IRISH MEDICINES BOARD

MEDICINAL PRODUCTS
news LETTER

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GENERAL

UPDATE TO THE IMB'S REGULATORY INFORMATION SYSTEM (RIO) AND ON-LINE SUBMISSIONS OF APPLICATIONS

Applicants are advised that RIO (Regulatory Information Online – the IMB's medicinal products submission and tracking portal) is being discontinued and will no longer be available from early February 2013. However, the facility to track the status of submissions submitted via RIO to the IMB will continue to be available.

The IMB will accept online submissions from March 2013 by means of a new and different system known as CESP (Common European Submission Platform). Details of this system may be found on the CESP website. It is a simple and secure mechanism for the exchange of information submitted over the internet between applicants and national regulatory agencies who are part of the Heads of Medicines Agencies (HMA) network.

The CESP website contains training material and a list of frequently asked questions (FAQs). Should you have any further queries, please direct them to customerservice@imb.ie.

The IMB's Guide to Electronic Submissions has been updated accordingly and is available in the publications section of our website.

HUMAN MEDICINES

CLINICAL TRIALS – NOTIFICATION OF ADVERSE REACTIONS

The IMB wishes to highlight that Section 7 of the Guide to Clinical Trial Applications has been updated to include a requirement that the sponsor or investigator when reporting a suspected unexpected serious adverse reaction (SUSAR) must indicate whether the SUSAR is associated with a breach or deviation from the approved protocol. Where the SUSAR is associated with a breach of the protocol, this must be clearly stated and detailed information provided with the SUSAR report.

PUBLICATION OF PILS FOR HUMAN MEDICINES

The publication of patient information leaflets (PILs) on the IMB website is due to commence from 1 March 2013. The publication applies to nationally authorised products (including decentralised and mutual recognition authorisations). The PIL for centrally authorised products is available on the European Medicines Agency (EMA) website.

From 1 March 2013, when a case is issued that results in a new or updated PIL, the PIL will be made available on the IMB website under the Human Medicines Products List within 14 days of the issuance of the case.

It is important that applicants exclude any confidential information,

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including signatures, when providing PILs to the IMB. This will ensure that such details do not appear on our website.

For any queries in relation to the publication of PILs, please contact customerservice@imb.ie.

QUALIFIED PERSON FOR PHARMACOVIGILANCE (QPPV) – PROVISION OF CONTACT DETAILS TO THE IMB

The IMB pharmacovigilance department maintains a database of contact details for QPPVs. Marketing authorisation holders are requested to ensure that the contact details for QPPVs, deputy QPPVs and local contacts (if applicable), are kept up to date with changes promptly notified to the IMB. Contact details including names, 24-hour contact telephone numbers, email and postal addresses, and fax numbers if available should be emailed to imbpharmacovigilance@imb.ie.

Please contact us at this email address if you have any queries regarding the pharmacovigilance contact details currently registered with the IMB for your company.

SENDER INFORMATION AS PROVIDED IN ICSR/SUSAR E2B FILES

The IMB wishes to highlight the fact that the 'Sender' information submitted in the E2B electronic format of ICSRs and SUSARs is automatically used as the contact information for follow-up/acknowledgement of case reports. It is considered a matter for individual companies to ensure that if this is not the person responsible for case follow-up that the correspondence is passed to the appropriate person in the company. It is recommended that procedures are in place to support timely provision of acknowledgements and or requests for follow-up to relevant staff as appropriate.

PHARMACOVIGILANCE AND RISK MANAGEMENT FOR MARKETING AUTHORISATION HOLDERS RELATING TO THE NEW EU PHARMACOVIGILANCE LEGISLATION

The IMB continues to provide regular updates on new documents released and guidance for marketing authorisation holders on its website under the section New EU Pharmacovigilance Legislation.

The legislation is underpinned by the European Commission implementing regulation (EU) No 520/2012 and a series of modules on good vigilance practice (GVP). The GVP modules, the annex to GVP module VIII on post-authorisation safety studies, which outlines Member States' requirements for transmission of information on non-interventional post-authorisation safety studies, and a Q&A document are available on the EMA website and on the Pharmacovigilance section of the CMDh website.

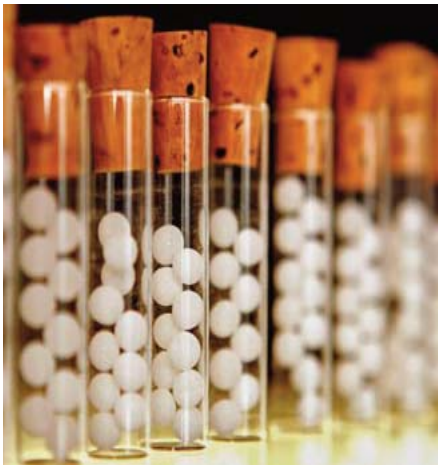
The Pharmacovigilance Risk Assessment Committee (PRAC) has been established at the EMA and is responsible for assessing all aspects of the risk management of medicines for human use. This includes the detection, assessment, minimisation and communication relating to the risk of adverse reactions, taking into account the therapeutic effect of the medicine. It also has responsibility for the design and evaluation of post-authorisation safety studies and pharmacovigilance audit.

The PRAC recommendations that affect centrally-authorised medicines are considered by the Committee for Medicinal Products for Human Use (CHMP). The PRAC recommendations that affect nationally authorised medicines are considered by the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh). PRAC recommendations are also provided to the EMA secretariat, Management Board and European Commission, as applicable.

The PRAC agenda, minutes and meeting highlights are published on the EMA website every month. The CHMP meeting highlights are also published. The pharmacovigilance part of the CMDh minutes is published on the CMDh section of the HMA website.

Marketing authorisation holders are reminded to routinely check the minutes of these meetings in order to maintain an awareness of emerging safety information and recommendations from the PRAC, which may have implications for their medicinal products.

For specific questions regarding the IMB's implementation of the new legislation, please contact vigilance_assessement@imb.ie.



VETERINARY MEDICINES

OUTCOME OF REFERRAL OF FLUKICIDES WITHOUT MRL FOR MILK

The IMB is currently accepting variation applications to give effect to the labelling changes of those products affected by the recent decision of the European Commission. This includes products containing clorsulon, closantel, nitroxinil, triclabendazole or rafoxanide. The decision relates to the use of products containing these substances in animals intended to produce milk for human consumption, including use during the dry period. The applications involved are being processed free of charge, provided that they are submitted before 31 March 2013.

The IMB notes that the EU decision relates only to products where the flukicide substance affected by the decision is present as the sole active substance in the product. Nevertheless, the IMB considers that the fundamental conclusions of the decision might be equally applicable to flukicide substances used in combination with other substance such as anthelmintics. Where relevant to such products, it may be necessary to include a prohibition on use of the products concerned in dairy cows as well as use in dairy ewes and goats producing milk for human consumption. The IMB is therefore reviewing the position of the affected substances when used in combination products to establish if any further clarification to the labelling instructions is necessary. Marketing authorisation holders affected by this matter will be contacted by the IMB over the coming weeks. Queries on this matter can be sent to Dr. Gavin Ryan at gavin.ryan@imb.ie.

COMPLIANCE

THE FALSIFIED MEDICINES DIRECTIVE AND THE REQUIREMENT TO APPLY TO THE IMB FOR REGISTRATION

Directive 2001/83/EC, relating to medicinal products for human use, has been amended by Directive 2011/62/EU (Falsified Medicines Directive) in order to further safeguard public health by protecting the pharmaceutical supply chain from infiltration with falsified medicinal products. This involves the introduction of additional regulatory requirements in order to enhance protection of the supply chain. The main provisions of the Falsified Medicines Directive involve the introduction of:

i. A new obligatory authenticity feature or safety feature which must appear on the outer packaging of particular medicinal products;
ii. More robust rules regarding the control of starting materials and the inspection of manufacturers of active substances and excipients used in medicinal products;
iii. More robust controls for the wholesale distribution of medicinal products including the introduction of controls, for the first time, on entities involved in brokering medicinal products;
iv. A common EU-wide logo to identify legal online pharmacies and to establish a notification system for entities offering to supply medicinal products to the public over the internet.

The following information relates specifically to provisions (ii) and (iii) and it applies to:

- Manufacturers of active substances
- Importers of active substances (from outside of the EEA)
- Distributors of active substances
- Brokers of finished medicinal products

Where the Directive applies to a company, there is a requirement to register with the IMB. This involves submission of an application for registration covering each of the above activities carried out by the company concerned. Where a company carries out more than one activity relating to active substances, it is acceptable to detail these on a single application form. An application fee of €250 will be payable for each activity for which registration is sought.

Relevant guides and forms relating to these registration schemes can be found on the following sections of the IMB website:

- The registration of active substance manufacturers, importers and distributors
- The registration of brokers of finished medicinal products

Note: the Falsified Medicines Directive does not apply to the manufacture of investigational medicinal products or veterinary medicinal products.

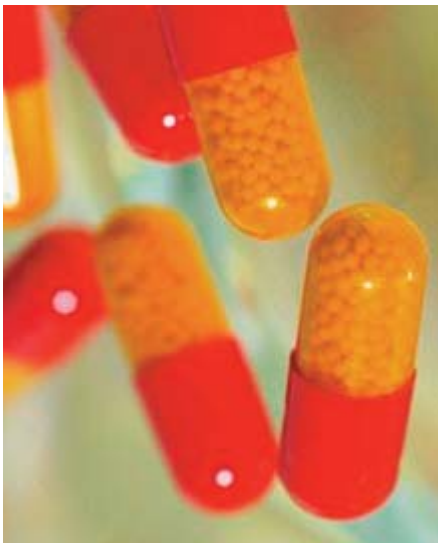
REVISED GUIDELINES ON GOOD DISTRIBUTION PRACTICE (GDP) OF MEDICINAL PRODUCTS FOR HUMAN USE

It is anticipated that the revised guidelines will be published during the first quarter of 2013. The guidelines, which are expected to come into operation within 6 months of publication, will replace the original Guidelines on GDP of Medicinal Products for Human Use published in 1994. Interested parties, including manufacturers, wholesalers and brokers, should monitor the European Commission website for updates in relation to the publication of the final document.

The revised guidelines will take into account amendments to the Community Code, which have been introduced with the amendment of Directive 2001/83/EU (relating to medicinal products for human use), by Directive 2011/62/EU (Falsified Medicines Directive). These amendments include measures intended to prevent the entry into the legal supply chain of falsified medicinal products and also advancements of practices in the European Union for storage and distribution of medicinal products.

THE VARIATIONS REGULATION AND APPLICATIONS FOR CERTIFICATES OF A PHARMACEUTICAL PRODUCT (CPP) AND FREE SALE CERTIFICATES (CFS)

The IMB has encountered difficulties with some applications for CPP and CFS. This is specifically due to the variations process and primarily concerns Type IA 'Do and Tell' variations. There have been some significant delays as a result and, in some cases, withdrawal of the certificate application.



In these instances, we have found that the marketing authorisation holder (MAH) has made 'do and tell' changes to the product specific details (PSD) and/or summary of product characteristics (SPC). Details such as MAH address, composition and manufacturing site have been updated but the MAH has either not submitted details of the amendments or has not had confirmation from the IMB that the variation has been assessed and approved. This has resulted in the product information that the IMB has on file not matching the information in the application.

While fully acknowledging the provisions of the Variations Regulation, the IMB can only issue a CPP or a CFS which accurately reflects the most recently approved information on the PSD and SPC for the product concerned.

Accordingly, prior to requesting certificates, applicants should verify with their own regulatory departments that all relevant variations have been submitted to, and approved by, the IMB and that the marketing authorisation details have been updated.

While we try, insofar as is possible, to assist applicants for certificates, the submission of product information that is not consistent with that currently in the marketing authorisation, as issued by the IMB, is likely to result in the application being invalidated and returned.

AGREEMENT ON CONFORMITY ASSESSMENT AND ACCEPTANCE WITH ISRAEL

The Agreement on Conformity Assessment and Acceptance (ACAA) of industrial products between the EU and Israel is now in force. This agreement recognises the equivalence between the regulation of medicinal product (human and veterinary) manufacture in the EU and Israel. Certain products are currently excluded from the terms of the ACAA and these include medicinal products derived from human blood or plasma, investigational medicinal products, homoeopathic medicinal products, medicinal gases and veterinary immunological products.

With regard to the importation of medicinal products the ACAA will function similarly to a Mutual Recognition Agreement (MRA) in that medicinal products which are manufactured and covered under the ACAA may be imported into the European Economic Area (EEA) without a requirement for testing to be performed in the EEA. However, each batch of product will have to undergo certification by a Qualified Person at the site which is named as the site of EEA batch release on the relevant marketing authorisation for that product. Recognition of testing for products covered under the ACAA will extend to Official Control Authority Batch Release certificates issued following testing at the Official Medicines Control Laboratory in Israel.

Separately, Israel has applied to the EU Commission to be listed as a country which is equivalent (under the terms of the Falsified Medicines Directive 2011/62 /EC) with the EU with regard to regulation of active substance manufacture. While the system of regulation of active substances may be considered equivalent with regard to manufacture of actives which are used domestically at Israeli sites for manufacture of medicinal products, the legislation does not currently cover actives exported from Israel for use elsewhere. This particular aspect is the subject of ongoing contacts between the EU Commission and Israel.

POINTS TO CONSIDER FOR IMPORTATION OF ACTIVE SUBSTANCES FROM OUTSIDE THE EEA

Commission Directive 2011/62/EU (Falsified Medicines Directive), which amends Directive 2001/83/EU (relating to medicinal products for human use), will introduce new regulatory requirements for the importation of active substances from outside the EEA on 2 July 2013. From this date onwards, active substances can only be imported into the EEA if accompanied by a 'written confirmation' from the Competent Authority of the exporting third country which confirms that the standards of GMP and control of the plant are equivalent to those in the EEA.

Two waivers from this requirement are provided for in the Directive:

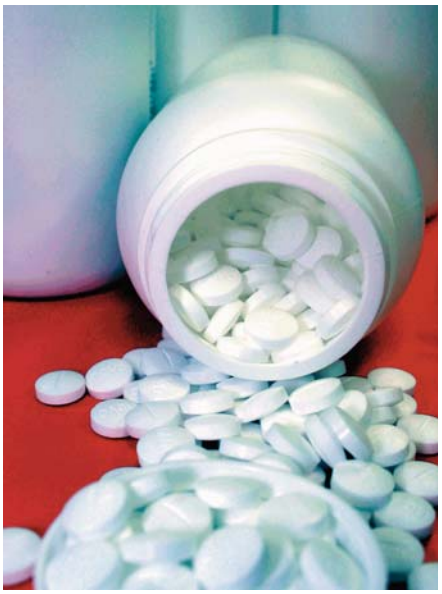
a. If the active substances have been sourced from countries listed by the Commission as having GMP standards equivalent to those of the EU; or

b. If the active substance manufacturer holds a valid GMP Certificate issued by an EU Competent Authority.

In order to maintain the continuity of supply of active substances and when considering sourcing active substances from new manufacturers, finished product manufacturers should assess if the active substance manufacturer is located:

i. In a country where the regulatory authority provides the 'written confirmation' of equivalence; or

ii. In a listed country.



Thus, as part of the supplier qualification process, companies should seek evidence early in the process from the active substance manufacturer as to whether the third country of origin is in either of the categories.

In some countries, it is possible that there may be different local regulatory requirements for active substances which are manufactured for export compared to those which are manufactured for use domestically. Where there are different requirements for manufacturers of active substances which are intended for export only from the third country then this may impact on the ability of the local regulatory authority to issue a 'written confirmation' in relation to those active substances. It is possible that the local regulatory authority may have no oversight of an active substance manufacturer unless that manufacturer has registered or is authorised by that local regulatory authority. Manufacturers of medicinal products in Ireland and importers of active substances should take these factors into consideration when selecting sources of active substances.

In exceptional cases, companies can apply to the IMB to request an inspection at a third country active substance manufacturing site that does not meet these two criteria (listed country or written confirmation). The IMB and other Competent Authorities in the EEA have finite inspection resources and it is unlikely that all requests for inspection could be facilitated. The IMB will consider requests from authorised manufacturers in Ireland and these requests will be assessed on a case by case basis.

Companies should provide advance notification to the IMB (by emailing compliance@imb.ie) of their intention to request an inspection and may be asked to provide background details on the process for selection of the active substance manufacturer. The following information should be provided with the request in order to accurately verify details of the active substance manufacturer:

i. Company name in English and, where applicable, in the local language. This is important as in some cases the company name in the local language may be different to the English version;

ii. Details of any authorisation or registration of the site with the local third country regulatory authority.

Further information is available from the relevant questions and answers document on the Commission's website.

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