HOW TO CHANGE THE LEGAL CLASSIFICATION OF A MEDICINE IN THE UK

CONTENTS

MHRA GUIDANCE

HOW TO CHANGE THE LEGAL CLASSIFICATION OF A MEDICINE IN THE UK

1. INTRODUCTION

This guideline is aimed at companies considering applying to change the legal classification of a medicine in the UK, to help optimise submission of applications and thereby facilitate assessment and outcome.

In the UK, the default legal classification of a medicine is Pharmacy medicine (P). However new medicines, when first authorised, are usually restricted for use under medical supervision and made available only with a prescription; a medicine restricted in this way is classified as a Prescription Only Medicine (POM). If experience gained during use gives evidence to demonstrate that the medicine is safe for use without prescription control, reclassification as a non-prescription product may be undertaken. In some cases availability may be limited to supply under the supervision of a pharmacist as a P medicine, however if further experience demonstrates that access to professional advice is not required for safe use of the medicine, it may then be reclassified as a General Sale List (GSL) medicine to allow sale from a wider range of retail outlets. Following reclassification from POM to P or P to GSL, some products may be limited to specific indications with appropriate restrictions on strength, dose and pack size.

This guide aims to provide general advice on the procedures for changing the legal classification of a medicine, to help ensure a simple, speedy and transparent process wherever possible; it is not a complete and authoritative statement of the law. The European guidance "A guideline on changing the legal classification for the supply of a medicinal product for human use" (revised January 2006) is also relevant and can be accessed via the Commission's website in The Rules Governing Medicinal Products in the European Community – Volume 2C: Guidelines.

Both Marketing Authorisation (MA) holders and other interested parties (professional organisations, patient groups, etc) may submit reclassification applications; however it is important they hold the appropriate data and/or MA.

Requests for change of legal classification of medicines and associated policy matters are dealt with by the Vigilance and Risk Management of Medicines (VRMM) Division of the Medicines and Healthcare products Regulatory Agency (MHRA). Applicants are strongly encouraged to apply for a Scientific Advice Meeting (SAM), initially for preliminary advice, and later, as the application develops, to discuss queries and seek guidance and advice relating to a proposed reclassification, prior to submission. Guidance and advice from key experts is also strongly recommended prior to Scientific Advice Meetings.

The procedures, criteria for classification and data requirements for reclassification applications are detailed in the following sections of this booklet. Only applications that fulfil the criteria listed will be accepted as valid. For further information on the procedures or if the guidance does not appear to describe adequately any particular circumstance relevant to an application, please send an email to: reclassification@mhra.gsi.gov.uk.

2. BACKGROUND

The sale and supply of medicines is controlled by the Medicines Act 1968 and Directive 2001/83/EC as amended. All medicines marketed in the UK are classified according to one of the three following categories:

- Prescription Only Medicines (POM) – available only on a prescription
- Pharmacy (P) – available under the supervision of a pharmacist
- General Sale List (GSL) – available in general retail outlets such as supermarkets.

Appendix 1 includes information on the legislation and other information resources in the UK and EU on sale and supply of medicines for human use.

The criteria for classification of medicines as POM and GSL are laid out in more detail in Appendix 2.

The presumption under law is that all medicines are P unless they meet the criteria for POM or GSL classification. Pack size restrictions for certain products are listed in The Human Medicines Regulations 2012; in particular, P pseudoephedrine products (regulation 237) and GSL products containing analgesics such as paracetamol (Schedule 15). Pack size restrictions may be a requirement for reclassification for other products, if they form part of the risk minimisation measures, and this will be reflected in the MA.

Under The Human Medicines Regulation 2012, legal status for all licensed medicines is determined by the MA. There should be a separate MA for each legal status of the medicinal product.

The UK Licensing Authority makes decisions on legal classification for products granted through National, Mutual Recognition (MR) and Decentralised (DC) procedures. The European Commission (EC) makes decisions for products authorised through the Centralised Procedure. For products authorised through the Centralised Procedure, where necessary, the appropriate UK legal status and other national information will be confirmed on the outer packaging (in a 'Blue box') as set out in Article 57 of Directive 2001/83/EC.

3. OVERVIEW OF PROCEDURE

The key elements of the procedure which may help contribute to a successful outcome are outlined in Figure 1.

Only major applications are likely to require all the above elements e.g. ‘standard’ and ‘simple’ switches may not require scientific advice meetings or post approval data generation (see section 5 for definitions of ‘major’, ‘standard’ and ‘simple’ applications). However, on-going dialogue between the applicant and the Agency is encouraged throughout the regulatory process for all types of reclassification application.

Key Elements

Before submission

- Company selection and internal evaluation of switch candidate
- Preliminary Scientific Advice Meeting (SAM) with MHRA
- SAM with MHRA (when application further advanced)
- Compilation of the switch application – taking into account SAM meetings

Submission of application and MHRA Assessment

- Preliminary assessment of the application and allocation to process type by MHRA
- Stakeholder consultation for some Major applications (all ‘first in class’ or ‘first-time P/GSL indication’ applications, and others as appropriate)
- Commission on Human Medicines (CHM) advice for Major applications
- Publication on MHRA website for comment

Decision (approval/ refusal)

- Licensing Authority decision
    - If positive – implementation of the **Risk Management Plan (RMP)** as necessary
    - If negative, the applicant would have had the opportunity to appeal under procedures laid down in Schedule 11 of The Human Medicines Regulations 2012.

Life cycle maintenance

- may include further **data generation**, e.g. usage studies (as appropriate).

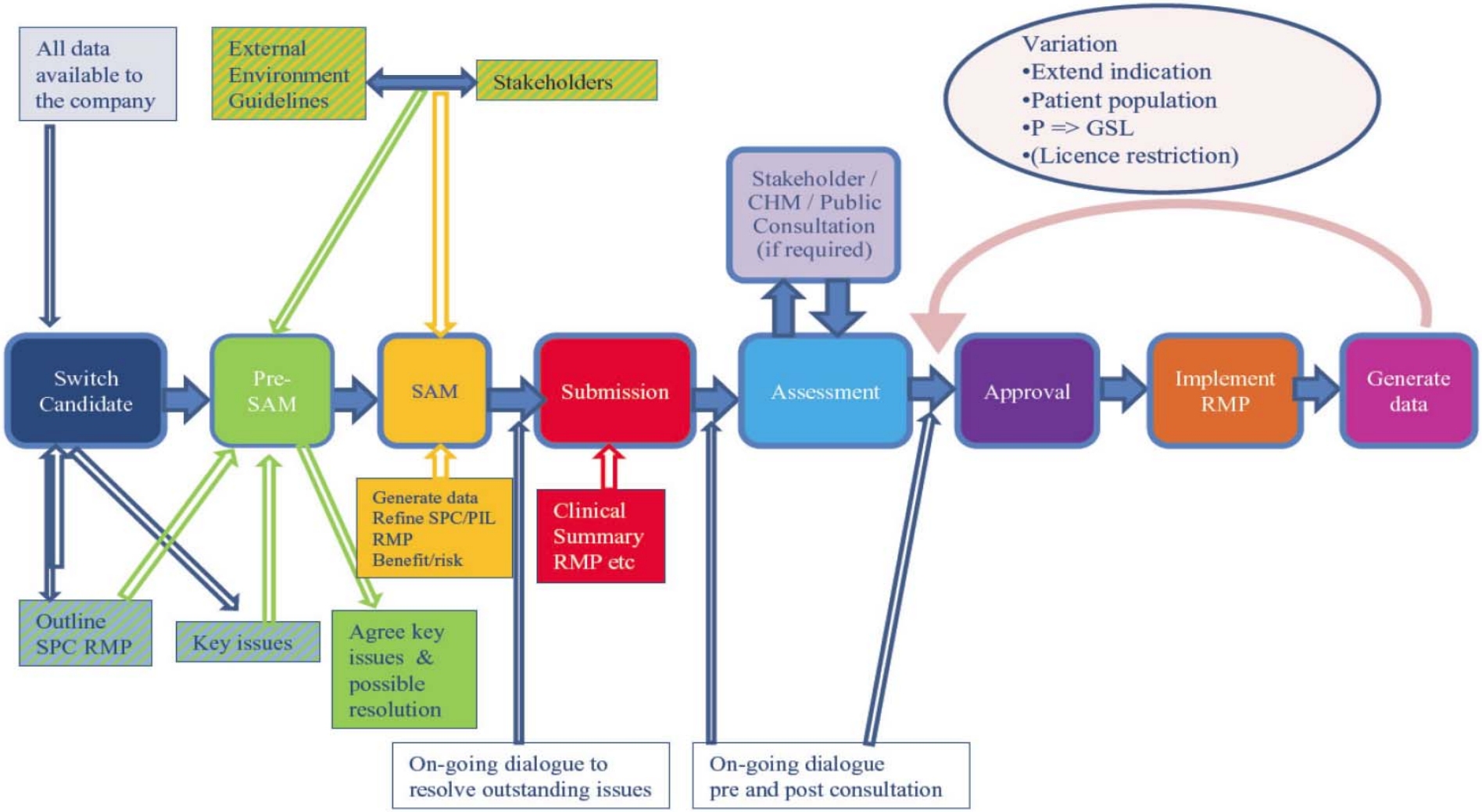


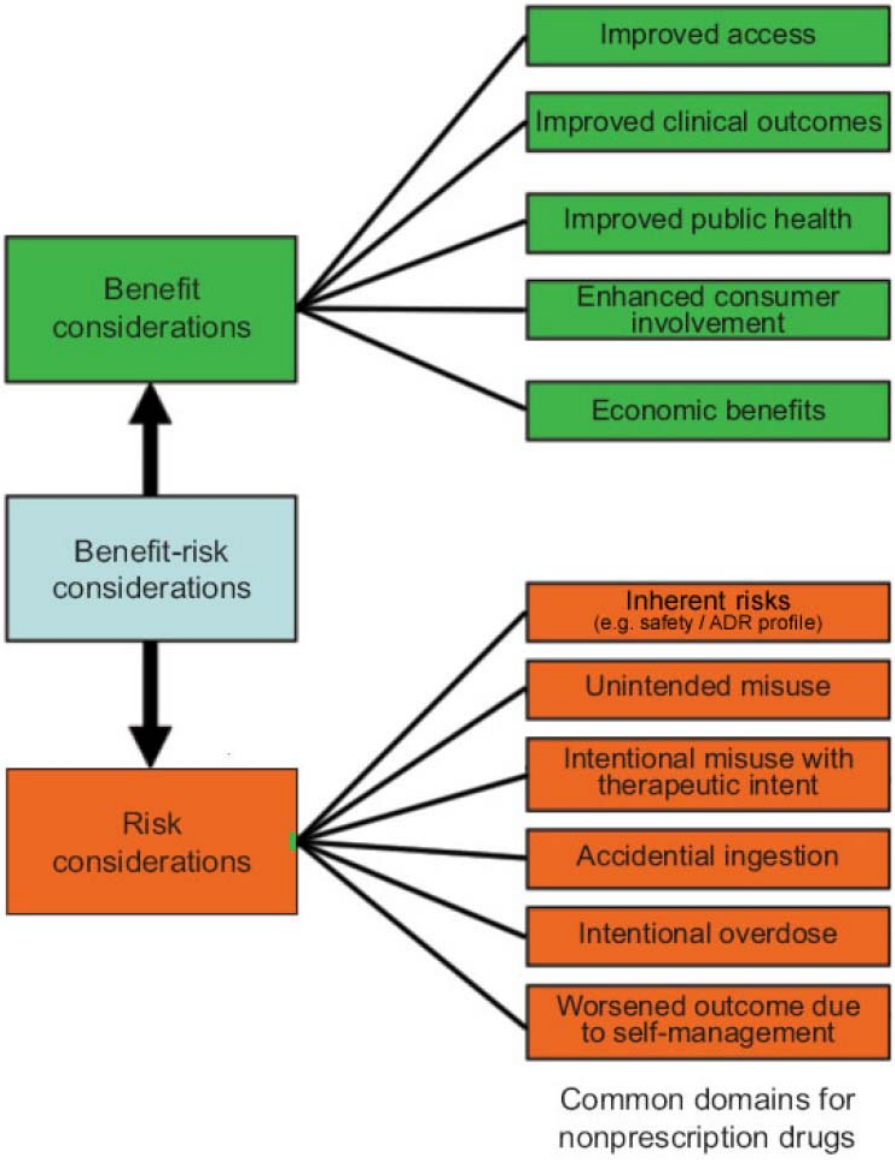
Figure 1: Key Elements of the Reclassification procedure

4 Before Submission

4.1 Evaluation of the switch candidate by applicant

It is essential that applicants thoroughly evaluate potential switch candidates prior to any meeting with MHRA. This early evaluation of the benefit: risk profile should take into account all data available to the applicant including; external expert advice, non-prescription availability in other countries and experience from previous switch applications. The evaluation will inform the production of a draft Summary of Product Characteristics (SPC), draft labelling and identification of potential gaps requiring further data generation.

A useful tool for conducting the benefit: risk analysis is shown below.



Common domains for nonprescription drugs

Based on Ref: E P Brass, R Lofstedt and O Renn. Improving the Decision-Making Process for Nonprescription Drugs: A Framework for Benefit – Risk Assessment
Clin. Pharmacol. Ther. 2011: doi: 10.1038/clpt.2011.231
A copy is available at: www.nature.com/clpt/journal/v90/n6/full/clpt2011231a.html

Early analysis using this framework will allow applicants to evaluate potential risk minimisation proposals which can then be discussed with MHRA. These might include for example proposals for reduced indications, pack sizes, target population, dose etc. Consideration should be given to refining the framework throughout the assessment process to take account of further information and advice, which may then be included as part of the application.

The evaluation of the switch candidate should include consideration of the potential for data exclusivity to be granted under Art 74a of Directive 2001/83/EC, as amended (see Section 5.5)

4.2 Scientific Advice Meeting(s)

For a Major reclassification application, the stage before submission is a key element of the procedure, during which the data requirements and content of the application will be established. An early stage preliminary SAM with MHRA is helpful to guide your approach to developing the proposed reclassification. Issues for discussion may include likely evidence required, additional studies, the Risk Management Plan (RMP) and potential for exclusivity. MHRA can also advise companies on the regulatory process and the timetable which might be followed including any expected public consultation time in any particular case.

The SAM phase (which may involve more that one meeting) is an important time to discuss the reclassification proposals in relation to e.g. drug, indication, dose, target population, pack size and name, and proposed controls for P or GSL supply as appropriate i.e. the RMP framework which may include changes to patient information, pharmacy training and educational materials (if required), data management and communications. The 'model' (proposed circumstances for non-prescription supply) should then be further developed by the company, based on the advice and input from MHRA.

In developing the 'model', it is strongly advisable in the case of innovative reclassifications, to have early involvement of interested stakeholders such as:

- Key opinion leaders
- General Practitioners with a special interest
- Pharmacists, representatives of pharmacy and/or other relevant professional organisations
- Practising healthcare professionals
- Patient representatives/organisations, as appropriate.

The aim would be to verify the non-prescription supply model, identify any special data requirements and highlight potential issues beforehand to ensure that a sound, well supported application is submitted with an appropriate risk minimisation plan.

The MHRA website includes information about how to apply for a SAM. When requesting a meeting, the applicant should specifically mention known issues relating to the proposed reclassification, so that appropriate MHRA staff can be identified at an early stage and take part in the meeting.

At the meeting the application type (Major, Standard, Simple) will be agreed provisionally and, where the SAM concerns a well developed reclassification proposal, an outline timetable for assessment will be defined by the MHRA identifying key milestones, with agreed timing and frequency of communications (in both directions).

Meetings designed to discuss POM to P switches may also address future P to GSL reclassification in which case the proposed timetable for any subsequent reclassification application may also be discussed.

Advice meetings are not compulsory but are at the discretion of the applicant and may be particularly helpful for POM to P (or POM to P, then GSL) than for P to GSL switches.

Advice meetings are less likely to be needed in the case of Simple applications.

The pre-submission phase may range between a few weeks and several years depending on the complexity of the proposed switch and available evidence.

Note: Fees for SAM meetings
Fees are payable for SAM meetings, as set out on the MHRA website (http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Informationforlicenceapplicants/Otherusefulservicesandinformation/Scientificadviceforlicenceapplicants/index.htm).

5. Application Development and Submission

When planning to submit a reclassification application it is important to identify:

- the correct type of application to be submitted, which depends upon the nature of the proposed reclassification
- the most appropriate route to achieve the desired outcome, e.g. new MA or variation to existing MA.

5.1 Types of Reclassification Application

There are three types of reclassification applications which reflect the process used to reach a decision. An applicant may decide on the appropriate application type based either on the advice given during a SAM, if one has taken place, or on the information below. In all cases the type will be confirmed by MHRA post validation of the application. Further information on the content of reclassification applications may be found in section 5.5 and Appendix 3.

MAJOR - a major change requiring referral for expert advice within the Agency will be allocated to this procedure, for example the first in a new therapeutic category or a new target population for an existing product. This would normally have been agreed during the SAM phase.

A 'Major' may be converted to a **STANDARD** application if during assessment it is decided that referral to an expert advisory committee is not necessary, for example for the second product in a therapeutic category, providing no significant differences in the safety profile. The standard category only applies to applications previously submitted as a MAJOR application. Advice on possibility of this route would have been considered during the SAM phase.

SIMPLE - a "me-too" application, based on an analogous product which has already completed the reclassification procedure, is submitted as a Reclassification variation (analogous product); this may be either a Type IB or Type II variation, depending upon the nature of the proposed changes to the product information.

For these purposes, an analogous medicinal product is a medicinal product which has a UK marketing authorisation or a marketing authorisation granted through the EU Centralised Procedure and which:

- has the same active ingredient, route of administration and use; and
- has the same strength or a higher strength; and
- has the same dosage or daily dosage, or a higher dosage or daily dosage; and
- is for sale or supply at the same quantity or a greater quantity, as the medicinal product in relation to which the application is made.

An application for a product with a different pharmaceutical form will be considered on an individual basis and may not be eligible to be considered an analogous product.

See section 6 for details of the assessment process.

5.2 Fees

For each of the above application types, the fee is based on the work involved. A higher fee is payable on all Major applications requiring referral to the CHM. For a Standard application the full Major fee is charged on initial submission but where the reclassification does not need to be considered by an advisory group or the CHM, half the fee will be refunded to give a Standard fee.

If there is an analogous product already granted with the proposed classification (see above), a Reclassification variation (analogous product) fee will be payable.

Actual fees may vary from year to year. Please check the MHRA website fees page.

Bulk fees are applicable when the same applicant makes the same changes to more than one product at the same time, having the same active(s).

5.3 Timetables

For major reclassifications, indicative timelines will be set out (for example following SAM meetings), to provide predictability in relation to the reclassification process as a whole. In general, the timetable will be based on the published timelines for the type of application submitted, with additional periods to allow for the time to arrange a Stakeholder Group meeting prior to CHM consideration and/or public consultation.

For analogous product variations, depending upon the route used to submit the application, i.e. Type IB, or Type II, the usual timelines will apply.

5.4 Application Routes

UK National, Mutual Recognition and Decentralised Procedures
For National, MR and DC products, reclassification applications may be submitted via the following routes:

- variation of an existing MA
- in conjunction with an abridged application (where retention of the POM or P MA is desired, see below)
- creation of a duplicate MA followed by a variation to change the legal classification.

To retain a POM product without some of the restrictions proposed for the non-prescription product (such as pack size or indication), a new MA application rather than a variation to the existing MA must be submitted. The applicant will then have a separate MA on which to base the reclassification application.

Please note that where products of identical composition exist as both POM and non-prescription products, with different indications, contraindications and/or warnings, the two MAs must be distinguishable by invented name since it would give rise to safety concerns for the two products to exist under identical names. Further information is available in the MHRA guidance on naming of medicines.

Where a change in legal classification is due only to a difference in pack size of the medicinal product but all other aspects of the marketing authorisations are the same, the same brand name can be used for the products. The two authorisations will need to be maintained such that no divergence between the authorisations will take place. If divergence takes place at a later date a new brand name will need to be used for the divergent authorisation.

Note:
The legal classification of MAs authorised via the Mutual Recognition (MR) or Decentralised (DC) procedures are determined nationally. Reclassification applications for such products are likely to require special consideration and applicants are advised to seek advice from MHRA at an early stage.

Centralised Procedure
Reclassification applications for centralised MAs are submitted to the European Medicines Agency (EMA). Applicants are advised to seek further information from EMA (www.ema.europa.eu).

5.5 Content of Reclassification Applications

Major and Standard Applications

The reclassification application should consist of the following elements. The content of the individual elements will vary depending on the type of application and whether it is POM - P or P – GSL. Appendix 4 contains full details.

- Product Information (SPC, labelling and patient information leaflet)
- Reclassification Clinical Overview - a critical evaluation of the proposed non-prescription product demonstrating that none of the prescription criteria apply or in the case of an application for GSL supply that the product can be sold or supplied with reasonable safety without pharmacist supervision
- Risk Management Plan (RMP) - outlining the important risks associated with the reclassification of the product and the proposals to manage these risks such as clear product information and in some cases other measures including any provisions for appropriate education and training for pharmacists and pharmacy staff.

Companies must provide all references in full.

Simple Applications

Depending upon the circumstances, these may be submitted as either Type IB or Type II applications and should be consistent with current variations guidance under change code C.1.5 which has been adopted in the UK.

A straightforward Type IB (change code C.1.5a) application should include:

- the details of the analogous product, e.g. SPC
- the SPC, updated as appropriate
- the proposed labelling
- the proposed patient information leaflet.

For SPC changes other than to Section 4 (e.g. name change, pack size) separate variations should be submitted, according to the usual procedures.

If the simple application involves a number of complex changes to the SPC, label and leaflet, or if additional evidence to support the application is required, such as bioequivalence data, a Type II application (change code C.1.5.b) would be more appropriate. This route provides greater flexibility in relation to timelines and opportunities to optimise the application.

Data Exclusivity

Article 54 of Directive 2004/27/EC amends Directive 2001/83/EC, inserting a new Article 74A which allows for one year's data protection following the change of classification of a medicinal product. Should an applicant submit the results of pre-clinical tests or clinical trials (normally this would be part of a Major application) and those data are the basis for the change in legal classification, the competent authority (in the UK, this is the MHRA) shall not refer to those data when examining an application by another applicant for the same substance for one year after the initial change. In order for this to be applied, the data must be pertinent, specific and integral to the argument for a successful switch. The data must be fundamental to the assessment of the switch application. MHRA guidance on the application for exclusivity for change in legal status of a medicine should be referred to.

6. Assessment by MHRA

6.1 Major Applications

Stakeholder Advice

After validation, applications allocated to the Major route will be assessed by MHRA and, subject to any further data being requested beforehand, may then be considered by a specially constituted Stakeholder Group of those most affected by the reclassification. Membership will include individuals with expertise in supply and usage of non-prescription medicines, supplemented by therapeutic expertise for the particular switch under consideration and patient group/lay representatives. The group will consider the regulatory issues, the clinical/pharmacy delivery and the patient view of the switch.

Referral to CHM

Following the Stakeholder meeting, if applicable, the application will be considered by the CHM for advice; views may also be sought from an EAG of experts in the field.

Further, the CHM will be asked to advise, when considering a POM to P reclassification application, whether subsequent P to GSL reclassification might be approvable; and, if so, under what conditions – these might include the extent of non-prescription usage (time on market, patient exposure or other conditions), monitoring of actual non-prescription use (e.g. appropriate selection, appropriate use), or other post-marketing data which may, in many instances, be linked to the RMP.

Public Comment

Publishing information about potential reclassifications prepares healthcare professionals, and the public, for a possible reclassification and provides an opportunity for new issues to be raised:

- this will generally take place if the product is the first in class to be reclassified or where the indication is new for P (or GSL) supply, but may take place in other instances depending on particular circumstances
- the MHRA will seek comments from interested parties, taking into consideration the key points which have already been raised in the Stakeholder and CHM advice (with a focus on seeking any additional points in relation to the proposed reclassification).

A report of the stakeholder consideration if any, the CHM advice, a summary of the RMP and the key issues discussed will be published on the MHRA website, consistent with transparency policies; it will be available for a fixed period of 21 days for comment.

The report will outline the terms of the reclassification (POM -P/GSL, POM-P or P-GSL) and seek views on whether the proposed reclassification model and RMP are sufficient to support the switch. Applicants will have an opportunity to contribute names of organisations/groups specifically to be approached for comment.

If new issues have arisen at any point MHRA may wish to refer them to CHM for review before the Licensing Authority determines the application. This may extend processing time.

When all outstanding issues have been resolved, the application will be approved.

6.2 Standard Applications

After validation any Major application will be reviewed to assess whether there is a suitable precedent already established to provisionally allocate it to the Standard route, without the need for expert advice, e.g.

- the second in a therapeutic class where the safety profile does not differ significantly from a product already available as a non-prescription medicine
- a pack size change which does not impact on the safety profile.

Following MHRA assessment of the application, the applicant may be approached for additional information to clarify specific issues.

On completion of the assessment of all data submitted, the applicant will be informed of the outcome.

Applications will be submitted for formal review by CHM if the assessment of the supporting data raises issues of sufficient concern that the application is not considered approvable, or expert advice would benefit the review. In such cases a separate stakeholder group would not be necessary, although use could be made of existing Expert Advisory Groups (EAGs) as necessary.

The applicant will be informed if expert advice is to be sought; it is likely that the time to final determination will be longer and the route outlined for a Major application will be relevant.

6.3 Simple Applications

Simple “me too” reclassifications (not supported by full data) for products where an analogous product has already been reclassified, are processed through the usual Type 1B (change code: C.1.5a) or Type II (change code C.1.5.b) variation procedure.

7. Decision

7.1 Completion of Application Procedures

The applicant will be informed of the outcome once a decision has been made. Where an application for POM – P with a proposal for eventual reclassification to GSL has been submitted an initial approval may be granted limiting supply to pharmacy only until such time as the conditions for GSL status are fully met.

Favourable decisions on applications will be implemented depending on the type of application submitted, by including the new legal classification in the grant of the new MA, or by variation to the existing MA. Successfully reclassified products assessed via the Major/Standard routes will then be listed on the MHRA website.

Where the CHM has advised against an application, the applicant will be sent the reasons, together with the assessment report. Applicants will be given the opportunity for a hearing before CHM.

When a reclassification involving a Major or Standard application is granted, a copy of the Public Assessment Report (PAR) will be available on the MHRA website.

8. Action after approval

8.1 RMP Implementation

See Appendix 3 Section c For information about the content of Risk Management Plans.

Certain reclassifications may be granted with conditions that require the applicant to undertake specific risk management activities after approval. The types of activities which may be required include training, education, pharmacy sales protocol, public advice, consumer support programmes, monitoring of actual non-prescription use. The detail and timelines for the activities together with any requirements for reporting will be agreed between the applicant and MHRA. Specific post marketing activities are more likely to be required for POM to P reclassifications than for P to GSL switches.

Where post marketing studies have been agreed, to confirm safe supply in a non-prescription setting, these may have an impact on the introduction of analogous or similar products while studies are on-going. For example, where a company has committed to undertake additional monitoring in order to validate the results of a study, there may be limited opportunity for further presentations not subject to the same controls. This is considered by MHRA on a case by case basis.

8.2 Data Generation

Additional restrictions to the product may be required (e.g. revisions to labelling) following the outcome of the RMP, such as the results of further studies conducted by the applicant and/or additional experience of the product in use. On the other hand generation of new data may allow for extensions of indications, target population or removal of the requirement for a sales protocol. Further, actual use experience in the pharmacy setting may support reclassification from P to GSL (see Appendix 2).

Appendix 1

LEGISLATION AND OTHER INFORMATION RESOURCES IN THE UNITED KINGDOM AND EU ON SALE OR SUPPLY OF MEDICINES FOR HUMAN USE

UK

- Council Directive 2001/83/EC as amended by Directive 2004/27/EC.
- The Human Medicines Regulations 2012
- The Prescription Only Medicines (Human Use) Order 1997 (The POM Order)
- Fees Regulations

EU

- Risk Management Plans: Good pharmacovigilance practices: Module V Risk management systems provides information on content and structure
- A GUIDELINE ON CHANGING THE CLASSIFICATION FOR THE SUPPLY OF A MEDICINAL PRODUCT FOR HUMAN USE (January 2006) (http://ec.europa.eu/health/files/eudralex/vol-2/c/switchguide_160106_en.pdf)

Other Resources

- E P Brass, R Lofstedt and O Renn. Improving the Decision-Making Process for Nonprescription Drugs: A Framework for Benefit – Risk Assessment *Clin. Pharmacol. Ther. 2011: doi: 10.1038/clpt.2011.231*
  An abstract is available at:
  www.nature.com/clpt/journal/v90/n6/full/clpt2011231a.html

Appendix 2

MEDICINES CLASSIFICATION CRITERIA

Criteria for classification as a Prescription Only Medicine (POM)

Article 71 of Directive 2001/83/EC as amended specifies the criteria by which Member States should classify medicines into those subject to medical prescription and those not subject to prescription control.

A medicine will be non-prescription unless it fulfils the criteria for prescription control as set out below.
Prescription only status will apply where:-

- a direct or indirect danger exists to human health, even when used correctly, if used without medical supervision; or
- there is frequently incorrect use which could lead to direct or indirect danger to human health; or
- further investigation of activity and/or side-effects is required; or
- the product is normally prescribed for parenteral administration.

In the UK the POM criteria are laid down in the Human Medicines Regulations 2012, regulation 62(3).

2. Exemptions from prescription control may be made having regard to:

(a) the maximum single dose;
(b) the maximum daily dose;
(c) the strength of the product;
(d) its pharmaceutical form;
(e) its packaging; or
(f) such other circumstances relating to its use as may be specified in the determination.

Criterion for General Sale List classification (GSL)

Under the provisions of The Human Medicines Regulations 2012, regulation 62(5), GSL is appropriate for medicines which can, with reasonable safety, be sold or supplied otherwise than by or under the supervision of a pharmacist.

The term “with reasonable safety” has been defined as: “where the hazard to health, the risk of misuse, or the need to take special precautions in handling is small and where wider sale would be a convenience to the purchaser."

Eye ointments are excluded from GSL and the following classes of products are not usually GSL but may be considered on a case-by-case basis: -

- Anthelmintics
- Parenterals
- Eye drops
- Enemas

- Irrigations used wholly or mainly for wounds, bladder, vagina or rectum
- Aspirin or Aloxiprin for administration wholly or mainly to children

Under The Human Medicines Regulations 2012, GSL medicines can be sold from a range of general sale premises, such as supermarkets, provided those premises can be closed to exclude the public (i.e. they are lockable) and the medicines are pre-packed in their original containers.

Appendix 3

CONTENT OF RECLASSIFICATION APPLICATIONS

1. POM to P Reclassification Application

a) Patient Information (CTD Module 1.3)

The proposed Summary of Product Characteristics (SPC) should be submitted, together with mock-ups of the proposed packaging and Patient Information Leaflet. The results of PIL User Testing Study will also be necessary, before approval of the application.

Labels and leaflets used for the existing product will normally require amendment to ensure safe use as a P or GSL product. Clear instructions to aid correct diagnosis and prevent misdiagnosis will be needed. Additional precautions and warnings may be necessary, e.g. the action to be taken if no response is obtained and the circumstances requiring pharmacist and/or medical advice.

Promotional material should comply with legislation and with self-regulatory procedures in operation. It is helpful for advertising plans to be briefly outlined and MHRA may further require pre-submission, of material for vetting before issue.

b) Reclassification Clinical Overview (CTD Module 2.5)

This should be included as part of the Clinical Overall Summary, or as appropriate. The Expert is expected to:

- provide a general overview of the product's efficacy,
- make an objective and impartial assessment of the application in the light of current scientific knowledge and
- to confirm that the safety data provided is adequate to support reclassification, evaluate the overall benefit: risk profile of the proposed reclassification (the benefit: risk model in Section 4.2.1 may be a useful reference) and discuss how the RMP addresses potential outstanding risks.

Risks and benefits, both direct and indirect, should be discussed with reference to the current usage of the product in the prescription setting or pharmacy setting, as appropriate. The proposed changes to the product information and supply of the product associated with the reclassification should be justified in the context of the existing circumstances of supply.

• Benefit Risk Profile:

Detailed information on undertaking a benefit risk assessment for non-prescription medicines may be found in a paper by Brass et al referenced on page 5 of this guide.

Undertaking a robust assessment of the benefit risk profile of the proposed switch is essential; it can facilitate a shared understanding of the proposal between the company and MHRA and will help inform decisions throughout the switch process.

Each proposed switch will have a unique set of 'benefits' and 'risks' and it is important that these are characterised and captured and then assessed.

Benefits
It is generally agreed that the benefits of non-prescription medicines relate to;

- Improved access
- Improved clinical outcomes
- Improved public health
- Enhanced consumer involvement in healthcare
- Economic benefits

Some of these are direct benefits for the individual themselves while others are indirect benefits to the wider population such as improvements in public health, for example the OTC availability of Emergency Hormonal Contraception enables prompt treatment (within 72hours) in a situation where efficacy decreases over time.

It is important that consideration is given to the overall public health benefit as well as potential benefits of wider access to the product and the potential for wider access to information by the public. Suitable justification should be provided for the use of all submitted data (which may include experience in other member states) to underpin the reclassification application

Risks

First POM Criterion:
Likely to present a danger either directly or indirectly, even when used correctly, if utilised without medical supervision

- **Direct danger**

A direct danger may be present if the product causes adverse reactions that are important because of their seriousness, severity or frequency or because the reaction is one for which there is no suitable preventative action such as the exclusion of a clearly identifiable risk group. In addition to the product's safety profile, it may be helpful to consider the benefit-to-risk in relation to that for similar products already available as Pharmacy medicines for the same indication. One member of a class that causes adverse reactions more frequently than other members of the class may be unsuitable for reclassification for the same indication.

Consideration should also be given to the danger arising from drug interactions with commonly used medicines and how these may be prevented.

- **Indirect danger**

An important example of an indirect danger is when symptomatic treatment might mask an underlying condition requiring medical attention, for example cancer or heart disease. Consideration should be given to whether an indirect danger might exist and if so, whether the risk, its frequency and the seriousness of the consequences would make reclassification unacceptable. Additional warnings such as a recommendation to seek medical advice if symptoms persist beyond a stated time period may be necessary in such instances.

Another important example of an indirect danger would be the increased risk of development of bacterial resistance in the community as a result of wider use of antibiotics without medical supervision. Consideration should be given to ways of ensuring or demonstrating that the risk will not be increased.

Treatments may also present an indirect danger when particular symptoms are outward manifestations of a diverse range of underlying pathologies. If the patient cannot easily self-diagnose the cause of such symptoms it may be inappropriate to provide symptomatic treatment without management of the underlying disease. Special attention should be paid to the possibility of serious asymptomatic damage in chronic conditions.

- **Self-diagnosis**

It is important that the conditions or symptoms for which the product is indicated can be correctly diagnosed without medical supervision or can be easily recognised following initial medical diagnosis. The problem of excluding conditions with similar symptoms but unsuitable for treatment with the product in question may need to be addressed. The ability to correctly self-diagnose may be influenced by:

- Appropriate product information (label and/or leaflet)
- A consultation with the pharmacist which may involve completion of a suitable questionnaire and/or use of a diagnostic kit.

Patients should be able to understand the natural course of the disease and the possibility and consequences of reoccurrence. They should also be able to recognise contraindications and understand essential precautions and warnings. Experience in such issues in relation to other medicines in a related therapeutic area may provide important supplementary information.

- **Risk of misuse**

A high incidence of conditions listed as contraindications, extensive precautions and warnings or a high rate of usage of interacting drugs in the population of patients likely to use the drug may increase the incidence and risk of misuse.

It is important that the danger to health is small if the patient uses the product when it is not indicated, exceeds the recommended dose or recommended length of treatment or fails to heed the contraindications or warnings. Consideration of the consequences of misuse is an important component of the overall safety profile of the product. Concerns over the risk of misuse are lessened where the product causes only few, non-serious side effects. In this situation, while the risk-to-benefit may be unfavourable to the patient who uses the product incorrectly, the overall benefit-to-risk for availability of the medicine in the community without prescription may be favourable.

It may also be necessary to consider whether incorrect use might lead to an indirect risk, e.g. a delay in seeking medical treatment, and if so, whether the consequences to the patient would be important.

Second POM Criterion:
Frequently and to a very wide extent used incorrectly, and as a result are likely to present a direct or indirect danger to human health

When a product or substance is known to be used frequently incorrectly, pharmacy status is not appropriate. Recognised widespread misuse of a product or substance classified as a pharmacy medicine could lead to its reclassification as a prescription medicine.

Third POM Criterion:
Contain substances or preparations thereof the activity and/or side-effects of which require further investigation

- **Limited experience**

Further investigation is likely to be necessary where the number of patients exposed is relatively small, for example when a medicine has only recently been authorised, because there is limited experience of the product under normal conditions of use. Even if clinical trial data are extensive and reassuring, it is important to have evidence of safety where the product is being used without the exclusion of certain groups of patients imposed by the design of clinical trials (e.g. the elderly, children and those with certain medical conditions).

- **New strength, dose, route of administration, age group or indication**

Further investigation is also necessary where it is proposed that the substance will be available without prescription as follows: -

- in a new strength,
- at a new dose,
- using a new route of administration,
- exposing a different patient age group, or
- for a new indication, particularly when the indication has not been previously authorised for a non-prescription product.

Even though the safety and efficacy profile of the medicinal product as it is presently marketed is relevant, re-evaluation of benefit-to-risk according to the proposed use is necessary. This may be difficult because the product will not have been widely available for the new indication or new dosage. It may nevertheless be possible to extrapolate from the known safety of the existing prescription product, particularly if there are few side-effects and/or where doses proposed for non-prescription supply are lower and the population is a sub-group of the patient group treated on prescription.

Fourth POM Criterion:
Are normally prescribed for parenteral administration

Parenteral administration involves breaching the skin or mucosa. As a general rule products for parenteral administration are not appropriate for availability without medical supervision because of the additional risks and complexity of this route of administration.

- **Additional Considerations for the Expert**

The Expert may need to take account of the other factors that influence legal status as outlined in Directive 2001/83/EC (see paragraph 2 & 3 of Appendix 1). This includes whether the substance is a narcotic or a psychotropic substance or might be abused leading to addiction or misused for illegal purposes. Supply without a medical prescription may be acceptable if additional restrictions are introduced. e.g. limiting the maximum single dose, the maximum daily dose, the strength, the pharmaceutical form, the circumstances of use, and the type of packaging and/or pack size.

If restrictions to the maximum dose or maximum daily dose are introduced in order to protect against a danger when the medicine is used either correctly or incorrectly, it is necessary to confirm that the restricted dose retains the efficacy and the favourable benefit-to-risk of the full dose.

Consideration should also be given to the need for restrictions on the strength, pharmaceutical form, circumstances of use, pack size, or a combination of these in order to provide a safeguard against incorrect use including overuse or overdose or against a delay in seeking medical attention. When pack size is restricted, the proposed pack must be compatible with the intended indication and its likely duration of use.

The Expert should critically evaluate the proposed non-prescription product in the light of the criteria for prescription control and demonstrate why none of the criteria apply.

Efficacy data is only required when indications, dosages or age ranges differ from the authorised product. Pharmacokinetic or pharmacodynamic data are required if a different pharmaceutical form is used. Any new data should be submitted in accordance with the existing CTD format.

Where relevant, the conditions for GSL availability should be considered at the time of reclassification from POM to P, with a wider review of the risk management tools that have traditionally been used - e.g. pack size, duration of use and patient population - to ensure that any restrictions in the P or GSL setting reflect the actual use of the product in those settings.

Proposal for Data Exclusivity

Where data have been submitted which form the basis of a proposal for data exclusivity under Art 74a of Directive 2001/83/EC as amended, expert comment should be provided. In particular, the significance of the data should be addressed with a justification for its importance to the proposed reclassification.

Expert comment on the Label and Patient Information Leaflet

In all cases labelling and patient information leaflets must be supplied which are compliant with Directive 2001/83/EC as amended.

The proposed product label and patient information leaflet are important elements of the application and should be reviewed by the Expert to confirm that clear and comprehensive information has been provided which will effectively protect patients from any safety hazards.

The patient information leaflet should take full account of the circumstances of use and should provide warnings, as appropriate for use without medical supervision. e.g. limiting duration of treatment, when to seek health professional advice etc.

The written information should effectively minimise the risk of use where a product is contraindicated or where problems could occur. The Expert should ensure that adequate instructions are included and that all contraindications, precautions and warnings are clearly described in lay terms and prominently printed in the leaflet. The patient is likely to need guidance on action to take if the medicine does not have the desired effect or causes adverse effects. The Expert should ensure that appropriate action by the patient is recommended to provide for the absence of health professional supervision.

c) Risk Management Plan (Reclassification) (CTD Module 1.8)

The Risk Management Plan (RMP) should include a Safety Specification, the Pharmacovigilance Plan a summary of efficacy and any plans for post-authorisation efficacy studies, Risk Minimisation Measures and a summary for the lay reader (which will be published). The aim of the RMP is to protect consumers from known risks, by suitable amendments to the product information and to put forward a plan for managing risks identified and safety monitoring, as necessary.

Regulatory and Scientific guidance concerning the content of the RMP is provided in the Good pharmacovigilance practices (GVP) section of the EMA website, Module V (Risk Management Systems).

The emphasis will be on using the RMP to structure the dossier: identifying the risks involved in non-prescription supply, perhaps in a new/wider patient population, and setting out the ways in which the risks can be minimised e.g. by providing more detailed information on packaging and in the Patient Information Leaflet.

As the Risk Management Plan is a living document, some requirements set out in it (such as a specific pharmacy protocol or a questionnaire introduced for example when a product was first reclassified from POM to P) may be simplified or may no longer be required once sufficient experience of non-prescription availability has been accumulated.

Unless there is a clear risk management rationale for restrictions in the GSL setting, with the exception of analgesics, all P pack sizes would be permitted for GSL supply if the P to GSL reclassification is approved.

Whilst it is a regulatory requirement to use the EU-RMP template to prepare an RMP there may be sections in the RMP that are not relevant for the purposes of the reclassification, this should be discussed and justified in the RMP, if appropriate seek advice from MHRA.

Part I – Product Overview
An introduction and background to the product.

Part II - The Safety Specification
This should define the knowledge about the safety of the product, how the product has been used within the current licensed indication and how it would be expected to be used in the situation of a reclassified product (i.e. the epidemiology of the indication). The identified and potential risks should be included here, together with a discussion of the limitations of the safety database.

The information provided here should:

- Be backed up by the safety profile of the drug, the cumulative exposure, taking account of data from clinical trials and post marketing experience (the most important aspect).
- Show how the proposed new non-prescription population might differ from the previous population, and how the safety data from the previous population is still applicable to the new non-prescription population.

Applicants should provide an estimate of the number of people using the product under the current legal classification compared to the anticipated number of people using the product under the proposed classification.

The extent of the supporting safety data required will depend on experience with the product and the availability to the applicant of recent Periodic Safety Update Reports (PSURs). Where available, summaries from PSURs already submitted to MHRA should be provided with full bridging data for the intervening period. If the application is made within 5 years of marketing, the PSUR summaries should be drawn together ahead of the 5-year date. It is not necessary to resubmit the complete PSUR.

Experience in terms of patient exposure to the product needs to be considerable allowing the safety profile to be fully established. Full details of availability, classification for sale and patient exposure should be provided for all countries where marketed. Data from non-prescription supply in another country may be of value. Normally, substances suitable for GSL classification will have been in widespread use in the UK, in P products. Comparison of safety with other drugs having GSL availability in the UK for similar indications may be helpful.

A safety profile should be drawn up based on the following data: -

- Spontaneous reports of adverse reactions
- Post-marketing surveillance studies
- Clinical trials
- Published literature
- Safety reviews
- Non-prescription supply of the same or similar products in other countries

Data obtained in the UK should be distinguished from that obtained from other countries and, for non-UK data, details must be provided in relation to differences in

product or usage characteristics. All cited references must be provided in full with translations where applicable.

Adverse drug reactions to non-prescription products should normally be minor and should cease on discontinuing therapy. Information concerning serious type A and type B reactions experienced should be given and discussed. The problems of extrapolating data from a 'prescription only' population to a 'non-prescription' population should be addressed, where possible. Comparison of safety with other drugs available in the UK without prescription may be helpful.

In the presentation of important identified and potential risks, a specific discussion of any risks associated with switch from POM to P status or from P to GSL status (e.g. use outside the proposed pharmacy model or off-label use) should be included.

Where pharmaceutical forms or doses to be used have received only limited use, it may be possible to extrapolate from data relating to other presentations and full justification for this approach must be given when used.

Reports of therapeutic overdose, misuse or abuse whether deliberate or accidental, should be reviewed. Symptoms and hazards of overdose and other misuse should be clearly described and recommended treatments given, where appropriate. In the case of misuse, the consequence of delay in seeking medical attention should be addressed.

Drug interactions may have additional consequence for non-prescription products and these should be reviewed in the light of the reclassification proposal. Attention should be paid to any OTC products the patient may already be using including herbal remedies and nutritional supplements.

A suitable time period for treatment should be given, with justification, and should be reflected in the pack size proposed for the non-prescription product.

Part III - Pharmacovigilance Plan

This Section should consider and comment on whether the current, routine Pharmacovigilance monitoring systems for non-prescription medicines, would be applicable to this product, such as pharmacist or patient reporting via the Yellow Card scheme.

For some proposed P medicines, depending on the product and potential areas of concern, consideration may need to be given to a more focussed post authorisation monitoring study, such as:

- a drug utilisation study
- a study patient demographics and/ or usage of the product, by questionnaire, for example
- validation of a diagnostic protocol (if not conducted prior to grant of licence).

Other safety studies may need to be considered, for example, use in special groups such as the elderly where the risk of a favourable benefit/risk balance is less clear. There may be instances where the safety data might all be based on the selective population recruited for clinical trials and has little usage in the wider population.

Part IV Plans for post-authorisation efficacy studies

This section includes a requirement for an efficacy summary. If necessary, a brief overview would be sufficient for a reclassification application.

Part V – Risk Minimisation Measures

Measures to minimise risks of non-prescription availability should be proposed in this section e.g. use outside the proposed pharmacy model or off-label use. These should be routine measures for proposed GSL products but additional measures may be necessary to ensure safe use of reclassified P products:

Routine:
Updated SPC, revised labelling and patient information leaflet

Additional measures could include:

- Provision of training and educational material for the pharmacist and pharmacy staff (see Appendix 3)
- Pharmacy diagnostic questionnaire and protocol, suitably validated
- Other measures as necessary.

This includes a section on the evaluation of the effectiveness of the risk minimisation measures.

Part VI - Summary of activities in the risk management plan
A summary of the RMP should be included, written for the lay reader and which is suitable for publication. For each indication, the summary should include an overview of disease epidemiology and a summary of existing efficacy data. For the medicinal product, there should be a summary of safety concerns (important identified and potential risks and important missing information). There should also be a summary of risk minimisation activities by safety concern, how risks will be monitored and any major changes to the RMP over time.

Part VII Annexes to the Risk Management

2. Content of P – GSL Reclassification Applications

The content of a P – GSL application is the same as for a POM to P application with the following exceptions:

- Consideration should be given to the criterion for GSL status and the elaboration of the statement “with reasonable safety” (see Appendix 2).
- Justification of how the product may be supplied safely without the supervision of a pharmacist must be provided.

The expert should discuss the indications, maximum dose and maximum daily dose considered suitable for GSL sale and should confirm that the proposed treatment length is justified and is reflected in the pack size. In addition, compliance with relevant clinical guidelines, where appropriate, should also be confirmed.

New pharmacokinetic, pharmacodynamic or efficacy data are not usually required as it would be unusual to consider a formulation or use as being appropriate for GSL supply where it had not been available previously as a P medicine.

It is important that the conditions or symptoms for which the product is indicated can be correctly diagnosed without professional supervision or can be easily recognised following earlier medical diagnosis. The problem of excluding conditions with similar symptoms but unsuitable for treatment with the product in question may need to be addressed. The ability to correctly self-diagnose may be influenced by appropriate product information (label and/or leaflet).

Patients should be able to understand the natural course of the disease and the possibility and consequences of reoccurrence. They should also be able to recognise contraindications and understand essential precautions and warnings. Experience in such issues in relation to other medicines in a related therapeutic area may provide important supplementary information.

The significance of the contraindications, warnings, ADRs, interactions, problems of overdose and other misuse should be discussed in the context of use without access to professional advice. Confirmation should also be provided that significant special handling precautions are not required.

The need for GSL classification should be reviewed in relation to the supply model under pharmacy supervision for the existing P product and focusing on the advantages arising from the convenience of general sale and why these are considered to outweigh the disadvantages arising from lack of access to professional advice at the time of purchase.

When considering the safety of a product for GSL, it is necessary to confirm firstly that the hazard to health and the risk of misuse is small and that significant special precautions in handling are not required.

If there are no safety impediments, it is then necessary to justify the need for wider sale with the reasons why the convenience to the purchaser outweighs the benefit of availability of professional advice at the point of sale.

Appendix 4

Pharmacy Sales Protocols, Questionnaires, Training and Educational Materials

It is important that pharmacy educational material is proportional to the training required and is not promotional or an unnecessary burden upon pharmacy staff.

Protocols are not required in all circumstances and the need for a protocol should in any case be re-evaluated as further experience with the switched product is gained.

Training and Educational Material for proposed P products

Applicants should review the information and training needs of health care professionals to enable them to confidently advise on the appropriate use of the product as well as support and monitor the patients and clearly identify how such needs will be met. Further advice on the information and training needs concerning potential candidates may be sought from the following:

- Professional bodies representing pharmacy
- Proprietary Association of Great Britain (PAGB), where appropriate
- Relevant patient representative organisations.

For certain products, where a new pharmacy diagnostic protocol is to be employed, consideration should be given to developing a suitable questionnaire to help the pharmacist ensure appropriate and safe supply to the patient. Where a questionnaire is developed, a suitable validation study should be conducted, unless otherwise justified.

Appendix 5

HOW TO AVOID SOME COMMON PROBLEMS

Advice Meetings: Ensure that your proposed strategy and the application type and associated process are fully understood before the switch application is made. This will allow MHRA time to form a special Expert Advisory Group if needed.

Benefit/Risk assessment: By providing a full account of benefits and potential risks, a balanced benefit/risk assessment can be made as opposed to a risk/safety assessment. New methods have been developed to help the benefit/risk assessment process (e.g. Brass EP, Lofstedt R, Renn O. Improving the decision-making process for non-prescription drugs: A framework for benefit-risk assessment. Clin. Pharmacol. Ther. 2011: doi: 10.1038/clpt.2011.231).

Benefits assessment: Fully describe the benefits of the proposed switch, taking into account benefits to the individual patient, overall public health benefit, wider access, and access to health information by the public.

POM to P-GSL: If a progression from POM to P and then P to GSL is foreseen as the ultimate goal, ensure that the proposal for switch takes this into account, considering POM criteria as well as conditions that may be required for meeting GSL criteria.

Potential risks assessment: Consider all potential risks arising from the medicine, direct or indirect, and from supply with or without pharmacist supervision (as appropriate), and demonstrate clearly that the legal criteria for P or GSL are applicable.

Product labelling: Avoid leaving this to the end of the switch process. There is often much detail to be sorted out, and to ensure this does not result in delay at the end, it is best to agree the product labelling with MHRA at an earlier stage.

Product Name: Define the proposed product name at an early stage in the switch process (i.e. advice meeting stage) in order to ensure agreement will be forthcoming.

Regular dialogue: Both Applicant and MHRA have a responsibility to keep in close touch at all stages of the switch process to ensure there are no unexpected developments or delays.

Regulatory strategy: Consider all possible application routes for achieving the switch and select the optimum for your needs. For example, a new Marketing Authorisation may be required for the switch product if more than one legal status product is required.

Risk Management Plan (RMP): Pay particular attention to this document, balancing in proportion the aspiration to risk minimisation against the need to optimise benefits, and taking into account the “real world practice” as the benchmark for current availability. The RMP is regarded as a pivotal element in the switch assessment.

Sales protocols and Questionnaires: Where a sales protocol or questionnaire is considered necessary for a new switch discuss with MHRA the role of the questionnaire as an aid for pharmacists, and the potential for simplification as further experience of supply in a pharmacy setting is gained..

Appendix 6

Frequently asked questions – and answers

1. Is there a list of medicines that are available as Prescription Only Medicines (POM)?
MHRA maintains lists relating to the conditions for POM supply. The lists that include circumstances under which substances are included in POM products are List A and List C.

2. Is there a list of medicines that are available as General Sale List (GSL) medicines?
If a drug is available GSL, it will be listed in List B with details of the conditions for GSL supply. For recently reclassified drugs (since 2002), additional information may also be contained in the (List C).

3. Is there a list of medicines that are available as Pharmacy (P) medicines?
No, there is no definitive list of Pharmacy medicines as a Pharmacy medicine is defined as a medicine that is not a Prescription Only Medicine or a medicine on the General Sale List. Please refer to the lists of substances, which provide exemptions for pharmacy supply, for further information.

4. How do I submit a 'me-too' reclassification application?
The variation change code C.I.5 may be used for a “me-too” reclassification. The variation may be a Type IB or Type II, depending on the data supporting the application, and grouping may be used where appropriate. The timelines would be as published, 30 days for a Type IB and 90 days for a Type II. Please note that as a Type IB application has very short deadlines, it is important that any application is fully consistent with the analogous, currently authorised cross reference product, particularly in terms of the Summary of Product Characteristics (SPC).

5. What is an analogous product?
For these purposes, an analogous medicinal product is a medicinal product which has a United Kingdom marketing authorisation or a Community marketing authorisation and which:

- has the same active ingredient, route of administration and use; and
- has the same strength or a higher strength; and
- has the same dosage or daily dosage, or a higher dosage or daily dosage; and
- is for sale or supply at the same quantity or a greater quantity, as the medicinal product in relation to which the application is made.

The pharmaceutical form is not listed in the above points and for an application where this is the only difference between the proposed and analogous products, it would be for the applicant to justify that there are no significant differences between the two pharmaceutical forms.

6. Is it possible to apply for two different legal statuses (e.g. POM and P or P and GSL) on a single marketing authorisation?
No, there should only be one legal status on any marketing authorisation (MA).

Therefore, if a MA holder requires more than one legal status for a product there are two options:

1. submit a simple abridged application to obtain a duplicate MA, then submit a reclassification variation application
2. submit a standard abridged application, which will essentially combine both the assessment of the simple abridged application together with incorporating the proposed legal status into one application.

For further information on fees please refer to the pages on MHRA's website relating to fees for licence applications and fees for reclassifications.

7. Is it necessary to submit a risk-management plan?
For a major or standard procedure it is necessary to submit a risk-management plan. This should include details of measures incorporated to ensure correct self-diagnosis/self-treatment together with any essential safeguards required in order to prevent incorrect usage. This information will include changes such as, but not limited to, additional advice or warning statements, any restrictions on indications, contraindications, dose, pack, length of treatment and clear statements about circumstances requiring physician intervention and the action needed if symptoms do not respond or if an adverse reaction occurs. It may also include reference to availability of suitable educational materials for pharmacists and pharmacy staff.

8. Is it possible to submit a national reclassification application for a marketing authorisation that has been approved via the Decentralised Procedure (DCP) or the Mutual Recognition Procedure (MRP)?
For products authorised via the DCP or MRP the legal status is decided at a national level. As such, it is possible that a product may be available without a prescription in some Member States while remaining prescription only in others. The SPC should remain harmonised across the Member States involved in the procedure. It is recommended that you seek a scientific advice meeting if you wish to submit an application of this kind.