

Guidelines for cultivating cannabis for medicinal purposes

Annex to the Regulation of the Minister of Health, Welfare and Sport of 9 January 2003, GMT/BMC 2340685, containing policy guidelines for the decision on applications for Opium Act exemptions (Policy guidelines Opium Act exemptions)

(authorised English translation)

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1 Introduction

Under certain conditions, the Dutch government permits the cultivation of cannabis for medicinal purposes. In the case of herbal drugs, the cultivation method and primary processing of the plant determines the ultimate properties of the active pharmaceutical ingredient. Starting materials of herbal origin have a complex composition and can only be characterised to a limited extent through chemical or biological analysis. Therefore, an effective quality assurance system in the steps leading up to the production of the active pharmaceutical ingredient is needed in order to guarantee reproducible quality. These steps are cultivation, harvesting and primary processing.

The following guidelines for cultivating, harvesting and primary processing of cannabis constitute a quality assurance system that meets these requirements. The Office of Medicinal Cannabis (Bureau voor Medicinale Cannabis) will test on the basis of these requirements.

These guidelines have been derived from the general rules for Good Agricultural Practice of the Working Group on Herbal Medicinal Products of the European Medicines Evaluation Agency (EMA).

This is a non-authorised translation of the official version in Dutch.

2 General

- 2.1 These guidelines apply to the cultivation, harvesting and primary processing of cannabis plants intended for medicinal use or the preparation of medicinal drugs. These guidelines must be read in connection with the European Good Manufacturing Practice (GMP) guidelines for active pharmaceutical products. They apply to all methods of production including organic cultivation. These guidelines also provide additional standards for the production and processing of herbal starting materials insofar as they identify the critical production steps that are needed to ensure good, reproducible quality.
- 2.2 The main objective of these guidelines is to increase the reliability of the medicines prepared from cannabis by establishing an appropriate quality standard for the herbal medicine cannabis. In particular, it is important that the cannabis:
 - is produced hygienically to keep microbiological contamination to a minimum;
 - is produced such that negative effects on the plants during cultivation, processing and storage are kept to a minimum;
 - is produced under conditions that ensure that the therapeutic properties of the end product are constant and reproducible.

3 Personnel and training

3.1 Training

- 3.1.1 Personnel must have received adequate botanical/horticultural training before performing the tasks given to them.
- 3.1.2 Production personnel must be trained in the production techniques used.
- 3.1.3 Primary processing procedures must comply with the regulations on food hygiene.

3.2 Hygiene

- 3.2.1 All personnel entrusted with handling the herbal material must maintain proper personal hygiene.
- 3.2.2 Persons suffering from infectious diseases transmittable via food, including diarrhoea, or carriers of these diseases must be forbidden access to areas where they could come into contact with the herbal material.
- 3.2.3 Persons with open wounds, inflammations and skin-infections must be suspended from areas where they could come into contact with herbal material, unless they wear protective clothing or gloves until they have recovered completely.
- 3.2.4 Personnel must be protected from contact with toxic or potentially allergenic herbal material by means of adequate protective clothing.

4 Buildings and facilities

- 4.1 Rooms used in the processing of harvested crops must be clean, well ventilated and must never be used for other activities.
- 4.2 Buildings must be designed in a manner that protects the crops against pests and domestic animals.
- 4.3 The medicinal cannabis must be stored:
 - in a suitable packaging
 - in rooms with concrete or similar floors which are easy to clean;
 - on pallets;
 - at a sufficient distance from walls;
 - well separated from other crops in order to prevent cross-contamination.Organic products must be stored separately from products not grown organically.
- 4.4 Buildings where plant processing is carried out must have changing facilities, toilets and hand-washing facilities.

5 Equipment

- 5.1 Equipment used in plant cultivation and processing must be easy to clean in order to eliminate the risk of contamination.
- 5.2 Equipment and machinery should be mounted such that they are easily accessible. Machines used in fertiliser and pesticide application must be calibrated regularly.
- 5.3 The equipment must be made from materials other than wood. If wooden materials (such as pallets) are used, they must not come into direct contact with chemicals and contaminated materials, in order to prevent contamination of the herbal materials.
- 5.4 Equipment and machinery used for harvesting must be clean and in very good working condition. Machine parts that come into direct contact with the harvested crop must be cleaned regularly and must be free from oil and contamination, including residual plant matter.

6 Seeds and propagation material

- 6.1 Seeds and propagation material must be botanically identified as to species, variety, chemotype and origin. The materials used must be traceable. Starting material must be free from pests and disease as much as possible in order to guarantee healthy growth.
- 6.2 Cuttings of female plants must be used as propagation material for the production of cannabis.
- 6.3 During the entire production process (cultivation, harvest, drying, packaging), the presence of male plants and of different species, different varieties or different plant parts must be monitored. Any impurities must be removed immediately.

7 Cultivation

- 7.1 Soil and fertilisation
 - 7.1.1 Cannabis for medicinal purposes must not be grown on soil contaminated with sludge, heavy metals, pesticide residues or other chemicals. Any chemicals used must therefore be kept to the minimum effective dose.
 - 7.1.2 Manure applied should be thoroughly composted and must be devoid of human faeces. Irrigation should be controlled and according to the needs of the cannabis plant. Fertilisers should be used in such a way that leaching is reduced to a minimum.
- 7.2 Irrigation
 - 7.2.1 Irrigation must be controlled and only as required by the cannabis plant.
 - 7.2.2 Irrigation water must contain as few as possible contaminants like faeces, heavy metals, pesticides and toxicologically hazardous substances.
- 7.3 All tillage must be adapted to plant growth and requirements. Using herbicides and pesticides must be avoided as far as possible. Use and storage of pesticides must be in accordance with the recommendations of the manufacturer and the relevant approval authorities. Only qualified personnel are allowed to use such substances using only approved material but not in a period preceding the harvest, as indicated by the buyer or producer.

8. Harvesting

- 8.1 Harvesting must be done when the plants have reached the best quality for the intended use.
- 8.2 Damaged, and dead plants must be removed.
- 8.3 Harvesting must take place under the best possible conditions, avoiding wet soil or extremely high air humidity. If harvesting occurs in wet conditions, additional care needs to be taken to avoid the adverse effects of moisture.
- 8.4 During harvesting, care must be taken that no other species or cannabis variety gets mixed with the crop.
- 8.5 The harvested crop must not come into direct contact with the soil. Directly after harvesting, it must be prepared for transport in clean, dry conditions (e.g. sacks, baskets, boxes).

- 8.6 All containers must be clean and free from any residues from previous harvests; containers that are not in use must be kept in dry conditions, free of pests and inaccessible to domestic animals.
- 8.7 Mechanical damage and compacting of the herbal drug that could result in undesirable quality changes must be avoided. In this respect, take care to avoid:
- overfilling sacks/containers;
 - stacking sacks/containers too high.
- 8.8 Freshly harvested herbal material must be delivered to the processing facility as quickly as possible in order to prevent thermal degradation.
- 8.9 The harvested crop must be protected from pests and domestic animals.

9 Primary processing

- 9.1 Primary processing includes washing, cutting before drying, freezing, distillation, drying, etc.
- 9.2 On arrival at the processing facility, the harvested crop must be directly unloaded and unpacked. Prior to processing, the material must not be exposed to direct sunlight (except in cases that specifically require this) and must be protected from rain.
- 9.3 Drying
- 9.3.1 Drying crops directly on the ground or under direct sunlight must be avoided.
- 9.3.2 Uniform drying speed and prevention of mold growth must be assured.
- 9.3.3 In the case that plant material is dried in the open air, it must be spread in a thin layer. To ensure good air circulation the drying racks must be placed at sufficient distance to the floor.
- 9.3.4 In the case plant material is not dried in the open air optimal drying circumstances like temperature and drying time must be chosen.
- 9.4 Waste bins must be available and must be emptied and cleaned daily. Waste must be collected in bags and/or in closable containers.

10. Packaging

- 10.1 Following repeated controls and removal of any material not meeting its requirements or of undesired objects, the product must be packaged in clean, dry and preferably new packaging. The label must be clear, firmly fixed and made from non-toxic material.
- 10.2 Reusable packaging material must be well cleaned and dried prior to use.
- 10.3 Packaging material must be stored in a clean, dry place that is free of pests and inaccessible to domestic animals. The packaging material must not contaminate the product.

11. Storage and distribution

- 11.1 Dried, packaged products and extracts must be stored in a dry, well-ventilated room in which daily temperature fluctuations are limited and good ventilation is ensured. Fresh products must be stored between 1°C and 5°C; frozen products must be kept at temperatures below -18°C (or below -20°C for long-term storage).
- 11.2 In the event of bulk transport, it is important to ensure dry conditions. To prevent mould formation or fermentation, it is advisable to use ventilated containers, transport vehicles and other ventilated facilities.
- 11.3 Decontamination of the storage area to combat pests must be carried out only where necessary and by authorised personnel only.
- 11.4 When frozen storage or saturated steam is used for pest control, the moisture content of the product must be controlled after treatment.

12. Special provisions for the production of cannabis intended for processing into a standardised herbal drug.

12.1 Herbs

- a. In these guidelines a herbal medicine is understood to mean any medicine that contains exclusively herbal drugs or herbal preparations as active ingredients.
- b. Herbal drugs are plants or parts of plants in an unprocessed state which are used for medicinal or pharmaceutical purposes. A herbal drug or a preparation is regarded as one active substance in its entirety whether or not the constituents with therapeutic activity are known.
- c. Herbal drug preparations are comminuted or powdered herbal drugs, extracts, tinctures, fatty or essential oils, expressed juices, processed resins or gums, etc. prepared from herbal drugs, and preparations that are produced through fractionation, purification or concentration.
- d. In departure from the above, chemically defined isolated constituents or their mixtures are not considered herbal drug preparations.
- e. Herbal drug preparations may contain other components such as solvents, diluents and preservatives.

12.2 If the cannabis is intended for processing into a standardised herbal medicine, the cannabis must be cultivated under such standardised conditions that the content of the constituents is constant. Protocols of the operations committed during the cultivation must be kept available.

12.3 The content of the main constituents, which includes Δ -9-tetrahydrocannabinol (Δ -9-THC) and cannabidiol (CBD), is determined quantitatively. For a selection of the other constituents, fingerprinting with a suitable technique, such as GC-MS, GC, HPLC or TLC will suffice.

12.4 Unless it is proven that omitting the standardisation of one of the following elements results in a constant and reproducible product, at least the following must be standardised during cultivation:

- a. cultivar of the cannabis plant;
- b. cultivation substrate;
- c. day length;
- d. light intensity;
- e. colour temperature of the lighting;
- f. atmospheric humidity;
- g. temperature;
- h. irrigation
- i. ventilation;
- j. plant age at the time of harvesting;
- k. time of day of harvesting.

12.5 Unless it is proven that omitting the standardisation of one of the following elements results in a constant and reproducible product, at least the following must be standardised during drying:

- a. atmospheric humidity;
- b. temperature;
- c. ventilation;
- d. drying time.

13. Documentation

- 13.1 All processes and procedures which may affect the quality of the product must be recorded in the documentation for each batch. The following in particular must be documented:
- a. the location of cultivation and the name of the cultivator in charge;
 - b. details on crops previously grown at that location;
 - c. nature, origin and quantity of the herbal starting materials;
 - d. the chemicals and other substances used during cultivation, such as fertilisers, pesticides and herbicides;
 - e. standard cultivation conditions, if applicable;
 - f. particular circumstances which occurred during cultivation, harvesting and production which may affect the chemical composition, such as plant diseases or temporary departure from standard cultivation conditions, particularly during the harvesting period;
 - g. nature and quantity of the yield;
 - h. date or dates, and time or times of day when harvesting occurred;
 - i. drying conditions;
 - j. measures for pest control.
- 13.2 Analysis reports of soil analysis must be kept available in the dossier
- 13.3 Location
- 13.3.1 All batches originating from one location must be clearly labelled (e.g. with a batch number). This must be done as early on in the process as possible.
- 13.2.2 Batches originating from different geographic locations may only be combined if guaranteed to be the same, and that the mixture is homogenous. Mixing of batches must be documented.
- 13.3 It must be recorded in the documentation for each batch that the cultivation, harvest and primary processing procedures were in accordance with these requirements.
- 13.4 All parties involved in the production process must demand that their suppliers document all relevant stages and elements of the production process for each batch.
- 13.5 Audit results must be recorded in an audit report. The audit report and concomitant analysis reports and other documents must be kept for at least ten years.

14 Safeguarding the material

- 14.1 The buildings in which the cannabis is cultivated, processed, packaged and stored must be sufficiently secured. This means that there must be security in force and that only authorised personnel is allowed access to the buildings.
- 14.2 The personnel involved in the production process of cannabis must be authorised for that purpose by the employer. When concluding the supply contract, the supplier designates authorised persons and indicates how this will be verified.
- 14.3 There must be a balanced administration of the cannabis.

14.4 Waste must be stored in such a way that theft is impossible. If waste is collected in bags it must be stored in a lockable container (for instance a pressing container) immediately.