

Guideline on variations to marketing authorisations for medicinal products for human use

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1. Introduction

This guideline covers variations to marketing authorisations for medicinal products for human use (also referred to as “human medicines”).

Variation means any amendment to the terms of an authorisation to market a human medicine as well as any change to the summary of product characteristics and the documents forming the basis for a marketing authorisation.

Under section 26(1) of the Danish Medicines Act, the holder of a marketing authorisation (hereinafter the “MAH”) must apply for authorisation of a variation pursuant to Commission Regulation (EC) No 1234/2008 as amended concerning medicinal products for human use and veterinary medicinal products (hereinafter the “Variation Regulation”).

This guideline provides general information on the rules for amending a marketing authorisation and offers practical instructions in special situations.

In the context of variations, “the same MAH” means applicants belonging to the same parent company or group of companies and applicants having entered into agreements on or exercising concerted practices in relation to the placing on the market of the medicinal product concerned. The term “same marketing authorisation” includes all pharmaceutical forms and strengths of a given medicinal product, i.e. one D.Sp.No. (Danish speciality number).

1.1 The rules on variations in brief

The Variation Regulation lays down rules for the examination of variations.

The Variation Regulation is supplemented by the European Commission’s “Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures” (hereinafter “the Classification Guideline”).

The Classification Guideline gives information on the procedure for applying for the approval of variations. The Classification Guideline also contains an annex with details on the classification of the different types of variations, see section 3.

1.2 Additional information on the website of the Danish Medicines Agency

Additional information about variations can be found on the website of the Danish Medicines Agency in the form of links to regulations, guidelines, etc. and questions and answers about variations. The information is updated regularly, and MAHs are advised to acquaint themselves with any relevant details.

2. The scope of this guideline

The guideline applies to variations to marketing authorisations for human medicines granted by the Danish Medicines Agency in accordance with section 8(1) of the Danish Medicines Act, including marketing authorisations for herbal medicinal products, strong vitamin and mineral preparations and radiopharmaceuticals.

The guideline covers marketing authorisations granted by the Danish Medicines Agency under the purely national procedure, the decentralised procedure (*DGP*) or the mutual recognition procedure (*MRP*).

The guideline does not cover variations of marketing authorisations granted by the European Commission under the centralised procedure (CP), unless the variation involves dose dispensing, see the special situation described in section 6.4.10.

In addition, the guideline covers variations to registrations of traditional herbal medicinal products granted by the Danish Medicines Agency under the purely national procedure, cf. section 17 of the Executive Order on Herbal Medicinal Products and Traditional Herbal Medicinal Products (Danish title: *Bekendtgørelse om naturlægemidler og traditionelle plantelægemidler*), as well as traditional herbal medicinal products authorised through MRP or DCP.

Variations involving traditional herbal medicinal products must be submitted in accordance with the legislation in the same manner as herbal medicinal products that have been granted a marketing authorisation. In the context of variations, a registration is thus considered equivalent to a marketing authorisation. Likewise, the documentation requirements for traditional herbal medicinal products are the same as the documentation requirements for authorised herbal medicinal products. When the Classification Guideline states specific requirements for »herbal medicinal products«, this applies to all medicinal products in which the active constituents are a vegetable herbal substance/herbal preparation.

For homeopathic medicinal products, any variation to the terms of the decision on registration and any change to the documents forming the basis for the registration must be applied for as a variation.

3. Types of variations

There are four types of variations: type IA, type IB, type II and extensions of a marketing authorisation (referred also to as an “extension”).

Type IA variations are minor changes with only minimal impact, or no impact at all, on the quality, safety and/or efficacy of a medicinal product. A type IA variation can be implemented without the prior approval of the Danish Medicines Agency but must be notified to the Danish Medicines Agency within 12 months of implementation. However, for administrative purposes, certain type IA variations must be notified to the Danish Medicines Agency immediately after implementation. These are IA variations with the suffix “IN” (IN = immediate notification), i.e. type IAIN. A change in the address of the MAH is one such example.

The so-called “annual report” is a notification of the implementation of one or several type IA variations, and an annual report may also include one or more a-groupings, see section 5.1.

Type IB variations are minor variations which are neither a type IA variation, a type II variation nor an extension.

Type II variations are major variations which are not extensions and which may have a significant impact on the quality, safety and/or efficacy of the medicinal product concerned.

Implementation of type IB variations and type II variations requires prior approval of the Danish Medicines Agency. For type IB variations, a few exceptions apply to DCP and MRP, cf. article 24(2) of the Variation Regulation – further details are given in section 6.2 of this guideline.

An extension of a marketing authorisation is considered a variation by default, but an application for an extension is evaluated in accordance with the application procedure of a

marketing authorisation. An exhaustive list of variations considered as extensions can be found in Annex I of the Variation Regulation.

Annex II of the Variation Regulation provides a non-exhaustive list of variations classified as type IA and type II variations, and in the Classification Guideline, the European Commission has classified a number of variations of type IA, IB and II. The Classification Guideline also clarifies the conditions that must be met for each type of variation and the documentation to be submitted with the application.

If a variation leads to consequential changes to the summary of product characteristics, labelling and/or package leaflet (the “product information”) any such changes are considered part of the variation concerned.

4. Unclassified variations

Variations that are not classified in the Classification Guideline should generally be classified as a type IB variation by default, but not if the variation could have a significant impact on the quality, safety and/or efficacy of the medicinal product. If the latter is the case, the variation must be submitted as a type II variation.

However, pursuant to article 5 of the Variation Regulation, the MAH may request the Danish Medicines Agency to provide a recommendation on the classification of a variation. The procedure for such a request is described in the guideline on classification requests from the CMDh (Coordination Group for Mutual Recognition and Decentralised Procedures for human medicines). The recommendations given through this procedure are, as standard, published on the respective websites of the European Medicines Agency (EMA) and the CMDh. Note in this respect that if a variation has no classification in the Classification Guideline, can only be classified as a type IA variation pursuant to a recommendation made pursuant to the procedure described.

5. Application procedure for variations

A variation application must be submitted to the Danish Medicines Agency via CESP (Common European Submission Platform).

The application must consist of a cover letter, a completed electronic application form and any required documentation, including an updated quality overall summary, expert opinion and CV of expert and where applicable the summary of product characteristics, labelling and package leaflet in the relevant language. If the MAH has obtained a classification recommendation on a variation from the CMDh or from the EMA (see section 4), a copy of that recommendation must be attached.

The variation application form must be downloaded from the website of the European Commission (esubmission.ema.europa.eu).

In case of medicinal products authorised under the purely national procedure, the summary of product characteristics, labelling or package leaflet are required in Danish only. This product information must be presented with the submitted variation application. Mock-ups or specimens should be made available as necessary.

In case of variations resulting in changes to the summary of product characteristics, the Danish Medicines Agency prefers the submission of a draft version of the updated summary of product characteristics in an electronic and editable format (Word). The same applies to the

draft versions of the package leaflet and labelling if the variation results in changes to these documents. The documents must be enclosed in an annotated version and a clean version.

Only one authorised summary of product characteristics with associated package leaflet and labelling can exist. If, for a medicinal product, several variation applications are submitted and reviewed simultaneously and which result in changes to the product information, each variation must be based on the authorised summary of product characteristics and the associated package leaflet and labelling. Immediately after the approval of one of the variations, the MAH is responsible for submitting a consolidated summary of product characteristics, package leaflet and labelling for the variations that are still in the review procedure. The purpose is to ensure that the product information is harmonised in line with all variations.

Generally, only one variation per application form can be applied for to the Danish Medicines Agency. It is possible, however, to derogate from this rule in connection with grouping of variations and worksharing procedures, where the MAH can submit all variations on the same application form.

5.1 Grouping

Grouping is a possibility provided in article 7 and article 13d of the Variation Regulation and can be used when the following applies:

- If the same minor variations of type IA to one or more marketing authorisations with the same MAH are submitted at the same time to the Danish Medicines Agency, or if several variations of type IA to one marketing authorisation are submitted at the same time to the Danish Medicines Agency, all variations may be submitted on the same application form (“a-grouping”).
- If several variations of the same marketing authorisation are submitted at the same time and if the variations otherwise comply with at least one of the conditions in Annex III of the Variation Regulation or have been agreed with the relevant authority, the variations can be submitted on the same application form (“b-grouping”). In a b-grouping, at least one of the grouped variations is a type IB variation, a type II variation or an extension of a marketing authorisation. A b-grouping is handled according to the highest variation type in the group. For instance, a b-grouping consisting of two type IB variations and three type IA variations will be handled according to the procedure applicable to type IB variations. If the same group also contains a type II variation, the procedure for type II variations will be followed.
- If one or more variations of several purely national marketing authorisations with the same MAH granted by the Danish Medicines Agency are submitted at the same time, all variations can be submitted on the same application form (“b-grouping”).

Variations to purely national marketing authorisations cannot be applied for in a grouping with variations to authorisations granted via MRP or DCP.

5.2 Worksharing

The worksharing procedure, cf. article 20 of the Variation Regulation, may be applied when the MAH wishes to submit a variation of type IB, type II or a b-grouping, and the change(s)

involve(s) several marketing authorisations from the same MAH. The worksharing procedure cannot be applied to b-grouping containing an application for an extension of a marketing authorisation. Worksharing can include MRP/DCP/CP/national variations.

If the variations concern only national marketing authorisations granted by the Danish Medicines Agency, worksharing is not a possibility, but submission as a grouping of variations is possible subject to agreement with the Danish Medicines Agency.

Worksharing does not require that the affected medicinal products have a harmonised dossier and/or summary of product characteristics, but it is a requirement that the review of the application does not, or only to a limited extent, involve product-specific assessments.

5.3 One medicine, several variation applications

If, for one single medicinal product, several variation applications affecting the same pharmaceutical form or several applications related to each other are submitted, this must be indicated in the section »Other applications« so that the applications can be reviewed together.

The sections »Precise scope and background for change and justification for grouping, worksharing and classification of unforeseen changes« as well as »Present« and »Proposed« must always contain a concise description of the purpose of the application, the current status and the actual changes applied for.

5.4 Review of the application

The Variation Regulation lays down the assessment times for the various types of variations. Generally, the assessment time is calculated from the procedure start date to the Danish Medicines Agency's final decision; for type IB and type II variations, the time it takes the MAH to respond to any questions posed by the Danish Medicines Agency is not included ("clock stop"). More information about assessment times is available on the website of the Danish Medicines Agency.

Type IA variations (including IAIN variations)

In principle, it is not possible for the MAH to present additional information for type IA variations. Applications that are deemed invalid upon receipt by the Danish Medicines Agency will not be accepted.

The Danish Medicines Agency will decide whether to accept or reject the application. The review of a grouped application covering several variations is closed with a decision in which the Danish Medicines Agency has considered each submitted variation. The decision may therefore include both accepted and rejected variations (partial approval).

In the case of a variation of a marketing authorisation granted by the Danish Medicines Agency via DCP or MRP with Denmark as Reference Member State (RMS), the Danish Medicines Agency will inform the MAH and the competent authorities of the relevant Member States as to whether the variation is accepted or rejected. The MAH will subsequently be informed of the decision by letter.

In the case of a variation of a marketing authorisation granted by the Danish Medicines Agency via DCP or MRP with Denmark as Concerned Member State (CMS), the Danish Medicines Agency does not send a letter with its decision (unless it concerns changes to the

product information). This is because it is the responsibility of the Reference Member State to inform the MAH as to whether the variation has been accepted or rejected.

If the variation concerns a marketing authorisation granted by the Danish Medicines Agency under the purely national procedure, the Danish Medicines Agency will always inform the MAH of its decision by letter.

If an approved variation concerns the summary of product characteristics, labelling and/or package leaflet, the Danish Medicines Agency will always send a letter to the MAH (regardless if Denmark is the RMS or CMS or if it is a national variation). This letter will detail the date by which the approved variation must be made in the labelling and/or package leaflet, and whether the MAH must notify the variation to Medicine Prices via DKMANet, see sections 6.2 and 6.3.

Type IA variations can be implemented without the prior approval of the Danish Medicines Agency, see section 3.

If the Danish Medicines Agency decides to reject a variation that has been implemented before the submission of the application, the MAH must ensure to revert matters to the situation existing before the implementation of the variation.

Type IB and II type variations

Upon receipt of an application, the Danish Medicines Agency acknowledges receipt of a valid application. If information and/or documentation is lacking in an application, the Danish Medicines Agency may set a deadline for the MAH to submit the missing information and/or documentation.

Once the Danish Medicines Agency has received a valid application, it will review the application.

If after the review, the Danish Medicines Agency requires additional information, it will request the MAH to submit a reply with additional information. This means that an application will be rejected if the Danish Medicines Agency has not received the relevant additional information within the deadline stated, unless special circumstances warrant that the deadline be extended. An extension of the deadline must always be agreed with the Danish Medicines Agency.

The Danish Medicines Agency will decide whether to accept or reject the application. The review of a grouped application covering several variations is closed with a decision in which the Danish Medicines Agency has considered each submitted variation. The decision may therefore include both accepted and rejected variations (partial approval).

In the case of a variation for a marketing authorisation granted by the Danish Medicines Agency via DCP or MRP with Denmark as Reference Member State, the Danish Medicines Agency will inform the MAH and the competent authorities of the relevant Member states as to whether the variation is accepted or rejected. The MAH will subsequently be informed of the decision by letter. In the case of a variation for a marketing authorisation granted by the Danish Medicines Agency via DCP or MRP with Denmark as Concerned Member State, it is the responsibility of the Reference Member State to inform the MAH as to whether the variation has been accepted or rejected.

If the variation concerns a marketing authorisation granted by the Danish Medicines Agency under the purely national procedure, the Danish Medicines Agency will always inform the MAH of its decision by letter.

If an approved variation concerns the summary of product characteristics, labelling and/or package leaflet, the Danish Medicines Agency will always send a letter to the MAH (regardless if Denmark is the RMS or CMS or if it is a national variation). This letter will detail the date by which the approved variation must be made in the labelling and/or package leaflet, and whether the MAH must notify the variation to Medicine Prices via DKMANet, see sections 6.2 and 6.3.

6. Implementation of variations, impact on labelling and/or package leaflet as well as notification of variations to Medicine Prices

For variations affecting the medicinal product's labelling and/or package leaflet, the implementation of the variation means the time when the Qualified Person (QP) releases the new packages. These variations are subject to a special process for implementation on the market of new packages with the changed labelling and/or package leaflet and in certain cases also a process for notification to Medicine Prices via DKMANet. The process is described in general in sections 6.2 and 6.3, whereas special situations are described in section 6.4. The special situations described in sections 6.4.1-6.4.4 can be read in conjunction with the additional information on the implementation process of certain administrative variations on the website of the Danish Medicines Agency.

For other variations not affecting the medicinal product's labelling and/or package leaflet, the implementation of the variation means the time when the MAH implements the change. For instance, in respect of changes related to quality, the implementation of the variation is the time when the MAH implements the change in the MAH's quality system.

6.1 Implementation of variations not affecting the medicinal product's labelling and/or package leaflet

If a variation affects only the content of the summary of product characteristics, not the labelling and/or package leaflet, the Danish Medicines Agency will generally update the summary of product characteristics at the time of approving the variation.

6.2 Implementation of variations affecting the medicinal product's labelling and/or package leaflet

A variation affecting the labelling and/or package leaflet must be implemented for the labelling and package leaflet simultaneously. Changes to the labelling and/or package leaflet must generally be implemented within one year of the Danish Medicines Agency's approval of the variation.

The implementation must comprise all medicinal products and associated pack sizes covered by the authorisation, including medicinal products that are currently not on the market.

However, the 1-year deadline requires that the following conditions are met:

- 1) It appears from the current package leaflet (in the packages) that the newest package leaflet is available at www.indlaegsseddel.dk, and

- 2) The updated package leaflet is uploaded to www.indlaegsseddel.dk no later than three months after the Danish Medicines Agency approved the variation.

In relation to condition 1, it is recommended to insert this information between the following two sections of the package leaflet: “Læs denne indlægsseddel grundigt” (“Read all of this leaflet carefully”) and “Oversigt over indlægssedlen” (“What is in this leaflet”). The standard sentence defined by the Danish Medicines Agency is: ”Se den nyeste indlægsseddel på www.indlaegsseddel.dk” (“See the newest package leaflet at www.indlaegsseddel.dk”).

If these two conditions are not met, the Danish Medicines Agency requires that the changes to the labelling and/or package leaflet be implemented within six months of the Danish Medicines Agency’s approval of the variation.

However, the Danish Medicines Agency may in each specific case always set a shorter or longer deadline for implementation of changes to the labelling and/or package leaflet. Any such special implementation terms will be established in connection with the approval of the variation.

Up until the deadline for implementation, both new packages reflecting the approved variation and old packages with the old labelling may be released. Upon expiry of the implementation deadline, only new packages with the updated labelling, etc. may be released.

If a change to the summary of product characteristics of a medicine involves matters related to the safety of using the medicinal product, the Danish Medicines Agency’s approval will detail if the package leaflet must be changed immediately and if a withdrawal of the medicinal product is required.

For type IA variations, the MAH may implement changes to the labelling and/or package leaflet before the variation is approved by the Danish Medicines Agency and an updated summary of product characteristics is submitted, cf. article 24(1) of the Variation Regulation. Correspondingly, the MAH may, in case of a type IB variation and when Denmark is the Concerned Member State in an MRP or a DCP implement changes to the labelling and/or package leaflet in accordance with the approval notified by the Reference Member State before the Danish Medicines Agency has submitted an updated summary of product characteristics, cf. article 24(2) of the Variation Regulation.

6.3 Notification to Medicine Prices of variations affecting the medicinal product’s labelling and/or package leaflet

After their approval certain variations affecting medicinal products on the market or previously on the market must also be notified to the Danish Medicines Agency to be changed in Medicine Prices via DKMANet – Prices & Packages. When the Danish Medicines Agency approves these variations, the approval is made subject to this notification requirement.

However, the notification requirement does not apply to radiopharmaceuticals, herbal medicinal products, traditional herbal medicinal products, homeopathic medicinal products as well as strong vitamin and mineral preparations as these types of medicinal products are not entered in Medicine Prices.

The following variations must be notified to Medicine Prices:

- Change in the name or address of the MAH or representative
- New representative or removal of representative

- New MAH
- New medicinal product name.

If a variation is subject to notification to Medicine Prices, notification must take place by the implementation deadline for changing the labelling and/or package leaflet in line with the approved variation, cf. section 6.2. When the MAH or the representative notifies the variation to Medicine Prices, they also indicate being ready to place on the market the first packages with the change. Notification for the entire D.Sp.No. (Danish speciality number) must be made at the same time. At the time of releasing the new packages, an updated package leaflet must be uploaded to www.indlaegsseddel.dk.

Based on the notification to Medicine Prices, the Danish Medicines Agency updates the summary of product characteristics and any other data registered with the Danish Medicines Agency.

6.4. Special situations

6.4.1 Change in the name or address of the MAH or the representative (type IAIN)

A change in the name or address of the MAH is a type IAIN variation.

A change in the name or address of a representative is not covered by the Variation Regulation. For practical reasons, it has been decided in Denmark to handle changes to the representative in the same manner as changes in the name and/or address of the MAH; consequently they are processed as type IAIN variations.

This is to ensure that the Danish Medicines Agency has updated knowledge about whom the MAH has appointed as representative as this is the person the Danish Medicines Agency communicates with. It is also to ensure that the summary of product characteristics is kept updated with information about the representative.

A type IAIN variation can be implemented without the prior approval of the Danish Medicines Agency but must be notified to the Danish Medicines Agency no later than immediately after the implementation of the variation.

As documentation for the change in address, the company can enclose with the variation application a copy of its request for change of address submitted to the Danish Business Authority. A copy of the acceptance from the Danish Business Authority would also be sufficient documentation.

The mentioned variations must be notified to Medicine Prices via DKMANet. Notification for the entire D.Sp.No. must be made at the same time with the exception of affected medicinal products that are not or have not previously been marketed. When making the notification, the MAH indicates being ready to place on the market the new packages with the approved variation.

From the time when the notification to Medicine Prices takes effect, there is an implementation period of two years. Within this period the new packages with the changed labelling and/or package leaflet must be implemented on the Danish market. During this period, both new and old packages within the relevant D.Sp.No. can be released on the market. For each implementation of a new package, the MAH indicates that going forward, only new packages of the specific package of medicine are released.

When new packages have been implemented for all the marketed medicine packages with the concerned D.Sp.No. or by the expiry of the implementation period, only new packages with the updated labelling etc. can be released. There is no requirement for withdrawing packages with the old labelling, unless the MAH is part of the medicinal product name, see section 6.4.4.

If the MAH changes its name, the marketed packages are not required to have a new product number pursuant to the rules of the Executive Order on Product Numbers for Human and Veterinary Medicinal Products, unless the MAH's name change affects the medicinal product name, see section 6.4.4.

6.4.2 New representative or removal of representative

A change to a new representative or removal of a representative is not covered by the Variation Regulation. For practical reasons, it has been decided in Denmark to review such changes as a national type IB variation, category A.z. In practice, this means ticking off only "National Authorisation" on the variation application form even if the medicinal product concerned has been authorised through MRP or DCP.

An application for the appointment of a new representative or the removal of a representative must be submitted by the MAH.

After approval, the variation must be notified to Medicine Prices via DKMANet. Notification for the entire D.Sp.No. must be made at the same time with the exception of affected medicinal products that are not or have not previously been marketed. When making the notification, the MAH indicates being ready to place on the market the new packages with the approved variation.

From the time when the notification to Medicine Prices takes effect, there is an implementation period of two years. During this period, both new and old packages within the relevant D.Sp.No. can be released on the market. For each implementation of a new package, the MAH indicates that going forward, only new packages of the specific package of medicine are released.

When new packages have been implemented for all the marketed medicine packages with the concerned D.Sp.No. or by the expiry of the implementation period, only packages with the new labelling can be released. Withdrawal of packages with the old labelling is not required.

Implementation of a change of representatives for parts of a D.Sp.No. must be notified for all the affected marketing authorisation numbers (MA numbers). The same implementation process and the same deadlines will continue to apply.

6.4.3 New MAH and any consequential changes to the medicinal product name

A change to a new MAH is not covered by the Variation Regulation. For practical reasons, it has been decided in Denmark to review such changes as a national type IB variation, category A.z. In practice, this means ticking off only "National Authorisation" on the variation application form even if the medicinal product concerned has been authorised through MRP or DCP.

An application for a new MAH must be submitted either by the current MAH or the new MAH. This applies in connection with mergers and sale of marketing authorisations.

The application must include confirmations from both the transferee and transferor of the marketing authorisation and also the revised summary of product characteristics, package leaflet and labelling in an electronic and editable format (Word).

When a medicinal product is transferred from one MAH to another, the entire medicinal product (the entire D.Sp.No.) must be transferred, i.e. all pharmaceutical forms and strengths.

If the name of the MAH is part of the name of the medicinal product (the common name), an application for approval of the variation to change the MAH must include an application to change the name of the medicinal product. An application to change the MAH and to change the name of the medicinal product can be submitted as a grouping on the same application form if the medicinal product has been authorised under the purely national procedure. When changes are made to both the MAH and the medicinal product name, the implementation process for changing the name of a medicinal product must be followed, cf. section 6.4.4 below.

After the approval of a new MAH, the variation must be notified to Medicine Prices via DKMANet by the implementation deadline for changing the labelling and/or package leaflet in line with the approved variation, see sections 6.2 and 6.3. Notification for the entire D.Sp.No. must be made at the same time with the exception of affected medicinal products that are not or have not previously been marketed. When making the notification, the MAH indicates being ready to place on the market the new packages with the approved variation.

From the time when the notification to Medicine Prices takes effect, there is an implementation period of two years. During this period, both new and old packages within the relevant D.Sp.No. can be released on the market. For each implementation of a new package, the MAH indicates that going forward, only new packages of the specific package of medicine are released.

When new packages have been implemented for all the marketed medicine packages with the concerned D.Sp.No. or by the expiry of the implementation period, only new packages with the updated labelling can be released. Withdrawal of packages with the old labelling is not required.

A transfer to a new MAH may result in the introduction of a new Pharmacovigilance System Master File (PSMF) and significant changes to the authorised Risk Management Plan (RMP). The new MAH is responsible for assessing whether these changes should be submitted in a separate variation application.

6.4.4 New medicinal product name

A change of a medicinal product name is a type IB variation. It covers both the change of an invented name and the change of a common name, i.e. a name in which the company name or logo is part of the medicinal product name.

A new medicinal product name must be applied for from the Danish Medicines Agency.

A change of medicinal product name must be notified to Medicine Prices via DKMANet after approval of the variation. Notification must take place by the implementation deadline for changing the labelling and/or package leaflet, see sections 6.2 and 6.3. Notification for the entire D.Sp.No. must be made at the same time with the exception of affected medicinal products that are not or have not previously been marketed. When making the notification, the MAH indicates being ready to place on the market the new packages with the approved change in name.

If the name of the MAH is part of the name of the medicinal product (common name + MAH), a transfer to a new MAH or change in name of the MAH implies that the name of the medicinal

product must be changed. If so, the change in the name of the medicinal product and the MAH must be notified to Medicine Prices simultaneously.

Changing the name of a medicinal product implies that the medicine packages concerned must receive a new product number.

Product numbers are administered by Danish Drug Information (Dansk Lægemiddel Information A/S) and can be ordered directly from the Pharmaceutical Information Center in Finland.

A new product number is not required for medicine packages which have a product number but have never been placed on the market, regardless if the name of the medicinal product is changed.

Upon notification of the change in the medicinal product's name, the old medicine packages must be removed (withdrawn) from the market. When making this notification, the companies can therefore also notify the product numbers of the new medicine packages being introduced. After that, only medicine packages with the new labelling are marketed.

6.4.5 Deregistration of a pharmaceutical form or strength

Deregistration of one or more pharmaceutical forms or strengths (partial deregistration) can take place without the submission of a variation but must be notified to the Danish Medicines Agency.

For medicinal products placed on the market, the notification must always be made to Medicine Prices via DKMANet – Prices & Packages.

For medicinal products not placed on the market, the notification can be made either to Medicine Prices via DKMANet – Prices & Packages, or alternatively by email to godkendelse@dkma.dk or by ordinary post to the Danish Medicines Agency, Quality Assessment & Clinical Trials, Workflow, Axel Heides Gade 1, 2300 Copenhagen S.

If the deregistration of a pharmaceutical form or a strength implies changes to the summary of product characteristics, the MAH must also send a revised summary of product characteristics to the Danish Medicines Agency by e-mail to godkendelse@dkma.dk.

If the deregistration is expected to influence patients, e.g. because no substitutable alternatives exist, the MAH must send a report about this no later than two months before the planned deregistration, to the Danish Medicines Agency, by email to shortage@dkma.dk. The report must contain information about the reason why the medicinal product is no longer to be marketed.

It may be relevant to send direct information to the relevant healthcare professionals with advice on how to deal with the supply shortage. Likewise, the Danish Medicines Agency may also provide information about the situation on the website of the Danish Medicines Agency.

6.4.6 Changed composition

If the composition of the medicinal product is changed, the MAH is obliged to ensure that the relevant stakeholders, e.g. doctors and pharmacies, have been duly informed of the changes prior to the placing of the altered version on the market. Likewise, the MAH is obliged to ensure that all relevant information about the changed composition has been provided on the packaging material.

If the product's appearance or active substances are changed, the Danish Medicines Agency requires that the change of the labelling and package leaflet takes place at the same time as the placing on the market of the packages with the implemented changes. The updated package leaflet must be uploaded to www.indlaegsseddel.dk by the time when the packages are placed on the marketed.

As regards variations implying changes to the appearance or taste of the medicinal product, the altered version may for a transitional period be affixed with a supplementary label, specifying that the product's appearance or taste has changed but that the content is otherwise the same. For a transition period of six months, it is acceptable that both compositions are on the market at the same time. The transitional period starts when the first new package is introduced.

6.4.7 Change in shelf life or storage conditions

Where the shelf life of a medicinal product is changed, the Danish Medicines Agency requires that the medicinal product currently on the market be withdrawn if its shelf life is longer than that of the new one. However, this does not apply if the change is not made for reasons of durability, but for instance to harmonise the shelf life in different countries.

Where storage conditions change, the currently marketed medicinal product must, in principle, be withdrawn.

In connection with a change of the medicinal product's shelf life or storage conditions, any change to the labelling and package leaflet must be implemented at the time the packages concerned are placed on the market.

6.4.8 Temporary repackaging of medicines

If the MAH temporarily needs to repackage medicinal products at a new site, the submission of a type IAIN variation classification B.II.b.1.a under the purely national procedure is required. This also applies to medicinal products authorised under MRP and DCP. In practice, this means ticking off only "National Authorisation" on the variation application form even if the medicinal product concerned has been authorised through MRP or DCP. Detailed information is available at the website of the Danish Medicines Agency.

6.4.9 Addition of a new manufacturing site outside the EU/EEA for a medicinal product authorised under the purely national procedure

If the variation application concerns the addition of a new manufacturing site (classification B.II.b.1) where the manufacturer(s) is/are located outside the EU/EEA and where no operational good manufacturing practice mutual recognition agreement exists between the country concerned and the EU, and where there is no satisfactory inspection in the last three years by an inspection service of an EEA authority, the application must, in addition to the requirements of the relevant guideline, include the following documents:

- Manufacturing authorisation from the local, national authority.
- Site master file(s) for the manufacturing site(s) in question
- Audit report on audit performed by/on behalf of the MAH at the manufacturing site
- Statement from the manufacturer, indicating that the premises are ready for regulatory inspection

6.4.10 Dose dispensing

The introduction or extension of the shelf life in connection with dose dispensing must be submitted as a type IB variation classification B.II.f.1.a.2 under the purely national procedure. This also applies to medicinal products authorised under CP, MRP and DCP. In practice, this means ticking off only “National Authorisation” on the variation application form even if the medicinal product concerned has been authorised through CP, MRP or DCP. Detailed information is available at the website of the Danish Medicines Agency.

6.4.11 Change of dispensing status

A change in dispensing status is a purely national matter. In Denmark, this change must be submitted as a national type II variation, classification C.I.4, because it implies a change to the summary of product characteristics with a significant impact on the safety of the medicinal product. This applies whether the medicinal product was authorised via MRP, DCP or the purely national procedure. In practice, this means ticking off only “National Authorisation” on the variation application form even if the medicinal product concerned has been authorised through MRP or DCP.

7. Fees

The Danish Medicines Agency charges fees pursuant to the Danish Executive Order on Fees in force at any time. The website of the Danish Medicines Agency provides information on the charging of fees. The information is regularly updated, and familiarisation with the relevant aspects is recommended.

8. Replacement of the previous guideline

This guideline replaces Guideline No 9846 of 24 November 2020 on variations to marketing authorisations for medicinal products with regard to human medicines.

Danish Medicines Agency, 15 September 2022

Mette Aaboe Hansen

/Pernille Rahbek

Annex 1

References

Danish Medicines Act: Consolidation Act No 99 of 16 January 2018 as amended.

Variation Regulation: Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products as amended

Classification Guideline: The European Commission’s Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products

for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures (2013/C 223/01)

Executive Order on Herbal Medicinal Products and Traditional Herbal Medicinal Products: Danish Executive Order No 1233 of 12 December 2005 on Herbal Medicinal Products and Traditional Herbal Medicinal Products (Danish title: *Bekendtgørelse nr. 1233 af 12. december 2005 om naturlægemidler og traditionelle plantelægemidler*) as last amended by Executive Order No 120 of 25 January 2022

Executive order on Product Numbers for Human and Veterinary Medicinal Products: Danish Executive Order No 767 of 22 June 2016 on Product Numbers for Human and Veterinary Medicinal Products (Danish title: *Bekendtgørelse nr. 767 af 22. juni 2016 om varenumre til lægemidler til mennesker og dyr*) as last amended by executive order no 2455 of 14 December 2021.