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# HPRA MEDICINAL PRODUCTS NEWSLETTER

ISSUE 49

## In this Issue



## General

# Herbal Medicines Information Seminar - 14th January

The HPRA held an information seminar on herbal medicines on Wednesday 14th January. This was the fourth event on herbal medicines held by the HPRA (formerly Irish Medicines Board, IMB) since the implementation of the EU directive on traditional herbal medicinal products in Ireland in July 2007.

There were over 70 attendees including industry authorisation and registration holders, manufacturers, distributors, retailers and herbal practitioners. Representatives from the Department of Health and the Food Safety Authority of Ireland (FSAI) also attended.

The purpose of the seminar was to promote compliance and there were presentations from the licensing, safety monitoring and compliance departments of the HPRA. Topics covered in the presentations included the quality and clinical requirements for authorisation or registration of herbal medicines, the pharmacovigilance requirements, observations from the HPRA quality defect and recall programme and the updated approach to compliance monitoring.

There was lively and interactive discussion and the feedback was highly positive. The presentations are available to registered attendees on our website.

HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2, Ireland
T: +353 1 676 4971 E: info@hpra.ie **www.hpra.ie**

# Proactive Approach to Reclassification (Switching)

The Health Products Regulatory Authority (HPRA) is responsible for the classification of medicines as prescription or non-prescription and their availability for sale in pharmacies only or in general retail outlets. This is often referred to as the Method of Sale and Supply (MoSS). The process for changing the MoSS is referred to as reclassification or switching.

## Background

In 2011 the HPRA, then Irish Medicines Board (IMB), established the independent Consultative Panel on the Legal Classification of Medicines to review policies relating to the legal classification of human medicines and to develop recommendations to address current unmet needs in the availability of non-prescription medicines.

The Panel concluded its work in 2013 and recommended that a proactive and transparent process to encourage applications for reclassification should be made, with a deeper and more direct engagement being undertaken between the HPRA and marketing authorisation holders (MAHs) in order to facilitate timely consideration and resolution of the issues which can arise in the course of examining such applications.

A proactive approach will ultimately increase the range of medicines that can be made available to Irish patients through pharmacies or general sale outlets without prescription. This approach is consistent with current Irish healthcare policy which aims, where appropriate, to provide patients with increased access to healthcare at the lowest level of complexity and cost.

In general, medicines appropriate for reclassification are those for conditions suitable for self-diagnosis and self-treatment, where there are clear instructions for use, a defined maximum dose and maximum daily dose and an appropriate duration of use, an appropriate safety profile in terms of contraindications, special warnings, interactions, use in pregnancy/lactation, sedation, adverse effects and potential for overdose.

## Progress

In July 2014, the HPRA published a list of twelve active substances (or combinations of substances) currently classified as prescription-only medicines (POM) for which it considers the MoSS classification could be safely switched from prescription only medicine (POM) to over the counter (OTC) pharmacy sale (not subject to medical prescription). This was the first occasion on which the Authority proactively invited the submission of reclassification applications. The list is available on our website.

The HPRA has been engaging with the relevant MAHs for these medicines and is progressing applications. Some MAHs have indicated that they are not interested in progressing applications for commercial reasons. While this is disappointing, the Authority is continuing to review the suitability of additional active substances for reclassification and is engaging directly with MAHs to establish their interest in submitting applications. The present focus involves reclassification of prescription medicines. This will be extended over time to include reclassification of medicines currently available for sale through pharmacies to make these available, where it is considered safe to do so, in general retail outlets. Notice of any reclassifications will be published, following approval of applications.

## Expressions of Interest and Applications

In addition to identifying medicines containing substances suitable for reclassification, the HPRA is requesting expressions of interest from MAHs in respect of other potential reclassifications. Expressions of interest should be made by email to moss@hpra.ie and should include details of the medicine, including the name and PA number, if the medicine is authorised.

Following receipt of expressions of interest, the HPRA will engage with each MAH in order to determine an appropriate timeframe for submission of the relevant switching application and supporting documentation. Pre-submission scientific and procedural advice on individual applications will be available to interested MAHs, in the form of telecon, email correspondence and face-to-face meetings with relevant HPRA staff.

The HPRA Guide to Reclassification (Switching) of Legal Supply Status of Human Medicines is available on our website.

For further information and to request scientific or procedural advice relating to switching the legal classification of a particular medicinal product, please email moss@hpra.ie.

# New EU Clinical Trials Regulations

The Clinical Trials Regulation (Regulation (EU) No 5036/2014) was published in the Official Journal of the EU (OJEU) in May 2014 and is available on the EU website (www.eur-lex.europa.eu).

The regulation, which will replace the existing EU Clinical Trials Directive, will streamline the authorisation process and further harmonise requirements for clinical trials in Europe.

Applicants will now submit a single application for a clinical trial, irrespective of the number of participating member states and there will be one application per member state. The European Medicines Agency (EMA) will host the portal for submission of applications.

A single decision on a clinical trial is required from each member state. In Ireland, this will mean that one decision will replace the current separate approvals given by the HPRA and the ethics committee.

The regulation will apply from 28 May 2016 unless the IT infrastructure that underpins the regulation is not fully functional.

The HPRA has been working closely with the Department of Health, the ethics committees, the EMA and EU member states in preparation for the implementation of the regulation. The HPRA will provide further information updates, as necessary, and plans to hold an Information Seminar, on the new Clinical Trials Regulation, later in 2015.

# Reminder to submit Marketing Status Notifications for all authorisations and certificates

Authorisation and Certificate holders are reminded of their obligation under The Medicinal Products (Control of Placing on the Market) Regulations, 2007, Article 24 (4) and (5) of Directive 2001/83/EC (the "Sunset Clause").

Holders are required to submit notifications of the current marketing status for all authorised products.

Holders must ensure to notify the HPRA of the date that the product was placed on the market and to notify the HPRA no less than two months in advance of a cessation in marketing, either temporary or permanent, unless there are exceptional circumstances.

**Notifications should be made using the form Notification of Marketing Status of Human Medicines** which is available on the HPRA website and should be submitted electronically to medstatus@hpra.ie

Further information is available in the Guide to Notification of Marketing Status of Human Medicines available on the HPRA website.

# Certificates of suitability and retest periods

**The HPRA would like to draw the attention of applicants to the following:**

When submitting a variation that includes a certificate of suitability for an active substance where no retest period is stated on the certificate of suitability, if the applicant wishes to register a retest period for the active substance, a separate Type 1B variation (B.I.d.1.a.4) to assess and approve the stability data is required. Similarly if new stability data is submitted to set/amend a retest date, a separate variation Type 1B variation (B.I.d.1.a.4) is required to assess the new stability data.

Applicants should note that where a defined retest period is not stated on the certificate of suitability and data to support a defined retest period for the active substance have not been submitted to and approved by the HPRA, it is required that the active substance is tested immediately prior to use.

# Declaration form for the 'Detailed Description of the Pharmacovigilance System' relating to applications for veterinary medicinal products

As part of efforts to reduce administrative burden and make best use of available resources, the Co-ordinating Group for Mutual Recognition and Decentralised Procedures - veterinary (CMDv) piloted a process in 2014 to avoid repeated assessment of the same version of the Detailed Description of the Pharmacovigilance System (DDPS) and consequently, try to reduce the number of questions posed on the DDPS.

A DDPS declaration form for use by applicants was developed to facilitate this process and is available for download from the CMDv pages of the HMA website (here) along with instructions on its use.

Following a 12 month pilot phase and based upon positive feedback, the CMDv agreed to continue the use of the DDPS declaration form on an indefinite basis. Although initially piloted in applications for new marketing authorisations using the Decentralised application procedure only, the CMDv agreed to extend the possibility to use the DDPS declaration in all application procedures for new marketing authorisations (but not variations), where use of such a declaration is appropriate.

The declaration form may be used by an applicant to notify National Competent Authorities (NCAs) of any previous assessment and approval of the same version of the DDPS and to allow NCAs reviewing that DDPS to decide whether it is necessary to re-assess and pose questions on the DDPS.

Consequently, the HPRA recommends that you utilise this possibility when submitting your application. If you decide to use the DDPS declaration form, it is recommended that the completed and signed DDPS declaration form is included as a supplementary annex 5.20 in the Part Ia –admin-info folder of your application and entitled 'DDPS-declaration'. Note that provision of a DDPS declaration form is in addition to, not instead of, the actual DDPS, which must still be provided in annex 5-20.

**Summary of how to use the DDPS declaration:**

1. Use of the DDPS declaration by applicants is optional. However, applicants are strongly encouraged to complete the declaration to facilitate avoidance of repeated assessment of the same version of the DDPS.
2. The DDPS declaration may be used for all new marketing authorisation application procedure types (not variations), where use of such a declaration is appropriate.
3. The DDPS declaration form should only be completed where an applicant intends to submit a version of their DDPS that has already been assessed and accepted within the context of a previous Mutual Recognition, Decentralised or Centralised application procedure.
4. The DDPS declaration is an additional document that may be submitted as part of an application and its inclusion in an application should be suitably highlighted to the Reference Member State.
5. The DDPS declaration may not be used to replace submission of the actual DDPS - the DDPS must continue to be submitted in Annex 5.20 of the application form as usual.
6. It is recommended that the declaration form be submitted as an additional document accompanying Annex 5.20 of the application form in the Part 1a – admin-info folder.
7. All sections of the DDPS declaration form should be completed as fully as possible.
8. Further information/advice may be obtained from the proposed Reference Member State for any forthcoming procedure.

# Veterinary Medicines

## **Capacity** planning

The Veterinary Sciences Department is currently formulating our business plans for 2015. Even if forecasting new applications is a difficult task, we are endeavouring to plan our resources for the year and would appreciate being informed of any requests for HPRA to act as Reference Member State during 2015. By interacting with the HPRA to advise us of upcoming procedures and timeframes we hope to better manage our resources and to facilitate applicants timelines in handling applications for mutual recognition and decentralised procedures. Please contact Ms. Elaine Hynes, Planning & Licensing Manager, (elaine.hynes@hpra.ie) in the first instance.

## **Feedback on Veterinary Medicines Department** Information Day

The HPRA held a Veterinary Medicines Info Day on the 2nd December 2014. The feedback on the meeting itself and on the venue and hospitality arrangements was overwhelmingly positive. We are grateful to everyone who supported the event. The main subject matter of the meeting was the new European proposal for the authorisation and monitoring of veterinary medicines. It is appreciated that the process of reviewing the proposal is complex and will take many months; HPRA will continue to monitor the position as it unfolds. For those who were unable to attend the event, the presentations for the meeting are now available, on request, from Ms. Michelle Sinnott (michelle.sinnott@hpra.ie).

# Compliance

## **New Tools for Manufacturers** to help prevent Medicines Shortages

In recent years, there have been a number of cases where shortages have resulted in critical medicines not being available for patients. Whilst Marketing Authorisation Holders have a responsibility to ensure availability of the medicinal products which they place on the market, shortages of medicines may also result from issues arising at the manufacturing site. Manufacturers have a role to play in preventing these shortages.

In November 2012 the European Medicines Agency (EMA) published a Reflection Paper on the subject of medicinal product supply shortages caused by manufacturing/Good Manufacturing Practice Compliance problems.

Industry representative bodies have also recognised the important role which manufacturers have in ensuring continued availability of medicines, and have recently collaborated, in the form of an Inter Association Task Force, to work on this area. The output from this work is a set of tools which may be used to:

- identify critical products in the context of a potential shortage;
- proactively guard against shortages arising;
- ensure effective communication to regulatory authorities should a potential shortage emerge.

The EMA, and a number of regulatory authorities, have also contributed to the development of these tools and manufacturers are encouraged to use these to prevent shortages of their products.

Contd.

# Compliance

The tools which are currently available are listed below, and links are also provided to the websites where these can be accessed.

**ISPE Website**

The ISPE Drug Shortages Prevention Plan is available on their website www.ispe.org

**PDA Website**

The following tools are available from the PDA website

- Drug Shortage Risk Register
- Drug Shortage Prevention and Response Plan - Risk Triage Approach for Proactive Management of Drug Shortage

**Tool under development**

A tool for standardising communication of shortages to regulatory authorities is being jointly developed by the following associations; EFPIA EGA, AESGP and PPTA, and will be published when finalised.

# **Amendment to the Misuse** of Drugs Regulations

The Minister for Health approved the Misuse of Drugs (Amendment) (No. 2) Regulations 2014 (S.I. No. 583 of 2014) on the 17 December 2014.

The Misuse of Drugs Regulations apply controls to the drugs specified in Schedules 1 to 5 of the Regulations (being drugs to which the Misuse of Drugs Acts 1977 and 1984, as amended, apply) the effect of which is to impose restrictions on the production, supply, possession, importation and exportation of the drugs in question. The restrictions applied to these drugs vary according to the extent to which these are used for medical or scientific purposes and having regard to the likelihood of their abuse.

S.I. No. 583 of 2014 amends the Regulations by adding certain substances to Schedule 1. In addition, it increases the extent of the controls applicable to 4-Hydroxybutanoic acid, also known as gamma-hydroxybutyric acid (GHB), and its sodium salt form, which is known as sodium oxybate. 4-Hydroxybutanoic acid, which was previously listed within Schedule 3 of the Regulations, is now listed within Schedule 2.

Accordingly, a registration, issued by the Department of Health, as was the case previously, will no longer suffice in respect of supplying, possessing, importing or exporting 4-Hydroxybutanoic acid. Companies which supply, possess, import or export 4-Hydroxybutanoic acid should contact the HPRA at controlleddrugs@hpra.ie as any of these activities now requires a licence which must be renewed annually.


Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2, Ireland
T: +353 1 676 4971 E: info@hpra.ie www.hpra.ie

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