

Guide to **Reclassification (Switching) of Legal Supply Status for Human Medicinal Products**

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This guide does not purport to be an interpretation of law and/or regulations and is for guidance purposes only.



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1 SCOPE

This guide provides an overview of the regulatory and administrative requirements for reclassification of the legal supply status for a medicinal product by a marketing authorisation holder (MAH). The guide applies to medicinal products for human use, granted a marketing authorisation (MA) by the HPRA, nationally, through the mutual-recognition (MR) or the decentralised procedure (DCP).

It does not address switching applications for products authorised through the centralised procedure other than to advise on specific national issues relating to their legal supply status.

Specific issues not addressed in this guideline should be directed to HPRA Customer Service (info@hpra.ie).

2 INTRODUCTION

Procedures for the legal classification of the supply of a medicinal product have been revised in line with the changes to the legislation effected by the coming into force of Council Directive 2001/83/EC, transposed into Irish law by the Medicinal Products (Prescription and Control of Supply) Regulations, 2003 (S.I. No. 540 of 2003) and Medicinal Products (Control of Placing on the Market) Regulations, 2007 (S.I. No. 540 of 2007). The legal status for supply of a medicinal product is now a condition of the marketing authorisation rather than being based on an entry in the active substance list (schedules) in Medicinal Products (Prescription and Control of Supply) Regulations 2003.

Following authorisation, a new medicinal product, in accordance with Title VI of Directive 2001/83/EC, is generally designated as having a prescription-only legal status. Application can be made to the HPRA to change the legal status from prescription-only to non-prescription. This procedure is referred to as '**reclassification**' or '**switching**' and both terms appear interchangeably throughout this document.

Switching involves a change from:

- prescription-only to pharmacy-only status, or
- pharmacy-only to general sale status.

Pharmacy-only status applies to medicinal products that can be sold in a pharmacy under the supervision of a pharmacist. General sale means that the medicinal product may be sold in pharmacies and non-pharmacy retail outlets e.g. supermarkets.

On occasion, a medicine, which was previously classified as having non-prescription status (pharmacy-only or on general sale) may be reclassified to prescription control or to pharmacy-only status if new risks are identified which alter the benefit/risk ratio and indicate

that it is no longer safe to supply without the supervision of a doctor or pharmacist (as appropriate).

3 LEGAL FRAMEWORK

European Council Directive 2001/83/EC was transposed into national legislation and came into force on 23 July 2007 as the Medicinal Products (Control of Placing on the Market) Regulations (S.I. No. 540 of 2007), 2007 and as the Medicinal Products (Prescription and Control of Supply) Regulations 2003 (S.I. No. 540 of 2003). This update to the legislation resulted in two key changes that impact on the classification of medicinal products:

- 1 The legal status for supply of a medicinal product is now a condition of the marketing authorisation and is product-specific.
- 2 The HPRA has assumed responsibility for classification/reclassification and maintenance of a record of legal status for supply of all authorised medicinal products (Regulation 12 of S.I. No. 540 of 2007).

Previously in Ireland the legal classification for an active substance was determined by its inclusion in the schedules appended to S.I. No. 540 of 2003.

Non-prescription status was determined by entries into the First and Second Schedules of this legislation. Conditions relating to maximum dose (MD), maximum daily dose (MDD), pack size etc. were outlined in columns 3, 4 and 5 of the First Schedule.

General sales status required an entry into the Second Schedule, part 2. Reclassification or switching of legal supply status involved an application to both the Department of Health and the HPRA. A successful application resulted in a change to the schedules appended to the Medicinal Products (Prescription and Control of Supply) Regulations S.I. No. 540 of 2003 and a parallel change to the marketing authorisation.

Since the legislation was updated, reclassification or switching now only requires an application to the HPRA for a change in legal supply status to the marketing authorisation.

4 CRITERIA FOR CLASSIFICATION OF LEGAL SUPPLY STATUS

4.1 Prescription control

In accordance with Regulation 12 of the Medicinal Products (Control of Placing on the Market) Regulations 2007, (S.I. No. 540 of 2007), medicinal products are classified either as:

- subject to medical prescription, or
- not subject to medical prescription.

A medicine comes under prescription control if it fulfils any of the following criteria:

- It is likely to present a danger either directly or indirectly, even when used correctly, if utilised without medical supervision, or
- It is frequently and to a very wide extent used incorrectly, and as a result is likely to present a direct or indirect danger to human health, or
- It contains substances or preparations, the activity and/or adverse reactions of which require further investigation, or
- It is normally prescribed by a doctor to be administered parenterally (for injection), or
- It emits radiation.

Examples of situations where prescription control generally applies:

- Medicinal products that are administered parenterally (by injection)
- Psychotropics or narcotics listed in any of the schedules to the Single Convention on Narcotic Drugs or the Convention on Psychotropic Drugs, products with a risk of misuse, abuse, dependence or withdrawal syndrome – requiring frequent monitoring by physician
- Antidepressants, antipsychotics, anxiolytics not listed in schedules of the Convention on Psychotropic Drugs
- Products with specific follow up measures required in their risk management plans to address particular on-going safety concerns
- Medicines containing new chemical entities that were authorised less than five years ago
- Antimicrobial agents with potential for development of resistance if used extensively without medical supervision

Prescription-only medicines are further sub-classified as:

- only on medical prescription for non-renewable supply
- on medical prescription for renewable supply.

In accordance with the Medicinal Products (Prescription and Control of Supply) Regulations 2003 (S.I. No. 540 of 2003), non-renewable substances are listed as Schedule 1A (A), whereas renewable substances are listed as Schedule 1B (B).

If a substance is listed in the Schedule 1B of the Regulation as outlined above, the sub-classification of an authorised product containing that substance is generally not changed by the HPRA unless the summary of product characteristics (SmPC) for a given product (e.g.,

indication, posology) requires that it be restricted, whereby its status may be changed for example from renewable to non-renewable.

Renewable and non-renewable status is determined by national precedence and in compliance with the content of the SmPC. This is assigned on a case-by-case basis to any given product authorisation.

Medicinal products that require specialist supervision, parenteral administration, or which are for short-term use where there is a risk of resistance (e.g. antimicrobials), are examples of the types of products usually classified as subject to prescription for non-renewable supply (A).

Prescription-only classification and further restriction to supply (non-renewable status (A)) also applies when the product is:

- a medicinal product that is reserved for use in certain specialised areas i.e. conditions requiring hospital based diagnosis, administration under medical supervision in hospital or outpatient setting
- a narcotic or psychotropic agent which, if the product is incorrectly used, presents a substantial risk of abuse or addiction (Misuse of Drugs Regulations 1988 (S.I. No. 328 of 1988)).

Most medicinal products subject to prescription control are classified for renewable supply.

4.2 Non-prescription status

If the criteria for prescription control are not met, the medicinal product may be classified as non-prescription.

In accordance with Regulation 12 of S.I. No. 540 of 2007, there are two subcategories of non-prescription medicine:

- Pharmacy-only status applies to medicinal products that are available under the supervision of a pharmacist.
- General sale products that, following review of the nature and intended use of the product, can, with reasonable safety, be sold without the supervision of a pharmacist.

In some instances, products which normally come under prescription control may be classified for supply without a prescription with certain restrictions e.g. a maximum single dose (MD), a maximum daily dose (MDD), a specified strength or pharmaceutical form, limited pack size or indications for use.

4.3 Centrally-authorised products

The legal status for supply of products authorised through the centralised procedure is determined in line with the provisions outlined in Council Directive 2001/83/EC and is outlined in Annex II to the SmPC. The sub-categorisation of renewable and non-renewable

supply is determined by Member States on a case-by-case basis in accordance with the EMA 'Guideline on Legal Status for the Supply to the Patient of Centrally Authorised Medicinal Products'. Centrally-authorized products with non-prescription status are classified as pharmacy-only medicines in the Irish setting. There is no provision for classifying centrally-authorized products as general sale medicines in Irish legislation.

5 APPLICATION FOR CHANGE IN LEGAL STATUS

5.1 Reclassification (switching) applications

Applications can be made to the HPRa to change the prescription status from:

- prescription-only to pharmacy-only
- pharmacy-only to general sale status

The HPRa has adopted a proactive approach to switching the method of sale and supply of medicinal products containing specified active ingredients in the interest of public health, MAHs are also encouraged to submit innovative switches. Expressions of interest can be made by e-mail to moss@hpra.ie and should include the PA number, the name of the medicinal product and any relevant documentation.

Following receipt of the expression of interest, the HPRa will engage with the applicant(s) to determine an appropriate timeframe for submission of the relevant switching application and supporting documentation.

Marketing authorisation holders are requested to engage with competent authorities at the earliest possible stage in the process.

For further information and requests for scientific or procedural advice relating to switching the legal classification of a particular medicine, please contact moss@hpra.ie.

Prescription-only to pharmacy-only status

In general, switching applications are only considered for products that have a well-known, long established safety profile as a prescription-only medicine. If favourable post-marketing safety experience for a product provides evidence that the medicinal product may be safely used without supervision by a physician, application can be made for reclassification from prescription-only to pharmacy-only status. The applicant must demonstrate that the medicinal product in question can be exempted from prescription control.

Pharmacy-only to general sale status

Over time, if the benefit/risk evaluation of increased availability of a given pharmacy-only medicine is considered positive, application for general sale status can be considered. In this

instance, sufficient evidence must be provided to ensure that such a medicine can be safely supplied without the intervention of a pharmacist. However, it is not considered that prescription-only to pharmacy-only to general sale status is a natural continuum for all products.

5.2 Application types

National procedures

Switch applications for nationally authorised products can be submitted as a:

- variation
- new application.

Following consideration by the HPRA the application is approved or rejected; if approved, the marketing authorisation is updated as appropriate.

Points to note:

- a) Applications to change from prescription-only status to non-prescription status (pharmacy-only or general sales) for a nationally authorised product should generally be submitted as a Type II switch variation.
- b) Citing 'well established use' (Article 10a of Directive 2001/83/EC) as the legal basis for a 'first-in-class' switch application, that will result in a product having a different legal classification to that listed in the schedules appended S.I. No. 540 of 2003, should be discussed with the HPRA in advance of submission.
- c) Applications that are based on an approved switch of a reference medicinal product (generic/hybrid medicinal products) can be submitted as Type IB variations. These applications must have the same indication, posology, route of administration, risk minimisation measures and pharmaceutical form as the reference product.
- d) The applicant should clearly indicate the legal basis for the submission of their application in the cover letter and application form. It is strongly recommended to discuss the proposed legal basis for the application in advance with the HPRA, in order to prevent difficulties at validation. Queries regarding the legal basis for the application should be directed to moss@hpra.ie.

A successful switch application applies only to that particular marketing authorisation. All other products with the same active substance require a separate application requesting change of prescription status.

It is possible to submit a variation to reclassify a medicinal product in parallel with an 'informed consent' application on a full dossier (Article 10c) or a 'duplicate' (same legal basis)

application. This mechanism may be used in circumstances where the applicant wishes to maintain product availability through the legal route via which it is currently authorised (e.g. maintain a prescription pack and also have a pharmacy-only pack on the market), which may be useful when the reclassified product has a different indication or is suitable for use in a different population. The new non-prescription product will require a new name or a distinct qualifier in these instances.

The product information (SmPC, package leaflet) for an informed consent or duplicate application should be identical to that of the authorised product. The variation should include the revised SmPC, package leaflet and label and proposals for the non-prescription name, indication and dose, as appropriate.

A dossier for a duplicate application should be identical to that of the reference product, and should be on the same legal basis. For further information on informed consent applications please refer to Annex II of this document.

Applicants are requested to submit the informed consent or duplicate application and variation application simultaneously and provide details in the cover letter for each application.

Mutual recognition/decentralised procedures

Switch applications of products that have been authorised through a mutual recognition (MR) or decentralised (DC) procedure require special consideration and should be discussed with the HPRA in advance of a submission. Where Ireland is either the Reference Member State (RMS) or a Concerned Member State (CMS), the HPRA will need to determine whether the change can be processed nationally or whether the change in legal status needs to be submitted through an MR or DC procedure.

A number of options are listed below; however, it should be noted that these are not exhaustive nor are they binding on Member States or applicants.

- If an applicant wishes to seek reclassification in Ireland of a product authorised by an MR or DC procedure and this will require **no** change to the harmonised dossier, or will only require additional national information on the labelling or package leaflet, the applicant may submit a national reclassification application. National changes required to the labelling or package leaflet can be accommodated locally with a label in the 'blue box' concept.
- Where Ireland is the RMS or the CMS for a product in an MR procedure and an applicant wishes to seek reclassification from prescription-only to non-prescription and it is established that **reclassification is possible in the RMS**, the applicant may do this firstly by obtaining a duplicate marketing authorisation. The changes to the product particulars required by the RMS for non-prescription status could then be made by variation to this

duplicate MA before starting an MR procedure. A product authorised in this way may require a new name or distinct qualifier in line with national procedures.

- Where Ireland is the CMS for a product in an MR procedure and an applicant wishes to seek reclassification from prescription-only to non-prescription and it is established that **reclassification is not possible in the RMS**, but one or more CMSs are supportive of reclassification, a change in the RMS can be undertaken in accordance with 'CMDh procedural advice on changing the Reference Member State'. The applicant should consult the 'CMDh best practice guide for authorisation of non-prescription medicines in the decentralised and mutual recognition procedure'. A product authorised in this way may require a new name or distinct qualifier in line with national procedures.

6 DATA REQUIREMENTS

The documentation concerning safety and efficacy required to support an application for a change in the legal classification for supply will vary from application to application and will depend on the nature of the active substance and the extent of change proposed for the product authorisation. Each application is evaluated on a case-by-case basis. Guidelines on the data required for switch applications for nationally held product authorisations are outlined below.

The documentation requirements for submission of an Article 10(c) application are included in Annex II.

6.1 Reclassification from prescription-only to pharmacy-only status

All applications should include:

- 1 A clinical expert report demonstrating that prescription control is not required for safe use
- 2 A safety/efficacy summary
- 3 Risk minimisation plan where necessary including appropriately justified education and training material
- 4 Full colour mock-ups of product information (label and package leaflet)
- 5 Results of user testing of the package leaflet or a justification for its omission.

Clinical expert report

The clinical expert report should justify the request for reclassification in the context of the criteria that determine classification for supply subject to a medical prescription.

The expert must:

- Provide a balanced critical analysis of the reasons why the given product should be exempt from prescription control.

- Discuss in detail each criterion and justify why the medicinal product does not meet these criteria and may therefore not be subject to a medical prescription (see section 4.1 detailing criteria for prescription control).

The benefit/risk evaluation must consider the following points:

- a) The potential for direct and indirect danger associated with use of the product in the context of self-assessment of symptoms and use without medical supervision. The condition or symptom must be self-diagnosable or easily identified following initial diagnosis by a doctor. Use of a product that has significant side effects or use by a patient who has incorrectly assessed his condition or symptoms must be considered along with the potential benefits to the patient of greater availability of the medicine. Measures proposed by the applicant to ensure correct self-diagnosis and treatment should be outlined and appropriately justified. Situations where the user should seek medical intervention need to be clearly outlined. The consequences for the patient of a delay in seeking medical intervention should also be discussed.
- b) Masking deterioration of an underlying condition by symptomatic treatment or the potential for development of resistance to antimicrobial agents if used extensively without medical supervision are examples of potential indirect risks.
- c) The potential for misuse. The extent of known incorrect use should be described and the potential risks of inappropriate use/misuse should be evaluated. The potential for 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
- d) The extent of the experience with the medication under normal conditions of use.
- e) Generally products should have five years post authorisation safety data available for review including data from all relevant patient populations. However, applications for products that are recently authorised or with limited exposure may be considered. In such cases the clinical expert report should clearly lay out and justify the rationale for such a request.
- f) Introduction of a new strength, dose, route of administration, indication or age group should be justified. The indications, proposed MD, MDD and duration of treatment and pack size should all be discussed and justified in the context of the known contraindications, warnings, interactions, side effects and potential for abuse/misuse.

Note: Further information on the factors that should be addressed in justifying exemption from prescription control is detailed in the EU Commission 'Guideline on changing the classification for the supply of a medicinal product for human use'.

Safety and efficacy summary

The clinical expert report should be supported by a comprehensive pre-clinical safety, clinical safety and efficacy summary as appropriate. An overview and summaries of all relevant pre-clinical and clinical studies should be provided for review.

The following key points should be addressed:

- a) A summary of all relevant completed and ongoing clinical trials and post marketing surveillance studies should be provided for review. The safety summary should include an overview of adverse reactions taking into consideration patient exposure, known indications for use, known interactions and extent and duration of use.
- b) Relevant PSUR data should be presented with appropriate bridging summaries.
- c) The relevance of data relating to prescription-only use in support of an application for non-prescription use should be discussed but the benefit/risk evaluation must focus on the proposed non-prescription use. An overview of the use of the product including the extent of exposure in other jurisdictions where the product has been available without prescription should be provided.
- d) A comprehensive literature review including a copy of all cited references should be included.
- e) The safety profile should be discussed in the context of any proposed change to the indications, dose, posology or population of use.

Supporting efficacy data should be provided where there is a change to the indications for use or the proposed posology for the non-prescription formulation. The MD, MDD and maximum period of treatment, the indications for use, and what would be considered a reasonable course of treatment should be justified. Evidence that a restricted dose retains efficacy and a positive benefit/risk ratio in the context of the new use should be provided. Any restrictions proposed for the pack size must reflect the intended duration of use. Other factors that need to be taken into consideration include whether the substance is a narcotic or a psychotropic, or might be abused or used for illegal purposes.

Risk minimisation plan

Where there are potential or identified risks relating to the reclassification of the method of sale and supply of a medicine and it is proposed that such risks can be managed with the intervention of a pharmacist, risk minimisation measures may be required in support of the application for reclassification. Risk minimisation strategies should be outlined where appropriate. In some situations, where an expanded role for the pharmacist is considered, details of any literature/educational materials that the pharmacist might use or provide to the

patient should be appropriately justified and included in the application. The SmPC, label and package leaflet are the primary reference documents for information and should form the basis for any educational materials.

Labels and package leaflet

Full colour mock-ups of labels and package leaflets should be provided for review. Particular emphasis is placed on labels and package leaflets in these applications in order to minimise the risk for patients who are inexperienced in the interpretation of medication labels or have difficulty reading and understanding the instructions or evaluating the risks and benefits of use for the product in question. The expert report must discuss in detail any changes to the labelling or package leaflet and outline measures taken to minimise the potential risks associated with the proposed change in classification.

User testing

The label and the package leaflet need to undergo user and readability testing or a clear justification for its omission should be provided.

Pre-launch or marketing material

All advertising material should comply with the provisions of Medicinal Products (Control of Advertising) Regulations, 2007, S.I. No. 541 of 2007. On occasion applicants may be requested to submit advertising/promotional materials to the HPRA Advertising Committee for review. To avoid confusion for stakeholders, potential status changes of products should not be promoted prior to their approval.

6.2 Reclassification from pharmacy-only status to general sales status

All applications require:

- 1 A clinical expert report demonstrating that this product can with reasonable safety be sold or supplied without the supervision of a pharmacist
- 2 A safety/efficacy summary
- 3 Full colour mock-ups of product information
- 4 Package leaflet or label user test (as appropriate) or a justification for its omission
- 5 Risk minimisation plan, where necessary

Clinical expert report

General sales status refers to availability of certain medicinal products that can with reasonable safety be sold other than by or under the supervision of a pharmacist, in pharmacies or non-pharmacy retail outlets. The product in question must have a well-established safety profile when used correctly. Normally products that have or are applying for general sales status are in widespread use at pharmacy level for a number of years prior to

the application for general sales status. The products in question are used for short term treatment of conditions which can be easily self-diagnosed. However, it is not considered that all products would necessarily progress from pharmacy-only to general sales.

The rationale for the proposed move from pharmacy-only to general sales status for the product in question must be clearly outlined in the application. The indications, proposed MD and MDD and duration of treatment in the general sales setting should all be discussed and justified in the context of the known contraindications, warnings, side effects and potential for abuse/misuse. Pack sizes intended for general sales should be justified and should reflect the intended duration of use.

The key factors that must be addressed in the clinical expert report are:

- a) The risk associated with the use and potential misuse of the product for patients who have self-assessed their symptoms and are selecting a medication without the guidance or assistance of a healthcare professional balanced with the potential benefit to the patient of greater availability of the medication.
- b) The risk of direct safety concerns such as a risk of a known serious side effect or incorrect use of a product.
- c) The risk of indirect safety concerns such as a delay in effective treatment of more serious medical disorders because symptoms are relieved by an OTC medication. It should be clearly outlined for the patient under what circumstances they should seek medical help.
- d) The clinical expert report must clearly justify such a proposed reclassification in the context of the known safety profile and the suitability of the product for more widespread availability.

Safety and efficacy expert report

An overview of the known safety profile should be provided including a bridging summary of relevant PSUR data and a summary of all relevant clinical safety and post marketing safety studies. Reports relating to overdose, misuse or abuse should be discussed.

Comparison with similar products with general sale status or data relating to general sales use in other jurisdictions may be provided for review but should take into consideration that differences in approach may be present between different countries' health systems. Risk minimisation proposals should be outlined in this summary if appropriate.

It is unlikely that new efficacy data should be required for an application for general sale status unless the applicant is proposing a new indication, route of administration or posology for the general sale list (GSL) product. A suitable duration of treatment should be identified

and justified along with a proposed pack size. A comprehensive literature review including a copy of all cited references should be included.

Full colour mock-ups of package leaflet and label

A key requirement for an application for general sale status is that the package leaflet and label must be clear, simple and readable so that consumers can easily access information about the product's benefits and risks and how the drug should be used most effectively so that they can choose the appropriate medicine for their condition in the absence of the intervention of a healthcare professional.

Points to note:

- a) Clear and adequate information must be available at the point of access (i.e. on the label) for the patient so that they can make an informed choice.
- b) The product information should also provide clear instruction on when to seek medical advice.

The expert report should detail how any proposed changes to the labelling facilitate safe use of the product while minimising the risk of potential hazards. Mock-ups of the package leaflet and label should be provided. User testing is required. It is strongly recommended that child resistant containers should be provided for all products that are available over the counter.

Risk minimisation

Where there are potential or identified risks relating to the reclassification of the method of sale and supply of a medicine, risk minimisation measures may be required in support of the application for reclassification. Risk minimisation strategies should be outlined where appropriate. Details of any literature/educational materials that might be used or provided to the patient should be included in the application as part of the risk minimisation plan if appropriate. The SmPC, label and package leaflet are the primary source documents for information for patients and should form the basis for any educational materials.

Pre-launch or marketing material

All advertising material should comply with the provisions of Medicinal Products (Control of Advertising) Regulations 2007, S.I. No. 541 of 2007. On occasion applicants may be requested to submit advertising/promotional materials to the HPRA Advertising Committee for review. To avoid confusion for stakeholders, potential status changes of products should not be promoted prior to their approval.

7 EXCLUSIVITY FOR CHANGE IN LEGAL STATUS OF A MEDICINE

Any application for reclassification of a medicinal product that includes results of pre-clinical tests or clinical trials that are the basis for the change of classification, entitles the applicant to one year's exclusivity. Article 74a of Council Directive 2001/83/EC, introduced by Directive 2004/27/EC states that "Where a change of classification of a medicinal product has been authorised on the basis of significant preclinical tests or clinical trials, the competent authority shall not refer to the results of those tests or trials when examining an application by another applicant for or holder of marketing authorisation for a change of classification of the same substance for one year after the initial change was authorised". In this case the one-year period of data protection starts from the date of issuing of the authorisation or variation relating to the reclassification.

The HPRA may not refer to this data when examining other applications for the same substance up to one year after the initial change. In order for the periods of exclusivity to be granted the HPRA must consider that the new data is critical for approval of the reclassification application.

Applicants wishing to claim exclusivity should highlight this in the cover letter accompanying the applications.

8 CONSULTATION AND ADVICE

Applicants are welcome to contact the HPRA in advance of any given application for specific advice if required.

Applications may be reviewed by external experts and advisory committees during the assessment procedure.

9 TIMELINES

Applications can be submitted at any time in the calendar year and adhere to the timelines for national or European procedures, as appropriate. All applications should be submitted to the Receipts and Validation Section of the HPRA. All applications should be clearly marked as 'SWITCH' applications.

The HPRA strongly recommends electronic submission of applications and related information in line with the 'Guide to Electronic Submissions - Human Medicines'. New applications should be submitted by CESP or e-mail to submissions@hpra.ie or be sent on CD/DVD or memory stick to:

Receipts and Validation,
Health Products Regulatory Authority,
Kevin O'Malley House,
Earlsfort Centre,
Earlsfort Terrace,
Dublin 2
D02 XP77
Tel: +353 1 6764971
Fax: +353 1 6767836

ANNEX I REFERENCE DOCUMENTS

Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (Consolidated version)

Medicinal Products (Prescription and Control of Supply) Regulations, 2003

Medicinal Products (Control of Placing on the Market) Regulations, 2007. S.I. No.540 of 2007,

Misuse of Drugs Regulations, 1988, S.I. No. 328 of 1988

Medicinal Products (Control of Advertising) Regulations, 2007, S.I. No. 541 of 2007

A Guideline on Changing the Classification for the Supply of a Medicinal Product for Human Use (The Rules governing Medicinal Products in the European Community Volume 2C: Guidelines Revision January 2006)

Guideline on Legal Status for the Supply to the Patient of Centrally Authorised Medicinal Products Doc. Ref. EMEA/186279/2006

The EU Guideline on the Readability of the Label and Package Leaflet of Medicinal Products for Human Use

HPRA 'Guide to Labels and Leaflets of Human Medicines'

HPRA 'Guide to Invented Names of Human Medicines'

CMDh Best Practice Guide for Authorisation of non-prescription medicines in the decentralised and mutual recognition procedures

CMDh procedural advice on changing the Reference Member State

EMA guideline on good pharmacovigilance practices (GVP) Module I – Pharmacovigilance systems and their quality systems (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129132.pdf)

ANNEX II NATIONAL INFORMED CONSENT APPLICATIONS

This Annex describes the steps to follow when submitting an informed consent (Article 10c of Directive 2001/83/EC) marketing authorisation application to the HPRA. An application is made for a medicinal product possessing the same qualitative and quantitative composition in terms of active substances and the same pharmaceutical form of an authorised product where consent has been given by the existing marketing authorisation holder to use their data in support of this application. The procedural time for the evaluation is reduced to 60 days.

The checklist approach is dependent on the reference marketing authorisation for which informed consent is provided, to aid compliance with current regulatory requirements including update of specifications in line with new or amended pharmacopoeial monographs and minimum requirements for particular SmPCs.

Product name: _____

Company name: _____

PA number: _____

Items to check
<p>SmPC</p> <p>The SmPC should be in line with the SmPC of the reference product, an authorised medicinal product in Europe. However, before submission the reference SmPC should have been updated in line with the EC Guideline on Summary of Product Characteristics and the format of the SmPC should be aligned with the QRD SmPC template.</p>
<p>Package leaflet</p> <p>The package leaflet should be in line with the package leaflet of the reference product, an authorised medicinal product in Europe. However, before submission the format of the package leaflet should be aligned with the QRD template.</p>
<p>User testing</p> <p>Provide results of user testing of the package leaflet in line with the EC Guideline on the Readability of the Labelling and Package Leaflet for Medicinal Products for Human Use, or a justification as to why these are not required.</p>
<p>Labelling</p> <p>Refer to the HPRA Guide to Labels and Leaflets of Human Medicines.</p> <p>For general guidance, the following EU and EMA guidelines are also applicable to labels and package leaflets:</p> <ul style="list-style-type: none">- EU guideline on excipients in the label and package leaflet of medicinal products for human use- EU guideline on readability of the label and package leaflet for medicinal products for human use- Note for guidance on Declaration of storage conditions A in the product information for medicinal products; B for active substances- EMA guideline on quality aspects included in the product information for vaccines for human use- EMA guideline on the warning on transmissible agents in summary of product characteristics (SmPCs) and package leaflets for plasma-derived medicinal products
<p>Provide representative colour mock-ups of all components, (e.g. label, carton, package leaflet, blister etc.) and ensure that the spaces for location of batch and expiry date details are identified. Provide mock-ups for all pack presentations in accordance with HPRA requirements.</p>

Ensure adequate differentiation between products in the same range.
OTC products with two or more active ingredients should include the international non-proprietary name (INN) and strength as part of the product name, clearly displayed on both carton and label with equal prominence to all active ingredients (see the HPRA Guide to Labels and Leaflets of Human Medicines available on www.hpra.ie).

Braille to be included plus an explanation of how the applicant will provide additional package leaflets in alternative formats.

Application form

Ensure the correct version is used.

Complete administrative data should be provided with consent to pharmaceutical, preclinical and clinical data. The authorised product and the informed consent application can have the same or different marketing authorisation holders.

Details of authorised product in the EU or Member State where the application is made:

- Product name, strength, pharmaceutical form;
- Marketing authorisation holder;
- Marketing authorisation number(s): Attach letter of consent from the marketing authorisation holder of the authorised product.

Ensure all sections of the form are completed. Where sections are not applicable, do not leave blank but state 'Not applicable' or 'N/A'.

The application form should address any requirements introduced since transposition of the Directive e.g. requirements for description of the Pharmacovigilance system, GMP requirements for active ingredients etc. (see specific details below), even if these were not included on the authorisation of the reference product.

In addition to the Annex checklist (Annexes 6.1 to 6.22), remember to include the following:

- Informed consent letter
- Manufacturers of active ingredient and finished product - each API manufacturer needs to have a statement by the QP of the product manufacturer in relation to GMP (Annex 6.22)
- If using a contracted service to submit the application, include a letter of access for direct communication concerning the application
- Letter confirming the applicant has access to all of the data supporting the application and is in possession of the quality section of the dossier
- If the product manufacturer is not the applicant, a letter from the manufacturer confirming that they are prepared to manufacture the product on the applicant's behalf
- Suppliers' statements concerning TSE risk (e.g. lactose, glycerol).
- Detailed description of the Pharmacovigilance System. Section 1.8.1 (Module 1).
- The Qualified Person for Pharmacovigilance (QPPV) should be included in section 2.4.4 of the MA form and a CV of the QPPV attached in Annex 5.5

Ensure all Ph Eur Certificates of Suitability for both active and TSE risk excipients are up to date by checking the EDQM website (www.edqm.eu).

Ensure expert statements/overall summaries and overviews (Module 2) with relevant signature pages and CVs are included (Module 1.4.1, 1.4.2 and 1.4.3).

- Statements are required from pharmaceutical, preclinical and clinical experts.
- Clinical experts should be registered medical practitioners within the European Community.

Environmental risk assessment (ERA)

Where the application does not present a different or additional environmental risk to the reference product currently approved, absence of an ERA may be justified but should be addressed in the Expert Report. See the CHMP guideline on environmental risk assessment of medicinal products for human use.

Ensure the HPRA's additional data requirements are included.

Specifications must comply with current pharmacopoeial monographs, unless otherwise approved by the HPRA and must include general monographs (e.g. substance for pharmaceutical use, residual solvents, uniformity of dosage units etc.).

Ensure the manufacturing process includes the maximum validated batch size.