IRISH MEDICINES BOARD
Bord Leigheasra na hÉireann

IMB NEWSLETTER

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GENERAL:

New Board Members of the Irish Medicines Board

On 2nd March 2001, the Minister for Health and Children, Mr. Michéal Martin appointed the new Irish Medicines Board members who are as follows:

Mr Pat O'Mahony (Chairman)
Mr Denis Cronin
Ms Breda Dooley
Dr Rory Lehane
Ms Aideen Murphy
Mr Aidan Murray
Ms Anne Nolan
Mr PJ O'Connor
Prof Kevin O'Malley

The Board has been appointed for a period ending 31st December 2005.

Implementation of Variations following their approval

All authorisation and manufacturing licence holders are reminded that the various national Regulations and the General Conditions of Authorisation require that a product complies with the terms of its authorisation at all times. Consequently, once a variation has been approved all lots of the product placed on the market should comply with the terms of the revised authorisation from the date of the approval. For changes in manufacturing processes or specifications, these will normally mean the next production batch released by the Qualified Person.

The IMB recognises that in certain instances there may be a finite timescale for making the transition for a variety of reasons. The IMB emphasises that it is essential that the authorisation holder explicitly identifies within the variation application

(a) when the variation will be implemented post approval and

(b) the rationale for any likely delay.

It is also recognised that implemented changes will take a finite period to reach the market place, but this period should not normally exceed 3-6 months. In certain cases when urgent safety and quality changes need to be made to labelling, a much earlier implementation time will usually be required. The IMB, in conjunction with industry associations, is in the process of developing a policy for urgent implementation of such changes, depending upon the category of associated risk.

Staff Changes at the IMB

Three new members of staff took up duty:

- Dr. Tracy Keane and Dr. Patrick Costello as additional Immunological Assessors in the Veterinary area,
- Dr. Lorraine Nolan as Project Manager – Controlled Drugs to oversee the transfer of that function from the Department of Health and Children to the IMB over the next twelve months,
- Ms Trina O'Neill as Assistant Accountant,
- Ms Kathleen O'Neill, Senior Pharmaceutical Assessor has rejoined the staff following a career break.

Human Medicines Information Day

The annual IMB meeting on Human Medicines was held in the Great Southern Hotel at Dublin Airport on 9th February 2001 and was attended by approximately 200 delegates.

The morning session was devoted entirely to clinical trials and was chaired by Dr. Pat Sullivan, Chairman of the IMB Sub-Committee on Clinical Trials. Representatives from the IMB Medical and Pharmaceutical Departments, ethics committees (Dr. Sean O'Briain, Chairman of Ethics Committee, St. James's Hospital and Secretary of the Association of Ethics Committees of Ireland), chief investigators (Prof. Brian Sheppard, Head of Department of Obstetrics & Gynaecology, Trinity Centre for Health Science), the pharmaceutical industry, (Ms. Leonie Clarke, Scientific and Regulatory Affairs Manager, Irish Pharmaceutical Healthcare Association), made presentations relevant to their area at the meeting. The results of a study conducted by the IMB on current practices on clinical trials in Ireland were presented. The study identified two areas of specific concern that impact on the number of clinical trials conducted in Ireland. These were delays in approval of trials and amendments by ethics committees, and lack of uniformity in the indemnity for clinical trials between the different academic institutions and health boards.

The presentations were followed by a short session on future legislative requirements for clinical trials in Ireland, namely the European Directive on Clinical Trials which has recently been adopted by the European Parliament.

During the afternoon session, a number of current topics were discussed which included residual solvents, TSE Directive, renewals and variations. With regard to residual solvents, the audience was reminded of the ICH guideline concerning acceptable levels for patient safety. With regard to the TSE Directive, it was noted that not all companies had yet responded to the request to complete the TSE declaration. This was identified as a major issue for the IMB and companies were asked to complete the TSE declaration as a matter of urgency. With regard to national renewal applications, the IMB stated that the present policy was to give priority to processing of renewals in a timely fashion. The companies were reminded that under the Irish legislation, once a PA is beyond its expiry date the licence for the product is no longer in existence.

An update was provided on the proposed changes to EU regulations on variations. Expected changes to Regulations 541/95 and 542/95 are the introduction of Type 0 changes, which could be implemented without official approval from the regulatory authorities 'tell and do variations' (for example, change of name/address of companies). For Mutual Recognition Type II variations, proposed amendments would allow the Reference Member State to notify approval to the applicant on behalf of all concerned member states.

Prior to the close of the meeting, there was a questions and answers session which allowed for active discussions between the audience and the staff of the IMB.

Website Updates

From August 2000, the editing and update of the IMB Website has been taken over by the IMB's IT Systems Section. Since then, some changes have been made to improve navigation through the site. It is expected that these enhancements will assist the user in keeping up-to-date with events within the Board.

A 'News Update' section has been included in our Home Page and News Section. This will act as a bulletin board announcing the most recent updates made to the site. There are direct links in this section for IMB recruitment advertisements and for the most recent IMB Press Releases.

For updates to the web site please see **http://www.imb.ie**

HUMAN MEDICINES

Legislation and Guidelines

Medicinal Products (Control of Paracetamol) Regulations 2001

The Minister for Health and Children has recently signed into law the Medicinal Products (Control of Paracetamol) Regulations 2000 which come into effect on 1 October, 2001. PA holders will be required to comply with the pack size, method of sale and supply and labelling requirements in the Regulations by that date. Further details will be given by the IMB in due course.

Adopted Notes for Guidance

- CPMP/QWP/159/01 (CVMP/271/01) Note for Guidance on Limitations to the Use of Ethylene Oxide in the Manufacture of Medicinal Products (CPMP/CVMP Adopted March 2001)
- CPMP/QWP/848/96 (EMEA/CVMP/598/99) Note for Guidance on Process Validation (CPMP/CVMP Adopted February 2001)
- CPMP/QWP/3015/99 Note for Guidance on Parametric Release (CPMP Adopted February 2001)
- CPMP/QWP/2934/99 Note for Guidance for In-Use Stability Testing of Human Medicinal Products – Annex to Note for Guidance on Stability Testing of Existing Active Substances and related Finished Products and Note for Guidance on Stability Testing of New Drug Substances and Products (CPMP Adopted February 2001)
- CPMP/EWP/552/95 Revision 1 Note for Guidance on Post Menopausal Osteoporosis in Women (CPMP adopted January 2001)
- Topic Q1A, Step 5 Note for Guidance on Stability Testing of New Drug Substances and Products (CPMP/ICH/2736/99 (Revision of CPMP/ICH/380/95), adopted – November 2000)
- CPMP/EWP/566/98 Revision 1 Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Epilectic Disorders (CPMP adopted November 2000)

Position Statement

- Position Statement (BWP)on the Use of Tumourigenic Cells of Human Origin for the Productiuon of Biological and Biotechnological Medicinal Products

Draft Notes for Guidance

- CPMP/QWP/158/01 (CVMP/115/01) Note For Guidance on Quality of Water for Pharmaceutical Use (Released for Consultation, Feb. 01)
- CPMP/EWP/QWP/1401/98 Note For Guidance on the Investigation of Bioavailability and Bioequivalence (Re-released for Consultation, Dec. 00)
- CPMP/QWP/2845/00 Note for Guidance on Requirements for Pharmaceutical Documentation for Pressurised Metered Dose Inhalation Products (Released for Consultation, November 00)
- CPMP/QWP/2820/00 (EMEA/CVMP/815/00) Note for Guidance on Specifications: Test procedures and Acceptance Criteria for Herbal Drugs, Herbal Drug Preparations and Herbal Medicinal Products (Released for Consultation by CPMP/CVMP, November 00)
- CPMP/QWP/2819/00 (EMEA/CVMP/814/00) Note for Guidance on Quality of Herbal Medicinal Products (Released for Consultation by CPMP/CVMP, November 00)
- Topic Q1D, Step 2 Note for Guidance on Bracketing and Matrixing Designs for Stability Testing of Drug Substances and Drug Products (CPMP/ICH/4104/00 – released for consultation November 2000)
- Draft Note For Guidance (QWP) on Quality of Water for Pharmaceutical Use.

The Notice to Applicants

Over the past six months, a number of documents have been revised in the Notice to Applicants, Volume 2 of *The Rules Governing Medicinal Products in the European Union.*

Chapter 2, Volume 2A

This chapter on the mutual recognition procedure has been revised to provide more details on the scope of the procedure and on repeat use. Minor changes have been made to the numbering system for MRPs. Information on national transfer procedures have been moved from this chapter to chapter 7.

Chapter 4, Volume 2A

This chapter on the centralised procedure has been revised in line with current practices at the EMEA and CPMP.

Part IA Application Form, Volume 2B

The application form for new applications has been substantially revised. The new form clearly distinguishes the legal basis of an application from the issue of whether or not the application is a line extension under Annex II of the variation regulations. New sections are included on orphan drug status, scientific advice, and paediatric development programmes. There have also been changes made to the section on manufacturers of the active and the finished product.

The form can be used from 1 April 2001. If the old form is used, applicants must ensure that the legal basis for the application and the TSE status are clearly indicated. From 1st October 2001, applications will not be accepted unless they include the new form.

Guideline on the categorisation of New Applications (NA) versus Variation Applications (V), Volume 2C

This guideline formed part of Chapter 5 of Volume 2A but is now a separate regulatory guideline in Volume 2C. It has been substantially revised to clarify the application procedure to be followed when making changes to the pharmaceutical form or strength of a medicinal product in accordance with Annex II of the variation regulations. Depending on the nature of the change to the product, the application follows either a new application procedure or a variations procedure.

The main change in the revised text relates to the definition of strength in a parenteral product. The strength of single-dose products has been defined as:

a) total use, where the amount of active substance in the container is given in total to the patient, or

b) partial use, where the dose is calculated according to the patient's weight or body surface area.

For parenteral products where the dose is independent of patient variables (total use), each container is a separate strength and a new strength must be applied for as a new application. Where the dose is patient-dependent, containers of different sizes represent different pack sizes and a new volume container can be applied for as a variation.

In relation to changes in the pharmaceutical form, the Ph. Eur. standard terms are used as the basis for defining

pharmaceutical form. A change to the pharmaceutical form results in a new application, except for deletion of a solvent. Other changes where the application procedure is clarified are changes from a single-dose to a multi-dose preparation or vice-versa, changes in presentation, changes in route of administration and inclusion of devices.

The guideline includes many examples to illustrate the classification. As in the previous text, there is a specific statement made that the classification does not have any impact on the fees to be charged, or on whether the procedure results in a modification of the Marketing Authorisation (MA) or a new MA, or on national authorities policies with regard to MA numbers.

The IMB has decided to adopt the classification in the guideline for the procedure to be followed when making an Annex II application, both for national applications and for applications through MR. Companies wishing to make such an application should follow the procedure outlined in the guideline (new application or variation) and pay the appropriate fee. The outcome of the application is either an endorsement to the original PA or a new PA; it is not necessarily dependent on the application procedure but is determined by IMB policies with regard to the issuing of product authorisations.

TSE Safety Compliance

In accordance with the terms of European directive, 1999/82/EC, the Irish Medicines Board has been reviewing compliance with the requirements of the note for guidance on Minimising the risk of transmitting Animal Spongiform Encephalopathy via medicinal products, February 2001 (EMEA/410/01). All products on the market in Ireland on 1st March 2001 have been reviewed following an extensive survey conducted by the IMB. Companies who have not responded to requests for information by this time have had their product authorisations suspended.

The survey showed that approximately 70% of the products do not currently contain materials of ruminant animal origin and that in general terms this percentage appears to be growing with time.

Those products for which certificates of suitability from EDQM are provided or have been applied for up to the end of February 2001 have been allowed to continue on the market until full certification has been provided. Similarly products for which scientific data has been submitted will be allowed to continue on the market during 2001 subject to regular review. Any products for which the certificates or queries remain outstanding by the end of 2001 will be suspended from marketing.

Renewals

Applications for renewals of product authorisation, which fall due on or after 1st March 2001 should indicate the TSE status of the products; otherwise these applications will not be validated. Applicants should submit TSE certificates which have been granted at the time of application and complete the tables which are included on the IMB website (**http://www.imb.ie**). Where scientific data has already been submitted as part of the review process, this can be cross-referred to in the renewal application with a reference to the type of data and the date of submission.

Variations

Requests to change the source of supply of materials of ruminant animal origin on or after 1st March 2001 should be accompanied by appropriate variation applications, either Type I (certification) or Type II (data submission). Wherever possible the certification route is always the preferred route. The impact of subsequent changes to new suppliers of starting materials of animal origin will need to be addressed on an ongoing basis.

Finally manufacturers of medicinal products are advised that where possible they should seek to move away from the use of ruminant animal derived materials.

Clinical Trials

As a general policy compliance with the TSE guideline is also required for products for clinical trials conducted in Ireland from January 2001.

Companies are therefore expected to address the issue of TSE safety in Category 3 applications for clinical trial permission or amendment to clinical trial permissions, indicating whether or not ruminant animal materials are present. A declaration form is required to be completed by all applicants for category 3 trials. The form is available from the IMB website (**http://www.imb.ie**) for use as an attachment to the clinical trial forms. Where ruminant animal materials are present, applicants for clinical trial

permission should indicate whether or not certification from EDQM (the preferred route) or data have been provided in the application. Where data have been evaluated separately e.g. in the context of the IMB review of marketed products or by other regulatory authorities in the European Union, this should be indicated in the declaration.

Once again it should be borne in mind that changes to the source of starting materials of ruminant animal origin will require re-evaluation in accordance with the CPMP guidelines on TSE risk.

Renewals and Variations

Hypericum perforatum

Further to extensive discussion at national and European level regarding the potential for medicinal products to interact with St. John's wort *(Hypericum perforatum)*, final agreement was reached at the end of last year on wording for inclusion in the relevant SPCs.

The medicinal products concerned include warfarin, cyclosporin, digoxin, theophylline, carbamazepine, phenobarbitone, phenytoin, trazodone, nefazodone, protease inhibitors, non-nucleoside reverse transcriptase inhibitors, selective serotonin re-uptake inhibitors, triptans and oral contraceptives.

In order to implement this agreed wording which affects a significant number of products, the IMB proposes to implement the recommendations in the following way:

1. Medicinal products due for renewal during 2001 will have the agreed wording implemented at time of renewal.

2. Recently renewed products for which the final authorisation documents have not yet been issued will have the wording implemented as an endorsement.

3. For medicinal products to which 1 and 2 above do not apply, relevant Product Authorisation Holders will be contacted and requested to submit variations to implement the wording as soon as possible.

4. Variations relating to products authorised through the centralised or mutual recognition procedures will have variations implemented via the Rapporteur/RMS.

Product Authorisation Holders are requested to review their products in order to identify those for which variations should be submitted.

A copy of the final wording is available from the IMB's website: **http://www.imb.ie**

Changes to labels and leaflets

Under directive 92/27/EEC, all proposed changes to labels and leaflets not connected with the SPC must be submitted to the competent authority. To avoid setting up a separate procedure for submitting these changes to the IMB, PA holders are asked to submit them as a Type II standard variation, a procedure which has the same timeframe as the 90 days laid down in the directive. Changes to labels and leaflets cannot be processed in any other way.
During the course of assessment of labels and leaflets, certain changes may be requested. In reviewing the amended texts, the assessor will focus on the revisions which have been made. If other changes have been made which were not requested, the PA holder should clearly identify them and bring them to the attention of the assessor, to ensure that these changes too are approved in the final marketed label or leaflet.

Periodic Safety Update Reports (PSURs)

As indicated in a previous issue of the Quarterly Newsletter (Winter 1998), PSURs covering the period since last renewal are required in support of all renewal applications, even if a product is not currently marketed in Ireland. PSURs should be provided in keeping with the format and content described in the Notice to Marketing Authorisation Holders (NtMAHs).

A clinical expert statement, including a concise benefit/risk analysis of the product since last renewal, must also be provided.

Applicants are reminded that they must undertake any recommendations made by the clinical expert in their report e.g. epidemiological studies, special monitoring, variations etc.

Declaration of Expiry Dates and Storage Conditions

The Irish Medicines Board wishes to remind all manufacturers that expiry dates and storage conditions for medicinal products should be declared as clearly as possible on

product labels and packaging leaflets as appropriate. The normal practice for declaration of expiry dates is to refer to the month and the year and it is preferred that the year is spelled out in full – '2001' – rather than simply the last two numbers. The month can be referred to numerically or by letters. It should be noted that where an expiry date refers to a month of a given year, this is understood to be the last day of the month and that the product can continue to be used throughout the month until the last day has been reached. Consequently, in assigning a specific month for expiry dates, the normal practice is to default to the end of the previous month and to add the shelf life in order to arrive at an accurate and valid expiry date. Thus, products with a two-year shelf life manufactured during March 1999 should state their expiry date as February 2001.

In certain cases it may be more pertinent to apply the specific day of the month of expiry for products such as radio-pharmaceuticals with a very short shelf life in order to give more accurate information.

In regard to storage conditions, these are normally stated in accordance with where applicable CPMP Guidelines (CPMP/QWP/609/96) in terms of the maximum storage temperature. The absence of a storage temperature means that the product meets the full ICH stability criteria and therefore can be stored at normal room temperature conditions throughout the European Union. Storage temperatures are particularly important for products which are intended to be stored in a refrigerator. The CPMP guideline on storage conditions is currently under revision in order to improve the clarity of the guidance.

Clinical Trials

The Clinical Trials Directive

After many years of negotiation, agreement was finally reached on the draft European Directive on the Conduct of Clinical Trials for Medicinal Products for Human Use at the European Parliament on 12th December 2000 and at the Health Council of the Council of Ministers on 14th December 2000. Formal adoption should follow shortly.

This Directive aims to protect clinical trial subjects by setting standards for Good Clinical Practice (GCP) and Good Manufacturing Practice (GMP) and ensuring that standards and procedures in Europe will provide an environment where new medicines can be developed safely and rapidly.

Many of the provisions of the Directive are in accordance with Irish legislation on clinical trials (Control of Clinical Trials Act 1987/1990). Statutory timescales similar to those laid down in the Control of Clinical Trials Act 1987/1990 are stipulated in the Directive for both regulatory authorities and ethics committees. In accordance with Article 7 of the Directive written authorisation must be obtained from the ethics committee. For multicentre trials a single opinion for each Member State must be given within 60 days. This will necessitate the establishment of a National Ethics Committee.

As a rule, authorisation from the competent authority should be implicit, i.e. if there has been a vote in favour by the Ethics Committee and the competent authority has not objected within the 60 day period, the clinical trial may begin. In exceptional cases, especially with complex issues (i.e. gene therapy products and products containing genetically modified organisms), explicit written authorisation will be required. The European Parliament introduced informed consent into the Directive, as in the Irish legislation, and insisted on general conditions and requirements for enrolling participants in clinical trials. The Directive also lays down the conditions under which clinical trials may be undertaken in populations where persons are unable to give consent, with particular emphasis on studies in the paediatric population.

The Directive will also control the manufacture of medicinal products used in trials and will require inspection to ensure compliance with its provisions.

Member States will have 36 months to comply with the provisions of the Directive.

'Six-Day' Rule and Informed Consent

The conduct of Clinical Trials in Ireland is regulated by the Control of Clinical Trials Act 1987 as amended in 1990. Before any clinical trial is commenced each participant must give full and informed consent. Section 9 of the Act outlines the criteria that must be fulfilled to ensure that each participant fully understands the nature, scope and purpose of the study. Consent to participate in a clinical trial is not valid unless it is given in writing and signed by the person who is participating in the trial.

Section 7 of the Act describes exceptions to this. In the case of an individual who is not able either temporarily or permanently to give informed and personal consent, written consent may be obtained from two witnesses and his/her general practitioner or an independent medical practitioner. This arrangement must receive full ethical approval.

The Act further stipulates that six days should elapse between the time the consent form is signed and the day the patient commences the clinical trial. The start of the trial refers to the first day the patient engages in any trial based activity (e.g. screening visit). The six-day rule applies to all category 3 trials (section 3(1) of the Act). It does not apply to Category 1 and 2 trials as described by section 2(2) and section 2(3) of the Act.

In certain circumstances this six-day period can be waived. This usually applies to clinical emergency situations. Any such request must be made in writing to the IMB and include a statement of justification.

The 1991 Guidelines issued by the IMB in relation to clinical trial applications are currently being reviewed. New guidelines will be issued taking into consideration the Clinical Trials Directive adopted on the 14 December 2000. The revised guidelines will be based on the final approved wording of the Clinical Trials Directive.

GCP Inspection issues

A total of 14 clinical trials authorised by the IMB were subject to a GCP inspection during 2000. These inspections involved both sponsor affiliate offices and investigator sites. The average inspection consists of one day at the sponsor office (if applicable) and two days at an investigator site. The main aim of the 2000 program was to conduct a sufficient number of inspections to give an overall view of the current level of compliance with the Control of Clinical Trials Act 1987 and 1990, ICH/GCP and related documents. Sufficient data were gathered from the inspections to further develop inspection processes and systems. Analysis of the data was performed to identify areas of significant non-compliance and to form a basis for measuring the effect of the inspection program on the overall quality of the conduct of clinical trials in Ireland.

On the whole, there was an acceptable level of compliance and quality of trials with regard to legislation, ICH/GCP and related standards and guidelines. It was very clear that all parties involved strive to achieve a high level of compliance.

A total of 178 findings were issued (of all grades) during 2000. These findings were categorised into 10 areas covered by the inspections and the rates of occurrence of non-compliances are given below. It should be noted that no Grade 1 (Critical) findings were observed during the inspections.

Interaction with Ethics Committees 23.6%
Informed Consent Procedures 19.7%
Investigational Medicinal Products 15.7%
Management of essential documentation
(including SOPs) 15.2%
Source Data Verification and Protocol Compliance .11.8%
Biological sample handling 6.7%
Investigator site resources and organisation 5.1%
Randomistation procedures and unblinding 1.1%
ADR / SAE reporting 0.6%
Extent and nature of monitoring 0.6%

The above table shows the aspects of the clinical trial processes which are giving rise to significant non-compliances. It is worth noting that many of the non-compliances are very common and well understood. Some of the main findings in relation to the above categories are as follows.

Interaction with Ethics Committees (IECs)(23.6%)

- No documentation to indicate that the IECs are organised and operate in accordance with GCP (ICH/GCP 5.11.1(b), 3.2.2, 8.2.8)
- Opinion letter did not clearly indicate the versions of the documents reviewed or approved. (ICH/GCP 5.11.1(c), 3.1.2, 3.3.9, 4.4.1)
- Not clearly documented that the Investigator Brochure was submitted (ICH/GCP 4.4.2, 5.18.4(f), 3.1.2)
- Changes to documents made on verbal request. (ICH/GCP 3.3.9, 5.11.2)

Informed Consent Procedures (19.7%)

- Patient signatures not personally dated (ICH/GCP 4.8.8, 5.18.4(e) and (q))

- No version date / number on the consent form (ICH/GCP 4.8.1, 5.1.1)
- Consent taken by unauthorised personnel (poor documentation) (ICH/GCP 4.1.5, 4.2.4, 4.8.5, 5.18.4(e), (h) and (q))
- Unclear if the patient agreed to their primary physician being informed of their participation. (ICH/GCP 4.3.3, 5.18.4(e))
- Only signature page retained at site, therefore unclear if patient received the correct version of the patient information. (ICH/GCP 4.8.8, 4.8.10, 4.8.11, 5.18.4(e)).

Investigational Medicinal Products (15.7%)

- Inadequate documentation on adherence to storage requirements (ICH/GCP 4.6.4, 5.13.2, 5.14.3, 5.18.4(c)(i))
- Non-adherence to the labelling requirements of annex 13 of the EU GMP guide (paragraph 17 and 18 and 19)
- Inadequate storage facilities.
- Lack of awareness of recall procedures. (ICH/GCP 5.14.3, 5.14.4(c))
- Discrepancies in accountability records (ICH/GCP 4.6.1, 5.14.3, 5.18.4(c)(iv))

Some of the other significant findings in relation to the other categories include:

- Inadequate documentation in relation to the delegation of responsibilities at the investigator site. (It is necessary that the actual responsibilities delegated are documented and not just the signature and job title.)
- Inadequate documentation as to requisition documents for the blood samples and documentation regarding the storage of frozen samples.

  Local working practices not included as part of the quality systems (SOP system).

  Inadequate documentation as to the extent and frequency of monitoring at the investigator site.

During the course of recent inspections, a concern has arisen in relation to the labelling of the investigational medicinal product when it takes the form of blister packs or small packaging units such as vials or ampoules where there is an outer secondary packaging. It is accepted, and indeed outlined in Annex 13 of EU GMP, that such small items cannot accommodate all of the requirements in paragraph 17 of Annex 13. Labels on small units should include a minimum of (a) the name of the sponsor, (b) the batch and/or code number to identify the contents and packaging operation and (c) the trial subject identification number, where applicable. It is very important that there is some way of identifying the unit with a particular patient so as to ensure accuracy of accountability records and dosing compliance. Where this is not applicable, the rationale should be clearly documented and the omission justified. In general the IMB does not have any special labelling requirements other than that outlined in Annex 13 of EU GMP.

For further details concerning the inspection findings and processes in general, please contact the IMB.

HERBAL MEDICINES

Herbal Medicines Project Update

The Herbal Medicines Project first interim report was submitted to the Department of Health and Children on the 28th November 2000, on target. The project is on going and details of recent achievements are listed below.

1. **Advertisement in National Press**
   An advertisement placed in the national press requesting public comment on the regulation of traditional and alternative medicinal products, including herbal medicinal products, yielded a total of 41 submissions. All submissions were reviewed by both the IMB and the Scientific Committee on Herbal Medicinal Products [SCHMP – see point 2.].

2. **Establishment of Scientific Committee on Herbal Medicinal Products**
   Following the placement of the advertisement in the national press, a committee of experts in herbal medicine and related areas was established, based on recommendations from the IMB and responses to the above consultative processes. The SCHMP is chaired by Dr. Desmond Corrigan, Trinity College Dublin and consists of ten other members [see **Table 1**].

3. **Transparency and open consultation**
   The IMB is committed to a policy of openness and transparency throughout the Herbal Medicines

Table 1. Scientific Committee on Herbal Medicinal Products

Member	Discipline	Role on the Committee
Mrs. Ingrid Hook	Pharmacognosy	Scientific Advisor
Dr. Helen Sheridan	Phytochemistry	Scientific Advisor
Professor Edzard Ernst	Complementary Medicine	Scientific/External Advisor
Dr. Dilis Clare	General & Herbal Medicine	Medical/Herbal Advisor
Ms. Helen McCormack	Herbal Medicine	Herbal Advisor
Ms. Nicola Darrell	Herbal Medicine	Herbal Advisor
Ms. Geraldine Lavelle	Pharmacy and Aromatherapy	Pharmacy and Aromatherapy
Dr. John Duignan	General Medicine	Medical Advisor
Dr. Katherine Chan Mullen	Chinese Herbal & General Medicine	Chinese Medicine Advisor

The SCHMP has met on three occasions and work is ongoing towards a final report due to be submitted to the Department of Health and Children later this year.

Project. Therefore, it is hoped that all interested parties and members of the public will be afforded an opportunity to comment on a draft report prior to submission of the final report to the Department of Health and Children.

4. Establishment of a herbal/traditional medicinal products database

The IMB is in the process of establishing an information database of all products likely to fall into the categories of alternative, traditional or herbal in order to determine the number of products on the market that will potentially be controlled under a new national licensing scheme. The product details required are as follows:

- Name of the Medicinal Product
  i.e. proprietary or trade name which appears on the product label.
- Product Description
  i.e. pharmaceutical form – tablet, capsule, tincture, syrup etc. and description of same.
- Composition
  i.e. qualitative and quantitative particulars of all active ingredients.
- Name and Address of Person Responsible for Placing the Product on the Irish Market
- Method of Sale or Supply
  i.e. general sale, health food store only, pharmacy-only, prescription only etc.
- Method of Sales Promotion
  i.e. whether the product is promoted/advertised to the general public or to professionals only and how this is achieved e.g. the pack label or leaflet only, advertisement in newspapers, advertisement in professional journals, accompanying in-store literature etc.
- Special Conditions (Special Labeling or other Requirements)
  i.e. any indication claim and any other special warnings on the label or package leaflet.

5. Irish Medicines Board involvement at EU Level

At a European level, the IMB continues to participate in the Herbal Medicinal Products Working Party of the EMEA and the Pharmaceutical Committee Herbal Working Group of the European Commission. The IMB response to the 'Provisions of a Directive on a

Traditional Medicinal Products' circulated by the Pharmaceutical Committee was submitted on December 15th 2000 as requested. Feedback is expected following the next meeting of the Pharmaceutical Committee scheduled for April 2001.

VETERINARY MEDICINES

Legislation and Guidelines

The following guidelines and position papers have been adopted by the CVMP from October 2000 to February 2001.

Notes for Guidance:

Note for Guidance: Stability testing of existing active substances and related finished products (EMEA/CVMP/846/99-Final).

Note for Guidance: Testing and evaluation of the efficacy of antiparasitic substances for the treatment and prevention of tick and flea infestations in dogs and cats (EMEA/CVMP/005/00-Final).

Guidelines for the conduct of bioequivalence studies for veterinary medicinal products (EMEA/CVMP/016/00-Final).

Note for Guidance on risk analysis approach for residues of veterinary medicinal products in food of animal origin (EMEA/CVMP/187/00-Final).
Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMEA/410/01-Final).

Position Papers:

Position Paper on the assessment of the risk of starting materials of ruminant origin in veterinary medicinal products intended for use in ruminants (EMEA/CVMP/121/01-Final).

Position Paper on the assessment of risk of transmission of animal spongiform agents by master seed materials used in the production of veterinary vaccines (EMEA/CVMP/019/01-Final).

Compliance of Veterinary Medicinal Products with EU Directive on Transmissable Spongiform Encephalopathies (TSE) – Directive 1999/104/EC

With effect from 1st June 2001, all VMP's marketed in Ireland, including IVMP's should conform to the requirements for TSE safety as stated in the joint CPMP/CVMP guideline on Minimising the Risk of Transmission of Spongiform Encephalopathies in medicinal products (reference EMEA/410/01). These guidelines were last modified and adopted by the CVMP in February 2001.

All companies have been written to on several occasions between August 2000 and March 2001. Authorisation holders are reminded that failure to respond or to provide satisfactory assurance of TSE safety, will result in removal of the products from the market with effect from 1st June 2001.

Fees

Companies are asked to note that if a risk assessment is to be conducted by the IMB, i.e. if the veterinary product either

- contains material of ruminant origin for which EDQM certificates have not been submitted but scientific data have or,
- contains material of ruminant origin and is indicated for use in ruminant animals

then a Type I variation fee of £240 per product will be requested. **(Please note that there is no requirement to fill in variation application forms).**

Fees should be submitted on request to Ms Maura O'Connell, Assistant Operations Manager, Irish Medicines Board, Email: **maura.oconnell@imb.ie. quoting fee reference IMB/606.**

Harmonisation Initiative between Ireland and UK

The harmonisation of Summaries of Product Characteristics (SPC's) and labelling for veterinary products marketed in both Ireland and the UK offers clear economical benefits to companies and helps to maintain the product portfolio for veterinary medicines in Ireland, which holds the smaller market share.

To date, significant progress has been made after the establishment of procedural guidelines to facilitate both the regulatory authorities and industry. The product authorisation must be valid prior to initiating the harmonisation procedure; therefore, if a product authorisation is undergoing renewal in either the UK or Ireland, the harmonisation process is postponed until after the renewed licence is issued.

The marketing authorisations will be marked in the records of both authorities as being harmonised so that all subsequent applications can be progressed in such a way as to maintain the harmonisation, unless the company wishes to proceed differently at a future point in time and diverge the authorisations.

The original intention was to invite the marketing authorisation holder to apply for harmonisation of products on the basis of pharmacological class. However, as interested companies approached the regulatory authorities to request harmonisation of certain products within their ranges, these companies were invited to submit applications.

Dry cow intramammary products were selected as the initial product group for harmonisation, as these products already had comparable SPC's and labelling between the two territories. Companies interested in the initiative were asked to submit applications with the current SPC and labelling in both countries and the proposed harmonised versions. In February, the first harmonised SPC's were agreed between the two authorities and the company involved for a range of dry cow products.

At the time of writing, 16 applications have been received in total with 3 applications complete, 5 in progress, 2 awaiting variation approval to bring the SPC's in line and 6 applications on hold until the renewed licenses are issued.

The IMB and VMD have selected the next product group for harmonisation as the anthelmintic products. Therefore, any company with products in this class, which are eligible for harmonisation, may now apply. We also encourage any interested companies to submit applications or discuss possible harmonisations, outside this product category, with the following contacts:

IMB: Karen Quigley Phone Number: +353-1-6764971 or e-mail **karen.quigley@imb.ie.** VMD: Heather Oliver.

Safety and residue testing

The IMB wishes to point out that in accordance with Council Directive 81/852/EEC all safety and residue studies must be carried out in accordance with the provisions relating to Good Laboratory Practice.

Validation of new veterinary product applications

The IMB has revised its validation procedure (effective since March 1st, 2000) to avoid premature applications being accepted for evaluation with subsequent long delays during the evaluation stage. Where applications have insufficient data to allow the evaluation to take place (e.g. stability data from labscale batches only, no drug master file available, inadequate residue studies or insufficient data to demonstrate compliance with Directive 1999/104/EC), the application will be recorded as invalid and will have to be resubmitted once the necessary data are available. It is expected that this amendment to the procedure will result in the achievement of improved timelines for the granting of authorisations for new products.

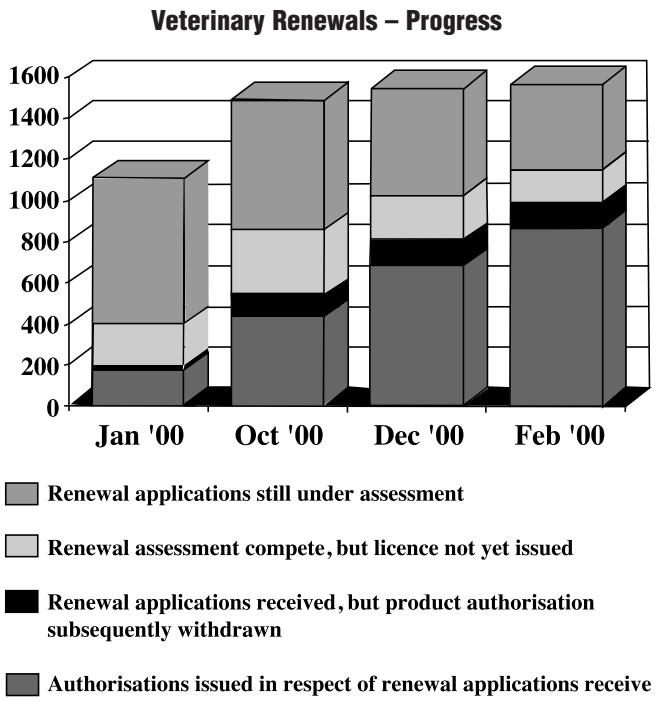
Receipt of authorisation schedule for checking by e-mail

Some applicants have requested the IMB to send them the final draft authorisation documents electronically in order to save time. The IMB will facilitate such requests but only on receipt of confirmation from the applicant that they do not object to receiving such documents routinely by e-mail. The IMB cannot be responsible for any breaches of confidentially caused by the transfer of documents to applicants electronically. Further information on this may be obtained from Ms. Fiona Smyth of the Veterinary Department at **fiona.smyth@imb.ie**

Method of supply on Part III of the Schedule (SPC)

Following in-house discussions with relevant personnel, it was agreed that it was not necessary to repeat the section Conditions of supply to Animal Owners on Part III of the schedule. The reasons for this are as follows:

1. There is no Section 7 in the Guideline for Summary of Product Characteristics (SPCs) agreed by the CVMP in April 1999. The inclusion of the provision for supply in this section has led to comments being raised by Concerned Member States to the SPC of products which were authorised under the Mutual Recognition System. In the interests of efficiency, both for



applicants and for the IMB, it is felt important to remove this unnecessary source of discussion on this aspect of the evaluation, which is a national issue for Member States.

2. The method of sale or supply is already included in Part II of the schedule.

3. Repetition of the text on supply adds to the work of the IMB secretariat.

All authorisations that are now being issued by the IMB for veterinary medicinal products indicate the method of supply on Part II of the schedule only. It is not necessary to return existing schedules which may contain the information on Parts II and III, except where it is intended to request the IMB to act as Reference Member State.

Veterinary Pharmaceuticals

Progress on Veterinary Renewals Backlog

At the beginning of 2000, one area highlighted by the veterinary division as requiring priority attention was that of veterinary renewals. At that time, authorisations had been issued in respect of only 16% of approximately 1,100 renewal applications received. Over the past 12 months, the number of renewal applications received has increased to approximately 1,600 and authorisations have been issued in respect of 56 % of those. In addition, approximately 8 % of the total number of renewal applications received to date have been withdrawn by applicants either on commercial grounds or in response to queries arising during the assessment process.

As can be seen from these figures, considerable progress has been made on this issue in a relatively short period of time. The IMB would like to take this opportunity to thank all those in the pharmaceutical companies responsible for dealing with renewal applications for their considerable efforts in assisting with this task. The IMB aims to eliminate the renewal application backlog as quickly as possible and has set a target of June 30th, 2001 for the processing of outstanding applications.

In relation to future applications for renewal, applicant companies are reminded that under the Animal Remedies Regulations, 1996, in order to maintain a marketing authorisation in force the application must be made to the IMB at least 90 days before the expiry date of the existing authorisation. It is the intention of IMB to issue renewed authorisations at the time of expiry of the current authorisation. To facilitate this procedure, applicants are requested to submit the renewal application 3 – 5 months ahead of the expiry of the existing authorisation. It is IMB policy to notify the Department of Agriculture, Food and Rural Development of lapsed authorisations. Failure to submit renewal applications 90 days before expiry may result in the authorisation lapsing (i.e. the product is deemed 'not authorised') with consequential effects for the supply of the product. Applications will not be considered eligible for renewal if they have not been received by the IMB before the expiry date of the existing authorisations.

Revised numbers of dossiers to be submitted

In respect of pharmaceutical applications for product authorisation and product renewal, it has been decided that only 2 complete sets of technical supporting documentation are necessary. However, 3 copies of the administrative details, SPC and product labelling are necessary, including when applicable, expert reports. In respect of amendment and variation applications for pharmaceuticals, 2 copies of the application form and supporting documentation should be submitted.

Further information on validation may be obtained from Ms. Mary Murphy of the Receipts and Validation Department at **mary.murphy@imb.ie.** Further information on either renewals or variations may be obtained from Ms. Sinead Barron of the Veterinary Department at **sinead.barron@imb.ie.**

Merging of Authorisations

Authorisations for identical products in different container sizes may only be merged at renewal if the request to do so is contained within the covering letter accompanying the renewal application. Alternatively, they may be merged on submission of a simple type I variation.

Veterinary Immunologicals

Immunological Review

The call-up date for companion animal products has been set for April 3rd 2001 through to June 30th 2001. The call up date for fish and all other products is from September 4th 2001 to November 24th 2001.

Further technical information may be obtained from Dr. Una Moore, Immunological Assessor at **una.moore@imb.ie.** Clarification of fee structure and submission details may be obtained from Ms. Fiona Smyth of the Veterinary Department at **fiona.smyth@imb.ie.**

Revised numbers of dossiers to be submitted

In respect of immunological applications for product authorisation, product review or product renewal, it has been decided that only one complete set of technical supporting documentation should be submitted to the IMB. One copy of Part I must be submitted to the Department of Agriculture, Food and Rural Development (DAFRD). In respect of amendment and variation applications, one copy of the entire documentation should be submitted to both the IMB and DAFRD.

Further information on validation may be obtained from Ms. Mary Murphy of the Receipts and Validation Department at **mary.murphy@imb.ie.** Further information on either renewals or variations may be obtained from Ms. Sinead Barron of the Veterinary Department at **sinead.barron@imb.ie.**

INSPECTORATE

Legislation and Guidelines

Adopted Notes for Guidance

- Note for Guidance (QWP) on Process Validation
- Note for Guidance (QWP) on Parametric Release
- Q7A " ICH Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients" - The document was adopted by ICH in October 2000. It is expected that the Guide will be implemented in the EU April 2001 and will become effective from the 1st June 2001.
- Revised Version of Annex 14 – Manufacture of medicinal products derived from human blood or plasma to the EU Guide to Good Manufacturing Practice (25/10/00)

Draft Notes

- Note for Guidance (QWP) on Quality of Water for Pharmaceutical Use
- Annex 15 'Qualification and Validation' - The draft document will be posted on the EU Commission web site. It is expected to be approved by the Pharmaceutical Committee in April 2001 and will come into force in June 2001.
- Revised Draft of Annex to the Guide to Good Manufacturing Practice for Medicinal Products: Certification by a Qualified Person and Batch Release (26/01/01)

In addition, the PIC/S website (**http://www.picscheme.org/pubs/pubs.htm**) has been updated so that the following guidelines are available free of charge:

- Pharmaceutical Inspection Cooperation Scheme (PIC/S 1/95)
- Guide to Good Manufacturing Practice for Medicinal Products (PH 1/97 (Rev) - December 2000)
- Site Master File Guidelines (PH 4/93)
- Sterility testing (PE 001-2)
- Validation - Master Plan, IQ, OQ, PQ, Cleaning (PR 1/99-2)
  Validation of aseptic processing (PE 002-2)
  Quality System Requirements for Pharmaceutical Inspectorates (PI 002-1)

Mutual Recognition Agreements (at the time of going to press)

Canada: There is no new date for the start of the operational phase.

US: The US plans to start assessment of Member States (MSs) with the UK and will only have the UK fully evaluated at the end of the transition period.

FDA agreed to provide a response by early 2001 to EU on a timetable for the evaluation of all MSs. They are currently reviewing their resources with regard to the evaluation of a number of MSs in parallel.

Japan: More clarity is required in regard to the preparatory and transition periods. No date is assigned for signing the agreement. A detailed work plan is required as to how the EU will determine Japanese equivalency.

Switzerland: New tentative date for coming into operation is the 1st July 2001.

Australia/ New Zealand: The agreement is in place for human medicinal products. Some assessment is being performed by the U.K. Veterinary Medicines Directorate on inspection of manufacture of veterinary medicinal products in these two countries.

Batch and GMP Certificates: At the last PIC/S meeting there was proposal to standardise batch and GMP certificates with all MR partners. This proposal is being reviewed.

GMP Observations

1. It has come to the attention of the Inspectorate that some companies may split a batch of product into a number of lots for sterilisation and then perform one sterility test for all of the lots together. This is not an acceptable practice.

   The definition of a batch in the Glossary of the EU GMP Guide refers to the Council Directive 75/318/EEC which provides a legal definition of a batch. This definition refers to sterile products as follows – 'A batch…….comprises all the units of a pharmaceutical form which are made from the same initial mass and have undergone…….a single sterilising operation'. In addition, the Ph. Eur. 2000 Supplement contains the following reference to batches of sterile products – 'a batch is defined as a homogenous collection of sealed containers prepared in such a manner that the risk of contamination is the same for each of the units contained therein'. These references require each steriliser load to be treated as a separate batch for sterility test purposes.

2. Holders of Manufacturer's Licences and/or Wholesalers Licences who are also PA holders should be familiar and compliant with their obligations regarding pharmacovigilance. Further details and references are available at **http://www.imb.ie/drug/drug.htm.**

TSE

In accordance with recently amended Annexes to Council Directives 75/318/EC and 81/852/EC, applicants for marketing authorisations are now legally obliged to demonstrate that medicinal products for human and/or veterinary use have been manufactured in accordance with the respective Notes for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products. Marketing Authorisation Holders were requested to provide information on the TSE risk of each of their products, using the agreed European format, by 1st March 2001 for medicinal products for human use and 1st June 2001 for medicinal products for veterinary use.

As a follow up to this, the data that have been submitted to the IMB will be verified by the inspectorate during the course of GMP inspections. Therefore it is expected that companies will have relevant information available at the site for both product authorised in Ireland and in other member states.

HUMAN PRODUCT AUTHORISATIONS ISSUED OCTOBER 2000 – MARCH 2001

PA Number	Product Name	PA Number	Product Name
PA0007/013/002	ASASANTIN RETARD	PA0568/011/001	PERINDOPRIL
PA0016/055/001	ALPRAZOLAM	PA0568/011/002	PERINDOPRIL
PA0016/055/002	ALPRAZOLAM	PA0568/012/001	PERINDOPRIL SERVIER
PA0016/055/003	ALPRAZOLAM	PA0568/012/002	PERINDOPRIL SERVIER
PA0017/098/002	FLOLAN	PA0577/038/001	EMCOLOL
PA0024/023/017	FLIXOTIDE EVOHALER CFC-FREE	PA0577/038/002	EMCOLOL
PA0035/090/001	FORTZAAR	PA0577/039/001	GERFORMIN 500
PA0037/069/003	ZOTON	PA0577/039/002	GERFORMIN 850
PA0043/006/003	NUROFEN MICRO-GRANULES	PA0678/012/004	AUGMENTIN
PA0044/076/010	ZANTAC 75 DISSOLVE	PA0678/076/001	INFANRIX - HIB
PA0044/101/001	NARAMIG	PA0678/076/002	INFANRIX - HIB
PA0050/147/001	ASPRO C	PA0696/010/001	RALGEX IBUPROFEN
PA0061/026/004	ZISPIN	PA0705/004/002	RHINOLAST HAYFEVER NASAL
PA0069/023/001	SETLERS ANTACID PEPPERMINT	PA0711/024/003	RANITIC
PA0069/023/002	SETLERS ANTACID SPEARMINT	PA0735/008/004	OMNISCAN
PA0077/145/005	SOLIAN	PA0735/008/005	OMNISCAN
PA0179/008/004	OSMOFUNDIN	PA0736/002/001	METRONIDAZOLE
PA0236/028/001	MYCOBUTIN	PA0749/004/001	CARBOPLATIN
PA0281/076/001	CANAZOLE CLOTRIMAZOLE	PA0810/002/004	OESCLIM
PA0281/095/001	BISOPROLOL FUMARATE	PA0810/002/005	OESCLIM
PA0281/095/002	BISOPROLOL FUMARATE	PA0815/002/001	TIMONIL RETARD
PA0320/005/002	COLGATE TOTAL FRESH STRIPE	PA0815/002/002	TIMONIL RETARD
PA0361/013/001	CHLORAMPHENICOL EYE DROPS BP	PA0822/001/007	LUSTRAL
		PA0823/010/008	CALPOL FAST MELTS
PA0361/013/002	CHLORAMPHENICOL EYE OINTMENT BP	PA0845/002/001	LACTECON
		PPA0465/041/004	BECOTIDE 250 INHALER
PA0522/009/001	HIGH POTENCY VITAMIN C	PPA0465/058/001	ZOTON
PA0540/012/001	ZOPICLONE	PPA0465/058/002	ZOTON
PA0540/012/002	ZOPICLONE	PPA0465/059/002	LIPOSTAT
PA0544/023/003	HB-VAX II	PPA0465/061/001	ZIRTEK
PA0566/019/010	INTRALIPID	PPA0465/065/001	ISTIN
PA0566/019/011	INTRALIPID	PPA0465/065/002	ISTIN
PA0566/019/012	INTRALIPID	PPA0465/067/001	COVERSYL

HUMAN CENTRALISED PRODUCT AUTHORISATIONS ISSUED OCTOBER 2000 – MARCH 2001

PA Number	Product Name	PA Number	Product Name
EU/1/00/147/001	HEXAVAC	EU/1/00/150/002	ACTOS
EU/1/00/147/002	HEXAVAC	EU/1/00/150/003	ACTOS
EU/1/00/147/003	HEXAVAC	EU/1/00/150/004	ACTOS
EU/1/00/147/004	HEXAVAC	EU/1/00/150/005	ACTOS
EU/1/00/147/005	HEXAVAC	EU/1/00/150/006	ACTOS
EU/1/00/147/006	HEXAVAC	EU/1/00/151/001	GLUSTIN-PIOGLITAZONE
EU/1/00/147/007	HEXAVAC	EU/1/00/151/002	GLUSTIN-PIOGLITAZONE
EU/1/00/147/008	HEXAVAC	EU/1/00/151/003	GLUSTIN-PIOGLITAZONE
EU/1/00/148/001	AGENERASE-AMPRENAVIR	EU/1/00/151/004	GLUSTIN-PIOGLITAZONE
EU/1/00/148/002	AGENERASE-AMPRENAVIR	EU/1/00/151/005	GLUSTIN-PIOGLITAZONE
EU/1/00/148/003	AGENERASE-AMPRENAVIR	EU/1/00/151/006	GLUSTIN-PIOGLITAZONE
EU/1/00/148/004	AGENERASE-AMPRENAVIR	EU/1/00/152/001	INFANRIX HEXA
EU/1/00/149/001	PANRETIN	EU/1/00/152/002	INFANRIX HEXA
EU/1/00/150/001	ACTOS	EU/1/00/152/003	INFANRIX HEXA

HUMAN CENTRALISED PRODUCT AUTHORISATIONS ISSUED OCTOBER 2000 – MARCH 2001

PA Number	Product Name
EU/1/00/152/004	INFANRIX HEXA
EU/1/00/152/005	INFANRIX HEXA
EU/1/00/152/006	INFANRIX HEXA
EU/1/00/152/007	INFANRIX HEXA
EU/1/00/152/008	INFANRIX HEXA
EU/1/00/152/009	INFANRIX HEXA
EU/1/00/152/010	INFANRIX HEXA
EU/1/00/152/011	INFANRIX HEXA
EU/1/00/152/012	INFANRIX HEXA
EU/1/00/152/013	INFANRIX HEXA
EU/1/00/152/014	INFANRIX HEXA
EU/1/00/152/015	INFANRIX HE
EU/1/00/152/016	INFANRIX HEXA
EU/1/00/153/001	INFANRIX PENTA
EU/1/00/153/002	INFANRIX PENTA
EU/1/00/153/003	INFANRIX PENTA
EU/1/00/153/004	INFANRIX PENTA
EU/1/00/153/005	INFANRIX PENTA
EU/1/00/153/006	INFANRIX PENTA
EU/1/00/153/007	INFANRIX PENTA
EU/1/00/153/008	INFANRIX-PENTA
EU/1/00/154/001	NEOSPECT
EU/1/00/154/002	NEOSPECT
EU/1/00/155/001	LUVERIS
EU/1/00/155/002	LUVERIS
EU/1/00/155/003	LUVERIS
EU/1/00/155/004	LUVERIS
EU/1/00/155/005	LUVERIS
EU/1/00/155/006	LUVERIS
EU/1/00/156/001	TRIZIVIR
EU/1/00/156/002	TRIZIVIR
EU/1/00/156/003	TRIZIVIR
EU/1/00/157/001	AZOMYR
EU/1/00/157/002	AZOMYR
EU/1/00/157/003	AZOMYR
EU/1/00/157/004	AZOMYR
EU/1/00/157/005	AZOMYR
EU/1/00/157/006	AZOMYR
EU/1/00/157/007	AZOMYR
EU/1/00/157/008	AZOMYR
EU/1/00/157/009	AZOMYR
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EU/1/00/160/007	AERIUS
EU/1/00/160/008	AERIUS
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EU/1/00/161/008	NEOCLARITYN
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EU/1/00/161/010	NEOCLARITYN
EU/1/00/161/011	NEOCLARITYN
EU/1/00/161/012	NEOCLARITYN
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EU/1/00/162/001	PRANDIN
EU/1/00/162/002	PRANDIN
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EU/1/00/162/006	PRANDIN
EU/1/00/162/007	PRANDIN
EU/1/00/162/008	PRANDIN
EU/1/00/162/009	PRANDIN
EU/1/00/162/010	PRANDIN
EU/1/00/162/011	PRANDIN
EU/1/00/162/012	PRANDIN
EU/1/00/162/013	PRANDIN
EU/1/00/162/014	PRANDIN
EU/1/00/162/015	PRANDIN

HUMAN CENTRALISED PRODUCT AUTHORISATIONS ISSUED OCTOBER 2000 – MARCH 2001

PA Number	Product Name	PA Number	Product Name
EU/1/00/162/016	PRANDIN	EU/1/00/167/004	PREVENAR
EU/1/00/162/017	PRANDIN	EU/1/00/168/001	TENECTEPLASE
EU/1/00/162/018	PRANDIN	EU/1/00/168/002	TENECTEPLASE
EU/1/00/163/001	XELODA	EU/1/00/168/003	TENECTEPLASE
EU/1/00/163/002	XELODA	EU/1/00/169/001	METALYSE
EU/1/00/164/001	NUTROPIN AQ	EU/1/00/169/002	METALYSE
EU/1/00/164/002	NUTROPIN AQ	EU/1/00/169/003	METALYSE
EU/1/00/165/001	OVIDRELLE	EU/1/00/170/001	FASTURTEC
EU/1/00/165/002	OVIDRELLE	EU/1/01/171/001	RAPAMUNE
EU/1/00/165/003	OVIDRELLE	EU/1/01/171/002	RAPAMUNE
EU/1/00/165/004	OVIDRELLE	EU/1/01/171/003	RAPAMUNE
EU/1/00/165/005	OVIDRELLE	EU/1/01/171/004	RAPAMUNE
EU/1/00/165/006	OVIDRELLE	EU/1/01/171/005	RAPAMUNE
EU/1/00/166/001	NEUROBLOC	EU/1/01/172/001	KALETRA
EU/1/00/166/002	NEUROBLOC	EU/1/01/172/002	KALETRA
EU/1/00/166/003	NEUROBLOC	EU/1/01/172/003	KALETRA
EU/1/00/167/001	PREVENAR	EU/1/01/176/001	ZOMETA
EU/1/00/167/002	PREVENAR	EU/1/01/176/002	ZOMETA
EU/1/00/167/003	PREVENAR	EU/1/01/176/003	ZOMETA

HUMAN NEW PRODUCT AUTHORISATIONS ISSUED (MUTUAL RECOGNITION) OCTOBER 2000 – MARCH 2001

PA Number	Product Name	PA Number	Product Name
PA0002/068/001	UFT	PA0521/004/002	OCTAPLAS
PA0012/089/001	GADOVIST	PA0544/032/001	PENTAVAC
PA0012/089/003	GADOVIST	PA0544/033/001	TETRAVAC
PA0012/090/001	GADOVIST	PA0568/007/002	GLICLAZIDE SERVIER MR
PA0012/090/003	GADOVIST	PA0568/013/001	DIAMICRON MR
PA0012/091/001	YASMIN	PA0568/014/001	AERODIOL
PA0013/099/001	ZADITEN	PA0568/015/001	ESTRADIOL SERVIER
PA0013/099/002	ZADITEN SDU	PA0577/035/001	INNOPRIL TABLETS
PA0024/025/004	VIANI 50 EVOHALER	PA0577/035/002	ENALAPRIL MALEATE
PA0024/025/005	VIANI 125 EVOHALER	PA0577/035/003	ENALAPRIL MALEATE
PA0024/025/006	VIANI 250 EVOHALER	PA0577/035/004	ENALAPRIL MALEATE
PA0024/026/004	SERETIDE 50 EVOHALER	PA0577/041/001	ZESGER
PA0024/026/005	SERETIDE 125 EVOHALER	PA0577/041/002	ZESGER
PA0024/026/006	SERETIDE 250 EVOHALER	PA0577/041/003	ZESGER
PA0035/085/003	SINGULAIR PAEDIATRIC	PA0593/022/001	OXYBUTYNIN STADA
PA0108/021/004	FEMOSTON-CONTI	PA0593/024/001	ENAPRIL STADA
PA0108/024/001	FEMUREST-CONTI	PA0593/024/002	ENAPRIL STADA
PA0111/004/001	AMOXYCILLIN	PA0593/024/003	ENAPRIL STADA
PA0111/004/002	AMOXYCILLIN	PA0593/024/004	ENAPRIL STADA
PA0118/046/001	“MINIMS PROXYMETACAINE W/V, EYE DROPS“	PA0736/019/001	TRACUTIL
		PA0748/025/011	EPREX
PA0218/025/006	ACTRAPID INNOLET	PA0795/003/001	DIVISEQ
PA0218/026/006	INSULATARD INNOLET	PA0815/003/001	ORFIRIL
PA0218/029/006	MIXTARD 30 INNOLET	PA0819/004/001	ENALAPRIL-RATIOPHARM
PA0224/022/001	TESTOSTERONE FERRING	PA0819/004/002	ENALAPRIL-RATIOPHARM
PA0281/080/001	COTRON CO-DANTHRAMER SUSPENSION 25/200	PA0819/004/003	ENALAPRIL-RATIOPHARM
		PA0819/004/004	ENALAPRIL-RATIOPHARM
PA0281/080/002	COTRON CO-DANTHRAMER SUSPENSION 75/1000	PA0819/005/001	ENALAPRIL
		PA0819/005/002	ENALAPRIL

HUMAN NEW PRODUCT AUTHORISATIONS ISSUED (MUTUAL RECOGNITION) OCTOBER 2000 – MARCH 2001

PA Number	Product Name	PA Number	Product Name
PA0819/005/003	ENALAPRIL	PA0966/004/002	BY-VERTIN
PA0819/006/001	CAPTOHCT-RATIOPHARM	PA0968/001/001	ALMOGRAN
PA0819/006/002	CAPTOHCT-RATIOPHARM	PA0969/001/001	EDNYT
PA0819/007/001	BISOPROLOL	PA0969/001/002	EDNYT
PA0819/007/002	BISOPROLOL	PA0969/001/003	EDNYT
PA0833/003/003	PROPOFOL ANTIGEN	PA0969/001/004	EDNYT
PA0833/003/004	PROPOFOL	PA0970/028/001	SYMBICORT TURBOHALER 100/6
PA0868/004/001	CALVIDIN	PA0970/028/002	SYMBICORT TURBOHALER 200/6
PA0899/018/001	FORTIPINE LA	PA0976/002/001	BISOPINE
PA0915/006/001	SOPROL	PA0976/002/002	BISOPINE
PA0915/006/002	SOPROL	PA0976/003/001	ACIDOPINE
PA0936/001/001	CYKLO-F	PA0976/004/001	FAMOTIDINE
PA0965/001/001	OMEPRAZOLE-RATIOPHARM	PA0976/004/002	FAMOTIDINE
PA0966/004/001	BY-VERTIN		

HUMAN PRODUCT AUTHORISATIONS WITHDRAWN OCTOBER 2000 – MARCH 2001

PA Number	Product Name	PA Number	Product Name
EU/1/00/142/001	NOVOMIX30	PA0021/005/001	BAYCARON
EU/1/00/142/002	NOVOMIX 30	PA0021/043/001	GAMIMUNE
EU/1/97/038/001	LIPROLOG	PA0023/060/002	INSUM BASAL FOR OPTIPEN CARTRIDGE
EU/1/97/038/002	LIPROLOG		
EU/1/97/038/003	LIPROLOG	PA0023/061/004	INSUMAN 25/75 FOR OPTIPEN CARTRIDGE
EU/1/98/059/001	TROVAN		
EU/1/98/059/002	TROVAN	PA0024/001/015	VENTOLIN EASI-BREATHE INHALER
EU/1/98/059/003	TROVAN	PA0024/005/009	BECOTIDE 50 EASI-BREATHE INHALER
EU/1/98/059/004	TROVAN	PA0024/005/010	BECOTIDE 100 EASI BREATHE INHALER
EU/1/98/059/005	TROVAN	PA0024/005/011	BECOTIDE 250 EASI-BREATHE INHALER
EU/1/98/059/006	TROVAN	PA0032/003/002	ASPRO CLEAR
EU/1/98/059/007	TROVAN	PA0032/031/002	PARACLEAR
EU/1/98/059/008	TROVAN	PA0033/020/001	STAYCEPT
EU/1/98/059/009	TROVAN	PA0033/020/002	STAYCEPT
EU/1/98/059/010	TROVAN	PA0037/008/003	MYAMBUTOL
EU/1/98/059/011	TROVAN	PA0037/021/001	CISPLATIN
EU/1/98/059/012	TROVAN	PA0037/021/002	CISPLATIN
EU/1/98/060/001	TROVAN IV	PA0038/031/001	VIDAYLIN
EU/1/98/060/002	TROVAN IV	PA0040/004/002	FLAGYL COMPAK
EU/1/98/060/003	TROVAN IV	PA0046/009/005	PONDOCILLIN
EU/1/98/072/001	ECHOGEN	PA0046/016/009	BURINEX
EU/1/99/105/001	ROTASHIELD	PA0046/025/001	MINIHEP CALCIUM
PA0007/015/003	ALUPENT	PA0046/025/003	MINIHEP CALCIUM
PA0007/015/005	ALUPENT METERED AEROSOL	PA0046/044/001	PUMP-HEP
PA0013/024/001	HYDERGINE	PA0046/060/001	INNOHEP
PA0013/024/002	HYDERGINE	PA0047/058/004	HUMULIN TM S
PA0013/039/003	SANOMIGRAN ELIXIR	PA0047/059/004	HUMULIN TM I
PA0013/048/001	NAVOBAN AMPOULES	PA0047/065/001	HUMULIN M 10/90
PA0013/048/002	NAVOBAN	PA0047/065/002	HUMULIN TM M1
PA0013/048/003	NAVOBAN	PA0047/065/004	HUMULIN M1 CARTRIDGE
PA0021/002/001	ALRHEUMAT	PA0047/066/002	HUMULIN M2

HUMAN PRODUCT AUTHORISATIONS WITHDRAWN OCTOBER 2000 – MARCH 2001

PA Number	Product Name
PA0047/069/001	HUMULIN TM M3
PA0047/070/001	HUMULIN TM M4
PA0047/070/004	HUMULIN M4 CARTRIDGE
PA0047/074/002	HUMULIN M5 CARTRIDGE
PA0047/074/003	HUMULIN M5 CARTRIDGE
PA0047/084/001	HUMAJECT M1 PEN
PA0047/085/001	HUMAJECT M2 PEN
PA0047/086/001	HUMAJECT M4 PEN
PA0047/087/001	HUMAJECT M5 PEN
PA0047/090/001	HUMULIN M1 PEN
PA0047/093/001	HUMULIN M4 PEN
PA0047/094/001	HUMULIN M5 PEN
PA0050/007/007	REDOXON
PA0050/007/008	REDOXON 200 MG
PA0050/007/009	REDOXON
PA0050/017/007	VALIUM
PA0050/051/002	KONAKION
PA0050/054/001	BECOSYM
PA0050/055/001	BENADON
PA0050/055/002	BENADON
PA0050/056/003	BENERVA
PA0050/056/006	BENERVA
PA0050/068/001	ROFERON-A
PA0050/068/002	ROFERON-A
PA0050/068/003	ROFERON-A
PA0050/068/007	ROFERON-A
PA0050/068/009	ROFERON A
PA0050/068/010	ROFERON A
PA0050/068/011	ROFERON A
PA0050/068/012	ROFERON A
PA0050/068/013	ROFERON A
PA0050/081/003	MANERIX
PA0050/102/001	SECADERM SALVE
PA0050/104/001	ZAM BUK
PA0050/112/001	CORSYM
PA0050/133/001	SYNTARIS HAYFEVER NASAL
PA0050/139/001	BIOVITAL
PA0051/009/001	FULCIN
PA0051/009/002	FULCIN
PA0051/025/002	MYSOLINE
PA0057/064/001	BECLOMETHASONE 50µg
PA0057/064/002	BELCLOMETHASONE 100µg
PA0057/064/003	BELCLOMETHASONE 250µg
PA0059/003/004	TOLECTIN
PA0059/009/007	PEVARYL
PA0059/021/001	TRINOVUM
PA0060/012/001	PARSTELIN
PA0077/129/001	INDAPAMIDE
PA0095/018/001	BENZYL BENZOATE APPLICATION B.P.
PA0108/015/002	DUPHALAC
PA0108/023/001	TEVETEN
PA0118/010/004	GANDA (1+0.2)
PA0126/048/001	CHLORDIAZEPOXIDE
PA0126/093/001	CLONDEPRYL
PA0130/015/004	ISMO RETARD
PA0130/019/001	LORON
PA0185/020/001	XURET
PA0240/001/001	SCINTADREN
PA0277/050/013	INTRON A
PA0277/050/014	INTRON A
PA0290/071/001	DIPIVEFRIN HYDROCHLORIDE OPHTHALMIC
PA0294/013/001	AMOLIN
PA0294/013/002	AMOLIN
PA0294/013/003	AMOLIN
PA0303/001/003	VERAMIL
PA0303/004/002	TOILAX
PA0303/016/001	TEMPOROL
PA0303/026/001	TRIDESTRA
PA0303/030/001	ANDROSTAT
PA0308/007/001	QUINODERM LOTIO-GEL
PA0408/033/001	RIMACID
PA0408/033/002	RIMACID
PA0408/034/001	RIMATHROCIN
PA0408/035/001	RIMADOPA
PA0408/035/002	RIMADOPA
PA0408/036/001	RIMAZOLE CO-TRIMOXAZOLE
PA0408/037/003	RIMAFLOX
PA0441/002/001	VICKS VAPORUB
PA0468/003/002	ALGICON
PA0468/009/002	UBRETID
PA0468/012/002	ANANASE FORTE
PA0473/004/001	ALVEOLEX GRANULES
PA0473/004/002	ALVEOLEX
PA0488/002/001	SOMAGARD (TM DESLORELIN)
PA0592/002/003	HUMAN ALBUMIN
PA0621/005/001	STERI-DROP HYPROMELLOSE
PA0700/005/001	INTROPIN
PA0700/008/004	NARCAN SYRINGE
PA0700/009/001	TRIDIL 500 MCG/ML
PA0700/009/002	TRIDIL 5 MG/ML
PA0732/001/001	CLONTERIC
PA0748/001/002	TYLEX
PA0748/003/003	RISPERDAL
PA0748/007/001	ORTHOFORMS CONTRACEPTIVE
PA0748/008/002	EVOREL SEQUI
PA0748/015/005	NIZORAL
PA0748/024/001	ORAP
PA0748/027/001	OVYSMEN ORAL CONTRACEPTIVE
PA0748/028/001	BINOVUM ORAL CONTRACEPTIVE
PA0748/036/001	ORTHO-DIENOESTROL
PA0748/037/001	PEVARYL
PA0748/045/001	ORTHO-NOVIN 1/50
PA0748/046/001	NEOCON 1/35
PPA0465/008/003	AMOXIL
PPA0465/008/004	AMOXIL FORTE

VETERINARY VACCINE REVIEW PRODUCT AUTHORISATIONS ISSUED OCTOBER 2000 – MARCH 2001

VPA Number	Product Name	VPA Number	Product Name
10857/031/001	MUCOBOVIN	10974/014/001	TORVAC RSV VACCINE

VETERINARY REVIEW PRODUCT AUTHORISATIONS ISSUED OCTOBER 2000 – MARCH 2001

VPA Number	Product Name	VPA Number	Product Name
10920/002/001	DERMCUSAL	10987/055/001	GULLIVERS FLEA AND TICK COLLAR FOR DOGS
10962/014/001	LARGE ANIMAL IMMOBILON		
10962/015/001	LARGE ANIMAL REVIVON		

VETERINARY NEW PRODUCT AUTHORISATIONS ISSUED OCTOBER 2000 – MARCH 2001

VPA Number	Product Name	VPA Number	Product Name
10988/062/001	PULMODOX	10835/008/004	PROGRAM PLUS
10047/013/002	APRALAN G200	10836/001/001	DALMAZIN
10894/005/001	ALFATRIM 40/200	10837/001/001	HEXIDIP
10999/089/001	PARAMECTIN DRENCH	10850/001/001	ERAQUELL
10999/079/001	CALCIVET	10878/001/001	EIRPET FLEA & TICK COLLAR FOR DOGS
10021/040/001	ADVANTAGE 40 FOR CATS		
10021/040/002	ADVANTAGE 80 FOR CATS	10879/013/001	TRIBEX 5%
10021/041/001	ADVANTAGE 40 FOR DOGS	10879/013/002	TRIBEX 10%
10021/041/002	ADVANTAGE 100 FOR DOGS	10879/014/001	IVERMECTIN
10021/041/003	ADVANTAGE 250 FOR DOGS	10881/007/001	BOB MARTINS FLEA POWDER FOR DOGS
10021/042/001	ADVANTAGE 400 FOR DOGS		
10021/039/001	BAYER DOG WORMER	10881/008/001	BOB MARTINS FLEA SHAMPOO FOR DOGS
10960/036/001	FORTEMEC		
10999/087/001	PARAMECTIN	10915/003/001	ARREST (SUSPENSION)
10999/088/001	PARAMECTIN	10915/007/001	GENESIS FOR CATTLE
10831/001/001	OSMONDS LINEOUT	10949/020/001	SEDALIN
10831/002/001	VETIMEC CATTLE	10949/020/002	SEDALIN
10028/041/001	MEGAMECTIN INJECTION	10954/010/001	ABACARE
10028/042/001	MEGAMECTIN	10960/035/001	BOMECTIN INJECTION
10126/066/001	ABINEX FORTE	10966/012/001	BOMATAK WHITE STRIPE
10277/073/001	SLICE	10976/016/001	OXYTETRAJECT
10545/022/001	VULKETAN WOUND GEL	10988/052/002	STABOX 50% OSP PIG
10831/006/001	MASTERMECTIN CATTLE	10989/049/001	CYCLO SPRAY
10835/008/001	PROGRAM PLUS	10996/138/001	VASOTOP
10835/008/002	PROGRAM PLUS	10996/138/002	VASOTOP
10835/008/003	PROGRAM PLUS	10996/138/003	VASOTOP

VETERINARY IMMUNOLOGICAL PRODUCT AUTHORISATIONS ISSUED OCTOBER 2000 – MARCH 2001

VPA Number	Product Name	VPA Number	Product Name
10861/064/001	POULVAC TRT	10996/129/001	NOBIVAC KC

VETERINARY IMMUNOLOGICAL PRODUCT AUTHORISATIONS WITHDRAWN OCTOBER 2000 – MARCH 2001

VPA Number	Product Name	VPA Number	Product Name
10996/106/001	ERYSORB PARVO	10996/121/001	PARVOSORB

VETERINARY PRODUCT AUTHORISATIONS WITHDRAWN OCTOBER 2000 – MARCH 2001

VPA Number	Product Name	VPA Number	Product Name
10019/017/001	ADVOCIN SOL	10021/024/001	TIGUVON 20%
10019/038/001	PENBRITIN VETERINARY INJECTABLE	10021/032/001	KILTIX DOG COLLAR - MEDIUM
10047/006/001	TYLAN 50	10021/032/002	KILTIX DOG COLLAR - LARGE
10895/001/001	DC 500	10021/035/001	ADVANTAGE 40 FOR DOGS
10946/028/001	PENBRITIN VETERINARY INJECTABLE	10021/035/002	ADVANTAGE FOR DOGS 100
10946/028/002	PENBRITIN VETERINARY INJECTABLE	10021/035/003	ADVANTAGE FOR DOGS 250
10946/036/001	PENDICLOX LACTATING COW	10021/036/001	ADVANTAGE 40 FOR CATS
10993/002/001	AMPIJECT	10021/036/002	ADVANTAGE 80 FOR CATS
10999/025/001	EDOMYCIN	10021/038/001	ADVANTAGE 400 FOR DOGS
10996/051/001	CARDIOVET (FOR DOGS)	10028/036/001	PROGRAM
10996/051/002	CARDIOVET (FOR DOGS)	10895/003/001	TRIVERZOLE
10996/051/003	CARDIOVET (FOR DOGS)	10973/002/001	STOCKMASTER WORM DRENCH
10996/051/004	CARDIOVET (FOR DOGS)	10996/117/001	PANACUR EQUINE GUARD
10996/051/005	CARDIOVET (FOR DOGS)	10857/021/001	IVOMEC (DRENCH FOR CATTLE)
10444/072/001	WINTER DIP 200	10996/018/001	PROGESTERONE
10962/020/001	COPAVET	10962/065/001	D 50 NO 8
10962/025/001	MULTIVET	10999/030/001	KETOSAID
10962/026/001	MULTIVET	10962/064/001	CALC NO 2
10007/032/001	METRASIL	10962/066/001	MS 25 NO 9
10007/033/001	METRASIL ORAL	10444/068/001	TIXOL
10040/039/002	KETOFEN 1%	10946/031/002	CLAMOXYL PALATABLE
10277/001/001	FINABIOTIC	10962/063/001	CALC NO 5

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