IRISH MEDICINES BOARD

news MEDICINAL PRODUCTS LETTER

SEPTEMBER – DECEMBER 2005 Issue No. 22

IRISH MEDICINES BOARD, KEVIN O'MALLEY HOUSE, EARLSFORT CENTRE, EARLSFORT TERRACE, DUBLIN 2 TEL: 01 676 4971 FAX: 01 6767836 EMAIL: FOI@IMB.IE

GENERAL

HUMAN MEDICINES INFORMATION DAY 14 OCTOBER 2005

The Human Medicines Information Day was held on the 14th October 2005 in the Great Southern Hotel, Dublin Airport.

The topics discussed were:

- Implementation of the New Medicines Legislation;
- Implications of the Coordination Group (DCP/MRP);
- Global MA;
- Legal basis and data/market exclusivity;
- Renewals and sunset clause;
- Product information;
- Key changes affecting manufacturers and wholesalers;
- Pharmacovigilance aspects; and
- Extranet services.

To view the presentations visit the IMB's website **www.imb.ie**

VETERINARY MEDICINES INFORMATION DAY 9 MAY 2006

The IMB's Veterinary Information Day 2006 will take place in the Great Southern Hotel, Dublin Airport on 9th May 2006. Registration will commence at 9.00am and presentations will commence at 9.45am, lasting until 4.00pm approx. Tea/coffee and lunch will be provided.

Please visit **www.imb.ie** for more information and registration form.

WORKSHOP FOR WHOLESALERS WHO SUPPLY TO GROCERY RETAIL SECTOR

A workshop for wholesalers involved in the supply of medicinal products to the grocery trade was held at the Crowne Plaza Hotel, Dublin on Friday 25th November 2005. The event attracted a wide attendance involving representatives who supply medicinal products to the grocery trade, representatives from the wider distribution/wholesale sector and other stakeholder groups.

Talks and presentations by IMB inspectors and staff were given on the following themes:

- The standard Good Distribution Practice (GDP) inspection agenda
- GDP deficiencies
- The responsible person
- Batch traceability and product recalls
- Quality systems

These presentations provided an overview of the principles and requirements of GDP for medicinal products, and also requirements for compliance with the terms and conditions of the wholesale licence issued by the IMB.

The presentations were followed by an active discussion session on GDP-related issues including recalls, counterfeit products and temperature-mapping. The discussion involved a high level of participation from the audience, reflecting the level of interest in the presentations and discussion topics.

STAFF CHANGES

Aibhne O'hAimhirgin was appointed Pharmaceutical Assessors in the Human Medicines Department.

Julie Lynch was appointed Scientific Officer in the Human Medicines Department.

Deirdre O'Regan was appointed GCP Inspector and *Gerard Sheridan* was appointed GMP Inspector in the Compliance Department.

Tim O'Neil was appointed Enforcement Officer in the Compliance Department.

Immunological Assessor, *Dr Joanne Gallagher*, will leave the Veterinary Medicines Department in February 2006 to take up a lecturing position.

The IMB would like to thank her for her contribution to the department and wish her every success in her new career.

CONTENTS

General
Human Information Day 14 October 2005 1
Veterinary Information Day 9 May 2006 1
Workshop for Wholesalers who supply to Grocery Retail Sector 25 November 2006 1
Staff Changes 1

Human Medicines
Legislation and Guidelines 2
E-mail Submission of ICSRs and SUSARs 2
Update on Electronic Reporting 2
Changes to the Membership of the Advisory Committee for Human Medicines 2
Notification of Changes to IMB Human Fees 3

Veterinary Medicines
Legislation and Guidelines 3
Changes in Administrative Procedures for Applications for Product Authorisations 3
New Animal Remedies Regulations 3
Classification Enquiries update 3
Changes to the Methods of Supply of Veterinary Medicines 4
Immunological Veterinary Medicinal Products 4
Supply status of IVMPs 5
Update on the Assessment of Review IVMPs 5
Changes to the Membership of the Advisory Committee for Veterinary Medicines 5
Notification of Changes to IMB Veterinary Fees 6

Compliance
QP Discretion 5
The Rule Governing Medicinal Products in the European Union (GMP) 5
Use of NIR for Identity Testing of Each Container of Material for Parenteral Products 5
Audits of Active Substance Suppliers 7
Guidance on conditions for storage, including cold storage for medicinal products 7
Revised Compliance Department Contact Details for Quality Defect, Product Recalls and Emergency Situations 7
Important Preliminary findings from IMB's Braille Market Compliance Work on Human Medicinal Products 7
Notification of Changes to IMB Human Fees 8

Statistics 9-12

HUMAN MEDICINES

LEGISLATION AND GUIDELINES

The following EU guidelines have been adopted:

CPMP/EWP/205/95 *Revision 3* Guideline on the Evaluation of Anticancer Medicinal Products in Man (Adopted by CHMP December 2005)
CPMP/EWP/633/02 *Revision 1* Guideline on the Clinical Development of Medicinal Products for the Treatment of HIV Infection (Adopted by CHMP November 2005)
EMEA/337053/05 Overview of Comments received in Draft Guideline on the Clinical Development of Medicinal Products for the Treatment of HIV Infection
CPMP/EWP/021/97 *Revision 1* Guideline on Clinical Investigation of Medicinal Products for Hormone Replacement Therapy of Oestrogen Deficiency Symptoms in Postmenopausal Women (Adopted by CHMP October 2005)
CPMP/EWP/329339/05 Overview of Comments received on Draft Guideline on Clinical Investigation of Medicinal Products for Hormone Replacement Therapy of Oestrogen Deficiency Symptoms in Postmenopausal Women CPMP/EWP/021/97 rev 1
Topic Q8, Step 4 Note for Guidance on Pharmaceutical Development (EMEA/CHMP/167068/04 - final approval by CHMP November 2005)
Topic S8, Step 4 Note for Guidance on Immunotoxicity studies for Human Pharmaceuticals (EMEA/CHMP/167235/05 - adopted October 2005)
CPMP/SWP/799/95 Guideline on the Non-Clinical Documentation for Mixed Marketing Authorisation Applications (CPMP adopted 12 October 2005)

E-MAIL SUBMISSION OF ICSRS AND SUSARS

In accordance with legislative requirements, companies are required to submit ADR reports electronically. These submissions must be made in accordance with the procedure described in the IMB's 'Guide to the Electronic Submission of ICSRs and SUSARs Associated with Use of Human Medicines' which can be found under the headings 'Pharmacovigilance' and 'Electronic Reporting' on the IMB's website **www.imb.ie** (see also below).

Companies are advised that submission of suspected adverse reaction reports as attachments to regular e-mails does not meet the standards for electronic reporting and cannot be considered to meet the regulatory reporting requirements in this regard. Furthermore, such transmissions may involve transfer of confidential data via insecure networks.

Accordingly, companies are requested to submit one paper copy of each relevant report by either fax or post, until testing of electronic transmission of adverse reaction reports has been carried out to the satisfaction of both parties.

UPDATE ON ELECTRONIC REPORTING OF ADRS

In accordance with EU legislation, companies are reminded of their obligation to submit adverse reaction reports electronically.

The IMB has been in production with Eudravigilance since November 2005 and since then has provided all suspected serious adverse reactions associated with the use of medicinal products occurring in Ireland, to the EMEA via Eudravigilance.

The IMB has initiated testing with a number of companies reporting Individual Case Safety Reports. This test phase is due to be completed by the end of March 2006, at which time companies that have been testing are expected to move into full production.

Detailed information regarding requirements for electronic reporting of adverse reactions, originating from both clinical trial and post-marketing environments, is available in the 'Guide to the Electronic Submission of ICSRs and SUSARs Associated with Use of Human Medicines' which can be found in the Pharmacovigilance section of the website www.imb.ie, under 'Electronic Reporting'.

The guide provides additional information and clarification on many aspects of electronic reporting of ICSRs and SUSARs, including technical requirements and standards, use of the Eudravigilance Gateway and EVWeb interface, testing and production phases, as well as links to a number of useful documents and websites.

Companies are requested to continue to provide paper copies of reports during the initial stage of this process. The IMB will notify companies when ready to accept 'electronic only' versions of reports.

Any company who has not yet contacted the IMB with regard to commencement of testing, or their proposals to meet their regulatory electronic reporting requirements, should do so as soon as possible, by contacting **eudravigilanceimb-test @imb.ie** .

Further information on electronic reporting is available in Part III of Volume 9 of the Rules Governing Medical Products in the EU – Pharmacovigilance-Medicinal Products for Human and Veterinary Use. Volume 9 has been revised in the context of the legislation and has been recently released for consultation by the European Commission (**http://pharmacos.eudra.org/F2/eudralex/index.htm**).

CHANGES TO THE MEMBERSHIP OF THE ADVISORY COMMITTEE FOR HUMAN MEDICINES

The end of 2005 signals the completion of the mandate of the current members of the Advisory Committee for Human Medicines. The management and staff of the IMB would like to thank the outgoing members and acknowledge their expertise and the time that was given voluntarily to the organisation over the last five years. It is expected that the membership of the new committee will be known in the coming weeks.

NOTIFICATION OF CHANGES TO IMB HUMAN FEES

The IMB wishes to advise all holders of product authorisations, manufacturing licences and wholesale licences that following consultations with the Department of Health and Children and with industry representatives, Statutory Instrument Number 882 of 2005 was signed by Mary Harney, An Tanáiste and Minister for Health and Children, on 23rd December 2005.

This Statutory Instrument provides for a general fee increase of 4.5%, an increase to maintenance fees to reflect additional pharmacovigilance requirements under Directive 2004/27/EC and some fee categories, effective from 1 January 2006. The IMB has applied these new fees to all applications received on or after this date. Amended versions of the Human Medicines Fee application Form and the Guide to Fees for Human Medicines are available on the IMB website, **www.imb.ie**.

VETERINARY MEDICINES

LEGISLATION AND GUIDELINES

The following EU guidelines have been adopted:

CVMP/743/00 rev 2 Revised Guideline on Requirements and Controls applied to Bovine Serum used in the production of Immunological Veterinary Medicinal Products (CVMP adopted revision November 2005)
CVMP/IWP/214680/05 Overview of Comments Recived on Draft Revised Guideline on Requirements and Controls applied to Bovine Serum used in the production of Immunological Veterinary Medicinal Products
CVMP/VICH/810/04 corr VICH Topic GL39 Step 7 Guideline on Test Procedures and Acceptance Criteria for New Veterinary Drug Substances and New Medicinal Products: Chemical Substances (CVMP adopted November 05)
CVMP/VICH/811/04 corr VICH Topic GL40 Step 7 Guideline on Test Procedures and Acceptance Criteria for New Biotechnological/Biological Veterinary Medicinal Products (CVMP adopted November 05)

CHANGES IN ADMINISTRATIVE PROCEDURES FOR APPLICATIONS FOR PRODUCT AUTHORISATIONS

Consequent to the roll-out of the new IMB computer system (NIMBUS) to the Veterinary Medicines Department on 5th December 2005, applicants should note that there will be some changes in the administrative procedures for processing applications. These changes include the following:

- Each application, whether new, variation or otherwise, will henceforth be identified on correspondence and on the computer database by means of a case reference number (CRN). Typically, the CRN is a 7-digit number (e.g. 7000001). Previous IMB numbering systems, such as variation numbers, will no longer apply. Applicants should cite the CRN in correspondence or in queries on particular applications. By means of the new system, the IMB may link similar applications from a single source with a single CRN, although each approval will be issued separately.

- The Receipts and Validations Unit of the IMB will henceforth receive and validate all renewal and variation applications, as has been the case for new applications. Only when an application has been accepted by the unit as having been validated will it be entered into the work schedule of assessors. Note that correspondence on applications under assessment should be addressed to the relevant assessors directly (citing the CRN). Such correspondence will be opened on receipt by administrative staff in the Veterinary Medicines Department and the date of receipt will be logged in the IMB database before the document is passed to the assessor. All other important milestones in the progress of the application are also recorded in the database.

- It is expected, in rolling out the new system (which has been in existence in the Human Medicines Department for more than two years) to the Veterinary Medicines Department, that there may be some interruption in service with minor delays in the issuing of some authorisations. The IMB is committed to ensuring that any such delays are kept to a minimum and expects that service levels will improve within a short period.

The new computer system is expected to contribute to improvements in the efficiency of the Veterinary Medicines Department's business processes.

NEW ANIMAL REMEDIES REGULATIONS

The Animal Remedies Regulations, 2005 (S.I. No. 734 of 2005), which implements Directive 2001/82/EC as amended by Directive 2004/28/EC, were signed into law on 17th November 2005. The new legislation will result in several changes to EU and national procedures for the authorisation of veterinary medicines and for the determination of products as animal remedies, as outlined below.

Classification Enquiries Update

Under the 1996 Animal Remedies Regulations, the IMB was obliged to consult with the Department of Agriculture and Food (DAF) when making a decision as to whether a borderline product could be classified as 'out of scope' of the veterinary medicines licensing scheme as

defined in EU Directive 2001/82/EC.

The revised legislation has been amended in this regard. As stated in Regulation 4(4), if the IMB determines that a substance does not come within the terms of the Directive, the Minister (i.e. DAF) must be notified, but there is no requirement for the IMB to consult formally with DAF before reaching its decision. It has therefore been decided that assessors' opinions on classification enquiries may be put before the IMB's Advisory Committee for Veterinary Medicines (ACVM) before a final decision of the IMB is given. The ACVM meets every 2 to 3 months.

The 'Guide to the Definition of an Animal Remedy' is currently being rewritten, and will include updates relating to the new legislation. It will be published on the IMB website as soon as it is available. Meanwhile the principles for deciding what constitutes an animal remedy as written in the guide remain applicable.

Changes to the Methods of Supply of Veterinary Medicines

Another consequence of the new Animal Remedies Regulations, 2005 relates to the designation of the method of supply of certain animal remedies. The VSO category has been changed and replaced by VPO and VPO-1 categories. These categories are defined as follows:

VPO-1: as an item for administration only by a registered veterinary practitioner,

VPO: as an item for administration only by a registered veterinary practitioner, or under the direct supervision of a registered veterinary practitioner.

As per the normal procedure, the VPO-1/VPO designation should be stated on the product label and packaging while the designation and the explanation should be stated on the package leaflet. Companies affected by this are requested to amend the authorisations and packaging of their products by submitting applications for variation (fee code 597, Type II standard variation, national) as soon as possible and in any case within one year from the date of signing of the legislation. It is expected that the timelines given for this change should minimise the impact on the animal health industry.

Another consequence of the new legislation is that the IMB will henceforth determine the appropriate method of supply of veterinary immunologicals in accordance with the policy adopted in 2004 (see Newsletter issue no. 17). Further advice in relation to the implementation of this policy is given below under the heading 'immunological veterinary medicinal products'.

The IMB is mindful of the ongoing discussions between the Department of Agriculture and Food (DAF) and the EU Commission in relation to possible exemptions for certain veterinary medicines from the restriction of prescription control and the uncertainty surrounding the timetable for an outcome of this issue. The IMB notes the position of DAF that the EU has not yet adopted a decision on the exemption criteria but must do so before 1 January 2007 and that pending this decision, existing national prescription and distribution arrangements can remain in place. Accordingly, the IMB awaits developments from DAF as to future changes to the method of supply of veterinary medicines. As soon as these changes are known, IMB will inform applicants so that any labelling and packaging changes required can be implemented in a timely manner.

In relation to the supply of intramammary antibiotics, the IMB notes that the 1996 Regulations have already been amended to remove the exception for intramammaries from the general rules on antibiotics and also to decouple intramammaries from controls under poisons legislation. The net effect of this change is that intramammary antibiotics, in common with all other antibiotics, will be subject to prescription control and designated POM. Applicant companies are requested to submit applications to give effect to this change before September 2006 so that the packaging of all intramammaries will be compliant on or before 1st January 2007. Companies affected by this are requested to amend the authorisations and packaging of their products by submitting applications for variation (fee code 597, Type II standard variation, national) as soon as possible and in any case within one year from the date of signing of the legislation. It is expected that the timelines given for this change should minimise the impact on the animal health industry.

IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS

As a result of the transfer of competency for Immunological Veterinary Medicinal Products (IVMPs) from DAF to the IMB, Veterinary Product Authorisation (VPA) Holders should note the following:

- The IMB will issue the marketing authorisations for all new product, renewal, variation, transfer and review applications granted from the 17th November 2005.

- The voluntary pre-clearance procedure currently in operation remains the responsibility of DAF. The IMB strongly recommends that applicants use the pre-clearance procedure in advance of submission of a new product application to the IMB to determine if there will be restrictions imposed on the availability of the product under the Diseases of Animals Act 1966 (Control on Animal and Poultry Vaccines) Order 2002. DAF has informed the IMB that it will take approximately four weeks for a pre-clearance application to be processed. In the event that restrictions on the sale, supply or use of the product apply, the application can still be forwarded to the IMB for assessment and, if the product meets the requirements of Directive 2004/28/EC, obtain a VPA, albeit that the product may not be permitted for use.

- Submission of dossiers: with the exception of products which are currently authorised under a Therapeutic Substance Act (TSA) licence, it is no longer necessary to copy DAF on applications for new products, renewals, variations or transfers. Such information need only be submitted to the IMB.

- Products licensed under the TSA: DAF maintains responsibility for all IVMPs currently licensed under the TSA until such

products are either issued with a VPA by the IMB, rejected by DAF or withdrawn by the applicant. Variation applications for TSA licensed products must be copied to DAF for information purposes. The application should be submitted to the IMB for assessment. Upon completion of the assessment of the variation the IMB will, as in the past, forward a recommendation to DAF for their consideration.

SUPPLY STATUS OF IVMPS

In March 2004, the IMB adopted a policy on the allocation of IVMPs to a supply category entitled 'Criteria for the Allocation of an immunological to a supply category'. This policy is based on the assignment of an IVMP to a supply category after a scientific risk:benefit analysis of the product has been conducted. It was developed in close collaboration with the DAF and in the belief that the POM(E) supply route would be removed from the Animal Remedies Regulations following its revision. However, the POM(E) supply route was not removed from the Animal Remedies Regulations 2005 (S.I. No. 734 of 2005).

All IVMPs licensed since April 2004 have been licensed in accordance with this policy. However, all immunologicals, including those licensed prior to April 2004, should be authorised in accordance with this IMB policy.

It should be noted that the DAF is currently engaged in discussion with the EU Commission on the controls needed for veterinary medicinal products intended for use in food-producing animals. These discussions may result in amendments being required to the supply routes of certain IVMPs.

Considering the current changing environment and the potential effect of change of labelling on the industry and on the availability of IVMPs, the IMB has therefore decided that a certain flexibility is currently required in the implementation of the IMB supply policy for IVMPs licensed prior to April 2004 and has made the following decisions:

- For new product applications and review product applications currently under assessment: to continue with the implementation of the IMB policy.
- For products licensed before April 2004: implementation of the IMB policy will await conclusion of the DAF/EU Commission discussions.
- By the end of December 2006 the supply routes of all IVMPs must be in line with EU and national requirements. Amendments to product authorisations, if required, must be conducted by way of variation to give effect to whatever changes are established in national legislation at that time.
- For products which have already changed the POM(E) supply category on the recommendation of the IMB: the IMB will accept applications from VPA holders to consider reinstatement of the POM(E) category. In considering any request to move products from POM to POM(E), the IMB will take note of any adverse drug reactions which may affect the risk: benefit balance. The IMB estimates that this will apply to approximately five products.
- The IMB will keep a watching brief on developments from the Commission regarding exemptions from the prescription requirement and update/implement IMB supply policy as soon as practically possible.

It is envisaged that the net result of this approach will be that the supply status of all authorisations will be compliant with IMB policy by 1st January 2007.

The IMB will require all authorisations issued in 2006, where the supply status is not in accordance with IMB policy, to have the following condition added to Section 8 of the Product Specific Details.

8. Special Conditions
Re: Route of Supply:
The authorisation must comply with the appropriate method of supply in accordance with national legislation by the 1st of January 2007.

Information should be sought from the DAF regarding the length of time that product released prior to January 2007 can remain on the Irish market with product literature bearing a supply status not in line with its authorisation.

A copy of the IMB policy document 'Criteria for the Allocation of an Immunological to a supply category' can be found on the IMB website. If further information on the allocation of supply routes to IVMPs is required please contact Dr. Una Moore, Senior Immunological Assessor in the Veterinary Medicines Department.

UPDATE ON THE ASSESSMENT OF REVIEW IVMPS (DEC 2005)

Approximately 160 applications were received, of which 152 were considered valid. Of these, 93 applications have been issued with a VPA, 9 applications were refused, 24 applications were withdrawn and 26 are under assessment. All review applications for ruminant and porcine species are completed. Of the poultry IVMPs, 24 of the 30 applications received are complete as are 28 of the 29 companion animal applications and 5 of the 19 equine applications. All of the piscine applications are under assessment (5 in total). It is anticipated that by the end of 2007 all review IVMPs applications will have been assessed.

CHANGES TO THE MEMBERSHIP OF THE ADVISORY COMMITTEE FOR VETERINARY MEDICINES

The end of 2005 signals the completion of the mandate of the current members of the Advisory Committee for Veterinary Medicines. The management and staff of the IMB wish to thank the out-going members and acknowledge their expertise and effort given voluntarily to the organisation over the last five years. It is expected that the membership of the new committee will be known in the coming weeks.

NOTIFICATION OF CHANGES TO IMB VETERINARY FEES

The IMB wishes to advise all holders of veterinary product authorisations and veterinary manufacturing licences that following consultations with the Department of Agriculture & Food, Department of Finance and with industry representatives, approval was granted for a change in the veterinary fees. This approval, which dates from 1st January 2006, has been implemented with effect from 1st February 2006.

This change provides for a general fee increase of 4.5%, an increase to maintenance fees to reflect additional pharmacovigilance requirements under Directive 2004/28/EC and some new fees, effective from 1st February 2006. The IMB has applied these new fees to all applications received on or after this date. Amended versions of the Veterinary Medicines Fee Application Form and the Guide to Fees for Veterinary Medicines are available on the IMB website, **www.imb.ie**.

COMPLIANCE

QP DISCRETION

Following the last meeting of the Heads of Medicines Agencies (HMA) in November 2005, a decision was taken to convene a group of representatives from both the Inspectors Working Party (IWP) and the Joint CHMP/CVMP Quality Working Party (QWP) to develop a common EU approach to the handling of minor deviations from the Marketing Authorisation in the context of batch certification by a Qualified Person. The working group, chaired by Mr. Pat O'Mahony (IMB) and Ms. Emer Cooke (EMEA), met on 11th January 2006 and a 'solution document' was subsequently agreed. This proposed solution document has been put forward to the IWP and QWP for further comment. This paper is tabled for adoption at the next HMA meeting at the end of February and if adopted will be published thereafter.

THE RULES GOVERNING MEDICINAL PRODUCTS IN THE EUROPEAN UNION (GOOD MANUFACTURING PRACTICES): PART I REVISIONS

Chapter 1 on Quality Management has been revised to include new requirements on Product Quality Review. These come into force in 1st January 2006.

Chapter 6 on Quality Control includes new provisions for an On-going Stability Programme and an update for reference samples, and these changes will come into operation on 1st June 2006. (In the last issue of the IMB Newsletter, it was stated that the new requirements for Chapter 6 would come into effect on 1st January 2006. The actual date for implementation is 1st June 2006).

Chapter 8 on Complaints and Product Recall was revised to raise awareness of the possibility that a reported quality defect may be the result of counterfeiting activity, and to clarify that the discovery of a counterfeit medicinal product should be reported to the competent authority. This revised version of Chapter 8 comes into operation on 1st February 2006.

A New Annex 19 to the GMP Guide provides guidance on the taking and holding of reference samples of starting materials, packaging materials and finished products, as well as for retention samples of finished products. The Annex provides definitions for the terms 'reference sample' and 'retention sample', which hitherto were often incorrectly considered as synonyms. Updated guidance is also given on the size of reference samples. Annex 19 will come into operation on 1st June 2006.

USE OF NEAR INFRARED FOR IDENTITY TESTING OF EACH CONTAINER OF MATERIAL FOR PARENTERAL PRODUCTS

A number of companies have requested guidance for situations where the registered specifications of starting materials include conventional or pharmacopoeial methods for the confirmation of identity, but where the companies wish to use Near Infrared (NIR) spectroscopy to perform identity testing on each container of starting materials used in the manufacture of parenteral products. Specifically, companies wish to know if the use of this alternative analytical methodology is acceptable.

The current position is that Annex 8 of the GMP Guide states that the identity of a complete batch of starting materials can normally only be ensured if individual samples are taken from all the containers, and an identity test performed on each sample. It is permissible to sample only a proportion of the containers where a validated procedure has been established to ensure that no single container of starting material has been incorrectly labelled. However, the Annex goes on to say that it is improbable that a procedure could be satisfactorily validated for starting materials for use in parenteral products.

Unless variations are submitted for all affected products, the regis-

tered method for confirming identity should be performed. However, there is no restriction on the performance of additional testing, and the use of NIR to provide container-wise confirmation of identity can provide useful information. Under the circumstances, the requirements of the marketing authorisation will be deemed to have been met by carrying out the registered method for confirmation of identity on a statistically representative composite sample, when this is supplemented with NIR analysis of every container.

The NIR method should be validated in line with the recommendations of the Note for Guidance on the Use of Near Infrared Spectroscopy by the Pharmaceutical Industry and the Data Requirements for New Submissions and Variations (CPMP/QWP/3309/01/EMEA/CVMP/961/01).

AUDITS OF ACTIVE SUBSTANCE SUPPLIERS

The EMEA and the GMP inspectorates of the national competent authorities are often asked questions about audits of active substance suppliers, as these are seen as the expected means whereby manufacturing authorisation holders should ensure that they only use active substances that have been manufactured in accordance with GMP. The EMEA has prepared a list of frequently asked questions and answers which is available at http://www.emea.eu.int/Inspections/GMPfaqAS.html. With further experience these may be added to in the future.

GUIDANCE ON CONDITIONS FOR STORAGE, INCLUDING COLD STORAGE FOR MEDICINAL PRODUCTS

Following the recent period of consultation, which ended on 27th January, 2006, the IMB Guidance Note for Manufacturers (Human and Veterinary), Wholesalers and Transporters of Human Medicinal Products in Ireland in relation to Conditions for Cold Storage and the Maintenance of the Cold Chain will be finalised and published on our

website by 28th February, 2006.

The guidance note also describes the conditions for both room (ambient) temperature storage and controlled room temperature storage.

REVISED COMPLIANCE DEPARTMENT CONTACT DETAILS FOR QUALITY DEFECTS, PRODUCT RECALLS AND EMERGENCY SITUATIONS

In light of the 2005 restructuring of the Inspectorate Department, which is now known as the Compliance Department, some minor changes have been made to the IMB's emergency contact details. See the table below. These contact details may be used for reporting and discussing with us quality defect issues, potential product recalls, and other emergency issues.

The new contact details are as follows:

All Licensed Wholesalers, and Licensed and Authorised Manufacturers are required to:

- Update their recall procedure and other related documentation to reflect the above details, and
- Send a paper copy of the updated recall procedure, together with company contact details, (including out-of-hours contact details) to the IMB within one month of the publication date of this newsletter, addressed to Ms. Fiona Doyle, Adminstrator, Compliance Department, Irish Medicines Board, Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2.

IMPORTANT PRELIMINARY FINDINGS FROM IMB'S BRAILLE MARKET COMPLIANCE WORK ON HUMAN MEDICINAL PRODUCTS

As outlined in the IMB Newsletter No. 21, in order to ensure improved access to information on their medicines for people with visual impairment, Article 56a of Directive 2001/83/EC, as amended by Directive 2004/27/EC, has been introduced.

Article 56a requires that the name of the medicinal product must be expressed in Braille format on the packaging, allowing for improved differentiation of medicines. It also requires that the marketing authorisation holder ensures that the package information leaflet is made available, on request, in formats which are suitable for people with visual impairment. The 'leaflet' provided should not be abridged in any way.

Name	*Position*	*Office contact details*	*Out-of-hours Contact Details*
Mr. John Lynch	*Director of Compliance*	*Tel: 01-676 4971 Fax: 01-676 4061 john.lynch@imb.ie*	*087-2347294*
*Mr. Kevin O'Donnell**	*Market Compliance Manager*	*Tel: 01-676 4971 Fax: 01-676 4061 kevin.odonnell@imb.ie*	*087-9562818*

** Primary Contact Person*

The Market Compliance Section of the IMB Compliance Department will check the compliance of labelling and arrangements in place at companies with the provisions of article 56a. As part of this work, the Market Compliance Section will obtain samples of relevant medicinal products from the marketplace for inspection, and will also perform on-site inspections, as necessary, in order to monitor compliance with the provisions of article 56a and with the Braille declaration provided by the MAH.

There are currently a number of medicinal products on the Irish marketplace which contain Braille on their outer packaging. (These products have been on the market for some time.) Several of these products have now been sampled and examined by the Market Compliance Section, for compliance with the requirements of article 56a. The following serious findings were observed:

- In some cases, the Braille text for the product strength did not differentiate between numbers and letters, and as a result, the Braille text was not readily readable to a Braille user. This is important because, in Braille, letters and numbers use the same Braille cells, but they are differentiated by the use of special indicator Braille cells, which show whether the next Braille cell is for a letter or for a number. For example, the Braille for '1g per 100ml' should indicate that the 'g' (for gram) is a letter and not a number. If it does not, the Braille reads '17' instead of '1g'. Likewise, the Braille for the above strength should indicate that the '1' (in 100) is a number and not a letter.

- In some cases, a decimal point in a product strength was incorrectly shown in Braille as a full stop. (In Braille, the cells for decimal points and full stops are different, and using these incorrectly can affect how numbers are interpreted.)

- In some cases, the Braille text for multi-strength products did not clearly state the strength of each product, as the units of measurement for the strength were missing.

- In some cases, the Braille dots on outer cartons were observed to be quite flat, and not easily read by the Braille user. This made the Braille difficult to read, and it also raised a concern that, over time, the height of the Braille dots might reduce further, and that the dots would become more flattened, making readability of the Braille even more difficult.

- Finally, in some cases, the Braille text was positioned very close to the edges of the sides of the outer packs. Braille text should, if possible, not be too close to the edges of the sides of outer cartons, because if the pack gets damaged or torn, the Braille can easily be impacted.

Marketing Authorisation Holders and manufacturers are requested to take the above findings into consideration when sourcing, designing and approving outer cartons and product labels which carry Braille text.

Details and guidance on the Braille requirements are available in IMB Newsletter No. 21, and in the European Commission guidance document titled 'Guidance concerning the Braille requirements for labelling and the package leaflet (Article 56a of Directive 2001/83/EC as amended)', available at

http://pharmacos.eudra.org/F2/pharmacos/docs/Doc2005/04_05/Braille_text20050411.pdf

NOTIFICATION OF CHANGES TO IMB HUMAN FEES

The IMB wishes to advise all holders of product authorisations, manufacturing licences and wholesale licences that following consultations with the Department of Health and Children and with industry representatives, Statutory Instrument Number 882 of 2005 was signed by Mary Harney, An Tanaiste and Minister for Health and Children, on 23rd December 2005.

This Statutory Instrument provides for a general fee increase of 4.5%, an increase to maintenance fees to reflect additional pharmacovigilance requirements under Directive 2004/27/EC and some new fees, effective from 1 January 2006. The IMB has applied these new fees to all applications received on or after this date. Amended versions of the Human Medicines Fee application Form and the Guide to Fees for Human Medicines are available on the IMB website, **www.imb.ie**.

Human New Product Authorisations Issued (October–December 2005)

PA Number	Product Name
PA0002/077/001	PRAVASTATIN SODIUM
PA0002/077/002	PRAVASTATIN SODIUM
PA0002/077/003	PRAVASTATIN SODIUM
PA0004/065/001	BOOTS BITE AND STING RELIEF ANTIHISTAMINE
PA0068/010/002	VASTAREL prolonged-release
PA0068/016/001	TRIMETAZIDINE Prolonged-Release
PA0074/051/001	ROMEP
PA0074/054/003	ONDANSETRON
PA0074/054/004	ONDANSETRON
PA0074/055/001	Ramipril
PA0074/055/002	RAMIPRIL
PA0074/055/003	RAMIPRIL
PA0074/055/004	RAMIPRIL
PA0074/058/001	Lamotrigine
PA0074/058/002	Lamotrigine
PA0074/058/003	Lamotrigine
PA0074/058/004	Lamotrigine
PA0172/037/001	ParaPlus
PA0290/077/001	Tobravisc
PA0361/018/001	HYDROMORPHONE HYDROCHLORIDE
PA0361/018/002	HYDROMORPHONE HYDROCHLORIDE
PA0926/001/001	fexofenadine
PA0926/001/002	fexofenadine
PA0966/012/001	QUINAPRO
PA0966/012/002	QUINAPRO
PA0966/012/003	QUINAPRO
PA0966/012/004	QUINAPRO
PA1017/003/001	DOXANE
PA1017/003/002	DOXANE
PA1017/003/003	DOXANE
PA1044/005/001	FLUCOMEL
PA1044/005/002	FLUCOMEL
PA1044/005/003	FLUCOMEL
PA1063/002/001	BIOFLOXCIN
PA1063/002/002	BIOFLOXCIN
PA1063/002/003	BIOFLOXCIN
PA1063/018/001	Lanafine
PA1063/018/002	Lanafine AFR
PA1064/001/001	PAMIDRONATE DISODIUM
PA1064/001/002	PAMIDRONATE DISODIUM
PA1124/001/001	Doxel
PA1125/001/001	FLUDEOXYGLUCOSE 18 F
PA1140/005/001	Doxapram
PA1140/005/002	Doxapram
PA1144/002/001	CONDROSULF
PA1148/001/001	GABAPENTIN
PA1148/001/002	GABAPENTIN
PA1148/001/003	GABAPENTIN
PA1164/001/001	Preventex
PA1267/001/001	Ketamine
PA1267/001/002	Ketamine multidose
PA1267/001/003	Ketamine
PA1267/001/004	Ketamine multidose
PA1284/001/001	Omeprazole
PA1284/001/002	Omeprazole
PA1284/001/003	Omeprazole
PPA0465/012/007	Adalat LA
PPA0465/116/003	Atacand
PPA0465/131/001A	RELIFEX
PPA0465/151/001	Lamisil
PPA0465/153/001	Seroquel
PPA0465/153/002	Seroquel
PPA0465/153/003	Seroquel
PPA0465/155/001	Arret
PPA0465/156/001	Calcichew
PPA0465/157/001	Panadol Extra
PPA0465/158/001	Panadol
PPA0465/159/001	Movicol
PPA0465/165/001	Actonel Once Weekly
PPA0465/167/001	Flixonase Aqueous
PPA0465/169/001	Xyzal
PPA0465/171/001	Omnexel

Human New Product Authorisations Withdrawn (October–December 2005)

PA Number	Product Name
PA0013/004/005	MELLERIL
PA0013/004/001	Melleril
PA0013/004/002	Melleril
PA0013/004/003	Melleril
PA0013/004/004	Melleril
PA0047/028/001	Doloxene
PA0013/064/001	APRESOLINE
PA1189/001/003	ZYDOL
PA1189/001/005	ZYDOL SOLUBLE
PA0913/009/001	CODAFEN CONTINUS
PA0185/032/001	Tricloryl
PA1077/028/001	Infanrix-Hib
PA1077/030/001	Infanrix Single-dose vial
PA1077/020/002	Boostrix

continued on next page ▶

Human New Product Authorisations Withdrawn (cont.) (October–December 2005)

PA Number	Product Name
PA1077/101/002	Boostrix Polio (glass vials)
PA0126/022/001	Meldopa
PA0126/022/002	Meldopa
PA0126/101/001	Vertamel
PA0126/101/002	Vertamel
PA0126/106/001	Morstel SR
PA0126/106/002	Morstel SR
PA0126/106/003	Morstel SR
PA0126/106/004	Morstel SR
PA0126/044/003	Napmel EC
PA0126/044/005	Napmel EC
PA0516/007/001	Verelan
PA0516/007/002	Verelan
PA0516/007/003	Verelan
PA0913/008/002	DHC Continus
PA0913/008/003	DHC Continus
PA0903/001/001	Brulidine
PA0903/002/001	Avomine
PA0903/003/001	Ceplac
PA0970/044/001	LOSEC
PA0970/044/002	Losec
PA0970/044/003	LOSEC
PA0936/043/001	Pharmorubicin 10
PA0936/043/002	Pharmorubicin 50
PA0936/043/005	PHARMORUBICIN
PA0007/043/004	ACTILYSE
PA0179/008/004	OSMOFUNDIN
PA0805/001/002	Serdolect
PA0805/001/006	Serdolect
PA0040/070/001	Oruvail-100 SR
PA0748/023/003	STUGERON FORTE
PA0046/024/006A	One-Alpha
PA0002/065/001	Cefzil
PA0002/065/002	Cefzil
PA0002/065/003	Cefzil
PA0002/065/004	Cefzil
PA0038/018/001	Ethrane
PA0062/038/001	Conotrane
PA0002/031/007	Modecate
PA0012/065/001	Triodene
PA0050/139/002	Biovital
PA0046/035/002	MINIHEP SODIUM
PA0218/029/001	MIXTARD 30 INSULIN
PA0218/033/004	MIXTARD 10 PENFILL 3ML
PA0218/036/004	MIXTARD 50 PENFILL 3ML
PA0298/004/001	Tetracycline
PA0086/008/005	Robinul
PA1077/033/003	Amoxil
PA1077/015/006	ZINNAT
PA0936/021/001	CO-BETALOC
PA0436/007/001	Salomol Inhaler
PA0282/042/001	Naproxen
PA0282/042/002	Naproxen
PA0484/013/001	CUREA
PA0484/026/001	Tar Pomade
PA0040/021/004	Neulactil
PA0054/009/002	Optimax without Vitamins
PA0022/037/001	Loramet
PA0038/079/001	Arythmol
PA0736/001/001	HEMOHES 6%
PA0736/001/002	HEMOHES 10%
PA0148/034/001	PREFERIN - A TOPICAL OPHTHALMIC
PA0947/001/001	TICINAN SUSTAINED RELEASE
PA0947/001/002	TICINAN SUSTAINED RELEASE
PA0947/001/003	TICINAN SUSTAINED RELEASE
PA0947/001/004	TICINAN SUSTAINED RELEASE
PA0947/001/005	TICINAN SUSTAINED RELEASE
PA0126/090/001	Amoxycillin
PA0126/090/002	Amoxycillin
PA0126/029/001	Cidomel
PA0126/097/002	Xanomel
PA0126/025/003	MELZINE
PA0126/124/001	PAROCETAN
PA0437/026/001	Doxorubicin Hydrochloride for Injection
PA0913/003/001	Phyllocontin Paediatric Continus
PA0043/038/001	Crookes Spot Treatment Cream Regular - Colourless
PA0043/038/002	Crookes Spot Treatment Cream Regular - Cover Up
PA0476/004/001	Cimetidine
PA0476/004/002	Cimetidine
PA0007/047/001	BONEFOS
PA0007/047/002	BONEFOS
PA0282/057/001	Tamoxifen
PA0282/057/002	Tamoxifen
PA0282/057/003	Tamoxifen

Human New Product Authorisations (Mutual Recognition) (October–December 2005)

PA Number	Product Name
PA0013/118/001	Co-Tareg
PA0013/118/002	Co-Tareg
PA0013/118/003	Co-Tareg
PA0043/027/002	Curatoderm
PA0126/124/001	PAROCETAN
PA0126/150/001	Azithromycin
PA0148/064/001	Combigan
PA0237/061/001	Simvastatin
PA0281/126/001	Ondansetron
PA0281/127/001	Ondran
PA0281/127/002	Ondran
PA0282/090/001	Nasofan Aqueous
PA0290/076/001	Miostat
PA0329/010/001	Nicopass Liquorice Mint
PA0329/010/002	Nicopass Fresh Mint
PA0410/005/001	Duodopa
PA0436/041/001	Lanziop
PA0436/041/002	Lanziop
PA0436/043/001	Simvastatin
PA0436/043/002	Simvastatin
PA0436/043/003	Simvastatin
PA0568/002/004	Coversyl
PA0568/002/005	Coversyl
PA0568/002/006	Coversyl
PA0577/072/001	Citalopram
PA0585/022/001	Omsil
PA0590/022/001	Clobetasol propionate Galderma
PA0688/005/001	Meloxicam Chanelle Medical
PA0688/005/002	Meloxicam Chanelle Medical
PA0711/076/001	Ketozol
PA0711/076/002	Ketozol Dandruff
PA0711/078/001	Amlode
PA0711/078/003	Amlode

PA Number	Product Name
PA0711/079/001	Tamsu
PA0736/021/001	Lipidem
PA0736/021/002	Lipidem
PA0749/010/001	Carvedilol
PA0749/010/002	Carvedilol
PA0749/010/003	Carvedilol
PA0749/010/004	Carvedilol
PA0749/014/001	Meloxicam
PA0749/014/002	Meloxicam
PA0891/003/002	Xyzal
PA0931/006/001	Potassium Chloride & Glucose IV Infusion
PA0931/006/002	Potassium Chloride & Glucose IV Infusion
PA0931/007/001	Potassium Chloride & Sodium Chloride IV Infusion
PA0931/007/002	Potassium Chloride & Sodium Chloride IV Infusion
PA0931/008/001	Potassium Chloride,Sodium Chloride & Glucose IV I
PA0931/008/002	Potassium Chloride, Sodium Chloride & Glucose IV I
PA0966/013/001	Ergha Mirtazapine
PA1058/006/002	Novolizer Budesonide
PA1063/020/001	Mobiglan
PA1063/020/002	Mobiglan
PA1077/111/001	Malarone
PA1130/003/001	Salbutamol
PA1130/003/002	Salbutamol
PA1130/004/001	Budeso-neb
PA1130/004/002	Budeso-neb
PA1242/001/001	Glucosamine Pharma Nord

Veterinary New Product Authorisations Issued (October–December 2005)

VPA Number	Product Name
10021/014/004	DRONTAL PLUS FLAVOUR TABLETS
10277/076/001	INSUVET NEUTRAL
10277/077/001	INSUVET PROTAMINE ZINC
10277/078/001	INSUVET LENTE

VPA Number	Product Name
10545/031/001	OXFENDEX ORAL SUSPENSION 2.265 %W/V
10802/001/002	AUROFAC SUIS 100 GRANULAR
10999/107/001	MACROMECTIN POUR-ON

Veterinary New Authorisation Issued (Mutual Recognition) (October–December 2005)

VPA Number	Product Name	VPA Number	Product Name
10861/089/001	CYDECTIN LA FOR CATTLE	10996/138/004	VASOTOP 0.625MG TABLET
10966/030/001	CLAVASEPTIN 50 MG PALATABLE TABLETS	10996/138/005	VASOTOP 10MG TABLET
10966/030/002	CLAVASEPTIN 250 MG PALATABLE TABLETS	10996/186/001	CEPHAGUARD DC 150MG INTRAMAMMARY OINTMENT
10966/030/003	CLAVASEPTIN 500 MG PALATABLE TABLETS		

Veterinary Product Authorisations Withdrawn (October–December 2005)

VPA Number	Product Name	VPA Number	Product Name
10007/031/001	VORDEXOL	10882/001/001	IODYPRO
10016/047/001	HYLARTIL VET	10889/001/001	WORM BAN
10095/006/001	VETSUL	10912/001/001	SEARGENTS FLEA COLLAR FOR CATS
10277/004/001	FINADYNE PASTE	10912/002/001	SEARGENTS FLEA COLLAR FOR DOGS
10277/011/004	NUFLOR	10912/002/002	SEARGENTS FLEA COLLAR FOR LARGE DOGS
10277/057/001	SAFFAN	10965/013/001	HARTZ RID FLEA SPRAY FOR CATS
10835/010/001	LIGNAVET PLUS	10966/026/001	TETRASEPTIN
10835/037/001	LARGE ANIMAL IMMOBILON	10966/026/002	TETRASEPTIN
10835/038/001	LARGE ANIMAL REVIVON	10988/050/001	CLOXADRY
10849/001/001	JECTAMEC INJECTABLE SOLUTION	10989/021/001	XYLAZINE
10857/012/001	SAGATAL INJECTION	10996/035/001	OXYTOCIN-S 10IU/ML SOLN FOR INJ
10857/053/001	CEFOVET L	10999/034/002	LIFE-AID P
10869/001/001	FLUNIXIN MEGLUMINE		

Veterinary Immunological New Authorisations Issued (National) (October–December 2005)

VPA Number	Product Name	VPA Number	Product Name
10846/005/001	HIPRABOVIS PNEUMOS		

Veterinary Immunological New Authorisations Issued (Mutual Recognition) (October–December 2005)

VPA Number	Product Name	VPA Number	Product Name
10857/065/001	GALLIMUNE 302 ND+IB+EDS		
10857/066/001	GALLIMUNE 303 ND+IB+ART	10857/069/001	DILUMAREX
10857/067/001	GALLIMUNE 407 ND+IB+EDS+ART	10861/088/001	DURAMUNE PUPPY DP+C

Veterinary Immunological Review Authorisations Issued (October–December 2005)

VPA Number	Product Name	VPA Number	Product Name
10277/084/001	INTRAC		
10857/036/001	EURICAN DHPPI	10996/153/002	PREVAC PRO
10996/094/001	NOBILIS IB+ND+EDS	10996/154/001	PREVAC T PRO
10996/153/001	PREVAC PRO	10996/154/002	PREVAC T PRO