LÆGEMIDDELSTYRELSEN
DANISH MEDICINES AGENCY

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

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 (**m**anufacturer's and **i**mporter's **a**uthorisation). In the following, an authorisation for wholesale distribution of medicines within the EU/EEA will be referred to as a wholesale dealer's authorisation.

For information on general requirements and guidelines on application for a company authorisation, see the Guidelines on 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.

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.

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 the Guidelines on requirements and expectations for the qualified person in a pharmaceutical company**.**

Contents:

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1. Guidelines on how to fill in the application form

The MIA application form is divided into 6 Annexes, of which Annex 1 and Annex 2 fall in two parts each.

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
Annex 6:	Responsible manager

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 EU/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.

1.1 Medicines for human or veterinary use

It should be indicated whether the manufactured medicines are for human or veterinary use.
Note, that some activities are only relevant to medicines 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.

1.2 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.

1.3 Completing Annex 1 and Annex 2 (activities)

Note, that a new MIA format was launched on 10 February 2015. This means that the activities in the form have been changed, and the form must be completed in a different way than previously.

> With the new format, all activities 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.

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 144-156 of Compilation of Community Procedures on Inspections and Exchange of Information.

Special situations:
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.

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

”1.5.2 Secondary packaging” covers the release of the packaging process. Thus, a manufacturer that repackages must also release the repacked medicines without having any further activities or comments on the authorisation.

1.4 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.

After 1 June 2011, the Danish Medicines Agency no longer indicates contract acceptors in Annex 3 or Annex 4.
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. 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.

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 based 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.

1.5 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 Guidelines on requirements and expectations for the Qualified Person in a pharmaceutical company. A Qualified Person is not required for analytical laboratories and manufacturers of medicated feed.
See item "2. Submission and requirements for applications" for a list of the documents that must be submitted.

1.6 Completing Annex 6 (responsible manager)
In this Annex, the name of the company's responsible manager is indicated. State the title of the responsible manager in Danish and English.
Note that prescribing doctors, dentists and proprietary pharmacists are legally bound to apply to the Danish Medicines Agency for permission to establish a relationship with or run a pharmaceutical company, cf. section 3(2) of the Danish Health Act., see Healthcare professionals' relationships with companies (in Danish).
Also note that according to section 8A of the Danish Veterinarian Act, practising veterinarians are not permitted to be associated with a company handling veterinary medicines, unless the Danish Veterinary and Food Administration has granted an exemption. More information in Danish is available here: Veterinarians' financial independence of pharmaceutical companies.

1.7 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 EU/EEA company within the same organisation) requires a wholesale distribution authorisation.

2. Submission and requirements for applications

For information on general requirements and guidelines for application for a company authorisation, see the Guidelines on 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 the Guidelines on 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 two types of company authorisations:

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

The application must be submitted with a detailed cover letter or cover email, describing the reason for the application, and must contain relevant additional material.

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 an organisation chart and 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
- Organisation chart
- 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

2.2.1 Change of name, change of activities, responsible manager etc.

If a company changes its name, an application to change the MIA must be submitted, see the Guidelines on requirements and deadlines for applications for company authorisations.
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 front page must also be completed.
If a company applies to change the responsible manager, it is sufficient to submit the front page of the application form as well as Annex 6.

The following documents must be submitted:

- Application form

2.2.2 Change of address, addition of new site

When applying for a change of address or addition of a new site, please submit an organisation chart and the Site Master File (SMF), if these documents have changed significantly.

The following documents must be submitted:

- Application form
- Organisation chart
- Site Master File (SMF)

2.2.3 Change of Qualified Person

If a company applies to change the authorised Qualified Persons, it is sufficient to submit the front page 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 Guidelines on requirements and expectations for the Qualified Person in a pharmaceutical company.

The following documents must be submitted:

- Application form
- Diploma, including a list of completed subjects
- CV, including a list of qualifications, relevant practical experience, relevant courses, etc.
- Training plan (if the person is newly employed in the company)
- Contract with consultant (if the consultant should be authorised as a qualified person)

2.3. Termination of authorisation

When a company is to terminate an MIA, the company will normally be contacted by an inspector to schedule a close-down inspection to ensure that the handling of complaints, withdrawals, storage of reference and retention samples, batch documentation etc. are adequately dealt with.

If the company continues to have GMP and GDP responsibilities for medicines, it must still hold a section 39 authorisation for a given time frame.

The termination of an MIA cannot be effected until the day the company no longer carries out GMP activities, including has responsibilities for storage of reference and retention samples as well as batch documentation. Pursuant to Annex 19 of the EU GMP rules, reference and retention samples must be stored at the original site of manufacture. Section 26 of the GMP executive order further specifies that reference samples of medicines must be stored for at least one year after the expiry date. Reference samples of an API used in the finished product must be stored for at least two years after batch manufacture. However, it is possible to enter into a contract with another manufacturing company regarding storage of reference and retention samples as well as batch documentation.

A company wishing to terminate its MIA and continue to store reference and retention samples as well as batch documentation must therefore first submit an application to change the authorisation, notifying the Danish Medicines Agency that all manufacturing activities are being stopped. The Danish Medicines Agency will then issue an altered MIA from which it appears that the company exclusively stores reference and retention samples as well as batch documentation at the address. As soon as the company is no longer obliged to comply with the rules above, the company must inform the Danish Medicines Agency in writing to effect an absolute termination of the MIA.

3. EudraGMDP

Manufacturing and Importation Authorisations are transferred by the Danish Medicines Agency to the EU's community database, see EudraGMDP.
The issued manufacturing and importation authorisation 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 radiopharmaceuticals