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Research on: Medicinal Cannabis

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1 GMP-compliant production of medicinal cannabis

With the law „Cannabis as medicine“, which came into force at the beginning of March 2017 as „ *Änderung betäubungsmittelrechtlicher und anderer Vorschriften* “, the German Federal Government has newly regulated access to cannabis as a medicine for patients with serious illnesses.

Doctors of all disciplines can now prescribe cannabis flowers and cannabis extracts using “*narcotic prescriptions*” (*Betäubungsmittel (BtM)-Rezept).* This makes it possible for patients to obtain cannabis, as a drug in standardized quality for therapeutic purposes in pharmacies, in addition to dose-standardized medicinal products containing cannabis extract as well as cannabinoid-containing extemporaneous- or medicinal products. Hence, it is not necessary for the patient to apply at the BfArM for an exemption according to *§3 Abs. 2 BtM* for the acquisition of a standardized cannabis extract preparation or of medical cannabis flowers for use in the context of a medically supervised self-therapy.

1.1 Cannabis plant

In the medically used cannabis varieties, the flowers are either male or female and are formed on different plants. Female and male plants differ greatly in their active ingredient content. Medicinal cannabis is made of cannabis flowers in form of whole or shredded, flowering, dried shoot tips of the female *Cannabis sativa L.*. These are particularly rich in non-psychoactive cannabidiol (CBD) and the carboxylic acid precursor of Δ^9-tetrahydrocannabinol (THC).

1.2 Application forms of medicinal cannabis

Medicinal cannabis and cannabinoids can be used in various forms (see Table 1) and may be prescribed by doctors in Germany.

Table 1: Forms of application of cannabis and cannabinoids

Drug	Forms of application
Medicinal products	Sativex® (Nabiximols): Application as a spray
	Canemes® (Nabilon, full synthetic THC derivative): Taking as capsules
Extemporaneous products	Cannabis flower: Smoking (with or without added tobacco), vaporizing, orally as tea or pastry
	Cannabis extracts: orally as capsules or drip solution or topically as tinctures, creams
	Dronabinol (semisytnetic THC): Taking as capsules or vaporizing

1.3 Guidelines for the cultivation and production of medicinal cannabis

Depending on the activity and use, the guidelines for the cultivation and production of medicinal cannabis listed in Table 2 apply (excerpt from EU GMP Guide Annex 7).

"Table 2: Overview of the application of the guidelines for the manufacture of herbal medicinal products

Activity	***Good Agricultural and Collection Practice*** **(GACP)**	**Part II EU GMP Guide[$]**	**Part I EU GMP Guide[$]**
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			

[$]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 authorization/registration. For those initial steps that take place in the field, as justified in the marketing authorization/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.

**Regarding the expression from plants and distillation, if it is necessary for these activities to be an integral part of harvesting to maintain the quality of the product within the approved specifications, it is acceptable that they are performed in the field, provided that the cultivation is in compliance with GACP. These circumstances should be regarded as exceptional and justified in the relevant marketing authorization/registration documentation. For activities carried out in the field, appropriate documentation, control, and validation according to the GMP principles should be assured. Regulatory authorities may carry out GMP inspections of these activities in order to assess compliance."

In addition to the *Good Agricultural and Collection Practice* (GACP) guidelines, the EU GMP Guide Part I and Part II, Annex 7 "*Manufacture of herbal medicinal products*" should be noted.

Table 3 lists the monographs relevant to the specification of medicinal cannabis.

Table 3: Relevant monographs for the specification of medicinal cannabis

Testing / Determination	Monograph
Identity	Monograph „Cannabis flowers" Monograph concept „ Adjusted cannabis extract "
Purity	Monograph „Cannabis flowers" Monograph concept „ Adjusted cannabis extract "
Content	Monograph „Cannabis flowers" Monograph concept „ Adjusted cannabis extract "
Mycotoxin content	Ph. Eur. 2.8.18 (Aflatoxin B1) Ph. Eur. 2.8.22 (Ochratoxin A)
Pesticide residues	Ph. Eur. 2.8.13
Heavy metal residues	Ph. Eur. 2.8.27
Microbial contamination	Ph. Eur. 5.1.4 Ph. Eur. 5.1.8 Ph. Eur. 2.6.12 Ph. Eur. 2.6.13 Ph. Eur. 2.6.31

1.4 Manufacturing methods and processes

By drying, storing or heating the plant material, the inactive carboxylic acid precursor Δ^9-tetrahydrocannabinol acid (THCA) is decarboxylated to the active Δ^9-tetrahydrocannabinol (THC).

The cannabinoids of the cannabis flowers are obtained by suitable extraction methods such as heptane, ethanol or CO_2 extraction. The extracts are refined if necessary and the cannabinoid content is adjusted by dissolving them in a suitable oil.

2 Guidelines for the cultivation, processing and marketing of cannabis as a narcotic

In Germany, compliance with drug regulations (GACP, GMP) and with legal requirements concerning narcotics (Narcotic Drugs Act – BtMG) has to be ensured. According to the guidelines of the 1961 *United Nations Single Convention on Narcotic Drugs*, a so-called *Cannabis Agency* was established in Germany, which is subordinated to the Federal Opium Agency and operates and controls cannabis cultivation for medicinal purposes in Germany. The Cannabis Agency commissions companies, selected within a Europe-wide solicitation, with cannabis cultivation (temporally and quantitatively limited supply agreements) and buys up their cannabis. Beyond that the Cannabis Agency is not responsible for the import of cannabis and, therefore, does neither buy nor distribute imported cannabis. The Federal Opium Agency is responsible for imports.

2.1 Trade of narcotic drugs in Germany

In Germany, trade of narcotic drugs (narcotics and psychotropics) and precursors is regulated by the Narcotic Drugs Act of 1981 (BtMG) with its related issued regulations (Narcotic Foreign Trade Regulation, Narcotic Domestic Trade Regulation, Narcotic Prescription Regulation) and by Regulation (EG) Nrn. 273/2004, 111/2005, the Delegates Regulation (EU) 2015/1011 and the Implementing Regulation (EU) 2015/1013 complemented by the Commodities Control Act.

According to § 11 par. 1 Narcotic Drugs Act (BtMG), imports and exports of narcotics require an import or export authorization by the Federal Institute for Drugs and Medical Devices (BfArM) for each im- or export, additionally to the required authorization according to § 3 Narcotic Drugs Act.

The procedure for granting authorization for imports and exports is regulated in the Narcotic Foreign Trade Regulation (BtMAHV).

2.1.1 Foreign Trade in Narcotics

To import narcotics into Germany, the importer (e. g. manufacturer, trader, importer and academic institution) requires an authorization for participation to narcotic trade. Additionally, the importer has to submit an import application according to §1 the BtMAHV for every imported cargo at the BfArM. This import application includes i. a. information about the applicant (importer), about the non-resident exporter including the narcotics number of the exporting country, the imported narcotic and the transport route. The BfArM considers the import application and gives a limited import authorization according to §3 BtMAHV if necessary (schematic overview in Figure 1).

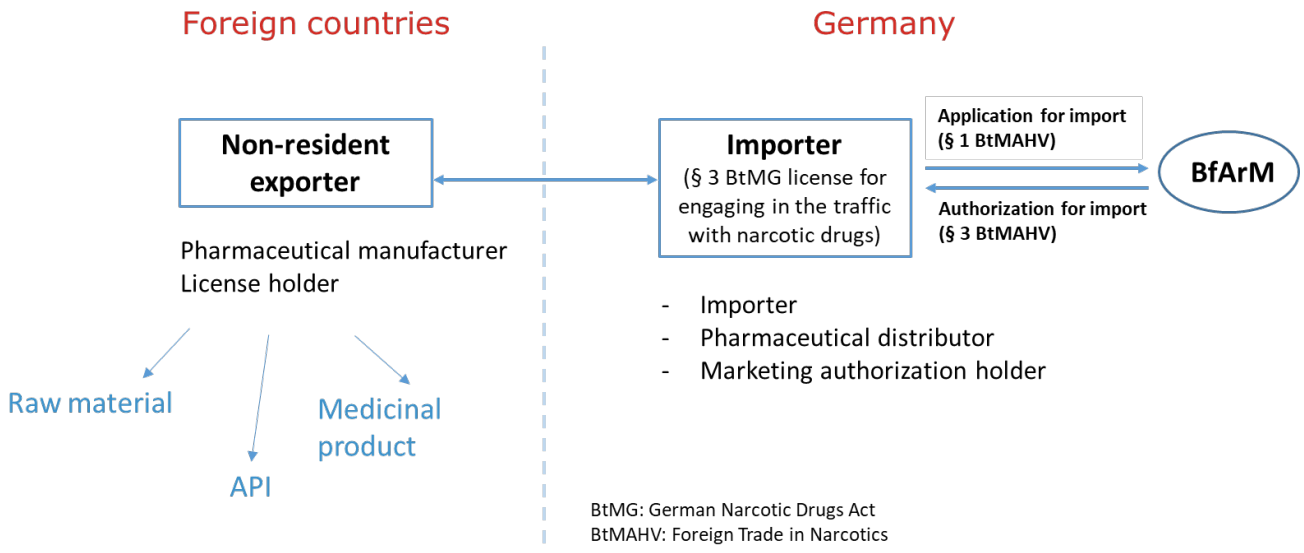

Figure 1: Schematic diagram of the narcotic foreign trade in Germany

3 Situation in Europe

The application of cannabis is limited worldwide for academic and medical use (UNODC, United Nations Office on Drugs and Crime; The International Drug Control Conventions 2013).

Countries of the European Union set up national agencies (in Germany Cannabis Agency) according to the 1961 United Nations Single Convention on Narcotic Drugs, which control cannabis production and provision for medical purposes.

There are no common regulations for the use of medicinal cannabis in the EU, as every country has its own regulations. Many EU member states have a kind of “compassionate access” program for non-authorized medicinal products. Therefore, cannabis preparations and medicinal products are mainly accessed by those “compassionate access” programs.

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