IRISH MEDICINES BOARD

news MEDICINAL PRODUCTS LETTER

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GENERAL

SIGNING OF MEMORANDUM OF UNDERSTANDING BETWEEN THE THERAPEUTIC GOODS ADMINISTRATION OF AUSTRALIA AND THE IMB

With the view of establishing a framework for cooperation in the area of the regulation of therapeutic goods, a Memorandum of Understanding between the Therapeutic Goods Administration (TGA) of Australia and the IMB was signed in Dublin on 8 June 2010 by Dr. Rohan Hammett, National Manager of the TGA, and Mr. Pat O'Mahony, Chief Executive of the IMB.

The purpose of the memorandum is to promote an understanding of both parties' framework, requirements and processes, to facilitate the exchange of information and documentation, to encourage collaborative activities and to enhance the parties' ability to provide efficient services relating to or in connection with public health while meeting the needs of their respective population.

Mr. Pat O'Mahony, Chief Executive of the IMB and Dr. Rohan Hammett, National Manager of the TGA, Dublin, 8 June 2010

HERBAL MEDICINES ON THE IRISH MARKET 2010

Under the provisions of the Medicinal Products (Control of Placing on the Market) Regulations 2007, S.I. 540 of 2007, as amended, no new herbal medicinal product can be placed on the market after July 2007 without the prior approval of the IMB. Products which were on the market at that time can remain on the market provided an application is made for registration under the Traditional Herbal Medicinal Products (THMP) registration scheme and registration is issued by the Irish Medicines Board by 30 April 2011. After this time, a herbal medicinal product may not remain on the Irish market legally without a marketing →

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authorisation or THMP registration. Further details of the authorisation and traditional registration schemes for herbal medicinal products may be found on the IMB's website.

As of mid-2010, the number of applications for the THMP registration scheme has been disappointingly small in comparison with the number of products actually on the market. In order to facilitate the registration process and give greater clarity to companies, some of which are continuing to place herbal medicinal products on the market inappropriately as food supplements, the IMB has proposed to publish two lists of herbal substances.

The first list is a list of herbal substances which are not considered to be suitable for inclusion in food supplements. These herbal substances are considered to be potentially toxic or have potent pharmacological action which makes them medicinal substances under the definition given in Article 1 of Directive 2001/83/EC as amended.

Products containing such herbs take the form of tablets, capsules, other solid and liquid dosage forms and the dried herbs themselves or teas made from these herbs. However, where concentrated extracts or tinctures are used or other parts of the plant, safety for use in food cannot necessarily be guaranteed and potential users are recommended to consult the IMB on individual cases.

In regard to the above, it should be understood that in order for herbal substances to be included in a food supplement, **no medicinal claim** can be made for the product on its packaging or associated literature. These two lists should not be considered exhaustive and will be added to or deleted from as experience is gained. Any queries on the contents or the usage of these lists or any comments should be addressed to herbalmedicines@imb.ie. The two draft lists can be accessed on the IMB's website.

AUTHORISATION OR REGISTRATION NUMBERING SYSTEM

The IMB has received queries about the format of the numbering system on the licence and on the IMB website. For PA, PPA, DPR, HNR, HOR, and TR numbers, the number displayed on the website takes the format e.g. PA0123/004/005, consisting of three distinct sections of 4 digits, 3 digits and 3 digits respectively. This format is due to the numbering generated automatically from our IT systems. When putting the number on packaging materials there is no requirement to include the preceding zeros, i.e. PA 123/4/5 may be used.

HUMAN MEDICINES

PROJECT TO UPDATE THE LEGAL STATUS OF CENTRALLY AUTHORISED MEDICINAL PRODUCTS

The IMB is currently undertaking a project to update the legal status (method of sale, supply and promotion) for centrally-authorised medicinal products (authorisation granted by the European Commission under Regulation (EEC) 2309/93 or Regulation (EC) No. 726/2004). This information is published on our website.

The classification of the method of sale, supply and promotion of centrally-authorised medicinal products is determined by the Committee for Medicinal Products for Human Use (CHMP) and annexed to the Opinion at the time of the marketing authorisation. Currently all centrally-authorised products default to S1B according to Regulation 7(10) (b) of the Medicinal Products (Prescription and Control of Supply) Regulations (S.I. No. 540 of 2003) as amended. However, according to the EMA 'Guideline on Legal Status for the Supply of Centrally Authorised Products', the sub-categories of non-renewable (S1A) and renewable (S1B) may be used at a national level in Member States. The guideline may be found on the EMA website.

In order to comply with the legislation and EMA guidance, centrally-authorised products are designated as S1A or S1B, with S1A having more restrictions with regard to dispensing. In general, all parenterals (excluding insulin) are classified as S1A. For products subject to medical prescription, where the EMA has assigned additional sub-categories of 'restricted' and/or 'special' these are generally classified by the IMB as S1A. A prescription for a product that is non-renewable (S1A) may be dispensed on more than one occasion subject to the restrictions outlined in Regulation 7 of the Medicinal Products (Prescription and Control of Supply) Regulations. In general, if a substance is listed in Schedule 1 of these Regulations as renewable (S1B), the classification of a centrally-authorised product containing that substance will not be changed unless it has been deemed 'restricted' and/or 'special' by the EMA, whereby the status of that particular product will change to non-renewable (S1A). Each product will be considered on an individual basis.

The IMB is updating its website to include the legal status of centrally-authorised products. Marketing authorisation holders of centrally-authorised products are currently receiving notification of the legal status of their products and are encouraged to review them and revert if they wish to seek clarification.

Any queries regarding this project should be submitted (by email) to customerservice@imb.ie clearly marked as 'Method of Sale, Supply & Promotion project'.

CHANGE IN THE PROCEDURE FOR REQUESTING IRELAND TO ACT AS REFERENCE MEMBER STATE (RMS) IN A DECENTRALISED PROCEDURE FOR A HUMAN MEDICINAL PRODUCT

The IMB would like to inform applicants of its plan to introduce a new 'window' system for managing requests for the IMB to act as RMS for human medicinal products. The window for requests will open at certain periods during the year and all requests received will be considered. Successful requests will be allocated a dedicated slot for assessment of their application. Guidance will be published on our website shortly and the first window for requests is due to open in September 2010.

VETERINARY MEDICINES

COLLECTION OF DATA ON VETERINARY CONSUMPTION OF ANTIMICROBIALS

The Veterinary Medicines Department has begun the task of requesting marketing authorisation holders (MAHs) to complete the template as required under the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) project. The IMB has populated a number of the required fields in the template with data from its own database and has forwarded the template to MAHs for their input. The completed information should be returned to the IMB **before 24 September 2010**, preferably by electronic means (**michelle.sinnott@imb.ie**). The necessary data, once received by the IMB, will be sent to the European Medicines Agency (EMA) for aggregation with those of other Member States.

UPDATE ON STATUS OF FLUKICIDES WITHOUT MRL FOR MILK

Stakeholders will be aware of the action taken by the IMB in February to update the Summary of Product Characteristics of flukicidal products for cattle which did not have a maximum residue limit (MRL) established in milk. This action was to clarify that the products in question were not permitted for use in animals producing milk for human consumption, including pregnant animals intended to produce milk for human consumption.

All involved marketing authorisation holders submitted the required variation applications to amend the product literature thus facilitating the IMB's response to the situation. Product in old livery should not be released from the manufacturer or wholesaler after 31 July 2010. Products with literature which have not been changed are liable to be seized by the Department of Agriculture, Fisheries and Food from that date.

The IMB has separately initiated Article 9 procedures under Regulation 470 EC 2009 requesting the European Medicines Agency (EMA) to establish MRLs for milk for the substances involved. This is the first time this particular procedure has been used. At the end of June, the EMA confirmed their acceptance of the eligibility of the substances closantel, nitroxynil, rafoxanide and triclabendazole for this procedure which is now underway.

STAFF CHANGES

Ms. Katarina Dankova left the Veterinary Medicines Department on 19 August. The IMB wishes her well in her new career.

COMPLIANCE

REQUIREMENT FOR QP DECLARATIONS FOR INCLUSION OF THIRD-COUNTRY CONTRACT MANUFACTURERS / TESTING FACILITIES FOR IMP AUTHORISATION

Under EU GMPs Annex 13, paragraph 39,

The duties of the Qualified Person in relation to investigational medicinal products are affected by the different circumstances that can arise and are referred to below...

b) Product imported directly from a 3rd country: the duties are laid down in article 13.3(b) of Directive 2001/20/EC. Where investigational medicinal products are imported from a 3rd country and they are subject to arrangements concluded between the Community and that country, such as a Mutual Recognition Agreement (MRA), equivalent standards of Good Manufacturing Practice apply provided any such agreement is relevant to the product in question. In the absence of an MRA, the Qualified Person should determine that equivalent standards of Good Manufacturing Practice apply through knowledge of the quality system employed at the manufacturer. This knowledge is normally acquired through participation in audit of the manufacturer's quality systems. In either case, the Qualified Person may then certify on the basis of documentation supplied by the 3rd country manufacturer.

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In cases where an authorised IMP manufacturer is intending to submit a variation to include a third-country contract manufacturing site or contract testing site and where no MRA exists with this third country, such variation applications should include a declaration that the QP is satisfied that the site operates in accordance with a standard equivalent to EU GMP at the time of submission of the application.

This determination by the QP should be based upon knowledge of the quality system employed at the manufacturer. This knowledge is normally acquired through participation in an audit of the manufacturer's premises and quality system.

The QP making the declaration should have sufficient knowledge of the processes concerned and documentary evidence should be available to support this. It is on the understanding that the declaration accompanying such applications affirms that the site operates in compliance with EU GMP that such variations are approved and the site is named on the IMP manufacturer's authorisation. The IMP authorisation holder should have a procedure in place describing the requirements for submission of such a declaration.

The IMB reserves the right to inspect any such third-country sites and also to request copies of audit reports to support such variation applications.

MEETING OF THE PIC/S EXPERT CIRCLE ON ACTIVE SUBSTANCES

The Third Meeting of the PIC/S Expert Circle on Active Pharmaceutical Ingredients was hosted by the IMB in Dublin on 26 – 28 May. This Expert Circle is focused on training of inspectors and development of guidance for inspection of APIs. Sixty-nine participants from 27 national agencies for medicines or international organisations attended the meeting.

The main subjects of the meeting were supply chain management and quality risk management for inspection planning. The format of the meeting consisted of a small number of presentations and workshops. The first two

days of the meeting were held at the Institute of Technology, Tallaght, and the IMB is particularly appreciative of the Institute's assistance which, in addition to the conference facilities, included a tour of the Institute's pilot scale manufacturing unit and laboratories.

The feedback from the meeting delegates was, in general, favourable. Tangible outputs from the meeting included a series of questions and answers on the distribution of APIs which will be proposed for publication on the PIC/S website. In addition, the draft quality risk management tool developed by the PIC/S expert circle on Quality Risk Management (QRM) was evaluated for application to the inspection of existing API sites and new API sites. The feedback and conclusions from this discussion will be outlined to the QRM Expert Circle.

PERSISTENT ORGANIC POLLUTANTS REGULATIONS 2010, S.I. NO. 235 OF 2010 ('POPS REGULATIONS')

There is worldwide concern at the continuing release of persistent organic pollutants (POPs) into the environment. These chemical substances are transported across international boundaries far from their sources and they persist in the environment, bio-accumulate through the food web, and pose a risk to human health and the environment. The aim of the POPs Regulations (effective from 31 May 2010) is to give effect to relevant provisions of Regulation (EC) No 850/2004 on persistent organic pollutants,[1] as amended ('Regulation 850/2004'). The objective of Regulation 850/2004 is to protect human health and the environment from POPs by prohibiting, phasing out, or restricting the production, placing on the market and use of specified POPs. It is intended that this will be achieved by minimising, with a view to eliminating where feasible, releases of such substances, and by establishing provisions regarding waste consisting of, containing or contaminated by any of these substances.

The Environmental Protection Agency (EPA) is the competent authority for the purposes of the POPs Regulations. The IMB is specified in the POPs Regulations as the *'public authority concerned'* for *'persistent organic pollutants used or intended for use in medicinal or veterinary applications'*.[2] As such, the IMB is required to have regard to the requirements of the POPs Regulations and Regulation 850/2004 in the exercise of its powers, functions and duties. The IMB is required to co-operate with the EPA. Provision is made for the EPA to enter into arrangements with the IMB regarding the implementation of and compliance with the POPs Regulations and Regulation 850/2004. These may include obligations on the provision of awareness programmes, public information and training, as well as monitoring and reporting. The IMB may bring summary proceedings for an offence under the POPs Regulations.

Many of the substances described in Regulation 850/2004, Annex I, Part A are pesticides. There are restrictions within the EU Guide to GMP regarding the processing of pesticides in facilities used for the manufacture of active pharmaceutical ingredients or medicinal products.

Subject to any arrangement with the EPA, IMB inspections may in future include monitoring for POPs during routine inspections of those sites where chemicals that are classified as POPs may be used for processing or for non-process applications. It is envisaged that any such activity will be incorporated into existing voluntary and mandatory inspections.

1 *Regulation (EC) No 850/2004 of the European Parliament and of the Council of 29 April 2004 on persistent organic pollutants and amending Directive 79/117/EEC*

2 *Persistant Organic Pollutants Regulations, Art 7(1)(b)*

REPORTING OF QUALITY DEFECTS

In 2009, the IMB investigated 614 reports of quality defects, of which 98 resulted in recall action on the Irish market. A total of 164 were classified as minor and posing minimal risk to patient safety. Following review of the regulatory oversight requirement, the IMB will shortly publish guidance on the occasions when it will not be necessary for some of these minor defects to be reported to the IMB. This guidance note is intended to help stakeholders to identify the quality defects that should be reported. These stakeholders include marketing authorisation holders, manufacturers and wholesalers.
The document will cover:

- Guidance on how to classify quality defects;
- Criteria to use to determine if a quality defect is reportable or not;
- The IMB's expectations of stakeholders when a quality defect is not reported to the IMB;
- Examples of quality defects which should be reported to the IMB;
- How to report quality defects to the IMB.

The document will be published in late September and will be available on the IMB website.

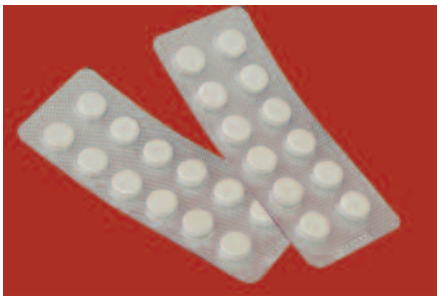
The guidance note will be covered at the GMP and Market Compliance Information Day on 14 October 2010, under the agenda topic '*New IMB Guidance Note – How to Determine if a Quality Defect Should be Reported to the IMB*'.

MICRONISATION OF ACTIVE SUBSTANCES

Micronisation of active substances may be carried out by an active substance manufacturer before supply of a material to an authorised medicinal product manufacturer or, alternatively, arrangements may be made by the medicinal product manufacturer to have the material micronised. In all cases, micronisation of an active substance should be an activity which is covered within the marketing authorisation dossier for the product.

Where the active substance is supplied in micronised form by the active substance manufacturer, the micronisation process (and site where the activity takes place, if different) is considered to fall within the scope of the GMP declaration for the active substance supplied by the Qualified Person in support of the marketing authorisation application.

Where micronisation is arranged by the medicinal product manufacturer, the site performing micronisation should be named as a contract manufacturer on the manufacturer's/importer's authorisation (MIA) held by the medicinal product manufacturer. This would be a technical variation to the MIA and should be supported by documentary evidence that the micronisation site has undergone a successful GMP inspection by an EU authority in relation to this activity.



CONTROLLED DRUGS – UPDATE TO MISUSE OF DRUGS REGULATIONS 2010

New legislation to control a range of drugs and substances was introduced under the Misuse of Drugs Acts on 11 May 2010. A primary focus of this legislation was to place control on certain synthetic cannabinoids, BZP derivatives, mephedrone and related cathinones, so called 'legal highs' which were being supplied in 'head shops' in Ireland.

However, the legislation has also controlled a number of other drugs and substances (see below) including some used in medicines, under the Misuse of Drugs Acts. These were already controlled under the UN Conventions on Narcotic Drugs and Psychotropic Substances. The new legislation has brought Ireland's control measures in line with existing international controls.

The drugs and substances now covered, including the Schedules under the Misuse of Drugs Regulations into which these have been placed, are set out within the following statutory instruments:

- Misuse of Drugs Act 1977
- (Controlled Drugs) (Declaration)
- Order 2010 (S.I. No. 199 of 2010)
- Misuse of Drugs (Amendment)
- Regulations 2010 (S.I. No. 200 of 2010)

This new legislation is of interest to medicinal product manufacturers and wholesalers as it introduces control under Misuse of Drugs Acts for the following active pharmaceutical ingredients: remifentanil, zolpidem and ketamine. The IMB has already communicated with the relevant sectors of those industries directly impacted by the changes. However, it is important that, within the wider industry, those manufacturers and wholesalers which may have future business interest involving these substances are also kept informed of the new controls now applicable to these substances, and can consider, in advance, the impact of these changes on their proposed activities.

If you require any further clarification or information regarding the legislation update, please do not hesitate to contact deirdre.ryan@imb.ie.

USE OF SMALL VOLUME COLD CHAIN INSULATED SHIPPERS

During recent wholesale inspections, a number of deficiencies have been cited relating to the use of insulated shippers to transport small volumes of product requiring 2-8°C storage and, in particular, the validation of these shippers.

Wholesalers are reminded that all deliveries using cold chain shippers should be completed within the time period for which the shippers were validated. To ensure this, the time of packing should be included on delivery documentation along with the maximum validated time for the shippers.

Should any material changes be made to the validated shipper (e.g. change in box, type or size of chill/frozen packs, change in assembly/configuration etc), the transportation system should be revalidated. Should the wholesaler believe that →

a revalidation is not required, documented justification should be available to an IMB inspector. In this regard wholesalers should also take into account the impact of use and 'wear-and-tear' on the continued validated status of the delivery system. This should also include periodic assessment of the need to replace the system or component parts.

Wholesalers should note that the temperature at which a chill/frozen pack is chilled/frozen will significantly impact on the temperature within the shipper. Therefore, it should be ensured that the temperature within the refrigerator/freezer is the same as when the shipper was originally validated. The duration for which chill/ice packs should be refrigerated/frozen should also be defined and validated. Refrigerators/freezers used for this purpose should be validated and the temperature of these routinely monitored.

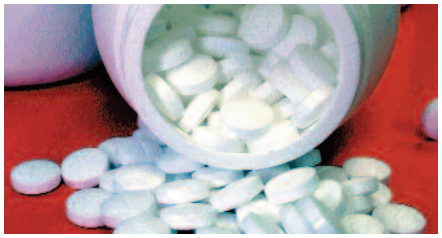
Information is available from the guidance document 'Guide to Control and Monitoring of Storage and Transportation Temperature Conditions for Medicinal Products and Active Substances', available on the IMB's website.

COSMETICS UPDATE

It is intended that legislation to transfer the Competent Authority role for cosmetics to the IMB from the Department of Health and Children is planned to come into effect in quarter four 2010.

On 15 September, the IMB hosted an information day, with the participation of key stakeholders involved in cosmetics control, in order to provide an overview of the transfer of the Competent Authority role for cosmetics as well as some practical aspects of compliance with the legislation.

All presentations from the information day are available on our website, as well as additional guidance on notification requirements, complying with the legislation and how to apply for certificates of free sale.



Once the legislation is in place, the IMB will carry out the functions of the Competent Authority for cosmetics, including:

- the maintenance of a notification database of cosmetic product manufacturers and importers;
- establishment of a market surveillance system involving market sampling and analysis and review of product information files;
- enforcement of the legislation, together with our partners in the HSE;
- generation of certificates of free sale; and participation in international activities, including relevant EU working groups.

The cosmetics function has been integrated into the Healthcare Products Distribution Section within the Compliance Department. For specific queries relating to manufacturing or placing cosmetic products on the market, please contact the Compliance Department at **compliance@imb.ie**.

JOINT INSPECTIONS WITH THE US FDA (NOTICE REPRINTED FROM EMA WEBSITE)

'11/08/2010 - The European Medicines Agency (EMA) and the Food and Drug Administration of the United States of America (US FDA – see website) continue to seek potential candidate companies for a joint GMP inspection pilot programme for manufacturers of medicinal products. Companies that have submitted in parallel two equivalent marketing authorisation applications for the same medicinal product to both the EMA and the US FDA can request to participate in the pilot programme for joint pre-approval inspection should such an inspection be considered necessary by both agencies.

The overall objective is to see whether greater international collaboration can help to distribute inspection capacity allowing more manufacturing sites to be monitored and reducing unnecessary duplication.

Companies can also participate in the pilot exercise by hosting a single joint re-inspection (routine surveillance) where both the EMA and the US FDA have separately planned routine surveillance inspections (re-inspections) to take place within a similar time period at a manufacturing site of a medicinal product authorised in the USA and centrally authorised in the European Union.

Companies that wish to participate should contact either **gmp@ema.europa.eu** and/or **CDERInternationalGMP@fda.hhs.gov**.

GMP AND MARKET COMPLIANCE INFORMATION DAY

This Information Day will take place on 14 October 2010 in the Crown Plaza Hotel in Santry. Further information on the agenda and on how to register for this event are available on the IMB website. Please note that the closing date for registration is 30 September 2010.

The IMB no longer publishes product statistics in this newsletter. The status of authorisations are updated regularly on our website, please use the link below for the most up to date details.
http://www.imb.ie/EN/Medicines/HumanMedicines/HumanMedicinesListing.aspx
http://www.imb.ie/EN/Medicines/VeterinaryMedicines/VeterinaryMedicinesListing.aspx

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