IRISH MEDICINES BOARD

MEDICINAL PRODUCTS
newsLETTER

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GENERAL

CHANGE IN THE PROCEDURE FOR ISSUING VARIATIONS

The IMB would like to take this opportunity to advise Marketing Authorisation Holders (MAHs) of a change to our existing process for issuing variations to marketing authorisations where the renewal of the authorisation remains outstanding.

Previously when the assessment of a variation to update to the Summary of Product Characteristics (SmPC) was completed but the renewal was still outstanding, the case was not issued and was held until the renewal of the authorisation had been completed and issued. The variation case was then issued independently of the renewal.

In the interest of ensuring that product information updates, particularly those relating to safety issues are made in a timely manner and that the updated information is available to healthcare professionals and patients, we are implementing a change to this practice. The IMB will now issue all approved variations even where the authorisation renewal is outstanding. However, the IMB wishes to emphasise to MAHs that this change does not in any way negate their responsibility to ensure renewal applications are submitted in a timely manner and at least 9 months before the renewal date.

CLARIFICATION OF THE REQUIREMENTS FOR MARKETING AUTHORISATION HOLDERS, REGARDING COMMUNICATIONS TO HEALTHCARE PROFESSIONALS

Communication with healthcare professionals (HCP) by way of a direct healthcare professional communication (DHPC) is a formal process which provides HCPs with information regarding new and emerging safety issues. National guidance for marketing authorisation holders (MAH) on DHPCs, which is in line with European guidance, is published on the IMB website here.

It is sometimes necessary to communicate with HCPs, in order to highlight changes to the product information or other significant issues. The IMB has decided to call these communications, Product Information Updates (PIUs), in order to distinguish them from DHPCs and 'Caution in Use' notifications. Examples of where the IMB may consider that a PIU is needed include:

- Following the outcome of a referral procedure (Article 30 or 31), which results in changes to indications, posology or contraindications.
- Following the outcome of a Type II variation resulting in changes to indications, posology or contraindications.
- Following the outcome of a Type II switch variation resulting in the first change in the method of sale and supply of an active substance.
- Following the IMB approval of a batch specific request procedure (BSR), where there are significant differences between the product information of the BSR-approved product and the currently authorised product on the Irish marketplace.

Where deemed necessary, the MAH will be requested to prepare a PIU for review by the IMB. The PIU should be entitled 'Important information for healthcare professionals'. The title should be prominent to distinguish the letter from other less critical mail received by HCPs. A subheading can be included to describe the issue that

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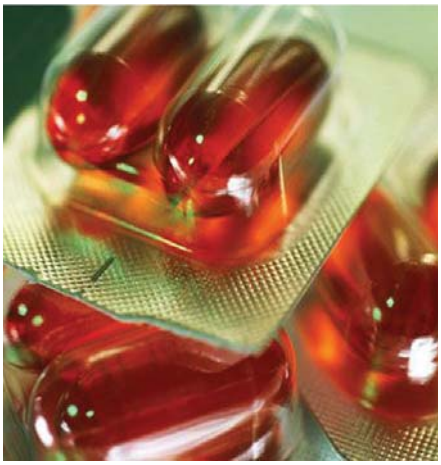
is the subject of the PIU e.g. 'Interruption to supply' or 'New Prescribing Information' etc.

Additional requirements for a PIU:

1. The product names and PA numbers and INN should be included at the top of the letter. Clarification around any non-marketed strength of the product can be provided in the letter e.g. 'The changes also apply to the X strength that is not currently on the Irish market'.
2. The reason for this communication needs to be made clearly described in the introductory paragraph. Where the letter relates to changes to the SmPC, the practical implications of those changes need to be explained in the subsequent text using the standard SmPC headings. The letter can state that it has been agreed with the IMB.
3. References to any documents or literature mentioned in the text should be provided.
4. In cases where alternatives medicines are proposed, it should be ensured that these are authorised in Ireland for the relevant indications and that they are available on the Irish market.
5. Details of the person who should be contacted in the event of queries should be provided.



6. Details of any anticipated duration of the disruption in supply, if relevant, should be included.
7. Provide the IMB with details of the categories of healthcare professionals and professional bodies to be targeted for distribution of the PIU. Clarify whether the MAH will distribute the letter using contact information provided by a professional body e.g. PSI or whether the professional body has agreed to distribute the letter on the MAH's behalf. The IMB should be included in the distribution list for the final agreed letter.

All queries and communications concerning PIUs should be sent to piu@imb.ie

The IMB may also publish PIU letters on its website.

IMB PHARMACOVIGILANCE INFORMATION DAY – 21ST NOVEMBER 2014

The IMB will hold a Human Medicines Pharmacovigilance Information Day on Friday 21 November 2014. The meeting will particularly focus on the European Pharmacovigilance legislation: Two years post implementation.

A preliminary agenda will be published shortly and stakeholders are welcome to propose any specific topics/areas they would like addressed, for consideration.

This information day will be of interest to those dealing with pharmacovigilance of human medicinal products (Marketing Authorisation Holders (MAHs) and Healthcare professionals (HCPs)).

The event will be held from 9am to 5pm at the Crowne Plaza hotel, Santry, Dublin. Details of the venue can be found on the website www.crowneplaza.com.

HUMAN MEDICINES

MINOR CHANGES TO PRODUCT INFORMATION

The IMB would like to clarify its procedure for minor changes to product labelling and package leaflets under Article 61(3) of Directive 2001/83/EC as amended. This Article states that 'all proposed changes to an aspect of the labelling or the package leaflet covered by this title and not connected with the summary of product characteristics shall be submitted to the authorities competent for authorising marketing'. The IMB previously published a list of minor amendments to the labelling and package leaflet which do not require prior notification to the IMB in the Guide to Labels and Leaflets of Human Medicines. Following a review, the IMB has identified some additional minor amendments to the labels and the leaflet which are not considered to require a formal assessment. Therefore the list has been expanded to include the following additional changes:

- Reorientation of a pictogram without any changes to the wording or meaning and with no impact on legibility.
- Change to the size, colour or font of a company logo or trademark on a carton that is similar in size to the currently approved logo/trademark and does not interfere with the legibility of the required text.
- Deletion of the MAH logo or trademark on the carton (but MAH still clearly identified).
- Change to the trademark statement on a carton/leaflet e.g. if a statement is changed from 'Product X is a registered trademark of Company Y' to 'Product X is a registered trademark', and there are no other changes to the text.
- Placing a previously non-marketed pack size on the market, where the

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content, font size and appearance of the label text are identical to the marketed pack, apart from the contents by weight/volume/number of units.

- Addition of a quick response (QR) code or 2D barcode to product labelling and/or package leaflets for internal control purposes or anti-counterfeit measures, with no addition or impact to the approved product information and provided that the conditions outlined in section 9.7 of the Guide to Labels and Leaflets of Human Medicines are met.

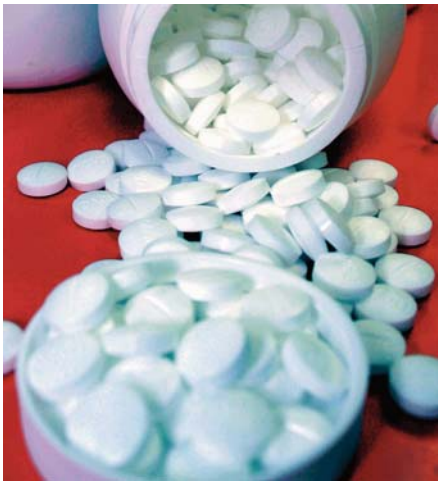
In such instances, the revised labels or patient leaflet should be submitted to the IMB at the next regulatory activity involving a change in the product information.

Any and all other changes to product labels or package leaflets, other than those minor changes listed in section 10.3 of the Guide to Labels and Leaflets of Human Medicines, will continue to require a formal notification, as before.

ONGOING IMPLEMENTATION OF THE PROVISIONS OF THE PHARMACOVIGILANCE LEGISLATION

IMPLEMENTATION OF TEXT HIGHLIGHTING ADDITIONAL MONITORING REQUIREMENTS AND STATEMENTS ENCOURAGING REPORTING OF ADVERSE REACTIONS

Information on the initial list of medicines subject to additional monitoring requirements and the symbol identifying them was published (25 April 2013) by the European Medicines Agency (EMA) on its website. This initial list will be reviewed and updated, as necessary, following consideration by the Pharmacovigilance Risk Assessment Committee (PRAC) at its monthly meetings. Medicinal products may be included or removed from this list either in the context of a regulatory procedure (e.g. marketing authorisation application, extension of indication, renewal), or



outside the circumstances of a regulatory procedure.

The EMA published an updated product information template for centrally authorised products to label medicines subject to additional monitoring. Applicants must implement the inverted black triangle, additional monitoring statement and statements encouraging the reporting of suspected adverse reactions for new marketing applications by complying with the QRD template and the country specific information as stated in Appendix V. December 31st 2013 was the timeline for implementation of these changes for existing centrally authorised marketing authorisations.

The Co-ordination Group for Mutual Recognition and Decentralised Procedures-Human (CMD(h)) has published guidance for MAHs in relation to the implementation of the inverted black triangle, additional monitoring statement and the statements encouraging reporting of suspected adverse reactions in MR/DC products. The guidance appears in their Questions and Answers document on variations and requires compliance with the revised QRD template and county specific information as stated in Appendix V.

For nationally authorised products which are subject to additional monitoring, the IMB will apply the same procedure as outlined in the CMD(h) guidance provided for products authorised through the MR/DC procedure. The text to be included should be identical to that outlined in the most recent version of the QRD template for MR/DC procedures published on the CMD(h) website.

All medicinal products (including those not subject to additional monitoring) should include a standard text in their product information requesting that healthcare professionals report any suspected adverse reactions in accordance with the national spontaneous reporting system referred to in Article 107a(1) (Art. 11 of Directive 2001/83/EC). Patients should also be requested to communicate any suspected adverse reaction to his/her doctor, pharmacist, healthcare professional or directly to the national spontaneous reporting system referred to in Article 107a (1). The text to be included for all products (centrally authorised products, MR/DC products and nationally authorised products) is outlined in the revised QRD template and country specific information is stated in Appendix V. The updates for nationally authorised products should implemented as soon as possible, but no later than April 2015 for products with regulatory activity and April 2016 for medicinal products with no regulatory activity.

The IMB has recently published a Guidance document for Marketing Authorisation Holders on implementation of text highlighting additional monitoring requirements and statements encouraging reporting of adverse reactions. This guidance document is available at www.imb.ie

VETERINARY MEDICINES

REPORT ON VETERINARY ANTIMICROBIAL CONSUMPTION IN 2012 AND UPDATE ON COLLECTION OF THE 2013 DATA

A report on the consumption of veterinary antimicrobials in Ireland during 2012 is available on the IMB website (www.imb.ie). The consumption data follow a similar pattern to previous years, although it appears that there has been an increase in overall consumption.

In accordance with the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) requirements, the IMB will shortly commence the collection of data on the supply of antimicrobials to the Irish market for the year 2013. The reporting form is expected to be largely similar to that of previous years. The Excel form will be released to marketing authorisation holders by the IMB as soon as it is finalised in early February 2014. Please note that the spread sheet contains in-built formulas, which might not work if the document is copied for completion elsewhere.

Any queries on the use of the form should be sent to the IMB (gavin.ryan@imb.ie). For those applicants who do not have access to the data collection form, it is available on request from the IMB (michelle.sinnott@imb.ie).

UPDATE ON NEW EU LEGISLATIVE PROPOSAL

The IMB understands that the proposal for new European legislation governing the authorisation, use, supply and monitoring of veterinary medicinal products is nearing finalisation by the EU Commission. Publication is expected during the first half of 2014. Once available, the IMB plans to host an IMB Veterinary Medicines Information Day to help communicate the key changes to stakeholders. Details of the event will be available on the IMB website in due course.

PILOT PHASE FOR USE OF A DDPS DECLARATION.

The Coordinating Group for Mutual Recognition and Decentralised Procedures-Veterinary (CMDv) has been exploring ways to improve the functioning of the Decentralised procedure whilst making best use of available resources and minimising administrative burden within the current legislative framework.

One area identified by the CMDv as having potential for improved functioning is the reduction of repeated assessment of the same Detailed Description of the Pharmacovigilance System (DDPS) and consequent questions during the Decentralised procedure.

Following a period of consultation by CMDv with those responsible for assessing DDPSs within the national competent authorities, the CMDv agreed at their November 2013 plenary meeting to pilot the use of a DDPS declaration as a means to avoid repeated assessment of the same DDPS and consequently try to reduce the number of questions posed on the DDPS.

Note that applications for marketing authorisations must still continue to submit the DDPS in annex 5.20 of the application form. However, applicants may now choose to additionally complete a DDPS declaration which provides minimum information on when the **same version** of their DDPS has previously been assessed by competent authorities during either a Mutual Recognition, Decentralised or Centralised application procedure. Member States reviewing the DDPS in a new Decentralised application procedure may then decide whether it is necessary to re-assess and pose questions on the DDPS.

The pilot phase is scheduled to be introduced by the end of January 2014 and will be for a twelve month period. This initiative relates specifically to the same version of a DDPS previously accepted by Member States and will initially be restricted to new applications submitted using the Decentralised procedure. The DDPS declaration form and information on its use will be available on the CMDv pages of the Heads of Medicines Agencies website before the pilot phase commences. Applicants may also obtain further information on its use from the Reference Member State of forthcoming Decentralised procedures.

COMPLIANCE

AMENDMENTS TO REGULATION (EC) NO. 273/2004 AND COUNCIL REGULATION (EC) NO. 111/2005

Updates to two key pieces of legislation relating to precursor chemicals (known as scheduled substances) have recently been published in the Official Journal of the European Union (L 330). The original pieces of legislation are Regulation (EC) No. 273/2004 (as amended) and Council Regulation (EC) No. 111/2005 (as amended). The amending regulations are Regulation (EU) No. 1258/2013 and Regulation (EU) No. 1259/2013 respectively.

The main objective of these amendments is to strengthen the rules for registration and licensing of operators and users of scheduled substances in order to prevent diversion of scheduled substances towards illicit drug production.

These amendments have an effective date of 30 December 2013 with the exception of the requirements for category 2A scheduled substances which will only become obligatory as of 30 June 2015.

The main amendments to Regulation (EC) No. 273/2004, which deals with trade within the EU that are relevant to operators are:

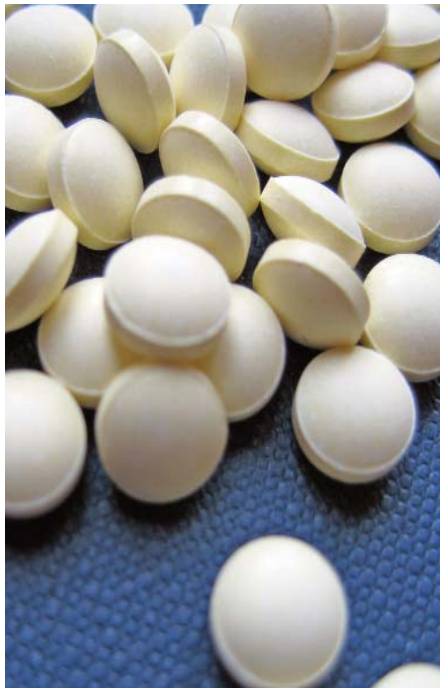
- Addition of alpha-phenylacetoacetonitrile (APAAN) to Annex I as a category 1 scheduled substance.
- Removal of category 2 of Annex I and its replacement within Annex I with two new categories, 2A and 2B. All previous category 2 scheduled substances will now be in category 2B with the exception of acetic anhydride which will be placed in category 2A.
- Requirement for end users of Annex I category 2A scheduled substances to obtain a registration in order to receive and/or possess a category 2A scheduled substance.
- Suppliers of acetic anhydride should note that they can only supply to those in possession of a category 2A registration.
- Creation of an EU database, to include a list of licensed and registered operators of scheduled substances, for licensing authorities.

The main amendments to Council Regulation (EC) No. 111/2005, which deals with trade between the EU and third countries, that are relevant to operators are:

- Addition of alpha-phenylacetoacetonitrile (APAAN) to the Annex as a category 1 scheduled substance.
- Creation of a new category for scheduled substances, category 4, in the Annex.
- Addition of human medicinal products and veterinary medicinal products containing ephedrine and pseudoephedrine into category 4.
- Requirement for all exports of scheduled substances listed in category 4 to obtain an export authorisation prior to export from the EU.

In order to comply with the above new requirements, operators within Ireland that meet any of the criteria identified below are requested to contact the IMB at controlleddrugs@imb.ie

- Possess, supply, or produce acetic anhydride and do not currently hold a registration with the IMB for this substance.
- Possess, supply or produce alpha-phenylacetoacetonitrile (APAAN).
- Export medicinal products (human or veterinary) containing ephedrine or pseudoephedrine to third countries.



GENERAL SALE WHOLESALE DISTRIBUTORS – UPDATE TO THE ANNUAL COMPLIANCE ASSESSMENT REPORT AND CHANGES TO THE INSPECTION PROCESS AND ITS FREQUENCY

The annual compliance assessment report forms part of the risk-based approach that is applied to determine the inspection frequency of those wholesalers who engage only in the supply of general sales medicinal products ('general sale wholesale distributors'). The template for this report has been amended in order to clarify when the completed report should be provided to the IMB. We now require that the report, capturing both changes made in the previous year and changes planned for the coming year, is provided during January and no later than 31 January of each year. Under this risk based approach, if a wholesaler doesn't submit the report by the due date, there is an automatic increase to the inspection frequency. The

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updated document can be found on our website under Publications for the page Wholesale Distribution. Changes have also been made to the inspection process and the frequency of inspection that is applied to general sale wholesale distributors. These changes are outlined in the IMB Guide to the Quality System for General Sale Wholesale Distributors. The main points are summarised below:-

- During inspection there will be an increased focus on how activities, such as medicinal product storage and record keeping activities are carried out in practice.
- We will determine the frequency at which a facility is inspected using the factors outlined in the guide as well as the annual compliance assessment report. This can result in the inspection interval ranging from 6 months to 5 years.

UPDATES TO IMB GUIDES FOR WHOLESALERS AND BROKERS OF FINISHED MEDICINAL PRODUCTS

The IMB has recently updated its 'guide to good distribution practice of medicinal products for human use'. This document provides additional clarification to wholesalers and brokers located within Ireland regarding the guidelines of 5 November 2013 on good distribution practice of medicinal products for human use (2013/C 343/01) published by the European Commission. Wholesalers should ensure that they comply in full with all requirements of both the European Commission guidelines and the IMB guidance document.

We have also published a second guide entitled 'Guide to Wholesaling and Brokering of Medicinal Products for Human Use in Ireland'. This document provides guidance on the regulations covering the wholesale distribution and brokering of medicinal products for human use in Ireland, including when authorisation / registration is required and the process for applying for such authorisations / registrations.

Both guides are available on the IMB website.

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