IRISH MEDICINES BOARD

news LETTER

MEDICINAL PRODUCTS

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HUMAN MEDICINES

IN-USE STABILITY TESTING

The *Note for Guidance on In-Use Stability Testing of Human Medicinal Products (CPMP/QWP/2934/99)* states that 'the registration dossier for a multidose product should either include the in-use stability data on which the in-use shelf life is based or a justification why no in-use shelf life is established'. The *Note for Guidance on Development Pharmaceutics (CPMP/QWP/155/96)* further states that for liquid and semi-solid preparations, 'large packs intended for dispensing may require more stringent testing. The testing programme should allow the assignment of an 'in-use shelf life' for the product which will subsequently appear on the product literature'. This period should be appropriate, especially for products intended to be sterile such as parenteral or ophthalmic preparations where there are specific micro-biological considerations. Examples of multidose products include multidose tablet and capsule containers, creams, gels, oral liquids, eye ointments and drops, multidose parenterals etc.

The IMB advises marketing authorisation holders that, where an in-use shelf life is not currently registered for a multidose product, they should conduct in-use stability testing to establish an acceptable period during which the product can be used once the container has been opened.

The new Variations Regulations (EC No. 1234/2008) provide for a reduction or extension of the shelf life of the finished product after first opening by way of a Type IAin B.II.f.1.a.2 or Type IB B.II.f.1.b.2 variation category respectively.

INCOMING MR/DCP APPLICATIONS

The IMB encourages finalisation of the national phase of incoming MR and DCP applications as promptly as possible.

Applicants are reminded below of several steps they can take which may facilitate this final stage of assessment for human products.

Applicants are requested to respond promptly when sent the draft schedule for their comments. If a product is not to be marketed immediately, text versions of the final national product information should be submitted. These should reflect exactly the harmonised text, adapted only to include the national specific elements such as name, PA number, MAH for Ireland etc. This will facilitate issue of the authorisation. When the product is then later to be marketed, an Article 61.3 application must be submitted to register mock-ups and Braille declaration prepared based on these text versions (as amended by any intervening variations).

If the product is to be marketed immediately, applicants should take into account when preparing mock-ups, IMB recommendations on labelling as stated in the IMB *Guide to Labels and Leaflets of Human Medicines* available on the IMB website, and the European Commission *Guideline on the Readability of the Labelling and Package Leaflet of Medicinal Products for Human Use* available on the European Commission website. All colour mock-ups, including those with non-finalised wording, may be submitted to the IMB pharmaceutical →

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assessor for initial review regarding layout and style prior to the EU end-of-procedure/commencement of the national phase of assessment – this should minimise correspondence required during the national phase to finalise mock-ups. Applicants are encouraged to carefully review mock-ups submitted against the harmonised end-of-procedure texts to ensure no omissions have occured e.g. that the INN still reflects the strength in the name etc. Formatting should be used judiciously to highlight important information, e.g., strength per total volume for parenterals or safety issues for powders for concentrates for solution highlighting the requirement that the product 'must be reconstituted and further diluted before use'. Applicants are reminded that even when a product is for administration by healthcare professionals only, a Braille declaration must still be submitted, as the sections on Braille exemption (Section 1b) and the provision of a patient-accessible leaflet for people who are blind or partially sighted (Section 2) must be completed (see IMB website for details).

It is highly recommended that applicants finalise the proposed name as early as possible in the MR/DCP procedure. Generic names can be generally accepted, except for modified release/prolonged release products. Where an invented name is required, the IMB *Guide to Invented Names of Human Medicines*, available on the IMB website, should be consulted and applicants are encouraged to provide a number of proposed invented names for review early in the procedure. However if a product is not to be marketed immediately, then a generic name can be used to finalise the national SPC, PL and label texts, if a commitment is also provided to submit a variation to register an invented name prior to marketing (especially for modified release/prolonged release products).

Close coordination between the applicant (for the EU phase) and local representatives (for the national phase) is recommended to avoid discrepancies from the approved procedural text and agreed positions during procedure e.g. batch release sites. Applicants are also recommended to carefully review mock-ups at this stage to ensure no changes other than those which are the subject of the discussion with the assessor have been introduced between submitted mock-up versions.

The IMB therefore welcomes the cooperation of applicants in this matter to facilitate finalisation of the national phase of MR/DCP new applications.

MINOR CHANGES TO PRODUCT INFORMATION

The IMB would like to clarify its procedure for minor changes to product labelling and package leaflets under Article 61(3) of Directive 2001/83/EC as amended. This Article states that 'all proposed changes to an aspect of the labelling or the package leaflet covered by this Title and not connected with the summary of product characteristics shall be submitted to the authorities competent for authorising marketing'. The requirement for submission of Article 61(3) notifications to register changes to approved product information remains unchanged.

However, the IMB has identified some minor amendments to the labelling and package leaflet which are not considered to require a formal assessment. With this in mind, marketing authorisation holders are advised that the following changes do not require notification to the IMB:

1. Moving the location of the batch number/expiry date on inner and outer packaging, provided no other details are changed.
2. Transfer of the entire text of a carton face to an opposing face, with no change to text, font size, layout, appearance or readability of text.
3. Any change to a barcode, e.g. number on the barcode that does not affect any other aspect of the labelling and does not change the location of the barcode.
4. Change to printing key lines on package leaflet or labelling with no change to text, font size, appearance or readability of information.
5. Change in the dimensions of the PIL resulting in an **increase** in the font size of the text.
6. Deletion of UK PL numbers and/or PL holder details, with no other changes to information.
7. Change/deletion of a product name in another member state in section 6 of the PIL (MRP products only).
8. Change in the details of a distributor/wholesaler.
9. Change to dimensions of carton with no change in layout or font size of text.
10. Relocation of Braille positioning (with no change to text).
11. Change to packaging code/internal reference code on packaging.

In such instances, the revised labels or patient leaflet should be submitted to the IMB at the next regulatory activity involving a change in the product information. Any and all other changes to product labels or package leaflets will continue to require a formal notification, as before.

UPDATE ON EUDRAVIGILANCE BUSINESS RULES

The IMB previously highlighted the requirements arising from introduction of the new EudraVigilance business rules for exchanging safety/acknowledgement messages and individual cases safety reports (ICSRs) in the EEA, in the January 2010 issue of the newsletter and on its website. These rules are detailed in a guidance entitled *Note for Guidance EudraVigilance Human – Processing of Safety Messages and Individual Case Safety Reports (ICSRs)* (Doc. Ref. EMEA/H/20665/04/ Final – Revision 2), which is available on the websites of the EMA and EudraVigilance.

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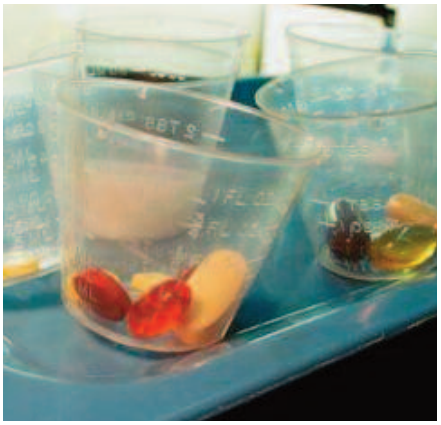
The business rules apply to **all** stakeholders involved in exchanging safety messages and ICSRs electronically at Community level in line with applicable legislation and guidance. Marketing authorisation holders (MAHs) and sponsors are requested to ensure that all adverse reaction reports submitted electronically to the IMB comply with these requirements.

The IMB in conjunction with the EMA has followed the proposed common implementation plan outlined in the document *Implementation Plan for The Note for Guidance EudraVigilance Human – Processing of Safety Messages and Individual Case Safety Reports (ICSRs)* (Doc. Ref. EMA/665231/2008 Revision 1), which is also available on the websites of the EMA and EudraVigilance. All stakeholders should follow this common approach, and should now have fully implemented the business rules in accordance with this plan.

The EMA performs routine data



quality control checks based on the business rules and validation process, providing senders with monthly listings of ICSRs which do not comply with the mandatory data elements and validation rules as described in the guidance for correction and appropriate retransmission electronically within 15 days following receipt of the listings.

Review of experience to date has shown that some of the non-compliances identified in rejected reports include cases coded with non-current versions of MedDRA, inconsistencies in handling of fatal cases, worldwide case IDs not in the appropriate E2B format, and missing seriousness criteria. From 7 February 2011, reports which are not submitted in accordance with the required standards and formats, will be classified as 'error reports' by the IMB, which will continue to monitor compliance with the business rules and will communicate with MAH/sponsors regarding non-compliance, as appropriate.

Further information on the business rules and the implementation plan are available on the EMA website and the EudraVigilance website.

If you have any questions concerning these business rules, please contact the EudraVigilance helpdesk (Tel. +44 (0)20 7523 7523; email: eudravigilance@ema.europa.eu).

VETERINARY MEDICINES

REPORT FROM THE WORKING GROUP ON THE METHODS OF SUPPLY OF COMPANION ANIMAL ANTIPARASITIC MEDICINES

The Board of the IMB endorsed the above report at their meeting on 1 September 2010. The report is now available on the IMB website. From now on, the principles set out in this report will form the basis of the approach to be taken to the designation of the method of supply for companion animal antiparasitic medicines.

In respect of the list of products for dogs, the report notes that the existing supply category was deemed satisfactory for 65 out of 75 medicines. For 10 medicines for dogs, a change from POM to CAM was recommended. In respect of the medicines for cats, the method of supply for 24 out of 27 medicines remain unchanged. For a single product, the report recommended that the supply route be changed from POM to POM(E) while for two products, a change from POM to CAM was recommended.

Applicant companies which are affected by the recommendation to change the method of supply have been invited to submit an application to vary the existing marketing authorisations in line with the policy. Applicants who chose to vary their authorisation to give effect to this change before 30 November 2010 benefited by having the applications processed free of charge.

COMPLIANCE

UPDATES TO THE EU GMP GUIDE

Chapter 5 (Production) and **Chapter 7** (Outsourced Activities) have been revised and issued for public consultation (see further details below). The draft text is available on the websites of the European Medicines Agency (EMA) and the European Commission. These documents are open for **public consultation until 28 February 2011** and any comments should be made using the form available on the EMA website and addressed to both SANCO-GMP@ec.europa.eu and ADM-GMDP@ema.europa.eu.

- **Chapter 5 – Production (revised draft guidance)**
  Changes have been proposed to the sections dealing with qualification of suppliers to reflect the legal obligation of manufacturers to ensure that active substances used have been →

produced in accordance with GMP. Requirements for ensuring traceability of the supply chain for starting materials have also been introduced. The revised guidance also clarifies expectations with regard to testing of starting materials. Further work on the sections of Chapter 5 dealing with control of cross contamination is ongoing and there will be a separate consultation on these aspects when the revised draft text becomes available.

- **Chapter 7 – Outsourced Activities (revised draft guidance)**
  This chapter has been revised to harmonise the terminology used with that included in the ICH Q10 guideline and also to reflect the wider scope of what are considered to be outsourced activities in the context of the manufacture and testing of medicines. The Chapter title has been changed to reflect this.

- **Chapter 6 – Quality Control (Concept Paper)**
  A concept paper on revision of Chapter 6 has been published on the EMA website. This concept paper proposes that Chapter 6 be revised to include guidance on the transfer of analytical methods. The document is open for **public consultation until 28 February 2011** and any comments should be addressed to ADM-GMDP@ema.europa.eu.

UPDATES TO OTHER GUIDANCE DOCUMENTS

A draft concept paper has been published on the EMA website regarding storage conditions during transport. The purpose of the document is to provide guidance on regulatory expectations to ensure that medicinal products and active substances are not damaged during transportation. This concept paper is open for **public consultation until 28 February 2011** and any comments should be addressed to ADM-GMDP@ema.europa.eu.

NEW Q&A ON QUALIFIED PERSON (QP) ROLE

Two new Questions and Answers have been published on the EMA website regarding the role of the Qualified Person. These questions had been raised at a meeting of Interested Parties with the inspectors' working group at the EMA.

NEW IMB GUIDANCE DOCUMENTS

The IMB will soon publish a series of guidance documents on its website relating to frequently asked questions on specific areas of interest. A brief summary of these documents is given below:

1. **Variation applications to authorisations / licence**
   This document highlights the documentation requirements that should be considered as minimum requirements for supporting documentation to accompany an application to vary a Manufacturing / Importation Authorisation or Wholesaler Authorisation.
2. **Guidance relating to attainment of Qualified Person (QP) status in Ireland**
   This document is intended to provide guidance to individuals considering a career in the pharmaceutical industry as a Qualified Person (QP). It identifies the educational requirements to become a QP and the manner in which the IMB approves QP candidates. The document also provides potential candidates with reading material which should be considered before embarking on further education.
3. **Guidance on requests to the IMB to perform inspections in third countries**
   The IMB, as Competent Authority in Ireland for the regulation of medicinal products, medical devices and healthcare products, is often requested to perform inspections in third countries. These countries are defined as being located outside the European Economic Area (EEA). This document is intended to provide guidance to holders of Manufacturing / Importation Authorisations (MIAs) or Marketing Authorisations (MAs) in the Republic of Ireland, that request an inspection to be performed at a third party manufacturer located outside the EEA. The legal basis for such inspections and planning logistics are described in the document.

ELECTRONIC APPLICATIONS FOR CONTROLLED DRUG LICENCES / LETTERS OF NO OBJECTION

From 31 January 2011, the IMB will no longer be accepting paper applications for annual licences, import/ export licences and 'letters of no objection' for controlled drugs from manufacturing and wholesaling companies. This will also apply to universities at a later date.

Pharmatrust is an electronic application system which allows companies to apply for licences online. As an online application system, the process of submission will be quicker and more efficient. Using Pharmatrust will mean applicants will benefit in the following ways:

- ✔ Ease of application;
- ✔ Quick and efficient application process;
- ✔ Less opportunity for errors;
- ✔ Secure online system;
- ✔ Environmentally friendly – less paper waste.

To register for Pharmatrust, the following information should be provided to controlleddrugs@imb.ie:

- Name of company;
- Name of contact person and e-mail address;
- A list of all controlled drugs and imported or exported products;
- The names and addresses of foreign companies from which drugs or products requiring a licence are imported or to which they are exported.

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Following the set-up of a Pharmatrust account, companies will be required to hold an account with the Department of Health and Children which should be maintained in credit by submission of a cheque, **payable to the Department**, posted to the Controlled Drugs section at the IMB, to cover anticipated fees for a number of licences. Each time a licence is issued, the appropriate fee will be deducted from the account. A licence cannot be issued if there is insufficient funding to process the application. Please forward any queries to controlleddrugs@imb.ie.

COSMETICS

Since October 2010, the IMB has undertaken responsibility for issuing certificates of free sale for cosmetics (see IMB website for more details). These were previously issued by the Department of Health and Children.

All companies wishing to apply for certificates of free sale should make themselves familiar with the new requirements for notification and for application for free sale certificates prior to first application.

Before applying for a certificate of free sale a company must complete the process of notification of their responsible person and submit the required notarised documents and spreadsheet. For more information on this, please consult the relevant guidelines on the IMB website. The new application form and guideline document regarding the completion of applications for cosmetic certificates of free sale can be found on the IMB website.

All guidelines should be thoroughly reviewed before making an application as they contain information and guidance on all aspects of the application; if an application is lacking any required information it cannot be processed until the omission is resolved by the company. The most common causes of non-validation of the application involve: inadequate completion of the notification process, omission of a cosmetics organisation number (allocated by the IMB), non-submission of the relevant fee, non-submission of Companies Registration Office document and failure to identify relevant product codes on the application spreadsheet which should match that declared to the IMB during the notification process.

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.

Human Medicines Products List

Veterinary Medicines Products List

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