IRISH MEDICINES BOARD

newsLETTER

MEDICINAL PRODUCTS

MAY – AUGUST 2011 Issue No. 39

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HUMAN MEDICINES

REMINDER – PHARMACOVIGILANCE INFORMATION DAY ON FRIDAY 2 DECEMBER 2011

As highlighted in the last issue of the Medicinal Products newsletter, the IMB will hold a Human Medicines Pharmacovigilance Information Day on Friday 2 December 2011 to address issues related to implementation of the new European Pharmacovigilance legislation, which comes into effect in July 2012.

The information day will cover a range of topics including the IMB's implementation plans, progress with the Joint EMA-MS implementation plans, as well as an update on the status of Implementing Measures and Good Vigilance Practice. There will also be presentations on the pharmacovigilance system masterfile, changes to adverse reaction reporting requirements, changes to periodic safety update reports, requirements for post-authorisation safety studies and additional risk minimisation.

For further information, including the agenda and registration details, see the IMB website.

CHANGES IN MARKETING AUTHORISATION HOLDER FOR HUMAN MEDICINES

The IMB wishes to highlight issues which should be addressed to facilitate the transfer process for applicants requesting a change to the marketing authorisation holder (MAH):

(a) Transfers of marketing authorisation holder before authorisation in DCP/MR/ national procedures

Applicants are reminded that during DCP/MR or national new product applications, any proposal to transfer the MAH for Ireland prior to the conclusion of the procedure should be clearly communicated as early as possible during the procedure. Revised application forms indicating the new MAH, and supporting Annexes e.g. 5.3, 5.4, and 5.19 as appropriate, should be provided during the DCP/MR/national procedure for the product, citing the IMB case number and the EU procedure number as relevant. Separately, but concurrently, an IMB 'Transfer Before Authorisation application form B' (available on the IMB website) should be submitted to IMB Receipts and Validation, also clearly indicating the relevant IMB case number, and the RMS procedure number for a DCP/MRP. When the applicant has been informed that the transfer has been processed and when they have received notification of the new PA numbers, the revised product information (summary of product characteristics (SmPC), package leaflet (PL) and mock-ups and an updated IMB Braille declaration including the new PA numbers and MAH details), should be provided for the ongoing new product application. As previously communicated in the issue 37 of the IMB newsletter, text versions of the national labels, which should include the updated national sections e.g. PA number, will be accepted if the product is not to be marketed. Similarly text versions of the national leaflet are accepted.

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Name changes before authorisation arising from MA transfer

If the applicant envisages prior to commencement of MR/DCP/new national application that an MA transfer will occur during the procedure and that this will result in a change in the product name, the initial name proposed in the original submission should consist of: INN + initial MAH (e.g. 'Paracetamol + firstMAH'), in order to minimise any redundant discussion of invented names.

If it is also intended to change the name of the product during the DCP/MR/national procedure as a result of an MA transfer before authorisation (e.g. from INN + MAH or from invented name relating to the first MAH to a different invented name), this should be clearly communicated as early in the procedure as possible to allow for IMB consideration of the name in line with the 'IMB Guide to Invented Names of Medicinal Products for Human Use'. An updated application form, annexes and product information as above, must be submitted. It should not be assumed that lack of comment on a name change implies acceptance of the name. Requests for name changes cannot be facilitated once the draft schedule has been sent to the applicant for comment (see IMB Newsletter, issue No. 28).

Applicants should also consider finalising the MRP/DCP/national new application with the initial MAH and initial name and providing product information in text format, and then submitting a post-approval request to transfer the MAH after authorisation ('Form A', see section **(b)** below) along with variations/notifications to register the new name and to update the product information, in particular where the initial approval is regarded as urgent.

(b) Transfers of Marketing Authorisation Holder after authorisation

The IMB would like to remind MAHs that, during the transfer of an existing product authorisation to a new MAH, no changes may be made to the labels and leaflet, other than the (P)PA/DPR number, the holder's name and address and the company logo, as applicable. Any changes to the layout and design of the product livery should be registered by way of a separate article 61(3) notification as they may affect the readability of the contents and therefore require review. Similarly, if mock-ups have not previously been registered with the IMB, an Article 61(3) notification is required.

Further guidance in relation to transfers may be found in the *Guide to transfers of marketing authorisations, parallel import licences and dual pack import registrations for human medicines* which is provided on the IMB website, along with transfer Forms 'A' and 'B'.

OTHER VARIATIONS/ NOTIFICATIONS AFFECTING PACKAGING

Notifications to change the name and/or address of the Marketing Authorisation Holder

Notifications to change the name and/or address of the MAH where the legal entity of the holder remains the same, are classified as Type IA.IN A.1 notifications. When submitting these notifications, we would like to remind all applicants that the only acceptable changes are those to the name and/or address of the MAH in the product information (SmPC, package leaflet and labels). No other changes can be included in the notification application. Any further changes (e.g. change in product livery, addition of Braille etc.) must be made by way of a separate notification application/ Article 61.3 application. In the case where one site is registered as both the MAH and manufacturer, changes to the name and/or address of the registered manufacturing site cannot be approved as part of a transfer of ownership or a Type IA.IN A.1 notification to amend the name and/or address of the MAH. A separate Type IA.IN A.5. notification is required.

VETERINARY MEDICINES

REVIEW OF THE DIRECTIVE 2011/82/EC

The EU Commission has stated that a new legislative proposal to amend and/or replace the existing Directive 2001/82/EC is expected to be ready in Quarter 3, 2012. Currently, the Commission is engaged with stakeholders and consultants in guaging the appetite for change and in undertaking an assessment of the possible impact of any new proposals. The review is expected to be wide-ranging, including not only the authorisation procedures and data protection, but also considerations relating to the off-label use of veterinary medicines, distribution, pharmacovigilance, and the regulation of new therapies. A detailed exposé of the regulatory aspects of the review as they might affect national stakeholders is expected to be given at the IMB Vet Information Day on 6 October 2011 (for details, visit the IMB website).

UPDATE ON STATUS OF FLUKICIDES WITHOUT MAXIMUM RESIDUE LIMIT (MRL) FOR MILK

After almost nine months of internal deliberation, the European Commission has confirmed that Article 9 (1) of Regulation (EC) No. 470/2009 is not applicable where an MRL has already been established for the species concerned. The Commission has stated that in the case of substances for which an MRL was established under Council Regulation (EEC) No. 2377/90, Article 27 of Regulation (EC) No.

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470/2009 offers the possibility to submit to the European Medicines Agency (EMA) a request for an opinion on extrapolation of MRLs to other species or tissues. Accordingly, the IMB's applications for the establishment of MRLs for active substances included in flukicides for which no MRL exists for milk have been deemed invalid by the Commission. New applications in accordance with the advice of the Commission will now be submitted to the EMA.

Separately, the EU Commission initiated an Article 35 (Directive 2001/82/EC) referral procedure on 10 March 2011 in respect of flukicidal products containing active substances for which no MRL has been established for milk. This procedure is expected to have implications not only for clorsulon, closantel, nitroxynil, triclabendazole and rafoxanide but also for other anthelmintics without an MRL for milk which might be present in combination with the flukicidal substances concerned and for ruminant species other than cattle producing milk for human consumption.

Pending further EU developments, the labelling of the concerned flukicidal products in Ireland will remain as is (i.e. products containing the substances clorsulon, closantel, nitroxynil, rafoxanide and triclabendazole are not permitted for use in dry cows and pregnant heifers intended to produce milk for human consumption).

UPDATED CMDV BEST PRACTICE GUIDE FOR THE REPEAT-USE PROCEDURE

Applicants are advised that the Co-ordination Group for Mutual Recognition and Decentralised Procedures – veterinary (CMDv) has recently updated their *Best Practice Guide for the Repeat-Use Procedure*.

The main revisions in the most recent edition relate to the introduction of further clarification concerning:

- updating of the dossier with new information/data and the requirement for a variation procedure prior to initiating a repeat-use procedure;
- handling of changes to the SPC (in exceptional circumstances) by way of a Type II variation post repeat-use procedure; and
- use of web conferencing (Vitero) to resolve concerns raised during the procedure.

The updated version of this Best Practice Guide is published since 9 June 2011 and can be found on the CMDv webpage of the Heads of Medicines Agency website.

COLD CHAIN STORAGE

A cold chain can be defined as a temperature controlled supply chain. An unbroken cold chain is an uninterrupted series of storage and distribution activities which maintain a given temperature range. In some instances, there is potential for the supply chain to become broken and this must be considered when assigning the conditions for storage and transport for a veterinary medicinal product.

VICH GL3 Stability Testing of New Veterinary Drug Substances indicates that 'the storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment, and subsequent use'.

Results of cold chain storage should be available for a given product, including the shortest and longest potential transportation times where refrigerated conditions are required to maintain the quality of the product. If storage conditions are given in the SPC as 'Store refrigerated (2-8°C)' then data must be available to show that the product is not affected by storage conditions foreseen for this product, i.e. the extreme of times and temperature must be accounted for during shipping studies for a representative number of batches as part of the ongoing stability studies.

Data from the accelerated storage condition and, if appropriate, from the intermediate storage condition, can be used to evaluate the effect of short-term excursions outside the label storage conditions (such as might occur during shipping).

If significant change occurs within the first three months testing at the accelerated storage condition, a discussion should be provided to address the effect of short-term excursions outside the label storage condition, e.g. during shipping or handling. This discussion can be supported, if appropriate, by further testing on a single batch of the drug substance for a period shorter than three months but with more frequent testing than usual.

Overall, data should be available to the Competent Authorities which supports the statement in section 6.4 of the SPC, Store and transport refrigerated (2°C-8°C).

COLLECTION OF DATA ON VETERINARY CONSUMPTION OF ANTIMICROBIALS

The Veterinary Medicines department has collected data in respect of usage of veterinary antimicrobials for 2009 as required under the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) project. A report on the IMB findings is available on the IMB website. The IMB is currently gathering and assessing usage data for the year 2010. Similar data will be gathered annually henceforth. The IMB expects that the data will be used in due course by the EMA and the European Commission to frame appropriate risk management strategies aimed at minimising the development of antimicrobial resistance.

CROSS AUTHORITY COOPERATION

The Veterinary Medicines department of the IMB and the Veterinary Medicines Directorate (VMD) in the UK have a number of initiatives in place to encourage pharmaceutical companies to maintain marketing authorisations (MAs) in both markets and thus increase availability of medicines. Two of these initiatives focus on enabling companies to have common packaging for products authorised in both countries. The third initiative is a national worksharing scheme which enables a single assessment of certain variations rather than the independent assessment of variations by each national authority. A clarification paper outlining the operation of each of these initiatives is available in the publications section of the IMB website. The purpose and scope of each initiative is summarised below and also in Table 1.

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Joint labelling

This initiative is a structured procedure for processing mock-ups at the end of an EU procedure where applicants have requested joint labelling between Ireland (IE) and the UK. The procedure is implemented immediately after conclusion of the EU procedure and does not require a separate application. If not initially requested on conclusion of the EU procedure, joint labelling may also be achieved by submission of a C.II.6 variation application, submitted simultaneously to each member state.

This procedure applies to immunological and pharmaceutical veterinary medicinal products authorised via the mutual recognition or decentralised procedure, including renewals and variations, where both the UK and Ireland have been involved as either reference member state or concerned member state.

Harmonisation

This initiative is a simplified procedure for harmonising the summary of product characteristics (SPC) and product literature of nationally authorised products (identical in terms of formulation, packaging and manufacture in both countries), so that these products can be marketed using the same labels and leaflets in Ireland and the UK.

This procedure applies to immunological and pharmaceutical VMPs authorised via the national procedure and is applied for by way of simultaneous variation in each member state.

Partnership Initiative

Marketing authorisation holders (MAHs) often submit the same national variation applications to a number of countries. Where the supporting data are identical, and the underlying data for the MA are very similar, it is possible using this procedure to request a single assessment of the variation application rather than the individual assessment of data by each national authority. MAHs benefit from receiving a consolidated list of questions from the involved countries within a defined timeframe.

This procedure applies to Type II variations to immunological and pharmaceutical VMPs authorised via the national procedure. The procedure was expanded to include Belgium in early 2011 and more recently to include the Netherlands.

Table 1

Procedure	Eligible products	Technical assessment	Impact on SPC/product literature	Comment
Joint Labelling	MRP/DCP authorised	No	Yes	SPC and label text already agreed during EU procedure. Procedure limited to agreement of mock-ups.
Harmonisation	Nationally authorised	No	Yes	No technical assessment. SPCs must be essentially similar. Outcome is common SPC/labelling.
Partnership Initiative	Nationally authorised	Yes	Yes/No	Co-ordinated technical assessment not limited to SPC/labelling issues.

SUBMISSION OF RESPONSES IN EUROPEAN PROCEDURES

With the move to electronic submission of marketing authorisation applications, the IMB would like to draw the attention of applicants to the following.

As part of the Mutual Recognition Procedure (MRP) and Decentralised Procedure (DCP), lists of questions (two in DCPs and one in MRPs) are forwarded to the applicant. The applicant is expected to insert their response(s) directly into this document (attachments providing further data/information may be referenced) and to return the document to the reference member state (RMS) in accordance with the procedure timetable. Subsequently, the RMS is required to insert their assessment of the applicant's responses directly into the same document. However, it has been noted that on a number of recent occasions where the IMB has acted as RMS, the document including the responses of the applicant has been provided in PDF or other non-editable format (i.e. not returned in the same editable format sent to the applicant by the RMS) with the result that the document is unusable by the RMS.

In order to facilitate the work of the RMS, applicants are kindly requested to ensure that such documents (requiring further input from the RMS) are submitted in an editable format e.g. Microsoft Word format. Note that updated SPCs and labelling/leaflet texts submitted with the aforementioned response document should also be provided in an editable format to enable the RMS to insert comments/track changes.

COMPLIANCE

FALSIFIED MEDICINES DIRECTIVE 2011/62/EU

The Directive on Falsified Medicines* has been published in the Official Journal of the European Union, and includes a broad range of new legislative requirements, the majority of which will be applicable from 2 January 2013.

The Directive aims to prevent falsified medicines from reaching patients by introducing harmonised, pan-European safety and control measures. These measures will ensure easier identification of falsified medicines, and improve verifications and controls at EU borders and within the EU.

New measures relating to activities within the remit of the IMB include:

- an obligatory authenticity (safety) feature on the outer packaging of certain medicines considered to be at risk of falsification: this feature will be decided upon at a later stage via a European Commission delegated act;
- strengthened requirements for control and inspections of plants manufacturing active pharmaceutical ingredients;
- strengthened record-keeping requirements for wholesale distributors and a requirement for registration of brokers;
- strengthened rules on inspections; and
- the obligation for manufacturers and distributors to report any suspicion of falsified medicines.

The Directive must be transposed by the Member States by January 2013 and will largely apply as of then. However, some measures, such as those related to the safety feature, have a longer implementation time in order to allow for the necessary technical adaptations.

* *Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products.*

GOOD DISTRIBUTION PRACTICE (GDP): IMB AND OTHER GUIDANCE UPDATES

IMB Guidance

A number of IMB guidance documents relevant to wholesalers have recently been updated and published. Wholesalers and other relevant parties are advised to read these documents and to update their own quality systems and processes where required. The updates include the following:

- The updated *Guide on Wholesaling of Medicinal Products for Human Use in Ireland* was published on 29 September 2011, following a period of public consultation and can be accessed on our website.
- The updated *Guide to Control and Monitoring of Storage and Transportation Temperature Conditions for Medicinal Products and Active Substances* was published on 4 October 2011 on the IMB website. The update does not involve any significant change in material content of this guide, and includes only updates on relevant legislative references which have been amended or put in place since the guide was originally published.

EU Guidelines on Good Distribution Practice

The European Commission has recently released for public consultation the revised *Guidelines on Good Distribution Practice of Medicinal Products for Human Use*. The consultation will run until 31 December 2011 following which the guideline may be updated further prior to final publication. The guideline will then come into operation six months after final publication and will replace the previous version of the guideline (94/C 63/03) which was published in 1994. The guideline is available on the EC website.

The revision provides a substantial update to the current GDP guidelines by both expanding on existing requirements and also describing new requirements including those to ensure compliance with the Falsified Medicines Directive (Directive 2011/62/EU – see separate article in this Newsletter). The format of the guideline has also been revised by structuring the requirements into chapters.

The process for revising the update has been ongoing for some time with the IMB contributing to the updates through the EMA Inspector's Working Group. The IMB views the revision as having an extremely positive impact on GDP and the protection of public health. The revised guideline will provide wholesalers with a clear picture of the requirements for compliance with GDP, given the continuing evolution and increased complexities involved within wholesaling. Examples of revised areas within the guideline include: the qualification of suppliers/customers, computer validation, requirements for contract operations, transportation and specific provisions for brokers of medicinal products.

The IMB has already notified all wholesale authorisation holders of this consultation process. It is advised that all wholesalers/distributors, brokers, and other relevant stakeholders, review the revised guidelines and participate in the consultation process by submitting any comments directly to the European Commission, EMA and IMB at the following email addresses:

SANCO-gmp@ec.europa.eu
ADM-GMDP@ema.europa.eu
compliance@imb.ie

ADVERTISING COMPLIANCE FAQS PUBLISHED

The IMB recently published a list of frequently asked questions (FAQs) on advertising compliance aimed at all persons involved in the advertising of human medicinal products in Ireland. This list is partly based on questions that have been received by the advertising compliance group since the programme formally began in May 2009. The document includes general questions on advertising compliance as well as requirements for the content of advertisements, record keeping requirements and the IMB's handling of complaints. This document is currently available on the IMB website and any queries can be sent to **compliance@imb.ie.**

TRAINING OF OPERATORS INVOLVED IN ASEPTIC OPERATIONS

Over the last number of years deficiencies have been identified that have related to the level of training being afforded to operators involved in aseptic processing. Some deficiencies issued have related to a lack of practical training in aseptic practices and to the fact that operators have been considered qualified after participating in a successful process simulation without due consideration being given to the need for more routine training events, e.g. additional off-line training and assessment relating to the more intricate and more difficult to perform aseptic manipulations.

> Annex 1 (Manufacture of Sterile Medicinal Products) of the EU Guidelines on Good Manufacturing Practice (GMP) specifies *'All personnel (including those concerned with cleaning and maintenance) employed in such areas should receive regular training in disciplines relevant to the correct manufacture of sterile products. This training should include reference to hygiene and to the basic elements of microbiology...'.*

Operator training is critical to aseptic operations. Accordingly, the training involved should not be restricted to unique events that are designed to render operators 'qualified' to perform aseptic operations based on such activities. The operator's ability to perform critical operations (such as aseptic set up, routine / significant interventions and filling) should be based upon a process of practical

training and assessment designed to ensure that he/she is able to routinely perform such activities competently. Subsequent participation in a successful process simulation is part of the overall competency assessment of the operator.

The IMB would expect that the initial parts of such a training regime should include, as a minimum:

- basic microbiology,
- garbing (microbiological evaluation and observational assessment),
- general cleanroom behaviour,
- asepsis (task oriented aseptic manipulations), and
- philosophy of process simulations.

These elements should be considered mutually complementary. The initial training should not be considered as a mechanism to render an operator 'qualified' to perform aseptic operations, but as a means for the operator to achieve a base level of competence that should be continuously built upon. In order to ensure that an operator achieves such a base level and can be deemed competent to perform aseptic operations, the operator should be afforded the time needed to practice such operations in advance of the initial process simulation.
Upon completion of such activities, operator competency should be further assessed by participation in process simulations.

Additionally, a system of ongoing routine training should be in place. Such ongoing training should incorporate elements such as:

- practical asepsis (it is important to afford operators the time to practise and hone their skills to be able to perform aseptic operations confidently and competently);
- gowning, including observational assessment of competency as well as a system for exclusion of operators from entry into the aseptic processing area depending on performance; and
- microbiology (e.g. updates on results from trend data for environmental monitoring (process and personnel), information relating to the types of flora isolated and their source).

Ongoing training of aseptic operators should be considered an iterative process and a system to continuously assess operator competency in asepsis should be in place.

COSMETICS: MARKET SURVEILLANCE FOR THE IRISH MARKET

It is just over a year since the IMB undertook the role of national Competent Authority for cosmetics in October 2010. As our role as Competent Authority continues to develop and take into account new regulatory requirements, we will be providing regular updates on cosmetics related activities in our newsletters.

One of our main focuses within the first year has been to ensure the provision of an effective system of market surveillance for cosmetic products. Market surveillance is one of the key mechanisms through which the regulatory system for cosmetics monitors and ensures the protection of consumer health. This is an activity which the IMB performs in partnership with the Health Service Executive (HSE). Operational market surveillance activities are performed by the HSE's Environmental Health Officers (EHOs), and sample analysis and testing is performed by the Public Analyst Laboratory (PAL) service based in Cork, Dublin and Galway.

A risk-based approach is taken when carrying out market →

surveillance and, as such, involves proactive and reactive investigative work. Accordingly, as we approach the end of 2011, scheduling of market surveillance activity for 2012 by the IMB, the EHOs and PALs is under way.

The range of products surveyed within the proactive part of the programme is based upon a number of risk factors determined jointly by the IMB and the HSE and routinely includes issues such as the objectives of the Platform of European Market Surveillance Authorities for Cosmetics (PEMSAC) and new developments in legislation. Experience from our own market, such as products which may present safety concerns, plays an important role in identifying other areas of focus for the programme. The programme is also structured to correspond with seasonal and other changes in the market place. For example, in October, the campaign includes a focus on children's make up sets in preparation for Halloween.

Reactive surveillance involves analysis of product or documentation due to information becoming available about a certain product or operator and may require unscheduled sampling and analysis from the Irish market. This

information can come to our attention through a number of sources, e.g. a RAPEX Alert (safety alert for general consumer products, including cosmetics) via the National Consumer Agency (NCA); notification of an undesirable effect experienced by a consumer or healthcare professional; concerns regarding product safety following review of a product information file. Sampling and analysis for a reactive case involves close cooperation between the EHOs and PALs as well as the IMB and the NCA. The NCA is the national contact point for RAPEX alerts (received from other EU member states) relating to consumer products and is a key stakeholder in the market surveillance of cosmetic products on the Irish market that may present a serious risk to consumers.

In addition to incoming RAPEX alerts, the work performed under our market surveillance programme can also be the trigger for the NCA issuing an alert, for cosmetics which present a risk to consumers, to other EU member states through the RAPEX system.

The IMB continues to maintain close liaison with the Department of Health on all aspects of the Board's discharge of the role of Competent Authority.

As the Competent Authority, the IMB is obliged to report on national market surveillance programmes to the European Commission. The Commission hosts a number of European meetings in the area of market surveillance. The PEMSAC group meets biannually to facilitate exchange of information, coordinate national campaigns and common projects and to communicate the legislative obligations to the member states in the area of cosmetics market surveillance. The IMB and HSE have representatives contributing to these working groups to help improve the safety of cosmetics for the Irish market.

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This Bulletin is designed by Ashfield Press Publishing Services for

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