IRISH MEDICINES BOARD

MEDICINAL PRODUCTS newsLETTER

JANUARY–APRIL 2013 Issue No. 44

IRISH MEDICINES BOARD, KEVIN O'MALLEY HOUSE, EARLSFORT CENTRE, EARLSFORT TERRACE, DUBLIN 2 TEL: 01 676 4971 FAX: 01 676 7836 EMAIL: FOI@IMB.IE

## HUMAN MEDICINES

# ONGOING IMPLEMENTATION OF THE PROVISIONS OF THE PHARMACOVIGILANCE LEGISLATION

## (DIRECTIVE 2010/84/EU AND REGULATION (EU) 1235/2010)

### *Update on medicines subject to additional monitoring requirements and texts for inclusion in product information on ADR reporting*

Information on the initial list of medicines subject to additional monitoring requirements and the symbol identifying them has recently been finalised and 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.

Updated templates have been developed by the Quality Review of Documents (QRD) group at the EMA. These include the relevant explanatory content regarding medicines subject to additional monitoring requirements as well as the text for the product information to encourage reporting of suspected adverse reactions by healthcare professionals and patients/consumers. The text encouraging the reporting of suspected adverse reaction applies to all medicinal products and not just those subjected to additional monitoring requirements. Further information, together with details of the relevant content, is available from the EMA website.

The additional local information and contact details for inclusion in the product information (SmPC and PL) is as follows:

### *SmPC text – Section 4.8: Reporting of suspected adverse reactions*

….Healthcare professionals are asked to report any suspected adverse reactions preferably through the online reporting option accessible from the IMB homepage. A downloadable report form is also accessible from the IMB website, which may be completed manually and submitted to the IMB via 'freepost', in addition to the traditional post-paid 'yellow card' option.

FREEPOST
Pharmacovigilance Section
Irish Medicines Board
Kevin O'Malley House
Earlsfort Centre
Earlsfort Terrace
Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.imb.ie
e-mail: imbpharmacovigilance@imb.ie

### *PL text – Section 4: Reporting of side effects*

….Reports may be made by following the links to the online reporting option accessible from the IMB homepage, or by completing the downloadable report form also accessible from the IMB website, which may be completed manually and submitted to the IMB via freepost, to the following address:

FREEPOST
Pharmacovigilance Section
Irish Medicines Board
Kevin O'Malley House
Earlsfort Centre
Earlsfort Terrace
Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.imb.ie
e-mail: imbpharmacovigilance@imb.ie

# CONTENTS

## QUALIFIED PERSON'S DECLARATION CONCERNING GMP COMPLIANCE OF ALL SITES INVOLVED IN THE MANUFACTURE OF THE ACTIVE SUBSTANCE

The ICH guideline (Q11) on the development and manufacture of drug substances (EMA/CHMP/ICH/425213/2011) states that the GMP provisions for drug substances described in ICH Q7 apply to all sites involved in manufacture from the first use of the starting material(s). Therefore, in providing the Qualified Person's (QP) declaration with a new application, renewal or variation requiring the submission of a declaration, all sites involved in the synthesis of the active substance, or an intermediate, subsequent to the use of the starting material(s) should be covered by the declaration.

The GMP provisions also apply to any site involved in the processing of the active substance during or subsequent to the synthetic steps but prior to finished product manufacture. For example, this would include sites involved in the milling, purification or blending of intermediate or drug substance. All sites involved in manufacture from the first use of the starting material should also be listed in the relevant application form and in section 3.2.S.2.1 of the dossier.

For active substances supplied to a certificate of suitability (CEP), only those manufacturing sites listed in the certificate will be required to be referenced in the dossier and have a declaration provided.

Applicants are reminded that section 3.2.S.2.1 of the dossier and the QP declaration relate to the actual manufacturing site(s). However, where the active substance is supplied to a CEP the IMB records the CEP holder's name and address in the Product Specific Details section of the schedule issued to applicants.

## UPDATE ON THE VARIATIONS REGULATION: NEW DEVELOPMENTS IN WORK-SHARING FOR NATIONALLY AUTHORISED PRODUCTS AND IMB WILLINGNESS TO ACT AS REFERENCE AUTHORITY

On 4 August 2013, the Variations Regulation (Commission Regulation (EC) No 1234/2008 as amended) will become fully applicable to nationally authorised products only. This will impact on the IMB's current processing of variations for nationally authorised products. From this time, EU timelines will be applied to these variations. Another significant impact will be the introduction of work-sharing procedures for variations for products that are authorised through national procedures within each Member State.

From August, purely nationally authorised products will be eligible to participate in work-sharing involving the same purely nationally authorised products in other Member States. Where suitable, nationally authorised products (provided that there is no, or minimum need, for product-specific assessment) will also be eligible for work-sharing with products authorised through the centralised and/or mutual recognition procedures. This development is intended to introduce further efficiencies and avoid duplication of work.

The reference authority for the work-sharing procedure will perform the assessment on behalf of the other concerned competent authorities. Where the procedure involves a centralised product, the reference authority will be the EMA. Where it involves a product authorised through the mutual recognition procedure, the reference authority will most likely be one of the Reference Member States. However, in the case of purely national products, where there is no obvious reference authority, marketing authorisation holders (MAHs) will be free to nominate their reference authority of choice to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh). The final decision on the choice of reference authority will be made by the CMDh.

The IMB would like to highlight its willingness to act as reference authority for variation work-sharing procedures, especially those involving purely national products. From August, experienced assessment resources and capacity will be available in both the quality and clinical assessment areas to participate in these work-sharing procedures. Interested parties are invited to approach the IMB with details of expected future work-sharing applications including the scope and nature of the proposed changes, the number of products and Member States that would be involved. Information should also be provided on the anticipated timeline for the submission of the variations. Details can be provided to following email address: **variationsworksharing@imb.ie**.

## EUROPEAN COMMISSION PUBLICATION OF REVISION 10 OF THE APPLICATION FORM FOR A MARKETING AUTHORISATION OF A MEDICINAL PRODUCT FOR HUMAN USE (APRIL 2013)

The European Commission has published revision 10 of the application form for a marketing authorisation of a medicinal product for human use. It will be a requirement that applicants use the form from June 2013 onwards.

Further information and an electronic version of this application form is available on the European Commission website.

The application form is to be used for an application for a marketing authorisation of a medicinal product for human use submitted to (a) the EMA under the centralised procedure or (b) a Member State (as well as Iceland, Liechtenstein and Norway) under either a national, mutual recognition or decentralised procedure.

VETERINARY MEDICINES

## REPORT ON VETERINARY ANTIMICROBIAL CONSUMPTION IN 2011 AND UPDATE ON COLLECTION OF THE 2012 DATA

A report on the consumption of veterinary antimicrobials in Ireland during 2011 has recently been published on the IMB website. The data follow a similar pattern to previous years, although it appears that there has been a slight reduction in overall consumption.

In accordance with the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) requirements, the IMB has commenced to collect data on the supply of antimicrobials to the Irish market for the year 2012. The reporting form is similar to that of previous years but has been modified to include drop down lists that facilitate completion of the information. The Excel form being released to marketing authorisation holders by the IMB contains in-built formulas which may not work if the document is copied for completion elsewhere.

It is expected that the data will be collected before **7 June 2013**. Any queries on the use of the form should be sent to gavin.ryan@imb.ie. For those applicants who do not have access to the data collection form, it is available on request from michelle.sinnott@imb.ie.

## IMB VETERINARY INFORMATION DAY 2013

The IMB is planning to host a Veterinary Medicines Information Day on Thursday 24th of October 2013. The event is contingent on the publication by the European Commission of a proposal on the new European legislation governing the authorisation, use, supply and monitoring of veterinary medicinal products. Marketing authorisation holders who would like to suggest other topics that might usefully be addressed during this event are requested to notify the IMB of their suggestions by emailing michelle.sinnott@imb.ie. Should the information day proceed, details concerning the date, venue and registration will be available on the IMB website over the coming months.

## PARTNERSHIP INITIATIVE BETWEEN THE UK, IRELAND, BELGIUM AND THE NETHERLANDS FOR NATIONAL VETERINARY APPLICATION PROCEDURES

Since 2008, Ireland and the UK have operated a national work-sharing scheme for variations known as the Partnership Initiative which was subsequently joined the Netherlands and Belgium. This scheme has been very successful and has enabled a single assessment of variation applications based on the same supporting data in the participating countries.

On 4 August 2013, the scope of the variation regulations will be extended to include products authorised on a national only basis. From that date onwards, national authorisations will be eligible to take part in EU work-sharing procedures and there will therefore no longer be any need to continue the Partnership Initiative. Therefore, no new applications will be accepted under the partnership initiative from **1 July 2013** and applicants will be expected to use the work-sharing procedure. Any applications that are submitted and pass validation in all involved countries **before** 1 July 2013 will be processed under the Partnership Initiative.

## PILOT PHASE OF A VALIDATION CHECKLIST TO BE USED BY THE REFERENCE MEMBER STATE.

The IMB will be participating in a new initiative to try and reduce the administrative burden and repetitive tasks faced by national competent authorities when validating applications for the mutual recognition (MR) or decentralised (DC) procedures.

The initiative was recently agreed at the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Veterinary (CMDv). It is planned that those agencies acting as the RMS in MR and DC procedures will use a validation checklist to validate such applications. Given the high frequency with which the IMB acts as RMS in MR/DC procedures, the IMB will participate in the pilot phase. Although yet to be confirmed, it is envisaged that the pilot phase for using the validation checklist will commence at the beginning of June, or shortly thereafter.

The use of a validation checklist is being trialled with the view to improving the validation phase of MR/DC procedures. As a result of participation in the pilot phase, the IMB will be introducing the use of a software validation tool. It should be noted that there will be no change in the validation requirements or timelines that applicants are expected to meet when submitting electronic applications using the MR/DC procedures to the IMB. However, in order to avoid any potential problems at the validation stage during the pilot phase, applicants are referred to the guidance on submission of electronic applications currently available on the Veterinary eSubmission section of the EMA website.

## STAFF CHANGES IN THE VETERINARY SCIENCES DEPARTMENT

Ms. Lisa Woods, Scientific Officer Pharmacovigilance, started a 12 month secondment at the EMA in February 2013. The IMB wishes her well in her new position. Lisa was replaced by Ms. Deirdre O'Keeffe. Deirdre was previously responsible for review of product literature and that position has been filled by Ms. Orla Hayden.

COMPLIANCE

## NEW IRISH LEGISLATION

The following amendment Regulations concerning placing on the market, manufacture and wholesale of medicinal products have been signed by the Minister of Health and give effect to Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011 (also known as the Falsified Medicines Directive)

- Medicinal Products (Control of Placing on the Market) (Amendment) Regulations 2013 **(S.I. No. 162 of 2013)**
- Medicinal Products (Control of Manufacture) (Amendment) Regulations 2013 **(S.I. No. 163 of 2013)**
- Medicinal Products (Control of Wholesale Distribution) (Amendment) Regulations 2013 **(S.I. No. 164 of 2013)**

The legislation concerning the application of fees by the IMB has also been amended (see below) to include details of the fees which will be levied for the registration processes described in Directive 2011/62/EU.

- Irish Medicines Board (Fees) (Amendment) Regulations 2013 **(S.I. No. 165 of 2013)**

## CONTROLLED DRUGS – LICENCE ENDORSEMENT REQUIREMENTS

The IMB, on behalf of the Department of Health, is responsible for the issuance of licences that allow operators to legally import and export controlled drugs to and from Ireland. The reconciliation of the import and export of controlled drugs is a critical activity and is one mechanism by which potential controlled drug diversion routes can be identified at a global level by the International Narcotics Control Board (INCB). To aid in the monitoring for diversion routes, the Department of Health, in conjunction with the IMB, has a responsibility to report quarterly and annually to the INCB on the quantities imported and exported to and from the state.

Operators that are granted import and export licences are reminded of their legal obligations under the Misuse of Drugs Act 1977 (as amended) and the conditions of their licences which require them to return both import and export licences to the IMB within **seven days** of using the licence (after the relevant associated import/export transaction has occurred). These licences must be endorsed, prior to their return, by way of signature and must also include a written amendment to accurately reflect any change in quantities imported or exported relevant to the amount for which the licence was issued. Where a licence expires prior to its use, it must be returned within seven days of the expiry date, advising the IMB that the licence was not used.

The failure, in a number of instances, to return endorsed licences within the required seven day timeline is of serious concern to the IMB and is a breach of the conditions of the licence. Accordingly, we will now be considering such a breach as a potential trigger for performing an inspection of any licence holder involved.

## REVISED GUIDELINES ON GOODS DISTRIBUTION PRACTICE (GDP) OF MEDICINAL PRODUCTS FOR HUMAN USE

The revised EU GDP guidelines were published in the Official Journal of the European Union by the EU Commission on 7 March 2013. This document will replace the current GDP guidelines published in 1994 (94/C 63/03). The revised guidelines come into operation six months from the publication date of 7 March 2013 and GDP inspections conducted by the IMB will be in accordance with the requirements of the revised guidelines from September 2013.

The guidelines will apply not only to wholesalers and manufacturers of medicinal products but will also incorporate specific requirements for brokers involved in activities relating to the sale or purchase of medicinal products. Other key changes include requirements relating to quality risk management, computerised systems, qualification and validation, management of outsourced activities and transportation. A requirement for contracted storage premises to be covered by a separate wholesale distribution authorisation is clearly stated and we will be further communicating with individual operators in this regard.

## FALSIFIED MEDICINES DIRECTIVE – WAIVER TO WRITTEN CONFIRMATION FOR AN IMPORTED ACTIVE SUBSTANCE

Directive 2011/62/EU (Falsified Medicines Directive), amending Directive 2001/83/EU, is being progressively implemented. After 2 July 2013, active substances may only be imported into the European Economic Area for manufacture of medicinal products for human use if one of the following criteria is satisfied;

1. The imported consignment of active substance is accompanied by a "written confirmation" issued by the relevant authority in the third country where the active substance manufacturer is located;
2. The active substance manufacturer is located in a country where the system for regulation of active substance

→

manufacturers in that country is considered equivalent to that in the EU. A list of third countries which are considered equivalent is available on the European Commission's website;

3. A waiver to the need for a written confirmation has been granted by the IMB for importation/use of an active substance from a third country manufacturer based on GMP certification of that manufacturer by a competent authority in the EEA.

Further information on the requirements for use of imported active substances is available on the EU Commission's website.

It should be noted that any manufacturer or importer intending to avail of a waiver, as referenced above, should apply to the IMB using the Waiver Application Form which is available on our website. The completed Waiver application should be sent to: Compliance Department, Irish Medicines Board, Kevin O'Malley House, Earlsfort Terrace, Dublin 2. A scanned copy of the completed waiver application may also be emailed to compliance@imb.ie.

The waiver may only be used to support importation or use of an active substance if granted by the IMB. Following assessment of the waiver application, the IMB will write to the applicant to confirm whether or not the waiver has been granted. It should be noted that, where a third country is known to issue written confirmations, it would normally be expected that a written confirmation, rather than a waiver, would be used as the basis for importation and use of active substances sourced from that third country.

Under Article 46 (b) of Directive 2011/62/EC, the IMB is required to notify the European Commission of its use of this waiver provision.

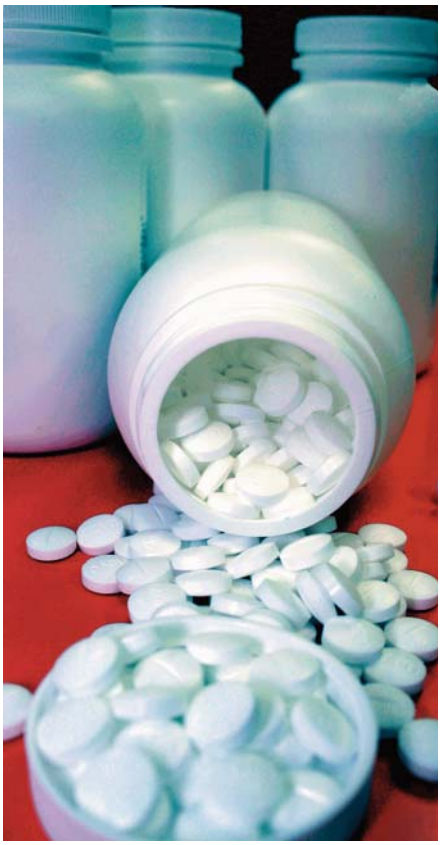
Any questions in relation to an application for, or the granting of, a waiver should be emailed to compliance@imb.ie.

## FALSIFIED MEDICINES DIRECTIVE – UPDATE ON REGISTRATION PROCESS

The registration process for companies involved in certain activities (see categories below), as required by Directive 2011/62/EU (Falsified Medicines Directive), began on the 2 January 2013. To date, we have received 61 registration applications. These are categorised as follows:

- 18 Manufacturers of active substances;
- 32 Importers of active substances;
- 10 Distributors of active substances;
- 1 Broker of finished medicinal products.

Technical assessment of the applications is in progress and the registration process will be completed when the Directive has been transposed into national legislation. Transposition is expected in the coming weeks following which registration documents will be issued where an inspection is not required. Where an inspection is required, the applicant will be contacted in order to arrange a suitable date and, in the event of a satisfactory outcome, a registration document will be issued. We intend to update the application form for registration and the existing associated guidance document to reflect new scenarios that have come to light. The main reasons for the revision of the form and guidance are outlined below:



- Inclusion of a requirement for active substance manufacturers and importers to register any distribution activities;
- Restructuring of guidance for authorised manufacturers and wholesalers of medicinal products;
- Clarification of instructions, particularly those relating to importation and distribution, within the text boxes on the form;
- Inclusion of additional worked examples and clarification of text for worked examples;
- Inclusion of guidance on fees.

The revised application form and guidance document will be available on the IMB website from June 2013.

## NEW EU REGULATION FOR COSMETIC PRODUCTS

The IMB, in conjunction with the HSE, is responsible for the regulation of cosmetic products in Ireland. All cosmetic products placed onto the Irish market are required to be safe and must comply with the legislative requirements.

Currently, cosmetic products placed on the EU market must meet the requirements outlined in the Cosmetic Directive 76/768/EEC. This legislation has been amended extensively over the years. In order to bring clarity, from 11 July 2013 it will be replaced by Regulation (EC) No 1223/2009. Some changes that arise from this new legislation include:

- Definition of a distributor, which incorporates retailers;
- Distributor obligations to maintain records and check the product labelling before making a product available on the EU market;

→

- A central notification portal harmonising product notifications which are made prior to placing cosmetic products on the market;
- Compulsory reporting by responsible persons and distributors of any serious undesirable effects (SUEs) to the IMB.

The IMB has drafted guidance documents to provide information for economic operators within the cosmetics sector in relation to Regulation 1223/2009. Their purpose is to provide practical advice in terms of meeting the regulatory requirements and ensuring consumer safety.

The IMB's *Guide to Distribution of Cosmetic Products in Ireland* has recently undergone a public consultation which ended on 19 April 2013. We would like to thank all those from whom we received comments. The finalised version will be published on our website by end of June.

IMB's *Guide to the Responsible Person for Cosmetic Products* has been published for stakeholder consultation and is now available on our website.

## STAFF CHANGES

Important staff changes that have occurred within the Compliance Department are outlined below. This information will be of particular interest to manufacturers and wholesalers of medicines which will need to update their recall procedures and contact listings accordingly.

**Aoife Farrell** has become Healthcare Products Distribution (HPD) Manager. The HPD section has responsibility for the management of the GDP inspection programme, as well as compliance programmes relating to controlled drugs, precursors, cosmetics and the monitoring of retail sales. Aoife was formerly Quality Defects and Recall Manager.

**Dr. Amy Kelly** has recently been appointed as Quality Defects and Recall Manager. Dr. Kelly is now the primary contact person for quality defects and recalls relating to medicinal products, investigational medicinal products and active substances and also manages the Exempt Medicinal Products programme. She was formerly a clinical assessor.

Please update your recall and other relevant procedures with this information, as required. Updated recall procedures should be sent to deirdre.breen@imb.ie.

Dr. Amy Kelly, Quality Defects & Recall Manager, Tel: +353 1 676 4971, Mobile: +353 86 027 8052, email: amy.kelly@imb.ie.

Aoife Farrell, Healthcare Products Distribution Manager, Tel: +353 1 676 4971, Mobile: +353 86 024 9808, email: aoife.farrell@imb.ie.

*This Bulletin is designed by Ashfield Press Publishing Services for*

IRISH MEDICINES BOARD

IRISH MEDICINES BOARD, KEVIN O'MALLEY HOUSE, EARLSFORT CENTRE, EARLSFORT TERRACE, DUBLIN 2
tel: +353 1 6764971 fax: +353 1 6767836 email: foi@imb.ie http://www.imb.ie