IRISH MEDICINES BOARD

MEDICINAL PRODUCTS
newsLETTER

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GENERAL

UPDATE ON HERBAL MEDICINES

The Traditional Herbal Medicinal Products Directive (2004/24/EC) was transposed into Irish law in 2007. This requires all products containing herbal substances coming onto the market after this time either to be authorised as for conventional medicines or to be registered under the Traditional Herbal Medicines (THM) scheme provided for by the Directive. From 30 April 2011, products that have not been either authorised or registered as THMs can no longer be lawfully marketed in Ireland. The IMB is in the process of moving to fully regulate the Irish market. Those herbal medicines which were subject of applications for THM registration as of the time of 30 April 2011 have been allowed to remain on the market pending the completion of the assessment process. The assessment process has been taking a long time, generally because of the poor quality of dossiers received.

As of 1 August 2012, six traditional herbal medicinal products have been registered using the new scheme and can be found on the IMB human medicines listing section. The easiest way to search for these is to use the advanced search facility and include the letters TR (Traditional Registration) in the licence number box. This will display all of the approved products which carry a TR number. Once the products have been registered by the IMB they will be allowed on to the market and the packaging will have appropriate labelling including the TR number.

To supplement the information available on the Traditional Herbal

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Medicinal Products Registration Scheme, the IMB has also produced two lists for illustrative purposes of herbal substances which can be and have been accepted for inclusion in Traditional Herbal Medicinal Products and the second list of herbs which, for various reasons, are not considered to be acceptable in THMPs. This second list includes herbs which are known to be toxic and therefore require medical supervision for their use. The existence of these lists has also been helpful in discussing with our colleagues in the Food Safety Authority which herbal substances are considered to be medicinal and which others may be acceptable for inclusion in food supplements when no medicinal claims are made on the label.

In the context of the discussion on the generation of the lists, the IMB has identified that products containing echinacea are primarily of use as medicinal products and should not be

marketed in Ireland as food supplements. The IMB is working closely with the Food Safety Authority to ensure that such products will only be marketed as medicinal products in the future.

In the course of the assessment of products containing echinacea, the IMB reviewed all information available regarding the safety and efficacy of products containing this herbal substance. The available safety data as well as guidance from the CHMP at the European Medicines Agency (EMA) were evaluated. Following this evaluation, the IMB concluded that the use of echinacea can be associated with rare side effects, mainly allergic reactions which in some cases may be severe. This review has led the IMB to conclude that the use of products containing echinacea is no longer recommended in children under twelve years of age. The IMB has taken the view that there are potential risks associated with the use of echinacea containing products in children under twelve years of age and there is limited evidence of benefit in this age group. Consequently, products containing echinacea specifically intended for use in children will no longer be acceptable on the Irish market and other products containing echinacea will be labelled accordingly to remove any references to use in children. While this is not considered a serious safety issue, nevertheless, these measures are being taken as a precaution, as with all medicines, to maximise the benefits of use and reduce the risks to users.

HUMAN MEDICINES

IMPLEMENTATION OF THE NEW EU PHARMACOVIGILANCE LEGISLATION: CHANGES TO REPORTING REQUIREMENTS

The revised European Union (EU) pharmacovigilance legislation Directive 2010/84/EU and Regulation (EC) 1235/2010 was adopted by the European Parliament and Council of Ministers in December 2010. Many of the new and revised provisions contained in the legislation have been effective since July 2012. The IMB has been providing, and continues to provide, regular updates on public consultations, new documents released and guidance for marketing authorisation holders (MAHs) on its website under the section New EU Pharmacovigilance Legislation. The legislation has also been transposed nationally and details of the relevant, national legal documents are also accessible via the above link.

For reporting of adverse reaction reports to the IMB, the following revised guidance has been issued in line with GVP Module VI. These national adverse reaction reporting requirements apply from July 2012 until the end of the transitional period (within six months of the functionalities of the Eudravigilance database being announced by the Agency).

Adverse Reaction Report Type	Source	Reporting requirements during transitional period
Serious Irish	Health Care Professionals	Continue to submit to IMB only, within 15 days[1]
	Consumer	Submit to IMB only, within 15 days[1]
Non-serious Irish	Health Care Professionals	No direct submission to IMB required[2]
	Consumer	No direct submission to IMB required[2]
Serious non-Irish	Health Care Professionals	No direct submission to IMB required[2]
	Consumer	No direct submission to IMB required[2]
Non-serious non-Irish	Health Care Professionals	No direct submission to IMB required[2]
	Consumer	No direct submission to IMB required[2]

1. Please note that the IMB will forward all Irish serious cases received directly to EudraVigilance. During the transitional period, MAHs should not report these Irish serious cases to EudraVigilance as this will lead to duplicate reporting.
2. Reports to EudraVigilance and other NCAs should be submitted in accordance with the European Medicines Agency document on Reporting requirements of Individual Case Safety Reports (ICSRs) applicable to marketing authorisation holders during the interim arrangements.

VETERINARY MEDICINES

STAFF CHANGES

Ms. Hazel Dunphy, Scientific Officer, left the Veterinary Medicines Department in June 2012. The IMB wishes her well in her new career. Hazel was replaced on 13 August by Ms. Anne McNaughton.

VETERINARY WEBSITE UPDATE

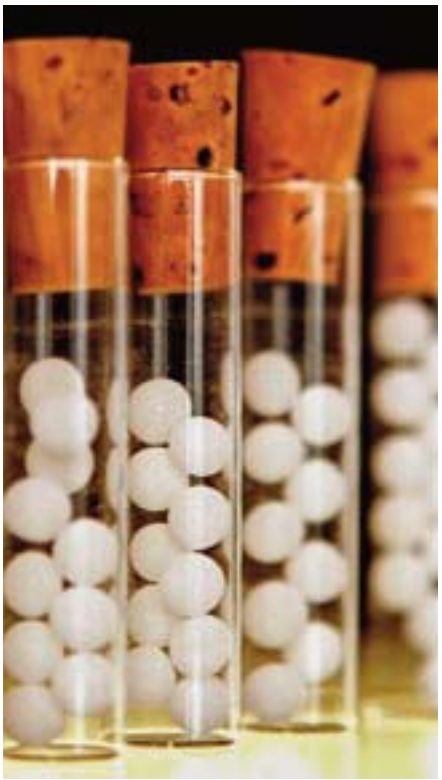
The IMB is experiencing some technical difficulties with the uploading of information concerning the list of authorised veterinary medicines on our website. In particular, the method of supply indicated on the website has not always been fully correct and in line with the marketing authorisation. The IMB apologies for this error and any confusion caused. Care is always taken to ensure the accuracy of information made available to the public. We are currently trying to resolve this issue.

The appointment of the IMB by the Minister for Health as competent authority for the protection of animals used for scientific purposes under Directive 2010/63/EU will necessitate some new changes to the website. This function will be effective from 2 January 2013 and preliminary work to undertake the activities has already commenced. As part of this work, the IMB will be developing a web presence and will be hosting relevant information on its web site. The changes are not expected to result in significant changes to the 'look and feel' of the existing site, but the information on veterinary medicines contained under the 'Veterinary' banner may have to be partitioned to accommodate information in respect of the new area of responsibility for scientific animal protection. It is also possible that the maintenance work required to accommodate the uploading of data in respect of the new activities will mean that some short-term disruption might be experienced. Queries relating to scientific animal protection may be sent to: **scientificanimalprotection@imb.ie.**

UPDATE ON FLUKICIDES FOR MILK-PRODUCING LIVESTOCK

Further to the establishment of maximum residue limits (MRLs) for milk in respect of clorsulon, closantel, nitroxinil, and triclabendazole earlier this year, a referral procedure of the products concerned was initiated by the European Commission. This procedure is aimed at harmonising the labelling of flukicidal products containing these active substances as well as rafoxanide for use in livestock intended to produce milk for human consumption. The net effect of the referral, which is nearing conclusion, will be:

1. Harmonisation of labelling warnings / withdrawal period recommendations in dry cows and pregnant heifers between products containing the same active substances and marketed in different EU Member States.
2. Introduction of new warnings/withdrawal period recommendations for other live stock intended to produce milk for human consumption in all Member States.



At the time of writing, we are waiting formal ratification of the referral procedure, following which MAHs will be requested to submit variation applications to bring their products into line with the Commission decision. The required variation is classified as a Type IA change under the variation category C.I.1.a.

Insofar as flukicidal products indicated for use in cattle are concerned, the existing warning "*Not permitted for use in animals producing milk for human consumption, including pregnant animals intended to produce milk for human consumption*" can continue in place on affected products marketing in Ireland (this warning being more conservative than that proposed by the Commission). However, the IMB is open to receiving applications from MAHs to be in line with the more precise and nuanced message contained in the Commission's decision, if desired.

It should be noted that the availability of MRLs for certain flukicidal substances is expected to stimulate MAHs to develop appropriate residue studies in pregnant or lactating livestock, thereby establishing appropriate withdrawal periods for milk for such animals. In the meantime, the availability of MRLs for the most of the substances concerned serves as a suitable reference point for national residue monitoring purposes.

COMPLIANCE

IMPORTANT INFORMATION IN RELATION TO GLYCERIN AND GLYCERIN-BASED STARTING MATERIALS

In July 2007 the IMB wrote to all Qualified Persons at authorised medicinal product and investigational medicinal product manufacturers and to all heads of quality units at active Ssubstance manufacturers in Ireland in relation to glycerin (also known as glycerol). That letter highlighted the need for increased vigilance to be exercised in relation to glycerin, particularly that manufactured in, or sourced from, China. The need for increased vigilance arose as a result of incidents in the United States where toothpaste and other dental products manufactured in China were found to be contaminated with diethylene glycol, which is known to have been used instead of glycerin. Diethylene glycol contaminated toothpaste had also been identified on the Spanish and UK markets.

There have also been cases in which containers labelled as glycerin (from China) actually contained diethylene glycol. Diethylene glycol, a common constituent of antifreeze, is sometimes used as a solvent and is hazardous when consumed, leading to potential liver and kidney failure, and possibly death. Ph. Eur. and USP monographs both specify a limit test for diethylene glycol (0.1%) that may be present in glycerin and provide a GC analytical method for its analysis.

The IMB now wishes to advise of another issue affecting glycerin that needs to be addressed and came to our attention via the US FDA.

Glycerin, as well as other oils and proteins commonly used in the production of human and animal food, medical products, cosmetics and other products, may contain toxins if they are derived from the *Jatropha* plant.

For more detailed information, please see the *Notification to Industry* issued in the US by the FDA on 6 July 2012. This is available at the following link: http://www.fda.gov/downloads/ForIndustry/GuidanceDocuments/UCM310867.pdf

Please be aware of the above information, and if the manufacturing site uses any glycerin or glycerin-based starting material, please check whether it was derived from the *Jatropha* plant. If it was, please ensure that there is evidence as to the compliance of the manufacturer of the material and that the necessary controls are implemented within the manufacturing operation to assure the quality of that material on receipt.

Please also be aware of the risks presented by the potential substitution or use of glycerin derived from the *Jatropha* plant. Steps should be taken to prevent the use of ingredients that might be intentionally, or otherwise, adulterated with *Jatropha*. Useful information in this regard is contained within the linked FDA Notification to Industry.

Glycerol/Glycerin that is intended to be used in medicinal products in the EU is expected to meet the requirements of the Ph. Eur. monograph on Glycerol (496) as well as the general monograph on substances for pharmaceutical use (2034).

The IMB wishes to reiterate the need for manufactures to review any reduced sampling and/or reduced testing programmes that are in place for glycerin or glycerin-based starting material at this time. This is to determine if there is still adequate assurance of the quality of those materials to support such reduced sampling and/or reduced testing activities.

The guidance in relation to Starting Materials as presented in Annex 8 (Sampling of Starting and Packaging Materials) to the EC Guide to GMP should be used as a basis for the above review. For active substance manufacturers, useful guidance in this regard is presented in Section 7 (Materials Management) of Part II of the EC Guide to GMP.

In addition, the guidance

presented in Annex 15 (Qualification and Validation) in relation to using a risk assessment approach to determine the scope and extent of validation should be applied when qualifying potential suppliers of any glycerin or glycerin-based starting material.

Appropriate personnel within manufacturing sites, such as quality control, validation and materials management staff, are requested to be aware of the above information and to take the actions outlined above.

HYDROGEN PEROXIDE IN TOOTH WHITENING PRODUCTS – NEW LEGISLATION FROM OCTOBER 2012

The IMB is highlighting changes in the EU legislation that will come into effect in October 2012 under Council Directive 2011/84/EU, the 'Tooth Whitening Directive', for the purpose of assuring a greater degree of

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protection of consumer health in this area.

An assessment by the European Commission's Scientific Committee on Consumer Safety published in 2007 (SCCP/1129/07) notes that particular care in using tooth whitening/bleaching products should be taken by persons with gingivitis and other periodontal diseases or defective restorations. A clinical examination by a dentist prior to using such tooth whitening products will ensure the absence of any conditions such as pre-existing oral tissue injury or pathology or concurrent use of tobacco and/or alcohol, which may exacerbate the possible toxic effects of hydrogen peroxide.

The assessment concluded that a limit of 0.1% hydrogen peroxide, present or released, is safe for products sold directly to consumers. Products containing more than 0.1% and up to 6% hydrogen peroxide, present or released, should be administered only by a dental practitioner. Because of the increasing risks of acute and long-term effects, tooth whitening products containing more than 6% hydrogen peroxide are not considered safe for use by the consumer. In light of this opinion, the Tooth Whitening Directive was adopted in September 2011 and will be in force from October 2012.

What does this new legislation mean for supply of tooth whitening products?

The Tooth Whitening Directive allows the use of hydrogen peroxide, present or released, in products sold directly to consumers up to a maximum concentration of 0.1%. Products containing greater than 0.1% and up to 6% hydrogen peroxide (present or released) must be applied under the supervision of a dental practitioner. A restriction on the sale of such products means that tooth whitening or bleaching products containing greater than 0.1% hydrogen peroxide can only be sold to dental practitioners. Distributors must therefore ensure that such products are only supplied to dental practitioners and are not supplied directly to retail. Products containing greater than 6% hydrogen peroxide (present or released) are

prohibited from use and should not be placed on the market.

Labelling requirements for tooth whitening products

The following information should appear in English on the packaging of tooth whitening products:

1. Name and address of the Responsible Person (EU address).
2. Nominal weight / volume.
3. Best before date or open jar symbol *(where applicable)*.
4. Precautions for use.[3]
5. Professional use only *(where applicable)*.
6. Batch number for traceability.
7. Product function.
8. List of ingredients.

Note: tooth whitening products that are CE marked as medical devices are incorrectly classified as such and should be brought to the attention of the IMB.

What precautions should be taken in sourcing tooth whitening products?

Due diligence and care should be taken in sourcing products from suppliers and confirmation of the strength of hydrogen peroxide present or released from the product should be sought from the supplier.

Product safety updates, listing products that pose a risk to consumers, are available on the European Commission's website.

What information should be requested from the supplier?

- Contact details of the European Responsible Person for each product supplied.
- Labelling information (see labelling checklist above) is present on the product packaging.
- The level of hydrogen peroxide present or released in the product and that it is not in excess of 6%.

Care should be taken with any of the following ingredients: hydrogen peroxide, carbamide peroxide, calcium peroxide, magnesium peroxide, zinc peroxide, sodium carbonate peroxide, sodium perborate, strontium peroxide and urea peroxide. All of these ingredients can release hydrogen peroxide

It is important that the above factors are appropriately accounted for within the relevant supplier agreements. In addition, wholesalers should carry out periodic goods-in checks to ensure that, on an on-going basis, products received continue to comply with the above. It is recommended that a sample pack from each in-coming batch is checked to ensure on-going compliance.

What other factors should be considered in terms of the distribution of tooth whitening products?

It is important to ensure that the onward supply of tooth-whitening products is compliant with the new legislative requirements. Wholesale distributors need to ensure that the supply of products containing between 0.1% and up to 6% hydrogen peroxide is confined to

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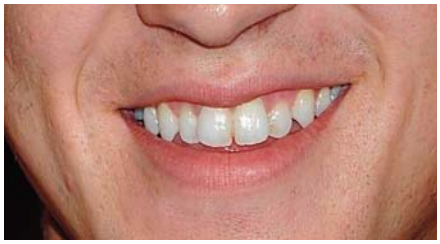
3 Specific precautions for use to appear on tooth whitening products containing between 0.1% and 6% hydrogen peroxide include:
- 'Contains hydrogen peroxide'.
- Concentration of hydrogen peroxide present or released indicated in percentage terms.
- 'Avoid contact with eyes, rinse immediately if product comes into contact with them'.
- 'Not to be used on a person under 18 years of age'.
- 'To be only sold to dental practitioners'.
- For each cycle of use, the first use to be carried out only by dental practitioners, or under their direct supervision if an equivalent level of safety is ensured. Afterwards to be provided to the consumer to complete the cycle of use.



dental practitioners only. In this regard, wholesalers should ensure that all products are appropriately identified and the necessary picking controls put in place to ensure that these higher strength products are not supplied to any other customers. Wholesalers will also need to consider how they may establish that the customer is a dental practitioner. The registration of dentists to professionally practice can be checked with the Irish Dental Council (www.dentalcouncil.ie).

Complaints and undesirable effects (adverse reactions)

It is recommended that all serious undesirable effects occurring on the Irish market be reported to the IMB as Competent Authority for cosmetics and to the responsible person (RP) for that tooth whitening or bleaching product in order to allow the effect to be investigated. The IMB can be contacted by e-mail at **cosmetics@imb.ie**.

FOR THE ATTENTION OF QUALIFIED PERSONS (QPS), MANUFACTURER /IMPORTER AUTHORISATION (MIA) HOLDERS AND ACTIVE SUBSTANCE MANUFACTURERS, IMPORTERS AND DISTRIBUTORS

From 2 July 2013, active substances may only be imported into the European Union if, inter alia, they are accompanied by a written confirmation from the Competent Authority of the exporting third country which – as regards the plant manufacturing the exported active substance – confirms that the GMP standards and control in the plant are equivalent to those in the EU [reference: Article 46b(2) of Directive 2011/62 that amends Directive 2001/83/EC]. In this context, the European Commission has issued an information leaflet as well as Q&A document, which can be downloaded from the Commission's web site:

Information on the importation of active substances:
http://ec.europa.eu/health/human-use/quality/index_en.htm#ias

Information leaflet:
http://ec.europa.eu/health/files/documents/active_pharmaceutical_ingredients_leaflet_en.pdf

Template for written confirmation:
http://ec.europa.eu/health/files/eudralex/vol-4/2012_06_19_template.pdf

Q&A:
http://ec.europa.eu/health/files/gmp/2012_06_04_qas.pdf

UPDATE TO THE IMB GUIDE TO REPORTING OF QUALITY DEFECTS IN MEDICINAL PRODUCTS FOR HUMAN AND VETERINARY USE

In September 2010, the IMB published a guidance note to assist stakeholders in assessing which quality defects should be reported to the IMB and which defects may be deemed non-reportable. Based on the experience gained and feedback received in the past two years, the guidance has been further developed and an updated version is due for publication.

The more significant changes to the document will be as follows:

- addition of active substance manufacturers to the scope of the document;
- new allowance for companies to, in certain specific circumstances, not report a quality defect to the IMB which has been classified as 'major';
- further guidance on initial defect investigation and information gathering; and
- additions to, and re-categorisation of, reportable and non-reportable defects.

The updated guidance note will be available shortly on the IMB website.

UPDATE TO THE GMP GUIDE

The revised text for Chapter 1 of the GMP Guide, which has been renamed as 'Pharmaceutical Quality System', has been published on the European Commission's website. The chapter was revised to align more closely with the terminology and concepts applied in the ICH Q10 guidance for a pharmaceutical quality system. The revised text will come into effect from 31 January 2013.

Chapter 7 of the GMP Guide also underwent revision and is now published on the EU Commission's website (it has been renamed as 'Outsourced Activities'). The text was revised principally to align more closely with terminology used in ICH Q10 and also to clarify the wider applicability of the guidance to outsourced activities in general. The revised text will come into effect from 31 January 2013.

Annex 2, which relates to manufacture of biological medicinal products for human use, underwent a substantial revision and the revised text has now been published on the EU Commission's website. The revised annex comes into effect from 31 January 2013.

Revision of the text of annex 15 (Qualification and Validation) and annex 17 (Parametric Release) will commence in 2013. The process will start will publication of concept papers outlining the reasons for revision of these annexes and these will be available for public consultation for a three-month period. It is anticipated that the concept papers will be published prior to the publication of the next IMB newsletter. Manufacturers should avail of the opportunity to comment on the scope of the revision to these annexes during the consultation period for these concept papers which will be published on the EMA website together with instructions on how to submit comments.

Manufacturer's/importer's authorisation (MIA)

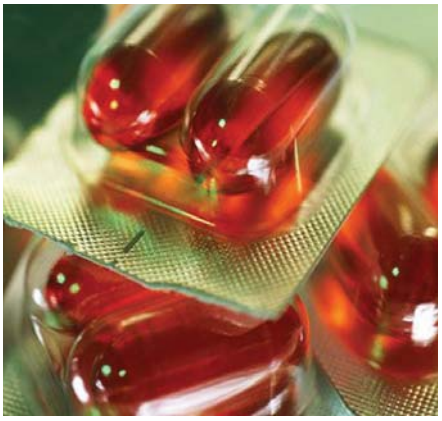
The IMB will be migrating MIAs from the current format to the new EU format which has been published in the EU Compilation of →

Community Procedures (see EMA website) and comes into effect in January 2013. The transfer of MIAs to the new format will include publication of certain details of the MIA, similar to those details which are publicly available for a GMP certificate, on the EudraGMDP database on the EMA website. The IMB will contact manufacturers prior to migration of their MIAs to the new format.

INVALID NEW AND VARIATION APPLICATIONS

The Compliance department aims to receive and validate new and variation applications as quickly and efficiently as possible. Our ability to meet this objective largely depends on the submissions we receive from industry. To this end, incomplete applications can lead to delays in the process as time is spent obtaining outstanding items.

When submitting new applications, guidance relating to supporting documentation is provided throughout the application form. Those submitting variation applications should refer to our 'Guide to applications to vary a manufacturing/importation authorisation or wholesaler authorisation' which is available on the IMB website.



Please note that, from 1 August 2012, all incomplete licensing applications will be marked with a status of 'invalid'. The applicant will be informed of the reasons for invalidation by e-mail or letter. The applicant will be given one month from the date of issue of IMB correspondence to provide all outstanding documentation or information. If any outstanding documentation or information has not been received within this timeframe, the application will be returned to the applicant and must be re-submitted in its entirety.

For assistance or information on completing a new or variation application, please contact compliance@imb.ie.

MEDICAL DEVICES CERTIFICATES OF FREE SALE

Following representations from the representative trade body and industry, the IMB has decided to extend the expiry date on medical device certificates of free sale from the present two years to five years in order to further facilitate regulatory approval processes for devices in non-EU markets. This change has been effective since June 2012. Applicants are reminded, however, that where a certificate of free sale has been issued and where device registration is not continued, for whatever reason, the potential is there for the free sale certificate to be used in non-EU markets up to its expiry date. To ensure that this does not happen, it is the responsibility of the organisation to which the certificate is issued to have in place a system which will withdraw from circulation certificates which list devices where device registration for the EU has ceased.

Applicants are also further reminded that it is beneficial when submitting applications for certificates that a current copy of the notified body certificate (if applicable) should be included in pdf format to ensure efficient processing of certificates.

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