

This is a translation of the Danish guideline on variations to marketing authorisations for medicinal products (Danish title: Vejledning om variationer af markedsføringstilladelser til lægemidler). Only the Danish version has legal validity.

Guideline on variations to marketing authorisations for medicinal products

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1. Introduction

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

According to section 26(1) of the Danish Medicines Act, the holder of a marketing authorisation issued by the Danish Medicines Agency must apply for authorisation of a variation to the summary of product characteristics and the documents forming the basis for the marketing authorisation, in accordance with Commission Regulation (EC) No 1234/2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (variation application). After authorisation of a variation, the change must be implemented within a specific time limit. The implementation must comprise all the package sizes covered by the authorisation, including packages that are currently not on the market.

Through regulation No 1234/2008 (the variation regulation), as amended by Commission Regulation (EU) No 712/2012, the European Commission has established rules on variations to marketing authorisations issued under the centralised procedure (CP), the decentralised procedure (DCP), the mutual recognition procedure (MRP) and authorisations issued under the purely national procedure.

The scope of this guideline

This guideline covers variations to marketing authorisations granted in accordance with section 8(1) of the Danish Medicines Act, including marketing authorisations for natural medicinal products, strong vitamin and mineral preparations and radiopharmaceuticals. Thus, the guideline covers authorisations granted under the decentralised procedure, the mutual recognition procedure and the purely national procedure.

In addition, the guideline covers variations to registrations of traditional herbal medicinal products issued by the Danish Medicines Agency under the purely national procedure, see section 17 of the executive order on natural medicinal products and traditional herbal medicinal products, as well as traditional herbal medicinal products authorised under the MRP and DCP procedures.

For traditional herbal medicinal products, variations must be applied for in accordance with legislation as is the case with herbal medicinal products, for which a marketing authorisation has been issued. As regards variations, a registration is equivalent to a marketing authorisation. Similarly, the documentation requirements for traditional herbal medicinal products are equivalent to the documentation requirements for herbal medicinal products authorised as natural medicinal products. When the European Commission's guideline on classification states specific requirements for »herbal medicinal product«, 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 as well as any change to the documents forming the basis for the registration must be applied for as a variation.

This guideline does not cover variations that only concern marketing authorisations issued under the centralised procedure, see regulation 726/2004, unless the variation concerns an introduction or extension of the storage period for dose dispensing.

Additional information on the Danish Medicines Agency's website

Additional information about variations is available at the website of the Danish Medicines Agency, including links to guidelines, etc. and questions and answers about variations. The information is updated regularly, and relevant persons are advised to familiarise themselves with relevant details before applying for authorisation of a variation.

Types of variations

There are four types of variations: type IA, type IB, type II and extensions of marketing authorisations (line extensions).

Type IA variations are minor changes having only a minimal impact, or no impact at all, on the quality, safety and/or efficacy of the medicinal product concerned. Type IA variations can be implemented without the prior approval of the Danish Medicines Agency, but the Danish Medicines Agency must be notified within 12 months from implementation. However, certain type IA variations must be notified to the Danish Medicines Agency immediately after implementation due to administrative circumstances. Type IA variations carry the suffix »IN« (IN = immediate notification). An example is if the address of the marketing authorisation holder changes.

An »Annual Report« is a notification about the implementation of one or more type IA variations, and an »Annual Report« can also include one or more a-groupings.

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

A type II variation means a major variation which is not an extension 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 by the Danish Medicines Agency. For type IB variations, a few exceptions apply to the decentralised procedure and the mutual recognition procedure, see article 24(2) of the variation regulation, and read more in chapter 5 of this guideline.

Extensions of a marketing authorisation are by definition considered variations, but an application for an extension is assessed according to the procedure for a new application for 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 to be classified as type IA and type II variations, and the European Commission has classified a number of type IA, type IB and type II variations in the *»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«* (the classification guideline). This guideline provides information about the conditions that need to be fulfilled for the respective classifications and describes the documentation that must accompany the application.

Variations that are not classified

In general, variations not classified in the variation regulation's classification guideline must automatically be classified as a type IB variation (type IB by default), unless variations may have a significant impact on the quality, safety and/or efficacy of the medicinal product concerned. Before applying for authorisation of an unclassified variation, the applicant may request the following authorities to provide a recommendation on the classification of the variation, see article 5 of the variation regulation:

- The Danish Medicines Agency, in case of a purely national marketing authorisation.
- The competent authority of the reference member state, if the marketing authorisation is granted under the MRP or DCP procedures.

The procedure for such a request is described in the coordination group's (CMD) guidelines, and the application form can be downloaded from the Danish Medicines Agency's website. On the CMD's website, there is a list of variations already classified upon request from an applicant or a member state. In this connection it should be noted that a variation, which is not classified in the variation regulation's classification guideline, can only be classified as a type IA variation on the basis of a recommendation, see above.

Definition of »same marketing authorisation« and »same holder«

In the context of variations, the term *»same marketing authorisation«* covers all pharmaceutical forms and strengths of a given medicinal product (one D.Sp.No.), and the term *»same holder«* covers applicants belonging to the same parent company or group of companies as well as applicants having entered into an agreement on or exercising concerted practices concerning the placing on the market of the medicinal product concerned.

2. The application

A variation application consists of a completed application form and the required accompanying documentation.

The application should be submitted to:

Danish Medicines Agency
Medicines Licensing, Workflow
Axel Heides Gade 1
DK-2300 Copenhagen S

The application form (eAF) can be downloaded in PDF format from the website of the European Medicines Agency. For variations to nationally authorised medicinal products, the form may be

completed in Danish or English, but for variations to medicinal products authorised under MRP or DCP the form must be completed in English.

On the Danish Medicines Agency's website, you can find explanations on how to complete the application form as well as information about electronic submissions.

Single application, grouping or worksharing

In general, only one variation per application form can be applied for to the Danish Medicines Agency. However, this rule may be departed from in connection with grouping of variations and worksharing procedures where all variations can be listed on the same form.

Grouping is a possibility, see article 7 of the variation regulation, and can be used:

1. If the same minor variations of type IA to the terms of one or more marketing authorisations owned by the same holder are notified at the same time to the Danish Medicines Agency, or if several variations of type IA to the terms of one marketing authorisation are notified at the same time to the Danish Medicines Agency, all the variations can be listed on the same application form (an »a-grouping«).
2. If several variations to the terms of the same marketing authorisation are submitted at the same time and if the variations otherwise comply with at least one of the provisions in Annex III of the variation regulation or have been agreed with the relevant authority, the variations can be listed on the same application form (a »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 processed on the basis of the procedure for the variation in the group with the highest complexity. For example, if a b-grouping contains two type IB variations and three type IA variations, the application will be processed 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.
3. If one or more variations to the terms of several purely national marketing authorisations owned by the same holder and granted by the Danish Medicines Agency are submitted at the same time, all the variations can be listed on the same application form (a »b-grouping«).

Variations to purely national marketing authorisations cannot be applied for in a grouping with variations to authorisations issued under the MRP or DCP procedure.

The review of grouped applications is closed with a decision from the Danish Medicines Agency in which all variations of the group are considered. The decision can include both approvals and rejections. This is also the case for worksharing procedures involving b-groupings.

The worksharing procedure may be applied when the applicant wishes to implement a variation of type IB, type II or a b-grouping, and the change(s) involve(s) several marketing authorisations owned by the same holder. Worksharing can contain MRP/DCP/CP/National variations. If the variations only concern national marketing authorisations granted by the Danish Medicines Agency, worksharing is not a possibility, but the variations can be applied for in a grouping, subject to agreement with the Danish Medicines Agency. It is not a requirement for worksharing 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 any product-specific assessments. The procedure cannot be applied to b-groupings containing an application for an extension of a marketing authorisation.

One medicinal product, several applications

If, for one single medicinal product, several applications affecting the same pharmaceutical form or several applications related to each other are submitted, this must be stated under 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 UNFORSEEN 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. In a grouped application, it must also be justified in the first section why the individual variations should be grouped.

Enclosed draft versions of updated summary of product characteristics, package leaflet and labelling

For variations resulting in changes to the summary of product characteristics, the draft version of the updated summary of product characteristics must be enclosed 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 complete with 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 accompanying package leaflet and labelling. Immediately after the authorisation of one of the variations, the applicant 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 across the variations.

In some cases, the variation only affects the contents of the summary of product characteristics and not the package leaflet or labelling, and it may be variations that do not have to be notified to Medicine Prices. In such cases, the Danish Medicines Agency usually updates the summary of product characteristics at the time specified by the applicant in the application form as the date of implementation of the change.

Other appendices

Relevant statements must be entered under the application form's section »Declaration of the Applicant«, and applicants are reminded that the section »Main signatory« is mandatory if the cover letter does not bear an original signature.

Note that all type II variations must be accompanied by an updated Summary (for example Quality overall Summary), an expert report or expert opinion as well as an expert CV.

3. The Danish Medicines Agency's processing of applications

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, and for type IB and type II variations the time it takes the applicant to respond to any questions posed by the Danish Medicines Agency is not included. More information about assessment times is available on the website of the Danish Medicines Agency.

Valid applications concerning type IA variations are authorised when the Danish Medicines Agency acknowledges receipt of the application.

Applications concerning type IA variations that are deemed invalid upon receipt by the Danish Medicines Agency will not be accepted.

Non-acceptance of variations implemented prior to application may oblige the holder of the marketing authorisation concerned to return the situation to the state before implementation.

If, after the initial assessment of an application concerning type IB or type II variations, the Danish Medicines Agency requires additional information, the applicant has the possibility of submitting additional documents. This means that an application will be refused if the Danish Medicines Agency has not received the relevant additional documents 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.

At the website of the Danish Medicines Agency, more information is available, including CMD's guidelines with information about assessment and deadlines for all procedures, including worksharing.

4. Fees

The Danish Medicines Agency charges a fee for the processing of variation applications. The fee is charged in accordance with the current Danish executive order on fees payable for medicinal products and pharmaceutical companies, etc. (the executive order on fees).

Fees are calculated by the Danish Medicines Agency in compliance with appendix 2 of the executive order on fees and are charged on the Danish Medicines Agency's receipt of applications.

The Danish Medicines Agency issues an invoice on receipt and registration of an application. Usually, the Danish Medicines Agency sends the invoice to the company specified in the application form. It is not possible to pay in advance, for example by bank transfer.

At the website of the Danish Medicines Agency, you can find more information about fees.

Timely payment of the annual fee implies that the medicinal product is considered to have been placed on the market under the »Sunset Clause«, see section 28 of the applicable Danish Medicines Act.

5. Marketing of medicinal products following the authorisation of a variation, including the implementation process

Implementation of a variation means the time when the new packages are supplied to the wholesaler. The variation must be implemented on the labelling and package leaflet of the medicinal product simultaneously.

If the variation needs to be notified to Medicine Prices via DKMANet, it will be considered implemented at the time when the notification took effect. In connection with the notification, the marketing authorisation holder or the representative informs Medicine Prices of the variation and signals that the first packages with the authorised change can be placed on the market.

All changes to an authorisation to market a medicinal product which implies a changes to the labelling and/or package leaflet must generally be implemented no later than one year after the Danish Medicines Agency's authorisation of/instruction to make the change. However, the 1-year deadline requires that

- it appears from the current package leaflet (in the packages) that the newest package leaflet is available at www.indlaegsseddel.dk, and
- the updated package leaflet is uploaded to www.indlaegsseddel.dk no later three months after the authorisation of the variation.

If these two conditions are not satisfied, changes to the labelling and package leaflet must be implemented within six months after authorisation of the variation.

However, the Danish Medicines Agency may always set a shorter or longer deadline for the implementation of changes to the labelling and package leaflet. If changes to the summary of product characteristics include matters related to the safety of using the medicinal product, it will

appear from the Danish Medicines Agency's decision whether the package leaflet needs to be changed immediately and whether a withdrawal is required.

Moreover, the Danish Medicines Agency has special processes for the authorisation and implementation of certain administrative variations. Read more about certain administrative variations in chapter 6.

As mentioned above, it must appear from the package leaflet that the newest package leaflet is available at www.indlaegsseddel.dk. We recommend that this information appears from the package leaflet, between the headings »Læs denne indlægsseddel grundigt« and »Oversigt over indlægssedlen«. (in English: »Read all of this leaflet carefully« and »In this leaflet«). As concerns package leaflets of veterinary medicinal products, we recommend to insert this information between the package leaflet heading and the section with the name and address of the marketing authorisation holder (MAH). The Danish Medicines Agency has not formulated a standard sentence for this piece of information.

However, it should be noted that for type IA variations, the MAH may implement changes to the labelling and package leaflet before the variation is authorised and an updated summary of product characteristics has been submitted, see article 24(1) of the variation regulation. Correspondingly, the MAH may, in case of type IB variations and when Denmark is the concerned member state in a mutual recognition or decentralised procedure, implement changes to the labelling and package leaflet in accordance with the reference member state's notified authorisation, before the Danish Medicines Agency has submitted an updated summary of product characteristics, see article 24(2) of the variation regulation.

6. Marketing of medicinal products following the authorisation of certain administrative variations, including the implementation process

Administrative variations do not concern the medicinal product, but the administrative information appearing from the summary of product characteristics, labelling and package leaflet of the medicinal product. Special circumstances apply to some administrative variations. For example, change of medicinal product name, change of marketing authorisation holder (MAH), changes concerning the representative as well as changes to the name and address of the MAH.

In the following paragraphs, the process applying to such administrative variations is specified, including a description of how to implement a variation.

Change of name or address of the marketing authorisation holder or the representative (Type IAIN)

A change of the address of the marketing authorisation holder (MAH) is a type IAIN variation. The same applies to a change of the MAH's name.

A change to the name and/or address of a representative is not covered by the variation regulation. For practical reasons, it has been decided in Denmark to review changes to the representative in the same way as changes to 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 with which the Danish Medicines Agency communicates and to ensure that the summary of product characteristics is kept updated with information about the representative.

Type IAIN variations must be notified to the Danish Medicines Agency immediately after the implementation at the latest.

As documentation for the change of address, the company's variation application can be accompanied by a copy of its request for a change of address to the Danish Business Authority. A copy of the acceptance from the Danish Business Authority would also be sufficient documentation.

Unless the affected packages have not previously been notified to Medicine Prices, the mentioned changes must be notified to Medicine Prices via DKMANet. Notification for the entire D.Sp.No. must be made at the same time. With this notification, the MAH signals that the new packages can be placed on the market and the variation can be implemented. Based on the notification, the Danish Medicines Agency updates the summary of product characteristics and any other data registered with the Danish Medicines Agency and affected by the change.

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 Danish market. For each implementation of a new package of medicine, the MAH signals that only new packages of the specific package of medicine will be released in future.

When new packages have been implemented for all the marketed medicine packages with the relevant D.Sp.No. or no later than at expiry of the implementation period, only new packages carrying the updated labelling etc. can be released. Withdrawal of packages with the old labelling is not required.

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 type IB variations, category A. Z.

An application for the appointment of a new representative or the removal of a representative must be submitted by the marketing authorisation holder (MAH).

Such changes must be applied for from the Danish Medicines Agency. When the Danish Medicines Agency has authorised the application, there is usually a notification period of one year. However, the 1-year deadline requires that

- it appears from the current package leaflet (in the packages) that the newest package leaflet is available at www.indlaegsseddel.dk, and
- the updated package leaflet is uploaded to www.indlaegsseddel.dk no later three months after the authorisation of the variation.

If the two conditions are not met, the notification period is six months after the authorisation of the variation.

During the notification period, the MAH or the representative must notify the change of representative to Medicine Prices via DKMANet, unless the affected packages of medicine have not previously been notified to Medicine Prices. Notification for the entire D.Sp.No. must be made at the same time. With this notification, the MAH signals that the new packages can be marketed and the variation can be implemented.

Based on the notification, the Danish Medicines Agency updates the summary of product characteristics and any other data registered with the Danish Medicines Agency and affected by the change.

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 Danish market. For each implementation of a new package of medicine, the MAH signals that only new packages of the specific package of medicine will be released in future.

When new packages have been implemented for all the marketed medicine packages with the relevant D.Sp.No. or no later than at expiry of the implementation period, only packages carrying 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 MT numbers. The same implementation process and the same deadlines still apply.

New marketing authorisation holder and any consequential changes to the medicinal product name

A change to a new holder of the marketing authorisation (MAH) is not covered by the variation regulation, but for practical reasons, it has been decided in Denmark to review such applications as type IB variations, category A. Z.

The application for a new MAH must include confirmations from both the entity holding the marketing authorisation and the entity to which ownership is to be transferred, including the corrected summary of product characteristics, package leaflet and labelling in an electronic and editable format (Word).

When a medicinal product is transferred from one holder to another, the entire medicinal product must be transferred, i.e. all pharmaceutical forms and strengths.

If the name of the MAH is included in the name of the medicinal product (the generic name), an application to transfer the ownership of the marketing authorisation to another holder must be accompanied by an application to change the name of the medicinal product at the same time. An application to transfer the ownership of a marketing authorisation and change the generic name can be applied for as a grouping on the same application form if the medicinal product has been authorised under the purely national procedure. Note that when changes are made to both the MAH and the medicinal product name, the implementation process for a change to the medicinal product name must be followed, read more in the chapter »New medicinal product name«.

A change to a new MAH must be applied for from the Danish Medicines Agency. This applies in connection with mergers and sale of marketing authorisations. When the Danish Medicines Agency has authorised the application, there is usually a notification period of one year. However, the 1-year deadline requires that

- it appears from the current package leaflet (in the packages) that the newest package leaflet is available at www.indlaegsseddel.dk, and
- the updated package leaflet is uploaded to www.indlaegsseddel.dk no later three months after the authorisation of the variation.

If the two conditions are not met, the notification period is six months after the authorisation of the variation.

During the notification period, the company must notify the change of MAHs to Medicine Prices via DKMANet, unless the affected packages of medicine have not previously been notified to Medicine Prices. Notification for the entire D.Sp.No. must be made at the same time. With this notification, the MAH signals that the new packages can be placed on the market and the variation can be implemented. Based on the notification, the Danish Medicines Agency updates the summary of product characteristics and any other data registered with the Danish Medicines Agency and affected by the change.

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 Danish market. For each implementation of a new package of medicine, the MAH signals that only new packages of the specific package of medicine will be released in future.

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

Note that a change of MAHs 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 holder is responsible for assessing whether these changes should be applied for in a separate variation application.

New medicinal product name

A change of a medicinal product name is a type IB variation, including a change of an invented name and a generic name, that is a name in which the company name or logo forms part of the medicinal product name.

A new medicinal product name must be applied for from the Danish Medicines Agency. When the Danish Medicines Agency has authorised the application, there is a notification period of one year.

During the notification period, the marketing authorisation holder (MAH) or the representative must notify the change of the medicinal product name to Medicine Prices via DKMANet. Notification for the entire D.Sp.No. must be made at the same time. With this notification, the MAH signals that the new packages can be marketed and the variation can be implemented. Based on the notification, the Danish Medicines Agency updates the summary of product characteristics and any other data registered with the Danish Medicines Agency and affected by the change.

When the new packages are implemented, an updated package leaflet must be uploaded to www.indlaegsseddel.dk.

A change of the medicinal product name also implies that the medicine packages must have a new product number according to the rules governing product numbers for medicinal products. When the notification takes effect in Medicine Prices, all the old product numbers covered by the relevant D.Sp.No. will be removed from Medicine Prices. Read more about new product numbers in chapter 10.

In connection with the implementation of the change of medicinal product name, all the old medicine packages must be withdrawn from the market, so that only medicine packages with the new labelling are marketed.

7. Notification to Medicine Prices

Certain variations must be notified to Medicine Prices via DKMANet – Prices & Packages as part of the implementation process. The relevant processes, including the notification date, appear from the individual chapters in the guideline and from the Danish Medicines Agency's website about Medicine Prices.

Notification of package sizes

All new package sizes to be marketed must be reported to the Danish Medicines Agency in order to implement changes in Medicine Prices. Notification must be sent to DKMANet – Prices & Packages.

However, this does not apply to radiopharmaceuticals, natural 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 included in Medicine Prices.

Notification of administrative variations

Administrative variations must be notified to the Danish Medicines Agency in order to implement changes in Medicine Prices via DKMANet – Prices & Packages. The relevant processes are described in the relevant chapters.

However, this does not apply to radiopharmaceuticals, natural 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 included in Medicine Prices.

8. Changed composition

If the composition of the product has been changed, the marketing authorisation holder (MAH) is obliged to ensure that the relevant stakeholders, e.g. doctors and pharmacies, have been duly informed of the changes prior to the placement 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 changes to the labelling and package leaflet must be made at the same time as packages with the new changes enter the market. The updated package leaflet must be uploaded to www.indlaegsseddel.dk when the new packages are marketed at the latest.

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 been varied but that the content is otherwise the same. For a transition period of six months, it is acceptable that both products are on the market at the same time. The transitional period starts when the first new package is introduced.

9. Change in shelf life or storage conditions

Where the shelf life of a medicinal product is changed, the medicinal product currently on the market must be withdrawn if the length of the previous shelf life is longer than the new one. However, this does not apply if the change is not made for reasons of durability, but for the reason of harmonising the shelf life in different countries.

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

In connection with a change of the medicinal product's shelf life or storage conditions, the changes to the labelling and package leaflet must be implemented simultaneously with the marketing of the affected packages.

10. New product numbers

If a medicinal product changes names, a new product number must be applied for.

A new product number is not required for medicine packages that have a product number but are not marketed yet, notwithstanding that the medicinal product name is changed.

If the marketing authorisation holder (MAH) changes names, the marketed packages do not need to have a new product number. If the medicinal product has a generic name and the change of MAH results in a change of the medicinal product name, medicine packages must, however, have a new product number. Implementation of the variation must follow the process for a new medicinal product name.

As part of the implementation of the change of medicinal product name, the company must notify the change to Medicine Prices via DKMANet. When the notification takes effect in Medicine Prices, all the old product numbers covered by the relevant D.Sp.No. will be removed from Medicine

Prices. As part of the notification, companies can also notify the product numbers of the new medicine packages.

Product numbers can be ordered from Danish Drug Information (Dansk Lægemiddel Information A/S).

11. Special situations

Conversion of documentation from previous Notice to Applicants format to CTD format for medicinal products authorised under the purely national procedure

Applicants requesting a conversion of all documents from the previous Notice to Applicants format (Part I-IV) to CTD format should apply for a type IA variation. A statement specifying that only the format has been changed must be available as documentation for the application.

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

In connection with the submission of a variation application to add a new manufacturing site (B. II.b. 1) where the manufacturer(s) is/are located outside the EU/EEA area and the country in question does not have an agreement with the EU on mutual recognition of good manufacturing practice and where the EEA authorities have not carried out an inspection with a satisfactory result within the past three years, the requirements appearing from the above guideline must be met and the following documents must be enclosed with the application:

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

Dose dispensing

Application for introduction or extension of the storage period for dose dispensing can be submitted as a type IB variation, no. B. II.f. 1.a2, under the purely national procedure. This also applies to medicinal products authorised under CP, MRP and DCP. Detailed information is available at the Danish Medicines Agency's website.

Temporary repackaging of medicines

If the marketing authorisation holder (MAH) temporarily needs to repackage medicinal products at a new location, the MAH must submit a type IAIN variation, no. B.II.b.1.a, under the purely national procedure. This also applies to medicinal products authorised under MRP and DCP. Detailed information is available at the Danish Medicines Agency's website.

Change of dispensing status

An application to change the dispensing status falls under national competence. In Denmark, the change must be applied for as a type II variation, no. C. I. 4, because this implies a change of 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.

Deregistration of a form or a strength

Deregistration of one or more forms or strengths of a medicinal product (partial deregistration) can take place without a variation application and can be notified in several ways. For marketed

products, the notification must always be sent via DKMAnet - Prices & Packages. For non-marketed products, notification can be made to the Danish Medicines Agency via DKMAnet – Prices and Packages, by email to godkendelse@dkma.dk or by ordinary post to the Danish Medicines Agency, Medicines Licensing, Workflow, Axel Heides Gade 1, DK-2300 Copenhagen S.

If the deregistration of a form or a strength implies changes to the summary of product characteristics, the marketing authorisation holder 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 the population, e.g. because no substitutable alternatives exist, the marketing authorisation holder must send a report about this, no later than two months before the planned deregistration, to the Danish Medicines Agency, by email to rapidalert@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 short supply situation. Likewise, the Danish Medicines Agency may also provide information about the situation on our website.

12. Commencement provisions

This guideline replaces guideline no. 9581 of 22 June 2016 on variations to marketing authorisations for medicinal products.

Danish Medicines Agency, 6 July 2017

Mette Aaboe Hansen

/ Karen Juul Jensen