IRISH MEDICINES BOARD

news LETTER

MEDICINAL PRODUCTS

MAY–AUGUST 2013 Issue No. 45

IRISH MEDICINES BOARD, KEVIN O'MALLEY HOUSE, EARLSFORT CENTRE, EARLSFORT TERRACE, DUBLIN 2 TEL: 01 676 4971 FAX: 01 676 7836 EMAIL: FOI@IMB.IE

HUMAN MEDICINES

LIST OF INTERCHANGEABLE MEDICINAL PRODUCTS (GENERIC SUBSTITUTION):

The Health (Pricing and Supply of Medical Goods) Act 2013 was commenced on 24 June 2013 and provides for the introduction of a system of generic substitution and reference pricing for medicinal products. The role of the IMB under this legislation is to establish, consult on, publish and maintain a list of interchangeable medicinal products on our website.

The initial list was published by the IMB on 7 August 2013, and included 96 atorvastatin products within four separate groups. The IMB has since added a further two active substances to the list. On 20 September, 46 esomeprazole-containing products within two separate groups were added while, on 24 September, 56 rosuvastatin-containing products within four separate groups were included.

The IMB will be adding further active substances to the list on a continual basis and at the time of going to print, ongoing consultations are taking place with omeprazole- and pravastatin-containing products. Further detailed information in relation to ongoing consultations and updates to the list can be found under the 'Generic and Interchangeable Medicines' section on the IMB's website homepage.

Interchangeable medicinal products are those that

(1.) have the same qualitative and quantitative composition in each of their active substances
(2.) are in the same pharmaceutical form
(3.) have the same route of administration and
(4.) have not more than two active substances. Such products will be included in a single group on the list. There will be certain circumstances where medicines are not considered interchangeable, for example, where there are clinically significant differences between medicines or where medicines cannot be safely substituted for other medicines. These criteria will always be taken into account in the decision-making process conducted by the IMB.

Medicines on the interchangeable list may be substituted for each other to assist in providing savings for those paying for medicines and for the health service. In practice, it is important to note that the list will not supplant the prescriber's discretion, to exempt a medicinal product from substitution for clinical reasons. In such instances, the prescriber will write, legibly and by hand 'do not substitute' on the prescription beside the name of the medicinal product.

As the objective of the legislation is to deliver savings to patients and the State, those medicinal products that result in the greatest cost will be reviewed first, having due regard to the terms of the legislation. The Department of Health has currently requested that the IMB prioritise the review of the interchangeability of the following 20 active substances contained in medicinal products that will achieve the greatest savings.

Anastrozole	Pantoprazole
Atorvastatin	Perindopril
Candesartan	Pravastatin
Clopidogrel	Quetiapine
Esomeprazole	Rabeprazole
Lansoprazole	Ramipril
Lercanidipine	Risperidone
Losartan	Rosuvastatin
Olanzapine	Simvastatin
Omeprazole	Valsartan

→

CONTENTS

Our initial focus in terms of reviewing interchangeability of medicinal products will be on the 20 active substances outlined above. Thereafter the IMB will continue to review further active substances and product groups (or products) for inclusion on the list of interchangeable medicinal products. Priorities may also continue to be determined based on needs identified by the Department of Health and/or HSE.

It is possible for the marketing authorisation holder to make an application to have a medicine added to the list of interchangeable medicines or add a group of medicines to the list. Applications of this nature will be considered by IMB following its review of the priority substances included in the table above. The maximum timeline for review of applications of this nature is 180 days.

The IMB has published a detailed guide outlining the process involved in establishing a list of interchangeable medicines and a questions and answers document. These documents are available on our website.

Queries on the list of interchangeable medicines can be sent to ICQueries@imb.ie

CLINICAL TRIALS – REFERENCE SAFETY INFORMATION (RSI)

The reference safety information (RSI) is used for assessing the expectedness of adverse reactions that occur during a clinical trial. The EU Heads of Medicines Agency Clinical Trials Facilitation Group (CTFG) has recently clarified the requirements for the RSI, as outlined in the European Commission guidance (CT-1 and CT-3).

For new clinical trial applications:

The cover letter should clearly indicate the location of the RSI in the application dossier. For authorised products, this will usually be within the Summary of Product Characteristics (SmPC) and for unauthorised products, within the Investigator's Brochure (IB).

If the reference safety information is within the **SmPC**, the list of expected adverse reactions is contained in Section 4.8 'Undesirable Effects'. Please note that relevant

safety information may also be contained in other sections of the SmPC, however only Section 4.8 should be used for the purposes of expectedness assessment. If the investigational medicinal product has marketing authorisations in several Member States with different SmPCs, the sponsor should justify its selection of the most appropriate SmPC for the RSI, with reference to subject safety.

If the reference safety information is within the **IB**, it should be in a clearly identified separate section. This section should include a list of expected adverse reactions clearly arranged according to their nature, frequency and severity (e.g. in tabular format). If different indications are being investigated for the investigational medicinal product, separate tables of expected adverse reactions by indication may be appropriate to avoid misinterpretation of information (e.g. oncologic indications and immune-mediated indications).

If an IB is used as the RSI for an authorised product, any differences between the list of expected adverse reactions in the IB and the SmPC should be highlighted and justified.

For ongoing clinical trials:

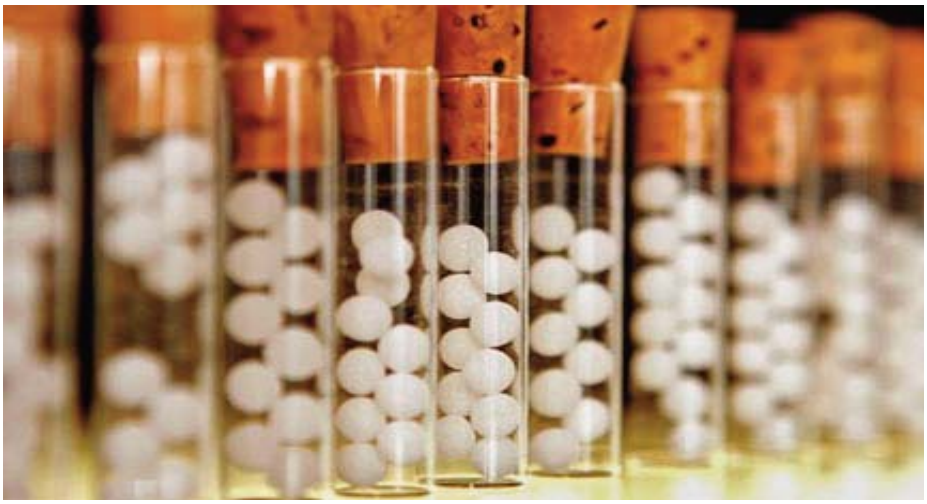
If the reference safety information is within the IB and there is not yet a clearly identified separate section, this should be implemented at the next routine yearly update. The location of the RSI should be clearly indicated in the cover letter.

Substantial amendment to a clinical trial:

When submitting a substantial amendment to an ongoing clinical trial, such as an IB update, any changes to the RSI should be clearly indicated using the track changes format. Proposed amendments to the RSI should be mentioned in the cover letter.

Any change to the RSI is considered a substantial amendment and should be justified with supporting data. If the RSI is required to be updated, it is recommended that this is done in alignment with the development safety update report (DSUR). In this way, the DSUR can act in part as justification for the RSI changes and the basis for expectedness can remain consistent for the reporting period. If the RSI is updated prior to the end of the reporting period of the DSUR, detailed justification with supporting data is required.

The Guide to Clinical Trial Applications has been updated to clarify these requirements.



VETERINARY MEDICINES

CHANGE IN NAME OF THE DEPARTMENT

Consequent to the IMB being designated as the competent authority for the regulation of animals used in scientific studies in Ireland on 1 January 2013, a unit was established to handle this work. The unit is located within the veterinary department which now considers a wide range of applications (not only those relating to veterinary medicinal products). Given the changed role of the department, it has been decided to change the name to the 'Veterinary Sciences Department'. Appropriate adjustments have also been made to the website which now includes both veterinary medicines or scientific animal protection sections.

IMB VET INFO DAY 2013

Even if it is the case that the long-awaited proposal for new European legislation governing the authorisation, use, supply and monitoring of veterinary medicinal products is not yet available, in the interest of our stakeholders the IMB has decided to host an IMB Veterinary Medicines Info Day on Thursday, 24 October 2013 at the Radisson Blu Hotel, Dublin Airport. The meeting venue and arrangements have been made to facilitate participation by stakeholders and to provide networking time for discussions with IMB personnel. The event will consider recent developments in relation to the authorisation of veterinary medicinal products and the performance of the IMB. Further details of the event are available on the IMB website. The IMB may consider hosting a special themed event relating to the elaboration of the new legislation in 2014 if there is interest amongst stakeholders for this.

IMB VETERINARY REGULATORY FEE CONSULTATIONS

As is usual around this time of the year, the IMB will shortly begin a public consultation in respect of its proposed fees for 2014. The overall objective of any new fee proposal will be to ensure that the IMB has adequate resources to meet its ongoing financial needs, both in respect of protecting public and animal health as well as customer service. Details of the fees will shortly be available on the IMB website.

QUICK RESPONSE CODES OR 2D BARCODES ON LABELLING AND IN PACKAGE LEAFLETS

The addition of a quick response (QR) code or 2D barcode to product labelling or package leaflets is permissible provided all three of the following conditions are met:

1. The QR code or 2D barcode is intended for internal manufacturing processing, stock control or anti-counterfeit measures.
2. Any additional information in the QR code or 2D barcode that can be read by members of the public must not contain information other than product information approved by the IMB for inclusion in the summary of product characteristics, label or package leaflet for the product.
3. The addition of the QR code or 2D barcode does not affect any other aspect of the label or leaflet and does not affect the legibility of the approved label or leaflet text.

Addition of QR codes or 2D barcodes fulfilling all three of the above requirements will not require submission of a variation application. However, where the addition of such a code or barcode meets conditions 1 and 2 but does not meet condition 3, a C.II 6 variation should be submitted along with amended mock-ups for consideration.

It is the responsibility of the MAH to ensure that all three of the above conditions are met. Inclusion of website addresses, or links to websites, within the QR code or 2D barcode is not currently permissible however this aspect is under review at present.

TRANSFERS OF MARKETING AUTHORISATION HOLDER BEFORE AUTHORISATION IN DCP/MR PROCEDURES

Applicants are reminded that during DCP or MR new product applications where Ireland is reference member state or a concerned member state, any proposal to transfer the MAH prior to the conclusion of the procedure should be clearly communicated as early as possible during the procedure. Revised application forms indicating the new MAH and supporting documentation should be provided during the DCP/MR procedure for the product, citing the relevant IMB case and EU procedure numbers. Separately, but concurrently, an IMB Transfer Before Authorisation application form B available on www.imb.ie should be submitted to IMB Receipts and Validation, also clearly indicating the relevant IMB case number and EU procedure numbers. When the applicant has been informed that the transfer has been processed and when they have received notification of the new VPA numbers, then revised product information (SPC, PL and mock-ups including the new VPA numbers and MAH details) should be provided for the DCP/MR procedure.

TRANSFERS OF MARKETING AUTHORISATION HOLDER AFTER AUTHORISATION

The IMB would like to remind MAH's that during the transfer of an existing product licence to a new MAH, no changes may be made to the →

labels and leaflet, other than the VPA number, the holder's name and address and the company logo, as applicable. Any changes to the layout and design of the product livery should be registered by way of a separate C.II.6 variation as they may affect the readability of the contents and therefore require review. Similarly if mock-ups have not previously been registered with the IMB, a C.II.6 variation is required. Further guidance in relation to transfers may be found in the 'Guide to transfers of veterinary product authorisations' which is provided on the IMB website.

COMPLIANCE

REVISIONS TO EU GMP GUIDANCE

Several sections of the GMP guide are undergoing revision at this time. All of the documents are accessible on the European Commission's website via: http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm

DOCUMENTS UNDERGOING PUBLIC CONSULTATION

Annex 16 – Certification by a Qualified Person and Batch Release

The Annex is undergoing revision to reflect the globalisation of the pharmaceutical supply chains and the introduction of new quality control strategies. The revision has been carried out in the light of Directive 2011/62/EU (the so-called 'falsified medicines directive') amending Directive 2001/83/EC as regards the prevention of the entry into the legal supply chain of falsified medicinal products, and to implement ICH Q8, Q9 and Q10 documents, and interpretation

documents, such as the manufacturer's/importer's authorisation (MIA) interpretation document, as applicable. In addition, some areas where the interpretation by member states has not been consistent, have been clarified.

Stakeholders are invited to comment on this draft (150 KB) by 5 November 2013 at the latest. Comments should be sent by email to: ADM-GMDP@ema.europa.eu and SANCO-pharmaceuticals-D6@ec.europa.eu

DOCUMENTS WHERE FINAL REVISED TEXT HAS BEEN PUBLISHED

Chapter 2 – Personnel

This chapter was revised to integrate the principles of 'Pharmaceutical Quality System' as described in the ICH Q10 tripartite guideline. A section has been added on consultants.

The final text has now been published and will come into operation from 16 February 2014.

DOCUMENTS WHERE THE REVISION PROCESS IS ONGOING FOLLOWING COMPLETION OF CONSULTATION

There are several sections of the GMP Guide where the revision process is ongoing to finalise text following completion of public consultation. These include the following documents:

Chapter 3 – Premises and Equipment

(Draft text – public consultation closed 18 July 2013)

The text in this chapter is undergoing revision to include improved guidance in section 6 on prevention of cross-contamination (involving also Chapter 5 – see below) and includes reference to a new complementary toxicological assessment guidance.

Chapter 5 – Production

(Draft text – public consultation closed 18 July 2013)

Changes have been made to sections 17 to 20 to improve the guidance on prevention of cross-contamination and to refer to guidance on toxicological assessment. Changes were also introduced in sections 26 to 28 on the qualification of suppliers in order to reflect the legal obligation of manufacturing authorisation holders to ensure that active substances are produced in accordance with GMP. The changes include supply chain traceability. Section 33 is inserted to clarify and harmonise expectations of

→

manufacturers regarding the testing of starting materials, while section 68 introduces guidance on notification of restrictions in supply.

Chapter 6 – Quality Control

(*Draft text – public consultation closed 18 July 2013)*
The draft text included a new section on technical transfer of testing methods and other items, such as, out of specification results.

Chapter 8 – Complaints and Product Recall

The draft text proposed revisions to reflect Quality Risk Management principles to be applied when investigating quality defects/complaints and when making decisions in relation to product recalls or other risk-mitigating actions. The revised text emphasises the need for the cause(s) of quality defects/complaints to be investigated and determined, and to ensure that appropriate preventative actions are put in place to guard against a recurrence of the issue. It also clarifies expectations and responsibilities in relation to the reporting of quality defects to the Supervisory Authority.

NEW LAWS REGULATING THE RETAILING OF COSMETIC PRODUCTS

On 11 July 2013, new laws[1] came into force impacting everyone who sells cosmetic products in Ireland. All retailers who sell cosmetic products should be aware of these new laws and the legal requirements now in place. The IMB has developed a leaflet to explain these important changes, which will be available on our website soon. The contents of the leaflet are summarised below.

What are cosmetic products?

These are products generally intended to cleanse or beautify a person. Some examples include deodorants, shampoos and soaps, hair dyes, toothpaste and make-up.

What do the new laws mean for me as a retailer?

As a result of the new laws, a retailer is now required to:

- confirm that certain important information has been included on the label of a cosmetic product;
- take due care and avoid any unnecessary risks in the purchase of cosmetic products from suppliers;
- take steps to make a product safe if there is a safety concern;
- inform suppliers and/or the IMB if a customer experiences an undesirable effect (adverse reaction) after using a cosmetic product;
- ensure products are stored and transported properly to avoid any negative impact on the safety of the products (while they are your responsibility);

Additionally, if you directly import a cosmetic product from outside Europe, you will have further responsibilities. Information on these additional responsibilities can be found in the IMB **Guide to Cosmetic Products for Responsible Persons**.

What do I need to check on the product label?

- That the text on the label is in English, in Irish or both.
- That the best before date, where this is relevant to the product, has not passed.
- That the information below is present on the label:
- an ingredient list
- a batch number or reference ID
- a European address

In the case of soap, a bath ball or any other small product where it is not possible to list the ingredients, this information should appear on a notice immediately beside the product.

What checks must I carry out if I purchase a cosmetic product over the internet for sale in my premises?

If you are buying a cosmetic product over the internet you must carry out the same checks as above.

1 This EU law is Regulation (EC) No. 1223/2009

What records do I need to keep?

Retailers should keep records of all their suppliers of cosmetic products. Invoices and/or delivery dockets should be kept for 3 years.

What actions should I take during a product recall?

In the event that an unsafe product is placed on the Irish market, a retailer is required to cooperate with their supplier and with the IMB in retrieving (recalling) the product from the market. This is when records become very important.

What do I do if a customer experiences an undesirable effect?

An undesirable effect is an adverse effect on human health that occurs from the normal or reasonably expected use of a cosmetic product. An undesirable effect is sometimes referred to as an adverse reaction. Examples of undesirable effects include irritant and allergic effects, sensitivity to light and itching. If a customer reports an undesirable effect, this information should be provided to the company at the European address on the label. Additionally, the information can be provided to the IMB using the undesirable effect report form.

A serious undesirable effect means an undesirable effect which results in temporary or permanent inability to function as normal, disability, hospitalisation, birth defects, an immediate risk to life, or death.

In the event of a *serious undesirable effect* occurring on the Irish market, the retailer *must*, without delay, contact the IMB *and* the company at the European address on the label. You should report the following details:

- the name of the relevant cosmetic product so it can be identified;
- all serious undesirable effects that you are aware of related to this product;
- any corrective action taken. This might include stopping a product from being sold.

Report forms can be downloaded from the cosmetics section of the IMB website.

→

What is the role of the IMB?

The IMB is responsible for the regulation of cosmetic products in Ireland. Our aim is to ensure all cosmetics on the Irish market are safe and comply with the new laws. We identify and address cosmetic product safety issues, in conjunction with the HSE, so that a cosmetic product will not compromise the health and safety of the consumer or the person applying the product.

Further information

See our **Guide to the Distribution of Cosmetic Products** for more details. This and other guides are available from the cosmetics section of **www.imb.ie** Copies of the form used to report serious undesirable effects to the IMB are also available.

If you have any queries about the information contained in this article, or any other questions concerning the regulation of cosmetic products, please e-mail: **cosmetics@imb.ie**

REQUIREMENTS REGARDING CPNP NOTIFICATION AND APPLICATIONS FOR COSMETIC CERTIFICATES OF FREE SALE

Cosmetic products which are intended to be placed on the market in the European Economic Area (EEA) must have a designated legal or natural person within the EEA entitled the Responsible Person (RP). If you manufacture a cosmetic product within the EEA or import a cosmetic product from outside the EEA you will most likely take on the role of the RP. The RP has a number of obligations under Regulation (EC) 1223/2009 one of which is cosmetic product notification.

All cosmetic products on the EEA market need to be notified via the Cosmetic Product Notification Portal (CPNP) prior to being placed on this market. Up to this point, cosmetic products were notified directly to the IMB or competent authorities in other Member States. This function has now been centralised across Europe. The European Commission has developed the CPNP as an online notification system and has published **guidance documents** on how to register and notify products. This notification has become a mandatory requirement since 11 July 2013 with the coming into force of Regulation (EC) No. 1223/2009 and it is the responsibility of the RP to ensure that all their cosmetic products are notified via CPNP. Importantly, this obligation extends to those products that have previously been notified to the IMB and are currently on the EEA market.

An application for a Cosmetics Certificate of Free Sale must only contain information which is identical to that which has been submitted via the CPNP, including CPNP reference numbers and descriptions. Corresponding company product identity numbers may also be included on the application. Discrepancies between information contained in the application versus the CPNP information for that product or product range will result in the application being returned.

An application for a Cosmetics Certificate of Free Sale for products which are intended for export outside the EEA only and would, therefore, not have been notified via the CPNP, must be accompanied by a letter signed by the manufacturer or the RP. This letter should state that the products are manufactured in accordance with the principles of GMP as set out in Regulation (EC) No. 1223/2009 and should list the products and their descriptions and site(s) of manufacture as they have appeared on the application. For applicants making an application for Cosmetics Certificates of Free Sale for the first time, this document should be notarised.

For reasons of transparency and efficiency, applications for certificates concerning these products should, ideally, be made separate from those made for products notified via the CPNP.

The Guidance note and application forms reflecting these changes will be updated shortly.

IRISH MEDICINES BOARD

This Bulletin is designed by Ashfield Press Publishing Services for

IRISH MEDICINES BOARD, KEVIN O'MALLEY HOUSE, EARLSFORT CENTRE, EARLSFORT TERRACE, DUBLIN 2
tel: +353 1 6764971 fax: +353 1 6767836 email: foi@imb.ie http://www.imb.ie