The European Directorate for the Quality of Medicines (EDQM) Annual Report of Activities - 2003

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

1) the European Pharmacopoeia, including the procedure for Certification of Suitability of monographs of the Pharmacopoeia and international relations,

2) the European network of Official Medicines Control Laboratories (OMCLs).

1. THE EUROPEAN PHARMACOPOEIA

PARTIES TO THE CONVENTION AND OBSERVERS

Now that Romania is a member state, the European Pharmacopoeia Convention has been signed by 32 parties: the European Union and the following countries: Austria, Belgium, Bosnia and Herzegovina, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Luxembourg, Netherlands, Norway, Portugal, Romania, Serbia and Montenegro (formerly Yugoslavia), Slovak Republic, Slovenia, Spain, Sweden, Switzerland, “The Former Yugoslav Republic of Macedonia”, Turkey, United Kingdom.

There are also 16 observers, namely the WHO, 6 European states (Albania, Bulgaria, Lithuania, Malta, Poland, Ukraine) and 9 non-European states (Algeria, Australia, Canada, China, Malaysia, Morocco, Senegal, Syria and Tunisia).

GENERAL ACTIVITIES

The European Pharmacopoeia Commission continued to update the 4th Edition, which entered into force on 1 January 2002. Four supplements (4.5, 4.6, 4.7 and 4.8) were published in 2003 and implemented on 1 July 2003, 1 January 2004, 1 April 2004, and 1 July 2004.

At its three Sessions in March, June and November 2003, the European Pharmacopoeia Commission adopted 219 monographs, of which 148 were revisions and 71 were new texts. The Commission also adopted 27 chapters and general methods, of which 20 were revisions and 7 were new texts. Overall, 246 texts were adopted (168 revised texts). The number of monographs prepared by the procedure for adaptation of national monographs or procedure III decreased slightly (14 in 2003 compared with 19 in 2002). The number of documents produced (new, revised) was stable (3150 in 2003). The new monographs can be broken down as follows: 59 on inorganic or organic products, 8 on vaccines, 5 on biologicals, 3 on herbal drugs or preparations, 1 on a homoeopathic preparation and 2 on radiopharmaceutical preparations.

A total of 196 days was devoted to meetings in 2003. This includes the three plenary sessions of the Commission and the corresponding preparatory meetings, the meetings of the Groups of Experts (46) and those of the ad hoc Working Parties (20). 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 (CPMP) and of the Committee For Veterinary Medicinal Products (CVMP) of the EMEA (nearly 20 meetings such as those of the Quality working party, Biotech working party, Veterinary Immunological products 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.

International harmonisation with the pharmacopoeias of the United States and Japan

Representatives of the United States Pharmacopeia, the Japanese Pharmacopoeia, the European Pharmacopoeia and the WHO met in Tokyo on 3-6 February 2003, in Brussels on 14-18 July 2003 and in Osaka on 11-14 November 2003 at the same time as the ICH meetings, which was useful for exchanging information on the progress of work.

Summary of agreements on harmonisation:

— chapter signed off on specific surface area;
— 12 monographs signed off on excipients:
  - 7 new: Hypermellose, Methylcellulose, Saccharin, Saccharin sodium, Saccharin calcium, Sodium starch glycolate, Talc;
  - 5 revised: Carmellose sodium, Cellulose acetate, Anhydrous citric acid, Citric acid monohydrate, Sodium chloride.

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 is published on the Internet site.


Annex 1 of Directive 2001/83/EC has been revised and adopted under the reference: Directive 2003/63/EC. This new directive maintains the mandatory character not only of specific monographs but also of general monographs and monographs on dosage forms in the European Pharmacopoeia for marketing authorisation dossiers on medicines for human use. It also refers to the use of certificates of suitability (active substance, excipients and TSE) of European Pharmacopoeia monographs when preparing marketing authorisation dossiers (see module 3, paragraph 2, points (5), (7) and (9)).

In addition, biological products, plasma derivatives and vaccines must also comply with the corresponding monographs of the European Pharmacopoeia. This is also the case for herbal medicines.

STANDARD TERMS

A revision of the list of standard terms was published on the Internet site with the addition of 2 new languages (Lithuanian and Latvian). In addition, a pilot phase is currently in place allowing the users to accede to an electronic list of standard terms from a specialised database. The addition of the Maltese language is under study in order to cover all the official languages of the 10 new countries acceding to the European Union.

COMMUNICATIONS AND PUBLIC RELATIONS

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

Symposium on cell and gene therapy products: strategies to improve the quality of the products and the safety of patients, Strasbourg (France), 24-25 February 2003

This scientific symposium was held on 24-25 February 2003 at the request of the European Pharmacopoeia Commission, with the close co-operation of the Commission of the European Communities and the European Agency for the Evaluation of Medicinal Products (EMEA). The aim of the symposium was to present the latest developments concerning these new therapies and the new quality and safety issues arising from these therapies.

Bringing together all the interested parties to exchange views in this way is part of an international consultative process to promote international harmonisation and facilitate the use of cell therapy and gene therapy products under conditions that ensure the protection of public health.

This symposium marked the official opening of the European Pharmacopoeia Commission’s work programme in these areas, which will be undertaken by experts appointed to two working parties that will meet regularly: the Gene Therapy Products Working Party (GTP) and the Cell Therapy Products Working Party (CTP).

The symposium was attended by 153 participants from 22 countries (mostly European countries but also Taiwan, South Korea, China, the United States and Canada).

Symposium on Foot-and-mouth disease vaccines, Strasbourg (France), 17-18 March 2003

Following recent epidemics of foot-and-mouth disease in Europe, this symposium was organised in order to give the opportunity for open debate on the provisions of 2 European documents, the revised Ph. Eur. monograph and the European guideline, which can then go forward for approval and implementation.

The group was made up of representatives from the Immunological Working party of the CVMP of the Commission of the European Communities, the World Organization for Animal Health (OIE) and the FAO-EUFMD. Representatives of manufacturers, the principal public and private research centres, universities, national authorities and Official Medicines Control Laboratories (OMCLs) participated in the discussions.

The symposium was attended by 43 participants from 16 countries (mostly European countries but also Bolivia, Colombia, Argentina and the United States).

Symposium on Microbiological control methods in the European Pharmacopoeia: Present and future, Copenhagen (Denmark), 5-6 May 2003

This scientific symposium provided a forum for exchanges between industry, raw-material and culture-media manufacturers, control laboratories and pharmacopoeias together with national authorities, licensing and Official Medicines Control Laboratories (OMCLs). Microbiological quality is an important aspect of the overall quality of medicines, for both sterile and non-sterile preparations.

At the conference, speakers had commented that the introduction of new methods was being hindered because of a lack of guidance on how they should be validated with respect to the existing Pharmacopoeia methods; one approach to improve the situation would be to draft a general chapter covering validation of alternative methods in microbiology. The Commission decided to add this item to the work programme.

The EDQM asked National Authorities to propose specialists to work on this item. Work began at the end of the year.

The symposium was attended by 146 persons from 26 countries (Europe, USA, Japan, Australia, Argentina).
3 Training sessions for users of the European Pharmacopoeia “How to use the European Pharmacopoeia” were organised on 6-7 March 2003 (subject: biological products), 26-27 June 2003 (subject: herbal products) and 4-5 December 2003 (subject: chemical products).

Following the success of the programme initiated in 2002 at the request of its users, the EDQM continued its programme for training and dialogue in different areas.

Nineteen participants from 9 countries including Canada attended the sessions on biological products; 44 participants from 16 different countries including the United States, Zimbabwe and Tunisia attended the sessions on herbal products; 59 persons from 20 different countries including the United States, Porto Rico and Zimbabwe attended the sessions on chemical products.

Visits and meetings at the EDQM

— PERF (Pan-European Regulatory Forum) (January 2003): work programme on veterinary immunologicals coordinated by the EMEA intended to facilitate the implementation of Community regulations in the 10 new acceding countries.

— Technical Pharmaceutical Union (UTIP) (January 2003): the European Pharmacopoeia was invited to present its activities during the events organised to commemorate the 50th anniversary of this professional association for continuing education of community pharmacists. 150 pharmacists attended the evening’s event which was covered in the specialised press.

— VICH, TAS Veterinary biological products expert working group (March 2003): at the group’s request, the 5th meeting of the group took place on EDQM premises.

— Russian delegation (July 2003): representatives of the Russian Pharmacopoeia and of Russian official control laboratories were welcomed to the EDQM.


Professional exhibitions

The EDQM participated in the following professional exhibitions and meetings:

— INDUSFARMA and ANVISA in August 2003 in Sao Paulo and Brasilia, Brazil;

— IDMA (Indian Drug Manufacturers Association) in September in Mumbai, India;

— CPHI (trade fair for producers of raw materials for the pharmaceutical industry) in December in Shanghai (China) and meeting with the Chinese Pharmaceutical Association (CPA).

These exhibitions provided an opportunity to meet users of the European Pharmacopoeia: from South America and Asia. The EDQM presented the 4th Edition, its publications and services to visitors through stands or 2-day training sessions tailored to the needs of associations and authorities. Partnerships were developed through successful exchanges with the local authorities.

WEBSITE http://www.pheur.org

The EDQM also continued to develop its Internet site; its publications can now be purchased online. Internet users can now order and directly pay for the publications of their choice by credit card, cheque or bank transfer at: https://book.pheur.org.

The Internet site for online sales is secure and credit card payments by Internet users are made through the bank’s secure site. This project has been successfully set up through collaboration between the EDQM and the Finance Directorate of the Council of Europe.

PROVIDING REFERENCE SUBSTANCES AND PREPARATIONS

130 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 1611. Extensive collaborative studies were required for 37 of these substances to determine the content of the substances used in the assays. In addition, 94 substances were replaced and the European Pharmacopoeia laboratory regularly monitored 355 substances and carried out quality control tests during the production of 391 batches. The number of chemical reference substances and biological reference preparations distributed to users continued to climb: 105 993 vials in 2003 (98 463 in 2002) and the number of orders increased from 13 832 to 15 722. Taking bulk substances selected by the European Pharmacopoeia Commission for use as reference substances, the Production Unit of the EDQM prepared 455 batches (filling 186 237 vials) and 8 batches by lyophilisation, filling 15 694 vials.

PREPARATION AND DISTRIBUTION OF SAMPLES

2439 (2190 in 2002) new samples were received by the EDQM this year. The total number of samples in stock was 15 509. 251 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 3 304 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, 9225 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 within the framework of the 3R concept (i.e. the Refinement, Reduction and Replacement 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 studies 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, 71 BSP projects have been initiated and 72 BRPs or replacement batches are being or have been established.

In 2003, the following projects have been started or pursued:

— Establishment of inactivated poliomyelitis vaccine (IPV) BRP batch 2
— Establishment of common in vitro potency assay for inactivated poliomyelitis vaccine (IPV)
— Establishment of rDNA hepatitis B vaccine (methods A and B) BRP batch 2
— Validation of alternatives to Auszyme ELISA kits, necessary for in vitro potency assay of rDNA hepatitis B vaccines
— Reporting phase for tetanus vaccine (for 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 bioassay for pertussis toxin
— Standardisation of test on “Molecular Size Distribution” of haemophilus influenzae type b conjugate vaccine
— Establishment of BRP and validation of methods for vaccinia immunoglobulin
— Reporting phase for antisera BRPs for potency assays of equine influenza vaccine
— Validation of in vitro potency assay for Newcastle Disease Vaccine
— Establishment of Newcastle Disease Vaccine BRPs
— 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 rabies vaccine for veterinary use BRP batch 4
— Establishment of anti-D immunoglobulin BRP
— Establishment of prekallikrein activator (PKA) BRP
— Establishment of BRP for normal human plasma for assay of SD-plasma and fibrin sealant kits
— Establishment of human coagulation factor VII concentrate BRP
— Establishment of human coagulation factor IX concentrate BRP batch 2
— Establishment of B19 virus DNA for NAT testing BRP
— Establishment of low molecular mass heparin BRP batches 4 & 5
— Establishment of an HPLC potency assay for interferon alfa2
— Establishment of rDNA erythropoietin BRP batch 2

The studies led to the adoption of the following reference preparations in 2003:

— Human anti-D immunoglobulin BRP batch 1
— B19 virus DNA for NAT testing BRP batch 1
— Heparin low molecular mass BRP batch 4 and 5
— Prekallikrein activator BRP batch 1
— Diphtheria toxin BRP batch 1
— Poliomyelitis vaccine (inactivated) BRP batch 2
— Hepatitis B vaccine (rDNA) Method A BRP batch 2
— Rabies vaccine for veterinary use BRP batch 4
— Erythropoietin BRP batch 2

The full reports on the concluded collaborative studies were published in Pharmeuropa Bio 2003-1 and 2003-2.

The project aiming at the establishment of the mycoplasma reference strains BRPs for validation of media and for the 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.
Six 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 prekallikrein activator 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 is now available.

CERTIFICATION OF SUITABILITY OF MONOGRAPHS OF THE EUROPEAN PHARMACOPOEIA

280 new applications (including 23 for products with TSE risk) and 305 requests for revision were received, in addition to the updates with respect to the publication of the 4th Edition. 529 new certificates were granted or revised (448 for chemical products and 81 for products with TSE risk).

In total, over 2000 applications have been received and 1487 certificates have been granted since the procedure became operational and these are regularly updated.

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, EGEA, 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, 2001/83/EC and 2003/63/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, the CVMP Immunological products Working Party and the Herbal Medicinal Products working party and representatives of the Commission of the European Communities, the EMEA and the EDQM. The Steering Committee met once this year thus ensuring that decisions involving licensing, pharmacopoeia and certification are taken in a coherent manner.

In addition to the Steering Committee, which is responsible for decisions on general policy, two 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 2003, 281 texts were translated from English to French (equivalent to 1155 pages with 300 words per page) and 234 from French to English (equivalent to 853 pages with 300 words per page).

In the area of publications, the year 2003 issues of Pharmeuropa comprise a total of 739 pages in French and 709 pages in English, Pharmeuropa Bio (issues in English only) comprised 70 pages, and the 4th Edition of the European Pharmacopoeia comprised 5258 pages in French and 4877 in English. The 4 supplements for 2003 of the 4th Edition comprise 1347 pages in French and 1274 in English.


The cumulative electronic edition of the European Pharmacopoeia is now available in 3 different formats: a CD-ROM version for individual use, an intranet version for use within networks and an online version accessible through the Internet. All 3 electronic editions are based on the same browser technology and feature a high-performance search engine, hyperlinks between monographs, general methods and reagents and a direct link to the online database for reference substances. All 3 electronic formats contain printable PDF files of the texts which are identical to those of the paper version. A demo version of the Internet version can be found at http://onlinedemo.pheur.org/demoh.htm.

2. 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 two 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 8th annual meeting was attended by 140 representatives from 70 laboratories from 30 countries and was held on 19-22 May 2003 in Warsaw (Poland). A representative of the EMEA was also present for direct contact with this Agency. Several scientific sessions took place during this meeting.

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.

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 28 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:

— valerian root (determination of the correction factor of dantron and finalisation of the study),
— liquorice root (determination of glycyrrhizic acid),
— amoxicillin (granules and powders for oral suspensions),
— aciclovir (tablets).

The study on valerian root showed that a large number of samples contained low concentrations of valerene acid and also that it was necessary to revise the monograph. The group of experts concerned had already examined the matter.

As regards liquorice root, about 30% of the samples analysed did not comply with the Ph. Eur. monograph.

The study on amoxicillin showed that about 14% of the products analysed were out of specifications with respect to the active substance. These results should nevertheless be confirmed by additional analyses.

The quality of the aciclovir tablets available on the European market seems to be satisfactory in terms of both content and purity.

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 Warsaw, Poland on 19-20 May 2003. This successful meeting included not only the traditional confidential exchange of information between OMCLs involved in batch release within the EU/EEA on issues related specifically to batch release but also the opportunity to interact with colleagues from the new Member States of the expanded European Union who will become part of the network as of 1 May 2004. The new Member States were represented by participants from Poland, the host of the meeting. As the mutual recognition agreement between Switzerland and the EU implemented in June 2002 includes the recognition of official batch release testing for biologicals, Switzerland participated fully in the meeting for the first time. In addition, in a broader context for the mutual exchange of expertise and experience on common issues there was an opportunity to interact with colleagues from other disciplines in the common sessions of the annual meeting on 20-22 May 2003.

Review of OMCL batch release activities since 2002 for both blood and vaccines and specific scientific presentations highlighted:

— continued evolution of the mutual recognition system emphasising improving transparency and the efficient resolution of common problems including use of the communication network, specifically the rapid information system, to exchange information on product-related issues,
— evaluation of the need for standardisation of methods and reference preparations through collaborative studies, in particular for hepatitis B and oral polio virus vaccines,
— development of methods and procedures to encourage the reduction of animal use for routine batch release activity,
— effective implementation of Quality Assurance systems in the OMCL network to improve mutual confidence amongst members.

Common procedures for batch release of biologicals

A common session to cover issues related to official control authority batch release (OCABR) relevant to both the blood and vaccines fields was held in the afternoon of the 19th and the morning of the 20th May 2003. Proposed revisions to annexes IIa, IIb, IId, III and IV of the Administrative Procedure for Batch Release of Biologicals were adopted. New internal procedures for dealing with discrepant results and quality control of documents and clarification on release specifications were also approved.

Blood products and plasma derivatives

The meeting of the network for batch release of human blood and plasma derivatives took place on 19 May 2003. Revision of the guideline on clotting factor concentrates, plasma inhibitor concentrates and fibrin sealants to include requirements for the release of preparations containing protein C has been
adopted. A new guideline for validation of nucleic acid amplification technology for quantitation of B19 virus DNA in plasma pools was adopted and revisions of the guidelines for human immunoglobulin and solvent detergent plasma to include reference to the new requirement for B19 testing were approved for external consultation and subsequently adopted by correspondence.

**Human Vaccines**

The meeting of the network for batch release of human vaccines took place on 19 May 2003. The revised guideline for meningococcal polysaccharide vaccine and a new guideline for yellow fever vaccine were adopted. A revision to allow for the possibility of reduction in animal testing by OMCLs for vaccines that require pyrogen tests was also adopted in the 7 guidelines where it was applicable.

The following 4 guidelines were approved for external consultation:

Smallpox vaccine, inactivated cholera vaccine and 2 separate guidelines for different formulations of hexavalent vaccines (diphtheria, tetanus, acellular pertussis, inactivated poliomyelitis, hepatitis B and haemophilus influenzae type b vaccines).

All adopted guidelines are available in a booklet that was published by the EDQM at the end of December 2003 and on the EDQM website.

**Immunological Veterinary Medicinal Products (IVMP)**

At a general meeting of OMCLs involved in evaluation of IVMPs, held in Strasbourg on 27-28 October 2003, the participants discussed the means to improve harmonisation and transparency of the OCABR system in the EU/EEA as implemented under the current legislation. Twenty-one specific guidelines were drafted to improve mutual recognition, and have been approved for external consultation. Drafting of 7 additional guidelines was commissioned. A revision of the administrative procedure for OCABR of IVMPs was also approved for external consultation.

**Preparation for entry of the 10 New EU member States into the OCABR network**

As of 1 May 2004, 10 new Member States will join the European Union and as such will be subject to the EU rules governing medicines. They will automatically become part of the EU OCABR network and may choose to implement OCABR in their Member State. In order to ensure a smooth entry into the system and to extend and foster the mutual recognition and confidence already established in the existing network, a meeting was held on 23-24 October 2003 in Prague. Nineteen representatives from 8 of the new Member States participated in discussions and saw presentations from representatives of several of the existing Member States, a representative from the European Commission and representatives of EDQM. This successful exchange was received with enthusiasm by all participants and laid the groundwork for open exchange and profitable co-operation in the future.

### II - Market surveillance for products with a centralised marketing authorisation

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 centrally authorised products (CAP) took place on 2-3 December 2003 in Strasbourg to discuss problems related to the testing programme for 2003.

The testing programme for 2003 included 37 medicines (14 biotech products, including 2 veterinary vaccines, and 23 synthetic products for human and veterinary use). In addition, tests were also carried out on the active substances of 10 of these products. This corresponded to an increase of about 30% compared with the programme for 2002. Samples of each product were collected from the markets of 3 member states of the EU/EEA. In total 17 countries provided samples, with the main contributors being France and Italy (10 products each) followed by Germany and Spain (9 products each). Sixteen countries participated in the testing phase, with 5 products on average being tested per country. France (11 products), Sweden (10 products) and Denmark (9 products) were the most active countries. All of the products collected by the national authorities from the markets as well as the reagents and reference materials provided by the marketing authorisation holders were centralised at the EDQM and then distributed to the national control laboratories. In 2003, this distribution meant handling 300 samples. The testing protocols were based on the marketing authorisation dossiers of the product licence holders. Technical comments on the testing methods and the documentation have been made in 17 cases so far. Only one product has been identified as being problematic and further investigations are now underway. All the results have been sent to the CPMP and CPVP (EMEA) for follow-up if necessary.

The upcoming integration of 10 new member states into the European Union was discussed at the annual meeting, and preparatory measures were decided.
Representatives of the OMCLs of the future member states participated in this meeting as observers. Starting on 1 May 2004, the OMCLs of the new member states will participate fully in the testing phase; the OMCLs of Cyprus, the Czech Republic, Hungary, Poland, Slovenia and Slovakia will each have one product to test during the programme for 2004.

The preparation of the testing programme for 2004 (covering 42 medicines) and its implementation were also discussed.

Another major activity during 2003 has been the organisation by the EDQM of a joint EMEA/EDQM Seminar on Sampling and Testing of Centrally Authorised Products (CAP) that took place in London at the EMEA premises on 18-19 September 2003.

This seminar was the first of its kind organised since the implementation of the CAP programme in 1999. It gathered together representatives from the national Agencies involved in the process of approving and supervising medicinal products within the EU/EEA: namely inspectors, representatives of OMCLs, (co-)rapporteurs and pharmaceutical assessors. Fifty participants attended the seminar including 7 observers from the acceding countries.

Based on the experience gained by all the actors involved since the beginning and feedback from industry, the seminar was organised with the following objectives:

— bring together representatives from the different actors of the programme (inspectors, OMCLs, pharmaceutical assessors, (co-)rapporteurs, EDQM, EMEA),
— foster communication between them and a better understanding of mutual needs,
— take stock of the situation,
— identify issues, if any and
— suggest ways to optimise the programme and its outcome, and move forward.

During these two days, a large number of ideas were shared and it provided an opportunity for an open and frank exchange of views. The outcome of this meeting is being currently further discussed within the Advisory group that has been established for the CAP programme, with a view to developing an action plan for optimising future programmes.

III. Market surveillance for products with a decentralised marketing authorisation

Further progress in the field of medicines licensed by the Mutual Recognition Procedure (MRP products) has been made during an enlarged trial phase where OMCLs from 10 Member States participated. This trial phase was launched in 2002 to apply the principle of work-sharing, concentrating on products that had received their marketing authorisation in the year 2000. On the basis of questionnaires distributed to the participants and evaluated by EDQM, a common testing plan was elaborated to avoid duplicate testing of the same products in different member states, which in several cases would have occurred without this co-ordinated planning.

This testing plan was made available on a web-based extranet site with restricted access to the participating OMCLs and their competent authorities. During meetings held in 2003, the reporting of results between the participants and making these results available in an on-line database was agreed and implemented by the EDQM.

The participants agreed unanimously to continue the successful trial phase to gain further experience and to extend the collaboration to all the MRP products that have been authorised so far.