LÆGEMIDDELSTYRELSEN
DANISH MEDICINES AGENCY

Guidelines on applications for authorisation to manufacture and import medicines and intermediates

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Introduction

These guidelines offer guidance on how to complete the application form for authorisation to manufacture and import medicines and intermediates.

In the following, an authorisation to manufacture and import medicines and intermediates will be referred to as an MIA (manufacturer's and importer's authorisation). In the following, an authorisation for whole- sale distribution of medicines within the EEA will be referred to as a wholesale distribution authorisation.

For information on general requirements and guidelines on application for a company authorisation, see Requirements and deadlines for applications for company authorisations. For information about activities requiring a company authorisation pursuant to section 39 of the Danish Medicines Act, see the Guidelines on activities subject to a section 39 authorisation.

For information on the requirements for the manufacture and import of medicines, see the Danish executive order on the manufacture and import of medicinal products and intermediate products (Danish title: "Bekendtgørelse om fremstilling og indførsel af lægemidler og mellemprodukter"), in the following referred

to as the GMP executive order, Regulation (EU) 2019/6 on veterinary medicinal products and Regulation (EU) 536/2014 on clinical trials on medicinal products for human use.

For information on the requirements for distribution of medicinal products, see the Danish executive order on the distribution of medicinal products (Danish title: "Bekendtgørelse om distribution af lægemidler"), in the following referred to as the GDP executive order, and Regulation (EU) 2019/6 on veterinary medicinal products.

For information on the specific requirements for batch release by the Qualified Person, see Annex 16 of the EU GMP guidelines, Certification by a Qualified Person and Batch Release, as well as Requirements and expectations for the qualified person in a pharmaceutical company.

1. Guidelines on how to fill in the application form

The MIA application form is divided into 5 Annexes, of which Annex 1 and Annex 2 fall in two parts each.

Introductory pages:	Application type, company information and signatures
Annex 1, part 1:	Manufacturing of medicines
Annex 1, Part 2:	Importation of medicines
Annex 2, Part 1:	Manufacturing of medicines for use in clinical trials
Annex 2, Part 2:	Importation of medicines for use in clinical trials
Annex 3:	Manufacturing activities contracted out
Annex 4:	Quality control (testing) contracted out
Annex 5:	Qualified Persons

1.1 Introductory pages

In the introductory pages, the applicant must first specify what the application is all about, i.e. whether it is a new application, a change to an existing authorisation or the termination of an existing authorisation. In addition, it must be stated when the company wants the change to apply. Please note that authorisations cannot be issued retrospectively.
Since it is often necessary to clarify what the application relates to, there is room in the following section to describe the application in free text.

When specifying company information for each site, the associated OMS LOC ID must be provided, and for the company's head office also OMS ORG ID must be indicated. OMS (Organisation Management Service) is the EMA's business register of pharmaceutical companies. The company is generally assigned an ORG ID, while each site is assigned a specific LOC ID. The company is responsible for ensuring that the information in this register is correct and to apply to the EMA for modification of the information, e.g. when the company is moving or changing name. This must be applied for and approved before the application for a company authorisation is submitted. New companies must apply to the EMA for registration in OMS, which must also be done before submitting an application to the Danish Medicines Agency. See information about OMS and how to apply for changes to the register here (in Danish only).

In the last paragraph, the company must sign the application. The Danish Medicines Agency does not have specific requirements as to who in the company must sign the application.

1.2 Annex 1 and Annex 2

Annex 1 concerns authorised medicines for sale at pharmacies and retail outlets, whereas Annex 2 concerns medicines for use in clinical trials.
Both Annex 1 and Annex 2 are split up in two parts. In Part 1, the applicant must indicate the company's manufacturing activities, in Part 2, the company's importation activities. Importation of medicines means

importation of medicines from a third country (countries outside the EEA).
If the company imports an intermediate for further processing, the relevant manufacturing activities in Part 1 as well as the relevant importation activities in Part 2 must be ticked.

1.3 Site(s)

Annex 1 and Annex 2 are site-specific. Annex 1 and Annex 2 must therefore be completed for each site at which manufacturing and/or importation activities are carried out. If no GMP activities take place at the main address, Annex 1 or Annex 2 should not be completed for the main address.
In Annex 1 and Annex 2, only the manufacturing activities carried out at the company's own address should be indicated. Activities that are carried out only by contract acceptor should not be indicated in Annex 1 and Annex 2.

1.4 Medicinal products for human or veterinary use

In the beginning of Annex 1 and Annex 2 it is ticked whether medicinal products are manufactured for human and/or veterinary use.
Please note that some activities are only relevant for medicinal products for veterinary use. This applies to the following activities: 1.2.1.15, 1.2.1.16, 1.5.1.15, 1.5.1.16.

1.5 Completion of activities

When completing Annex 1 and Annex 2 all activities performed at the address must be indicated separately. So, if you manufacture bulk tablets, engage in primary and secondary packaging, perform quality control testing and batch release the tablets, all these activities must be ticked in the application form, and they will also appear from the authorisation.

In the "Special Requirements" box, you can indicate if some of the products which the company manufactures, packages, tests or batch releases contain active substances subject to special requirements. The relevant special requirements must be ticked, and it must be indicated which items in the application form (e.g. 1.1.1.4 or 1.2.1.13) the special requirements apply to. Please note that special requirements should not be specified for the following activities: 1.1.3 and 1.2.2 (release), 1.5.2 (secondary packing), 1.6.1-1.6.4 (quality control) and in whole Part 2 (importation).

At the end of Part 1 and Part 2 in Annex 1 and Annex 2, it is possible to add comments, if necessary. Use this field if some of the selected activities need further elaboration.
A further description of the individual activities is available in the European Medicines Agency's (EMA) guidelines: Interpretation of the Union Format for Manufacturer/Importer Authorisation, on pages 172-188 of Compilation of Community Procedures on Inspections and Exchange of Information.

1.5.1 Special situations

Production of intermediates

The manufacturing of intermediate products is included in the individual manufacturing activities for bulk products in the application form. However, if a company exclusively manufactures intermediates that contain one or more active substances, the company must apply for authorisation of item "1.4.1.3 Other" and indicate the formulations (e.g. granules, powder, fluid, etc.) that are manufactured.

Storage

The storage of intermediate products and bulk products requires an MIA. Storage of own manufactured intermediate products and bulk products is included in the manufacturing activities on the company's MIA. Please note, that this applies to individual sites, so if, for example, an intermediate product is produced on one site and transferred to another site, the storage at the latter site must appear on the authorisation for this site

as mentioned below.
For storage of intermediate products or bulk products only, the company must apply for authorisation of item "1.4.3 Other" and indicate the formulations (e.g. granules, powder, fluid, etc.) that are stored. This also applies to the storage of unreleased medicinal products that are manufactured and packaged. The point "1.4.3 Other" with a description of the storage is also used here.
Note, that all components released for the manufacture of a medicinal product are considered as intermediates. Consequently, an MIA is required to store released raw materials and packaging components, if such components are not released again prior to the manufacture of the medicinal product.

Quality control and release
Quality control testing of APIs and intermediates is included in the individual manufacturing activities under 1.1.-1.4.

Packaging
"1.5.2 Secondary packaging" covers the release of the packaging process. Thus, a manufacturer that re-packages is also allowed to release the repacked medicines without having any further activities or comments on the authorisation.

Inactive activities
An MIA must be up-to-date in relation to the company's current activities. In exceptional cases, there may be a need for a company to have activities on the authorisation that are inactive. An example could be a contract manufacturer who wants to offer an activity to its customers but does not have a current customer for the activity. It is a prerequisite that the company has other active activities on the authorisation and that procedures, premises, equipment and training of staff are maintained for all activities on the authorisation, including for inactive activities.

It is not permitted to hold an authorisation consisting exclusively of inactive activities. When a company no longer has activities, the authorisation must be withdrawn, see Section 2.3. In the case of a shorter period, where all activities are inactive, the company may contact the Danish Medicines Agency in order to maintain the authorisation. The Danish Medicines Agency's general position is that there can be a maximum of 6 months without any activity. When the Danish Medicines Agency receives the company's argument for the wish to maintain the authorisation, a specific assessment of the current situation will be made.

1.6 Completing Annex 3 and Annex 4 (contract manufacturers and contract laboratories)

Under contract work, the contract giver (the company) outsources GMP activities to a contract acceptor (another company holding an MIA). The contract between the two parties is called a technical agreement. Under contract work, the contract giver has overall responsibility for compliance with the GMP and GDP rules, also for the activities carried out by the contract acceptor. The outsourcing of activities not included on the application form (e.g. cleaning) is not contract work in the meaning of section 39 of the Danish Medicines Act. Likewise, if a marketing authorisation holder (MAH) pays a manufacturer to manufacture and batch release a product, and the MAH does not have responsibilities in relation to the GMP and GDP rules, this is not contract work in the meaning of section 39 of the Danish Medicines Act, but instead a commercial agreement.
Only manufacturing or testing activities can be contracted out. Activities related to batch release cannot be outsourced pursuant to section 28 of the GMP executive order.

The Danish Medicines Agency does not pre-approve contract acceptors, and contract acceptors do not appear on the issued MIA. Whenever a new application for an MIA is submitted, the applicant must instead submit a list of all contract acceptors (contract acceptors as well as contract laboratories) with the application.

The list must include the following details about each contract acceptor:

- Name and precise address of the contract acceptor (the address appearing from the regulatory approval)
- The activities (items from the application form) that have been contracted out
- The date of the latest audit of the contract acceptor
- The date of the next scheduled audit of the contract acceptor
- The expiry date of the contract acceptor's regulatory approval
- The date when the contract between the contract giver and contract acceptor was concluded (date of signatures)
- The date when the first batch was released, in which the contract acceptor was used for manufacturing or testing activities
- Medicines in which the contract acceptor is involved in manufacturing or testing activities

The Danish Medicines Agency prefers companies to use the Template for the List of contract acceptors (in Danish only). See the "Guidelines" tab in the template for guidance on how to fill out the list.

This list replaces Annex 3 and Annex 4. The list must be updated on a current basis and should be readily available at inspections. Companies is not required to inform The Danish Medicines Agency when chances in the list of contract acceptors are made.

An activity can appear in Annex 1 or Annex 2 and in the List of contract acceptors if the activity takes place both at the company's own address and at the contract acceptor.

The conditions on which manufacturing and testing activities can be outsourced to a contract acceptor are described in section 28 of the GMP executive order. The obligation to audit contract acceptors is described in section 31(3) of the GMP executive order. The following must therefore be in place before a company is permitted to use a new contract acceptor:

- The contract giver must ensure that the contract acceptor holds a valid regulatory approval (MIA or GMP certificate). The contract giver must therefore not release medicines where a new contract acceptor is involved before it is ensured that the contract acceptor has a valid regulatory approval.
- The contract giver must as part of the self-inspection programme audit its contract acceptors on a regular basis. The contract giver must therefore not release medicines where a new contract acceptor is involved before the contract acceptor has been audited in accordance with the EU GMP rules with a satisfactory result.
- There must be a contract between contract giver and contract acceptor according to the provisions of section 28 of the GMP executive order. The contract giver must therefore not release medicines where a new contract acceptor is involved before the contract between contract giver and contract acceptor has been signed.

1.7 Completing Annex 5 (Qualified Person)

In this Annex, the company's Qualified Persons are indicated. If a Qualified Person has not been authorised internally to carry out batch release activities for all types of formulations released by the company, the Qualified Person's areas of responsibility are indicted here. State the title of the Qualified Person in Danish and English.
Qualified Persons must, as a minimum, meet the criteria of applicable law, see the Danish Medicines Agency's Requirements and expectations for the QP in a pharmaceutical company. See section "2. Submission and requirements for applications" for a list of the documents that must be submitted.
There are no requirements for Qualified Person for 1) analytical laboratories or 2) blood banks, that exclusively engage in activities concerning fractionation of whole blood and the freezing, quality control and storage of plasma.

1.8 An MIA also permits wholesale distribution of own manufactured medicines

The MIA also allows the holder to wholesale distribute medicines manufactured and batch released at the company's own address. In these guidelines, these medicines are referred to as own manufactured medicines. Wholesale distribution of medicines batch released by another manufacturer (also another EEA company within the same organisation) requires a wholesale distribution authorisation.

Storage of own manufactured medicines at one of the company's sites that has not been part of the manufacture of the medicine, requires a wholesale distribution authorisation at this site.

2. Submission and requirements for applications

For information on general requirements and guidelines for application for a company authorisation, see Requirements and deadlines for applications for company authorisations. In these guidelines, you can find information on how to submit the application, on assessment times, including the concept of *clock stop*, electronic issuance and the validity of authorisations as well as fees.

In Requirements and deadlines for applications for company authorisations you can read about our expectations for a company prior to the submission of an application for the three types of company authorisations:

1. Application for new company authorisation (first application)
2. Application for change of an existing authorization
3. Application for withdrawal of existing company authorisation

There may be different requirements for the documentation to be submitted, depending on the type of application. The special requirements for documentation when applying for an MIA are described below.

2.1 Application for new company authorisation

When submitting a new application for an MIA, you must enclose a Site Master File (SMF). The SMF is a brief description/overview of the manufacturing sites that manufacture marketed products. The SMF can be prepared according to the *Explanatory Notes on the preparation of a Site Master File*, EudraLex, Vol. 4 2010. At the same time, the documentation required for the authorisation of a Qualified Person must also be submitted.

The following documents must be submitted:

- Application form
- Site Master File (SMF)
- Documents for the authorisation of a Qualified Person (see this item)
- Overview of contract acceptors (Template for the List of contract acceptors)

2.2 Application for changes

If a company wishes to change one or more conditions of the MIA, an amendment to the MIA must be applied for in accordance with the guidelines for the application for change, see Requirements and deadlines for applications for company authorisations. The different application changes will be reviewed in the following sections. Please note that the initial pages of the application form must always be filled in at the time of application.

Companies that have an MIA issued before 1 October 2015 must submit a fully completed application form for all sites, regardless of what the application is about. This is because the interpretation of the format at EU level changed.

2.2.1 Change of name and activities

When applying for a change of company name it is sufficient to complete the introductory pages of the application form, and therefore no need to complete Annex 1-5.

When applying for a change of activities in Annex 1 or Annex 2, the entire Annex for the site concerned must be completed (all tick marks must be put - activities to be added and activities to be continued). If changes only involve one site, it is sufficient to complete the relevant Annex for the site in question. The introductory pages must also be completed.

2.2.2 Change of address or addition of new site

When applying for a change of address or addition of a new site, please submit the Site Master File (SMF), if these documents have changed significantly. Annex 1 and Annex 2 for the site should also be submitted as well as the introductory pages of the application.

2.2.3 Change of Qualified Person

If a company applies to change the authorised Qualified Persons, it is sufficient to submit the introductory pages of the application form as well as Annex 5.
When new Qualified Persons are to be authorised, their diplomas, including a list of completed subjects, and CVs must be submitted with the application, including a list of their qualifications, relevant practical experience, relevant courses, etc.
Qualified Persons must, as a minimum, meet the criteria of applicable law, see the Danish Medicines Agency's Requirements and expectations for the QP in a pharmaceutical company.

The following documents must be submitted:

- Application form
- Diploma, including a list of completed subjects. If no teaching has been received in all basic subjects, see guidance above, documentation of acquired knowledge within the missing basic subjects must be submitted. Feel free to use this form (in Danish only).
- CV listing relevant practical experience, relevant courses, etc. It should be clarified in the CV what experience is relevant for the specific application.
- Training plan (if the person is newly employed in the company)
- Contract with consultant (if a consultant should be authorised as a qualified person).

2.3. Termination of authorisation

Termination of an MIA can only take place on the day the company no longer has GMP activities, including the storage of reference and retention samples and batch documentation. In accordance with Annex 19 of the EU GMP rules, reference and retention samples shall be kept at the manufacturer. Section 26 of the GMP executive order further specifies that reference samples of medicinal products must be kept for at least one year after the expiry date. Reference samples of APIs used in the finished product shall be kept at least 2 years after batch production. However, it is possible to enter into a contract with another manufacturer for the storage of reference and retention samples and batch documentation.

When applying for the withdrawal of the MIA, the company must fill out the initial pages of the application form. Under the description of the application, it must be clarified how the company has ensured that the handling of complaints, recalls, retention of reference and retention samples, batch documentation, etc. for medicinal products manufactured by the company continues to be handled. As a rule, the company will be contacted by an inspector who will plan a closure inspection.

If the company continues to have GMP and GDP responsibilities for medicinal products, it still needs a MIA for a given period of time.

Therefore, a company that wishes to withdraw its MIA but wishes to keep reference and retention samples and batch documentation must first submit an amendment application informing the Danish Medicines Agency that all manufacturing activities are stopped. The Danish Medicines Agency will then issue an amended MIA stating that only reference and retention samples and batch documentation are kept at the address. As soon as the company is no longer obligated under the above rules, the company must submit an application for discontinuation as described above.

3. EudraGMDP

MIAs are transferred by the Danish Medicines Agency to the EU's community database, EudraGMDP, see: http://eudragmp.eudra.org/.The issued MIAs will be published in EudraGMDP.

4. Exemptions from applying for an MIA

Exemption from section 39(1) and (2) of the Danish Medicines Act applies to the following:

1. Hospital wards which only perform additive service
2. Hospital wards which only perform simple labelling and preparation of registered radioactive pharmaceuticals.

5. Change log

Dato	Version	Ændring
01-12-2022	Guide-GMP-10	Inserted reference to regulation (EU) 536/2014 on clinical trials on medicinal products for human use. Annex 6 (the responsible management person) has been removed from the MIA application form. Relevant sections have been deleted or updated accordingly. It has been clarified in section 2.2.3 about the QP that the CV should list the information relevant for the application.
13-12-2021	Guide-GMP-09	Inserted reference to Regulation (EU) 2019/6 on veterinary medicinal products, which enters into force on 28 January 2022. New section on filling in the introductory pages of the application form. New section on inactive activities. In the section on contract manufacturers and laboratories, it is added that companies are not required to inform the Danish Medicines Agency when the list of contract manufacturers and contract laboratories is updated. In the section on qualified person, it is stated that blood banks are exempt from the requirement of qualified person. Similar information on manufacturers of medicated feed has been removed. In the section on responsible management person, prescribing pharmacists have been added to the list of professions that are obliged to apply for authorisation to be affiliated or operate a pharmaceutical company. In addition, general update e.g. inserting change logs.