IRISH MEDICINES BOARD

# news LETTER

MEDICINAL PRODUCTS

JANUARY – MAY 2003 Issue No. 14

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GENERAL

## 2003 IMB Information Days

An information day on Human Medicines is scheduled to take place Monday 29th September 2003 in the Great Southern Airport Hotel.

Proposed topics for discussion are:

- Implementation of CT Directive
- IMB IT Strategy
- ADR Reporting

Registration forms for this day can be downloaded from our Website at www.imb.ie or please contact Ms Margaret Miley. The cost will be €250 per person.

An information day on: '*The Simplified Registration Scheme for Homeopathic Medicines*', is being planned, to take place later in the year.

## Staff Changes at the IMB

The Irish Medicines Board is delighted to announce the following recent appointments which arise from reorganisation and the NIMBUS programme and involve transfer of some roles and responsibilities. These appointments will come into effect on a phased basis over the coming months (see 'The NIMBUS Programme' in this Newsletter)

| | |
|---|---|
| Dr. Joan Gilvarry | *Director of Human Medicines* |
| Dr. J. Michael Morris | *Technical Director* |
| Ms Rita Purcell | *Director of Finance and Corporate Affairs* |
| Dr. Elaine Breslin | *Medical Assessment Manager* |
| Ms Caitriona Diviney | *Workflow Manager* |
| Dr. Caitríona Fisher | *Quality Systems and Regulatory Affairs Manager* |
| Ms Muireann Lydon | *Pharmaceutical Assessment Manager* |
| Ms Rachel Mahon | *Post-Licensing Manager* |
| Ms Margaret Miley | *Administrative Manager – Technical Directorate* |
| Ms Mary Murphy | *Receipts and Validation Manager* |
| Ms Maura O'Connell | *Training and Development Manager* |
| Ms Alison O'Toole | *Licensing Manager* |
| Ms Brigid Sheridan | *Scheduling and Customer Support Manager* |

### OTHER RECENT APPOINTMENTS

Mr Chris Cullen took up duty as Senior Inspector in February and Mr Greg McGurk joined the Inspectorate team at the end of March. Dr. Cormac Dalton has also recently joined the staff as Pharmaceutical Assessor.

Recruitment advertisement for current vacancies appended to this publication – closing date Friday 30th May

## CONTENTS

## UPDATE ON THE TRANSFER OF THE CONTROLLED DRUGS FUNCTIONS FROM THE DEPARTMENT OF HEALTH AND CHILDREN TO THE IMB.

The preparation of the legislative amendments to the Misuse of Drugs Acts, necessary to confer responsibility for the controlled drugs licensing and inspection functions to the IMB, are currently being progressed by the Department of Health and Children. The transfer of these functions to the IMB will take place once these amendments are set in place. Further update on the legislative amendments and the transfer of functions will be made available through the IMB website (**www.imb.ie**) and future newsletter editions.

## THE NIMBUS PROGRAMME

The Irish Medicines Board is currently working on the development and implementation of the NIMBUS programme of work. NIMBUS incorporates both organisational and technological change for the IMB and will be implemented in the human medicines area initially.

The reorganisation of the Human Medicines Licensing area has now been agreed and will be fully implemented over the coming months. Dr. Joan Gilvarry will head the Human Medicines division supported by a multidisciplinary team.

All licensing activities will be managed through the new licensing and post-licensing functions with case managers responsible for tracking individual applications. Resource management will be handled through the new workflow function and over the coming year, a dedicated customer service function will also be established.

Overall this new structure is designed to reflect the streamlining of licensing activities and the most effective and efficient use of resources to provide a quality service to all stakeholders.

The information technology project within NIMBUS is now at the design stage with pilot implementation commencing in Q3/2003.

Workflow management is central to the new technology infrastructure and combined with improved web based applications and communications mechanisms, will provide proactive management of licensing activities and associated services. The project is also focused on EU initiatives on electronic exchange of data and will be capable of handling the eCTD at a very early stage.

All stakeholders will be provided with regular updates on the progress of the NIMBUS programme and if there are any queries or you require further information please contact **Suzanne.McDonald@imb.ie**

# HUMAN MEDICINES

## LEGISLATION AND GUIDELINES

### Adopted Notes for Guidance

- CPMP/EWP/633/02 Note for Guidance on the Clinical Development of Medicinal Products for treatment of HIV infection (CPMP) adopted March 2003)
- CPMP/EWP/49/01 Appendix to the Committee for Proprietary medicinal Products (CPMP) Note for Guidance on the Clinical Investigation of Medicinal Products in the Treatment of Schizophrenia, on the Methodology of Clinical Trials concerning the Development of Depot Preparation of Approved Medicinal Products in Schizophrenia CPMP adopted February 2003)
- CPMP/QWP/3309/01 (EMEA/CVMP/961/01) Note for Guidance on the Use of Near Infrared Spectroscopy by the Pharmaceutical Industry and the Data to be forwarded in the Part II of the Dossier for a Marketing Authorisation (Adopted by CPMP/CVMP February 2003)
- CPMP/QWP/130/96 Note for guidance on Chemistry of the New Active Substance. (CPMP adopted February 2003)
- Topic Q3B, Step 2 Note for Guidance on Impurities in New Drug Products (CPMP/ICH/2738/99 (*Revision of CPMP/ICH/282/95*), approval by CPMP 2003
- Topic Q1E, Step 3 Note for Guidance on Evaluation of Stability Data (CPMP/ICH/420/02 – final approval by CPMP February 2003)
- Topic Q1F, Step 3 Note for Guidance on Stability Data Package for Registration in Climatic Zones III and IV (CPMP/ICH/421/02 – final approval by CPMP February 2003)

## CHANGE IN POLICY FOR ISSUING CHANGES TO PRODUCT AUTHORISATIONS

### Current Policy

As companies will be aware, it is the policy of the IMB to issue the updated authorisation schedule (including the Part I and the SPC) at the date of first issue of the product authorisation, the date of renewal and date of transfer (if relevant). Changes (variations) to the details of the product authorisation schedules are issued by endorsement which while forming part of the authorisation, is not normally incorporated into the text until the time of the next renewal.

### New Policy

Following a variation to the PA schedule, the IMB intends to issue a revised schedule which incorporates the change, so that the product authorisation schedule is current and correct at all times. This is a considerable project for the IMB and will have two phases:

*Phase 1 - Updating all existing schedules to reflect endorsements issued since the date of issue or last renewal.*

The IMB has in excess of 6,000 authorisations for human medicines and we plan to update schedules by company in numeric sequence i.e. ▼

starting with the holder of PA001. We will contact each company as we start on their PA schedules and we would be grateful if you could nominate somebody in your company to deal with any queries that may arise. As each schedule is completed it will be e-mailed to your company and any proposed correction of errors should be marked up on the word document sent to you, either manually or by using the track changes option available in Word. Your proposed changes will be accepted if consistent with the endorsements issued, and the new version of the schedule sent to you. Companies *may not* use this process to include anything other than approved variations in their authorisation and other changes must be submitted via the normal variation procedure.

Product Authorisations that have been issued, renewed or transferred in 2003 will also be maintained as updated schedules.

### *Phase 2 – Issue of endorsements to updated schedules.*

Once your company's schedules have been updated, an updated schedule will be issued whenever a variation is approved which changes the schedule. The signed authorisation page will remain the same but will be accompanied by the full schedule. Our new planned IT system will allow online transfer of this information but in the interim we will be sending hard copies of the schedule.

In this area we would ask for your help and co-operation. When we issue a new schedule to you, you will need to take the time to compare it to the previous version to establish which variations have been incorporated into the new version. The signed and dated licence page includes the IMB variation reference number which is issued to each individual variation. Because these numbers are internal, there is no easy way in our current system to indicate which variations have been incorporated, however this will be apparent from reviewing the schedule. Our new systems will address this issue but in the meantime we would ask that you take the time to review the schedule as the IMB does not have the resources to process significant numbers of queries in this area. We will of course endeavor to help where you are unable to reconcile changes to the schedule with variations submitted.

### *Benefits of the New Policy*

We believe that this policy will bring significant benefits to the PA holders, the IMB and the users of product authorisations. The primary benefit is that the currently approved text will be accurately reflected in the schedule. It will also have the longer-term benefit of speeding up renewals and transfers. In the meantime however, we would ask for you patience and assistance. It is a substantial body of work for the IMB and your co-operation will be appreciated.

## MRA WITH CANADA

The Mutual Recognition Agreement with Canada has been in operation since 1 February 2003. The agreement relates to prescription and non-prescription products, medical gases, vaccines immunologicals, stable medicinal products derived from human blood or blood plasma and biotherapeutics. Products manufactured in Canada and sold in the EEA can be tested only in Canada and do not have to be re-tested on importation into the EEA. However, removal of the retesting on entry into the EU may constitute a variation to the Product Authorisation if these details have been given in the dossier and a Type II standard variation application should be submitted to change them. It should be noted that batches imported into the EEA must still be released by a manufacturer within the EEA.

For further details concerning the MRA, please refer to the Inspectorate section of this newsletter.

## COMMON TECHNICAL DOCUMENT (CTD)

As notified in previous newsletters, the date for implementation of the CTD is 1 July 2003. After this date, no new applications will be acceptable in the old format. Any documentation submitted in the old format will not be validated and the applicant will be required to collect the dossier from IMB offices.

Variations and responses to queries on on-going applications will also have to be submitted in CTD format.

For further details on procedural issue, please see the Questions and Answers document on the EU Commission's website, **http://pharmacos.eudra.org/F2/eudralex/vol2/B/ctdqa_032003.pdf.** PA holders should note that, contrary to the advice given in this document, the IMB does not wish to receive re-formatted dossiers of existing PAs, as we do not have the storage capacity to accept them. This does not affect the requirement to submit variations and responses to queries in CTD-format.

## RENEWAL APPLICATIONS

PA holders are reminded that full shelf-life stability data under ICH controlled temperature and humidity conditions are required for older products, even those not marketed in Ireland. As these requirements have been in place for many years, failure to supply such data may lead to a refusal to renew the authorisation or a restriction in the shelf life or storage conditions. When submitting updated stability studies, PA holders should confirm that the formulation, packaging materials and analytical methods used were those previously approved and include a conclusion based on the results of the studies.

For quality defect reports, it is important to include full details of the probable cause and of any corrective action taken, in order not to cause delays in the renewal process.

## PARALLEL IMPORTS AND GENERIC PRODUCTS

The IMB wishes to inform (P)PA holders of parallel import products and generic products that they are required to maintain up to date information in their Summary of Product Characteristics (SPC) and package leaflet that is in line with that of the reference product. When the reference product information is updated, then the parallel import and generic product information should be brought in line by submission of variations.

This issue is of particular importance with regard to the updating of safety information within the SPC. Such information should be com- ▼

municated to the patient without delay in the leaflet.

(P)PA holders should note that chapter 1, volume 24 of *The Notice to Applicants* states that the Marketing Authorisation Holder 'shall inform authorities of any information brought to his attention that could lead to a modification in the … SPC.'

Furthermore, the General Conditions relating to Product Authorisations state that the authorisation holder shall inform the Board of any additional information received by him which may alter the validity of data provided in support of the application or may further the understanding of the substance and its effects, or may alter the directions for use of the medicinal product which is the subject of the authorisation.

## PHARMACOVIGILANCE

### Homeopathic Medicinal Products containing *Chelidonium majus* L.

The IMB recently requested a voluntary withdrawal of herbal products containing Greater Celandine for oral use, due to findings on hepatoxicity of such products. Following on from this, the issue of homeopathic preparations of celandine (*Chelidonium majus* L.) was also considered. It was decided that preparations containing celandine at a potency lower than D4 have a negative benefit risk ratio. Accordingly, a request for voluntary withdrawal of such products, including mother tincture, 1x, 2x and 3x, has been sent to manufacturers and suppliers of homeopathic medicines.

### Submission of ADR Reports

The IMB would like to inform companies that it *not necessary* to submit a company report form or CIOMS form for cases which have been initially notified by the IMB, unless the company has been notified of the same case independently and has additional information on the case.

It is sufficient to inform the IMB by e-mail of the company-generated reference number for such cases.

### Implementation of Electronic Reporting of Individual Case Safety report (ICSR's) to the IMB

Update from Newsletter 13 (September – December 2002)

As a follow up to the article that appeared in the last Quarterly Newsletter of the IMB, we are pleased to inform companies that the IMB is now actively testing Electronic submission of ICSR's. A number of companies are now transmitting XML files to the IMB via the Estri gateway in accordance with the guidance detailed in the last newsletter.

Additional companies interested in initiating electronic submission of ICSR's to the IMB should contact Ms. Shirley Mulvey at **smulvey@imb.ie** for further information and testing details.

## HERBAL MEDICINES PROJECT

Comment on the IMB Herbal Medicines Project report and on the report on the IMB Herbal Medicines Seminar held in May 2002 is still awaited from the Minister for Health and Children.

### EU Directive on Traditional Herbal Medicinal Products

The European Parliament Committee for the Environment Public Health and Consumer Policy submitted in excess of 20 proposed amendments to the Directive to the European Commission in December 2002. The Commission position is awaited, although early reaction indicates that the Commission is favourably disposed to extending the scope of the Directive, an issue of considerable importance from the IMB point of view.

Once published, the Commission position paper will form the basis for discussion at the next Council Working Group [date to be confirmed].

### *Chelidonium majus* L. [Celandine]

In January 2003 following reports from a number medicines agencies of the EU regarding the potential association between the use of medicinal products containing celandine and liver damage the IMB, its *ad hoc* Scientific Committee on Herbal Medicinal Products and the Advisory Committee for Human Medicines considered the issue.

In February 2003 the IMB requested a voluntarily withdrawal of celandine-containing products for oral use from the Irish market. The organisations representing manufacturers, health food stores, pharmacists, medical doctors and Chinese and Western herbalists agreed to the withdrawal. The issue will be reviewed in six months time.

## HOMEOPATHIC MEDICINES PROJECT

### Launch of the Homeopathic Medicines Simplified Registration Scheme.

Final preparations are underway for the launch of the registration scheme as laid down in the EU Directive 2001/83/EC. This scheme covers homeopathic medicines for human use, which are placed on the market without specific therapeutic claim and at a dilution that guarantees the safety of the medicinal product. In addition this scheme covers only those products that are administered orally or externally.

The following documentation will be sent to all manufacturers and suppliers in the coming month:

- Guidance Notes for Manufacturers and Suppliers.
- Guidance Notes on the Control and Quality of Homeopathic Stocks.
- The Manufacture and Control of Dosage Forms for Homeopathic Products.

This documentation, and application forms, will also be available on the IMB web site at **www.imb.ie**, in the near future.

Due to the wide variety of starting materials used in the preparation of homeopathic medicines, applications for registration will be accepted in the following order: homeopathic medicines of mineral origin only, followed by plant-based products, and then animal-based products. When these are processed more complex preparations (two or more stocks) will be accepted. This procedure will facilitate the efficient operation of the scheme.

An information day on: 'The Simplified Registration Scheme for Homeopathic Medicines', is being planned, to take place later in the year.

# VETERINARY MEDICINES

## NIMBUS ROLL-OUT TO THE VETERINARY DEPARTMENT

Work on the new IMB IT Strategy (NIMBUS) is currently underway in respect of the authorisation of human medicines. It is envisaged that the technology adopted by the Human medicines area will be adapted for the management of applications for veterinary medicines following its implementation in the human medicines area. However, a few of the personnel changes supporting the management of applications for human medicines will impact on the Veterinary Department within the coming months. In particular, Dr. Mike Morris in his new role as Technical Director, will cease to have direct responsibility for the pharmaceutical aspects of the authorisation of veterinary pharmaceutical medicines, which will now be the responsibility of Ms. Mary O'Grady, Senior Pharmaceutical Assessor. At a procedural level, it is expected that the current systems for the receipt, validation, evaluation, management and authorisation of veterinary medicines will continue as heretofore. Once the NIMBUS programme becomes operational to veterinary medicines a further update from the Veterinary Department will be provided. In the meantime, any queries on this matter should be addressed to the Veterinary Director, Dr. J.G. Beechinor.

## LEGISLATION AND GUIDELINES

The following guidelines have been adopted by the CVMP from January 2003 to April 2003:

- Revised guideline for the conduct of efficacy studies for intramammary products for use in cattle, (EMEA/CVMP/344/99-FINAL-Rev.1)
- Note for Guidance on the Use of Near InfraRed Spectroscopy by the Pharmaceutical Industry and the Data to be forwarded in the Part II of the Dossier for a Marketing Authorisation (EMEA/CVMP/961/01)
- Note for Guidance on the Declaration of Storage Conditions for Medicinal Product Particulars and Active Substances (EMEA/CVMP/422/99-Rev.1)

### Common EU Pharmacovigilance Reporting Form for MAHs

- Common EU Pharmacovigilance Reporting Form for MAHs, Points to Consider regarding reporting of suspected Serious Adverse Reaction to Veterinary Medicinal Products was adopted by the CVMP. This form will be applicable to MA holders from August 2003 (EMEA/CVMP/601/02-Final)

These documents are available on the EMEA web site:
**http://www.emea.eu.int**

## CLARIFICATION OF TESTING REQUIREMENTS FOR ANTIMICROBIALS SUBSTANCES SUBMITTED UNDER ARTICLE 13 (1)(A) II OF DIRECTIVE 2001/82/EC

The Veterinary Department would like to draw the attention of readers to a guideline relating to the efficacy testing of antimicrobials substances which was elaborated by the Committee for Veterinary Medicinal Products which will come into effect on 11th June 2003. The guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances, (EMEA/CVMP/627/01 – Final) specifies the data requirements for a new application containing either new or established antimicrobial substances. The EMEA has pointed out that while the guideline does not apply to abridged applications which are based on the specific requirements laid down in Article 13 (1) (a) (i) or (iii) of Directive 2001/82/EC they do apply to those applications submitted under Article 13 (1) (a) (ii) of this directive. The EMEA has stressed in this context that the reference to published scientific literature of a bibliographic application refers to information available in the public domain which of course can include data to provide the information which the guideline seeks to require in the context of the antimicrobial resistance.

## BIOCIDAL PRODUCTS

A recent Commission Guidance Document (Doc-Biocides-2002/01) addresses the issue of some types of borderline products which may fall between the Veterinary Medicines Directive (2001/82/EC) and the Biocidal Products Directive (98/8/EC). While not legally binding on competent authorities, this guidance document was the subject of recent discussions between the IMB and the Department of Agriculture (DAF). The Pesticides Control Service of the DAF is the competent authority for the Biocidal Products Directive.

As a result of that meeting, some products which were previously classified as veterinary medicines may be dealt with under the Biocidal Products Directive, as long as no medicinal claims are made. These include disinfectants for use on animals for general hygiene purposes, and insect repellants for use on animals which have no lethal effect on insects. Companies wishing to market such products are recommended to make the usual classification enquiry to the IMB in the first instance, using the application form available on our website. It should be noted that the Biocidal Products Directive requires the submission and evaluation of very similar data to those required by the Veterinary Medicines Directive.

Teat dips are not included in the above decision and will continue to be subject to IMB assessment as veterinary medicines, under the terms of Directive 2001/82/EC.

The IMB Guide to the Definition of an Animal Remedy is being updated to take account of these and other changes, and the revised version (2nd Edition, 2003) will shortly be available on the IMB website.

### Renewals of Marketing Authorisations for Veterinary Medicinal Products

In order to further improve business processes in the veterinary department, it has been decided not to

send out drafts of the authorisation schedules for renewal applications which are about to issue from the IMB. Up to now, it had been IMB practice to allow applicants a period of two weeks to formally agree the authorisation schedule ahead of the Management Committee meetings at which renewal of the authorisation was formally approved. As the renewed authorisation schedule should be the same as that existing previously, it was rare for comments to be received from applicants on the draft schedule. It has been decided therefore to remove this step from the procedure. In future, on satisfactory completion of assessment of the application for renewal, a recommendation concerning renewal will be forwarded directly to the Management Committee for approval and subsequent release of the renewed authorisation to the applicant.

The procedure of sending draft schedules to applicants for new applications for product authorisation will continue as before.

### TRANSFERS

Companies are reminded that transfer of a marketing authorisation to a new Veterinary Product Authorisation (VPA) Holder will automatically mean that a new VPA number is required. The new number will appear on the revised authorisation schedule which is issued on approval of the transfer, and it follows that the new number should be included on revised packaging, along with the name and address of the new VPA Holder.

In the case of transfers, revised mock-ups are not required by the IMB before issue of the new authorisation. However, there are legal considerations which require the correct VPA Holder and VPA number to appear on the labels of veterinary medicinal products. Therefore, as set out in the IMB 'Guideline for the implementation of packaging changes to authorised veterinary medicinal products' and on the Transfer Application Form, it is expected that within a six-month period of approval of the transfer, all supplies leaving the VPA Holder's distribution point (company warehouse or agent) should carry appropriately amended packaging.

### MUTUAL RECOGNITION AGREEMENT (MRA) WITH CANADA

As a result of the MRA with Canada coming into effect earlier this year, product manufactured in Canada no longer needs to be retested on entry into the EU. This is also applicable to product manufactured in Australia, Switzerland and New Zealand which already have operational MRA's with the EU. However, removal of the retesting on entry into the EU constitutes a variation to the Veterinary Product Authorisation for which the company must submit a Type II standard variation application and appropriate fee. It should be noted that batches imported into the EEA must still be released by a manufacturer within the EEA.

For further details concerning the MRA please refer to the Inspectorate section of this newsletter.

### HEVRA WEBSITE

The website of the Heads of Veterinary Regulatory Authorities can be visited at **http://www.hevra.org/what.asp**. From here there are links to the websites of all European Agencies.

The website also includes the official site of the Veterinary Mutual Recognition Facilitation Group (VMRFG) which is regularly updated to take account of policy and other decisions. A brief report of every monthly VMRFG meeting is posted, as well as many procedural documents. There is a facility for applicants to ask questions of the Group, and answers to those questions are posted on the site under 'Frequently Asked Questions'.

Recent updates include the latest edition of the Best Practice Guide (VMRF/033/03), a list of the contact points for Mutual Recognition Procedures in Member States, European Commission and EMEA (VMRF/032/01), and new start dates for 2003/04. Answers to a number of questions have also recently been added.

## INSPECTORATE

### GUIDANCE ON RECALL & CAUTION-IN-USE LETTERS

It is requested that all written communications to healthcare professionals and wholesalers on the subject of batch or product recalls, be discussed and agreed with the Inspectorate Department in advance of their issue. This also applies to written communications providing cautionary advice to physicians, pharmacists and other healthcare professionals on a product or batch quality defect. The latter communications are normally called *Caution-In-Use Letters, (or Dear Doctor Letters where physicians are the intended recipients).*

Communications are requested to be short (preferably no more than one A4 page in length), informative, (providing all the necessary information to the reader), and free of unneceassary information and promotional statements.

The communications should contain simple, unambiguous language, and the overall subject matter (for example, a batch recall of a particular product) should be prominantly displayed at the top of the letter in bold, centered text. The following three documents (Appendices 1-3, pages 11-13) provide examples of letters showing the formats and text elements which are generally requested for such communications.

The Inspectorate Department is available to provide assistance and advice on the text and format of such communications.

Please note also that all agreed, written communications concerning product or batch recalls, and Cau-

tion-In-Use notifications, should carry a statement to the effect that the actions being undertaken, or the advice being provided, have been agreed with the Irish Medicines Board. This provides assurance to the reader that the instructions or advice being provided are in agreement with the IMB.

## REVIEW OF PROPOSED PLANS FOR NEW FACILITIES AND FACILITY EXPANSIONS

Any company intending to engage in construction activities in relation to their GMP or GDP activities are advised to meet with the Inspectorate Department in order to review the plans. It is preferable that such plans are reviewed prior to initiation of construction. The expectation of the Inspectorate from such meetings is that any obvious design failures will be identified at a point where corrective actions may be implemented. However, the review of plans by the Inspectorate does not imply acceptance of the plans and would not prejudice the outcome of any future inspection.

The plans for review should include the building outlay, pressure differentials and process flows for materials, personnel and waste. Note that the term 'process flows' refers to a plan of the building overlaid with different coloured lines showing the sequence of rooms used for each part of the process.

Companies wishing to avail of this review by the Inspectorate should contact Stan O'Neill at **stan.oneill@imb.ie**

## QUALIFIED PERSON RELEASE OF BATCHES FOR MARKETS OUTSIDE THE EU

Qualified Persons should note that the certification requirements for batches of medicinal products apply to all batches manufactured in Ireland, regardless of the destination of the batch or intermediate material. For example, it is required that Qualified Persons formally release batches for the US, although the FDA would not require such a declaration or entry into the batch register.

## MUTUAL RECOGNITION AGREEMENTS (MRAS)

We wish to advise that the operational phase of the EC–Canada MRA, Sectoral Annex on GMP, commenced on 1 February 2003.

The Sectoral Annex covers human and veterinary medicinal products, with the exception of stable medicinal products derived from blood and plasma and veterinary immunologicals. Pre-approval inspections are also currently excluded from the operational phase. Full details of the MRA are available from the EMEA website at **www.emea.eu.int**

We wish to draw your attention to the following issues which relate to the operation of the EC – Canada MRA:

### 1. Medicinal Products manufactured in Ireland and exported to Canada

(i) The Canadian Authority may request from IMB details regarding the GMP compliance of a manufacturer based in Ireland and exporting products to Canada. This information will be provided directly by the IMB inspectorate to the Canadian Authority in the format of the EU certificate of GMP compliance of a manufacturer (ref. EMEA/MRA/48 /02 Rev 2 Final;– this document can be downloaded from the EMEA website).

(ii) The manufacturer must issue a Batch Certificate with each batch exported. The format of the Batch Certificate must be as per the internationally harmonised requirements for Batch Certification (ref. EMEA/MRA/23/01;– this document can be downloaded from the EMEA website).

### 2. Medicinal Products manufactured in Canada and imported into Ireland

(i) Batches of product imported from outside the EU must undergo certification by a qualified person and batch release in accordance with the requirements set down in the Medical Preparations (Licensing of Manufacture) Regulations, 1993–1996 and in annex 16 to the EU Guide to Good Manufacturing Practice. This requirement continues to apply to each batch of medicinal product imported from Canada. However as the MRA is operational, it is no longer necessary to carry out analytical testing on importation of medicinal products covered by the sectoral annex of the EC–Canada MRA on GMP.

Please note that in situations where the marketing authorisation for the product specifies the analytical testing to be carried out on import, a variation should be submitted to the relevant competent authority to remove this requirement.

The latest updates on all of the MRAs are available from **http://www.emea.eu.int/htms/technical/mra/mra.htm**

## Human New Product Authorisations Issued (January - April 2003)

| PA Number | Product Name | PA Number | Product Name |
|---|---|---|---|
| PA0007/059/001 | PHARMATON VIT-AL PLUS | PPA0465/091/001 | SERETIDE DISKUS |
| PA0030/044/002 | LAMISIL AT | PPA0465/091/002 | SERETIDE DISKUS |
| PA0043/025/001 | STREPSILS INTENSIVE | PPA0465/091/003 | SERETIDE DISKUS |
| PA0061/026/005 | ZISPIN SOLTAB | PPA0465/092/001 | LAMICTAL |
| PA0061/026/006 | ZISPIN SOLTAB | PPA0465/092/002 | LAMICTAL |
| PA0061/026/007 | ZISPIN SOLTAB | PPA0465/092/003 | LAMICTAL |
| PA0111/001/001 | CURAM | PPA0465/092/004 | LAMICTAL |
| PA0111/001/002 | CURAM | PPA0465/096/001 | LAMISIL |
| PA0144/042/001 | ISOTREXOL | PPA0465/097/001 | NEURONTIN |
| PA0144/042/002 | ISOTREXOL | PPA0465/097/002 | NEURONTIN |
| PA0365/074/003 | ASACOLON | PPA0465/098/001 | PROSCAR |
| PA0495/012/001 | SOOTHAKE TOOTHACHE TINCTURE | PPA0465/100/001 | PULMICORT |
| PA0522/005/001 | SURE-LAX SENNA TABLETS 25 MG | PPA0465/100/002 | PULMICORT |
| PA0711/027/001 | AMBROL | PPA0465/100/003 | PULMICORT |
| PA0844/002/001 | POTASSIUM IODATE | PPA0465/101/001 | VALTREX |
| PPA0465/088/001 | BRICANYL TURBOHALER | | |

## Human Product Authorisations Withdrawn (January - April 2003)

| PA Number | Product Name | PA Number | Product Name |
|---|---|---|---|
| PA0004/025/001 | BOOTS HEALTHCARE HOT LEMON COLD RELIEF | PA0035/041/001 | CONCORDIN |
| | | PA0035/041/002 | CONCORDIN |
| PA0009/050/001 | IMTACK | PA0035/057/001 | MINTEZOL |
| PA0012/035/001 | BILOPTIN | PA0037/020/001 | ZADSTAT |
| PA0013/002/004 | PARLODEL | PA0037/020/005 | ZADSTAT |
| PA0013/013/001 | ZADITEN | PA0037/039/001 | ASENDIS |
| PA0013/019/001 | SYNTOPRESSIN | PA0037/039/002 | ASENDIS |
| PA0013/033/002 | SANDIMMUN | PA0037/039/003 | ASENDIS |
| PA0013/045/002 | LAMISIL | PA0037/045/004 | CALCIUM LEUCOVORIN |
| PA0013/054/005 | NEORAL | PA0037/045/005 | CALCIUM LEUCOVORIN |
| PA0013/078/003 | CIBACEN | PA0037/053/001 | PIPRIL |
| PA0013/090/003 | AREDIA DRY POWDER | PA0037/053/002 | PIPRIL |
| PA0013/106/003 | FAMVIR | PA0037/053/003 | PIPRIL |
| PA0017/017/001 | DICONAL | PA0037/053/004 | PIPRIL |
| PA0022/042/003 | TEMAZEPAM | PA0037/053/005 | PIPRIL |
| PA0022/042/004 | TEMAZEPAM | PA0037/053/006 | PIPRIL |
| PA0035/002/002 | TRYPTIZOL | PA0037/053/007 | PIPRIL |
| PA0035/002/003 | TRYPTIZOL | PA0037/053/008 | PIPRIL |
| PA0035/002/004 | TRYPTIZOL | PA0037/074/001 | PNU-IMUNE VACCINE |
| PA0035/002/006 | TRYPTIZOL | PA0037/074/002 | PNU-IMUNE VACCINE |
| PA0035/012/001 | BENEMID | PA0040/026/006 | STEMETIL |
| PA0035/016/003 | DECADRON | PA0046/017/001 | BURINEX K |
| PA0035/016/004 | DECADRON SHOCK PAK | PA0050/128/002 | NAPROSYN |
| PA0035/024/001 | EDECRIN | PA0050/128/003 | NAPROSYN |
| PA0035/026/001 | HYDROSALURIC | PA0050/148/001 | LORON FOR INFUSION |
| PA0035/028/001 | MIDAMOR | PA0054/053/001 | MULTIBIONTA |

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## Human Product Authorisations Withdrawn (continud) (January - April 2003)

| PA Number | Product Name |
|---|---|
| PA0077/077/001 | RESONIUM A |
| PA0118/029/001 | EPPY MULTIDOSE |
| PA0148/010/001 | HMS LIQUIFILM |
| PA0271/002/003 | ISOKET |
| PA0271/002/004 | ISOKET |
| PA0271/002/006 | ISOKET |
| PA0271/002/011 | ISOKET 0.05% I.C. 10ML PREFILLED SYRINGE |
| PA0271/009/001 | VIRIDAL |
| PA0271/009/002 | VIRIDAL |
| PA0271/009/003 | VIRIDAL |
| PA0281/006/002 | FUROSEMIDE |
| PA0281/007/001 | DIAZEPAM |
| PA0281/007/003 | DIAZEPAM |
| PA0281/015/003 | IBUPROFEN |
| PA0281/036/003 | PINAMOX |
| PA0281/036/004 | PINAMOX |
| PA0281/045/001 | TRANTALOL ATENOLOL |
| PA0281/047/001 | AZOPINE |
| PA0281/054/003 | PINAMET CIMETIDINE |
| PA0365/055/001 | VIVOTIF |
| PA0437/011/008 | FLOUROURACIL ONCO-VIAL |
| PA0437/041/001 | ASTRIX |
| PA0469/005/001 | MINOXIDIL BIOGLAN |
| PA0488/007/003 | ISORDIL |
| PA0582/014/001 | MIOCHOL |
| PA0620/001/003 | HAVRIX JUNIOR |
| PA0620/001/004 | HAVRIX JUNIOR |
| PA0621/002/001 | STERINEB SODIUM CROMOGLYCATE |
| PA0678/041/001 | ENOS FRUIT SALTS |
| PA0678/046/001 | VALDA PASTILLES |
| PA0678/053/001 | BEECHAMS HOT LEMON DECONGESTANT |
| PA0678/057/001 | TUMS ASSORTED FLAVOUR |
| PA0678/060/001 | BEECHAMS COLD RELIEF |
| PA0711/022/003 | TAMOX |
| PA0769/001/001 | CHYMODIACTIN |
| PA0769/009/001 | DILAUDID |
| PA0810/002/001 | OESCLIM |
| PA0810/002/002 | OESCLIM |
| PA0810/002/003 | OESCLIM |
| PA0810/002/004 | OESCLIM |
| PA0810/002/005 | OESCLIM |
| PA0823/030/001 | ABIDEC |
| PA0936/030/001 | REHIDRAT |
| PA1009/009/001 | MENOGON |
| PA1047/002/001 | PLASMATEIN |

## Human New Product Authorisations (Mutual Recognition) (January - April 2003)

| PA Number | Product Name |
|---|---|
| PA0002/069/001 | PERFALGAN |
| PA0021/048/002 | AVELOX |
| PA0021/048/003 | AVELOX |
| PA0022/080/001 | ALESSE |
| PA0035/085/004 | SINGULAIR |
| PA0050/068/025 | ROFERON-A PRE-FILLED SYRINGE 18MIU/0.5ML |
| PA0050/153/001 | COPEGUS |
| PA0144/046/001 | OILATUM |
| PA0167/008/015 | SODIUM CHLORIDE 0.9% |
| PA0167/051/009 | POTASSIUM CHLORIDE 0.15% AND GLUCOSE 5% |
| PA0167/051/010 | POTASSIUM CHLORIDE 0.3% AND GLUCOSE 5% |
| PA0167/052/011 | POTASSIUM CHLORIDE 0.3% & SODIUM CHLORIDE 0.9% |
| PA0167/055/007 | COMPOUND SODIUM LACTATE INTRAVENOUS INFUSION B.P. |
| PA0167/063/005 | COMPOUND SODIUM LACTATE & GLUCOSE 5% |
| PA0167/108/001 | LIDOCAINE HYDROCHLORIDE |
| PA0167/109/009 | OLICLINOMEL N4-720E |
| PA0170/020/003 | ACTONEL ONCE A WEEK |
| PA0172/019/002 | SECLODIN |
| PA0185/041/001 | MENORING 50 |
| PA0281/113/001 | STATCOR |
| PA0281/113/002 | STATCOR |
| PA0281/113/003 | STATCOR |
| PA0282/080/001 | VASODUR |
| PA0282/080/002 | VASODUR |
| PA0282/080/003 | VASODUR |
| PA0282/081/001 | EMVASC |
| PA0282/081/002 | EMVASC |
| PA0437/050/001 | MITOXANTRONE (MITOZANTRONE) |
| PA0454/002/002 | APO-GO AMPOULES |
| PA0549/011/001 | DOLFLASH |

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## Human New Product Authorisations (Mutual Recognition) (continued) (January - April 2003)

| PA Number | Product Name | PA Number | Product Name |
|---|---|---|---|
| PA0577/046/001 | HISTACLAR | PA0969/004/001 | FLUCONAZOLE |
| PA0577/046/002 | HISTACLAR ALLERGY | PA0969/004/002 | FLUCONAZOLE |
| PA0677/017/001 | FLUCIS | PA0969/004/003 | FLUCONAZOLE |
| PA0678/071/010 | NIQUITIN CQ | PA0970/028/003 | SYMBICORT TURBOHALER 400/12 |
| PA0678/071/011 | NIQUITIN CQ | PA0970/057/001 | CRESTOR |
| PA0711/046/001 | DOMERID | PA0970/057/002 | CRESTOR |
| PA0711/046/002 | DOMERID, ROWEX | PA0970/057/003 | CRESTOR |
| PA0805/003/001 | ENTACT | PA0970/058/001 | ROSUVASTATIN ASTRAZENECA |
| PA0805/003/002 | ENTACT | PA0970/058/002 | ROSUVASTATIN ASTRAZENECA |
| PA0805/003/003 | ENTACT | PA0970/058/003 | ROSUVASTATIN ASTRAZENECA |
| PA0805/003/004 | ENTACT | PA1059/001/001 | UBISTESIN |
| PA0819/018/001 | CETIRIZINE | PA1059/001/002 | UBISTESIN FORTE |
| PA0819/021/001 | OMEPRAZOLE-RATIOPHARM | PA1072/001/001 | ANAPEN JUNIOR |
| PA0865/010/001 | HYPOLOC | PA1072/001/002 | ANAPEN |
| PA0891/004/001 | BUTENAFINE HYDROCHLORIDE 10 MG/G | | |

## Veterinary New Product Authorisations Issued (January - April 2003)

| VPA Number | Product Name | VPA Number | Product Name |
|---|---|---|---|
| 10007/029/003 | VETMEDIN | 10999/096/002 | NOROCARP 50 MG TABLETS |
| 10999/096/001 | NOROCARP 20 MG TABLETS | 10830/006/001 | INTERJECT |

## Veterinary Mutual Recognition Authorisations Issued (January - April 2003)

| VPA Number | Product Name | VPA Number | Product Name |
|---|---|---|---|
| 10021/045/001 | TOP DROP FOR SMALL CATS | 10021/046/004 | TOP DROP FOR EXTRA LARGE DOGS |
| 10021/045/002 | TOP DROP FOR LARGE CATS | 10820/001/001 | APIGUARD GEL (25% THYMOL) |
| 10021/046/001 | TOP DROP FOR SMALL DOGS | 10277/074/001 | NUFLOR SWINE INJECTABLE |
| 10021/046/002 | TOP DROP FOR MEDIUM DOGS | 10835/042/001 | CAPSTAR 11.4MG, TABLETS FOR CATS AND SMALL DOGS |
| 10021/046/003 | TOP DROP FOR LARGE DOGS | | |
| 10983/039/001 | PRILIUM 75 MG POWDER FOR ORAL SOLUTION | 10835/042/002 | CAPSTAR 57 MG, TABLETS FOR LARGE DOGS |
| 10983/039/003 | PRILIUM 300 MG POWDER FOR ORAL SOLUTION | 10983/039/002 | PRILIUM 150 MG POWDER FOR ORAL SOLUTION |

## Veterinary Product Authorisations Withdrawn (January - April 2003)

| VPA Number | Product Name | VPA Number | Product Name |
|---|---|---|---|
| 10019/065/001 | RIMADYL | 10981/008/001 | VITAMIN E + SELENIUM (FOR VET USE) |
| 10277/034/002 | STREPTOPEN INJECTION | | |
| 10960/042/001 | KEELOGANE WORM DRENCH | 10996/070/001 | DUPLOCILLIN LA |

## Veterinary Immunological Review Authorisations Issued (January - April 2003)

| VPA Number | Product Name | VPA Number | Product Name |
|---|---|---|---|
| 10277/062/001 | LEPTAVOID-H | 10019/070/001 | SPIROVAC |
| 10996/136/001 | NOBILIS IB MA 5 | 10996/146/001 | HEPTAVAC P PLUS |
| 10861/057/001 | POULVAC PAST M | 10996/149/001 | OVIVAC P PLUS |
| 10996/140/001 | COLISORB | 10996/133/001 | NOBILIS GUMBORO D78 LIVE |
| 10996/141/001 | PORCOVAC PLUS | 10996/150/001 | TETANUS ANTITOXIN BEHRING |

## Appendix 1 – Sample Batch Recall Letter

[COMPANY HEADED PAPER]

Batch Recall

Product Name, Pharmaceutical Form & PA Number

Batch Number(s) and Expiry Date(s)

Date of Mailing

Dear Pharmacist/Doctor/Wholesaler (use as appropriate)

We wish to advise you that batch no. _____ of product _____ , PA No. _____ is being recalled with immediate effect. [*If more than one batch is being recalled, a table showing the batch numbers may be appropriate here.*]

This action has been agreed with the Irish Medicines Board.

The reason for the recall is that _____

Please immediately quarantine any units of this batch which you have in your possession. [*Instruction is now provided to the reader on the return or on the direct uplift of quarantined stock**]

We apologise for any inconvenience this action may cause. Should you have any queries, please contact _____ at telephone number _____ .

Yours sincerely,

_____

NAME AND POSITION

* *Wholesalers are usually requested to return their quarantined units to their distributor. A Fax-Back form may be attached with the letter, so that wholesalers may notify their distributor by Fax of the number of units which are held in quarantine.*

*Pharmacists are usually requested to return their quarantined units to their wholesaler. However, there are cases where quarantined items must be uplifted directly by a wholesaler or distributor – this is generally where the batch defect is of a serious nature. The Inspectorate Department will provide guidance in this regard.*

*If the recall will result in an out-of-stock situation arising in the marketplace, this should be stated in the letter. The Inspectorate Department will provide guidance on details which may need to be provided in this regard.*

## Appendix 2 – Sample Product Recall Letter

[COMPANY HEADED PAPER]

Product Recall

Product Name, Pharmaceutical Form & PA Number

All Batches

Date of Mailing

Dear Pharmacist/Doctor/Wholesaler (use as appropriate)

We wish to advise you that all in-date batches of product _____ , PA No. _____ are being recalled with immediate effect.

This action has been agreed with the Irish Medicines Board.

The reason for the recall is that _____

Please immediately quarantine any units of this product which you have in your possession. [*Instruction is now provided to the reader on the return or on the direct uplift of quarantined stock**]

We are endeavouring to make replacement stock of this product available as soon as possible. It is expected that replacement stock will be available again in ___ weeks (or months). Until then, this product will be unavailable. [*See note below* **]

We apologise for any inconvenience this action may cause. Should you have any queries, please contact _____ at telephone number _____ .

Yours sincerely,

_____

NAME AND POSITION

* *Wholesalers are usually requested to return their quarantined units to their distributor. A Fax-Back form may be attached with the letter, so that wholesalers may notify their distributor by Fax of the number of units which are held in quarantine.*

** *Pharmacists are usually requested to return their quarantined units to their wholesaler. However, there are cases where quarantined items must be uplifted directly by a wholesaler or distributor – this is generally where the batch defect is of a serious nature. The Inspectorate Department will provide guidance in this regard.*

## Appendix 3 – Sample Caution-In-Use Letter

[COMPANY HEADED PAPER]

Caution-In-Use Notification

Product Name, Pharmaceutical Form & PA Number

Batch Number (if appropriate)

Date of Mailing

Dear Pharmacist/Doctor (use as appropriate)

Following discussions with the Irish Medicines Board, we wish to alert you of the following:

[*The cautionary message is now provided. If the issue relates to a quality defect, it would be appropriate here to describe the defect, to state what batches are affected, and to provide the cautionary advice or instructions as agreed with the Inspectorate Department of the IMB. If the issue relates to something other than a quality defect, the Inspectorate Department will provide guidance on how best to address the issue.*]

We are endeavouring to address this matter in the following way: [*Information would now be given in this regard. It may be appropriate to provide information on replacement stock here.*]

We apologise for any inconvenience this issue may cause. Should you have any queries, please contact _____ at telephone number _____ .

Yours sincerely,

_____

NAME AND POSITION

NOTE:

*Caution-In-Use letters are very much written and agreed on a case by case basis with IMB. They are usually required in order to communicate the presence of a quality defect on a batch or product, when a batch or product recall is either not warranted or not possible. The Inspectorate Department will provide detailed guidance on the information which may need to be provided in all Caution-In-Use communications.*

## Appendix 4 – Recruitment Advertisement

IRISH MEDICINES BOARD

EARLSFORT CENTRE, EARLSFORT TERRACE, DUBLIN 2.
TEL: +353 1 676 4971 FAX: +353 1 676 7836

The Irish Medicines Board is the regulatory agency for human and veterinary medicines in Ireland as well as Competent Authority for Medical Devices. Vacancies now exist for:

### GMP INSPECTOR

Reporting to the Director of Inspection, the appointee will be responsible at a National and European level for assessing the compliance of manufacturers and wholesalers of medicinal products with Good Manufacturing Practice (GMP) and Good Distribution Practice (GDP) respectively.

Candidates must hold a degree in pharmacy, microbiology, biochemistry, pharmaceutical chemistry, chemistry or other biological sciences and have a minimum of two years experience in relation to the manufacture, Quality Assurance and/or Quality Control of medicinal products. A thorough knowledge of computer validation and/or auditing would be an advantage. There is a requirement for travel within Ireland and, possibly, abroad and a full clean driving licence and use of a car is required.

### PHARMACEUTICAL ASSESSORS

Reporting to the Pharmaceutical Assessment Manager, assessors are required to carry out evaluation of pharmaceutical data submitted in support of applications for the granting, variation and renewal of marketing authorizations for human and veterinary medicinal products. Candidates must hold a degree in pharmacy or other relevant scientific discipline. They should also have relevant experience in Quality Assurance, regulatory affairs or pharmaceutical analysis in the pharmaceutical industry or in a regulatory authority.

### SENIOR PHARMACEUTICAL ASSESSOR – BIOLOGICAL PRODUCTS

(1 year job-share)

Reporting and duties as for Pharmaceutical Assessors outlined above. Candidates must hold a degree in pharmacy and have relevant biological /biotechnology experience in regulatory affairs.

*The Board is an equal opportunities employer.*
*Shortlisting of applicants will be undertaken.*

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Applications in writing with a current curriculum vitae should be submitted to the Human Resources Manager at the above address from whom details of posts may be obtained

**Closing date for receipt of applications is Friday 30th May 2003.**