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CMDh Best Practice Guide for authorisation of Non-Prescription Medicines in the Decentralised and Mutual Recognition Procedures

1. Introduction

~~In February 2011 a CMDh Task Force on Self Medication was set up by the CMDh working party on the Future of CMDh, with a mandate from the Heads of Medicines Agencies (HMA) to explore ways of making the Mutual Recognition and Decentralised Procedures (MRP/DCP) more practical for medicines classified as not subject to medical prescription (hereafter referred to as Non-Prescription medicines) This is in addition to the general matters for improvement of MRP/DCP that are addressed by the Future of CMDh Working Party. This task recognises a long-standing concern of the self-medication industry and reflects the importance HMA and CMDh place on ensuring that the MRP/DCP route of authorisation is equally used by all industry sectors.~~

~~Annual statistics for the years pre-dating 2011 show that MRP/DCP is significantly underutilised by the self-medication sector. However,~~ MRP/DCP can be an important regulatory route for Non-Prescription medicines whilst recognising that:

- classification of a medicinal product remains a national competence;
- different healthcare systems exist in Member States (MSs);
- procedures for determining the classification of a medicinal product differ between MSs – e.g. classification can be product based or substance based;
- product names of Non-Prescription medicines may differ between MSs; and
- arrangements for access to Non-Prescription medicines differ between MSs.
- specific MSs can be selected in any one procedure to address the requirements of a non-prescription market;

Therefore, procedures should be put in place that support companies wishing to access the European market and maximise the use of MRP/DCP to facilitate choice of markets, while respecting differing markets within MSs.

Simple, consistent procedures are needed that support Non-Prescription medicine companies wishing to access the European market through MRP/DCP and to assist authorisation by National Competent Authorities (NCAs) of national marketing authorisations (MAs) reflecting the classification and product information agreed for national markets.

The objective is not to harmonise classification of medicinal products between MSs as this remains an important distinction between MRP/DCP and Centralised procedures.

NCAs use different approaches to managing Non-Prescription medicines within the MRP/DCP system, while still operating properly within legislative requirements.

The ultimate aim is to identify processes for NCAs to authorise MAs for Non-Prescription medicines that will be acceptable to all parties.

~~This Best Practice Guide was revised in the light of experience of use when the Task Force was re-convened in 2016.~~

2. Aim and Scope

This document aims to improve the functioning of MRP/DCP for authorising Non-Prescription medicines. It provides information about best practice MRP/DCP procedures as well as details of approaches to managing Non-Prescription medicines within the MRP/DCP system, in order to inform all NCAs, applicants and Marketing Authorisation Holders (MAHs) of the options available. Guidance is also given on the role of the Reference Member State (RMS) specific to procedures involving a Non-Prescription medicinal product. This guidance is additional to the *CMDh Best Practice Guide for the Decentralised and the Mutual Recognition Procedures*, which applies to applications for both medicinal products subject to medical prescription (Prescription-Only) and Non-Prescription medicinal products. Annex 1 additionally addresses points to consider for reclassification from Prescription-Only to Non-Prescription of a medicinal product authorised through MRP/DCP.

3. References and Related Documents

- Directive 2001/83/EC as amended;
- The Rules Governing Medicinal Products in the European Union, Volume 2;
- Best Practice Guide for Decentralised and Mutual Recognition Procedures;
- Guideline on Changing the Classification for the Supply of a Medicinal Product for Human Use (The Rules Governing Medicinal Products in the European Community, Notice to Applicants, Volume 2C);
- CMDh Procedural Advice on Changing the Reference Member State;

4. Best Practice in Processing Applications for new MAs of Non-Prescription Medicines

4.1. Non-Prescription Contact Point

CMDh recommends that an identifiable Non-Prescription resource or contact point exists within an NCA to be used for assessment and/or as a reference point for other departments of the NCA.

4.2. Pre-procedural Phase

~~Pre-submission procedures set out in the CMDh Best Practice Guide for the Decentralised and the Mutual Recognition Procedures should be applied.~~

~~In addition, to~~**Scientific and/or regulatory advice**

To establish mutual interest in working together on an application and to facilitate a supportive role of the RMS, applicants ~~have the opportunity~~are encouraged to get scientific and/or regulatory advice with the proposed RMS well in advance but at least six months prior to submission of an application that include novel non-prescription properties in order to discuss the regulatory strategy and the timing for the submission.

CMDh rules for slot booking still apply. ~~-~~However, where it can be accommodated within a NCA's procedures, a slot may be agreed at the meeting.

The applicant should submit in advance a comprehensive briefing document with specific questions to focus discussions and so that the NCA can ensure that assessors with the relevant knowledge and expertise are present at the meeting. ~~-~~It is valuable for the RMS to know the ~~intended~~intention of the applicant regarding the classification of the specific medicinal product for which a MA is sought in all MSs concerned ~~MSs involved~~ in the procedure at this stage of providing advice. ~~-~~Therefore, the applicant should present the situation in the respective CMSs in the briefing document, in particular if they are proposing a novel classification in one or several MSs. Such an engagement is however not a pre-assessment.

~~As module 1 is the regional part of the dossier, the content should be harmonised across the EU. NCAs should not raise any national requirements beyond those they have stated in the most current version of the CMDh table of 'Additional Data Requested' (as detailed in the application form or published on the CMDh website).~~

~~Classification should not be part of the validation process, as it is to be considered during the assessment phase. However, acceptance of a valid application by an NCA should not be regarded as an agreement of the proposed classification which is a national issue. In circumstances where the proposed classification is not accepted by an NCA due to a conflict with the national rules, the applicant can withdraw their application if they do not want the MA to be granted with a different classification to that proposed in their application.~~

Discussions around the ~~brand~~product name are also part of the assessment and should not lead to invalidation or delay in the MRP or DCP timelines.

In relation to an application for authorisation of a generic product, as with all European procedures, where there is no Reference Medicinal Product authorised in a MS, the NCA should accept as a Reference Medicinal Product, a product that is authorised by another NCA or by the EC i.e. a European Reference Product (ERP). ~~-~~The classification of the ERP has no bearing on the classification of the ~~medicinal~~generic product; this remains a national issue.

Applicants should book a slot/submission date well in advance especially where specific manufacturing timelines are important for the Applicant (e.g. for seasonal products or on expiry of data exclusivity) Where possible, NCAs should seek to accommodate an appropriate submission date.

For new DCP applications, where the acceptability of the prescription status in CMSs is uncertain and it is **anticipated that the OTC and Prescription-Only SmPCs would differ,** two parallel DCP procedures should be initiated with an aim to having a Prescription-Only outcome in one stream and an

OTC outcome in the other. It is preferable, but not mandatory to keep both procedures with the same RMS.

The CMSs to be added to each stream should be considered accordingly.

For one product there can only be one set of common product information. Different strengths for a product can however have separate common product information.

4.3. The Application Submission

~~*4.3. 1.1. The Application Submission*~~

In addition to the documentation required for an application for a Marketing Authorisation through the DCP, a document should be submitted, which is separate from the clinical documentation, providing justification for Non-Prescription classification~~.~~ if the non-prescription classification is novel in any of the Member States concerned by the application, or the non-prescription properties of the product is extended, e.g. other indication or population (novel in this context is understood as new properties of a medicine regarding e.g. active substance, the therapeutic indication, the pharmaceutical form and the strength or the route of administration).

The justification document is essential for assessing non-prescription legal status.
Entitled, "Justification for Non-Prescription Classification" this document would be located in ~~Module~~module 1.2 and should contain all the supporting data and evidence required to justify classification of the medicinal product as not subject to medical prescription as set out in the *Guideline on Changing the Classification for the Supply of a Medicinal Product for Human Use*.

Having a specific place in the eCTD for documentation supporting non-prescription classification will facilitate the NCAs ~~validation and~~ assessment of ~~submisisons~~submissions.

If there are scientific supporting documents to be placed in the module 2-5 of the eCTD structure, for example a Clinical Overview in 2.5, the leaf title should indicate the purpose of the content (e.g. clinical-overview-OTC).

In case documents are placed in the module 2-5 of the eCTD structure, this should be indicated in the administrative background documents in ~~M~~module 1.2.

For further details see the CMDh Best Practice Guide on the use of the Electronic Common Technical Document (eCTD) in the Mutual Recognition and Decentralised Procedures (~~http://www.hma.eu/277.html~~http://www.hma.eu/277.html).

Validation phase

As module 1 is the regional part of the dossier, the content should be harmonised across the EU. NCAs should not raise any national requirements beyond those they have stated in the CMDh table of 'Additional Data Requested' as published on the CMDh website.

Classification should not be part of the validation process, as it is to be considered during the assessment phase. Therefore, validation of an application by a NCA should not be regarded as an agreement of the proposed classification which is a national issue.

4.4. Evaluation

~~4.4.1. Adherence to Timelines~~

~~As set out in the *CMDh Best Practice Guide for the Decentralised and the Mutual Recognition Procedures*, it is important that timelines are respected by all parties in all steps of the procedure, and that agreements made during MRP/DCP are respected by the MSs concerned after closure of the procedure.~~

~~Applicants should book a slot/submission date well in advance especially where specific manufacturing timelines are important for the Applicant (e.g. for seasonal products or on expiry of data exclusivity) Where possible, NCAs should seek to accommodate an appropriate submission date.~~

~~4.4.2.~~ 4.4.1. Assessment of the classification of a Medicinal Product

Assessors should have relevant experience and an appreciation of the specific nature of patient information for Non-Prescription medicines, which plays an important role in ensuring the medicines will be taken appropriately, safely and effectively without medical supervision.

To facilitate the assessment of classification of the medicinal product, anything affected by the ~~brand~~proposed non-prescription classification, e.g. the product name and patient information, should be addressed as part of the initial dossier and made available at the beginning of the procedure. ~~-~~These are key parts of the assessment.

In addition to complying with national requirements, the assessment should be undertaken with reference to the Commission Guideline: *Guideline on changing the classification for the supply of a medicinal product for human use*"

~~https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-2/c/switchguide_160106_en.pdf~~

https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-2/c/switchguide_160106_en.pdf

In circumstances where the proposed classification is not accepted by a CMS due to a conflict with its national rules, the applicant can withdraw their application if they do not want the MA to be granted with a different classification to that proposed in their application.

Sharing of classification Assessments

Where the application is for a product that contains an active ingredient, which would be classified as non-prescription for the first time in the RMS or had previously been reclassified in the RMS, the RMS is encouraged to provide to all CMSs, their full preliminary or previous assessment of the change of classification or a summary of their preliminary or previous assessment of the proposal from the applicant for non-prescription classification, where available. A summary of the RMS preliminary or previous assessment (clearly stating that this is their national position) should preferably be included in the Overview (section Legal Status) of the Assessment Report.

~~4.4.3.~~ 4.4.2. Role of the RMS

During assessment, reference should be made to the relevant Directive, ~~NtA~~Notice to Applicants and/or CMDh guidance documents as appropriate to resolve any disputes that may arise~~,~~. Early discussion at CMDh ~~should~~could be initiated by the RMS if any clarification is required e.g. where a consensus cannot be reached by MSs involved in the procedure~~.~~ regarding details in the common product information necessary to obtain non-prescription classification in one or more MS.

CMDh recognises that detailed discussion may be needed amongst NCAs concerned to reach consensus on indications~~, strength, dose~~ (including population), posology and safety information that may enable Non-Prescription classification to be possible when this is considered in the national phase. The RMS has an important role in facilitating the consensus on the SmPC for basis of approval and maximising opportunities for dialogue amongst NCAs but also involving the applicant as appropriate.

It is, however, recognised that consensus on classification is not required during assessment as classification remains a national competence.

5. Tracking of Legal Classification

~~The RMS should keep the MRI Product Index up to date in relation to the legal classification of products within the RMS.~~

~~CMDh recognises that whilst this does not provide a complete picture of legal classification across all CMSs, applicants~~Applicants will have access to limited but accurate information in the RMS and can build up a picture by searching on similar products/actives with different RMS and tracking the information on the NCA's website or from other national sources.

Annex 1

Applications for Reclassification of Medicines from Prescription Only to Non-Prescription

1. Clarity on Classification Procedures

Classification is a national matter and individual MSs have different procedures and fee structures for reclassification of medicines. ~~Applicants~~MAHs should ensure they understand the procedures in all MSs involved in the application. ~~-~~Details of national reclassification procedures ~~can~~may be found on each NCA's website.

2. The Application Submission

~~The~~A document providing data and evidence to justify non-prescription classification should be submitted and should be entitled, "Justification for Non-Prescription Classification" and ~~should~~shall be located ~~Module~~module 1.2 of the eCTD. If supporting documents are placed in the module 2-5 of the eCTD structure, this should be indicated in the administrative background documents in ~~M~~module 1.2. (See section 4.3 of the main document for more details)

3. Reclassification Process – Best Practice Points

3.1. Pre-submission Scientific Advice/ Regulatory Meetings

~~Applicants~~MAHs should indicate, at an early stage, their intention to seek reclassification of their product in the RMS and, as soon as possible, contact other MSs in which Non-Prescription classification of the medicinal product/active substance would require prior change of the ~~classification.~~product information. If it is established that it ~~–~~might be problematic to reclassify a product to Non-Prescription in the RMS and there is a realistic view to obtain non-prescription in at least 2 CMS, the applicant should consider starting a new MRP/DCP procedure for a Non-Prescription version of the product~~.~~ (See point ~~2~~5.3).

Any briefing document submitted at pre-submission stage should address all the requirements that need to be satisfied for a medicinal product to be reclassified from Prescription Only to Non-Prescription as detailed in the *Guideline on Changing the Classification for the Supply of a Medicinal Product for Human Use*. Risk minimisation measures and patient needs should be identified early. Therefore, at this stage, the conditions for Non-Prescription classification should be discussed – i.e. the combination of appropriate indication(s), target population, posology, pack size, warnings etc – to ensure safe and effective use in the non-prescription setting.

To ensure the NCA is best placed to discuss with the ~~applicant~~MAH the possibility of a successful procedure, the ~~applicant should also~~MAH is strongly recommended to prepare, for the advice meeting an overview of the classification of the product in all CMSs, including details of the differences between the SmPCs (Section 4.1, Section 4.2) and the relevant parts of the Package Leaflet (PL) in those MSs.

Where a reclassification application will involve assessment by different teams both at ~~applicant~~MAH and MS level, MSs and ~~applicants~~MAHs are encouraged to be flexible in their approach to pre~~-~~-submission meetings and facilitate input from all teams.

3.2. Specific Competence within NCAs in the Regulation of Non-Prescription Medicines

For reclassification applications, ~~applicants~~MAHs and NCAs should follow the principles in the *Guideline on Changing the Classification for the Supply of a Medicinal Product for Human Use*. In the regulatory process there are specific factors to consider in relation to the assessment of non-prescription medicines:

- A critical analysis of the medicinal product against the criteria for classification of a medicinal product as being subject to medical prescription;
- A benefit:risk analysis (to address the criteria for classification of a medicinal product as being subject to medical prescription) may be needed when deciding the suitability of a product for use without medical supervision;
- The product information (SmPC, label and package leaflet) need to be assessed for suitability for use without input from a prescriber;

3.3. Role of the RMS

As for all applications the RMS should lead the procedure, acting as the interface between the ~~applicant~~MAH and the CMSs and it is important that there is open, transparent and constructive dialogue between the ~~applicant~~MAH and the RMS. While there is no guarantee that the application for reclassification can be approved until full assessment of the ~~dossier~~application, the RMS is better placed to be supportive of the application if it has agreed the proposed Non-Prescription ~~model~~status in principle at the pre~~-~~submission/scientific advice meeting, and the ~~applicant~~MAH has submitted ~~a dossier~~an application in accordance with current requirements of legislation and European guidelines.

4. Sharing of Reclassification Assessments

To gain a better understanding of NCAs' approaches to Non-Prescription classification of medicines, NCAs are encouraged to share experiences and approaches to the assessment of applications for these products~~, for example, through Non-Prescription medicine workshops for assessors and Interested Parties~~.

~~For previously approved national reclassification applications, the RMS should be prepared to share, on request, its reclassification assessment with other NCAs who subsequently receive reclassification applications.~~

Where the application is for a product that contains an active ingredient, which would be classified as non-prescription for the first time in the RMS or had previously been reclassified in the RMS, the RMS is encouraged to provide to all CMSs, their full preliminary or previous assessment of the change of classification or a summary of their preliminary or previous assessment of the proposal from the applicant for non-prescription classification, where available. A summary of the RMS preliminary or previous assessment (clearly stating that this is their national position) should preferably be included in the Overview (section Legal Status) of the Assessment Report.

5. Examples of Possible Approaches to Reclassification

Where a request for reclassification of a product within a MRP/DCP cannot be accommodated by all NCAs, the following approaches can be considered. These are only suggestions, are not exhaustive and are not binding on MSs or Applicants.

5.1. Reclassification of an MRP/DCP product in a MS which requires no change or minimal change to the product particulars

If an applicant wishes to seek reclassification in a MS, of a product authorised by MRP/DCP and this will require no change to the harmonised dossier, or will only require additional national information on the labelling/package leaflet, the applicant may submit a national reclassification application. National changes required to the labelling/leaflet can be addressed by the NCA via the 'Blue ~~Box'concept~~Box' concept

5.2. Reclassification of an MRP/DCP product which requires more than minimal change to the product particulars and where the RMS is supportive of the reclassification

If an applicant wishes to seek reclassification from Prescription Only to Non-Prescription of a product authorised by MRP/DCP in the RMS and it is established that reclassification is possible in the RMS, the applicant may do this firstly by obtaining a duplicate MA. The changes to the product particulars required by that MS for Non-Prescription status could then be made by variation to this duplicate MA before starting a new MR procedure. A product authorised in this way may require a new name or distinct qualifier in line with national procedures.

5.3. Reclassification of an MRP/DCP product which requires more than minimal change to the product particulars and where the RMS is unable to support the reclassification

If an applicant wishes to seek reclassification from Prescription Only to Non-~~-~~Prescription of a product authorised by MRP/DCP and it is established that reclassification is not possible in the RMS, the applicant may apply for a separate DCP for a Non-Prescription version of the product, involving one or more of the CMSs and choosing a CMS to be the RMS for this procedure. This will result effectively in duplicate MAs in the chosen RMS and CMS(s) with separate prescription and non-prescription product particulars (SmPC, label and leaflet). In doing so the applicant must fully justify why a change in RMS is requested.

A product authorised in this way may require a new name or distinct qualifier in line with national procedures. If this procedure is adopted the RMS for the original Prescription Only product would not need to change as well.

The choice of the additional RMS should be undertaken in accordance with *CMDh Procedural Advice on Changing the Reference Member State*.