Medicines & Healthcare products
Regulatory Agency

MHRA guidance on the reclassification of medicines in the UK

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Contents

Acronyms

List of Acronyms used in this document

CHM	Commission on Human Medicines
DCP	Decentralised Procedure
EAG	Expert Advisory Group
GSL	General Sale List
LA	Licensing Authority
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MHRA	Medicines and Healthcare products Regulatory Agency
MRP	Mutual Recognition Procedure
P	Pharmacy Medicine
PASS	Post Authorisation Safety Study
PAR	Public Assessment Report
PIL	Patient Information Leaflet
POM	Prescription Only Medicine
RFI	Request for Further Information
RMP	Risk Management Plan
SAM	Scientific Advice Meeting
SmPC	Summary of Product Characteristics

Supporting Documents

1. Reclassification Validation Checklist
2. Flow diagram showing the timescales for national major reclassification applications

1. Purpose and Scope

This document aims to provide guidance on the reclassification of a medicine in the UK.

Validation processes precede application review, emphasising the submission of complete supporting documents. The reclassification validation checklist, which outlines all documents required for a reclassification application submission, which should be referenced.

The timetable for the assessment of reclassification applications is summarised in the supporting document named flow diagram, and is explained in section 4.

2. Introduction

In the UK, there are three legal statuses that a medicine can be classified within:

- **Prescription-Only Medicine (POM)** - must be prescribed by a doctor or other authorised health professional and must be dispensed from a pharmacy or from another specifically licensed premises.
- **Pharmacy Medicines (P)** - can be bought only from pharmacies and under a pharmacist's supervision.
- **General Sale List Medicines (GSL)** - may be purchased without the supervision of a pharmacist and are available in retail outlets, such as a newsagent, a supermarket, or a vending machine in a shop.

Multiple legal statuses cannot exist on a single marketing authorisation (MA), i.e. it can either be POM, P or GSL.

New medicines, when first authorised, are usually restricted for use under medical supervision as a POM.

Once there has been sufficient use of a medicine, such that there are sufficient post-marketing data to demonstrate that the medicine can be safely supplied and used without prescription control, reclassification to a non-prescription product may be undertaken.

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.

An applicant submitting a reclassification application must hold the relevant marketing authorisation (MA); alternatively, a new marketing authorisation application (MAA) could be submitted in combination with a reclassification application.

The procedures, timetable, and criteria for supply status, for reclassification applications are detailed in the following sections of this guidance.

3. Scientific Advice Meetings

It is strongly advised, although not compulsory, that applicants for all major reclassifications seek scientific advice prior to submission. To apply for scientific advice, see 'Get scientific advice from the MHRA' in conjunction with Fees for scientific advice meetings.

Examples of issues advised on at SAMs include:

1) The proposed conditions of supply of the medicine
2) The proposed changes to the product information
3) Product name proposals
4) Submission strategies

It is not possible to provide a guarantee of successful reclassification or to pre-empt the outcome of the reclassification process, without conducting a full assessment of the submitted application.

Requests for a SAM should be made well in advance of anticipated applicant deadlines.

Applicants may alternatively wish to book a broader scope meeting.

4. Process and Timetable of Reclassification

4.1 Flow diagram

The flow diagram published on the MHRA website and attached in Annex 2 of this document provides an overview of the timetable for national major reclassification applications. Each of the steps from the flow diagram is described in section 4.2.

4.2 Timetable for assessment

It is important to note that timetables may change, as not all steps delineated below may be applicable to each submission. On occasion, it may not be possible to adhere to the timetable if there are unforeseen circumstances, which may cause delays. Any such delays will be communicated to the applicant.

The assessment team will not assess any documentation outside of the timetable, including via email. Assessment will only take place once the application or response documents have been formally uploaded and submitted to the MHRA.

All days are presented as calendar days and not working days.

Step 1: Application received by the MHRA and awaits validation.

- Application is validated internally by the MHRA.
- All documents listed in the reclassification validation checklist must be submitted. If any necessary documents are omitted, the application will not be validated.

Step 2: Validation of application completed, and assessment of application starts **(Day 0)**

- Applicants will be notified of the initial timetable once an assessor/assessment team has been allocated to assess the application.
- A full initial assessment of the application will be undertaken within 60 days.

Step 3: Assessment completed and RFI letter issued **(Day 60)**

1st RFI:

- By or on Day 60, the 1st Request for Further Information (RFI) letter will be sent to the applicant, if necessary, which consolidates all outstanding issues to address from all assessors involved in the assessment of the application.
- The applicant will have 60 days to respond in full.

- Once the applicant submits the response to the RFI, the assessor(s) will have 30 days to assess the response.

2nd RFI (Optional):

- If there are outstanding issues to resolve, a 2nd RFI letter may be issued **(Day 90)**
- The applicant will have 60 days to respond in full.
- Once the applicant submits the response to the RFI, the assessor(s) will have 30 days to assess the response.

A maximum of two RFI letters can be issued before the application is considered by the Commission on Human Medicines (CHM).

Step 4: Assessment of RFI response completed **(Day 90 if only one RFI letter was issued, Day 120 if a second RFI letter was issued)**

- The assessor(s) will determine whether the application will continue as a major or be downgraded to a standard (at Day 90 or at Day 120 if a second RFI letter is issued). This decision will be communicated to the applicant via an ad hoc letter.

Major:

- The reclassification application will continue as a major application if advice needs to be sought from the CHM.
- There are two possibilities at this stage for a major reclassification:
  1. The application will be presented to the CHM.
  2. A stakeholder group will be held with selected healthcare professionals and members of the public to seek views on the proposed reclassification. Stakeholder groups are organised for innovative reclassifications, and the decision to set up the meeting is considered on a case-by-case basis. The time taken to plan and hold the meeting can vary and is likely to take a maximum of 60 days, however, this time may be extended if necessary. Following the stakeholder group, the application will be presented to the CHM.

Standard:

- A major reclassification application will be downgraded to a standard application if no advice is sought from the CHM.
- The application will proceed to approval at **Day 120**.

Step 5: CHM meeting (and EAG meeting if required)

- Expert advice will be sought from the CHM and the relevant EAG if required.

Step 6: CHM advice letter issued.

Positive opinion from CHM

- If the CHM advise in favour of the reclassification, the advice letter may include conditions under which the application is approvable, requiring changes to be made to the SmPC or patient information, or other documents. In this scenario, the applicant will

have 28 days to respond. Once the response is submitted, the assessor(s) will have 30 days to assess the response.
- Once the response has been assessed, if none of the optional steps (see below) are undertaken, the application will proceed to approval (Day 160).

Optional steps:

The following optional steps may be undertaken before the application is approved:
- Internal administrative process (maximum of 20 days) (Day 160)
- Public consultation period (Day 180) - Public consultations are conducted on a case-by-case basis. Public consultations for reclassification applications usually run for 21 days.
- Assessment of responses received from public consultation **(Day 181)** - The assessor(s) will have 30 days to assess the responses received.
- RFI letter issued following public consultation (Day 210): If there are issues raised during the public consultation, an RFI letter will be issued. The applicant will have up to 28 days to respond in full. Once the RFI response has been submitted, the assessor(s) will have up to 15 days to assess the response.
- If the assessor(s) are satisfied with the response, the reclassification application will be approved **(Day 225)**, and the applicant will be issued with a grant letter.

Negative opinion from CHM

If the CHM advise against the reclassification, the applicant will have 28 days to notify the MHRA on whether they intend to appeal the decision. In accordance with *Paragraph 18; Part 2 of Schedule 11 of The Human Medicines Regulations 2012, (SI 2012/1916)*, the applicant may notify the Licensing Authority (LA) in writing to request the opportunity to make written or oral representations to the CHM in relation to the grounds set out in the refusal letter. The applicant must make this request within 28 days of the day on which the notification is given, unless otherwise indicated. If the applicant wishes to appeal, the documentation must be provided within 6 months of the date that the applicant notified the MHRA of their decision to appeal. The applicant can request to extend the deadline up to a maximum of 12 months (from the date that the applicant requested to appeal). If the documentation is not provided within the 12-month deadline, the application will be refused.

5. Application Type and Submission Strategy

The types of reclassification application are:

1) A reclassification variation, which is:

    a) Simple

    b) Standard (this is **not** a route of submission - see section 5.2)

    c) Major

2) A reclassification variation combined with a marketing authorisation application (MAA) (simple/standard/complex) (see section 5.3).

5.1 Simple reclassification

A simple reclassification is based on an analogous product which has already completed the reclassification procedure.

An analogous product is a medicinal product which has a MA in the UK and:

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

The analogous product should have been on the market during the previous six months and must not have been removed for reasons of safety, quality, or efficacy. Exceptionally, it may be possible to accept certain products which have not been on the UK market for over 6 months as analogous products. Applicants are advised to contact the MHRA (variationqueries@mhra.gov.uk) to seek guidance on the eligibility of these products. In these circumstances, acceptance of the proposed analogous product will be determined on a case-by-case basis.

Two products containing different active substances cannot be used as an analogous product for a combination product containing those active substances.

How to submit a simple reclassification:

If a simple reclassification only involves the assessment of the product information (Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Label), a

Type IB application should be submitted. Type IB applications follow the timetable outlined here.

If a simple reclassification involves the assessment of the product information and further assessment of supporting documents or changes, a Type II (analogous product) application should be submitted. Examples of supporting documents include the user testing of the PIL, or bioequivalence data where the analogous product is a different pharmaceutical form to the proposed product to be reclassified. Type II applications follow the timetable outlined here.

Refer to **part B** of the reclassification validation checklist of all documents needed at submission for a simple reclassification.

5.2 Major reclassification

If there is no analogous product to base the reclassification on, the application must be submitted as a major reclassification.

A decision will be made by the assessment team on whether expert advice is required from the CHM, once a full assessment has taken place.

If advice is required from the CHM, the application will proceed as a major. If no advice is required from the CHM, the application will be downgraded to a standard application (see below).

Commission on Human Medicines

The Commission on Human Medicines was established in October 2005; its functions are set out in *regulation 10 of The Human Medicines Regulations 2012 (SI 2012/1916*).

The CHM is an **independent advisory body** to the Licensing Authority (LA)[1]; they do not make the final decisions with respect to grant or otherwise of applications; this falls to the LA. The assessment team will present their recommendations to the CHM on a particular application based on a full and thorough assessment of the data or evidence provided by the applicant against the criteria set out in the regulations (*The Human Medicines Regulations 2012*). The CHM provides expert advice and make recommendations to the LA having considered the evidence or data provided to them by the LA.

[1] The MHRA operates as the Licensing Authority (LA) on behalf of the Secretary of State with a mission to protect patient and public health through effective regulation of medicines and medical devices

How to submit a major reclassification:

A major reclassification application is classified as a Type II variation.

See **part C** of the reclassification validation checklist for all documents required to be submitted for a major reclassification.

Downgrading a ‘major’ reclassification to a ‘standard’ application

Applicants cannot submit a reclassification as a standard application. If a major reclassification application undergoes a full assessment and no advice is sought from the CHM, it will be downgraded to a standard application.

The decision as to whether an application is downgraded to standard will be on a case-by-case basis. *The Medicines (Products for Human Use) (Fees) Regulations 2016* specify that 50% of the major reclassification fee is refunded if the LA is satisfied that the application does not require consideration by the CHM.

5.3 Reclassifications combined with initial marketing authorisation applications

Reclassification applications may be submitted in combination with an initial MAA.

Reclassification applications combined with a simple abridged are submitted if there is a desire to copy and retain an existing marketing authorisation.

Reclassification applications combined with a standard or complex abridged are submitted if the MAH wishes to apply for the reclassification in tandem with the initial MAA.

Reclassification variations can be combined with a simple, standard, or complex initial MAA, if required. The following combinations are possible:

	Simple abridged	**Standard abridged**	**Complex abridged**
Major POM to P reclassification	✓	✓	✓
Major P to GSL reclassification	✓	✓	✓
Analogous product (Type II) reclassification	✓	⊗	⊗
Analogous product (Type IB) reclassification	⊗	⊗	⊗

Due to timetable restrictions, it is not possible to combine a Type IB reclassification with a simple abridged.

For any of the above combined applications, guidance on documentation related to the MAA of the combined submission should be sought from the MHRA website.
Types and Submission

5.4 International Recognition Procedure

On 1 January 2024, the EC Decision Reliance Procedure (ECDRP) was replaced by the new International Recognition procedure (IRP). The legal status of supply and thus the reclassification of medicines remains a national competency.

A major reclassification application can be submitted in parallel with an initial marketing authorisation application via IRP and will be considered at the same time by the two assessment teams. Alternatively, the reclassification application can be submitted following the approval of the initial MAA.

5.5 Fees

Please refer to the MHRA fees page for current reclassification fees.

In some instances, it may be possible to submit a POM to GSL application; this will incur a POM to P fee.

5.6 Submission strategy

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

a) the correct type of application to be submitted; and

b) the most appropriate route to achieve the desired outcome, e.g. a new MA combined with a reclassification or variation to an existing MA.

Reclassification applications may be submitted via the following routes:

1) reclassification variation to an existing MA

2) reclassification variation combined with an initial MAA

3) creation of a duplicate POM or P MA, which, once approved, can be followed by a reclassification variation to change the legal supply status. Types and Submission

5.7 Proposed modifications within the scope of reclassification applications

The following changes may be included as part of a reclassification application:

Change of the name of the medicinal product

A new invented name or a change in the product name can be submitted as part of a major or simple reclassification application. The MHRA Guideline for the Naming of Medicinal Products and Braille Requirements for Name on Label should be referred to when considering a name for the product.

Change in the pack size

Changes to the pack size that are consequential to the reclassification are acceptable, provided there are no changes to the immediate packaging. If there are changes to the immediate packaging, a separate variation to change the pack size with the new packaging must be submitted in parallel to the reclassification application.

5.8 Proposed modifications outside the scope of reclassification applications

The following changes are not within the scope of a reclassification application:

Change in the indication

Additional indications or extensions to indications, are outside the scope of a reclassification variation. The indication proposed for the product must already have been approved on the MA prior to submitting the reclassification variation. A restriction or a more limited indication that is a subset of an already approved indication is permitted, and is common, as part of a reclassification variation.

Change in the posology

Any changes which widen the posology is outside the scope a reclassification variation. The posology proposed for the product must already have been approved on the MA prior to submitting the reclassification variation. A restricted or a more limited posology which corresponds to the proposed indication or target population is permitted.

Changes to the pharmacological properties of the SmPC

Changes to sections 5.1, 5.2 and 5.3 of the SmPC are outside the scope of a reclassification variation. Any changes to these sections should be submitted via a separate variation.

Addition of an Own Label Supplier (OLS) and associated changes such as a new product name and livery

The addition of an own label supplier (OLS) and consequential addition of a product name (applicable to the registered OLS) is outside the scope of a reclassification variation. A separate variation to add an OLS and the consequential product name is required. A separate submission to the Product Information Quality (PIQ) team will also be required to introduce the OLS livery; this can be submitted at the same time as the variation to add the OLS as part of a Composite Co-ordinated Collection (CCC). Please refer to the MHRA Guidance on packaging, labelling and patient information leaflets.

Reclassification variations cannot be included as part of a CCC or a grouping.

5.9 European Marketing Authorisations

Changes to product information for a decentralised procedure (DCP) or mutual recognition procedure (MRP) MA require agreement from the relevant member states. It is advised that reclassification variations take place on a national UK MA. The applicant should refer to the MHRA guidance on handling of decentralised and mutual recognition procedures which are approved or pending for advice on how to obtain a UK MA.

5.10 Invented Name

When products with identical compositions are available both as POM and non-prescription medicines, but with differing indications, contraindications, and/or warnings, they must have distinct invented names for each MA. This is essential to mitigate safety concerns from identical names being associated with two different products. More guidance is available from MHRA Guideline for the Naming of Medicinal Products and Braille Requirements for Name on Label.

Where a change in legal status is due solely to a difference in pack size of the product, but all other aspects of the MAs and the SmPC 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 any time, a new brand name will need to be used for the divergent authorisation.

6. Criteria for Supply Status

The sale and supply of medicines is controlled by *The Human Medicines Regulations 2012.*

6.1 Criteria for supply status as a Prescription Only Medicine

A medicine will be non-prescription unless it fulfils the criteria for prescription control as set out below. Prescription only status will be applicable under the following conditions:

1. When there is a direct or indirect danger to human health, even when used correctly, if used without medical supervision.

2. In cases where there is frequent incorrect use that could lead to direct or indirect danger to human health.

3. When further investigation of activity and/or side-effects is necessary.

4. If 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).*

First POM Criterion:

(a) The potential for **direct danger** associated with correct and incorrect use of the product without medical supervision, for example:

I. *adverse drug reactions* that are important because of their seriousness, severity, or frequency.

II. the benefit-to-risk of the *safety profile* of the product in relation to that for similar products already available as P medicines for the same indication.

III. *Interactions* with commonly used medicines.

The proposed indications, maximum dose, maximum daily dose, duration of treatment and pack size should all be discussed and justified in the context of the proposed contraindications, warnings, interactions, side effects and potential for abuse or misuse.

(b) The potential for **indirect danger** associated with correct and incorrect use of the without medical supervision, for example:

I. Consideration should be given to symptomatic treatment which might *mask* an underlying condition and potentially delay a diagnosis or conditions which may be exacerbated by the treatment.

II. The condition or symptom must be *correctly diagnosed* without medical supervision or can be easily recognised following initial medical diagnosis by a doctor.

III. 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. Evidence to assess the understanding is likely to be useful to support the application. Experience in such issues in relation to other medicines in a related therapeutic area may provide important supplementary information.

IV. The extent of *known incorrect use* should be described, and the potential risks of inappropriate use or misuse should be evaluated. The potential for and consequences of misuse to lead to an indirect risk should also be considered. Any restrictions on indications for use, duration of use, dose or pack size or additional warnings to limit the risk of misuse should be outlined.

Potential risk mitigations may be to include additional referral criteria such as a recommendation to seek medical advice if symptoms worsen or persist beyond a short, fixed duration.

Second POM Criterion:

When a product or substance is known to be or likely 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 POM.

Consideration should be given to the consequences of using the product when contraindicated or off-label, used incorrectly or for prolonged periods of time. Any potential for such abuse or misuse should be discussed.

Third POM Criterion:

Further investigation into the activity and/or side effects of the active ingredient may not be necessary. Usually, the active ingredient is well understood by the time a reclassification is considered, so this criterion may not be applicable.

The extent of experience under normal conditions of use must be considered. Applications for products that were recently authorised or with limited exposure may be considered. In such cases, the reclassification clinical overview should clearly lay out and justify the rationale for such a request.

Fourth POM Criterion:

Parenteral administration entails piercing the skin or mucous membranes. Products intended for parenteral administration are unsuitable for reclassification due to the heightened risks and complexities associated with this route of administration, making medical supervision necessary for their availability.

6.2 Criterion for supply status as a General Sales List medicine

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." Precise GSL product eligibility details can be found in *The Human Medicines Regulations 2012, regulation 62 (Schedule 1, Part 2).*

Normally products with, or seeking, GSL status are in widespread use in pharmacies for several years prior to the application. The GSL products are used for short term treatment of conditions which are easily self-diagnosed. However, not all products would necessarily progress from P to GSL. Any proposed indications, posology (including maximum dose/maximum daily dose), and duration of treatment, should be discussed and justified in the context of the known contraindications, warnings, side effects and potential for abuse or misuse. Pack sizes should be justified and should reflect the intended duration of use.

The default legal status will be P if a medicine does not meet the POM criteria and is suitable as a non-prescription medicine but does not meet the GSL criterion.

7. Other Useful Resources

7.1 Advertising

The MHRA may ask to see all advertising and promotional material for legislative compliance prior to publishing. This will happen for most major reclassifications, and for others on a case-by-case basis. Further information can be found in the MHRA guidance on the vetting of promotional material, MHRA guidance on advertising of medicines and the MHRA Blue Guide.

7.2 Public Assessment Report (PAR)

Following the approval of a major or standard reclassification, the MHRA will publish a Public Assessment Report (PAR) on the MHRA website within 60 days of approval.

7.3 Data Exclusivity

The MHRA guidance on exclusivity for change in legal status of a medicine can be found on the MHRA website.

7.4 Risk Management Plan (RMP)

Certain reclassifications may be granted with conditions that require the applicant to undertake specific risk minimisation activities after approval. The risk management plan (RMP) aims to mitigate known risks through appropriate product information adjustments and to outline a plan for managing risks and safety monitoring as needed. Training materials and post-authorisation safety studies that will be approved as part of a reclassification, are an additional risk minimisation measure (aRMM). Advice on the format and content of RMPs can be found MHRA Guidance on Pharmacovigilance Procedures (Updated 14 October 2021). For simple reclassifications, training materials do not need to be provided even if they were included as aRMMs for the analogous product.

7.5 Post-Authorisation Safety Study (PASS)

A post-authorisation safety study (PASS) is a study that is conducted after a medicine has been authorised to obtain further information on a medicine's safety, or to measure the effectiveness of risk-management measures. For certain proposed reclassified medications, depending on the product and potential areas of concern, it may be necessary to consider a more targeted post-authorisation monitoring study., e.g. evidence that pharmacy support or training materials can be followed appropriately, and key messages are understood. Advice on PASS can be found in the MHRA Guidance on Pharmacovigilance Procedures (Updated 14 October 2021).

7.6 Queries

Questions regarding the reclassification of a medicine should be directed to variationqueries@mhra.gov.uk.