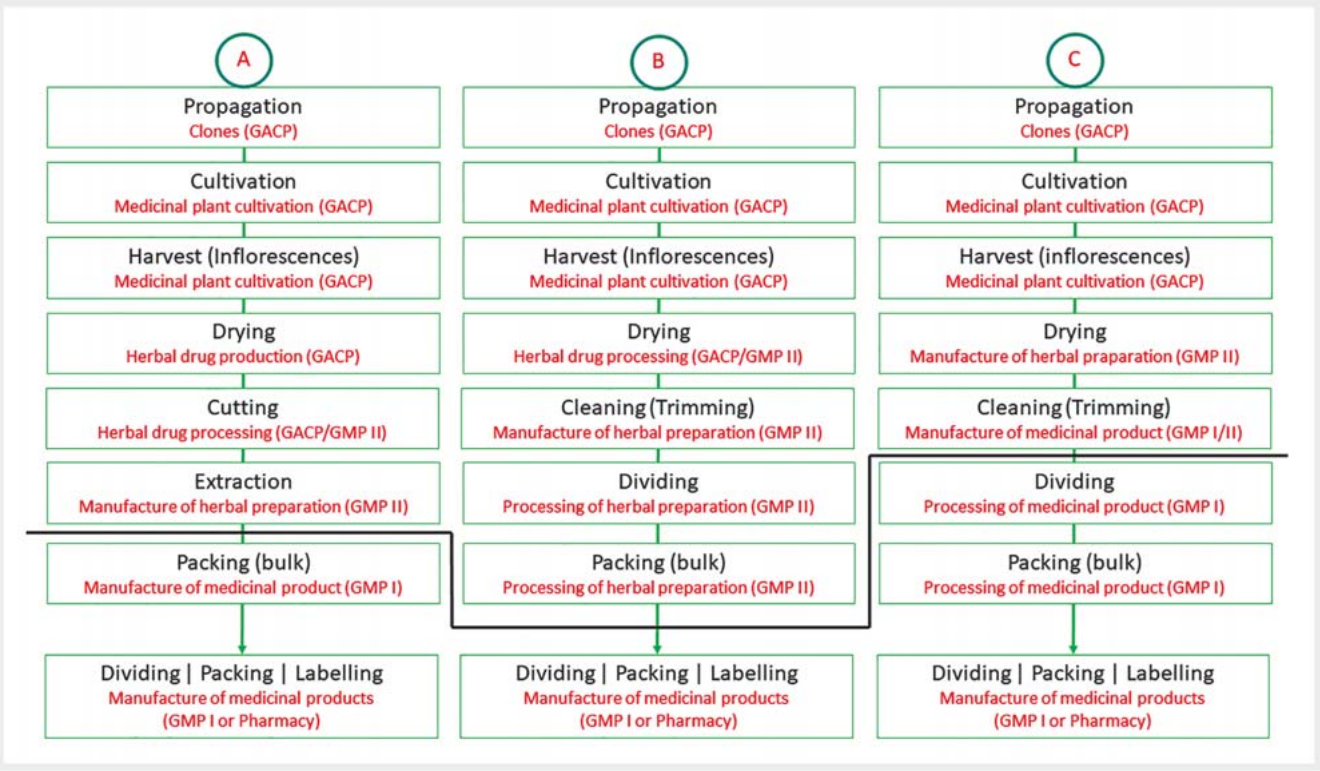

▶ **Fig. 4** Concepts followed by local competent authorities in the EU for the different stages of the manufacture of medicinal cannabis (A: Liquid medicinal preparations, B and C: Flowers) with different demarcation between EU GMP Part I and II. Some of these concepts are in conflict with existing concepts for the manufacture of herbal medicines in the EU and the demarcations as provided by ICH Q7. For imports of medicinal cannabis as flowers in bulk in the EU, concept B follows the requirements for the import of APIs and thus only a notification together with a "written confirmation" is required; concept C follow the requirements for medicinal products and thus an import permit and wholesale licence are required. The latter also applies in the case of liquid bulk extracts under concept A. Data partly from [30].

importing into Europe and companies trading in cannabis medicines in Europe need a wholesale permit from the EU member state in which they are located.

Delimitation of the Quality Assurance Systems GACP, GMP Part I, and GMP Part II

For herbal medicinal products, concepts have been developed as to when production should be carried out under GMP (as distinct from GACP) and which processing steps should be carried out under GMP Part II or GMP Part I. Such a concept exists, for example, for the manufacture of medicinal teas, which has been successfully practiced in the EU for many years and is recognized by the authorities. Here, the cultivation of the herbal starting material as well as the initial drying and comminution are performed under GACP. The production of the actual herbal preparation, in particular the fine cutting and the homogenization, is carried out according to EU-GMP Part II and its packaging and labelling, according to EU-GMP Part I or local requirements for pharmacies. Such a concept can easily be transferred to purified cannabis flowers (▶ **Fig. 2**).

If cannabis flowers are used as herbal starting materials for the manufacture of herbal preparations, i.e., extracts, the equally well-established concept for the production of herbal medicinal products with herbal preparations as active ingredients applies. The cultivation and the first processing steps of the herbal starting material are carried out under GACP. The production of the active ingredients (preparations, e.g., extracts) is carried out under EU GMP Part II, whereas the production of the medicinal product is carried out under EU GMP Part I. The GMP manufacturing steps are also covered by the manufacturing authorization of a pharmacy (▶ **Fig. 2**). The responsibility for GMP supervision of the production of medicinal products in manufacturing facilities including pharmacies lies with the respective competent authorities of the EU member states, which also issue the corresponding GMP certificates in which the production of herbal medicinal products must be explicitly stated.

In the case of cannabis flowers as active ingredients for the preparation of flower-based prescription or magistral medicinal products in the pharmacy, the situation is complex and the requirements of the authorities regarding demarcation between EU GMP Part II and Part I are not harmonized between the EU member states. National peculiarities apply when it comes to the stage of production at which cannabis flowers are considered starting materials, active ingredients, or (intermediate) medicinal products. Today, three distinct concepts are followed (▶ **Fig. 4a–c**). This also results in the problem that the existing requirements in pharmacopoeias in Europe are partly applied to cannabis flowers as active substances and partly as medicinal products. Partic-

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ularly disconcerting is the position of individual authorities in Europe who consider the monograph for cannabis flowers in the German Pharmacopoeia (DAB) to be also applicable when extracts are produced from cannabis.

For cannabis medicinal products imported into the EU, a full EU release is required, which must be done by a "Qualified Person (QP)". This release is often carried out for purified ("trimmed") cannabis flowers and cannabis extracts (as far as they are covered by the monograph), on the basis of the DAB monographs. This release testing can also be carried out in an external laboratory with an EU manufacturer's authorization. Formally, the release requires the verification of all GMP obligations in the entire value chain; this normally also includes audits. Compliance with the GACP requirements must be guaranteed by the distributor of the medicinal product.

For the manufacturing steps that must be conducted under GMP, it is quite a complex project to integrate in detail steps such as harvesting, drying, and trimming into a GMP-compliant quality assurance concept. This is made even more difficult by the fact that cultivation and further processing are currently carried out in the countries of origin, such as Canada or Israel, under cannabis-specific quality assurance concepts but not under GMP. In this context, some requirements of the EU GMP Guide are not mapped, others differ. It will usually be the case that essential requirements of the EU-GMP Guide have to be established locally before an inspection by European inspectors can take place.

Preparation of GMP Inspections for Medicinal Cannabis

The implementation of GMP specifications and requirements for the manufacture of preparations from cannabis flowers, in particular extracts, follows established standards based on many years of experience with GMP concerning the production of herbal preparations and herbal medicinal products. However, such generally recognized standards are lacking for the production of medicinal cannabis. The inspections carried out in the meantime by the European competent authorities, especially in Canada and Israel, prove that it is certainly possible to also map corresponding standards for the production of medicinal cannabis. The underlying process, in the course of which several inspections are usually carried out, begins with a supplier qualification. At the end, the responsible person of the importing company must give a positive vote before an inspection can be applied for at the competent authority of an EU member state. When implementing the GMP requirements, challenges arise especially in the following areas:

Batch definition and batch homogeneity: In the GMP environment, the definition of a batch affects the resulting activities in many ways. This concerns the control strategy, in-process controls, release testing, and traceability, as well as cleaning and process validations. It must first be decided what is to be defined as a batch. This will usually be based on propagation and cultivation cycles, origin and age of clones or cultivars, and defined cultivation areas or spaces. In each case, a set of plants obtained in the same form must be defined. As the inflorescences are not cut and further crushed when producing the flowers as medicinal cannabis, complete homogenization is not possible, and therefore a certain variability of the cannabinoid contents must be expected. This ranges from ± 10 to 20% for the cannabinoids THC and CBD to be declared. However, this is only possible if the plants are spread, cultivated, and harvested under strictly controlled conditions and stable clones are used as cultivars and, so far, usually only when cultivation takes place indoors. This variation has a number of consequences that need to be taken into account in quality control and stability testing. Central to this is an appropriate sampling schedule for quality control and the examination of appropriate samples in stability studies, as the mean content of cannabinoids of packaged stored stability samples may well differ by 10 to 20% from pack to pack. Distinct from medicinal cannabis, cannabis (flowers) used for the manufacture of extracts represent herbal starting material. They need not be obtained under GMP; the manufacture under GMP (Part II) starts with the initial comminution before extraction.

Risk management system: Manufacturing under GMP requires the establishment of a pharmaceutical risk management system with a risk-based approach for all GMP activities. This requirement is often difficult to communicate to medicinal cannabis manufacturers in third countries and is not infrequently part of deficits identified during audits and inspections.

Zone concepts: The individual manufacturing zones must clearly be separated from one other. This particularly applies to the demarcation between the GACP and GMP areas in the production of purified ("trimmed") cannabis flowers. The GMP area requires appropriate clean room concepts. This represents an area of tension in the manufacture of medicinal cannabis insofar as harvested and dried cannabis flowers always have an inherent microbial contamination, which at the same time represents a critical quality attribute.

Supply systems: All supply systems (heating, ventilation, air conditioning, water, lighting, waste) must be adequately designed, qualified, and maintained.

Hygiene concepts: Due to the inherent bioburden of cannabis, appropriate hygiene concepts must be established. Part of such concepts must also be the rooms as well as equipment and facilities, their cleaning, and equipment storage before and after cleaning.

Control strategy: The control strategy includes all measures that ensure quality and batch conformity required under GMP. Sufficient controls must be defined for this purpose. These include, among others, in-process and material controls, controls of environmental conditions, the control of cleaning, and the control of processes.

Process validation: The GMP manufacturing process is subject to validation according to the requirements of Annex 15 of the EU GMP Guide.

Cleaning validation: The cleaning of surfaces in contact with the product and, where appropriate, rooms, must be validated. In the case of cannabis flower production, this includes the drying facilities and rooms, machines used to clean (trim) the inflorescences, vessels used for bulk storage, and equipment used in packaging.

Qualification: All equipment and instruments used in the GMP process must be qualified according to the requirements of Annex 15 of the EU GMP Guideline. If processes are computer-controlled

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(e.g., drying), the GMP requirements for software and computer validation must be observed. To ensure qualification, life cycle concepts are required that also depict maintenance and repairs.

Analytical test methods (thin-layer chromatography, microscopy): In third countries, there is often no experience with microscopic tests or thin-layer chromatographic test methods, which are well established in Europe. The establishment of such test methods in the third country can be associated with considerable effort, so that it may be necessary to forego the use of these methods in the release test for shipment. The corresponding tests are then carried out downstream as part of the EU release.

Analytical test methods and analytical method validation: It must be assumed that not only the manufacturing plants (possibly in the third country) are inspected, but also external control laboratories. This also applies if the external control laboratories are subject to local GMP supervision and they are third countries with which mutual recognition agreements exist (Australia, Canada, New Zealand, Switzerland, USA), since herbal active substances and/or medicinal products are not included in these agreements.

Documentation and document management: GMP-compliant documentation must be ensured. All GMP documents must be managed and appropriate processes for the creation, approval, management, distribution, and archiving of documents must be established. In this context, many aspects of data integrity are also touched upon.

Supplier qualification: All suppliers must be qualified. This also applies to all outsourced activities and often includes external testing facilities. All quality control and stability testing must be carried out in GMP-supervised testing facilities.

Certificates: After a GMP inspection by an EU-competent authority, a certificate is issued to the inspected establishments, facilities, or persons if the inspection has shown that the corresponding principles and guidelines are complied with. The period of validity of the certificate shall not exceed 3 years and will be withdrawn if it subsequently becomes known that the requirements were not met, and revoked if the requirements are no longer met. The certificates issued by the inspecting EU authorities in case of success are uploaded to the public GMDP database of the EMA.

Good Distribution Practice (GDP)

GDP is a GMP-analogous quality assurance system for the area of active pharmaceutical ingredient or medicinal product distribution. It comprises the following aspects to be covered by the distributors:

- requirements for the quality and risk management system
- requirements for instruments, rooms, transport vehicles, or containers and facilities
- requirements for personnel
- documentation requirements
- tasks of the person responsible for distribution
- appropriate procedures for handling complaints, returns, and recalls, as well as precautions to prevent counterfeiting
- outsourced activities
- transport requirements
- specific rules for intermediaries

The GDP requirements for active pharmaceutical ingredients [11] apply to the transport of active pharmaceutical ingredients in a (manufacturing facility or for the production of medicinal products in the pharmacy. Trade in active ingredients in the EU internal market is subject to notification, i.e., pharmaceutical manufacturers and pharmacies may only purchase active ingredients from appropriately registered active ingredient distributors and must cover the required GDP specifications in their quality assurance system. Additional obligations from national legislations on narcotics must be followed, which are not explained in detail here.

In the event that authorities categorize cannabis and preparations made from it as medicinal products, the GDP specifications for medicinal products apply [12]. These are mapped within the framework of the wholesale license that is then required.

The manufacturing authorization for finished medicinal products also includes the authorization to distribute the medicinal products it covers Manufacturers who also distribute their own products must therefore also comply with good distribution practice.

Quality Requirements for Cannabis Flowers

General quality requirements for herbal drugs in Europe

The herbal drug batch in question must be suitable for the intended use. This intended use is their further processing into preparations or their use as starting material for the extraction of ingredients. The pharmaceutical quality of a drug batch is ensured if it complies with the requirements of the European Pharmacopoeia or the national pharmacopoeias of a member state of the Council of Europe (e.g., DAB and Ph. Helv.) or other EU national pharmacopoeias. If no corresponding requirements exist in a specific case, the pharmaceutical manufacturer or distributor must draw up their own quality specifications. Relevant specifications for this can be found in the Ph. Eur. monograph “Herbal drugs” and in the guideline “Test procedures and Acceptance Criteria for Herbal Substances, Herbal Preparations and Herbal Medicinal Products/Traditional Herbal Medicinal Products” [13].

In the monograph “Herbal drugs”, of the Ph. Eur., the critical steps in drug production are mentioned in the section “Production” and appropriate procedures are required. Furthermore, the reference is also included here that when a decontaminating treatment has been used, it must be demonstrated that the constituents of the herbal drug are not affected and that no harmful residues remain. The use of ethylene oxide is prohibited for the decontamination of herbal drugs. The following quality attributes are specified (references to the corresponding chapters of Ph. Eur. in brackets):

Foreign matter (2.8.2): A test for foreign matter shall be carried out unless otherwise specified or except in justified and approved cases. The content of foreign matter shall not exceed 2% (m/m) unless otherwise specified or except in justified and approved cases. Appropriate specific testing of a dried herbal drug may be required to exclude possible adulteration.

Loss on drying (2.2.32): The determination shall be carried out unless otherwise prescribed or justified and authorized.

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Water (2.2.13): For dried herbal drugs with a high essential oil content, a determination of the water content may be carried out instead of a determination of the loss on drying. This is relevant for cannabis.

Ash (2.4.16) and hydrochloric acid insoluble ash (2.8.1): The determination serves in particular to detect mineral impurities. In the case of cannabis flowers, this is of little relevance, as mineral impurities do not play a role. Thus, with appropriate justification these tests might be omitted.

Pesticide residues (2.8.13): Dried herbal drugs shall comply with the requirements of the test. The requirements take into account the type of plant, the preparation for which the plant is intended, if necessary and, if information is available, full documentation on the treatment of the batch.

The mandatory scope of testing for pesticides in the EU and Switzerland is given in Ph. Eur. monograph 2.8.13. As cannabis cultivation is carried out under strict application of the GACP rules, the scope of testing can be limited to the pesticides that are actually used and documented. Not all limits for pesticides in herbal drugs are specified in the Ph. Eur.; thus, the requirements of Regulation 396/2005/EC with all its annexes and updates are additionally applicable. If a certain pesticide is not listed there either, a corresponding acceptable limit value must be calculated via the acceptable daily intake (ADI). In order to obtain a meaningful result, sampling and sample preparation are at least as important as the actual determination. Sampling must be carried out according to the specifications of Ph. Eur. monograph 2.8.20. In the food sector, standardized procedures for sample preparation have been developed and published for all conceivable situations. In Ph. Eur. monograph 2.8.13, reference is made to the validated analytical methods of the EU ("Quality control procedures for pesticides residues analysis"), namely to document N° SANCO/10232/2006 and subsequent revisions of this document, as represented by document N° SANTE/11312/2021 (implemented on 01.01.2022) [14].

Heavy metals (2.4.27): Unless otherwise specified in the individual monograph or except in justified and authorized cases, the following limits apply:

- cadmium: maximum 1.0 ppm
- lead: maximum 5.0 ppm
- mercury: maximum 0.1 ppm

If necessary, limit values for other heavy metals may be specified.

If needed, dried herbal drugs must comply with further tests. Relevant for cannabis flowers are:

Aflatoxins (2.8.18) and other mycotoxins: The Ph. Eur. monograph "Herbal drugs" indicates that the establishment of a limit may be necessary, in particular for aflatoxin B1 and ochratoxin B. Determining whether a test is needed must be based on a risk assessment and on experience with batch results available. As cannabis is known for possible contamination with mycotoxins, aflatoxins and ochratoxin A should be tested. In the risk assessment, the type of drying and the residual water content or water activity also play an essential role; if the water content is below 10% and the drying process guarantees a fast and homogeneous drying of the plant material, a low risk can be assumed. If this low risk is reflected in the respective batch results, skip testing might be used. When assessing the risk of contamination, the determination of water activity can also provide valuable data. The generally accepted limit below which germ growth is very unlikely is $a_w = 0.60$.

Because of their special risk potential, there is a whole series of national regulations specifically for aflatoxin contamination, in addition to the pharmacopoeia, with the aim of establishing limits for food. According to Ph. Eur. monograph 2.8.18, a limit value of 2 mg/kg applies to aflatoxin B1 for herbal drugs. In addition, it is stated that the total amount of aflatoxins B1, B2, G1 and G2 can be set at 4 mg/kg by the authorities. Herbal drugs that may be contaminated by aflatoxins must be tested by a validated method. The method described in the Ph. Eur. has been shown to be suitable for devil's claw root, ginger, and senna and is given as an example. Its suitability for other herbal drugs, including cannabis flowers, must be demonstrated, or a different validated method must be used. Sampling should be carried out according to monograph 2.8.20 of Ph. Eur. If the herbal drugs are used for the production of preparations, e.g., extracts, the test is usually not only carried out on the herbal drugs used for extraction only. Due to the formation of nests, which cannot be detected with reasonable effort during a sampling procedure, it may be necessary to perform this test on the extract as well.

Microbial contamination: In the case of dried herbal drugs that are part of a medicinal product in whole, cut, or powdered form, microbial contamination must be controlled (5.1.8. Microbiological quality of herbal medicinal products for oral use and extracts used in their preparation, or 5.1.4. Microbiological quality of non-sterile pharmaceutical preparations and substances for pharmaceutical use (e.g., for cutaneous use).

Fumigants: Treatment with ethylene oxide is not allowed in EU member states. This is also stated in the Ph. Eur. monograph "Herbal drugs". If other fumigants are used, appropriate residue studies must be carried out. Overall, the "Reflection paper on the use of fumigants" of the HMPC (EMEA/HMPC/125562/2006) [15] should be taken into account.

Specific Quality Requirements for Cannabis Flowers in Europe

The specific quality requirements in Europe result from the monographs of the German Pharmacopoeia (DAB 2020), the Swiss Pharmacopoeia (Ph. Helv.) and requirements defined by the Danish [16] and Dutch cannabis authorities [17]. In the latter case, this is a testing regulation for the varieties traded in the Netherlands. There is also a rather extensive monograph by the WHO [18]. A panel of the United States Pharmacopoeia (USP) has also prepared a commentary-like publication with numerous details [19], and draft monographs for the USP have been published in the Pharmacopoeial Forum [20]. In EU member states where no national specifications exist, the DAB monograph is frequently used for the definition of quality requirements.

The *definition* provided in the DAB is: "Whole or cut dried flowering growing tips of the female plants of *Cannabis sativa* L. (Cannabaceae).

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Content: 90.0 per cent to 110.0 per cent of the declared amount of cannabinoids, such as Δ^9-tetrahydrocannabinol and cannabidiol, and cannabinoid-carboxylic acids, such as Δ^9-tetrahydrocannabinolic acid and cannabidiolic acid, calculated as Δ^9-tetrahydrocannabinol ($C_{21}H_{30}O_2$; M_r 314.5) or cannabidiol ($C_{21}H_{30}O_2$; M_r 314.5), based on the dried drug."

The definition in the DAB approximately corresponds to that in the Ph. Helv.; in the Danish monograph a content corridor of 80.0 to 100.0% is given for THCA/THC and CBDA/CBD; in the Dutch monograph and the WHO monograph defined content ranges are missing.

Identification

The identification is carried out by a combination of microscopy, thin-layer chromatography and color reactions.

Microscopic examination: DAB, Ph. Helv. and the Danish monograph contain detailed macroscopic and microscopic descriptions, which allow clear identification of the drugs and are also suitable for detecting adulterations. The latter, however, are of little importance, as medicinal cannabis must always come from controlled cultivation. A comprehensive description of macroscopic and microscopic characteristics can also be found in the USP publication.

Thin-layer chromatographic determinations: Identical thin-layer chromatographic determinations are included in the DAB and Ph. Helv. monographs. These are separations on RP phases; detection is with vanillin reagent. They focus on the identification of the bands for THC and CBD and do not represent fingerprints, not least because the extraction is not exhaustive. The use of THC acid and CBD as reference substances has proven to be problematic from the pharmacies' point of view in this thin-layer chromatographic test. Procurement is difficult and cost-intensive in practice. For this reason, in October 2018, the German Medicines Codex (DAC/NRF) [21] published an alternative test method more suitable for pharmacy practice, the advantage of which results from the use of Rf-marker substances (menthol and bornyl acetate) instead of the reference substances. However, this method can only be used for THC-type flowers. Other tests for THC based on color reactions and immune assays are available [22], which can be used in addition, or alone if sufficiently selective. For CBD-type flowers, a TLC test is currently standard, although here, too, ELISA-based tests have meanwhile come to market. The Dutch monograph describes a TLC on normal phase, followed by detection using fast blue salt. Fast blue salt, however, should no longer be used as a detection reagent because of its toxicity. In none of the monographs is an HPTLC method described, although it would be obvious to use one in everyday pharmacy. Details of an HPTLC method that actually also enables a fingerprint and with which individual chemotypes and cultivars can be distinguished can be found in the USP publication.

In the Danish monograph, a UHPLC-DAD fingerprint (ultra-high-performance liquid chromatographic-diode array detection) is required to detect THCA/THC and CBDA/CBD. As an additional criterion, a comparison of the online UV spectra with the respective reference standards is required.

Color reactions and immunoassays: There are a number of color reactions that are specific for cannabinoids and are also applied for forensic identification (p-dimethylaminobenzaldehydes, DMAB; true blue salt B and Duquenois or Duquenois-Levine reaction) [22]. In addition, more and more specific immunoassays for cannabinoids are available, which are used in various commercial rapid tests. For identification testing in the pharmacy as incoming testing, immunoassays with test strips or kits with color reactions from qualified suppliers (with corresponding proof of validation) can replace the TLC test.

Purity

The purity tests listed above generally applicable for herbal drugs are also binding for cannabis flowers, according to the Ph. Eur. Specific requirements exist in the monographs for the following parameters:

Foreign matter (2.8.2): Not more than 2% (DAB, Ph. Helv., Danish monograph)

Loss on drying (2.2.32): Not more than 10% (DAB), not more than 15% (Ph. Helv.)

Ash (2.4.16): Maximum 20% (Danish monograph)

Heavy metals (2.4.27): As specified in the monograph "Herbal drugs". In the Dutch test guideline, limit values deviating from Ph. Eur. are found.

Water (2.2.13): Not more than 10% (Danish monograph, as an alternative to Ph. Eur. 2.2.32)

Loss on drying (2.2.32): Maximum 10 per cent (DAB, Danish monograph), maximum 15 per cent (Ph. Helv.).

Pesticides (2.8.13): As specified in the monograph "Herbal drugs". As cannabis flowers for medicinal purposes are always obtained under controlled conditions, it is possible to limit the scope of testing to the pesticides used in cultivation.

Aflatoxins (2.8.18): As specified in the monograph "Herbal drugs".

Microbiological quality

The monographs do not contain specific requirements for microbiological quality. The Danish monograph states that, depending on the route of administration, the requirements of Ph. Eur. monographs 5.1.4 or 5.1.8 must be met. If cannabis flowers are dispensed in pharmacies for oral use, and this is done by preparing a decoction, only in this case is it possible to specify the microbiological quality of such flowers. This would be based on category A of monograph 5.1.8 of Ph. Eur., as a treatment resulting in a germ reduction takes place during application. Monograph 5.1.8 strictly applies to oral herbal medicinal products only. However, cannabis flowers are often administered as vape or smoke, which is also associated with germ reduction. In the absence of specific requirements for this application, some authorities now require compliance with the requirements of the category "inhalation products according to Ph. Eur. monograph 5.1.4 (special requirements apply to liquid preparations for nebulization)". These are the strictest requirements that exist for non-sterile medicinal products because the aerosols depicted in this monograph are associated with a high risk due to their direct entry into the respiratory tract and the lungs. However, due to the heat-induced germ reduction, this risk does not exist in this form when cannabis flowers are administered as vape or smoke, so that this requirement is not appropriate. This is especially important because the strict microbiological

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requirements for medicinal products to be administered by inhalation can usually only be met by treating the cannabis flowers with gamma-radiation. For such treatments, specific rules exist in some EU member states. In Germany, for example, a formal authorization is needed for such a treatment. Applications must be submitted by the person placing the product on the market. This leads to the paradoxical situation that each importer has to submit an independent application, even if identical varieties coming from the same producer are imported. An interesting constellation in Germany arises in the administrative area of the Government of Upper Bavaria, where cannabis flowers are classified as active substances, while in other parts of Germany local authorities classify cannabis flowers as a(n) (intermediate) medicinal product. Only for the latter case is the authorization needed. Apart from the administrative effort associated with irradiation, the authorities accept the risk that the irradiation of the flowers may lead to changes that negatively influence the risk-benefit ratio. In a multi-substance mixture, such as in cannabis flowers, it is impossible to definitely ascertain whether radiolysis products do not have an influence on efficacy and/or safety, and whether the data to be generated in the context of the irradiation authorization are actually representative. The monograph "Pharmaceutical preparations" of the European Pharmacopoeia states: "During the manufacture/preparation of non-sterile pharmaceutical preparations, appropriate measures are taken to ensure the microbiological quality of the preparation. Recommendations in this respect are given in General Texts 5.1.4 'Microbiological quality of non-sterile pharmaceutical preparations and of substances for pharmaceutical use', and 5.1.8 'Microbiological quality of herbal medicinal products for oral use and of extracts for their preparation'." Accordingly, these are strictly spoken binding specifications, but recommendations. It is therefore up to the manufacturer or distributor to set appropriate specifications for cannabis flowers, which may not require irradiation of the flowers. The limits of category B of Ph. Eur. chapter 5.1.8. seem appropriate for this purpose. However, the risk of contamination with *Aspergillus* spp. should be considered. Inhalation of cannabis contaminated with *Aspergillus* spp. can have serious effects, if the germs are not killed, especially in immunocompromised patients [23]. It is to be hoped that with the development of a monograph for cannabis flowers in the European Pharmacopoeia, the requirements for microbiological quality will also be adequately defined and thus a proper handling of this quality attribute can be achieved. It is undisputed that the microbiological quality should be optimized by appropriate measures during cultivation, processing, and storage, as well as by the selection of suitable packaging materials and transport conditions. This also corresponds to the requirements of the "Reflection paper on microbiological aspects of herbal medicinal products and traditional herbal medicinal products" [24].

Degradation products

Cannabinol: Not more than 1.0% (DAB 2020; Ph. Helv.). Cannabinol is the main degradation product of THC. The cannabinol content correlates with the degradation of THC in the flowers. It is thus also an indirect quality attribute that gives indications of appropriate processing, packaging, and storage of cannabis flowers.

Assay

The content of the target cannabinoids Δ9 -THC and CBD is determined by HPLC or UHPLC. The methods described in the various monographs differ with regard to the specified columns and gradients, and sometimes also with regard to the mobile phases used. It is not uncommon for testing laboratories to use in-house methods that have been optimized and cross-validated with the DAB or Ph. Helv. method. As a rule, the content of cannabis flowers is determined without a complete decarboxylation of the pure acids in the course of sample preparation. Therefore, the sums of CBDA/CBD and/or THCA/THC are evaluated. In the DAB monograph, three flower types are distinguished: THC >> CBD, THC ≈ CBD; THC << CBD. With the methods (GC and HPLC) described in Annex 3 of the USP publication [19], further cannabinoids can be quantified (CBC, CBD, CBDA, CBDV, CBDVA, CBG, CBGA, CBN, THCA, THCV, THCVA, Δ8-THC, Δ9-THC). A GC method for the determination of volatile terpenoids is also included there. Quantified terpenoids are *α*-pinene, *β*-myrcene, D-limonene, *α*-terpinolene and *β*-caryophyllene. All methods can also be used for fingerprint analysis. They are therefore very well suited to distinguish or characterize individual cultivars.

Stability

The processing of cannabis flowers has an influence on the potential degradation of cannabinoids that should not be underestimated. In intact glandular hairs, these are well protected from oxidative degradation as accumulation structures. The same applies to the loss of terpenoids. Therefore, during processing, care should be taken to ensure that the glandular hairs remain as intact as possible. Appropriate measures must therefore be taken to ensure sufficient transport and storage stability.

As a first step, the cannabinoid acids genuinely contained in the cannabis flowers can decarboxylate. This process depends on light and temperature. In dried drugs, 10 to 20% of the THCA is decarboxylated. When stored at up to 25 °C, this proportion hardly increases [25]. Above 50 °C, the acids are completely decarboxylated within a few hours. For medicinal cannabis, the decomposition of the cannabinoid acids is of little relevance, as the pharmacological activity comes from the decarboxylated cannabinoids. The oxidative degradation of THC can be prevented or at least slowed by protection from atmospheric oxygen. This can be achieved, for example, by using suitable packaging materials as well as transport and storage under protective gas. Oxidative degradation is thermodynamically controlled and slows down at low storage temperatures. The latter also slow down microbial growth and thus prevent secondary contamination of the dried cannabis flowers. However, storage temperatures at or below freezing point should be avoided, as the glandular hairs as accumulation structures are then destroyed, which may expose the cannabinoids accumulated there to oxygen, which may result in increased degradation of THC. The same applies if dried cannabis flowers are stored too dry. Ideal storage conditions range between 55% and 62% relative humidity, which avoids drying out and brittleness of the glandular hairs. The water content, or better the water activity, also plays a decisive role in preventing secondary microbial growth; it should not exceed $a_w = 0.6$. There is a method of the American Society for Testing and Materials (ASTM method

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no. D8196) [26] for determination. For the theory of the determination and for practical aspects, please refer to the new USP chapters <922> and <1112>.

Within the framework of the stability testing, all quality attributes that can change during transport and storage should be tested:

- content of the target cannabinoids
- cannabinol content
- microbiological quality
- water content
- water activity
- mycotoxins (at least at the end of the stability studies)

and, if applicable, chromatographic fingerprints. Stability studies must be conducted strain-specifically. In the DAB monograph, a storage temperature below 25 °C is specified. The Ph. Helv. contains no specification in this regard. Based on the data obtained from the stability studies, a shelf life and, if necessary, a use-by period after opening, as well as suitable storage conditions, must be determined.

Sampling

In the qualitative and quantitative analysis of a batch of herbal drugs to be tested, the composition of the sample used must be ensured to be representative for this batch, so that the sampling procedure used has as little effect as possible on the test results. This is a particular challenge for cannabis flowers, as the flowers or parts of the inflorescences are obtained as whole herbal drugs and are only crushed immediately before use, if necessary. Also, when taking samples for validation of the manufacturing process (incl. drying) and for stability studies, it must be carefully evaluated whether the intended sampling leads to representative samples. These basic requirements are defined in Ph. Eur. chapter 2.8.20 “Herbal drugs: sampling and sample preparation”. There, possible procedures for obtaining bulk samples are described, which represent the minimum requirements for the sampling of herbal drugs:

If the external inspection of the containers, markings, and labels of the batch shows that it can be assumed to be homogeneous, sampling is carried out depending on the number of containers, with the resulting number of containers then to be selected at random. In the case of larger containers, sampling is carried out at the bottom, in the middle, and at the top, and in the case of bags in the middle. The minimum total mass to be taken is specified as a function of the mass of herbal drug per container, and a minimum mass of the samples is defined as a function of the size of the drug batch. If a batch cannot be assumed to be homogeneous (which might be the case for cannabis), it shall be divided into sub-batches, each as homogeneous as possible. Each sub-batch shall be treated as a homogeneous batch and samples shall be taken from at least the number of randomly selected containers specified in Ph. Eur. This approach is hardly feasible for cannabis flowers, as it can rarely be assumed that batches or even sub-batches are “homogeneous”. Due to the high costs, increasing the number of samples and/or quantity is also not an option. A minimum sample quantity of 20 g/kg batch size (2 %) must be considered. It must therefore be decided on a case-by-case basis how representative samples can be obtained – ideally, based on validation data on batch homogeneity. In this context, samples for the determination of pesticides, aflatoxins and microbiological quality are particularly critical, as is the obtaining of representative samples in the context of stability studies. It must always be taken into account that the variability of test results depends not only on batch variability, but also on the quality attributes examined in each case.

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The samples are to be combined in such a way that, ideally, several representative sub-samples are obtained. With these, it can be assessed during analysis to which extent the sampling was representative. During sample preparation and comminution, the instability of THC must always be taken into account; ground or powdered samples must be processed immediately and should not be stored.

Further information can be found in the ASTM guideline (No. D8334) “Standard Practice for Sampling of Cannabis/Hemp Post-Harvest Batches for Laboratory Analyses” [27].

General Quality Requirements for Herbal Preparations in Europe

For herbal preparations, the Ph. Eur. contains the general monograph “Herbal drug preparations”. They are defined as follows: “Herbal drug preparations are homogeneous products obtained by subjecting herbal drugs to treatments such as extraction, distillation, expression, fractionation, purification, concentration, or fermentation.” In the case of medicinal cannabis and respective products purified (“trimmed”) cannabis flowers and cannabis extracts are used as herbal preparations. For the extracts the Ph. Eur. contains a distinct monograph “Extracts from herbal drugs”, in which the following definition is provided: “Herbal drug extracts are liquid (liquid extraction preparations), semi-solid (soft extracts and oleoresins) or solid (dry extracts) preparations obtained from herbal drugs using suitable solvents. An extract is essentially defined by the quality of the herbal drug, by its production process (extraction solvent(s), method of processing, etc.) and by its specifications.” Different types of extracts can be distinguished:

- Standardized extracts are adjusted to a defined content of one or more constituents with known therapeutic activity. This is achieved by adjustment of the extract with inert excipients or by blending batches of the extract.
- Quantified extracts are adjusted to one or more active markers, the content of which is controlled within a limited, specified range. Adjustments are made by blending batches of the extract.
- Other extracts are not adjusted to a particular content of constituents. For control purposes, one or more constituents are used as analytical markers. The minimum content for these analytical markers is given in an individual monograph.

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Cannabis extracts are usually liquid extracts that are adjusted to a certain content of cannabinoids (so far THC and CBD) and therefore belong to the group of standardized (= adjusted) extracts. The standardization, i.e., the adjustment to the specified content, is done by adding inert excipients. In the case of cannabis extracts, medium-chain triglycerides are often used for this purpose, or the adjustment is made by mixing several (specification-compliant) batches of the native extracts. The deviation from the adjusted content to be specified corresponds to ± 5 % of the permissible deviation for chemically-synthesized active substances.

In the monograph "Herbal drug extracts", under the section "Manufacture", the critical points in the manufacture of extracts and requirements for the materials used in the process, including the herbal drugs used in the manufacture, are presented in an overview. For example, the herbal drugs, solvents, and other materials used in the manufacture of extracts must be of suitable quality and, where applicable, must comply with the requirements of the relevant monographs of the European Pharmacopoeia. In justified cases, herbal drugs used for the preparation of extracts may exceed the limits for heavy metals laid down in the monograph "Herbal drugs", provided that the extract prepared therefrom complies with the test for heavy metals. This concept could be also applied to other requirements for the testing of contaminants.

Prior to extraction, different batches of the herbal drug, meeting the requirements of the relevant monograph or, in the absence of a single monograph, appropriate specifications, may be mixed. This may be necessary, for example, to obtain the amount of drug required for the production process or, in the case of standardized and quantified extracts, to ensure that the content of one or more constituents of the herbal drug to be extracted lies within a certain range. The herbal drug may also be subjected to a pre-treatment, it may be comminuted or defatted, or certain enzymes may be inactivated. In addition, unwanted ingredients (e.g., toxic ingredients) or undesirable components (e.g., insoluble components) may be removed at an appropriate stage of the manufacturing process. Solvents already used in the production process and subsequently recovered or recycled may be reused, provided that the recovery processes are controlled and monitored to ensure that the solvents meet appropriate specifications before being reused or mixed with other approved materials. Water for the preparation of extracts shall comply with the Ph. Eur. monograph "Water for the preparation of extracts". If applicable, extraction liquids (miscella) are thickened to the desired consistency using appropriate methods, usually under reduced pressure and at a temperature that minimizes the degradation of the ingredients. Essential oils that have been separated during processing can be added back to the extract in a suitable manufacturing step. This might be used to conserve terpenoids from cannabis, which can be lost in the course of the extraction and/or purification process. For technological reasons (for example, to simplify the drying process or to improve the homogeneity or consistency of the extract), suitable excipients may be added at various stages of the manufacturing process. Appropriate inert excipients may also be added to adjusted extracts to adjust one or more ingredients to a defined level. Suitable stabilizers, antioxidants, and antimicrobial preservatives may also be added in justified and authorized cases.

Extraction with a particular solvent results in a typical distribution pattern of extracted ingredients in the extract. During the production of adjusted and quantified extracts, purification procedures that increase the content of these ingredients compared to the expected values may be used; such extracts are referred to as "purified". In the case of preparations from cannabis flowers, this is achieved by adding excipients as "modifiers" or by distilling the volatile cannabinoids.

The following quality attributes are relevant for herbal drug extracts:

Identity

Identification testing is performed using suitable methods. According to the DAB and Ph. Eur., TLC is almost exclusively used to check the identity of extracts. Other chromatographic techniques or specific reactions might also be used. The chromatograms obtained could be used as fingerprints.

Purity

Depending on the analytical results of the herbal drug used for extract production and the manufacturing process used, testing of the extracts for the following contaminants may be necessary (reference to the respective Ph. Eur. chapters in brackets):

Heavy metals (2.4.27): Determination is only carried out in exceptional cases if there is a risk of accumulation. It is usually sufficient to determine heavy metals only in the herbal drug to be extracted. If an extract is tested for heavy metal content, the limits listed in the monograph "Herbal drugs" shall apply, unless other values are given in an appropriate extract monograph, and except in justified and authorized cases.

Aflatoxins (2.8.18) and other mycotoxins: Testing is usually done on the herbal drugs used for extraction. Because of the formation of nests, which cannot be detected with reasonable effort in a sample draw, it may be necessary to perform this test on the extract as well. Aflatoxins are also heat stable and soluble in hydroalcoholic solvents and lipophilic extractants. There is therefore a potential risk of carry-over of aflatoxins from the herbal drug into the herbal preparation or medicinal product, which could lead to the presence of higher aflatoxin concentrations in the herbal preparation or medicinal product. This risk should be fully assessed by validating the extraction process of a herbal preparation.

Pesticide residues (2.8.13): Testing is usually done at the herbal drug stage. As part of the development of a preparation, it should be demonstrated that no enrichment occurs as a result of the manufacturing process. In the case of the lipophilic extraction agents used for cannabis, there is at least such a risk. If this is confirmed, the permissible limits must be ensured to be complied with. The limits set for dried or fresh plants are also applied to preparations made from them, taking into account the drug-extract ratio. In the Ph. Eur. corresponding calculation formulae are given in chapter 2.8.13.

Testing for solvent residues: The solvents used for extraction cannot be completely removed during extract manufacture, at least not without immense technical effort. Small residual

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amounts remain in the extract. It must be ensured that the residual quantity is harmless. ICH guidelines (ICH: International Conference on Harmonisation) on limits for organic solvents in active substances and medicinal products stipulate the maximum permissible quantities for active substances, excipients, and finished products. The central guideline CPMP/ICH/283/95 [28] (based on the ICH Q3 guidance) has been implemented in Ph. Eur. chapter 5.4. For the manufacture of cannabis extracts, the solvents ethanol, hexane, cyclohexane, and n-heptane are used. In principle, it is only necessary to test for such solvents that are used for extraction or in other production steps. In Ph. Eur. chapter 2.4.24 a general method "Identification and determination of solvent residues" is given. This is a headspace gas chromatography method. This method must be validated for the substance or product to be tested.

Pyrrolizidine alkaloids: For some years now, pyrrolizidine alkaloids (PAs) have played a major role as possible contaminants in herbal medicines. They originate as secondary substances from various weeds, especially from the Asteraceae family and here from *Senecio* species. There are about 400 known substances, about half of which are hepatotoxic and hepatocarcinogenic [29].Their content is limited in the EU to a maximum of 1.0 µg/day for herbal medicinal products for oral or cutaneous use over a maximum of 2 weeks for adults (50 kg b. w.), and to a maximum of 0.5 µg/day for herbal medicinal products for oral or cutaneous use over a maximum of 2 weeks for children (20 kg b. w.) as well as pregnant women and nursing mothers. In the case of medicinal cannabis, contamination with PAs hardly plays a role, as the plant source material is obtained from strictly controlled cultivation, whereby weediness with PA-containing weeds can be avoided. However, it is not excluded that cannabis flowers from field cultivation are also used for the production of THC-free preparations. For this reason, a risk assessment of possible contamination with PAs is always required. As a rule, this is carried out within the framework of a GACP audit. If, on the basis of the available data, it can be verifiably demonstrated that the content of PAs in the medicinal product is usually ≤ 0.1 µg/day, the risk is categorized as low. The classification in this category is acceptable if the measured value is below this limit in 90 % of the samples tested and no sample is above a value of 0.35 µg pyrrolizidine alkaloids related to the daily dose. For this category, only random sampling is required. The specific level is to be derived from the available data. In the case of in-house cultures, testing may be dispensed with altogether.

A new general chapter 2.8.26 of Ph. Eur. describing 28 target PAs is implemented in the 10th edition. It allows for the use of any method consisting of chromatography coupled with MS/MS or high-resolution MS for the determination that meets the validation requirements specified in the chapter. In addition, it contains validation requirements that must be met to demonstrate that the suitability of the method remains valid during routine analysis.

Microbiological quality

According to Ph. Eur. chapter 5.1.8, "Extracts" must generally meet the acceptance criteria of category B for herbal medicinal products. However, if it can be demonstrated that the manufacturing process does not achieve a sufficient reduction in the number of microorganisms to meet the category B criteria, the extracts must meet the requirements for category C herbal medicinal products. The recommended acceptance criteria apply to extracts that are part of herbal medicinal products for oral use. For extracts that are part of pharmaceutical preparations for another route of administration, more stringent acceptance criteria may be required in order for such preparations to meet the criteria for the applicable route of administration (see General Text in Ph. Eur. Chapter 5.1.4). Where a risk of contamination may arise in certain cases during the course of extract manufacture, additional microbiological monitoring should be provided as in-process controls for each major sub-operation. Testing for microbiological purity is then also part of the purity testing of the final product. If extracts are used for vaping issues discussed above regarding the required microbial quality of flowers is relevant in analogy for these extracts, too.

Assay

The content of the target constituents in extracts must be determined using an appropriate method. Today, HPLC and GC methods are preferably used for content determination. The content of cannabis extracts is usually determined for cannabinoids, especially for CBD and THC. However, it is conceivable that based on pharmacological and/or clinical data, other cannabinoids or other constituents are also defined as target constituents; for example, terpenoids or flavonoids. In this context, the establishment of content corridors for a quantified extract would also be conceivable.

Stability

Stability tests are carried out on extracts with a focus on the target constituents and with regard to all parameters that can change during transport and storage. For extracts, these are usually:

- content of the target constituents
- degradation products
- microbiological quality
- water content
- water activity, if applicable
- chromatographic fingerprints

Chromatographic fingerprints are important, as herbal preparations are considered in their entirety as an active substance and as a complex multi-component system. This also applies in the case of standardized extracts; thus, the study is not focused solely on the standardized target constituents. Stability studies should always be conducted in a packaging material that is equally protective as the product-specific primary packaging material, if the packing material used for commercial shipment cannot be used.

Specific Requirements for Preparations from Cannabis in Europe

A DAB monograph "Cannabis extract, standardized" has also been published for extracts.

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The definition provided in the monograph is: "The standardized is extract made from the whole or comminuted, dried shoot tips of the flowering female plants of *Cannabis sativa* L.

Content: Δ^9-Tetrahydrocannabinol (THC; $C_{21}H_{30}O_2$; M_r 314.5): Minimum 1% and maximum 2% (m/m) for the extract and 90 to 110% of the label specified nominal content. Cannabidiol (CBD; $C_{21}H_{30}O_2$; M_r 314.5): 90 to 110% of the nominal content given in the label." The monograph appears to be in need of revision: Currently the monograph only covers extracts adjusted to a content of 1 to 25% THC. In the meantime, however, extracts are available in Europe that contain less than 1% THC and are adjusted to the active ingredient CBD (CBD extracts). There are also extracts available with contents above 25% THC (refined THC extracts obtained by distillation with up to 85% THC). Those extracts are not yet covered by the DAB monograph. Moreover, it is unclear whether the monograph specifies an active substance or an intermediate medicinal product. It remains unclear how the content corridor of 90 to 110% of the label specified in the monograph for THC and CBD is to be understood. Since pharmacopoeial monographs always depict shelf-life specifications, it can be understood as a content specification for the shelf life. This, according to the HMPC guideline on specifications for herbal preparations [13], would imply that 95 to 105% as content specification would then be an appropriate release specification. A different picture emerges if the monograph is also applied to preparations categorized as (intermediate) medicinal products. Here, the amount of active substance in the medicinal product would have to be specified in any case with a content corridor of 95 to 10%. Thus, for magistral preparations, this would for example imply that pharmacists need to perform normalization using the assay value provided in the certificate if they use a cannabis extract. Further aspects which should be addressing in a revision will be addressed for other requirements provided in the monograph.

The DAB monograph contains the following requirements:

Manufacture

The extract is stated to be extracted by a suitable extraction process, preferably a CO_2 extraction, and that the obtained extract is optionally refined and adjusted to the defined content by suitable excipients, preferably with medium-chain triglycerides. It is unclear why the definition focuses on CO_2 extracts, which do not have sole market significance in Europe as ethanol is also frequently used for extraction. It should be mentioned that standardization could generally not only be achieved by using inert excipients but also by mixing batches having the same specification.

Identification

In the DAB, the identity test is carried out by thin-layer chromatography. In the current version of the monograph, the identification test provided is not suitable for detecting counterfeit extracts (artificially mixed from cannabinoids).

Purity

Cannabinol: Maximum 2.5%. This specification is illogical, as cannabinol is a degradation product of THC. The limit should be related to the THC content. Otherwise, different limits would result, depending on the THC content.

Water (2.5.12): Not more than 0.5%. A determination according to Ph. Eur. chapter 2.5.32 instead of 2.5.12 seems more appropriate here because of the small amount of water to be determined; if this is even a critical quality attribute at all, because water is often absent in cannabis extracts, as they are manufactured with extracting agents that do not contain water. In this context, the limit of 0.5% stated in the DAB monograph is irrelevant. This limit actually generically applies to dry extracts as described in the European Pharmacopoeia and does not necessarily make sense for the cannabis extracts that occur as fluid extracts.

Solvent residues: The residues must comply with the specifications according to Ph. Eur. chapter 5.4.

In the case of extracts that are pure CBD or THC extracts, consideration must be given to how the residual contents for CBD or THC are specified in each case, respectively. This can be done, for example, by following the specification for related substances as it is done for chemically defined active substances. It must also be taken into account that THC or CBD content of less than 1% may still have pharmacological activities specific to the respective cannabinoid; this applies in particular to THC. In any case, for the respective limit provided for the minor of both cannabinoids, a corridor of 90 to 110% is not appropriate and could be impossible to be established as this would constitute a two-fold standardization.

Assay

The content is determined by means of HPLC.

For preparations that are not yet covered by the DAB monograph, the scope of testing is to be determined individually and in-house specifications must be established. For extracts not covered by the DAB monograph, other cannabinoids and/or additionally terpenoids might be specified.

Stability

Storage conditions are defined in the DAB monograph: Tightly closed, protected from light, below 25 °C, preferably at 2 to 8 °C.

In any case, product-specific stability studies have to be carried out according to the European guidelines. For cannabis, this would imply that any strains used for an extract must be considered. At least a risk assessment should be performed, if different strains used for the manufacture of a particular extract could constitute differences in the stability of the target compounds. Based on these data, a product-specific storage temperature and either a retest date if the cannabis extract is categorized as an active substance or an expiry date in the case of categorization as a(n) (intermediate) medicinal product must be established. For cannabis extracts, the following quality attributes are tested in the context of stability studies:

- THC/CBD content (or further cannabinoids)
- cannabinol content (if relevant, further degradation products)
- microbiological quality
- water content, if relevant
- chromatographic fingerprints
- leachables, if relevant (for plastic primary packaging materials)

The consideration of fingerprints is relevant because the stability of the entire extract must be demonstrated. The fingerprint chro-

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matograms obtained in the course of the stability study must match the initial chromatograms obtained for batch release.

This is also relevant for development, e.g., in the evaluation of suitable packaging materials, evaluation of antioxidants, or investigations on the influence of decontamination treatments (e.g., ionizing radiation). The investigation of fingerprints is certainly also required when the comprehensive characterization of a preparation is necessary, e.g., to ensure the traceability of preparations in pharmacological and clinical investigations.

When determining the shelf-life specification, a content corridor of 90 to 110 % should ensure that the preparations in the pharmacy still contain at least 95 % of the declared active substance content for THC and/or CBD when dispensed to the patient.

If plastic primary packaging materials or closure systems are used, the risk of extractables and leachables must be assessed, and confirmatory data collected on these aspects as part of the stability studies, if applicable.

In addition, the requirements defined in other monographs of the pharmacopoeia apply; for example, for certain dosage forms, if medicinal cannabis preparations are used as specific dosage forms. It is worth mentioning that there is no monograph yet for vaporization (or smoking) products as a dosage form.

Perspective for the Future

Frequently the clinical data published for medicinal cannabis are not accompanied by a complete characterization of the preparations used. As far as flowers and preparations made from them are concerned, these are mixtures of many constituents, including cannabinoids, terpenes, and possibly also flavonoids. It is by no means sufficient to determine only the THC and CBD content as quality attributes, as other constituents can also be involved in the pharmacological activity and clinical efficacy. Clinical data without complete phytochemical characterization are thus worthless or at most hypothesis-generating; they cannot be used for the authorisation of medicinal products.

The “no-label use” of cannabis flowers and other prescription drugs dispensed as pharmacy formulations in Germany is today, at least to a large extent, not based on sufficiently robust pharmacological and clinical data. Its usage can be assumed to be often empirical. In the case of cannabis flowers, this applies not only to the posology, but also to the individually prescribed cultivars and the corresponding THC and CBD contents and their mixing ratio. The THC content of medicinal cannabis flowers available in Germany ranges between < 1 % and 22 %, and the CBD content ranges between < 0.1 % and 10 %. The administration of flowers as medicinal cannabis is increasingly criticized, for which the following reasons can be given:

- The rates of transition into a decoction are variable and generally poor (only about 10 % of cannabinoids pass into tea).
- The preparation of a decoction (15 minutes boiling time) are difficult to integrate into the daily routine of the patient with a rational administration (several times a day).
- Exact dosing is not possible. This is particularly true when flowers are delivered in multi-dose containers but is also because decarboxylation is not always complete during tea preparation.
- There is an increasing number of cultivars, which is confusing for the doctor, and there is no clinical evidence for the individual cultivars.
- In the cultivars, the composition of cannabinoids is not consistent and sometimes not stable.
- The prescription of the cultivars does not follow any rationale but is at best empirical and is probably more often based on availability, rather than on the actual spectrum of constituents.
- In the event of shortages of individual cultivars, supply is (again empirically) switched to other cultivars.

Smoking of cannabis flowers is not included in the list above, as it must be considered not appropriate for medicinal purposes. Thus, it can be anticipated that medicinal cannabis in the form of flowers will decline in popularity in prescriptions and will increasingly be replaced by extracts, which will be formulated in suitable dosage forms, such as liquids, solid oral dosage forms, and products for vaporization. In these products, a much better consistency and dosing, and thus robust and reliable safety and efficacy, can be achieved for the patient. Quality requirements of such preparations, which are relevant for batch-to-batch consistency, should also comprise appropriate fingerprints of cannabinoids. This must be reflected in the monographs, which are needed in the European Pharmacopoeia, for cannabis flowers as an herbal drug used as starting material for extract preparation, and in a separate monograph for medicinal cannabis as well as for different types of cannabis extracts. In this context, it would be helpful for microbial quality attributes for such products to be established if used for vaporization. Regarding the quality assurance concepts, there is a need for an EU-wide harmonized approach clearly defining at which stages of manufacture of medicinal cannabis GACP, GMP Part II and GMP Part I is applicable and which criteria must be considered for demarcation. Normally it ought to be the role of the herbal medicinal product committee at EMA in cooperation with the quality working party and GMP/GDP inspectors’ group to define such criteria.

Contributors’ Statement

There are no other contributing authors.

Conflict of Interest

The authors declare that they have no conflict of interest.

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