

European Directorate for the Quality of Medicines (EDQM)

Annual Report of Activities - 2002

The European Directorate for the Quality of Medicines has two main areas of responsibility:

- 1) The European Pharmacopoeia, including the procedure for Certification of Conformity of monographs of the Pharmacopoeia and international relations,
- 2) The European network of Official Medicines Control Laboratories (OMCLs).

I. THE EUROPEAN PHARMACOPOEIA

PARTIES TO THE CONVENTION AND OBSERVERS

The European Pharmacopoeia Convention has been signed by 31 parties: the European Union and the following countries: Austria, Belgium, Bosnia and Herzegovina, Croatia, Cyprus, The Czech Republic, Denmark, Estonia, Finland, "The Former Yugoslav Republic of Macedonia", France, Germany, Greece, Hungary, Ireland, Iceland, Italy, Latvia, Grand-Duchy of Luxembourg, Norway, The Netherlands, Portugal, Serbia and Montenegro, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, The United Kingdom.

The number of observers increased by one state to 17 after Senegal's application was approved, namely the WHO, 7 European states (Albania, Bulgaria, Lithuania, Malta, Poland, Romania, Ukraine) and 9 non-European states (Algeria, Australia, Canada, China, Malaysia, Morocco, Senegal, Syria and Tunisia).

A NEW BUILDING

On 21 February 2002, the Committee of Ministers of the Council of Europe decided to open the procedure for construction of two new Council of Europe buildings near the Palais de l'Europe, the headquarters of the Council of Europe, in the very heart of Strasbourg's European district to accommodate the expansion of its activities - one to meet the organisation's general requirements, the other entirely dedicated to the growth of the EDQM/European Pharmacopoeia.

The City of Strasbourg gave the Council of Europe the best possible conditions for doing this by providing two sites, close to the Palais de l'Europe and the European Court of Human Rights.

The selection of design teams began with an international architecture competition. This phase was

completed at the end of 2002 with the Jury's selection of the winning team in the competition for each of the buildings. A new phase has now begun, which will allow Aukett-Europe, the winning team, to finalise the two projects.

GENERAL ACTIVITIES

The European Pharmacopoeia Commission continued to update the 4th Edition, which entered into force on 1 January 2002. Three supplements (4.2, 4.3 and 4.4) were published in 2002, and implemented on 1 July 2002, 1 January 2003 and 1 April 2003, respectively. The Commission decided that the 4th Edition will be completed in 2004 with a maximum of 8 non-cumulative supplements. The 5th Edition will be published in the summer of 2004 and enter into force on 1 January 2005.

At its three Sessions in March, June and November 2002, the European Pharmacopoeia Commission adopted 262 monographs, of which 191 were revisions and 71 were new texts. The Commission also adopted 25 chapters and general methods, of which 21 were revisions and 4 were new texts. Overall, 288 texts were adopted (212 revised texts). The number of monographs prepared by the procedure for adaptation of national monographs or procedure III increased (19 in 2002 compared with 17 in 2000). The number of documents produced (new, revised) is slightly higher (3150 compared with 3050 in 2001). The new monographs can be broken down as follows: 45 on inorganic or organic products, 6 on vaccines, 2 on biologicals, 13 on herbal drugs or preparations, 2 on homoeopathic preparations and 3 on radiopharmaceutical preparations.

A total of 315 days was devoted to meetings in 2002. This includes the three plenary sessions of the Commission and the corresponding preparatory meetings, the meetings of the Groups of Experts (114) and those of the *ad hoc* Working Parties (12). This total also includes the participation of members of the Secretariat in various other meetings: meetings of the Pharmaceutical Committee (Brussels) on medicines for human and veterinary use, meetings of the various working parties of the Committee for Proprietary Medicinal Products and of the Committee For Veterinary Medicinal Products of the EMEA (nearly 20 meetings such as those of the Quality working

party, Biotech working party, Veterinary Immunology working party, Inspectors working party and Herbal Medicinal Products working party). Members of the Secretariat also attended meetings of the Pharmacopoeial Discussion Group for International Harmonisation with Japan and the United States, preparatory meetings of the Quality Working Party for ICH6, meetings of VICH working parties and meetings to organise and take part in international scientific conferences and congresses.

The following activities are particularly noteworthy:

4TH EDITION

FORM

The 4th Edition is now published in printed form, as a CD-ROM and online (Internet).

CONTENT

a. Revision of the monograph on Substances for pharmaceutical use / Impurities

On 19-20 December 2001, the European Pharmacopoeia Commission organised a seminar on control of impurities in active substances that dealt not only with current revisions through ICH, but also with the application of the new monograph on substances for pharmaceutical use.

Following the seminar, the European Pharmacopoeia Commission decided at its March 2002 session to make a thorough review of:

- monographs where impurities control could be enhanced, notably by improved chromatographic techniques,
- monographs that do not have an Impurities section or where the section requires improvement,
- terminology and the presentation of the monographs, to improve clarity.

An action plan will be drawn up to deal with these, in co-operation with regulatory bodies, notably to set priorities.

IMPURITIES section of monographs

The Impurities section in monographs is an important feature that allows all users to be aware of the degree of control of impurities provided and the nature of the impurities that may occur.

Wherever possible the section is enhanced by division of the list into 'Qualified impurities' (now renamed 'Specified impurities') and 'Other detectable impurities'. The content of this section and the subdivisions is based on information obtained during elaboration.

Monograph specifications are based on batch analysis of active substances for products authorised in Europe and the qualification levels of the impurities. Acceptance criteria are stated for impurities found in

these batches. Such impurities are qualified either as a result of regulatory approval of the products by the competent authority or by use, or both. Manufacturers who co-operate in drafting of monographs may also provide information on qualification of impurities and should be encouraged to do so in all cases.

An Impurities section with full information related to products authorised at the time of preparation of the monograph is an essential part of a public standard if it is to be used effectively. This will require co-operation with marketing authorisation bodies, who are able to verify the statements on qualified impurities published in Pharmeuropa. This co-operation should form part of the future action plan on impurities.

Where a monograph has a fully informative Impurities section, this will be kept up to date by systematic application of the certification procedure. Marketing authorisation bodies will then have at all times an effective standard as the basis for approvals.

Wherever full information is available, the monograph can be aligned with the ICH approach:

- Limitation of qualified impurities to at most the level at which they are qualified (to be stated in the Impurities section),
- Limitation of other impurities to not more than the identification threshold, e.g. 0.1 per cent.

Identification of impurities

The approach outlined above poses the question of identification within the framework of monographs, particularly for those who have to apply the public standard without having background information on the monograph tests and the impurity profiles covered. At present a hierarchy of methods is applied for identification of impurities:

1. Using chemical reference substances.
2. Using relative retention.
3. Using representative chromatograms.

The application of these options will in future be further codified and described fully in the information chapter on impurities.

Information chapter on impurities

A clear conclusion of the EDQM Seminar on impurities in December 2001 was the need for an information chapter on impurities to explain how the various parts of the Pharmacopoeia are applied to ensure control of impurities. The information chapter is intended to clarify the use of monographs by:

- Pharmaceutical manufacturers;
- Assessors in marketing authorisation bodies;
- Inspectorate;
- Official medicines control laboratories;
- Suppliers of the pharmaceutical industry (chemical industry).

This general chapter was adopted by the Commission in November 2002. It is published for information in the present issue of *Pharmeuropa*.

Description of chromatographic systems

An improvement in the description of chromatographic systems and performance testing will facilitate the changes that the Commission wishes to make. A project for this has been initiated.

Scope

Monographs are designed to cover impurity profiles from all current routes of synthesis. This leads to complex LC tests whereas a simpler test could be used for a given route of synthesis/impurity profile. The single test has advantages for laboratories that do not have background information on the route of synthesis and expected impurity profile. The European Pharmacopoeia Commission will now explore the possibility of linking the test to the impurity profile. This will be acceptable if the Impurities section gives the information needed to choose the appropriate test system.

Terminology

At present, the terminology for impurities used in monographs differs in some parts from that in ICH guidelines. It will be aligned as far as possible with the guidelines (see Information chapter on impurities).

b. International harmonisation with the pharmacopoeias of the United States and Japan

Representatives of the United States Pharmacopoeia, the Japanese Pharmacopoeia, the European Pharmacopoeia and the WHO met in Brussels on 3-7 February 2002 and in Washington on 9-12 September 2002 at the same time as the ICH meetings, which was useful for exchanging information on the progress of work.

Summary of agreements on harmonisation:

- 5 chapters signed off on the testing of products of biotechnology: amino acid analysis, capillary electrophoresis, isoelectric focusing, protein determination, peptide mapping;
- test for sterility signed off (apart from some information in footnotes); this is one of 11 high-priority chapters required by ICH partners for the application of guideline Q6A. This agreement brings the number of signed off texts to 5;
- 2 new monographs signed off on excipients: anhydrous lactose and lactose monohydrate.

These texts will subsequently be recognised and formally implemented in accordance with the legal system of each partner.

The harmonisation procedure and its various stages have been re-assessed so that it can be streamlined to

speed up the international harmonisation process. It will soon be published on the Internet.

A hearing was held for the associations of the pharmaceutical and chemical industries (PhRMA, JPMA, EFPIA, IGPA, AHI, AESGP and representatives of manufacturers and users of excipients IPEC Europe, Americas and Japan). Following this hearing, the three pharmacopoeias decided to each integrate a “user friendly” presentation of the texts that would allow the harmonised and therefore “interchangeable” parts of each pharmacopoeia to be easily identified.

MONOGRAPHS ON NEW ACTIVE SUBSTANCES

The European Pharmacopoeia Commission has decided to schedule its work on active substances so that monographs are produced a few years before the patent expiry date, thus making it possible to assess dossiers on generics on the basis of existing monographs and related certificates of suitability.

STANDARD TERMS

A new revision of the list of standard terms was published in 2002 with the addition of a new language (Macedonian) and 3 new terms for medicines for human and veterinary use.

COMMUNICATIONS AND PUBLIC RELATIONS

The European Pharmacopoeia Commission reinforced its communications activities by organising the following international scientific conferences, seminars, workshops, training sessions and visits of the EDQM.

— **International symposium on Excipients: Classical quality requirements and functionality related testing, Brussels (Belgium), 4-5 April 2002**

As part of its international activities, the European Directorate for the Quality of Medicines of the Council of Europe (EDQM) organised this scientific symposium in collaboration with IPEC (International Pharmaceutical Excipients Council). 115 participants from 25 countries (Europe, USA, Japan, India and South Korea), from academia, national and supra-national licensing authorities and manufacturers attended the symposium.

The aim of the symposium was to make excipient suppliers and manufacturers familiar with trends in this field and to provide an opportunity, via workshops, to give feedback to ensure that future excipient monographs are compatible with industrial practice and needs as well as regulatory requirements. Present practice and licensing requirements in Europe, Japan and the United States of America (USA) were presented and the important role of IPEC in the preparation of specifications and introduction of quality systems was highlighted.

— **Symposium on the Replacement, reduction and refinement of the use of animals in the QC of vaccines, Strasbourg (France), 7-8 November 2002**

This scientific symposium within the VACTRAIN Project, sponsored by the European Commission was organised by the EDQM; it brought together the main research centres, official control laboratories and the vaccine manufacturers. It was attended by 80 persons from 16 countries (including EU and CEEC countries, Canada, Israel and the United States). This action of exchanging viewpoints of all interested parties is an important part of an international consultative process promoting continued progress in international harmonisation and facilitating free movement of vaccines while guaranteeing public health.

It was important to survey recent developments in the field of alternatives to the use of animals in the quality control of vaccines for both human and veterinary use and to examine the progress made in the 3Rs (Replacement, Reduction, Refinement of animal testing). Lectures and workshops reviewed present possibilities and future orientations and priorities.

— **Training session for users of the European Pharmacopoeia “How to use the European Pharmacopoeia – case of chemical products” 12-13 December 2002**

At the request of its users, the EDQM initiated in 2002 a cycle of 4 training sessions to convey the new concepts in the 4th Edition of the European Pharmacopoeia to its users.

50 participants from 13 countries (Europe, Korea, India and Taiwan) attended the sessions.

— **Visits and meetings at the EDQM: VICH (March 2002); Académie française de Pharmacie (March 2002); Chinese Licensing authorities (April 2002); Midwest Compendial Group (October 2002); Direction Générale de la Concurrence, de la Consommation et de la Répression des Fraudes DGCCRF [French directorate for action against fraud]; European Generics Association (EGA) and Japanese Pharmacopoeia (December 2002)**

The EDQM organised these visits and meetings on its premises as part of its regular exchanges with its partners. These meetings encourage the sharing of views and facilitate the EDQM's work in the area of international harmonisation.

— **Professional exhibitions**

The EDQM participated in the following professional exhibitions and meetings: *Drug Information Association* (DIA) in March in Basel (Switzerland), *Congresso y Exposicion de Tecnologia Farmaceutica* (ETIF) in October in Buenos Aires (Argentina), DIA in October

in Goa (India) and *American Association of Pharmaceutical Scientists* (AAPS) in November in Toronto (Canada).

These exhibitions provided an opportunity to meet users of the European Pharmacopoeia: from Europe, South America, North America and India. The EDQM presented the 4th Edition, its publications and services to visitors through stands, oral presentations or posters.

INTERNET SITE <http://www.pheur.org>

The EDQM also continued to develop its Internet site. This site helps implement the EDQM's transparency policy by making the following available to its users in real time:

- the summary of decisions of the Commission;
- the resolutions of the Public Health Committee on the suppression of monographs and the implementation dates of supplements;
- the programme of work of the Commission: a specialised database allows users to find out whether a given substance or general method is on the Commission's programme of work, how far the work has advanced and the implementation date of the official text; this database also includes the names of the reagents and chromatography columns that were considered suitable when the monograph was elaborated, if the information exists; it is possible to search the database by the number or the English, French or Latin name of the monographs and general methods;
- the list of adopted reference substances, the corresponding safety data sheets, the conditions of use of substances and preparations, and the public information on certificates of suitability are also published in 2 databases that can be accessed from the site.

PROVIDING REFERENCE SUBSTANCES AND PREPARATIONS

87 new chemical reference substances (or spectra) and biological reference preparations were adopted during the year, bringing the number of substances available to users of the European Pharmacopoeia to 1481. Extensive collaborative studies were required for 37 of these substances to determine the content of the substances used in the assays. In addition, 104 substances were replaced and the European Pharmacopoeia laboratory regularly monitored 164 substances and carried out quality control tests during the production of 444 batches. The number of chemical reference substances and biological reference preparations distributed to users continued to climb: 98 463 in 2002 (82 086 in 2001) and the number of orders increased from 12 149 to 13 832. Taking bulk substances selected by the European Pharmacopoeia Commission for use as reference substances, the

Production Unit of the EDQM prepared 427 batches (filling more than 114 386 vials) and 17 batches by lyophilisation, filling 23 221 vials.

PREPARATION AND DISTRIBUTION OF SAMPLES

2190 (2125 in 2001) new samples were received by the EDQM this year. The total number of samples in stock was 13 927. Nearly 695 studies were carried out by the European Pharmacopoeia laboratory to compare or check the analytical methods proposed for new monographs or for revisions of monographs at the request of the groups of experts of the Commission. The Production Unit had to prepare 1858 samples for these laboratory studies to check the quality of the substances available on the market (multisource substances for the adaptation of national monographs procedure) or to check the robustness of national monographs proposed as draft European monographs. In addition, nearly 4998 samples were prepared for distribution to the various experts of the European Directorate for the Quality of Medicines (for the elaboration of monographs and the organisation of collaborative studies, market surveillance studies, biological standardisation projects).

BIOLOGICAL STANDARDISATION

The Biological Standardisation Programme (BSP, Division IV) continued to pursue the following goals in the area of standardisation of biologicals:

- The establishment of European working standards,
- The development and validation of new analytical methods,
- The validation of alternative methods in the framework of the 3R concept (i.e. the **R**efinement, **R**eduction and **R**eplacement of animal experiments).

To this end, projects are run and collaborative studies are performed involving all interested partners (e.g. OMCLs and manufacturers). Participation in the collaborative study is not restricted to members or observers of the Ph. Eur. Commission. The results of the collaborative studies are published in *Pharmeuropa-Bio* which, since 2001, is referenced in MEDLINE and Index Medicus of the National Library of Medicines (USA).

Since its start in 1992, 64 BSP projects were initiated and 66 BRPs or replacement batches are being/have been established.

In 2002, the following projects have been started or pursued:

- Establishment of **inactivated poliomyelitis vaccine (IPV)** BRP batch 2,
- Establishment of **oral poliomyelitis vaccine (OPV)** BRP batch 3,

- Establishment of **hepatitis A vaccine** BRP (type B) batch 2,
- Establishment of **rDNA hepatitis B vaccine** BRP (methods A and B) batch 2,
- Reporting phase for **tetanus vaccine (human use)** BRP batch 2 and WHO 3rd International Standard,
- Validation of serological method for potency assay of **diphtheria vaccine**,
- Establishment of diphtheria toxin BRP for test for absence of residual toxin in **diphtheria vaccine**,
- Reporting phase for **acellular pertussis vaccine, mouse anti-serum** BRP,
- Validation of HPLC method as alternative to bio-assay for **pertussis toxin**,
- Standardisation of test on “Molecular Size Distribution” of **haemophilus influenzae type B conjugate vaccine**,
- Reporting phase for antisera BRPs for potency assays of **equine influenza vaccine**,
- Validation of *in vitro* potency assay for **Newcastle Disease Vaccine**,
- Establishment of BRPs for **Newcastle Disease Vaccine**,
- Establishment of **mycoplasma reference strains** BRPs,
- Validation of *in vitro* potency assay for **Clostridium perfringens vaccine**,
- Establishment of BRPs for *in vitro* potency assay of **Clostridium perfringens vaccine**,
- Establishment of BRP batch 4 for **rabies vaccine for veterinary use**,
- Establishment of **anti-D immunoglobulin** BRP,
- Establishment of BRP for prekallikrein activator (PKA),
- Establishment of BRP for normal human plasma for assay of **SD-plasma and fibrin sealant** kits
- Establishment of BRP for **human coagulation factor VII** concentrate,
- Establishment of BRP for **B19 virus spiked plasma** for NAT testing,
- Establishment of BRP batch 2 for **low molecular mass heparin**,
- Establishment of an HPLC potency assay for **interferon alfa2**,
- Establishment of BRP batch 2 for **rDNA erythropoietin**.

The studies led to the adoption of the following reference preparations in 2002:

- Oral poliomyelitis vaccine (OPV) BRP batch 3,
- Hepatitis A vaccine BRP (type B) batch 2.

The project aiming at the establishment of an HPLC potency assay for interferon alfa2 was also concluded in 2002. The data from the concluded collaborative studies were published in *Pharmeuropa-Bio* 2002-1.

The project aiming at the establishment of the mycoplasma reference strains BRPs for validation of media and for test for inhibitory substances is performed in the context of international harmonisation (VICH). The resulting BRPs will be made available globally to all interested parties.

10 new projects were started. As in previous years, co-operation with international partners continued; projects to establish common standards were set up whenever possible with the WHO Expert Committee on Biological Standardisation (ECBS); examples include the establishment of standards for PKA and low molecular mass heparin. The project for the establishment of the anti-D immunoglobulin reference material was a tripartite project, conducted together with WHO and FDA/CBER. As a result, a common global reference preparation will be available in 2003.

A workshop on the quality control of OPV was jointly organised by WHO, EDQM (BSP) and AFSSAPS and took place in Lyon (20-22 November 2002). A practical workshop for histopathologists who read slides from the monkey neurovirulence test was organised in parallel. A meeting report will be submitted to the WHO ECBS. The conclusions and recommendations from the meeting will also be considered by the Ph. Eur. during the revision of the OPV monograph, thereby promoting international harmonisation in the area of biological standardisation and control.

CERTIFICATION OF SUITABILITY OF MONOGRAPHS OF THE EUROPEAN PHARMACOPOEIA

258 new applications (including 42 for products with TSE risk) and 180 requests for revision were received, in addition to the updates with respect to the publication of the 4th Edition. 879 new certificates were granted or revised (579 for chemical products and 300 for products with TSE risk).

In total, 1207 certificates have been granted since the procedure became operational and these are regularly up-dated.

Steering Committee

The procedure illustrates the exemplary collaboration between the partners, namely the working parties of the CPMP, CVMP, and the European Pharmacopoeia Commission, which while consulting Industry (EFPIA, AESGP, CEFIC, FEDESA, EGEE, EAPPI,

IPEC), worked together to find practical solutions to improve quality assurance without complicating the administrative procedures for evaluation. The licensing authorities have clearly expressed their preference for the certification procedure when there is a European Pharmacopoeia monograph (Guideline on Requirements in relation to active substances and implementation of directives 2001/82/EC and 2001/83/EC).

The 3 Cs (Consultation, Co-ordination, Co-operation) that characterise the procedure are implemented by a Steering Committee consisting of the Chairs of the European Pharmacopoeia Commission, the Joint CPMP/CVMP Quality Working Party, the CPMP Biotech Working Party and CVMP Veterinary Immunology Working Party and representatives of the Commission of the European Communities, the EMEA and the EDQM. The Steering Committee met 4 times this year thus ensuring that decisions involving licensing, pharmacopoeia and certification are taken in a coherent manner.

Following exchanges with the "Herbal Medicinal Products" working party (EMEA), it was decided to extend the procedure to herbal preparations.

In addition to the Steering Committee, which is responsible for decisions on general policy, 2 technical advisory boards have been set up, one for chemical substances and the other for TSE risk substances. They consist of expert rapporteurs who participate in the evaluation of dossiers. These boards deal with any technical or scientific questions raised by the rapporteurs.

TRANSLATIONS AND PUBLICATIONS

It should be noted that the European Pharmacopoeia is published in both official languages of the Council of Europe, namely English and French. The EDQM therefore has its own specialised translation service. In 2002, 302 texts were translated from English to French and 226 from French to English.

In the area of publications, the year 2002 issues of *Pharmeuropa* comprise a total of 771 pages in French and 734 pages in English, *Pharmeuropa Bio* (issues in English only) comprised 108 pages, and the 4th Edition of the European Pharmacopoeia comprised 4164 pages in French and 3836 in English. The 3 supplements 2002 of the 4th Edition comprise 1030 pages in French and 950 in English.

The electronic version of the European Pharmacopoeia 4th Edition has been improved with the use of new software. This CD-ROM makes it possible to view all 1640 monographs, 220 general methods of analysis and 2000 reagents. The CD-ROM has a hierarchic table of contents and a keyword search. Hyperlinks in the text of a monograph give access to the relevant general methods and reagents and to an online database for reference substances.

An "online" electronic version was launched with the 4th Edition; it is available in 3 versions: a single-user version, an intranet version and an Internet version. All the versions use a Web browser interface to present the information. A demo version of the Internet version can be found at <http://online.pheur.org/demo.htm>.

II. NETWORK OF OFFICIAL MEDICINES CONTROL LABORATORIES (OMCLS)

The network (set up in 1995) is open to all countries that have signed the European Pharmacopoeia Convention and also to European observers at the European Pharmacopoeia Commission.

There are 2 levels of collaboration:

- general activities involving all the member states of the Convention and the observer states; all the official control laboratories are invited to meetings and are asked to participate in collaborative studies in all the areas of general interest,
- activities restricted to the European Economic Area.

A number of activities take place within the more restrictive regulatory framework for medicines in the European Union, notably those connected to the centralised Community procedures.

This approach means that know-how can be shared and all parties can progressively attain the same level of quality assurance while respecting each party's constraints.

GENERAL CO-OPERATION BETWEEN OFFICIAL CONTROL LABORATORIES

An annual meeting of the plenary network brings together the various participants and allows them to summarise the year's activities and decide on an action plan for the coming year. It is organised by one of the members of the network on a rotating basis so that the partners get to know each other better and interact more. The seventh annual meeting was attended by 150 representatives from 48 laboratories from 31 countries and was held on 13-16 May 2002 in Bilthoven (The Netherlands). A representative of the EMEA was also present for direct contact with this Agency.

Much work was done in the area of quality assurance systems. This resulted in the adoption of a programme to harmonise the quality assurance policies of all the members of the network and a specific programme for interlaboratory audits and for visits to provide assistance.

In October 2002 an evaluation meeting for the Mutual Visit/Audit programme was held in Strasbourg with the participation of experts. 48 experts from 28 different countries. It should be recalled that since 1999, 21 Mutual Joint Visits and 9 Mutual Joint audits have been performed at individual OMCL sites by independent auditors recruited from a pool of highly

specialised experts within the Network specifically trained for the purpose (European guidelines and ISO 17025).

Proficiency Testing Studies (PTS) are now being carried out regularly and this year 6 studies were organised in the physico-chemical area with the participation of 49 national laboratories on average while in the biological area 4 studies were organised, involving 14 national laboratories on average.

In addition, general studies on market surveillance of products commercialised in countries in the network were organised for the following preparations, with the participation of 12 national laboratories on average:

- Erythromycin base and salts,
- Valerian root,
- Liquorice root,
- Linseed: cadmium content.

As an important outcome of the Linseed study it was found that 28 per cent of the samples analysed contained more than 0.3 ppm of cadmium (Maximum Permissible Concentration according to WHO). As a follow-up of the study, the European Pharmacopoeia Commission agreed to revise the monograph to include a limit for the cadmium content.

ACTIVITIES RESTRICTED TO THE EUROPEAN ECONOMIC AREA

These were the following:

I – Official batch release of biologicals

The annual meetings for batch release of blood and plasma derivatives and vaccines were held in conjunction with the annual meeting for the OMCL general network. The meeting took place in Bilthoven, The Netherlands on 13 May 2002. This successful meeting included not only the traditional confidential exchange of information between OMCLs involved in batch release on issues related specifically to batch release but also the opportunity to interact with colleagues in a broader context for the mutual exchange of expertise and experience on common issues.

Review of OMCL batch release activities since 2001 for both blood and vaccines and specific scientific presentations highlighted:

- development of methods and procedures to encourage the reduction of animal use for routine batch release activity;
- continued use of the communication network, specifically the rapid information system, to exchange information on product-related issues, thus improving transparency and the efficient resolution of common problems;
- evaluation of the need for standardisation of methods and reference preparations through collaborative studies, in particular for hepatitis A and B vaccines;

- effective implementation of Quality Assurance systems in the OMCL network to improve mutual confidence amongst members.

Common procedures for batch release of biologicals

Proposed revisions to annexes III and IV of the Administrative Procedure for Batch Release of Biologicals were adopted. In addition, all of the guidelines and the administrative procedure have been updated to include the new references to Community directive 2001/83/EC and to the new and revised monographs of the European Pharmacopoeia.

These guidelines are available in a guide that was published by the EDQM at the end of December 2002 and on the EDQM Web site.

As the mutual recognition agreement between Switzerland and the EU (implementation in June 2002) includes the recognition of official batch release testing for biologicals, Switzerland was invited for the first time to participate in these meetings for confidential exchanges of data on vaccines and blood products.

Blood products and plasma derivatives

The meeting of the network for batch release of human blood and plasma derivatives took place on 13 May 2002. Requirements for the release of preparations containing protein C have been included in a revised version of the guideline on clotting factor concentrates, plasma inhibitor concentrates and fibrin sealants; this guideline has been approved for external consultation.

Human Vaccines

The meeting of the network for batch release of human vaccines took place on 13 May 2002. 2 new guidelines on vaccines were adopted:

- Meningococcal C polysaccharide protein conjugate vaccine;
- Multivalent pneumococcal polysaccharide conjugate vaccine.

3 other guidelines on yellow fever vaccines, meningococcal (multivalent) vaccines and hexavalent vaccines were approved for external consultation.

Immunological Veterinary Medicinal Products (IVMP)

At a general meeting of OMCLs involved in evaluation of IVMPs, held in Strasbourg on 15 October 2002, the participants discussed the means to improve harmonisation and transparency of the official control authority batch release system (OCABR) in the EU/EEA as implemented under the current legislation. Various proposals for action were made to improve mutual recognition, including the development of a number of specific guidelines, mainly for viral vaccines. A revision of the administrative procedure for OCABR of IVMPs was also undertaken with the Commission of the European Communities.

II - Market surveillance for products with a centralised Community marketing authorisation for European Union countries

After a contract was signed in June 1999 between the EMEA and the EDQM, an annual programme was implemented for the surveillance of all the medicines that had received a Community marketing authorisation 3 years before and of any medicines identified as requiring urgent attention by the CPMP or CPVP.

For these medicines, the network decided in its procedure that sampling from 3 different countries on average would be sufficiently representative of the European Union market. Samples are collected in principle throughout the medicines distribution system (manufacturers, wholesalers, community or hospital pharmacies) by national inspectors. Samples of each product are sent to the EDQM, which distributes them to 2 national control laboratories which carry out the required laboratory tests at the same time.

The analyses and results are collected by the EDQM. A report is established and sent to the EMEA for any follow up that might be needed. The system is now operating satisfactorily.

The annual meeting of the market surveillance programme for products with a centralised Community marketing authorisation took place on 3 December 2002 to discuss problems related to the testing programme.

The testing programme for 2002 included 30 medicines (10 products on the A-biotech list and 20 on the B list) and involved over 150 samples which were distributed to the various national official control laboratories for study according to well established protocols derived from marketing authorisation dossiers.

The results, which had been sent to the CPMP or CPVP (EMEA), were used to make sure that the quality of these substances was good and to check the reproducibility of the methods of analysis. The future accession of the CADREAC countries to the system has been discussed and some preparatory actions have been agreed during a break-out session dedicated to this item during the Annual OMCL meeting. A representative of CADREAC OMCLs could already participate in the Annual CAP meeting in December 2002.

Discussions are taking place so that samples collected from these central and eastern European countries can be included in the studies.

The testing programme for 2003, which covers 39 medicines, was discussed.

Progress was also made in the field of the medicines licensed by the Mutual recognition procedure (MRP products). An enlarged trial phase with OMCLs from 10 countries has been initiated in order to apply the principle of work-sharing also in this field of growing interest.