MALTA MEDICINES AUTHORITY

General Guidelines for importers and/or wholesale distributors to place cannabis-based products or synthetic cannabinoid products on the market in accordance with the Medicines Act and the Drug Dependence (Treatment not Imprisonment) Act

Contents

1 Introduction

The Regulatory Authority reserves the right, at its discretion, to update and/or revise these guidelines, from time to time, as deemed necessary. The guidance is not intended to, does not, and may not be relied upon to create any rights or obligations, substantive or procedural, enforceable at law by any party in any matter civil or criminal.

This document is solely intended to serve as guidelines and should not be construed as legislation. This document should not be considered as an exhaustive description of the instrument nor a substitute thereof or a legislative supplement to it and does not purport to be a replacement of the legislation. Please refer to the related legislation for a more comprehensive understanding. Should there be a conflict between these Guidelines and the related legislation, the related legislation prevails.

The Regulatory Authority retains its supervisory discretion in accordance with all applicable laws and regulations. Notwithstanding any licence, permit or authorisation granted by the Licensing Authority or any other authority, the Commissioner of Police and the Office of the Attorney General retain investigative and prosecutorial discretion in accordance with all applicable laws and regulations.

2 Scope

This general guideline is issued to provide guidance on the importation and/or wholesale distribution of cannabis-based products or synthetic cannabinoid products in accordance with Article 10 of the Drug Dependence (Treatment not Imprisonment) Act (Chapter 537 of the Laws of Malta) and the Medicines Act (Chapter 458 of the Laws of Malta).

3 Terms, Definitions and Abbreviations

“Advertisement” includes any representation by any means for the purpose of promoting, directly or indirectly, the prescription, supply, sale or consumption of cannabis;

“Broad spectrum” means selectively stripped from cannabinoids and non-cannabinoid matrix components;

“Cannabis” shall be construed as medicinal preparations of the plant cannabis and synthetic cannabinoid products as defined in the Drug Dependence (Treatment not Imprisonment) Act (Chapter 537 of the Laws of Malta);

“Cannabis waste” includes any form of cannabis which may be generated due to damage/recall/rejection/expiration and/or other justifiable reason, of finished products;

"Clock-stop" means any period during which the Regulatory Authority is awaiting the applicant’s submission of documents or information it has formally requested;

“Contribution” means a payment per unit product marketed, made to the Regulatory Authority for corresponding research and education activities;

“(EU)GMP certificate” has the same definition as “GMP certificate” in article 2 of the Medicines Authority (Fees) Regulations (S.L. 458.46);

“Full spectrum” means representation of the main cannabinoid and non-cannabinoid matrix components that are retained from the original cannabis plant in the finished product;

“Importation’’ means any one or more of the following activities: procuring, holding, selling and release of imported medicinal products in any part of Malta notwithstanding any provisions in any other Act, but does not include imported medicinal products that are in transit where the whole consignment of the said products remains fully intact and its status is not changed for free circulation; (in accordance the Medicines Act (Chapter 458 of the Laws of Malta);

“Licensing Authority” means the Superintendent of Public Health or its delegate in accordance with article 3 of the Medicines Act (Chapter 458 of the Laws of Malta);

“Licence Holder” means the holder of a Wholesale Dealer’s Licence issued in accordance with the Medicines Act (Chapter 458 of the Laws of Malta and its S.L. 458.37);

“Notification of Approval” means a product-specific notification issued by the Licensing Authority, certifying the authorisation for licensed wholesale distributors to source finished EU-batch released cannabis-based products for medicinal use and place them on the market in Malta;

“Approval Holder” means the holder of a Notification of Approval;

“Person” means either a physical or legal person;

“Qualified Person” (QP) means any person who is a qualified person as provided by regulation 9 of the Manufacture and Importation of Medicinal Products for Human Use Regulations (S.L. 458.36 of Chapter 458 of the Laws of Malta);

“Regulatory Authority” means the Malta Medicines Authority, referred to as the Agency inthe United Nations Single Convention on Narcotic Drugs (1961) articles 23 and 28;

“Responsible person” means a person registered as a pharmacist with the Pharmacy Council and recognised as suitable by the Medicines Authority since such person possesses adequate knowledge of the conditions required for the storage and distribution of medicinal products in order to avoid their deterioration or damage, has adequate knowledge of the regulations concerning the distribution of medicinal products, and has knowledge and understanding of good distribution practice, as provided in article 2 of the S.L. 458.37 of the Medicines Act (2003);

“Total Tetrahydrocannabinol (THC)” means the sum of Δ9-tetrahydrocannabinol (Δ9-THC), and Δ9-tetrahydrocannabinolic acid (Δ9-THCA) expressed as Δ9-tetrahydrocannabinol);

“Total Cannabidiol (CBD)” means the sum of cannabidiol, and cannabidiolic acid (CBDA) expressed as cannabidiol);

“Total Cannabinol (CBN)” means the sum of cannabinol, and cannabinolic acid (CBNA) expressed as cannabinol;

"Unit product" means final product pack as authorised for release, which pack shall in any case not exceed 100 grams in weight or 400 millilitres in volume, or as otherwise approved by the Regulatory Authority taking into consideration composition and intended market;

"Wholesale Distribution" also referred to as "Distribution" includes any one or all activities consisting of procuring, holding, and supplying medicinal products or cannabis-based products, apart from supplying such products to the public.

Abbreviations:

CBD: Cannabidiol

CBDA: Cannabidiolic acid

EU- GACP: EU Good Agricultural and Collection Practices

EU-GDP: EU-Good Distribution Practice

EU-GMP: EU-Good Manufacturing Practice

QP: Qualified Person

NoA: Notification of Approval

RA: Regulatory Authority

RP: Responsible Person

THC: Tetrahydrocannabinol

THCA: Tetrahydrocannabinolic acid

4 General Guidelines

4.1 Application process

The Drug Dependence (Treatment not imprisonment) Act (Chapter 537 of the Laws of Malta) and the Medicines Act (Chapter 458 of the Laws of Malta), provide the legislative measures enabling the importation and/or wholesale distribution of cannabis-based products or synthetic cannabinoid products. A Wholesale Dealer's Licence covering narcotics and psychotropics and a Notification of Approval (NoA) issued by the Licensing Authority, are required in order to trade in cannabis-based products for medicinal use. Holders of a Wholesaler Dealer's Licence and NoA must also comply with the relevant sections of the European Union Good Distribution Practice (EU-GDP) Guidelines published by the European Commission.

Interested parties shall electronically submit complete applications to the Regulatory Authority in English for the importation and/or wholesale distribution of cannabis in accordance with the Drug Dependence (Treatment not imprisonment) Act and the Medicines Act, including supporting documentation as requested. Translated documents submitted in fulfilment of the application requirements, shall be notarised. The application form may be accessed online.

Proof of payment of the applicable fees and contributions specified in the Production of Cannabis for Medicinal and Research Purposes (Fees) Regulations (S.L. 578.01 of the Laws of Malta), is mandatory and the respective provisions apply. The application fee shall be paid on first application and an annual renewal fee must be paid thereafter. The renewal fee shall be submitted 3 months before expiry of the NoA. The annual maintenance fee shall be paid upon the issuance of the NoA. For the purpose of financial reconciliation, payment transactions shall clearly specify reference to regulatory service being rendered (e.g., description of service, invoice number and/or application reference number). Fees are not refundable.

Applications are subject to ongoing review, at the discretion of the Regulatory Authority. Each application shall be reviewed following a validation period, during which the Regulatory Authority may request further information/documents, as deemed necessary. At renewal stage, updated application documents shall be submitted in full.

All documentation shall be provided with the application to avoid delays in processing the application. An application may be refused at any stage. The applicant should not assume that the application is complete and approved at any time during the application process. All activities shall be in conformity with the relevant legislation and guidelines at all times.

4.2 Obligations

Cannabis-based products shall be sourced from authorised entities and sold to authorised licenced wholesale distributors and/or pharmacies. Each finished product batch manufactured under EU-Good Manufacturing Practice (EU-GMP) shall be released by an EU Qualified Person and the approved product(s) shall be released on the local market by the company's Responsible Person (RP). A wholesale dealer's license only authorises the wholesale dealer to trade in or hold medicinal products which have been purchased or otherwise obtained from a licensed manufacturer or wholesale dealer site situated within the EU/EEA. Product(s) sourced through wholesale distribution shall be intended for the Maltese market. Export transactions to foreign market(s) are permitted by NoA Holders for locally produced units only, at the discretion of the production Licence Holder.

The product(s) shall only be sold from licensed pharmacies and in accordance with the prescribing requirements set out under the Medicines Act and the Dangerous Drugs Ordinance. Dispensing should be done in line with the Standard Operating Procedure of the Licensing Authority on the subject of Cannabis prescribing. The preparations may not be indicated for smoking or in any form meant for smoking.

The Approval Holder is obliged to inform the Regulatory Authority immediately of any information that comes to their attention on the product, on the manufacturer/s and on the source country wholesale distributor or exporter that may have changed from the information given in the application form which is the basis for the issuance of the NoA to place a cannabis-based product on the local market. The Approval Holder is bound to provide updated licences/certificates/approvals once the originally submitted have expired and/or are no longer valid. The NoA is not intended to be interpreted as being an authorisation in accordance with the Medicines (Marketing Authorisation), Regulations. Any obligations set out in the Dangerous Drugs Ordinance (Chapter 101 of the Laws of Malta), in relation to these products shall be met, as applicable.

The suspension, withdrawal, revocation, cancellation, or expiry of any of the following: the Wholesale Dealer's Licence, EU-GMP/certificates of the manufacturer and/or Licence for any reason, including for the protection of public health, safety, or security, and prevention of cannabis being diverted to an illicit market or use, shall preclude the carrying out of any activity related to cannabis.

Holder of the Notification of Approval

The company name set out in the NoA shall be included on the means by which the

applicant identifies themselves in relation to the importation and/or wholesale distribution of cannabis-based products, including, but not limited to, orders, transaction, transfer, shipping documents and sales invoices.

Responsible Person

The holder of a Wholesale Dealer's Licence shall engage a RP who meets the requirements specified in the Medicines Act, and must be a pharmacist registered with the pharmacy council and recognised by the Medicines Authority to act as a RP.

The RP is responsible to ensure that the licence conditions are adhered to and that storage conditions are in line with product requirements, and all storage and distribution areas are monitored, and records maintained. A quality system shall be in place in line with EU-GDP standards. Whether local or overseas, cultivation and manufacturing of cannabis must be in accordance with EU Good Agricultural and Collection Practices (EU- GACP) and EU-GMP standards respectively, in line with EU guidelines.

The RP shall be permanently and continuously at the disposal of the Approval Holder and shall assume responsibility that the quality requirements for the sourced products are met by reviewing the relevant quality documentation of batches being sourced to Malta and ensure that test results are in line with the approved product specifications, and the European Pharmacopoeia, as applicable, and that the standards of good practice are complied with at all times (refer to Appendix I for analytical parameters).

Sourcing of Products

A Licence Holder is responsible for obtaining the import documentation and permits required and shall comply with Maltese customs laws and International Conventions on cannabis. The application form for import permits may be accessed from the Office of the Superintendent of Public Health. Holders of an authorisation issued by the Superintendent of Public Health for consignment(s) from abroad, shall be in line with Customs legislation and with procedures set out by the Customs Department.

The relevant provisions of the United Nations Single Convention on Narcotic Drugs (1961) apply. The Approval Holder shall take the relevant steps and precautions necessary to ascertain quality assurance, safekeeping, security, and non-diversion of cannabis when shipping, delivering, or transporting it from the port of entry in Malta to the local licensed site.

Destruction

An Approval Holder shall destroy cannabis waste in accordance with environmental and waste management legislation without exposing persons and/or the environment to any hazard. Destruction of cannabis waste shall not occur at any unauthorised site and double-signed records/certificate(s) of destruction should be kept to account for cannabis waste being disposed of or destroyed. Destruction records shall be retained and presented accordingly to the Authority, with the annual reconciliations.

Approval Holders shall have standard operating procedures that account and allow for the traceability of cannabis waste material. Unit products intended for destruction secondary to rejection, damage, recall, expiration and/or other justifiable reason, shall be returned to the Approval Holder and destroyed, documenting evidence for the return. Root cause for the return shall be determined, devising a risk assessment and management plan including the corrective and preventive action(s) that shall be implemented, as applicable.

Approval Holders shall provide details on waste management such as closed incineration or other waste disposal systems. The Approval Holder shall qualify/audit the service provider and have a written agreement in place. The cannabis waste shall be transported directly to the site of destruction unless it is transiently stored in a locally authorised site in accordance with the Production of Cannabis for Medicinal and Research Purposes Act (Chapter 578 of the Laws of Malta). The Approval Holder remains responsible until a certificate of destruction issued by the service provider and corresponding RP declaration is provided to the Regulatory Authority.

The Approval Holder shall make a request for clearance with the Regulatory Authority prior to the company carrying out any destruction of cannabis waste, which notification shall include the product details and quantities of cannabis-based products intended to be destroyed or disposed of, and should be followed by documentary evidence of destruction covering the respective quantities, as prescribed by the Regulatory Authority.

Loss or theft

If the Approval Holder experiences theft, loss, irregular generation of waste, or misplaced cannabis material that cannot be accounted for in the normal course of business, the Approval Holder shall file a police report in accordance with national legislation and provide a written report to the Regulatory Authority immediately upon becoming aware of the occurrence.

Conformity with the Laws of Malta

An Approval Holder shall comply with all applicable Laws of Malta, including occupational health and safety, employment, environmental, sanitary and waste management, electrical safety, tax, and anti-money laundering legislation.

4.3 Security measures

The Approval Holder must ensure that sufficient security measures are in place. The Approval Holder shall have reasonable measures in place to avoid counterfeit or falsified products from entering the legal supply chain and to prevent the diversion of cannabis material in the illegal supply chain. Transportation and storage shall follow the same procedures and measures as adopted for narcotics and psychotropic substances, and shall comply with the conditions of the Wholesale Dealer's Licence and EU-GDP guidelines.

4.4 Packaging and labelling requirements

The Approval Holder shall provide specifications, technical drawings, and certificate(s) of compliance from supplier(s) for product packaging. Information for preparation of the product prior to administration shall be provided, as applicable.

The unit product label must contain information that includes as a minimum:

- Name and address of:
  - Manufacturer and EU batch release site of the finished product, as applicable;
  - Local distributor;
- Product name;
- Batch number;
- Expiry date;
- Net weight or volume;
- Storage conditions;
- Total THC and total CBD expressed in % w/w for cannabis inflorescence (Ph. Eur. 3028) and % w/w and % w/v for cannabis oils/extracts;
- Mode of use (route of administration);
- Extraction solvent(s) used, as applicable;
- Dosage formulation;
- Claim indicating that the product is intended for medicinal use (Ph. Eur. 3028);
- Claim indicating in-use shelf-life;
- Bioburden reduction (e.g. irradiation), as applicable;
- Contact details of the Approval Holder for product(s) safety monitoring.

Where applicable, the Approval Holder shall provide approved instructions on the product mode of use to the managing pharmacists and/or end users and to supply the approved label in English with each product for over-labelling at pharmacy level. The Approval Holder shall ensure that the serial number on the tamper-evident labels shall remain readable at all times, and documented at dispensing stage.

4.5 Possession and transactions

Each unit product pack sourced for the local market shall display the respective unique serial number prior to any transactions related to the product. The Approval Holder shall indicate the number of product-specific serial numbers through a request form (published online).

In cases where the serial numbers are requested in label format, the company is responsible for the supplied tamper-evident labels which are to be affixed on each pack (as approved for dispensing to the patient) sourced by the company, within ten (10) days of receipt of the products, and prior to any further transactions related to the product. The Authority shall be notified should the tamper-evident labels be affixed after the 10-day window has elapsed, supported with valid justifications. The import permit (as applicable) covering the quantities received, together with a delivery note(s)/transaction record(s) (indicating date of receipt of goods) and proof of payment for the research and education contribution specified in the Production of Cannabis for Medicinal and Research Purposes (Fees) Regulations (S.L. 578.01 of the Laws of Malta), shall accompany the submission of the serial numbers request form.

In cases where the serial numbers are requested in electronic format, an RP-endorsed declaration shall be provided to the Regulatory Authority stating that the product shall not be released for the local market prior to the submission of the import permit (as applicable) and delivery note(s)/transaction record(s) (indicating date of receipt of goods). Proof of payment for the research and education contribution specified in the Production of Cannabis for Medicinal and Research Purposes (Fees) Regulations (S.L. 578.01 of the Laws of Malta), shall accompany the serial numbers request form.

The storage and possession of the sourced cannabis-based products shall satisfy the requirements set out in the relevant legislation. Any trade related to cannabis for medicinal purposes should be in line with the legislation and the policies outlined by the Regulatory Authority, with all transactions being subject to the necessary approvals and permits.

4.6 Reporting

Traceability, reconciliations and estimates

The Approval Holder shall implement procedures and systems to retain an audit trail of the sourced cannabis-based unit products. Detailed records should be kept on the shipment, transport, holding, distribution and sale of the products. Complete batch records should allow traceability and reconciliation of the unit products released by the RP for distribution to authorised licensed operators.

The reporting of transacted units shall be aggregated at the batch number level. This is

contingent on the company's obligation to retain all necessary records which allow for the linking of batch data to the individual unit product serial numbers, therefore ensuring traceability and maintaining reconciliation across the supply chain. On an annual basis, as prescribed by the Regulatory Authority, the Approval Holder shall inform the Regulatory Authority on the number of unit product packs that are intended to be sourced over the subsequent year, together with details and quantities of unit product packs transacted during the previous year (if applicable). For the latter, as a minimum, the following records shall be kept and submitted to the Regulatory Authority in a timely manner and at the defined frequency:

i. name of product;
ii. pack size;
iii. batch number;
iv. strain name(s);
v. date of receipt of goods;
vi. import permit number;
vii. number of units sourced;
viii. number of units distributed;
ix. number of units intended for destruction;
x. number of units destroyed;
xi. number of units remaining in stock (excluding units intended for destruction);
xii. name and address of licensed operator(s) receiving the distributed goods.

Safety and quality monitoring

The Approval Holder shall ensure that the means for receiving and reporting adverse events for the marketed products are in place and that the Regulatory Authority is notified of any safety and quality defects. The Approval Holder shall relay to the Regulatory Authority all safety and quality reports within fifteen (15) calendar days of receipt.

The Approval Holder shall investigate every report received in respect of the safety and quality of products, and if necessary, take proportionate corrective and preventive measures, or any action as requested by the Regulatory Authority. The Approval Holder shall set up a system permitting the complete and rapid recall of every batch of products and provide the Regulatory Authority with all the information and reasons surrounding the recall.

Record-keeping should comply with local legislation and principles of EU-GMP and EU-GDP guidelines and general data production legislation. Records shall be kept at the licensed site in a manner that enables timely auditing by the Regulatory Authority. Records should be kept for at least five (5) years or one (1) year after product expiry, whichever is the longest.

4.7 Transmission of information

The Approval Holder shall provide to the Regulatory Authority all information and documentation requested, which information/documentation may be relayed to the Malta Police Force, Customs officials, the Licensing Authority, and other local bodies as deemed necessary by the Regulatory Authority or upon request, as well as foreign entities, including other Competent Authorities, European Authorities and the International Narcotics Control Board.

4.8 Advertising

Information as per approved unit product(s) listed on the NoA, may be provided to persons who are qualified to prescribe in line with the Drug Dependence (Treatment Not Imprisonment) Act (Chapter 537 of the Laws of Malta). In such case(s), advertisement of cannabis as a treatment, prevention, or cure, for any diseases, disorders, illnesses, or medical conditions is forbidden. Any claim regarding character, value, quantity, composition, merit, or safety of cannabis that is erroneous, misleading, or false and is not in line with the approved product label, is strictly prohibited.
Advertisement of cannabis to the public is strictly prohibited.

5 Related Legislation

Medicines Act (Chapter 458 of the Laws of Malta)
Medicinal and Kindred Professions Ordinance (Chapter 31 of the Laws of Malta)
Dangerous Drugs Ordinance (Chapter 101 of the Laws of Malta)
Drug Dependence (Treatment not Imprisonment) Act (Chapter 537 of the Laws of Malta)
Production of Cannabis for Medicinal and Research Purposes Act (Chapter 578 of the Laws of Malta)

For regulatory support and assistance please contact the MMA Cannabis for Medicinal and Research Purposes Unit on cannabis.medicinesauthority@gov.mt or +356 23439273.

6 Revision history

Signatures on file

7 Appendix I - Quality requirements

7.1 Identification

Cannabis plants shall be positively identified using macroscopic examination, microscopic identification and chromatographic procedures.

7.2 Chemical testing

Tests should be carried out in line with the European Medicines Agency (EMA) guidelines:

(a) Guideline on quality of herbal medicinal products/traditional herbal medicinal products EMA/HMPC/201116/2005, as amended from time to time; and
(b) Guideline on specifications: test procedures and acceptance criteria for herbal substances, herbal preparations and herbal medicinal products/traditional herbal medicinal products EMA/HMPC/162241/2005, as amended from time to time.

7.2.1 Cannabinoid assay limits

Inflorescence – the average content of total THC and total CBD in a representative sample of the product batch shall have a relative deviation not exceeding ±10% of the

stated content, as per the product specifications and labelling. Should this deviation be exceeded, batch-specific labelling may be considered by the Regulatory Authority subject to approval, given that the label shall reflect the cannabinoid content in the assay results at release.

Oils/extract – the average content of total THC and total CBD in a representative sample of the product batch shall have a relative deviation not exceeding ±10% of the stated content, as per the product specifications and labelling.

7.2.2 Periodic/Skip testing

The Regulatory Authority may consider proposals for a less-than-full finished product batch testing schedule which shall be accompanied by relevant supporting documentation, including data and comprehensive risk assessments, with the understanding that those batches not being tested shall still meet all acceptance criteria established. The number of batches required to justify skip testing depends on the proposed testing interval and level of impurities. Longer intervals require more batches. The data presented should preferably be from testing of consecutive batches. Periodic/skip testing schemes can only be applied if justified and approved by the Regulatory Authority.

7.3 Microbiological testing

Guidelines and limits specified in the below European Pharmacopeia sections apply:

Microbiological quality of finished products for oral use

Inflorescence, oils and extracts: Ph. Eur. 5.1.8B acceptance criteria
Inflorescence which has not undergone bioburden reduction: Where Ph. Eur. 5.1.8B acceptance criteria cannot be attained, the Regulatory Authority may consider accepting the Ph. Eur. 5.1.8C acceptance criteria.

Microbiological quality of finished products for inhalation

Inflorescence, oils and extracts: Ph. Eur. 5.1.4 acceptance criteria**.**

7.4 Summary of mandatory analytical tests

The certificate of analysis (CoA) must be specific for the following parameters: product name, strain, pack size, formulation and concentration. The CoA shall include, as a minimum, the following tests (as applicable), using the respective *European Pharmacopoeia General Monograph on Herbal Drugs* methods, specifications and limits which shall accompany the test results:

Table 1:Mandatory analytical tests by formulation

Cannabis inflorescence†	Cannabis oils/extracts†
i. Aflatoxins (Ph. Eur. 2.8.18) ii. Pesticides (Ph. Eur. 2.8.13) iii. Foreign matter (Ph. Eur. 3028) iv. Heavy metals (Ph. Eur. 3028) v. Microbiology (refer to section 7.3 above) vi. Loss on drying (Ph. Eur. 3028) vii. Total Tetrahydrocannabinol (THC) (Ph. Eur. 3028) viii. Total Cannabidiol (CBD)**Error! Bookmark not defined.** (Ph. Eur. 3028) ix. Total Cannabinol (CBN)**Error! Bookmark not defined.** (Ph. Eur. 3028) x. Identification (Ph. Eur. 3028)	i. Aflatoxins (Ph. Eur. 2.8.18) ii. Pesticides (Ph. Eur. 2.8.13) iii. Heavy metals (Ph. Eur. 2.4.27) iv. Microbiology (refer to section 7.3 above) v. Residual solvents‡ (Ph. Eur. 2.4.24) vi. Total Tetrahydrocannabinol (THC) vii. Total Cannabidiol (CBD) viii. Identification

Assays for the content of Tetrahydrocannabinol (THC) and Cannabidiol (CBD) should be carried out using validated chromatographic methods following sampling as per Ph Eur 2.8.20.

For cannabis inflorescence, should the cannabinoid assay exceed the analytical range for which the assay procedure has been validated as per Ph. Eur. 3028, or for cannabis oils/extracts for which pharmacopeial assay testing procedures are not established, testing should be carried out using validated chromatographic methods. Testing criteria listed above should be performed following sampling as per Ph. Eur. 2.8.20. Descriptions of the validated analytical procedures shall be available together with the specifications and the limits applied.

For CBD anhydrous substance (content 98.0 per cent to 102.0 per cent) which is isolated from *Cannabis sativa* L. plant, specifications as per Ph. Eur. 3151 shall apply.

7.5 Stability testing

7.5.1 Shelf-life of finished product

Stability tests shall include as a minimum, assays for total THC, total CBD, total CBN (as applicable), loss on drying, and microbiology (refer to section 7.3). Stability testing

† *Additional quality requirements may be requested by the Regulatory Authority for alternative formulations.*

‡ Note: *In case of solvents being used in the extraction process, Residual Solvents (Ph. Eur. 5.4) and Identification and Control of Residual Solvents (Ph. Eur. 2.4.24) are applicable. Further tests may be required by the Regulatory Authority which may include fumigant residues and radioactivity, among others.*

shall be carried out in line with the relevant sections of the guidelines:

a) Guideline on stability testing: stability testing of existing active substances and related finished products CPMP/QWP/122/02, as amended from time to time;
b) Guideline on quality of herbal medicinal products/traditional herbal medicinal products EMA/HMPC/201116/2005, as amended from time to time;
c) Guideline on specifications: test procedures and acceptance criteria for herbal substances, herbal preparations and herbal medicinal products/traditional herbal medicinal products EMA/HMPC/162241/2005, as amended from time to time;
d) Note for guidance on stability testing: stability testing of new drug substances and products. ICH Topic Q 1 A (R2) (CPMP/ICH/2736/99);
e) Note for guidance on evaluation of stability data. ICH Topic Q1E (CPMP/ICH/420/02);
f) Stability testing of active pharmaceutical ingredients and finished pharmaceutical product. WHO (Technical Report Series, No. 1010, 2018);
g) Note for guidance on in-use stability testing of human medicinal products. EMA/CPMP/QWP/2934/99.

Assay limits throughout the duration of the shelf-life shall follow those specified under section 7.2.

A minimum of a total of 3 batches for inflorescence and 2 batches for oils and extracts are required for long-term stability studies, covering the proposed shelf-life.

In-use stability testing

For finished multidose products intended for the local market, in-use stability testing shall establish the utilisation period after opening. A 30-day in-use period shall be considered acceptable without further supporting data, subject to a label claim specifying this in-use period. Should the in-use period claimed on the product label exceed 30 days, a stability study should be designed to simulate the use of the finished product in practice, taking into consideration relevant product characteristics. At intervals comparable to those that occur in practice, appropriate quantities should be removed by the withdrawal methods normally used. A minimum of two batches should be placed on stability for the purpose of the in-use study. At least one of these batches shall be chosen towards the end of its shelf life.

Stability commitments

- **Incomplete batches -** Should the above requirement for the minimum total number of batches not be fulfilled, the Regulatory Authority may consider approving a provisional shelf-life based on long-term stability studies for at least one batch covering the proposed shelf-life, subject to the provision of a stability commitment by the Approval Holder to provide long-term

stability studies for the remaining batches.

- **Strain similarity –** In the absence of stability studies for the proposed strain(s), stability data of the reference strain(s) may be considered, if similarity between the proposed and reference strain(s) is demonstrated through statistically equivalent terpene profiles. By means of a stability commitment endorsed by the company's RP, long-term stability studies shall be provided for products with the approved profiled strain(s). The requirement for terpene profiling and related stability commitments may be waived depending on the nature of the manufacturing process, at the discretion of the RA.

- **Shelf-life extrapolation –** For an established product shelf-life to be eligible for extrapolation, the requirements specified in *Appendix A of the ICH Topic Q1E (Evaluation of Stability Data),* shall be fulfilled. 'Significant change' shall be construed as failure of the product to meet its specifications.

- **Reduced design approach (bracketing) –** Stability studies shall be eligible for bracketing subject to the fulfilment of the following criteria:
  - Only one variable at a time may be considered;
  - Full stability data is required at a minimum, for the uppermost and lowermost limits of the bracket for the variable under study;
  - The approved product granted a shelf-life through bracketing, shall undergo long-term stability studies for a minimum of 1 batch, through a stability commitment endorsed by the company's RP.

- **Stability waiver for oils and extracts -** Stability waiver for oils and extracts - In the absence of stability data for oils and extracts, such products may qualify for a stability waiver whereby a conservative 6-month shelf-life may be assigned conditional to a stability commitment by the Approval Holder to provide long-term stability studies.

Progress on stability commitments shall be reported at a frequency as prescribed by the Regulatory Authority.