In July 2011, the CMDh endorsed the PhVWP report on ACE inhibitors, angiotensin II receptor antagonists (AIIRAs) and hydrochlorothiazide and their use in pregnancy and lactation and recommended the implementation of the agreed PhVWP wording for the SPC and package leaflet for all concerned products.

All marketing authorisation holders are asked to review the PhVWP agreed wording which is available on the CMDh website under product information, PhVWP recommendations, and to ensure that the SPC and package leaflet for concerned products, for which they hold marketing authorisations, are in compliance with these recommendations.

Marketing authorisation holders that have not already implemented the changes in SPC and package leaflets are asked to follow the timetable below:

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 April 2012</td>
<td>Variation applications requested through CMDh</td>
</tr>
<tr>
<td>29 June 2012</td>
<td>Variation applications submitted by MA holders</td>
</tr>
<tr>
<td>30 July 2012</td>
<td>Variation applications approved by RMS</td>
</tr>
</tbody>
</table>

If you require any further clarification or information, please do not hesitate to contact vigilance_assessment@imb.ie.
The IMB wishes to report that during March 2012, the European Commission published various Implementing Regulations (201/2012, 221/2012, 222/2012) allowing for the establishment of maximum residue limits (MRLs) for milk in respect of nitroxinil, closantel and triclabendazole. The IMB had previously submitted a request to the European Medicines Agency for the extrapolation of the MRLs to milk for these substances. The MRLs are as follows:

<table>
<thead>
<tr>
<th>Substance</th>
<th>Marker residue</th>
<th>Animal species</th>
<th>MRL for milk</th>
<th>Other provisions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitroxinil</td>
<td>Nitroxinil</td>
<td>Bovine, ovine</td>
<td>20 µg/kg</td>
<td>Final MRL</td>
</tr>
<tr>
<td>Closantel</td>
<td>Closantel</td>
<td>Bovine, ovine</td>
<td>45 µg/kg</td>
<td>Provisional MRL expires on 1 January 2014</td>
</tr>
<tr>
<td>Triclabendazole</td>
<td>Sum of the extractable residues that may be oxidised to ketotriclabendazole</td>
<td>All ruminants</td>
<td>10 µg/kg</td>
<td>Provisional MRL expires on 1 January 2014</td>
</tr>
</tbody>
</table>

For each of the substances concerned, the net effect of the above changes is to remove the existing provision ‘Not for use in animals from which milk is produced for human consumption’ from the MRL Regulation. However, until withdrawal periods are set, it should be noted that the existing prohibition on use of the products concerned in dairy cows remains in place.

The establishment of MRLs for milk in relation to these substances is, nonetheless, a welcome development because:

- the availability of an MRL is expected to lead to some of the companies concerned commissioning new residue studies in dairy animals producing milk for human consumption to establish appropriate withdrawal times (time between treatment and the production of milk for human consumption); and
- the MRL for milk provides a more suitable reference level for residue monitoring purposes.

Pending further ongoing developments, we will provide a further update on the situation in due course.

### PRODUCT LITERATURE

**Format**

In order to facilitate processing and storage of product literature by the IMB, applicants are requested to submit the final colour mock ups as individual unprotected pdf documents. Separate pdf documents for each component of the product literature (label, carton, package leaflet, blister pack etc) are required rather than a single pdf which includes all product literature.

For further information please contact Deirdre O’Keeffe (deirdre.okeeffe@imb.ie).

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**UPDATE ON MRLS FOR FLUKICIDES**

A guideline on the creation of mock ups can now be found on the IMB website. This standard is intended as a guide for both applicants when they are creating mock-ups for submission to regulatory authorities, and for regulatory authorities when they are assessing mock-ups. This reference standard is a joint document between the IMB and the UK’s Veterinary Medicines Directorate (VMD) and followed discussions with industry representatives.

The main body of this Standard includes requirements and guidance that are common to both the VMD and the IMB. Separate annexes have been created that deal with requirements specific to the individual competent authorities:

- annex A deals with the requirements specific to the VMD; and
- annex B deals with the requirements that are specific to the IMB.

This standard brings together existing requirements into one overall document for convenient reference rather than setting new requirements for product literature.

This document is available on the IMB website.

For further information, please contact Deirdre O’Keeffe (deirdre.okeeffe@imb.ie).
VISITORS TO THE IMB WEBSITE WILL KNOW THAT EACH MONTH WE UPLOAD A LIST OF VETERINARY MEDICINES AUTHORISED FOR THE FIRST TIME DURING THE PRECEDING MONTH. WE ALSO UPLOAD THE SUMMARY OF PRODUCT CHARACTERISTICS AS WELL AS OTHER PERTINENT INFORMATION (E.G. METHOD OF SUPPLY) WITHIN 7 DAYS OF THE DATE OF AUTHORISATION. OTHER CHANGES TO AUTHORISED PRODUCTS ARE UPLOADED WITHIN DAYS OF THEIR APPROVAL. MARKETING AUTHORISATION HOLDERS ARE ENCOURAGED TO CHECK THAT THE PUBLISHED DETAILS OF THEIR PRODUCTS ARE FULLY CORRECT. ANY ERRORS SHOULD BE IMMEDIATELY NOTIFIED TO THE VETERINARY MEDICINES DEPARTMENT (VETINFO@IMB.IE).

SUMMARY INFORMATION AND PARTICULARS OF AUTHORISED VETERINARY MEDICINES ON THE IMB WEBSITE

However, it is envisaged that their existing GMP certificates will continue to apply and the existing re-inspection process of these sites will become part of the programme of mandatory inspections of all API sites. Accordingly, they will not require immediate re-inspection when the new legislation is enacted.

There are a small number of API manufacturers in Ireland which have not requested GMP certification to date and, therefore, have not been the subject of voluntary inspections. We strongly encourage these companies to contact us as soon as possible with a view to scheduling inspections and, if found to be compliant, facilitating the GMP certification of these sites, thus avoiding any potential for disruption of business when the new legislation is enacted. Companies should indicate their interest and submit requests for information to compliance@imb.ie.

In addition, importers and distributors of APIs will be required to be registered with the IMB and will be subject to inspection on a risk-based approach. We will be contacting finished product manufacturers in due course, to obtain details of these parties. In the meantime, finished product manufacturers that use the services of third-party importers and distributors of APIs should ensure that these ‘agents’ are aware of the new legislative changes affecting APIs.

COMPLIANCE


It is envisaged that a registration process for all manufacturers, importers and distributors will be established and that mandatory inspections and certification to GMP will be part of the new legislation. Many of the API manufacturing sites operating in Ireland are already participating in a voluntary inspection programme, and hold GMP certificates from the IMB for the products they manufacture. These sites will be required to register when the registration process is established.

GMP AND MARKET COMPLIANCE INFORMATION DAY 2012

THE IMB WILL HOLD AN INFORMATION DAY, PRIMARILY FOR MANUFACTURERS OF ACTIVE SUBSTANCES AND MEDICINAL PRODUCTS, ON THURSDAY 27 SEPTEMBER 2012 AT THE CROWN PLAZA HOTEL IN SANTRY. FULL DETAILS OF THE PROGRAMME, INCLUDING HOW TO REGISTER, WILL BE ANNOUNCED ON THE IMB WEBSITE FROM EARLY JUNE. THOSE INTERESTED IN ATTENDING SHOULD CHECK THE ‘EVENTS’ SECTION OF THE WEBSITE FOR UPDATES.

ANYONE INTERESTED IN ATTENDING THIS INFORMATION DAY SHOULD RESERVE PLACES AT AN EARLY STAGE AS THERE IS USUALLY A SIGNIFICANT INTEREST AND PLACES ARE LIMITED.

IT IS PLANNED TO HAVE TOPICS WHICH SHOULD BE OF GENERAL INTEREST FOLLOWED BY PARALLEL SESSIONS ON MORE SPECIFIC TOPICS. WE ARE CONSIDERING HOLDING A SHORTER GENERAL MORNING SESSION WITH MORE TIME FOR PARALLEL SESSIONS.

THE GENERAL TOPICS COVERED ON THE DAY WILL INCLUDE A REGULATORY UPDATE ENCOMPASSING:

• GMP UPDATES, AND
• LEGISLATION (FALSIFIED MEDICINES DIRECTIVE).

QUESTIONS MAY BE SUBMITTED AND...
WHOLESALE DISTRIBUTION
INFORMATION DAY 2012

The Compliance Department will hold an Information Day for wholesale distributors of medicinal products on the 28 September 2012 at the Crowne Plaza hotel in Santry. Full details of the programme, including details on how to register, will be available on the IMB website from early June. Those interested in attending should check the ‘Events’ section of the website for updates and are advised to reserve a place at an early stage as a large number of attendees is expected and places will be limited.

The main purpose of the information day is to provide an overview of regulatory updates under the Falsified Medicines Directive and to discuss changes to the Commission Guidelines on Good Distribution Practice of Medicinal Products for Human Use. The guidelines are expected to become effective during 2013 and will take into account advancements of practices for appropriate storage and distribution of medicinal products in the European Union and amendments under the above Directive.

GUIDANCE FOR MARKETING AUTHORISATION HOLDERS
WHEN DEALING WITH PHARMACY LEVEL RECALLS ON THE IRISH MARKET

Currently, the most widely used method of providing recall communications to healthcare professionals in Ireland is by hard-copy post. During certain recalls, particularly those where an electronic communication has not already been sent, it is essential that the postal mailing is 100% successful so that the message and instructions in the recall communication are received by all intended recipients.

In a recall to pharmacy level, communications may be sent to a targeted list of pharmacies using a known customer listing or, where this is not possible, a blanket recall to all pharmacies in Ireland will be carried out.

In targeted listings, where the marketing authorisation holder (MAH) will be addressing the envelopes, it is important that it is addressed for the attention of the supervising pharmacist or the pharmacy department in the case of hospital pharmacies. Recent correspondence with community and hospital pharmacists has highlighted some cases where recall communications have failed to reach their intended target(s). It is important that recall letters are opened immediately so that recall actions can be undertaken quickly, as failure to get the message to the intended recipient(s) can cause defective product to remain available and expose patients to unnecessary risk.

In the case of a blanket recall to pharmacy level, the MAH will be requested by the IMB to obtain a pharmacy listing from the Pharmaceutical Society of Ireland (PSI), which is provided in the form of pre-printed labels by the PSI to the MAH. The PSI listing is updated on a regular basis, and so, to ensure that recall communications are issued to all intended recipients, it is essential that a current listing is obtained from the PSI at the time of the recall. Some private hospital pharmacies may not be included in this listing and this should be taken into account by the MAH when compiling the recipient listing.

Adherence of MAHs to the above guidance helps facilitate effective recall actions. Additional guidance on dealing with recall issues can be obtained from recallsandqualitydefects@imb.ie or from the ‘Product Recalls’ section on the IMB Website.

SAMPLING AND ANALYSIS:
IMPORTANT INFORMATION FOR MANUFACTURERS AND MARKETING AUTHORISATION HOLDERS (MAHS)

The IMB’s Market Compliance section operates a risk-based sampling and analysis programme as part of the IMB’s pre- and post-marketing product surveillance activities. This involves the sampling and analytical testing of human and veterinary medicinal products, active substances, products intended for export, enforcement-related samples and borderline medicinal/non-medicinal products. Examination of the packaging and labelling of medicinal and other products is also undertaken.

A key element of the programme involves evaluating the suitability of company analytical methods. Consequently, most of the surveillance testing work that is performed employs the company’s own quality control laboratory methods and reference materials. We routinely requests companies (MAHs or manufacturers) to provide it with copies of their own QC test methods, as well as reference standards and other items for use during the analysis work.

The purpose of this newsletter article is to highlight some issues that arise in relation to the provision of such items to us and to highlight important points that companies should be aware of when they receive requests for these items:

- The IMB uses form No. SUR-F0032, entitled ‘Request for Sampling and Analysis Supporting Items’ when requesting such items from companies. When this form is received by a company, it should...
be read in full and all of the items requested in it should be provided to the IMB within the time specified.

• The company must sign the form, declaring that the items being provided comply with the list of items requested, that the analytical methods being provided are those currently in use at the company’s testing laboratory and that they reflect those currently registered in the relevant marketing authorisation.

• The company should return the signed form, together with the items that were requested, to the IMB within the timeframe specified on the form.

• Several recent changes have been made to the form, as follows.

— Where related substances and/or chirality testing is to be performed by the IMB, the form will now contain a request for an unused chromatographic column to be provided for this analysis. The column will be returned by the IMB to the company upon request. In certain circumstances, we may also request a column to be provided for other types of analysis.

— When assay testing is to be performed by titration and an auto-titrator is used, the form will now contain a request to provide a copy of a typical titration curve and details of instrument settings (stir time etc.) along with the method.

— When Karl Fischer testing is to be carried out or when it is required for assay testing, the form will now request the company to specify the exact titrant/solvent system used by the company’s QC laboratory and to provide a statement that the titrants have been shown to be suitable according to Ph. Eur. Section 2.5.12 Water: Semi-Micro Determination.

Please also note the following:

— When HPLC or TLC is to be carried out, companies are requested to provide clear and legible representative chromatograms. For related substances testing in particular, chromatograms of blank, placebo, standard and sample should be provided.

— For UV and IR analysis, the relevant spectra should be supplied.

— When reference standards are provided, companies should ensure that enough material is supplied to perform testing in triplicate. The reference standard should have a minimum of 6 months left on its expiry date.

— Where specific TLC plates, SPE cartridges or filters are mentioned in the method these may also be requested.

• When reference standards are provided, companies should ensure that a reference standard which requires cold storage is sent directly to the laboratory contact person at the address on the request form.

• In cases where customs clearance is necessary when sending items to the IMB, companies should ensure that all necessary customs clearances are obtained in a timely manner.

• Companies should also advise the IMB as soon as possible if there will be a delay in supplying any of the items requested, with the reasons for same. The Market Compliance section can be contacted on + 353 (0) 1 6764971.

TOOTH-WHITENING PRODUCTS – NEW LEGISLATION ON HYDROGEN PEROXIDE

The IMB is highlighting upcoming changes in the legislation on the use of tooth-whitening or bleaching products containing hydrogen peroxide.

An assessment by the European Commission’s Scientific Committee on Consumer Safety was carried out to determine a safe level of hydrogen peroxide in oral hygiene and tooth whitening products with a report being published in 2007 (SCCP/1129/07). 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, Council Directive 2011/84/EU was adopted in September 2011 and will be in force from October 2012.

Directive 2011/84/EU 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. Furthermore, for each cycle of use, the first application is performed by a dental practitioner (as defined under Directive 2005/36/EC on qualifications for dentists), or under his/her direct supervision if an equivalent level of safety is ensured. Dental practitioners may then provide the product to the consumer to complete the cycle of use. In addition, such products should not be used on persons under 18 years of age and must be labelled with the following information:

- Contains hydrogen peroxide.
- Concentration of hydrogen peroxide present or released must be 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.

Tooth-whitening products containing greater than 6% hydrogen peroxide (present or released) are prohibited from use and should be withdrawn from the marketplace. Tooth-whitening products are classified as cosmetic products and not as medical devices. Products bearing a CE mark and marketed as medical devices are incorrectly classified as such and should be withdrawn from the market.

Further information on tooth-whitening products can be obtained from the Healthcare Products Distribution section of the Compliance Department at cosmetics@imb.ie.