

European Directorate for the Quality of Medicines (EDQM) Annual Report of Activities - 2004

The activities of the European Directorate for the Quality of Medicines (EDQM) are described in terms of its 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

With the accession of Bulgaria, Lithuania and Malta in 2004, the European Pharmacopoeia convention has been signed by 35 parties including the European Union and the following countries: Austria, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, the Czech Republic, Denmark, Estonia, Finland, "The Former Yugoslav Republic of Macedonia", France, Germany, Greece, Hungary, Ireland, Iceland, Italy, Latvia, Lithuania, the Grand-Duchy of Luxembourg, Malta, Norway, the Netherlands, Portugal, Serbia and Montenegro (formerly Yugoslavia), Romania, the Slovak Republic, Slovenia, Spain, Sweden, Switzerland, Turkey, and the United Kingdom.

There are also 14 observers, namely the WHO, plus 4 European states (Albania, Georgia, Poland, Ukraine), and 10 non-European states (Algeria, Australia, Canada, China, United States (FDA), Malaysia, Morocco, Senegal, Syria, Tunisia). There were 3 fewer European observer states than last year (these 3 states have since signed the Convention), and there was one more non-European observer state: the United States, represented by the FDA which had requested observer status, in particular for issues related to blood products. This official request follows many years of scientific exchanges and partnership to improve and standardise biological methods.

GENERAL ACTIVITIES

The European Pharmacopoeia Commission continued its work on the preparation of the 5th Edition, which entered into force on 1 January 2005. Two supplements (5.1 and 5.2) were published in 2004 and implemented on 1 April 2005 and 1 July 2005.

A "Certificate of Authenticity" for EDQM publications was developed. This certificate contains visible and hidden security features. In addition these certificates contain a unique "EDQM Publication ID", which serves for registration of the electronic version and allows users to verify their genuine EDQM publication using an online registration.

At its three Sessions in March, June and November 2004, the European Pharmacopoeia Commission adopted 196 monographs, of which 114 were revisions and 82 were new monographs. It also adopted 25 texts and general methods, of which 17 were revisions and 8 were new texts. Overall, 221 texts were adopted (including 131 revised texts). The number of monographs prepared by the procedure for adaptation of national monographs or procedure III was stable (14 in 2003 and 2004), while the number prepared by the groups of experts decreased slightly. The new procedure (procedure IV), set up for new products based on collaboration with the manufacturers and national control laboratories, yielded encouraging preliminary results (5 monographs prepared within short deadlines). The number of documents produced (new, revised) was stable: 3190 in 2004. The new monographs can be broken down as follows: 52 on inorganic or organic products, 3 on vaccines, 1 on a biological, 16 on herbal drugs or preparations, 8 on homoeopathic preparations, 1 on a radiopharmaceutical preparation, and 1 on a dosage form.

A total of 210 days were devoted to meetings in 2004 (196 in 2003). This includes the three plenary sessions of the Commission and the corresponding preparatory meetings, and the meetings of the Groups of Experts (81) and the *ad hoc* Working Parties (26). This total also includes the participation of members of the Secretariat in various other meetings: of the Pharmaceutical Committee (Brussels) on medicines for human and veterinary use; of the various working parties of the Committee for Medicinal Products for Human Use (CHMP); 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 (PDG) for International Harmonisation with Japan and the United States, preparatory meetings of the Quality Working Party for ICH (Q4B), meetings of VICH working parties, and meetings to organise and take part in international scientific conferences and congresses.

International harmonisation with the pharmacopoeias of the United States and Japan

The PDG [European Pharmacopoeia (Ph. Eur.), Japanese Pharmacopoeia (JP) and United States Pharmacopoeia (USP)] met in Madrid (Spain) on 16-19 February 2004 in conjunction with the WHO International Conference of Drug Regulatory Authorities (ICDRA), in Washington (United States) on 7-10 June 2004, and in Yokohama (Japan) on 15-18 November 2004 at the same time as the ICH meetings, which was useful for exchanging

information on the progress of work. These meetings were set up to finalise the harmonisation of a number of general chapters and monographs. The WHO attended as an observer.

Summary of agreements on harmonisation:

- 7 new general chapters signed off: uniformity of dosage units, dissolution, disintegration, flowability (powder flow), particle size distribution estimation by analytical sieving, optical microscopy, tablet friability;
- revision of 3 chapters for which it had been agreed to include new information that appeared at the time of transcription into the Pharmacopoeias of the United States and Japan: extractable volume of parenteral preparations, particulate matter in injectables, sulphated ash/residue on ignition;
- 8 monographs signed off on excipients: microcrystalline cellulose, powdered cellulose, methyl, ethyl, propyl and butyl parahydroxybenzoates, anhydrous calcium hydrogen phosphate, calcium hydrogen phosphate dihydrate.

The total number of signed-off, harmonised monographs is now 31 and the number of general texts is 19.

It should be noted that the signed-off texts must next be adopted, published and implemented in accordance with the legal system of each partner. The licensing authorities of the United States, the European Union and Japan cannot legally consider the texts to be interchangeable between the three pharmacopoeias until they have been published and implemented in all three, (provided that the texts conform to the signed agreements).

To facilitate and accelerate the implementation of an appropriate procedure, the ICH Steering Committee has set up a new ICH Expert Working Group Q4B (*Regulatory acceptance of pharmacopoeial interchangeability*). On 16 November 2004, the PDG held a joint meeting with Q4B to discuss the regulatory acceptance of harmonised monographs and general chapters, particularly those of relevance for the ICH Q6A guideline; working procedures, mechanisms of co-operation and the future programme were discussed; three examples were studied: extractable volume of parenterals, residue on ignition/sulphated ash, and the sterility test; examination of the test for extractable volume was completed and the Q4B group agreed that the methods of the three pharmacopoeias will be interchangeable once the harmonised text has been published and implemented in all three regions.

The PDG developed important aspects of the working procedure as a result of experience and the needs of regulators for recognition of the harmonisation status of monographs and general chapters. The PDG members will make every effort to identify as soon as possible any local requirement that will be unique to an individual pharmacopoeia; these local requirements and any non-harmonised aspects will be recorded on the sign-off sheet to facilitate the task of each pharmacopoeia in informing its users of harmonisation status.

Indication of harmonisation status

The PDG has developed a standard system of notation for indication of harmonisation status and information on residual differences to be applied by each pharmacopoeia

in its publication; non-harmonised items will be indicated by a standard symbol (♦).

2004: reinforcement of the EDQM's role in European Union Legislation

Directive 2001/83/EC and Directive 2001/82/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human and veterinary use were amended by directives 2004/27/EC article 111 and 2004/28/EC article 80 (Official Journal No L 136 of 30/04/2004 p. 34-57 and p. 58-84). Some of these amendments are related to several activities that have been developed on a practical basis through networks co-ordinated by the Council of Europe and which have now been granted legal recognition in the revised Community legislation:

- under the procedure for certification of suitability of monographs of the European Pharmacopoeia, the EDQM can ask the national inspection services to collaborate on the inspection of manufacturing sites and distribution sites for raw materials for pharmaceutical use. It should be noted that an extensive network for collaboration has been set up involving inspectors from over 15 countries participating on a voluntary basis; it is now in the pilot phase.
- the role played by the European network of OMCLs of the Council of Europe, in the area of independent testing, has been confirmed and consolidated in the European legislation on medicines for human and veterinary use.

STANDARD TERMS

The list of standard terms has been translated into 5 more languages (Lithuanian, Estonian, Latvian, Maltese and Romanian), so that these terms are now available in 27 languages; this includes all the official languages of the 10 new European Union member states. An electronic version of the list of standard terms is already available on the EDQM internet site, in a specialised database, and a printed version is currently being prepared.

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 or specialised exhibitions for professionals working in the area of quality control of medicines. Events of media interest were organised to commemorate the 40th anniversary of the European Pharmacopoeia to convey to the general public the importance of the activities of the EDQM/European Pharmacopoeia for the quality of all medicines and the fight against counterfeit products.

Symposium on Process Analytical Technologies (PAT), 3-4 May 2004, Cannes Mandelieu, France

The symposium was the occasion for industry and regulators from Europe (regulatory authorities and European Pharmacopoeia) and the United States of America (FDA and USP) to present their viewpoints.

The pharmaceutical industry currently manufactures a large volume of high quality medicines. To achieve greater reliability and efficiency the industry is developing better quality control and a deeper

understanding of the production process via Process Analytical Technology (PAT). This will involve a paradigm shift for the industry and regulatory (licensing) and control authorities (Inspection and OMCLs), encouraging the concept of quality by design and real-time monitoring of manufacturing processes.

The conference set the scene for wide-scale introduction of PAT in the pharmaceutical industry, which will have an impact on the pharmacopoeias in their role of setting public standards for the protection of public health. Pharmacopoeias can play a role for the whole of the industry and regulators by describing the best practice for, and the benefits of PAT.

Conference on "Quality on the Move: Dynamics of the European Pharmacopoeia", 4-6 October 2004, Budapest, Hungary

This international conference, organised by the EDQM, marked the 40th anniversary of the European Pharmacopoeia, and the publication of the 5th Edition. More than 350 participants from 40 countries heard presentations on achievements during the last 3 years and future challenges in all fields related to the quality of medicines.

Most of the areas of activity of the European Pharmacopoeia were covered in the interactive workshops, and EDQM staff and European Pharmacopoeia experts were available for individual consultations during the conference.

The outcome of the discussions at the conference will be taken into account by the European Pharmacopoeia Commission in future policy decisions and in decisions on the work programme.

Symposium on Diphtheria Vaccine: Serological Potency Tests, 6-7 October 2004, Budapest, Hungary

The symposium, organised within the Biological Standardisation Programme (BSP) of the EDQM, was attended by 57 participants from 16 countries.

It started with an account of a major validation study of serological potency tests for diphtheria vaccines, with the aim of improving animal welfare. The present official potency tests require challenge with toxin.

The study demonstrated that the serological potency model is a valid alternative to the challenge model, and both tetanus and diphtheria vaccines can be assayed in the same group of animals. This opens up perspectives for both a reduction of the total number of animals needed for control tests and for refinement of test conditions.

As an immediate result of the symposium, a revision proposal of the European Pharmacopoeia general chapter describing the assay of diphtheria vaccine can be expected in 2005.

3 training sessions were organised in Strasbourg on biological products (4-5 March 2004), herbal-based products and preparations (1-2 July 2004) and chemical products (2-3 December 2004)

Small groups (maximum 50 persons) were shown, through interactive discussions, how to make the best use of the European Pharmacopoeia. Special emphasis was placed on themes/case studies and the use of the electronic version.

Training sessions: official visits organised in response to invitations from the National Authorities and Professional Associations of the Pharmaceutical Industry

11 March 2004: a training session was organised in Switzerland at the invitation of the Swiss Medicines Agency and the Swiss Pharmacopoeia (Swissmedic). About 200 persons attended this one-day session.

Similarly, training sessions were organised in Morocco in September 2004, in China (Shanghai and Beijing) in October 2004 and in India in November 2004. These training sessions covered the European Pharmacopoeia and the Certification procedure. A large number of people (600 in all) attended the sessions.

Training sessions for pharmacy students

EDQM agents are often invited to participate in training sessions organised by pharmacy faculties in Europe. Students from the Strasbourg Faculty of Pharmacy who were enrolled in a postgraduate programme (Inter-University Diploma) attended a training session in October 2004; this training session took place on EDQM premises and gave an overview of European regulations on medicinal products. The EDQM also participated in University Day, a day of conferences jointly organised by Alsace BioValley and which involved industry in the Rhine basin (France, Germany and Switzerland) and the Strasbourg Faculty of Pharmacy, organised on 19 October 2004. This day was also open to pharmacy students. The two themes chosen for this day were the European Pharmacopoeia and Drug Discovery.

EDQM visits and meetings

As part of its regular exchanges with its partners, the EDQM organised the following visits on its premises:

Norwegian Medicines Agency (September 2004)

About 20 members of this agency were welcomed to Strasbourg for presentation of the activities of the EDQM/European Pharmacopoeia, in particular those concerning herbal-based products and biologicals. The procedure for Certification of Suitability of Monographs of the European Pharmacopoeia was also presented.

Chinese delegations (September/October/November 2004) and relations with China

Although China obtained observer status in 1994 a few years after relations began to develop, few exchanges took place between 1998 and 2002. However, exchanges with the Chinese authorities have intensified over the last two years, during which the EDQM has been visited twice by Chinese delegations. The first delegation consisted of representatives of the national authorities: the Chinese Pharmacopoeia and the State Food and Drug Administration (SFDA) based in Beijing. The presentations and discussions dealt with biological products (notably vaccines). These second delegation was sent by the Shanghai control laboratory authorities with which a programme for scientific exchange is being developed.

The EDQM also made an official visit to the Chinese Pharmacopoeia in Beijing in November 2004.

A partnership is being set up between the EDQM and the various Chinese authorities responsible for quality control of medicines, at both the national and provincial levels. One of the main subjects of discussion is the fight against

counterfeit medicines. Under this partnership, the EDQM welcomed a trainee on its premises in December 2004: Mr Ning Baoming, assistant professor at the National Institute for the Control of Pharmaceutical and Biological Products, in Beijing.

Japanese and Filipino authorities (October 2004)

The purpose of this visit was to initiate relations between the EDQM/European Pharmacopoeia and the Filipino authorities. Japan, which supports the creation of a Filipino pharmacopoeia also participated in this meeting, organised with the aim of setting up a collaboration as part of international harmonisation and relations between states in the area of quality of medicines.

Turkish delegation (December 2004)

The EDQM received a delegation consisting of scientific managers from the "Refik Saddam Institute", Central Laboratory for Control of Biological Medicines. The Turkish authorities had sent this delegation so that they could familiarise themselves with European standards, and procedures for the testing and batch release of human blood products and plasma derivatives. Turkey wished to set up an appropriate system for surveillance of these products with a control mechanism similar to that of the OMCL network of European Union member states.

Exhibitions and professional meetings

The EDQM also participated in the following:

- FARMA ANALISIS COSME 2004 (exhibition and conferences for the pharmaceutical, chemical, food and cosmetic industries) 23-26 March 2004 in Mexico City (Mexico);
- congress organised by FEBRAFARMA (Brazilian pharmaceutical industry federation) on 17 October 2004 in Sao Paulo (Brazil). The EDQM had been given half a day to present new aspects of the 5th Edition of the European Pharmacopoeia. This Congress was attended by about 50 representatives of the pharmacopoeia, universities and Brazilian pharmaceutical industries;
- ETIF (Congress and trade fair on pharmaceutical technologies and equipment) from 19-22 October 2004 in Buenos Aires (Argentina). This provided an opportunity to meet the national authorities, in particular the Argentine National Institute for Medicines (INAMED);
- IPC (trade fair for producers of raw materials for the Chinese pharmaceutical industry) from 28-30 October 2004 in Shanghai (China).

These exhibitions and professional meetings provided an opportunity to meet users of the European Pharmacopoeia from central America and Asia. The EDQM presented the 5th Edition, its publications and services to visitors through stands, oral presentations or training sessions adapted to the needs of associations or authorities.

Events related to the 40th anniversary of the European Pharmacopoeia (1964-2004)

The official ceremony on 15 June 2004 took place in the hemicycle of the Council of Europe; it was attended by about 300 persons: all of the delegations of the member

states and observer states of the European Pharmacopoeia, professionals working in the area of pharmacy, and members of the scientific community and of the general public interested in the subject. The 40th anniversary of the European Pharmacopoeia was also commemorated in a national ceremony held by the Netherlands in Utrecht on 5 June 2004, and by public debates organised by the Council of Europe and the EDQM in Strasbourg.

14 June 2004, "Medicines, the key to European public health policies" was the theme of a public debate in the city of Strasbourg. The special guest was Mr Fernand Sauer who had played an instrumental role in the accession of the European Union to the European Pharmacopoeia 10 years ago. Issues related to the provision of health care were also discussed. Mr Daniel Riot, the European editor of a French television station, moderated the discussions; questions were taken from about 60 persons, who communicated their expectations concerning health and medicines.

From 19 to 29 June 2004 an exhibition targeting the general public on the theme "Find out about the European Pharmacopoeia and Medicines" was held at the Chamber of Commerce and Industry of the Bas-Rhin department in France. The exhibition used displays to show the general public and specialists the results of the work carried out at the European level to guarantee the quality of medicines and the implications for public health in Europe. The exhibition also took visitors on a journey through the world of medicines and medical knowledge: from the first medicines obtained from nature (plant, mineral or animal products) to modern medicines produced by chemical synthesis, biotechnology or genetic engineering. The exhibition was warmly received by the general public and by more specialised groups of visitors such as community pharmacists and their assistants, representatives of the pharmaceutical industry, and representatives of local companies and associations. The exhibition, which is also available in English, can be borrowed on request.

WEBSITE <http://www.pheur.org>

The EDQM also continued to expand its Internet site in 2004. There was further development of on-line services for users, in particular the "KNOWLEDGE" database. The KNOWLEDGE database is a major advance in the area of scientific and technical support for users. This database contains information on the substances or methods of analysis on the programme of work of the European Pharmacopoeia, the state of work, the draft texts that have been published in *Pharmeuropa* for public inquiry with the corresponding issue number, and the volume of the European Pharmacopoeia in which the official text in force is found. The user can also find out whether a reference text is undergoing revision. The KNOWLEDGE database provides free technical information on the texts of the European Pharmacopoeia such as: trade names for reagents, eg, the names of the chromatographic columns or biological kits used to carry out some of the tests when the monograph was being elaborated; downloadable reference chromatograms; practical technical information on how to carry out certain tests. It is also now possible to obtain for each substance the list of reference substances used in the monograph and the certificates of suitability that have been granted. The availability of all this information in a single database is an important step

forward in the implementation of the EDQM/European Pharmacopoeia's policy of transparency for users.

PROVIDING REFERENCE SUBSTANCES AND PREPARATIONS

100 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 1681. Extensive collaborative studies were required for 27 of these substances to determine the content of the substances used in the assays. In addition, 92 substances were replaced, and the European Pharmacopoeia laboratory regularly monitored 449 substances and carried out quality control tests during the production of 451 batches. The number of chemical reference substances and biological reference preparations distributed to users continued to climb: 135 431 vials in 2004 (105 993 in 2003) and the number of orders increased from 15 722 to 17 903. Taking bulk substances selected by the European Pharmacopoeia Commission for use as reference substances, the Production Unit of the EDQM prepared 581 batches (filling 259 120 vials) and 8 batches by lyophilisation, filling 17 667 vials.

PREPARATION AND DISTRIBUTION OF SAMPLES

2651 (2439 in 2003) new samples were received by the EDQM this year. The total number of samples in stock was 17 512. 403 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 3197 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, 8552 samples were prepared for distribution to the various experts of the EDQM (for the elaboration of monographs and the organisation of collaborative studies, market surveillance studies, and 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 Pharmacopoeia (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 Refinement, Reduction and Replacement of animal experiments).

To this end, 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, 81 BSP projects have been initiated and 75 BRPs or replacement batches have been established.

In the year 2004, the following projects have been pursued:

- feasibility study for establishment of common *in vitro* potency assay for **inactivated poliomyelitis vaccine (IPV)**;
- establishment of **rDNA hepatitis B vaccine (method B) BRP batch 2**;
- validation of **alternatives to Auszyme ELISA kits**, necessary for *in vitro* potency assay of rDNA hepatitis B vaccines;
- validation of serological method for potency assay of **diphtheria vaccine**;
- validation of *in vitro* method as alternative to bio-assay 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** (new);
- validation of *in vitro* potency assay for **Newcastle Disease Vaccine**;
- establishment of **Newcastle Disease Vaccine BRPs** for *in vitro* potency assay;
- establishment of **mycoplasma reference strains BRPs**;
- establishment of **equine influenza antiserum BRP batch 2** (new);
- 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 1a**;
- establishment of **human normal immunoglobulin BRP batch 3** (new);
- establishment of **BRPs for determination of levels of anti-D immunoglobulin in normal immunoglobulin** (new);
- establishment of an HPLC potency assay for **interferon alfa2**;
- establishment of **low molecular mass heparin for calibration BRP batch 2** (new).

The studies led to the adoption of the following reference preparations in 2004:

- hepatitis B vaccine (rDNA) Method B BRP batch 2;
- newcastle disease vaccine BRPs batch 1;
- human coagulation factor IX concentrate BRP batch 1A.

The full reports on the concluded collaborative studies were published in Pharmeuropa-Bio 2004-1.

In 2004, the project on the development of serological assays to replace *in vivo* challenge as the batch potency

test for vaccines containing diphtheria components was completed. The project was complementary to the previously concluded project on alternative assays for tetanus vaccine. The general goal was to enable the performance of the potency assay for vaccines containing diphtheria and tetanus components using serum from the same animals. This will tremendously reduce the number of animals needed for these assays.

The outcome of the project and its implications were presented and discussed at a satellite meeting to the EDQM conference "Quality on the move" in Budapest (6-7 October 2004) with all interested parties (manufacturers, WHO, non-European authorities) as mentioned above.

Seven new projects were started. As in previous years, co-operation with international partners continued, and projects to establish common standards were set up whenever possible with the WHO Expert Committee on Biological Standardisation (ECBS), for example, the establishment of a standard for low molecular mass heparin for calibration. The project for the establishment of the reference materials for determination of the anti-D immunoglobulin content in normal immunoglobulin is a joint project with FDA/CBER.

CERTIFICATION OF SUITABILITY OF MONOGRAPHS OF THE EUROPEAN PHARMACOPOEIA

317 new applications (280 in 2003) (including 33 for products with TSE risk) and 350 requests for revision (305 in 2003) were received, in addition to the regular updates of certificates that are made following the publication of revised monographs. 578 new certificates were granted or revised (505 for chemical products and 73 for products with TSE risk).

In total, over 2400 applications have been received and 1700 certificates have been granted since the procedure became operational, and these are regularly up-dated.

The procedure illustrates the exemplary collaboration between the partners, namely the working parties of the CHMP, CVMP, and the European Pharmacopoeia Commission, which while consulting Industry (EFPIA, AESGP, CEFIC/APIC, IFHA, 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, and co-operation) that characterise the procedure are implemented by a Steering Committee consisting of the Chairs of the European Pharmacopoeia Commission, the Joint CHMP /CVMP Quality Working Party, the CHMP Biotech Working Party, the CVMP Immunological products Working Party the Herbal Medicinal Products Working Party and Inspection Working Party, and representatives of the Commission of the European Communities, the EMEA and the EDQM. The Steering Committee met twice 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 2004, 290 texts were translated from English to French (equivalent to 1205 pages with 300 words per page) and 263 from French to English (equivalent to 853 pages with 300 words per page).

In the area of publications, the year 2004 issues of *Pharmeuropa* comprised a total of 654 pages in French and 631 pages in English, *Pharmeuropa Bio* (issues in English only) comprised 80 pages, and the 5th Edition of the European Pharmacopoeia comprised 2976 pages in French and 2779 in English. The 2 supplements for 2004 of the 5th Edition comprise 564 pages in French and 553 in English.

The 5th edition consists of 1851 monographs, 286 general texts, and 2243 descriptions of reagents, and is published in both electronic and book form.

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 powerful 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 Acrobat 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://online.phEur.org/demo.htm>.

2. NETWORK OF OFFICIAL MEDICINES CONTROL LABORATORIES (OMCLs)

The network was set up in 1995 by an initiative of EDQM in close cooperation with the Commission of the European Union, and is open to all countries that have signed the European Pharmacopoeia Convention, as well as to observers at the European Pharmacopoeia Commission.

There are two levels of collaboration:

- *general activities* involving all member states of the Convention and the observer states; all the OMCLs are invited to meetings and are asked to participate in collaborative studies in all the areas of general interest;
- *EU/EEA specific activities*; a number of activities take place within the more restrictive regulatory framework for medicines in the EU, notably those connected to the Centralised Marketing Authorisation Procedure, the Mutual Recognition Procedure (MRP) and the Official Control Authority Batch Release

(OCABR) of blood and plasma derivatives and human and veterinary vaccines.

“Networking” means sharing of know-how within a pool of experts, work sharing and consequently saving of resources and costs in testing of medicinal products as well as mutual recognition of test results based on commonly agreed procedures. For that purpose the implementation and maintenance of harmonised Quality Management Systems (QMSs) within the network members based on ISO/IEC 17025 are sought and the assessment of established systems, based on commonly agreed procedures, is required. Since 1997 two instruments are in place to help OMCLs working towards these goals, namely Tutorials (former Mutual Joint Visits) and Mutual Joint Audits. Another contribution to “networking” is the organisation of annual meetings, which brings together representatives throughout the network to discuss and exchange viewpoints of common interest in the fields of testing medicines by independent OMCLs, to summarise the year’s activities and decide on an action plan for the coming year. They are organised by EDQM and hosted by one of the members of the network on a rotating basis.

GENERAL CO-OPERATION BETWEEN OFFICIAL CONTROL LABORATORIES OF THE PLENARY NETWORK

Annual meeting of the plenary network

The 9th annual meeting of the plenary network (General European OMCL Network, GEON) was held on 10-14 May 2004 at the Paul-Ehrlich-Institute in Langen (Germany) and was attended by 198 representatives from 61 OMCLs from 34 countries. A representative from both the European Commission and the EMEA were also present. 2004 was a specific landmark of the network, as for the first time the ten new EU Member States were present in the areas for which specific control regulations, such as Batch release for Human Biologicals-OCABR, are optionally applicable.

Quality Management Systems

The work in the area of QMSs for the OMCLs continues to proceed intensively.

Mutual Joint Audit/Visit and Tutorial Scheme

During the year 2004, 4 Mutual Joint Visits (MJV), 1 Tutorial and 13 Mutual Joint Audits (MJA) have been performed at OMCL sites under the coordination of Division IV of EDQM. This creates a total of 25 MJAs, 37 MJVs and 1 Tutorial carried out since the beginning of the programme by highly qualified experts from the Network specifically trained for the quality aspects (peer reviewing). Several requests have already been received for the year 2005 (10 audits and 6 tutorials). These figures show the strong commitment of the OMCL Network towards quality and harmonisation.

A reasonable number of OMCLs from the accession countries were assessed during 2004 and the process will continue in 2005 at the same intensive level.

In addition, discussions with representatives of the European co-operation for Accreditation (EA) concerning

the recognition of the contribution of OMCLs in setting up QMSs within their domain were intensified and are now progressing towards a common agreed understanding with a possible proactive cooperation.

Training sessions for the OMCL Network: the EDQM is currently organising two types of training sessions for the period 2005-2006. One type of training will be dedicated to the pool of auditors participating in the MJA/MJV/Tutorial scheme. The other type of training sessions will be open to all interested OMCLs, and the programme will include topics related to Quality Assurance and technical matters.

OMCL Network Guidelines

A new guideline has been created by a group of experts from the OMCL Network for the Qualification of Equipment. This document provides a practical and comprehensible tool for OMCLs willing to carry out the qualification of equipment, and it will replace the former guideline based on a compilation of publications. Other guidelines are under preparation and will also be presented to the Network for adoption in 2005.

Proficiency Testing Studies (PTS)

These studies have become a regular programme within the network and in 2004 six studies were organised in the physico-chemical field, with the participation of 45 national laboratories on average, while in the biological area 4 studies were organised, involving 13 national laboratories on average. In 2004, for the first time, manufacturers were given the possibility to participate in PTS studies in the biological field.

A third PTS programme agreement was signed with WHO. Five studies, the first of which started in August 2004, will be organised between July 2004 and June 2006. An average participation of 42 governmental control laboratories from Africa, Asia, East and South East Europe and Central and South America is expected.

General studies on market surveillance (MSS)

Such studies are aimed at screening the quality of products commercialised in countries of the Network were carried out for the following preparations, with the participation of 14 national laboratories on average: ibuprofen, omeprazole, matricaria flower and scored tablets.

In addition, an MSS on uniformity of dosage units (European Pharmacopoeia general method 2.9.40) involving all the OMCLs of the Network was initiated.

Where a need is identified, the results of these studies will support revision of the relevant European Pharmacopoeia monographs and/or general chapters and methods.

EU/EEA SPECIFIC ACTIVITIES

The general activities of pre- and post-authorisation testing of medicinal products on the European market by OMCLs are now laid down in the new European legislation (directive 2001/83/EC as amended by directive 2004/27/EC (human code), articles 19, 111 and 114 – and directive 2001/82/EC as amended by directive 2004/28/EC (veterinary code), articles 23, 80 and 82), which further strengthens the role of the OMCLs and the network.

Official Control Authority Batch Release (OCABR) of biologicals

The annual meeting was the first occasion on which all of the new EU Member States, integrated as of 1 May 2004, took part in the traditional confidential exchange of information on issues related specifically to batch release.

In addition, in order to facilitate the entry of new Member States into the system and to extend and foster the mutual recognition and confidence already established in the existing network, training workshops on OCABR have been arranged in the different disciplines.

The first workshop, for the blood network, was held at the Austrian Federal Institute for Medicines (BiFA) in Vienna on 1-3 December 2004. 16 representatives from 8 of the 10 new Member States and 2 participants from the candidate States of Croatia and Romania participated in discussions and saw presentations from representatives of several of the existing Member States, with a focus on practical application of batch release techniques including laboratory sessions and visits of laboratories sites. This successful exchange was received with enthusiasm by all participants. A similar workshop is planned for the vaccine network in April 2005.

Human Biologicals

At the annual meeting, the review of OMCL batch release activities of the past year for both blood and vaccines, and special scientific presentations were highlighted. Of key importance was the use of the established communication network.

Common procedures for batch release of human biologicals

Revision of the Administrative Procedure for Batch Release of Biologicals and all product-specific guidelines to update the legal references and adapt to current practice were adopted. A new internal procedure for fast track revision of guidelines to apply Ph. Eur. monograph revisions was also approved. Consistent with the network's terms of reference, elections were held for 2 positions of the 4 member advisory group (1 for blood and 1 for vaccine). Ellen Voets (Belgium - blood representative) and Phil Minor (United Kingdom - vaccine representative) were newly elected for a 4-year term. In addition, to aid in the integration process, a temporary, *ad hoc* group of new Member State representatives was created.

Blood products and plasma derivatives

A revision of all blood guidelines, to allow use of the Plasma Master File where available, was adopted. In addition, a proposal to review documentation of plasma pools at the time of testing by the OMCL was put forward, and will be pursued subject to clarification with the European Commission. An additional annex to the administrative procedure (annex IIf), concerning a certificate for ancillary blood and plasma-derived products in medical devices, was also adopted for application of Article 1 of Directive 2000/70/EC.

Human Vaccines

4 new guidelines were adopted as follows:

- Cholera vaccine (oral, inactivated);

- 2 separate guidelines for different formulations of hexavalent vaccines (diphtheria, tetanus, acellular pertussis, inactivated poliomyelitis, hepatitis B and haemophilus influenzae type b vaccines);
- vaccine containing vaccinia virus derived from cell culture (smallpox vaccine).

In addition revisions to the following guidelines were adopted by the fast track procedure. These will be in application in line with the relevant monograph revision as indicated:

- BCG vaccine (01/01/05);
- Influenza vaccine (01/04/05);
- Multivalent pneumococcal conjugate vaccine (01/04/05);
- Yellow fever vaccine (01/04/05).

The following guidelines were approved for external consultation:

- Hepatitis A/Typhoid polysaccharide vaccine (mix at use);
- Poliomyelitis vaccine (oral)- monovalent bulk;
- Poliomyelitis vaccine (oral) - trivalent vaccine.

All adopted guidelines and the revised Administrative Procedures are available in a booklet published by the EDQM at the end of December 2004. They are also available for download on the EDQM website.

Immunological Veterinary Medicinal Products (IVMPs)

This year, for the first time OMCLs involved in control of veterinary immunological products took part in the annual meeting in conjunction with the other branches of the OMCL network.

The veterinary participants discussed the means to formalise procedures for harmonisation and transparency of an OCABR system in the EU/EEA as implemented under the current legislation. A representative from the EU Commission participated in the discussion. There was an opportunity to present annual reports of activity in the field of batch release and in addition a number of interesting scientific presentations were given. A visit to the PEI animal facilities was a further highlight of the meeting.

A Working Group met in Strasbourg, 14 September 2004, to follow up on the agreements reached at the annual meeting. The group established proposals for an administrative procedure and 15 product-specific guidelines as well as a roadmap for implementation to be presented to the Veterinary Pharmaceutical Committee before being sent for external consultation by manufacturers.

Meeting with manufacturer's associations

Each of the sub-networks for OCABR of biologicals held separate meetings in Strasbourg with the relevant manufacturers association in the course of 2004 to allow for exchange and feedback and to ensure transparency and good will.

Representatives from the veterinary network for IVMPs met with representatives from the International Federation for Animal Health (IFAH) – Europe on

23 March 2004. Representatives from the vaccine network met with members of the European Vaccine Manufacturers' (EVM) Association on 29 June 2004 and representatives from the blood network met with representatives from the European Plasma Fractionators Association (EPFA) and the Plasma Protein Therapeutics Association (PPTA) on 5 November 2004.

Market surveillance for products with a centralised marketing authorisation

The programme for Sampling and Testing of Centrally Authorised Products (CAP) was successfully continued in 2004 and entered into its 5th consecutive year. Each product, is selected by expert groups from the European Medicines Agency (EMA) in London, is sampled in 3 European Economic Area (EEA) Member States and tested by 2 OMCLs, independently from the manufacturers. The role of the EDQM is to organise the collection of samples on the EEA market, to centralise all market samples as well as non-commercially available standards and specific reagents that are provided by the manufacturers, to distribute the test materials to the OMCLs, and to provide a compiled testing report to the EMA and its expert groups.

The CAP programme covers medicinal products for both human and veterinary use and included 43 products in 2004: quality-indicative test parameters from 12 biotech products and 31 chemical/pharmaceutical products were controlled by OMCLs. In addition, controls were also carried out on the active substances of 9 of these products. Overall, all incoming and outgoing market samples, reagents and reference materials represented the handling and storage of about 300 stock items. About 120 medicinal samples were analysed, representing an increase in work of about 16% compared to the 2003 programme.

All Member States from the former (15 in total) EU, as well as Norway and Iceland, actively participated in the sampling and/or testing phases. In addition, further to the enlargement of the European Union in May 2004, OMCLs from 6 of the new Member States countries (the Czech Republic, Cyprus, Hungary, the Slovak Republic, Slovenia and Poland) were successfully integrated into the testing phase on a voluntary basis.

As regards the outcome of the testing, the controls have highlighted that all the products tested are of an appropriate quality. Nevertheless, minor issues mainly related to the quality of the testing documentation were reported. Among the 43 products tested, only 3 raised questions which were referred to the EMA and its

scientific experts, in order for them to assess whether further actions are required.

The annual meeting of the EEA OMCLs involved in the CAP programme took place on 9-10 December 2004 in London on the EMA premises: this meeting enabled participants to discuss issues of common interest and prepare in detail the programme for 2005. It is anticipated that next year most of the new Member States will actively take part in both the sampling and testing phases.

As a follow-up to the CAP Seminar, which was held in London in September 2003, a series of documents which aim to optimise the existing system were elaborated in 2004. For instance, one document that has been adopted by the Network introduces a progressive switch for all chemical/pharmaceutical products from 2 testing OMCLs to one single testing OMCL. This change will take place over several years and is possible thanks to the on-going efforts of all members of the Network to steadily implement a QA policy, continuously maintained at a high level through efficient auditing.

Market surveillance for products with a marketing authorisation according to the Mutual Recognition Procedure (MRP)

The testing programme on MRP products, which had entered an enlarged trial phase in 2003, now covering all products authorised so far, has been continued in 2004. 15 OMCLs from 10 Member States participate in the programme. The programme was initiated in 2001 to apply the principle of work sharing, concentrating as a first step on products that had received their marketing authorisation in 2000. On the basis of questionnaires distributed to 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 coordinated planning. This testing plan was made available on an intranet-based extranet site with restricted access to the participating OMCLs and their competent authorities. In 2003 an additional on-line database of test results accessible to all participants was implemented by EDQM. Meanwhile, reports of results for about 280 products covering different dosage forms and strengths have been registered at EDQM and put on the extranet. As from next year, regular updates of all MRP products registered on the European market will be made available on the global MRP product database. It is planned to examine the outcome of the extended trial phase with a view to deciding on the implementation of a regular MRP testing programme, during the next annual meeting of the plenary Network (end of May 2005).