LÆGEMIDDELSTYRELSEN
DANISH MEDICINES AGENCY

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FAQ – Production and activities with cannabis primary products and intermediate products

This FAQ is for companies that apply for or have been granted a licence to produce cannabis primary products and cannabis intermediate products.

The specific rules appear from the executive order on cultivation, production and distribution of cannabis bulk and production of cannabis primary products and the executive order on import of cannabis primary products and production of cannabis intermediate products. Both executive orders are issued pursuant to the Act on a Medicinal Cannabis Pilot Programme.

It is important to draw a distinction between whether the cannabis primary products and cannabis intermediate products are based on imported products or Danish-grown cannabis, because substantially different rules apply.

What measures must be taken in relation to safety?

The company must maintain a system to ensure that safety risks are dealt with. A risk assessment of safety must be documented. If safety situations arise, the company must consider if there is cause for taking further safety measures.

The company must ensure that access is restricted. Unauthorised persons may only access the premises where cultivation, production or handling of cannabis takes place if they are duly escorted.

There are no specific requirements for the height of fences, number of cameras or the like.

What is expected of the safety responsible person?

The safety responsible person is a key figure, and attention will be paid to whether this person has the needed resources to complete his or her tasks adequately. The only requirement is that the person can obtain a certificate of good conduct from the Danish National Police.

Must the packaging material and labelling of Danish-produced cannabis primary products meet the labelling requirements of the executive order also if these primary products are exported to other countries?

The executive order on cultivation, production and distribution of cannabis bulk and production of cannabis primary products does not specify any labelling requirements for cannabis primary products to be exported. However, it is required that the

products can be traced, which the manufacturer must ensure. This will impact the labelling of the packs, e.g. with respect to batch number and company information.

The authorities of the import country may impose specific requirements for the labelling of the exported cannabis primary products, which the Danish companies must comply with. We refer to the competent authorities in the import country.

Please note that the exported products must not have been admitted to the Danish Medicines Agency's (DKMA's) list or share their name with a cannabis product admitted to the list.

Must each individual subcontracted analysis of a cannabis primary product have its own contract, or can a framework agreement on analysis be concluded?
It is not required to complete a separate contract for each individual analysis of a cannabis primary product made from Danish-grown cannabis. However, the contract must detail all the analysis tasks being subcontracted to a contract acceptor.

Can the company perform analysis itself?

A licensed company is permitted to carry out the required analyses of the cannabis primary products based on cannabis cultivated in Denmark. Reference standards must be used to validate the company's analytical methods.

How is the shelf life determined if there are no stability studies?

It must be ensured that the cannabis primary product cultivated in Denmark meets the established specifications, before it is used to produce a cannabis intermediate product.

The shelf life (storage time and conditions) is usually determined based on stability studies conducted by the company itself. In determining the shelf life, analogies may be drawn with similar products or possibly with any excipients used. It is determined from product to product based on its formulation. If no data on shelf life are available, the company must set a preliminary shelf life and storage conditions, following which the company will initiate stability studies to document a more accurate shelf life and storage conditions.

The studies must be completed in compliance with relevant ICH guidelines. See, for example, CHMP/QWP/122/02 rev. guideline on stability testing: *"Stability testing of existing active substances and related finished products"*.

Why is it not possible for an exported primary product and a primary product applied for inclusion on the DKMA's list to share the same name?

The requirement that the name of the two cannabis primary products cannot be identical is to avoid confusion between exported primary products and primary products for Danish patients.

What is allowed with respect to marketing of the primary products admitted to the DKMA's list?

Generally, it is not allowed to advertise for any cannabis primary products, intermediate products or end-products. We refer to the advertising provisions of the Act on a Medicinal Cannabis Pilot Programme, Part IX and the explanatory notes to the act which describe the rules in detail.

How will doctors, patients, etc. know about cannabis products if advertising is not allowed?

When products are admitted to the DKMA's list of cannabis primary products for treatment of Danish patients, a product sheet is prepared with specifics about the product. This product sheet will be available on our website together with any instructions on how to prepare the product once the cannabis intermediate product has been admitted to the list.

Can a primary product be admitted to the DKMA's list and exported under another name at the same time?

Cannabis primary products with the same specification can be produced for Danish patients as well as for export as long as the products do not share the same name.

Why is it required to have a competent person?

The requirement for a competent person reflects the qualified person employed by pharmaceutical companies pursuant to the rules of good manufacturing practice for medicinal products (GMP). A competent person must be present to ensure patient safety by vouching for the quality of the products, including that all requirements and rules have been complied with for every batch.

Why must the competent person be independent of the company's management and sales?

The competent person should be separated organisationally from the company's management and sales as it will support that the competent person releases only products of a quality matching the rules. The requirement for a competent person is essential to ensure patient safety and quality, which is why this person's qualifications and independence are of high importance.

The competent person must be at the company regularly – what is meant by regularly?

The competent person must be at the company regularly, and not only in connection with the release of products. The number of hours is for the company to assess, but the Danish Medicines Agency estimates that at least 10 hours a week is required to justify that the person has been at the company regularly.

Can a competent person be approved in advance?

A competent person cannot be approved before a new application or an application to vary an existing application is submitted. Thus, the approval of a competent person takes place in connection with the review of applications. Having a competent person approved should generally not be a problem as long as you fulfil the requirements of the executive order and the guide Requirements for and expectations of the competent person in a cannabis company (in Danish only).

In case a competent person does not fulfil the requirements completely, you should generally not expect the Danish Medicines Agency to disregard the rules since this person is very important for the company in ensuring the quality of the products.

What is required to be granted a licence to export cannabis primary products?

The company must comply with the requirements of the rules and must be able to document that cultivation in Denmark complies with GACP and is produced in compliance with GMP, etc. Furthermore, the company will be inspected before a licence to produce cannabis intermediate products is issued.

Note that an imported cannabis primary product cannot be exported, neither as a cannabis primary product nor a cannabis intermediate product.

For information about the export of cannabis bulk, please also see the FAQ on cultivation and production of cannabis bulk here.

Is export of products for research purposes in other countries allowed?

It is only possible to export primary products – and thus not finished intermediate products for dispensing to patients.

Likewise, the cannabis primary products may only be exported to countries in which the authorities permit the import of cannabis products for medicinal use. To find out if it is possible to export to a specific country, we advice you to contact the authorities in the country concerned.

What is a site?

A site is a geographical location. The manufacturing licence is site specific, which means that all geographical locations must appear on the licence with addresses and with a description of the activities carried out at each individual site.

May a cannabis intermediate product manufacturer subcontract the storage of products?

From 1 January 2019, it is permitted to subcontract activities, including storage, in Denmark. The requirements appear from section 40 of the executive order on import of cannabis primary products and production of cannabis intermediate products.

To whom can a manufacturer of cannabis intermediate products distribute its product?

A manufacturer of cannabis intermediate products may distribute its own registered cannabis intermediate products to wholesale distributors, pharmacies and hospital pharmacies.

In case of transport only

Via own transport or by use of a carrier. A carrier can be used for the transport of products from a manufacturer of cannabis intermediate products to a pharmacy without the need of a contract.

This is not considered a subcontracted activity. The manufacturer of the cannabis intermediate product is responsible for the transport.

In case of sale

A manufacturer of cannabis intermediate products can sell cannabis intermediate products to companies having an authorisation for wholesale distribution of medicinal products and having an authorisation for handling euphoriant substances on Schedule A.

In terms of GDP, cannabis intermediate products are equated with finished pharmaceutical products.

Transport from pharmacy back to the manufacturer of a cannabis intermediate product in case of complaints

After the receipt of cannabis intermediate products, the pharmacy owns the products.

Thus, the pharmacy must arrange for the return of the product to the manufacturer via a carrier. This must take place according to the GDP rules, including without undue delay.

Can I have samples of cannabis primary products analysed in laboratories abroad?

After 1 January 2019, analyses of Danish-grown cannabis primary products can be subcontracted to laboratories in EU/EEA countries as long as they have a Manufacturing and Importation Authorisation (MIA). These can be found in the EudraGMDP database. The related requirements appear from the executive order on the cultivation, production and distribution of cannabis bulk and production of cannabis primary products.

What licenses must a laboratory in Denmark have to analyse cannabis primary products?

Activities, including analyses of medicinal cannabis, can be subcontracted pursuant to section 33 of the executive order on cultivation, production and distribution of cannabis bulk and production of cannabis primary products. However, the laboratory is required to have one of the following licenses:

1) A licence to cultivate and produce cannabis bulk
2) A license to produce cannabis primary products and cannabis intermediate products
3) A manufacturer's authorisation pursuant to section 39(1) or (2) of the Danish Medicines Act.

In addition, the laboratory must have an authorisation pursuant to the executive order on euphoriant substances, Schedule A.

What tests is the laboratory required to carry out?

The requirements for analysis, etc. in relation to cannabis primary products cultivated in Denmark are described in the executive order on cultivation, production and distribution of cannabis bulk and production of cannabis primary products, particularly in section 48(1)(vi) and (ix) to (xi). Companies wishing to produce primary products must establish a specification, which will also provide a framework against which to carry out relevant tests. There is a minimum requirement for analysis of active substances, cf. section 48(1)(xi).

The Danish Drug Standards have been extended with a monograph for cannabis flower.

What are pesticides?

A pesticide is also called a plant protection product or a herbicide. Pesticides are used to protect plants or plant products from pests such as fungi or insects or to prevent infestation from such pests. It can also be used to control weeds or prevent the growth of unwanted plants.

Pesticides can be both chemical substances and microorganisms. Thus, it is the use of a substance that places it under the pesticide definition. It is not a question of whether the substance is chemical or of natural origin – or if it can otherwise be used in food products.

The use of natural predators is not considered as pesticide use.

The Pesticide Regulation belongs under the Ministry of Environment and Food of Denmark. If a company is not sure if a substance is a pesticide or not, the Ministry of Environment and Food of Denmark should be contacted for a clarification in the specific case. If the Ministry of Environment and Food of Denmark assesses it not to be a pesticide, the substance is not covered by the ban on pesticide use in the Act on a Medicinal Cannabis Pilot Programme.

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What pesticides are allowed in the cultivation of imported cannabis primary products?

From 1 January 2019, it has been allowed to import cannabis that has been cultivated by means of certain permitted pesticides.

First of all, pesticides are only permitted in the cultivation of cannabis primary products for oral use (i.e. cannabis products taken by mouth and absorbed by the body through the gastrointestinal system in the same way as food products).

In addition, all the active substances (the exterminating/controlling substances) contained in the pesticide used must meet the following three conditions:

1) all active substances must be approved in the EU pursuant to Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market (the Pesticide Regulation), and
2) all active substances must appear from Annex IV of Regulation (EC) No 396/2005 of the European Parliament and of the Council of 23 February 2005 on maximum residue levels of pesticides in or on food and feed of plant and animal origin, and
3) all active substances must appear from Annex 2 of the Danish Agricultural Agency's Guide on organic agricultural production (in brief: permitted active substances for organic agricultural production).

The importer (manufacturer of cannabis intermediate products) must be able to document that the active substances contained in the pesticides used meet the three conditions in relation to each individual cultivated cannabis batch to be imported.

How will the importer ensure that the pesticides used in cultivation meet the three conditions?

The importer (the manufacturer of cannabis intermediate products) must go through the following steps:

1) The importer must obtain the exact chemical name, (ISO) common name or CAS number of the active substances contained in the pesticides used in the cultivation of the imported cannabis.

2) The importer must ensure that every active substance has been approved for use in the EU in the European Commission's database of approved active substances. An exact search requires that the importer knows the exact chemical name, ISO common name or CAS number.

   http://ec.europa.eu/food/plant/pesticides/eu-pesticides-database/public/?event=activesubstance.selection&language=EN

3) The importer must check if every active substance also appears from Annex IV of the MRL regulation (Regulation (EC) no 396/2005 of the European Parliament and of the Council of 23 February 2005 on maximum residue levels of pesticides in or on food and feed of plant and animal origin). This check can also be run in the European Commission's database of approved active substances.
4) The importer must check that every active substance is on the list in the Danish Agricultural Agency's Guide on organic agricultural production, Annex 2 – the list of products that may be used for plant protection in special cases.

   https://lbst.dk/tvaergaaende/oekologi/jordbrugsbedrifter/vejledning-om-oekologisk-jordbrugsproduktion/#c5462

All the checks run by the company must be documented by way of a print-out from the database and references to the exact number in the MRL Regulation, Annex IV as well as the Guide on organic agricultural production.

How will the importer document that there are no other residues from other pesticides in the imported cannabis product?

When manufacturers of cannabis intermediate products apply for admission of a cannabis intermediate product and its related primary product, they must submit documentation that includes, for example, batch analysis results including analyses pursuant to the European Pharmacopoeia, Ph.Eur. 2.8.13, documenting that there are no pesticide residues in the cannabis primary product. This analysis is to establish that the product contains no other pesticides than those allowed.

How is the responsibility for the pesticide rules split between the Danish Medicines Agency, the Danish Agricultural Agency and the Danish Environmental Protection Agency?

The Danish Medicines Agency is responsible for the rules on the import of cannabis to Denmark, including the rules on the permitted pesticides.

The Danish Environmental Protection Agency assesses if a substance classifies as a pesticide, cf. the Pesticide Regulation, which falls under the agency's competence.

The Danish Agricultural Agency publishes the Guide on organic agricultural production.