MALTA
MEDICINES
AUTHORITY

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, at any 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.

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 sale or disposal of cannabis;

"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 hemp;

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

"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);

"Malta Industrial Parks" refers to a limited liability company (C. No. 28965), responsible for the administration of the government-owned industrial parks and related facilities around Malta and Gozo;

"Person" means either a physical or legal person;

"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;

"Unit product pack" is the individual pack of final product, in the approved weight/volume.

3. General Guidelines

3.1 Application process

Applications for the production of cannabis for medicinal and research purposes must be completed and the licence and EU-GMP certificate (as applicable) must be granted before activities related to cannabis production and research in terms of the Production of Cannabis for Medicinal and Research Purposes Act (Chapter 578 of the Laws of Malta) are carried out. The complete application form and supporting documents should be submitted electronically to the regulatory authority in English. Translated documents must be notarised.

Proof of payment of the applicable fees and contributions specified in the Production of Cannabis for Medicinal and Research Purposes (Fees) Regulations, L.N. 391 of 2018, is mandatory and the respective provisions apply. The application/renewal fee must be paid on first application and on renewal of the licence every 3 years or as determined by the regulatory authority from time to time. The annual fee must be paid upon the first issuance of the licence and is due every 12 months thereafter. Fees 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. All documentation must 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 any time during the application process.

Production of cannabis at the approved site may only be initiated once the relevant approvals, certificates, licences and permits are issued. A licence holder is only permitted the production of cannabis for medicinal and/or research purposes and all activities must be in conformity with the relevant legislation and guidelines at all times. Where the approved/certified site is intended for the production and/or testing of medicinal-products not related to cannabis for medicinal and/or research purposes, such production and/or testing 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 the letter of intent, EU-GMP Certificate 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.

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 must 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, transaction, transfer and shipping documents, product labels and sales invoices.

Qualified Person

The licence holder must 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 is resident in Malta. The qualified person 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 material coming from third countries undergoes all checks and analysis necessary to ensure quality and that the manufacturer applies standards of good manufacturing practice. 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.

Site

A licence holder must produce, store, package, and label cannabis only inside the 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 must comply with Maltese customs laws and international conventions on cannabis. Exportation of cannabis is restricted to finished products intended for medicinal use and must 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. The relevant provisions of the United Nations Single Convention on Narcotic Drugs (1961) apply and the applicant is responsible to obtain the necessary authorisations from the Office of the Superintendence of Public Health. A licence holder must 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 licensed site to a port of exit from Malta and vice-versa.

Destruction

Licence holders must provide details on waste management, such as closed incineration or composting, or other waste disposal systems. A licence holder should destroy cannabis in accordance with environmental and waste management legislation without exposing persons and/or the environment to any hazard. Destruction of cannabis must not occur at any unauthorised site and double-signed records should be kept to account for cannabis being disposed of or destroyed.

Loss or theft

If a licence holder experiences theft, loss, unusual waste, or disappearance of cannabis that cannot be explained to be in the normal course of business, the licence holder must 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 must comply with all applicable laws, including 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), directors, management, qualified person(s), responsible officers and any other persons with a financial interest and persons with decision making powers of influence. Due diligence reports should be submitted with the application and are subject to the requirements stipulated by the regulatory authority and shall include as a minimum, the nature of involvement and responsibilities of all parties, full personal credentials, permanent address, notarised copy of photo identification document and evidence attesting no past, pending or threatened crimes including environmental crimes, claims, proceedings, lawsuits, financial misconduct, activities which involve the proceeds of unlawful activities, any drug-related offenses, fraud or bankruptcy as well as full name, registers and jurisdiction in which legal entity is incorporated or otherwise created, and reference letters, as applicable. The regulatory authority may additionally refer any case(s) for security screening whereby the applicant is expected to provide all requested documentation, pay the related expenses, and consider the application review process to be on clock-stop pending the conclusion of the exercise(s). The licence holder is responsible to request and retain clean police conducts for all personnel, with up-to-date certificates being accessible to the regulatory authority as required. The regulatory authority retains the right to ask for any further clearance as it deems fit from time to time.

Security compliance

Access to areas within the licensed site must be physically restricted to authorised persons whose presence is strictly required in virtue of their work responsibilities and with adequate managerial supervision. The facility must be designed in such a way that prevents unauthorised access and visitors must be accompanied, at all times, by designated personnel whilst on premises. The four eyes principle should be applied for the product storage vault that must incorporate a two-person rule law for access. A licence holder must 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, are in place.

Monitoring

The perimeter of a licensed site, and particularly areas within a site where cannabis is present, must 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, or unusual movement in the site, or suspected illicit activity, or tampering with the security system. The visual recording devices should be backed up at least every two (2) weeks and historical records retained.

Management or designated personnel must:

i. record the identity of every person entering or exiting the premises; ii. monitor the intrusion detection system; 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.

Members of local law enforcement agencies, in particular those pertaining to the Malta Police Force, whilst in active duty and in relation to investigations or security checks pertaining to any issues related in any way to the production of cannabis for medicinal and research purposes in those same premises; and/or in relation to any investigations pertaining to any company employee/s working within such premises; are to be allowed free and unlimited access to all areas of the premises itself without any reservations whatsoever and without prior notice.

3.4 Manufacturing

Products must be consistently produced and controlled in accordance with the quality standards appropriate to their intended use and in line with the current good manufacturing practice guidelines published by the European Union Commission. The licensed site shall be inspected by the regulatory authority, as deemed necessary, to attest European Union Good Manufacturing Practice (EU-GMP) compliance.

Whether local or overseas, cultivation of cannabis to be subsequently manufactured in Malta, must be in accordance with Good Agricultural and Collection Practices (GACP), backed by a documented quality system. Refer to Appendix III for guidance on local cultivation. Cannabis must comply with any applicable European Pharmacopeia

monograph. Active substances, as dried flower in bulk, must be handled under GMP. In cases where the active substance is purchased from an outside source, the local 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. Intermediates, as oil containing cannabis that shall undergo further manufacturing steps, must have an EU-GMP certificate issued by an EU competent authority.

A licence holder must ensure that:

i. the finished product packaging prevents contamination and/or adulteration of cannabis;
ii. not more than the equivalent of the approved unit product pack of cannabis is in the container or package;
iii. the unit product pack label contains information that includes as a minimum: name and contact details of the licence holder; product name; batch number; expiry date; net weight or volume; and the percentage of cannabidiol and/or tetrahydrocannabinol.

At periodic intervals, determined by the regulatory authority, the licence holder shall be requested to submit estimates of the amount of cannabis (including corresponding quantity of cannabidiol and/or tetrahydrocannabinol, as applicable) that the manufacturer intends to import, over an upcoming stipulated period, for further processing in Malta.

3.5 Possession and transactions

The storage and possession of the harvest from local cultivation must satisfy the requirements set out in the relevant legislation. A licence holder must inform the regulatory authority of the number of finished product packs that shall be produced over the subsequent quarter, 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, L.N. 391 of 2018 must be submitted to the regulatory authority which shall consider approving the generation of an equivalent number of serial numbers, or otherwise, as determined by the regulatory authority. Each finished unit product pack shall display the respective serial number, in a tamper-evident manner, as established by the regulatory authority, prior to any transactions related to the product. 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.

3.6 Reporting

A licence holder must keep record of cannabis transactions to ensure traceability. As a minimum, the following records must be kept and submitted to the regulatory authority on a quarterly basis:

i. the source from which cannabis was received at the local licensed facility;
ii. the quantity and form of cannabis received, including copy of import permit;
iii. the number of finished unit product packs produced;
iv. the name of the entity to which the products are sold or provided (the client) and the site to where the cannabis is transported or delivered, including copy of export permit for exported products.

Record keeping should comply with local legislation and EU-Good Manufacturing Practice and EU-Good Distribution Practice guidelines.

A licence holder must investigate every report received in respect of the quality of products, and if necessary take corrective and preventive measures, or any action requested by the regulatory authority. A licence holder must relay, to the regulatory authority, all adverse reaction reports within fifteen (15) days of being received. A licence holder must 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.

A licence holder must keep a copy of each quarterly notice submitted to the regulatory authority and of any supporting information or documentation requested by the regulatory authority for at least five (5) years, or one (1) year after expiry, whichever is the longest. Records must be kept at the licensed site in a manner that enables timely auditing by the regulatory authority.

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 as deemed necessary by the regulatory authority or upon request, as well as foreign entities, including other competent authorities and the International Narcotics Control Board.

3.8 Advertising

Advertising of cannabis to persons qualified to prescribe must be in line with the advertising regulations in the Medicines Act (Chapter 458 of the Laws of Malta) and its subsidiary legislation, Medicinal Products (Advertising) Regulations, 2005 S.L. 458.32.

Advertisement of cannabis to the public 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 is strictly prohibited.

3.9 Research and development

Research and development activities related to cannabis may be carried out in licensed sites, subject to approval by the regulatory authority and other relevant bodies such as the ethics committee as may be applicable. A detailed description of such activities is to be submitted to the regulatory authority before initiation. A record of the research undertaken and the findings, including the source, quantity and form of cannabis used in the course of the research, must be documented. The site where the research is undertaken may be subject to inspections and audits, at the discretion of the regulatory authority.

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, L.N. 391 of 2018
Medicinal Products (Advertising) Regulations, 2005 S.L. 458.32

5. Revision history

Issue no.	*Issue date*	*Reason for revision*	*Prepared by*
1	December 2018	First version	Advanced Scientific Initiatives Directorate, MMA
2	December 2019	Review	Advanced Scientific Initiatives Directorate, MMA
3	July 2022	Update to section 3.1	Cannabis for Medicinal and Research Purposes Unit, MMA

6. Appendix I

6.1 Identification

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

6.2 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; 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.

The certificate of analysis must include, as a minimum, the following tests, using the respective European Pharmacopoeia methods and corresponding limits. The limits in the European Pharmacopeia General Monograph on 'Herbal Drugs' apply.

i. Aflatoxins (Ph Eur 2.8.18) ii. Pesticides (Ph Eur 2.8.13)
iii. Foreign matter (Ph Eur 2.8.2) iv. Heavy metals (Ph Eur 2.4.27)
v. Loss on drying (Ph Eur 2.2.32) vi. Content Tetrahydrocannabinol (THC)
vii. Content Cannabidiol (CBD)

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. Descriptions of the validated analytical procedures must be provided together with the specifications and the limits applied.

6.3 Assay Limits

Cannabis flowers – the average content of THC and CBD, including any corresponding acid, in a representative sample of the product must be not less than 90.0 per cent and not more than 110.0 percent of the stated content, as per the product specifications and labelling.

Cannabis oil or any other dosage form – the average content of THC and CBD in a representative sample of the product must not be less than 95.0 per cent and not more than 105.0 per cent of the stated content, as per the product specifications and labelling.

6.4 Microbiological Standards

Guidelines and limits specified in the below European Pharmacopeia sections apply:
Ph Eur 5.1.8 Microbiological quality of herbal medicinal products for oral use and extracts used in their preparation;
Ph Eur 5.1.4 Microbiological quality of non-sterile pharmaceutical preparations and substances for pharmaceutical use (for other routes of administration).

6.5 Stability

Stability tests must include as a minimum, assays for Tetrahydrocannabinol (THC), Cannabidiol (CBD), Loss on Drying, and Microbiology. Stability testing must 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;
b) Guideline on quality of herbal medicinal products/traditional herbal medicinal products EMA/HMPC/201116/2005, as amended;
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.

6.6 Summary of mandatory tests

CERTIFICATE OF ANALYSIS

1. Content THC
2. Content CBD
3. Loss on Drying
4. Microbiology
5. Pesticide Analysis
6. Heavy Metal Analysis
7. Aflatoxins
8. Foreign Matter
9. Identity tests

STABILITY TESTING

1. Content THC
2. Content CBD
3. Loss on Drying
4. Microbiology

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. In case of raw materials coming from an outside source, further tests may be required by the regulatory authority. These may include fumigant residues and radioactivity, among others.*

7. Appendix II

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 should be in place, but should not be perceived as exhaustive since the security approach adopted should 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 should 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 must 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) should be present at the site perimeter and all areas where cannabis is present, which devices must be monitored at all times and records of CCTV footage kept for a minimum of 30 days. All areas of the licensed premises must 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 should be used for the storage of cannabis raw material and finished products. The vault/strong room should be equipped with a dual-combination locking system using the four-eye principle. Vaults for harvested material should have a security system in place which caters for the release of the harvest, as determined by the regulatory authority. Cannabis waste material should be stored in a separate receptacle in the vault/strong room or a similarly secure, locked area.

Any glass panels considered as roof structures must be equipped with detection sensors. Cannabis, in whatever form or stage in the process, should not be visible from street level. An architect's declaration in this regard is required. The facility should bear no signs, names, logos, or cannabis connotations on the exterior of the building. The

external areas must have adequate lighting and standby generators should be available on site. Cultivation/production sites must be physically separated from offices, administration and break areas, which should nonetheless have an access-control system and monitoring. Pocket-less clothing must be used within production and cultivation areas, and personal bags and other containers should not be permissible in such areas. The number of entrances to areas holding cannabis must be kept to a strict minimum, which entrances must be secured and appropriate doors/frames in place.

7.3 Control systems

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

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

Licensees should have an agreed set of Standard Operating Procedures (SOPs) to cover emergency procedures, inventory and reconciliation, stock control, unauthorised access, intrusion and theft.

7.4 Transportation

Licensees should ensure that the level of security of cannabis during transportation is equivalent to that of the licensed premises. Cannabis in transit remains under the responsibility of the licensee 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 licensee uses a third party carrier. Delivery of goods on special sales conditions/transit terms such as exworks (EXW) and freight-on-board (FOB) terms is strictly prohibited. Any outsourced transport activities must be audited for standards and requirements at least equivalent to those of the manufacturer. Licensees should have an agreed set of Standard Operating Procedures (SOPs) covering responsibility, record keeping, reconciliation, reporting and emergency procedures. This document presents nonexhaustive 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 should 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 should not contain any visible signs suggesting the presence of cannabis and the products should not be visible from outside

the vehicle. Tamper-evident containers or packages should be used for all consignments. For consignments with a very high risk of diversion, the parties involved should consider additional security measures such as a separate secured area equivalent to a safe, that should be bolted down to the vehicle, police/security staff escorts and CCTV coverage at risk points.

The details of deliveries should be restricted to personnel that are required to know them. Licensees should ensure that a qualified person is designated to verify and sign out the consignment for delivery and similarly recipients should 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 should have comprehensive instructions covering routine and emergency situations during transit. Carrying unauthorised passengers and making visits to unauthorised locations should be strictly prohibited. Wherever an accident occurs that requires the attendance of the emergency services, the police should be made aware of the incident and the vehicle's content as soon as possible.

8. Appendix III

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 must be made to the European Medicines Agency Guideline on Good Agricultural and Collection Practice (GACP) for starting materials of herbal origin (EMEA/HMPC/246816/2005) and to the EU Good Manufacturing Practice (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 the Community Code relating to medicinal products for human use, the agricultural practices relating to the cultivation and primary processing of cannabis plants determine the quality of the finished products intended for patient administration.

8.2 Facilities

The cultivation site must be a defined, enclosed structure having permanent walls, within a licensed production and/or research facility. Such authorised sites must be situated within industrial zones managed by Malta Industrial Parks or in any other zones that hold a permit to operate an industrial activity. The facility must 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 of

cannabis plant material. The facility should incorporate a system which protects the cannabis plants from pests, diseases and domestic animals. Critical areas must be equipped with appropriate traps that must be logged into a system, checked periodically, documented and any findings reported immediately.

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

8.3 Personnel and training

Personnel working with the propagation, maintenance, growing, inspection and harvesting of the cannabis plants must either possess a post-secondary qualification related to horticultural practices or else must 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 should be received prior to their involvement in the day-to-day running of the 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 must comply with the regulations on food hygiene. Adequate clothing should be provided to protect the personnel from any toxic 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, must be forbidden to come in contact with the plant material. If a person is suffering from an infectious episode, he/she may be allowed to return to work not before a physician certifies that the person is free from the disease. If a person is a carrier of a disease, he/she must 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, must be cleaned in order to eliminate the risk of contamination and cross-contamination during the process. Equipment that is used to apply fertilisers must be calibrated regularly to ensure the prescribed delivery of the agrochemical to the cannabis plants, when needed. Preferably, equipment should 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, must 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 must be taken into account for electrical equipment with due consideration given to the high humidity and irrigation water within the growing environment. Equipment must 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, must be botanically identified. Record keeping must include the species name, variety, chemotype and place of origin. The material must 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 must be used as material for the cloning of cannabis varieties/chemotypes. If the female flowering tops are required as a finished product or as an API for further processing, male plants must 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 must be monitored. Within the growing premises, artificially-induced hermaphrodites may emerge. Personnel must be instructed to inspect the plants regularly for such possibilities.

8.6 Growing

Inert support media, such as rockwool, must be certified free from the presence of contaminants and microorganisms. Ideally, medicinal cannabis plants should 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 must 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 must be stated, and the physicochemical characteristics and the levels of heavy metals, pesticide residues, plant pathogens and pests, must be declared. Initially the source of the soil must be tested for potential radioactivity. If the soil and/or compost is subjected to sterilization, the method should 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 must be avoided. Artificial fertilisers with declared contents on the label and instructions for use should have a certificate of analysis which must be available at hand, upon inspection. Personnel should be instructed to apply fertilisers and agrochemicals to a minimum and only as and when the need arises. Any amounts used must be logged stating the date, purpose of use, location of use, and dose and duration of use.

Fertilisers and agrochemicals must be safely stored in cabinets with appropriate hazard signs affixed on the doors of such cabinets. Personnel must 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 must be well ventilated, cool and dry. Use and storage of agrochemicals must be undertaken, by qualified personnel only, in accordance with the recommendations of the manufacturer and the relevant authorities.

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

Qualified personnel must 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 should 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, should be removed and transported in a sealed plastic container to the disposal area.

8.7 Harvesting

The growth of the cannabis plants should be followed throughout the whole cycle. Prior to harvesting, environmental conditions such as high air humidity and high soil moisture content should 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 must be removed and disposed of immediately.

Harvesting must 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 must 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 must be immediately transferred to clean, dry boxes. Any reusable boxes must be thoroughly cleaned with 70% alcohol, and checked for any plant residues before re-use. The filling of these boxes must be done in such a way that the material is not compacted unnecessarily in the containers and no material must 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 should 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 must be kept clean, dry and protected from plant pests and domestic rodents and crawling insects. Appropriate traps must be placed outside and inside the storage facility to control the possible presence of these organisms. The harvested material should 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 must 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 finished 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 must 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 must 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, must be disposed of in sealable bags that must be placed in closable waste bins outside the drying area. Such waste bins must 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, must be:

i. Of food grade (specifications of which must 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 must be well cleaned and dried, ensuring that there are no residual disinfecting 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, must 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 must be stored at temperatures between 1°C and 5°C (ensuring no degradation of materials/active metabolites occurs within that temperature range); frozen products must be kept at temperatures below -18°C (or below -20°C for long-term storage).

The storage area must be:

i. A dry, well-ventilated designated area, which is temperature, light and humidity controlled, for which fluctuations must 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 must be controlled for residues before material is introduced and if saturated steam is used, humidity levels must 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 must 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 must 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 must be in order to prevent unauthorised movement of cannabis material or semi/finished cannabis products within or outside the premises. Only authorised personnel must be allowed to access specific designated areas as stated in their job description. Personnel must observe hygiene regulations at all times. Waste material must not be treated with negligence, and 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 finished products, the material must be shredded into 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 must be documented, stored for future reference and presented upon inspection. Documentation should be signed and countersigned in order to verify its validity. For safety reasons, the documentation must 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 must 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.

Signatures on file