General Guidelines on the Production of cannabis for medicinal and research purposes

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1 Introduction and Scope

These general guidelines, issued in accordance with Article 12 of the Production of Cannabis for Medicinal and Research Purposes Act (Chapter 578 of the Laws of Malta) are set to provide guidance on the production of cannabis for medicinal and research purposes in Malta. The Regulatory Authority reserves the right, at its discretion, to update and/or revise these guidelines, from time to time, as deemed necessary. The Guidelines are 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 Terms and definitions

“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” has the same definition as “cannabis” in the Production of Cannabis for Medicinal and Research Purposes Act: (a) fresh or dried cannabis; (b) cannabis oil; (c) cannabis plant or seeds; (d) derivatives of cannabis excluding synthetic derivatives;and, or (e) any substance and, or product set out in guidelines issued by the Regulatory Authority, all of the foregoing to be used exclusively for manufacturing of products for medicinal and, or research purposes; for the purpose of these guidelines the definition also includes extracts and hemp;

“Cannabis waste” includes any form of cannabis which may be generated due to failure in batch quality, generation of superfluous waste during cultivation, harvest, trimming, production and/or analysis and recall/rejection/expiration of bulk starting material and/or 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 Malta 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);

"Letter of Intent (LOI)" has the same definition as “letter of intent” in the Production of Cannabis for Medicinal and Research Purposes Act: a letter issued by Malta Enterprise which shall constitute a preliminary approval and may include *inter alia* the regulating of assistance under the Malta Enterprise laws. A letter of intent that includes assistance under the Malta Enterprise laws shall be subject to the provisions of the Malta Enterprise laws, which shall, *mutatis mutandis*, apply;

“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 licence issued in accordance with the Production of Cannabis for Medicinal and Research Purposes Act (Chapter 578 of the Laws of Malta);

“Malta Enterprise” means the Corporation established under Article 7 of the Malta Enterprise Act (Chapter 463 of the Laws of Malta);

“Person” means either a natural person or a legal person in accordance with article 1A of the Civil Code (Chapter 16 of the Laws of Malta);

“Purified extract” means a refined standardised extract where the assay value of the active cannabinoid(s) is greater or equal to 70% v/v;

“Preceding year” means the period of twelve (12) consecutive months commencing on the date an annual fee becomes due and ends on the day immediately preceding the next annual fee due date, provided that for the purpose of calculating the first annual fee, the twelve (12) month period shall be deemed to commence on the date on which the license is officially granted in accordance with the Act and these regulations;

“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 (Subsidiary Legislation 458.36 of the Medicines Act Chapter 458 of the laws of Malta);

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

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

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

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

"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.

3 General Guidelines

3.1 Application process

Chapter 578 of the Laws of Malta provides the legislative measures enabling the permitted activities on cannabis for medicinal and research purposes by this legal basis.

Applications for a Licence in accordance with Chapter 578 of the Laws of Malta shall be completed and the complete application form including all supporting documents shall be submitted electronically to the Regulatory Authority in English. Translated documents submitted in fulfilment of the application requirements, shall be notarised . Application forms, together with other details, may be accessed from: http://www.medicinesauthority.gov.mt/cannabisformedicinalandresearchpurposes

The Letter of Intent (LOI), the Licence for the Production of Cannabis for Medicinal and Research Purposes, the EU-Good Manufacturing Practice (GMP) certificate (as applicable) and the Facility Security Clearance Certificate(s) shall be granted before activities related to cannabis production and research, in terms of Chapter 578 of the Laws of Malta are carried out.

Prior to obtaining a Licence in accordance with Chapter 578 of the Laws of Malta, the Regulatory Authority may issue a no-objection statement for the handling of cannabis material for validation and/or testing purposes only, in the process of meeting the requirements for EU-GMP certification. To this effect, a request shall be submitted to the Regulatory Authority, including but not limited to, a plan with timelines, indicating when the premises will be ready to commence validation, security measures implemented at the local facility, relevant SOPs, and details of the pharmacist responsible for these activities. Details are to be provided on the source and quantities required, reflecting the amounts intended for validation purposes. An import permit is to be obtained from the Superintendence of Public Health, as applicable and in terms of the applicable legislation. Qualification of security measures, including access controls, shall be completed prior to receiving the material at the facility and there shall be full traceability and accountability of the process (refer to Section 3.6 and 7).

Proof of payment of the applicable fees and contributions specified in the Production of Cannabis for Medicinal and Research Purposes (Fees) S.L. 578.01 as amended, is mandatory and the respective provisions apply. For the purpose of financial reconciliation, payment transactions shall clearly specify reference to the regulatory service being rendered (e.g. description of service, invoice number and/or application reference number). The application/renewal fee shall be paid on first application and upon the renewal of the licence three (3) years after the granting of the licence or as determined by the Regulatory Authority from time to time. The annual fee shall be paid upon the first issuance of the licence and is due every 12 months thereafter. The annual fee shall be waived when the renewal fee is due. All fees and contributions are not refundable.

Applications are subject to on-going review, at the discretion of the Regulatory Authority. The Regulatory Authority reserves the right to request further information/documents, as deemed necessary and for providing a period within which the information/documents shall be provided to the Regulatory Authority. All

documentation shall be provided with the application to avoid delays in processing the application. An application may be refused at any stage.

Activities on cannabis for medicinal and/or research purposes in accordance with Chapter 578 of The Laws of Malta at the approved site may only be initiated once the relevant approvals, certificates, licences and permits are issued. A Licence Holder shall be in conformity with the relevant legislation and guidelines at all times.
Where the approved/certified site is intended for the production, quality control testing and/or research and development of medicinal–products and related substances not associated to cannabis for medicinal and/or research purposes, such activities shall be permitted upon endorsement by the Regulatory Authority of a company's QP-signed declaration stating the nature of the alternative products and including a risk assessment with measures taken to ensure physical and secure stock segregation during the different manufacturing and/or testing operations.

The suspension, withdrawal, revocation, cancellation, or expiry of any of the following; the LOI, EU-GMP/ Facility Security Clearance Certificate(s) 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. A Licence Holder will have the right to be heard, the right to appeal, and the right to redress in accordance with the Laws of Malta, with the exception of the LOI which is to be specifically regulated in terms of the Business Promotion Act, the Malta Enterprise Act and other applicable legislation.

3.2 Obligations

In line with the provisions of the applicable legislation, a Licence Holder, subject to the necessary approvals, certificates, licences and permits, may possess, manufacture, provide, ship, sell, deliver, transport, and destroy cannabis as defined by Article 2 of Chapter 578 of the Laws of Malta exclusively in relation to the production of cannabis for medicinal and/or research purposes, provided that all records are documented.

Licence Holder name

The name set out in the licence shall be included on the means by which the Licence Holders identify themselves in relation to the production of cannabis for medicinal and/or research purposes, including, but not limited to, orders, transactions, transfers and shipping documents, product labels and sales invoices.

Qualified Person

The Licence Holder shall engage a Qualified Person (QP) who meets the requirements specified in the Medicines Act and its subsidiary legislation, is recognised by the Medicines Authority to act as a QP, is a pharmacist registered with the Maltese Pharmacy Council and resides in Malta. The QP shall be permanently
and continuously at the disposal of the Licence Holder to ensure that standards of good practice in manufacturing are complied with at all times and that each batch of products has been manufactured, tested and complies in all respects with any established requirement, the approved specifications, and laws in force. The QP is responsible to

ensure that sourced material undergoes all checks and analysis necessary to ensure quality and that the manufacturer applies standards of Good Agricultural and Collection Practice (GACP) and GMP, in line with EU guidelines. Refer to Appendix I for analytical parameters. The QP, among other duties, is responsible to keep an up-to-date register to document and certify each production batch. The QP shall act in this capacity for manufacturing and/or importation activities depending on the eligible dosage forms.

Site

A Licence Holder shall perform activities on cannabis for medicinal and/or research purposes in accordance with Chapter 578 of The Laws of Malta only inside an approved designated site and any activity related to the production of cannabis at a private residence or at any other unauthorised site is strictly prohibited.

Import and export

A Licence Holder is responsible for obtaining the import and export documentation and permits required and shall comply with Maltese customs laws and International Conventions on cannabis and all the applicable legislation. The application form for import/export 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/to abroad, shall be responsible to lodge a Customs declaration, listing details of any cannabis-based material that is being brought into or imported into Malta or which is exiting or is being exported from Malta, as may be required in line with Customs legislation and with procedures set out by the Customs Department.

Exportation of intermediate and unit products is restricted to cannabis intended for medicinal and/or research purposes and shall be in conformity with import permits issued by the Competent Authority of the country of final destination and comply with the laws of the country of final destination or country of transit or transhipment, as applicable. The relevant provisions of the United Nations Single Convention on Narcotic Drugs (1961), as amended from time to time, apply and the applicant is responsible to obtain the necessary authorisations from the Office of the Superintendence of Public Health.

A Licence Holder shall take all 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 and from the local licensed site to any recipient.

Destruction

A Licence 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 shall be kept to account for cannabis waste being disposed of or destroyed. Destruction records shall be kept for the duration of the licence.

Licence Holders shall have robust standard operating procedures (SOPs) that account for cannabis waste material. The process shall be fully traceable and auditable. Traceability in this regard relates to a list of procedures and documentation that allow tracing the history of the plant material. Destruction practices with respect to rejected and/or recalled and/or returned material shall include documented explanations of why the rejection/recall/return occurred, determining the source of the problem, the level of risk associated, and corrective and preventive action to reduce the risk, and prevent future rejections/recalls/returns.

Licence Holders shall provide details on waste management such as closed incineration, composting or other waste disposal systems. If the destruction is outsourced, the Licence 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 stored transiently in a local site authorised by the relevant Authorities. The Licence Holder remains responsible for such waste until a certificate of destruction issued by the service provider and corresponding QP declaration is provided to the Regulatory Authority.

The Licence Holder carrying out any destruction of cannabis waste, shall seek approval from the Regulatory Authority through a notification prior to carrying out any destruction of cannabis waste, which notification shall include the details and quantities of cannabis-based products intended to be destroyed or disposed of, and shall be followed by documentary evidence of destruction covering the respective quantities, as prescribed by the Regulatory Authority.

Cannabis waste material may be inactivated in the local licensed site. A certificate of analysis indicating the presence of any residual cannabinoids shall be submitted to and reviewed by the Regulatory Authority as evidence of the inactivation process.

Loss or theft

If a Licence Holder experiences theft, loss, irregular generation of waste, or misplaced cannabis material that cannot be accounted for in the normal course of business, the Licence 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

A Licence Holder shall comply with all applicable Laws of Malta, including but not limited to occupational health and safety, employment, environmental, sanitary and waste management, electrical safety, tax, and anti-money laundering legislation.

3.3 Security measures

Due diligence

Due diligence procedures are applicable to company shareholders, ultimate beneficial owners (UBOs) (direct or indirect), directors, management, QP(s), responsible officers and any other persons with a financial interest and persons with decision making powers

of influence. The applicant shall furnish the Regulatory Authority with all requested documentation, and pay the related fees. Following the issuance of the licence, new personnel holding positions as listed above are required to undergo security screening and shall provide all the requested documentation and pay the related fees. Failure/non-compliance of security screening to said personnel shall preclude the individual from holding the said position.

It is the responsibility of the Licence Holder to perform regular background checks, to request and retain up-to-date clean police conduct certificates for all personnel. Up-to-date police conduct certificates shall be made accessible to the Regulatory Authority. The Regulatory Authority retains the right to ask for additional information/documentation, as necessary. All records shall be kept for the duration of the licence and in terms of general data protection legislation. The Licence Holder is responsible to ascertain that third party contractors, including but not limited to those for security surveillance, transportation and disposal of cannabis material, implement these provisions for personnel related to the Licence Holder's operations.

Security compliance

Access to areas within the licensed site shall be physically restricted to authorised persons whose presence is strictly required in virtue of their work responsibilities and with adequate managerial supervision. The facility shall be designed in such a way that prevents unauthorised access. Visitors shall be accompanied by designated personnel whilst on the premises at all times. The four eyes principle shall be applied for the product storage vault that shall incorporate a two-person rule for access. A Licence Holder shall ensure that sufficient security measures, in accordance with these General Guidelines (refer to Appendix II) and any further regulations and guidelines issued by the Regulatory Authority from time to time, are in place.
Licence Holders engaging solely in testing and/or research activities shall be exempt from the security requirements as specified in these Guidelines, provided that a facility security review process shall be undertaken as prescribed by the Regulatory Authority.

Monitoring

The perimeter of a licensed site, and particularly areas within a site where cannabis is present, shall at all times be visually monitored by suitable visual recording devices and secured by an intrusion detection system to detect any attempted or actual unauthorised access, any unusual movement, any suspected illicit activity, or any tampering with the security system. The visual recording devices shall be backed-up at least every two (2) weeks and historical records retained and/or in terms of any general data protection legislation.

In terms of general data protection legislation, the management or designated personnel of the Licence Holder shall:

i. record the identity of every person entering or exiting the premises;
ii. monitor the intrusion detection and security systems;
iii. determine the appropriate steps to take in response to security concerns, and;
iv. keep documented records which are accessible to those with a legitimate need to assess the procedures.

The Licence Holder shall allow free and unlimited access to all areas within the premises without any reservations to members of local law enforcement agencies, in particular those pertaining to the Malta Police Force, whilst in active duty and whilst carrying out investigations or security checks in connection with any issues related in any way to the production of cannabis for medicinal and research purposes and/or in relation to any investigations in connection with any of the Licence Holder's employee(s) working within such premises and this without the members of such local law enforcement agencies having to give prior notice.

3.4 Manufacturing

Products shall be consistently produced and controlled in accordance with the quality standards appropriate to their intended use and in line with the current GMP guidelines published by the European Union Commission. The licensed site shall be inspected by the Regulatory Authority, as deemed necessary, to attest EU-GMP compliance.

Planned or unannounced inspections/audits of the facility to check the level of compliance with EU-GMP, approved tests and specifications, and/or security procedures may be carried out from time to time. All necessary data and/or samples shall be made available upon request by the Regulatory Authority.

Whether local or overseas, cultivation of cannabis to be subsequently manufactured in Malta, shall be in accordance with GACP, backed by a documented quality system. Refer to Appendix III for guidance on local cultivation. Cannabis shall comply with any applicable European Pharmacopeia monograph. Active substances, as dried inflorescence in bulk, shall be handled under EU-GMP. In cases where the active substance is purchased from an outside source, the local/EU-QP is responsible to audit source, perform quality and identity checks on batches, hold certificates of analysis, document transactions and all other relevant activities as applied for active pharmaceutical ingredients (APIs) intended for medicinal products, in accordance with an adequate quality system. The performance of the audit may be delegated to third parties with appropriate knowledge in EU-GMP, however the local/EU-QP shall bear the ultimate responsibility of the report. Intermediates, containing cannabisthat shall undergo further manufacturing steps, shall have a GMP certificate issued by an EU Competent Authority.

A Licence Holder shall ensure that:

i. all active substances used in the manufacture of cannabis-based products shall not contain any substance that is not derived from the cannabis plant;
ii. the unit product packaging prevents contamination and/or tampering of product contents (packaging specifications shall be approved by the Regulatory Authority);
iii. not more than the equivalent of the approved unit product pack of cannabis is in the container or package;
iv. the unit product is released by the QP with a certificate of analysis in line with approved analytical tests, test procedures and specifications, in compliance with EU-GMP, as per the approved batch release SOP/documentation;
v. batch-release certificates and certificates of analysis shall be made available on request by the Regulatory Authority;
vi. The unit product label must contain information that includes as a minimum:

- Name and address of:
  - Manufacturer of the finished product;
  - EU batch release site of the finished product, as applicable
- Product name;
- Batch number;
- Regulatory Authority serial 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, as applicable
  (Ph. Eur. 3028);
- Bioburden reduction method (e.g. irradiation), as applicable;
- Claim indicating in-use shelf-life;
- Contact details of the Licence Holder for product(s) safety monitoring.

3.4.1 Third country EU-GMP Inspections

Requests for the Regulatory Authority to perform third country EU-GMP certification inspections of medicinal cannabis facilities shall be considered on the basis of schedule and resource availability at time of request. The following criteria shall be addressed as applicable, to support any requests made in this regard:

- QP audit report qualifying the proposed supplier against the required EU-GMP certification standard(s);
- Proof that the facility/site to be inspected shall supply material and/or products to a local licensed site intended for local processing and/or marketing;
- Submission of necessary licensing application(s);
- Evidence from concerned third party Competent Authority(ies) on their national requirements related to EU-GMP certification(s), as applicable.

3.5 Possession and transactions

The storage and possession of the harvest from cultivation shall satisfy the requirements set out in the applicable local and international legislation. A Licence Holder shall inform the Regulatory Authority of the number of unit product packs that will be

produced over the subsequent year, whether intended for the local market or export. Proof of payment of the corresponding research and education contribution specified in the Production of Cannabis for Medicinal and Research Purposes (Fees) Regulations, S.L. 578.01 as amended, shall be submitted to the Regulatory Authority, when requesting serialisation numbers. Each unit product pack shall display the respective serial numbers, in a tamper-evident manner, or as established by the Regulatory Authority, prior to any transactions related to the product. The serial numbers shall, at minimum, be visible on the outer packaging shall there be a tamper-evident seal. In the absence of the anti-tampering device, the serial numbers shall be displayed, at minimum, on the primary packaging. Any trade related to cannabis for medicinal purposes shall be in line with the legislation and regulatory requirements , with all transactions being subject to the necessary approvals and permits. At the discretion of the Licence Holder, locally produced units may be transferred directly to foreign client(s) or transacted to market(s) overseas via licensed local operator(s).

3.6 Reporting

Traceability, reconciliations and estimates

A Licence holder shall implement procedures and traceability systems to enable tracking/tracing of cannabis active ingredient, intermediates and unit products across the supply chain. Detailed records shall be kept on the cultivation, import, sale, distribution and export of cannabis. Complete batch records shall allow tracing of the batch from cultivation to unit product release by the QP and distribution to the licensed entities.

The reporting of transacted units shall be aggregated at the batch number level. This is contingent on the Licence Holder'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.

Reconciliations of all cannabis-based material shall be submitted to the Regulatory Authority on a quarterly basis. The Regulatory Authority shall provide specific templates according to the Licence Holder's authorised operations, to capture the quantities and movement of the cannabis-based material before, during and after processing within the local facility/site.

On a yearly basis, the Licence Holder shall submit projected quantities of cannabis-based material to be utilised for production and/or research activities. The Regulatory Authority shall supply templates according to the individual authorised operations, which shall specify, as a minimum, estimates of:

i. the amount of cannabis-based products intended to be consumed domestically and/or for export;
ii. the quantity of unit products to be manufactured locally, and
iii. the quantity of cannabis to be held in stock.

A Licence Holder shall keep a copy of each quarterly notice and annual forecast submitted to the Regulatory Authority and of any supporting information or documentation requested by the Regulatory Authority for the duration of the licence.

Reporting of Adverse Reaction Reports, Quality Defects and Recalls

A Licence Holder shall investigate every report received from any person in respect of the safety and quality of products, and if necessary take corrective and preventive measures, or any action requested by the Regulatory Authority. All safety and quality reports shall be notified to the Regulatory Authority within fifteen (15) calendar days of being received. A Licence 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 shall comply with local legislation and EU-GMP and EU-Good Distribution Practice (GDP) guidelines and general data protection legislation. Records shall be kept at the licensed facility/site in a manner that enables timely auditing by the Regulatory Authority. Such records shall be retained for not less than five (5) years from the date of manufacture or for a period of one (1) year following the labelled expiry date of the cannabis-based product, whichever is the longer period.

3.7 Transmission of information

The applicant or Licence 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 Superintendence of Public Health, and other local bodies or Authorities as deemed necessary by the Regulatory Authority or upon request, as well as foreign entities and Authorities , including other Competent Authorities , European Authorities and the International Narcotics Control Board.

3.8 Advertising

Information as per the approved unit product(s) listed on the licence, 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 strictly 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.

3.9 Research and development activities

Research and development activities related to cannabis may be carried out in licensed sites/facilities, subject to approval by the Regulatory Authority and other relevant bodies such as the ethics committee as may be applicable. A detailed description/research protocol, inclusive of an in-depth process flow chart of the intended research activities, is to be submitted to the Regulatory Authority before

initiation, together with other submission criteria as deemed necessary by the Regulatory Authority. A record of the research undertaken and the findings, including the source, quantity and form of cannabis used in the course of the research and intended timelines, shall be documented. A QP declaration indicating that any processed cannabis material is strictly intended for research purposes shall be submitted. The site/facility where the research is undertaken may be subject to inspections and audits, at the discretion of the Regulatory Authority.

3.10 Testing activities

Testing activities related to cannabis may be carried out in licensed sites/facilities, subject to approval by the Regulatory Authority and any applicable conditions imposed by the Regulatory Authority. Products shall be consistently tested and controlled in accordance with the quality standards appropriate to their intended use and in line with the current GMP guidelines published by the European Union Commission. The licensed site/facility will be inspected by the Regulatory Authority, as deemed necessary, to attest EU-GMP compliance.

Planned or unannounced inspections/audits of the facility to check the level of compliance with EU-GMP, approved tests and specifications, and/or security procedures may be carried out from time to time. All necessary data and/or samples shall be made available upon request by the Regulatory Authority.

3.11 Variations

The Licence Holder shall notify the Regulatory Authority of any amendments to the application and supplementary documentation, submitted during the review process for the granting of the licence for the Production of Cannabis for Medicinal and Research Purposes, through the relevant variation procedure. Only one variation type may be specified per variation application. The Licence Holder may benefit from fast-track processing of a variation application.

4 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
Production of Cannabis for Medicinal and Research Purposes (Fees) Regulations, S.L. 578.01

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

5 Revision History

Signatures on file

6 Appendix I – Quality Requirements

6.1 Identification

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

6.2 Chemical testing

Tests shall 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.

6.2.1 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/extracts – 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.

6.2.2 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.

6.3 Microbiological testing

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

Microbiological quality of starting/intermediate material:

- **Inflorescence:**
  - The Ph. Eur. 5.1.8C acceptance criteria shall apply for bulk material which is intended to undergo further processing (e.g. extraction) before being released in its finished product state (oil, extract).
    The Regulatory Authority may consider Ph. Eur. 5.1.8A criteria if a robust, evidence-based risk assessment is provided by the company demonstrating that the processing method sufficiently lowers the bioburden to meet the finished product microbial limits.
  - The Ph. Eur. 5.1.4 (inhalation use) and/or Ph. Eur. 5.1.8B (oral use) acceptance criteria shall apply for bulk material which is not intended to undergo further processing (e.g. extraction) and shall be presented in the inflorescence state within the finished product unit pack.
    In the absence of bioburden reduction processes (e.g. irradiation), 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.

- **Oils/extracts:**
  - The Ph. Eur. 5.1.8B acceptance criteria shall apply for bulk material.

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.

6.4 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 (Ph. Eur. 1433; Ph. Eur. 0765)* and the *European Pharmacopoeia Cannabis Monograph (Ph. Eur. 3028)* 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 6.3 above) vi. Loss on drying (Ph. Eur. 3028) vii. Total Tetrahydrocannabinol (THC)† (Ph. Eur. 3028) viii. Total Cannabidiol (CBD)†(Ph. Eur. 3028) ix. Total Cannabinol (CBN)† (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 6.3 above) v. Residual solvents (Ph. Eur. 2.4.24)‡ vi. Total Tetrahydrocannabinol (THC) vii. Total Cannabidiol (CBD) viii. Identification

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 shall 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.

6.5 Hold-time and stability testing

6.5.1 Hold-time studies

The period of time during which the starting and/or intermediate material is expected to remain within its specification under the defined conditions and therefore can be used for further processing, shall be established. After this period, a batch of starting and/or intermediate material destined for further processing, shall be re-tested for compliance with the specification and then used immediately (within 30 days). A batch of starting and/or intermediate material can be re-tested multiple times and a different portion of the batch used after each re-test, as long as it continues to comply with the specification.

Hold-time studies of the starting and/or intermediate material shall include as a minimum, cannabinoid assay, microbiology and loss on drying (as applicable). The latter two criteria shall apply, at a minimum for starting inflorescence in

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

† *May be excluded for cannabis inflorescence which is intended to undergo further processing (e.g. extraction).*

‡ *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.*

bulk, which is intended to undergo further processing (e.g. extraction).

6.5.2 Shelf-life of finished dosage form

The shelf-life of finished dosage forms shall in principle follow the EMA Note for Guidance on Start of Shelf-life of the Finished Dosage Form (CPMP/QWP/072/96, as amended from time to time). The expiration period of a production batch shall be calculated from the date of release of that batch. The date of such a release shall, under normal circumstances, not exceed 30 days from the date of production of that batch. If batches are released, exceeding 30 days from the production date, the date of production defined as the initial date of filling operations, shall be taken as the start of the shelf-life.

6.5.3 Stability studies of finished products

Stability tests of the finished product shall include as a minimum, assays for total THC, total CBD, total CBN (as applicable), loss on drying (as applicable) and microbiology (refer to section 6.3). Stability testing 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 6.2.1.

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

<u>In-use stability testing</u>

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 Licence 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 QP, long-term stability studies shall be provided for products with the approved strain(s). The requirement for terpene profiling and related stability commitments may be waived depending on the nature of the manufacturing process, as prescribed by the Regulatory Authority.
- **Shelf-life extrapolation –** For an established product shelf-life to be eligible for extrapolation, the requirements specified in *Appendix A of the ICH Topic Q 1 E (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 upfront stability data covering the proposed shelf-life is required, at a minimum, for the uppermost and lowermost limits of the bracket for the variable under study;
- The intermediates that fall in between the uppermost and lowermost limits of the bracket shall be granted the proposed shelf-life through bracketing, subject to the provision of a QP-endorsed commitment to perform, at a minimum, single batch stability studies under long-term conditions for any of the intermediate value(s).

- **Stability waiver for oils/extracts -** In the absence of stability data for oils/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 Licence Holder to provide long-term stability studies.

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

6.6 Stability requirements for export-only products

Conformity to the overall quality criteria as defined in this guideline shall be followed for commercial goods regardless of the destination market(s). For product(s) intended exclusively for export, the Regulatory Authority may, however, consider accepting the stability requirements of the receiving territory(ies) provided that the following conditions are met:

- Adequate evidence is presented by the Licence Holder to the Regulatory Authority that the relevant Competent Authority in the importing country permits the marketing of the said product(s) within their territory on the basis of the quality data submitted.
- For each distinct formulation, at least one reference product must be registered in Malta in compliance with local stability requirements. The locally registered product must be representative of the cannabinoid assay range applicable to the export-only product(s). The cannabinoid assay ranges that shall be considered for this purpose are as follows:
    1. THC-dominant type[§]:
        - total tetrahydrocannabinol, expressed as Δ^9-tetrahydrocannabinol ($C_{21}H_{30}O_2$; M_r 314.5): minimum 5.0 per cent (dried drug);
        - total cannabidiol, expressed as cannabidiol ($C_{21}H_{30}O_2$; M_r 314.5): maximum 1.0 per cent (dried drug).

    2. THC/CBD-intermediate type[§]:
        - total tetrahydrocannabinol, expressed as Δ^9-tetrahydrocannabinol ($C_{21}H_{30}O_2$; M_r 314.5): minimum 1.0 per cent (dried drug);
        - total cannabidiol, expressed as cannabidiol ($C_{21}H_{30}O_2$; M_r 314.5): minimum 1.0 per cent (dried drug);
        - total tetrahydrocannabinol / total cannabidiol ratio: 0.2 to 5.0 (dried drug).

    3. CBD-dominant type[§]:
        - total tetrahydrocannabinol, expressed as Δ^9-tetrahydrocannabinol ($C_{21}H_{30}O_2$; M_r 314.5): maximum 1.0 per cent (dried drug);
        - total cannabidiol, expressed as cannabidiol ($C_{21}H_{30}O_2$; M_r 314.5): minimum 5.0 per cent (dried drug)

[§] Products with total THC and/or total CBD concentrations falling outside the defined cannabinoid concentration brackets shall be subject to review by the Regulatory Authority for eligibility.

7 Appendix II - Security

The Licence Holder is responsible to ensure that the security measures in place at the facility are fit for purpose, maintained and monitored, as required. The below points may offer guidance on the minimum security standards that shall be in place, but shall not be perceived as exhaustive since the security approach adopted shall be pursuant to the type of operations and risk involved, which rests within the responsibility of the Licence Holder.

7.1 Security plan

A detailed security plan shall be documented and followed, including security SOPs,list of security devices located onsite, CCTV, procedures for handling personnel and visitors, access controls, internal security floor plans, protocols for vaults and intrusion detection systems.

7.2 Physical requirements

Premises shall have an intruder detection system which is monitored at all times and covers the perimeter and all the areas within the facility. Surveillance devices (CCTV) shall be present at the site perimeter and all areas where cannabis is present, which devices shall be monitored at all times and records of CCTV footage kept for a minimum of 30 days. All areas of the licensed premises shall have electronic authentication access control.

A climb-proof perimeter security fence and reinforced walls may be necessary, to separate the facility from adjacent buildings, depending on the type and scale of operations related to the respective facility. The areas for storing all cannabis material shall not share a wall with the exterior of the building unless the wall is reinforced. A strong room or vault shall be used for the storage of cannabis raw material and unit products. The vault/strong room shall be equipped with a dual-combination locking system using the four-eye principle. Vaults for harvested material shall havea security system in place which caters for the release of the harvest, as determined by the Regulatory Authority. Cannabis waste material shall be stored in a separate receptacle in the vault/strong room or a similarly secure, locked area.

Any glass panels considered as roof structures shall be equipped with detection sensors. Cannabis, in whatever form or stage in the process, shall not be visible from the street level. An architect’s declaration in this regard is required. The facility shall bear no signs, names or logos with cannabis connotations on the exterior of the building. The external areas shall have adequate lighting and standby generators shall be availableon site. Cultivation/production sites shall be physically separated from offices, administration and break areas, which shall nonetheless have an access-control system and monitoring. Pocket-less clothing shall be used within production and cultivation areas, and personal bags and other containers shall not be permissible in such areas. The number of entrances to areas holding cannabis shall be kept to a strict minimum, which entrances shall be secured and have appropriate doors/frames in place.

7.3 Control systems

Intrusion detection systems shall be operational at all times and shall be adequately maintained. There shall be real-time notices of breaches in security and in the event of an alarm activation the person(s) receiving the alert shall immediately notify the local law enforcement Authorities. Staff shall be trained on procedures to respond to intrusion and regular drills shall be carried out.

There shall be no access to the general public and a visitor policy shall be in place.The electronic access control shall be limited to the job description of personnel and hours/days of required access. The access control system shall be audited, with regular and random checks of access logs. All access records shall be kept for the period of the licence.

Licence Holders shall have an agreed set of Standard Operating Procedures (SOPs) to coveremergency procedures, inventory and reconciliation, stock control, unauthorised access, intrusion and theft.

7.4 Transportation

Licence Holders shall ensure that the level of security of cannabis during transportation is equivalent to that of the licensed premises, as applicable. Following the local receipt of stock, any cannabis in transit remains under the responsibility of the Licence Holder at all times, under whatever circumstances and sales arrangements, until the goods physically reach the client's end and ownership and responsibility is transferred to the recipient. This still applies if the Licence Holder uses a third-party carrier. Delivery of goods to the Licence Holder's clients on special sales conditions/transit terms such as ex- works (EXW) and freight-on-board (FOB) terms is strictly prohibited. Any outsourced transport activities shall be audited for standards and requirements at least equivalent to those of the manufacturer. Licence Holders shall have an agreed set of Standard Operating Procedures (SOPs) covering responsibility, record keeping, reconciliation, reporting and emergency procedures. This document presents non-exhaustive examples to be followed as a minimum for the transportation of cannabis and specific circumstances are likely to require specific measures.

Vehicles used for the transportation of cannabis shall be tracked and have adequate locking systems and anti-theft systems such as alarms and immobilisers appropriate to the level of risk of the consignment. The vehicle shall not contain any visible signs suggesting the presence of cannabis and the products shall not be visible from the outside the of vehicle. Tamper-evident containers or packages shall be used for all consignments. For consignments with a very high risk of diversion, the parties involved shall consider additional security measures such as a separate secured area equivalent to a safe, that shall be bolted down to the vehicle, police/security staff escorts and CCTV coverage at risk points.

The details of deliveries shall be restricted to personnel that are required to know them. Licence Holders shall ensure that a QP is designated to verify and sign out the consignment for delivery and similarly recipients shall ensure that the responsible person accepts the consignment and verifies that all goods have been delivered/received. Any thefts and losses are to be reported immediately to the Police and any other local law enforcement Authorities, including any thefts and losses during

transit. Drivers shall have comprehensive instructions covering routine and emergency situations during transit. Carrying unauthorised passengers and making visits to unauthorised locations shall be strictly prohibited. Wherever an accident occurs that requires the attendance of the emergency services, the police shall be made aware of the incident and the vehicle's content as soon as possible.

8 Appendix III - Good Agricultural and Collection Practices

8.1 Overview

Appendix III to the Production of Cannabis for Medicinal and Research Purposes Guidance Memorandum relates to the growing, harvesting and primary processing of cannabis plants intended for the production of cannabis for medicinal and research purposes in Malta. Reference shall be made to the European Medicines Agency Guideline on GACP for starting materials of herbal origin (EMEA/HMPC/246816/2005, as amended from time to time) and to the EU-GMP guidelines for active pharmaceutical products. In the case of herbal drugs, including the herbal substance and herbal preparations as defined in Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on theCommunity Code relating to medicinal products for human use as amended from time to time, the agriculturalpractices relating to the cultivation and primary processing of cannabis plants determinethe quality of the unit products intended for patient administration.

8.2 Facilities/Sites

The cultivation site shall be a defined, enclosed structure having permanent walls, within a licensed production and/or research facility. Such authorised sites shall be situated within industrial zones that hold a permit to operate industrial activity. The facility shall have security measures that include, but are not limited to, adequate CCTV, appropriate personnel logging and restricted-access, with a vault system being adopted for the safe storage ofcannabis plant material. The facility shall incorporate a system which protects the cannabis plants from pests, diseases and domestic animals. Critical areas shall be equipped with appropriate traps that shall be logged into a system, checked periodically, documented and any findings reported immediately.

Each area within the facility shall be segregated from the rest and shall not be used to carry out other activities that do not pertain to the specific designated area. The cannabis plant shall be stored in coded packaging, on appropriate shelving, at a sufficient distance from the walls. Proper container closure reduces the risk of cross-contamination. To maintain the hygienic standards of the site, personnel shall have adequate toilets, hand-washing and changing facilities. Collection and removal of contaminated/disposed material shall be carried out frequently.

8.3 Personnel and training

Personnel working with the propagation, maintenance, growing, inspection and harvesting of the cannabis plants shall either possess a post-secondary qualification related to horticultural practices or else shall be provided with adequate training in horticultural practices and botanical knowledge on the cannabis plant, and the biotic and abiotic factors that may affect the quality of the plant and therapeutic properties.

The training shall be received prior to their involvement in the day-to-day running ofthe plant production system. The Licence Holder and personnel are expected to ensure that the raw material, work-in-progress, finished goods and waste material, is not accessible to third parties, within or outside the premises.

Appropriate documentation and reporting is necessary for all activities related to the plant production system.

Procedures carried out for primary processing shall comply with the regulations on food hygiene. Adequate clothing should be provided to protect the personnel from anytoxic or potentially allergenic plant material. Personnel who in some way are related to infectious diseases (including diarrhoea and skin conditions) that are transmissible via food, including disease carriers, shall be forbidden to come in contact with the plant material. In case of personnel suffering from an infectious episode, he/she shall not be allowed to return to work before a physician certifies that the person is free from the disease. If a person is a carrier of a disease, he/she shall not be granted access to areas related to the plant material throughout the plant production system.

8.4 Equipment

Equipment and tools used in the cultivation of the cannabis plant from propagation to harvest and processing, shall be cleaned in order to eliminate the risk of contamination and cross-contamination during the process. Equipment that is used to apply fertilisers shall be calibrated regularly to ensure the prescribed delivery of the agrochemical to the cannabis plants, when needed. Preferably, equipment shall be made out of materials that can be easily cleaned and that will not either release or adsorb chemicals. Such materials exclude wood, unless the wood material is not in direct contact with agrochemicals and/or plant materials. Equipment that operates with petrochemicals, such as oils and fuels, shall be checked regularly for any leaks, such as to prevent any possible plant contamination and for the safety of the personnel working on site or in the vicinity. Shock hazards shall be taken into account for electrical equipment with due consideration given to the high humidity and irrigation water within the growing environment. Equipment shall be calibrated, maintained in good working conditions and stored away in a designated area when not in use, with equipment checks being recorded.

8.5 Seeds and propagation material

Propagating material, including seeds and cuttings, shall be botanically identified. Record keeping shall include the species name, variety, chemotype and place of origin. The material shall be certified free of pests and diseases by the presentation of a phytosanitary certificate, if the material is procured from a third country, or a plant passport, if the material is obtained from within the European Union. For ease of reference, a code may be assigned to a specific variety/chemotype to be used throughout the growing of the plant till the plant material is released.

Cuttings of selected female plants shall be used as material for the cloning of cannabis varieties/chemotypes. If the female flowering tops are required as a unit product or as an API for further processing, male plants shall not be present within the flowering area of the cannabis growing premises. If male plants are required either to produce new

cultivars (within the R&D area, subject to the approval of the Regulatory Authority) or else to produce seed and seed-derived extracts, then the presence of such plants shall be monitored. Within the growing premises, artificially-induced hermaphrodites may emerge. Personnel shall be instructed to inspect the plants regularly for such possibilities.

8.6 Growing

Inert support media, such as rockwool, shall be certified free from the presence of contaminants and microorganisms. Ideally, medicinal cannabis plants shall not be grown in soil or any medium that may potentially harbour possible contaminants and microorganisms. In case soil and/or compost are used for the growing of the plants, it shall be ensured that these media are free from the presence of contaminants and microorganisms by the presentation of certificates of analysis. The origins of the soil and/or compost shall be stated, and the physicochemical characteristics and the levels of heavy metals, pesticide residues, plant pathogens and pests, shall be declared. Initially the source of the soil shall be tested for potential radioactivity. If the soil and/or compost is subjected to sterilisation, the method shall be specified.

The use of organic fertilisers including animal manure, human wastes, farm slurry or other forms of liquid or solid natural fertilisers obtained from farms or municipal waste shall be avoided. Artificial fertilisers with declared contents on the label and instructions for use shall have a certificate of analysis which shall be available at hand, upon inspection. Personnel shall be instructed to apply fertilisers and agrochemicals to a minimum and only as and when the need arises. Any amounts usedshall be logged stating the date, purpose of use, location of use, and dose and durationof use.

Fertilisers and agrochemicals shall be safely stored in cabinets with appropriate hazard signs affixed on the doors of such cabinets. Personnel shall read carefully the instructions of storage so as to segregate agrochemicals that would otherwise cause fire or explosion hazard if stored within the same cabinet. The area designated for the storage of such agrochemicals shall be well ventilated, cool and dry. Use and storage of agrochemicals shall be undertaken, by qualified personnel only, in accordance with the recommendations of the manufacturer and the relevant Authorities.

Irrigation shall be supplied through an irrigation system which is controlled according to the needs of the plants. Irrigation water shall not contain any natural/organic fertilisers. The minimum water grade for irrigation shall be potable water. Initially the source of water shall be tested for potential radioactivity. The quality of the water shall be monitored frequently and periodically analysed for the presence of microorganisms, heavy metals and potential contaminants such as nitrates and pesticide residues.

Qualified personnel shall examine the different growth chambers for cannabis plants that are showing abnormal growth, irregular morphology and defects which indicate mechanical or biological damage. Such plants shall be removed immediately from the batch, and details for their removal recorded for future reference. Dead plants and plants which do not recover with an implemented measure, shall be removed and transported in a sealed plastic container to the disposal area.

8.7 Harvesting

The growth of the cannabis plants shall be followed throughout the whole cycle. Prior to harvesting, environmental conditions such as high air humidity and high soil moisture content shall be considered, as these may result in problems, particularly the emergence of post-harvest spoilage organisms. The material is checked for the presence of other cannabis varieties and/or weeds that may adulterate and alter the content of the cannabinoids present in the original plant or may introduce other phytochemicals that do not pertain to the cannabis plant and that may be possibly toxic. Any defective plants shall be removed and disposed of immediately.

Harvesting shall be done when plants have reached the optimum quality for the intended use. Flowers usually shrivel and turn brown when ripe. Harvesting is done when about 75% of the stigmas are brown and the trichomes are milky white. If whole plants are harvested (for the drying of whole plant materials), the plants shall be cut well above the soil to prevent contaminating the plant material with the soil and/or the contamination of the tool which is used to cut other cannabis plants. Ideally the pruning shears are dipped in a 70% alcohol solution between cuts. The harvested plants shall be immediately transferred to clean, dry boxes. Any reusable boxes shall be thoroughly cleaned with 70% alcohol, and checked for any plant residues before re-use. The filling of these boxes shall be done in such a way that the material is not compacted unnecessarily in the containers and no material shall be allowed to hang out of the containers. Such instances may lead to the damage of the plant material which could result in an inferior product.

The harvested material shall be transferred immediately to a storage area which is locked with a coded-door system as per the requirements of the Regulatory Authority. The storage area shall be kept clean, dry and protected from plant pests and domestic rodents and crawling insects. Appropriate traps shall be placed outside and inside the storage facility to control the possible presence of these organisms. The harvested material shall be transferred as soon as possible to the processing facility to initiate material drying so as to prevent degradation of the material and loss of quality due to prolonged holding times.

8.8 Primary processing

Whether in-house or procured from other sources, the harvested material shall be checked to ensure that the whole consignment has been delivered and directly unloaded and unpacked in a dedicated space, with a low (white) light intensity, under controlled humidity conditions and at a temperature of 20-25°C. Primary processing includes plant manipulation that may lead to the production of the API or unit product(s). Such processes would include: washing the plant material; cutting before drying; freezing; distillation; drying. The material can be dried either as:
(i) whole plants suspended in inverted position without contact with any surface or ground, or (ii) fresh flower heads placed in trays. The material shall be dried at a uniform temperature (or temperature range) to ensure that the active metabolites do not degrade with delayed drying or during slow drying, moulds and other post-harvest opportunistic microorganisms do not grow and mycotoxins do not build up, in the visual presence or absence of moulds. During open drying (if applicable), the material shall be spread evenly in thin layers in clean trays and in an environment that is clean and free from any air-borne pathogens, their toxins or contaminants. Any possible waste

generated from contaminated material, shall be disposed of in sealable bags that shall be placed in closable waste bins outside the drying area. Such waste bins shall be emptied and cleaned on a daily basis.

8.9 Packaging

The packing material which comes in contact with the product to be stored for further in-house processing or presented to the patient, shall be:

i. Of food grade, in accordance with Regulation (EC) No 1935/2004 as amended from time to time (specifications of which shall be kept for inspection purposes);
ii. Clean and free from any possible contaminants;
iii. Stored in a suitable storage area, away from contaminated areas/bins, and growing/production areas, away from pests and/or domestic animals;
iv. Accompanied by appropriate labelling, indicating the contents of the packaging; for in-house purposes a coding system may be used.

If reusable packaging is used, it shall be well cleaned and dried, ensuring that there are no residual disinfectants and/or other chemicals that would come in contact with the product.

8.10 Storage and distribution

The storage of dried material, packaged products and extracts, shall be:

i. In different designated areas to avoid cross-contamination of material at different states of processing;
ii. According to the specific requirements - fresh materials shall be stored at temperatures between 1°C and 5°C (ensuring no degradation of materials/active metabolites occurs within that temperature range); frozen products shall be kept at temperatures below -18°C (or below -20°C for long-term storage).

The storage area shall be:

i. A dry, well-ventilated designated area, which is temperature, light and humidity controlled, for which fluctuations shall be monitored, minimized and recorded;
ii. Cleaned prior to the introduction of a new batch of dried material, packaged products and extracts - any form of disinfection shall be controlled for residues before material is introduced and if saturated steam is used, humidity levels shall be monitored;
iii. Located away from contaminated areas/bins, and growing/production areas, away from pests and/or domestic animals.

The vehicle involved in transport or distribution shall be well-ventilated but not accessible to pests and domestic animals; emptied and kept clean, when not in use; inspected prior to loading of a new consignment; appropriately disinfected after use; free from any other material (the vehicle used to transport dried material, packaged products and extracts shall not be used to transport agrochemicals and other materials that may contaminate the products); and equipped to suit the material being transported, i.e. refrigeration or freezing capability (1-5°C and below -18°C, respectively), as applicable.

8.11 Security

Security systems shall be in order to prevent unauthorised movement of cannabis material or unit cannabis products within or outside the premises. Only authorised personnel shall be allowed to access specific designated areas as stated in their job description. Personnel shall observe hygiene regulations at all times. Waste material shall not be treated with negligence, and shall be stored in a lockable container to prevent theft, if it cannot be treated immediately. In case of cannabis material, cannabis extract wastes and defective cannabis unit products, the material shall be shreddedinto small pieces/diluted with other cultivation wastes and composted immediately, if possible. Incineration is not recommended due to the release of the active cannabinoids during the incineration process unless a closed system is used.

8.12 Documentation

All activities carried out within the premises shall be documented, stored for future reference and presented upon inspection. Documentation shall be signed and countersigned in order to verify its validity. For safety reasons, the documentation shall be duplicated (soft or hard copies, verified as true copies) and stored in a secure location in the licenced site. The documentation and any audit reports shall be kept for at least ten (10) years.

In summary the following documentation is mandatory:

i. Details of the location and person in charge of the propagation and production sites;
ii. The origin, nature and quantity of cannabis starting material;
iii. Agrochemicals used during the growing of the cannabis plants (including: time,purpose, dose and duration);
iv. Cultivation conditions for the particular cultivars, if applicable;
v. Any contingency from standard operating procedures;
vi. Analytical report(s) of the growing medium, if applicable;
vii. Analytical report(s) of the irrigation water;
viii. Harvest date and time for each particular cultivar;
ix. Time, duration and conditions of drying;
x. Checks on pest control traps and measures taken for any incident;
xi. Record keeping of quantity of cultivar subdivision into batches;
xii. Record keeping of waste generated from the propagation and production of the cannabis plants, including the method of destruction or disposal.