

Annual Report of Activities of the EDQM - 2007

The activities of the European Directorate for the Quality of Medicines & HealthCare are described in terms of its 5 main areas of responsibility.

- The European Pharmacopoeia, including publication and communications activities and international relations
 - European Pharmacopoeia Department
 - Communications and Public Relations
 - Provision of reference substances and preparations
 - Preparation and dispatching of samples
 - Biological Standardisation Programme
- The Procedure for Certification of Suitability
- The European network of Official Medicines Control Laboratories (OMCLs)
- Blood Transfusion
- Organ Transplantation

The year 2007 was another leap forward in the development of the EDQM: new missions in the field of blood transfusion and organ transplantation, a new 19 500 m² building, a new edition of the European Pharmacopoeia and the appointment of a new Director. These events have attracted growing interest not only from traditional partners of the EDQM (authorities, pharmacopoeias and regulatory agencies around the world), but also from a wider audience that is increasingly concerned with issues relating to medicines.

1. THE EUROPEAN PHARMACOPOEIA

PARTIES TO THE CONVENTION AND OBSERVERS

The European Pharmacopoeia convention has been signed by 37 parties including the European Union and the following countries: Austria, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Montenegro, the Netherlands, Norway, Poland, Portugal, Romania, Serbia, the Slovak Republic, Slovenia, Spain, Sweden, Switzerland, "The former Yugoslav Republic of Macedonia", Turkey and the United Kingdom.

20 observer states regularly participate in the work of the European Pharmacopoeia Commission, namely: the World Health Organisation (WHO) plus 6 European countries (Albania, Georgia, Belarus, Kazakhstan, the Russian Federation and Ukraine) and 13 non-European countries (Algeria, Australia, Brazil, Canada, China, Israel, Madagascar, Malaysia, Morocco, Senegal, Syria, Tunisia and the United States of America (FDA)).

1.1. EUROPEAN PHARMACOPOEIA DEPARTMENT

GENERAL ACTIVITIES

The European Pharmacopoeia Commission continued its work on the preparation of the 6th Edition, which was

published on 16 July 2007 and implemented on 1 January 2008. Supplements 6.1 and 6.2 were published in 2007, with implementation dates of 1 April 2008 and 1 July 2008, respectively.

At its 3 Sessions in March, June and November, the European Pharmacopoeia Commission adopted 280 new and revised monographs and general chapters. The adaptation of the requirements for microbiological quality in monographs to the new harmonised methods developed in collaboration with the Japanese Pharmacopoeia (JP) and the United States Pharmacopoeia (USP) was completed with the adoption of 66 revised monographs; the previous methods will consequently be phased out during 2008. A new general chapter on functionality-related characteristics of excipients was adopted. This chapter will support the large programme of work undertaken by the Commission for the introduction of functionality-related characteristics into excipient monographs. A revised version of the general monograph Substances for pharmaceutical use was adopted, extending the scope to all products, irrespective of whether they are covered by a specific monograph. This general monograph was the only one with limited scope and the extension aligns it with current regulatory practice. A monograph on coccidiosis vaccine for chickens was adopted, the first monograph on a parasite vaccine. In 16 monographs on active substances, the test for impurities using TLC was replaced by a modern HPLC test in order to align the monographs with modern requirements. 33 new items (monographs and general chapters) were added to the work programme during 2007.

At the March Session, the Commission elected a new Chair, Prof. H J de Jong, formerly First Vice-chair; at the June Session, 2 new Vice-chairs were elected, Mrs M Ek (Swedish delegation) and Dr G Lee (United Kingdom delegation). At the November Session, the chairs and membership of all groups of experts and working parties were renewed. Prior to these elections and renewals, the Commission adopted revised versions of the basic documents governing the work: the Rules of Procedure and the Guide for the Work of the European Pharmacopoeia. In addition, the Commission adopted formal Terms of Reference for all groups of experts and working parties and a Code of Practice with a Declaration of Interest applicable to all participants in the work of the European Pharmacopoeia.

The Commission appointed 3 new working parties: Glycan mapping, Precursors for radiopharmaceutical preparations, and Traditional Chinese medicines. A meeting of an *ad hoc* group to develop a policy on the control of genotoxic impurities was held in July 2007. It will result in the adoption of a policy document that reflects the approach of the EMEA guideline on this matter.

At the March Session, the Commission received a document from the Secretariat showing animal welfare

progress in monographs over the 20 years since the adoption of the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes and the corresponding directive (86/609) of the European Union. This document is published in *Pharmeuropa* 19.3 and demonstrates the considerable success of the efforts made by the Commission to replace, reduce and refine the use of animals in monographs.

When a harmonised chapter (Ph. Eur., JP, USP) on uniformity of dosage units was adopted some years ago, the Commission agreed that a transition period should be allowed for existing products before application of the new chapter. The regulatory authorities have indicated that they expect the previous method to be gradually phased out. The Commission has now published an enquiry paper in *Pharmeuropa* to gather views and data on the phasing out, with a projected date of 1 January 2013.

During 2007, the European Pharmacopoeia Department (Scientific Secretariat) organised over 50 meetings of groups of experts and working parties, 3 Sessions of the Commission and 6 meetings of the Presidium. Members of the Secretariat regularly attended as observers and actively participated in meetings of EMEA committees and working parties: Committee on Herbal Medicinal Products, Biologicals Working Party, Immunologicals Working party, Quality Working Party. At the beginning of 2007, the annual EDQM-EMEA joint forum was held in Strasbourg with representatives of the EDQM, the EMEA and the chairs of the latter's working parties to discuss items of common interest and compare work programmes.

Members of the Secretariat continue to participate in training courses on the use of monographs. These well-attended courses not only provide information to participants but also give interesting feedback to the Secretariat on the concerns of users.

INTERNATIONAL HARMONISATION WITH THE PHARMACOPOEIAS OF JAPAN AND THE USA

The Pharmacopoeial Discussion Group met on 7-10 May 2007 in Brussels and on 28 October to 1 November 2007 in Yokohama. A newly harmonised monograph on sucrose was signed off together with a series of general chapters on powder characterisation: bulk and tapped density, gas pycnometric density of solids, powder fineness, porosimetry by mercury intrusion, X-ray powder diffraction and laser-diffraction measurement of particle size. In 2002, a harmonised sterility test was signed off but with a number of residual differences. The PDG has made a particular effort to remove these differences, and a completely harmonised version of the test was signed off at the Yokohama meeting.

The role of the ICH Q4B working group in defining regulatory acceptance of harmonised texts was described in the 2006 annual report. The PDG again had joint sessions with Q4B and there is now a good prospect of smooth progress to regulatory acceptance of a number of harmonised texts: extractable volume, particulate matter in parenteral preparations, dissolution test, disintegration test, microbiological quality.

Meetings were held in Brussels and Yokohama with Tri-PEC (IPEC Europe, IPEC Americas and the Japanese Pharmaceutical Excipients Council), who are important stakeholders in the work on harmonisation of excipient monographs. The active involvement of these stakeholders in the PDG process is encouraged, particularly for inter-regional collaborative testing to further the harmonisation process.

STANDARD TERMS

Since 2006, national authorities are responsible for entering the translations of standard terms into the specialised database via the EDQM website. Standard terms are now available in 29 languages, including Chinese. Russian is currently being worked on.

TRANSLATIONS AND PUBLICATIONS

The European Pharmacopoeia is published in both official languages of the Council of Europe, namely English and French. A Spanish version is also available, but for now only on the internet (up to Supplement 5.5). A paper version is planned for the 6th Edition. In 2007, 217 texts were translated from English to French (equivalent to 1302 pages with 300 words per page) and 265 from French to English (equivalent to 658 pages with 300 words per page).

In the area of publications, the 2007 issues of *Pharmeuropa* comprised a total of 720 pages in French and 682 in English, *Pharmeuropa Bio* (issued in English only) comprised 68 pages, and *Pharmeuropa Scientific Notes* (issues in English only) comprised 46 pages. The 2 principal volumes of the 6th Edition of the European Pharmacopoeia comprised 3538 pages in French and 3308 in English. The 2 supplements published in 2007 for the 6th Edition comprised 632 pages in French and 598 in English.

The 6th Edition consists of 2046 monographs, 322 general texts and 2407 descriptions of reagents, and is published in both electronic and book form.

A hologram for the EDQM publications has been developed to protect against unauthorised copying. It contains a number of security features (see <http://www.edqm.eu/site/Hologram-699.html>). In addition, each publication has a unique 'EDQM Publication ID' (EPID), which serves for registration of the electronic versions and allows users to verify their genuine EDQM publication using an online registration. For some paper publications access to additional online services is granted after registration (Standard Terms and *Pharmeuropa*).

The cumulative electronic edition of the European Pharmacopoeia is available in 2 different formats: a CD-ROM version intended mostly for individual use and an internet version. Both electronic editions are based on browser technology and contain powerful search engines. Hyperlinks between monographs, general methods, reagents, printable PDF files of the texts, which are identical to those of the paper version, and links to the online database for reference substances and the Knowledge database are established. For the online version of the 6th Edition a new publication platform has been implemented, in order to cope better with the increased number of customers using this version. More advanced searches and export functions have been

implemented in this new online version. The licensing system is now based on the registration of computers.

Pharmeuropa (including Pharmeuropa Bio and Pharmeuropa Scientific Notes) are available online. All issues back to Volume 10 (1998) have been indexed and are available as searchable PDF files. The online access is included for subscribers of the paper version of Volume 19 (2007). The necessary access code can be generated using the information from the label on the back cover of Pharmeuropa 19.1.

Access to the online version of Standard Terms is included in the subscription to the paper version and this access is handled in the same way as for Pharmeuropa by using the EPID number (in this case on the Certificate of Authenticity) on the inside-front cover.

1.2. COMMUNICATIONS AND PUBLIC RELATIONS

The EDQM continued its comprehensive communication policy with its partners, giving priority in 2007 to the redesign of its website and organising and participating in many conferences, training sessions and visits.

Events for the general public were organised to convey the importance of the activities of the EDQM/European Pharmacopoeia in ensuring the quality of all medicines and in the fight against counterfeit medicines.

In its international relations, the EDQM strived to consult all its partners by meeting with them or participating in major specialised exhibitions.

Website

The EDQM is working actively to improve and expand its online services not only in scientific and technical areas but also in the areas of training and informing its users about EDQM products and services.

The number of visitors and visits to the EDQM website continued to increase in 2007, reaching a monthly average of 17 000 visitors and 53 000 visits per month (data from the statistics tool AWSTATS).

A number of new features were introduced in 2007 that were greatly appreciated by users.

- A 'News' section using RSS technology (Really Simple Syndication). It is available upon subscription and allows visitors to be automatically updated on the latest changes by checking RSS feeds.
- A thematic navigation based on areas of interest to visitors. 6 major themes were identified and are shown on the homepage: 'EDQM' to introduce the missions of the organisation; 'HealthCare' covering new activities such as blood transfusion and organ transplantation; 'European Pharmacopoeia'; 'Certification of Pharmaceutical Substances'; 'Medicines Control' focusing on the activities of the OMCL network that are still poorly understood; and finally 'Products & Services'.
- Technical databases continue their development: the pharmaceutical reference substances database was further improved and now provides information on the date of availability, the CAS and UN codes, and additional information that might indicate a chemical name for an impurity or a synonym.

The certification database has incorporated the following new features: the status of each certificate is displayed (valid or suspended), and for suspended certificates, the reason for the suspension is also provided.

Organisation of symposia on current issues

International Conference on 'New Frontiers in the Quality of Medicines', June 2007, Strasbourg, France

The main objectives of this conference were to review the technical and scientific advances in all areas covered by the European Pharmacopoeia to identify future priorities of the Commission. This event was an opportunity for the EDQM to strengthen its ties with a number of national authorities on a global scale. More than 350 participants from 50 countries heard presentations from stakeholders in the activities of the EDQM as well as from related organisations. Scientists from academia, regulatory bodies and industry shared their expertise in plenary sessions, workshops and one-to-one sessions (consultations by EDQM staff and European Pharmacopoeia experts).

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

- further improvement in communications;
- strong support for international harmonisation;
- work on biologicals;
- traditional medicines;
- participation in anti-counterfeiting actions (e.g. Council of Europe initiatives and WHO IMPACT (International Medical Products Anti-counterfeit Taskforce)).

Symposium on 'European Cooperation and Synergy in Quality Standards beyond the European Pharmacopoeia', June 2007, Strasbourg, France

This symposium examined the interest and the relevance of the general chapters of the European Pharmacopoeia and the general methods of analysis in the case of pharmaceutical products not covered by a marketing authorisation. Examples include the manufacture of 'small-scale' preparations, extemporaneous preparations and certain radiopharmaceutical products.

The quality aspects of these products or preparations are particularly important for both hospital and community pharmacies, national health authorities and inspectorates due to the high number of applications throughout Europe. The problem of potential differences in quality concerns thousands of patients in Europe who expect and require similar quality and control guarantees in all European countries.

More than 100 representatives from all the parties concerned, from 18 countries, took part in this symposium to debate and evoke new prospects for European harmonisation based on a better knowledge of the various national initiatives. Collaboration and sharing of efforts are required in order to guarantee the quality of these types of products.

Conference and symposia proceedings are published on the EDQM website (<http://www.edqm.eu>).

Training sessions / presentation of the missions of the EDQM

The EDQM organised 2 training sessions in 2007, in Warsaw (September 2007) and in London (December 2007).

These training sessions are very much appreciated by users of the European Pharmacopoeia and each drew the participation of 70 to 80 people from more than 15 countries. Since 2006, individual technical consultations with EDQM staff members are offered to participants at the end of the presentations.

4 other visits presenting the missions of the EDQM were also organised in response to invitations from national authorities and professional associations of the pharmaceutical industry.

Visits were organised to countries that are major producers of pharmaceutical raw materials: Hyderabad (India) with Prescription Pharma (150 participants, May 2007); Mumbai (India) with the Indian Pharmaceutical Association (IPA) (270 participants, November 2007); as well as Buenos Aires (Argentina) with the Argentinean authorities (INAME) (150 participants, October 2007). A session was also organised in Tunis (Tunisia) by the Tunisian Health Ministry (100 participants, November 2007).

A training session for quality auditors in the European Network of Official Medicines Control Laboratories (OMCLs) was also held in Vienna (November 2007). 25 participants from 13 countries attended this very specific session.

Inauguration of the new EDQM Building

To mark this event, an official ceremony was held on 20 March 2007. All partners of the EDQM were invited and approximately 450 people attended. The new 19 500 m² premises include 1500 m² of meeting space, 1800 m² of laboratories and 3200 m² of office space.

Award for blood transfusion activities

On 26 June 2007, the Council of Europe received an award from the International Society of Blood Transfusion (ISBT) in recognition of its intensive and continuous involvement in blood transfusion activities through its Expert Committees on Blood Transfusion and the guide for the preparation, use and quality assurance of blood components. The award was delivered by Prof. Shigeru Takamoto (President) and Dr. Paul Strengers (Secretary General) of the ISBT, in an official public ceremony on the occasion of their annual assembly.

9th European Day for organ donation and transplantation, 13 October 2007, Dublin, Ireland

On the occasion of the European Day for Organ Donation and Transplantation, the Council of Europe organised an international conference on 'Organ transplantation: experiences in Europe, the role of the Council of Europe and the Committee director on organ transplants, the impact of national legislation and an analysis of limiting factors and new strategies' with the Irish Kidney

Association (IKA). This conference was an opportunity to discuss both nationally and internationally these issues, where huge disparities still exist in the various European states. The President of the Republic of Ireland, Mrs Mary McAleese, opened the conference.

Group visits

In keeping with its policy of openness and transparency, the EDQM welcomed various groups of visitors to its premises.

- Permanent representatives at the Council of Europe (May 2007)
- Canadian and Chinese delegations (March and June 2007)
- 16 visiting groups representing both the target groups of the EDQM and a wider audience, totalling 360 people
- Open day of the Council of Europe on the occasion of the Heritage Day, 16 September 2007. Nearly 3,000 people came to visit and discover the activities of the EDQM on Heritage Day. During the day, institutional films, information panels and entertainment, such as sketches, were offered to the public.

Exhibition on the European Pharmacopoeia for the general public

Upon request, since 2004, the EDQM has been providing exhibition panels such as 'Find out about Pharmacopoeias and Medicine' that can be used as educational tools or for a particular event. Other panels explaining what a pharmacopoeia is and how it guarantees the quality of medicines, and describing all the activities of the EDQM in its European and global environment are also available.

This exhibition was used in various places and presented to various audiences in 2007.

- at the Maritime Museum, in May 2007, Rijeka, Croatia;
- at the EDQM's Open Day in September 2007, Strasbourg, France;
- on display at all times and accessible to all visitors in the main hall of the EDQM building.

International relations

Relations with the European Medicines Agency (EMA)

In addition to the yearly consultation meeting between the 2 institutions, co-ordination and co-operation activities with the agency continued throughout the year. EDQM representatives participated as observers in all the working parties relevant to the EDQM, notably the Biologicals, Inspection and Immunological working parties and the Committee for Herbal Medicinal Products. Representatives of the Agency were also invited to participate in symposia organised by the EDQM in areas of common interest to both institutions and to take part in relevant expert groups of the European Pharmacopoeia as observers.

The EDQM also gives all of the EMA and its experts on the Agency's premises free access to the electronic versions of its publications to facilitate the work of its European partners.

Relations with the World Health Organisation (WHO)

Representatives of the EDQM participated in the work of the WHO Expert Committee on Biological Standardisation (ECBS) and the Expert Committee on Monographs, Guidelines and Reference Standards for the Quality of Pharmaceuticals (ECSP). The ECBS is responsible for elaborating quality control requirements for biological products for human use (such as vaccines, blood products, hormones, biotechnological products and antibiotics). The EDQM plays an important role in this area and manages several common projects that are developed together with the WHO for the establishment of Biological Reference Standards. The EDQM has also been designated as a WHO collaborating centre for International Standards for Antibiotics (ISA). 2007 represented the first full year of operating this activity, for which a detailed report has been presented.

In September 2007, EDQM took part in a meeting on global strategic reflection on batch release of vaccines by the authorities, organised by the WHO in Ottawa (Canada); the Batch Release System (OCABR) already in place in Europe and coordinated by the EDQM was perceived as an interesting model that could inspire future WHO approaches.

Furthermore, the EDQM was involved in several technical expert committees on subjects of common interest in the field of vaccines, blood products and quality of medicines, addressing issues related to the development of methodology for tests and assays aimed at controlling the quality and stability of those products, or establishing standards and reference materials.

The EDQM also participated in the 2nd meeting of the WHO International Medical Products Anti-Counterfeiting Taskforce (IMPACT) in December 2007 in Lisbon (Portugal). This meeting was organised to evaluate the first steps undertaken by the different task force groups involved in the action plan to fight counterfeit medicines.

The EDQM has continued to develop a close co-operation in the field of Quality Assurance of Official Medicines Control Laboratories (OMCLs) through customised programmes of proficiency testing studies (PTS), as well as special training sessions for the implementation and maintenance of quality management systems (QMS). Representatives of several WHO member state control authorities attended dedicated quality assurance (QA) training sessions in Strasbourg and Vienna in September 2007. Due to the great interest these training sessions found among WHO participants, 2 additional sessions were co-organised between the WHO and the EDQM for QA issues in OMCLs in Africa. These took place in December 2007 in Rabat (Morocco) for French-speaking participants and Dar es Salaam (Tanzania) for English-speaking participants.

In the remit of its new activities of transfusion and transplantation medicines, the EDQM has participated in the meetings of the corresponding WHO Committees (Global Collaboration for Blood Safety (GCBS), Organ Transplantation Committee).

The EDQM was also invited to the 1st Regional Meeting of Directors of Blood Transfusion Services in Europe organised by the WHO Regional Office for Europe in Copenhagen.

Throughout 2007, the EDQM has reciprocally welcomed the participation of WHO officers and experts in its relevant meetings, conferences and workshops dealing with similar subjects of common interest.

Relations with the World Anti-Doping Agency (WADA)

The World Anti-Doping Agency (WADA) is the independent international organisation created in 1999 to provide, co-ordinate and supervise the fight against all forms of doping in sport. WADA is engaged in an education programme for athletes, research projects, producing standards and technical documents for all aspects of doping control, accreditation of anti-doping laboratories, etc.

A member of the EDQM staff has participated as an independent member of the laboratory committee since its inception and the EDQM assists particularly with the analysis of the results of the proficiency testing scheme for anti-doping analysis.

Meetings and consultations with partner authorities*Annual meeting of the European Network of Official Medicines Control Laboratories (OMCLs), May 2007, Prague, Czech Republic*

At the invitation of the EDQM, 216 participants from 33 countries attended the annual meeting of the European Network of OMCLs.

This annual meeting was organised in Prague with the help and support of the State Institute for Drug Control of Human Medicines and the Institute for the State Control of Veterinary Biologicals and Medicaments in the Czech Republic.

As usual, issues of particular importance were the harmonisation of testing programmes, exchange of experience and results, policy- and guideline-development for fostering mutual recognition, quality assurance, risk analysis and combating counterfeit medicines (see Chapter 3 for more information).

Relations with the Heads of Medicines Agencies (HMA) group

The EDQM contributed to the finalisation of the HMA strategy paper by providing their comments on how to reinforce co-operation and synergy between the various partners in Europe.

Relations with the secretariats of national pharmacopoeias (May 2007, Rijeka, Croatia)

The annual meeting of the national secretariats of pharmacopoeias was attended by 30 participants representing 22 national authorities. The meeting had been organised with the help of the Croatian Agency for Medicinal Products and Medical Devices.

Relations with the Argentinean authorities, (October 2007, Buenos Aires, Argentina)

An EDQM staff member was invited by the Argentinean authorities, the Argentine Pharmacopoeia and ANMAT (*Administracion nacional de medicamentos, alimentos*

y tecnologia medica) to participate in a conference on microbiological issues.

Relations with the Brazilian authorities (October 2007, Sao Paulo, Brazil)

An EDQM staff member was invited by the Brazilian Federation of the Pharmaceutical Industry (Febrafarma).

Relations with the Canadian authorities (March 2007)

The EDQM continued its regular exchanges with the Canadian authorities, not only in the area of the European Pharmacopoeia Commission and its groups of experts, but also in the area of certification of suitability of monographs of the European Pharmacopoeia. The EDQM and the Health Products and Food Branch (HPFB) of Health Canada signed a memorandum of understanding on 20 March 2007 that sees the official incorporation of Certificates of Suitability (CEP) granted by the EDQM into the evaluation of drug substances by the Therapeutic Products Directorate (TPD) of the HPFB.

The signing of this arrangement will allow applicants to file CEPs with the TPD, certifying the chemical purity and microbiological quality of a drug substance, in their marketing authorisation applications in Canada. The EDQM grants CEPs to manufacturers or suppliers of substances for pharmaceutical use when they have demonstrated compliance with the monographs of the European Pharmacopoeia. This CEP procedure is aimed at facilitating and simplifying exchanges between the partners to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia while avoiding duplication of work by regulatory authorities.

Relations with the Chinese authorities (March and June 2007)

A team from the EDQM was invited to the Shanghai Institute for Food and Drug Control (SIFDC) in Shanghai, China, under the framework of co-operation agreements already signed or being finalised. A memorandum of understanding was signed between the EDQM and the Chinese authorities, represented by the SIFDC, which facilitates access for Chinese users to European Pharmacopoeia reference standards necessary for the control of pharmaceutical substances. Chinese companies can contact the Shanghai Oriental Pharmaceutical Science and Technology Co. Ltd. (SOPST), a branch of the SIFDC, which is now responsible for taking orders for European Pharmacopoeia reference standards. The SOPST is an authorised distributor for the EDQM on the territory of the People's Republic of China for European Pharmacopoeia reference standards.

Relations with the Indian authorities (November 2007)

An official meeting was held with the Indian Pharmacopoeia (IPC) in November 2007 to provide an update on possible future collaborations and exchanges between the 2 organisations.

Relations with Tunisia (November 2007)

At the invitation of the Director of the Laboratory for Medicines Control (LNCM), a representative from the EDQM laboratory was invited to make a presentation to LNCM staff on the activities of the EDQM and its laboratory.

Special co-operation programme for scientists and correspondents of national authorities around the world

The EDQM hosted representatives from national authorities from Malaysia, Sweden and China, for periods ranging from half a day to several weeks. Each time the program was adapted depending on the profile of the participant.

Consultations of partner associations

EFPIA (European Federation of Pharmaceutical Industries and Associations), EVM (European Vaccine Manufacturers), IPFA (International Plasma Fractionation Association) and IFAH (International Federation for Animal Health)

The EDQM participated in the annual meetings of these associations to examine the results obtained in these areas, analyse new needs as they arose and envisage new developments.

CEFIC/APIC (European Chemical Industry Council/ Active Pharmaceutical Ingredients Committee)

A representative of the EDQM was invited to the annual meeting of the Committee in Warsaw, Poland, in October 2007, to present public health activities of the EDQM in the area of quality control of active substances for pharmaceutical use and to discuss the certification scheme.

PIC/S (Pharmaceutical Inspection Cooperation Scheme)

In July 2007, the EDQM and PIC/S signed a Memorandum of Understanding.

Transatlantic Administrative Simplification Workshop

The EDQM participated in the Transatlantic Administrative Simplification Workshop, jointly organised by the European Commission, the US Food and Drug Administration (FDA), the EMEA and the HMA under the auspices of the Transatlantic Economic Council, as foreseen in the Framework for Advancing Transatlantic Economic Integration between the European Union and the United States of America, signed by President Bush, President Barroso and Chancellor Merkel in April 2007. Proposals discussed for administrative simplification through transatlantic and international collaboration and harmonisation included ideas for a quicker harmonisation of pharmacopoeial requirements up to the vision of a unified pharmacopoeia.

Professional exhibitions in the pharmaceutical world

Various professional exhibitions provided an opportunity to meet users of the European Pharmacopoeia from Europe and Asia. Each time, the EDQM presented the 6th Edition, its publications, its products and its services to visitors, with the use of exhibition stands and, where appropriate, using presentations in satellite symposia.

The EDQM participated in the following:

CPhI Worldwide, October 2007, Milan, Italy

The EDQM participated in the Congress of Pharmaceutical Ingredients Worldwide (CPhI) fair/exhibition, which was attended by approximately 15 000 visitors in 2007. The EDQM stand received a reasonable number of visitors (450 visitors in 3 days) who were able to obtain answers to their questions on European

regulations concerning raw materials for pharmaceutical use and on the publications and services of the EDQM.

2nd CPhI India, November 2007, Mumbai, India

More than 10 000 visitors attended this event, confirming the success of this initiative, and the EDQM stand received 850 visitors in 3 days. Although most of the participants were Indian, other countries were also represented in this event. Local distributors of EDQM publications were invited to the stand and the presence of the EDQM at this conference was publicised by an extensive mailing campaign.

A special service offering free technical consultations was made available to companies holding certificates of suitability of monographs of the European Pharmacopoeia or to those that wish to apply for a certificate.

1.3. PROVISION OF REFERENCE SUBSTANCES AND PREPARATIONS

147 new CHEMICAL reference substances (or spectra) and biological reference preparations (including 14 for plants) were adopted in 2007, bringing the number of substances available to users of the European Pharmacopoeia to 2027. Extensive collaborative studies were required for 40 of these substances (including 12 for plants) to determine the content of the substances used in the assays. In addition, 122 reference substances were replaced and the EDQM laboratory regularly monitored 464 substances and carried out quality control tests during the production of 331 batches. The number of chemical reference substances and biological reference preparations distributed to users continued to climb: 203 976 vials in 2007 (184 564 vials in 2006), and the number of orders increased from 24 094 to 26 075. Taking bulk substances selected by the European Pharmacopoeia Commission for use as reference substances, the Production Unit of the EDQM prepared 455 batches (filling 318 649 vials).

1.4. PREPARATION AND DISTRIBUTION OF SAMPLES

2826 (2895 in 2006) new samples were received by the EDQM in 2007. The total number of samples in stock was almost 22 000. 403 studies were carried out by the EDQM 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 1987 samples for these laboratory studies to check the quality of the substances available on the market (multisource substances) or to check the robustness of draft European Pharmacopoeia monographs. In addition, 5674 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).

1.5. BIOLOGICAL STANDARDISATION PROGRAMME

The Biological Standardisation Programme (BSP), run by the Department of Biological Standardisation, OMCL Network and HealthCare (DBO), 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. 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 Medicine (USA).

Since its start in 1992, 97 BSP projects were initiated and 92 BRPs or replacement batches have been established.

In the year 2007, the following projects have been pursued.

In the field of vaccines for human use:

- validation of alternatives to Auszyme ELISA kits for *in vitro* potency assay of rDNA hepatitis B vaccine;
- validation of serological method for potency assay of acellular pertussis vaccine;
- standardisation of human influenza vaccine serology;
- validation of NMR methods for quality control of polysaccharide vaccines;
- establishment of (non-adsorbed) hepatitis A vaccine BRP;
- establishment of varicella vaccine BRP;
- establishment of diphtheria vaccine BRP replacement batch.

In the field of plasma-derived products:

- establishment of BRP for assay of SD-plasma and fibrin sealant kits;
- validation of *in vitro* assay method for tetanus immunoglobulin;
- establishment of von Willebrand factor BRP for ristocetin cofactor assay;
- establishment of BRPs for determination of anti-A, anti-B haemagglutinin titres in human normal immunoglobulin for intravenous administration;
- establishment of human coagulation factor IX BRP replacement batch;
- establishment of BRP replacement batches for determination of prekallikrein titres in human albumin.

In the field of biotechnology products:

- establishment of an HPLC assay for interferon alfa-2;
- establishment of low-molecular-mass heparin for calibration CRS replacement batch;
- establishment of erythropoietin BRP replacement batch;

- establishment of BRPs and ELISA assays for 2 major recombinant allergens (Bet v 1, Phl p 5a);
- establishment of filgrastim BRP;
- establishment of low-molecular-mass heparin for assay BRP replacement batch.

The studies led to the adoption of the following reference preparations by the Ph. Eur. Commission in 2007:

- Low-molecular-mass heparin for calibration CRS batch 2;
- Erythropoietin BRP batch 3.

The full reports on the concluded collaborative studies are published in Pharmeuropa Bio 2007-1 (available in early 2008).

In the field of vaccines for human use, the 2nd phase of a project was started that aims at a better standardisation of the serological methods used for clinical evaluation of influenza vaccines during the annual licensing procedure according to the EMEA Committee for Medicinal Products for Human Use (CHMP) guidelines; this has been requested by the CHMP Biologics Working Party (BWP) of the EMEA. In the 1st part of the project, which was completed in 2006, the influence of test variability on compliance with the CHMP guidelines for inter-pandemic influenza vaccines was investigated. Sera from elderly patients were tested using the haemagglutination-inhibition (HI) test. The study showed that reproducibility of the HI test is not satisfactory for this purpose and that standardisation of the serological methods is urgently needed. The 2nd part of the project will examine the influence of the use of a sheep serum standard on the variability of the HI and single-radial-haemolysis (SRH) tests and how this affects compliance with the CHMP criteria. The study will start in early 2008. Results are eagerly awaited by vaccine manufacturers and licensing authorities.

The strong efforts to apply the 3R concept to the field of quality control of biologicals were continued. Two 3R projects were significantly advanced in 2007. One project aims at the replacement of the *in vivo* challenge assay for tetanus immunoglobulin by an *in vitro* assay; for this project a collaborative study was run and concluded. The 2nd project extends to acellular pertussis vaccine previous projects on the development of serological assays to replace *in vivo* challenge as batch potency test for vaccines containing diphtheria and tetanus components. The goal is to enable the performance of the potency assay for vaccines containing all these components using serum from the same animals. This will considerably reduce the number of animals needed for these assays. In this case, the extensive feasibility study, in which a large number of sera obtained by immunisation with a wide variety of vaccines were used, was successfully completed and the collaborative study will start in early 2008. For both projects, initial results will be presented at the EDQM meeting 'Alternatives to animal testing: new approaches in the development and control of biologicals', which will be held in Dubrovnik, Croatia on 23-24 April 2008. The efforts of the EDQM and the Biological Standardisation Programme in the 3R field are gathered together with those of the EPAA (European Partnership for Alternative Approaches to Animal Testing) initiative, a high-level joint initiative of the European Commission and industry.

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 a standard for low-molecular-mass heparin for calibration that was adopted at the ECBS meeting in October 2007, and the establishment of replacement batches for the diphtheria vaccine BRP and International Standard (IS). The projects for the establishment of standards for determination of anti-A and anti-B haemagglutinin titres in immunoglobulins and for replacement batches of human coagulation factor IX are run as tri-partite studies with the WHO and FDA/CBER.

EDQM activities as WHO collaborative centre for international standards for antibiotics

Since May 2006 the EDQM has been the WHO Collaborative Centre for the WHO International Standards for Antibiotics (ISA). At the same time, the EDQM took over the responsibility for the establishment, storage and distribution of ISA from the National Institute for Biological Standards and Control (NIBSC). Batches that were held and distributed by the NIBSC are now being distributed by the EDQM.

The ISA are essential for the standardisation and quality control of antibiotic drug substances and pharmaceutical drug products. They are supplied for use in the microbiological assays performed for quality control.

In 2007, the collaborative study that aimed at the establishment of a replacement batch for the current IS for amphotericin B, the stocks of which will soon be exhausted, was completed. The establishment report was adopted by the WHO Expert Committee on Biological Standardisation (ECBS) at its session in October 2007. At the same time, the establishment report for nystatin was adopted by the ECBS. The nystatin collaborative study had been run in 2006 but the report was completed only after the 2006 ECBS meeting. At the 2007 meeting, the ECBS also approved proposals for replacement of the current batches of the IS for dihydrostreptomycin sulphate, gramicidin, teicoplanin and vancomycin, for which the stocks will soon be depleted. The respective collaborative studies will be initiated in 2008. Information on the availability and ordering of ISA is available on the EDQM website (<http://www.edqm.eu/site/WHO-International-Standards-for-Antibiotics-ISA-665.html>).

1.6. QUALITY MANAGEMENT SYSTEM

The EDQM continued the development of its quality management system based on the ISO 9001 standard (general administration), ISO 17025 standard (laboratory), ISO Guide 34 (reference standards) and ISO Guide 43-1 (PTS activities) to guarantee optimal service to interested parties while improving the efficiency of working methods.

The EDQM provides Safety Data Sheets (SDSs) for all reference standards available. 1957 SDSs are now available through the EDQM website or upon request. These SDSs have been redrafted to be compliant with REACH regulation (EC/1907/2006).

2. CERTIFICATION OF SUITABILITY OF MONOGRAPHS OF THE EUROPEAN PHARMACOPOEIA

361 new applications and 641 requests for revision were received, in addition to the regular updates following the publication of revised monographs in the supplements of the European Pharmacopoeia. More than 1000 certificates (new or revised) were granted after assessment. In total, over 3400 applications have been received and 2380 certificates granted since the procedure became operational. These are regularly updated according to a procedure that is in line with the procedures for variations to the marketing authorisations of medicines.

The certification procedure illustrates the exemplary collaboration between different partners, namely the working parties of the CHMP, CVMP and the European Pharmacopoeia Commission, which, while consulting industry (EFPIA, AESGP, CEFIC/APIC, IFHA, EGA, 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 whenever a specific substance is covered by a European Pharmacopoeia monograph (see Guideline 'Summary of Requirements for Active Substances in the Quality Part of the Dossier' and implementation of directives 2001/82/EC, 2001/83/EC and 2003/63/EC, as amended).

The Steering Committee, which consists of representatives of all concerned authorities, is responsible for decisions on general policy (see Terms of Reference, PA/PH/CEP (01) 1), met twice in 2007, thus ensuring that decisions involving licensing, the Pharmacopoeia and certification are taken in a coherent manner.

In addition to the Steering Committee, 4 meetings of the 2 technical advisory boards (for chemical and for TSE applications) were organised. These boards consist of expert assessors who participate in the evaluation of dossiers and deal with any technical or scientific questions, in particular elaborating or revising the technical documents needed for the procedure to function effectively.

Operating on the basis of the mandate given to the EDQM by the European Commission, the programme for inspection of manufacturing sites covered by certificates of suitability is an important tool to supplement the evaluation of the quality of substances for pharmaceutical use. In 2007, 34 inspections were carried out with the participation of inspectors from different national agencies. Most of these inspections took place in India and China, countries which represent approximately 80 per cent of the production of pharmaceutical substances used in Europe today. Procedures have been established in collaboration with the EMEA GMP/GDP Inspection Working Group for cases where critical/major deficiencies are noticed leading to a conclusion of GMP non-compliance or failure of declaration (e.g. refusal of inspection, major discrepancies compared to the dossier) and to potential actions regarding the validity of granted CEPs and on-going applications. In case of suspension of CEPs/applications, the national competent authorities concerned are informed so that necessary action on

related marketing applications/authorisations can be taken.

The Certification division (DCEP) participated in several events (conferences, fairs/exhibitions, meetings with national delegations) in particular in Europe but also in India and China (see above) to improve the EDQM's visibility and reinforce co-operation with its various partners (manufacturers and authorities). The efforts to enhance communications were further strengthened by offering confidential consultations to the industry (one-to-one meetings offered during these events, technical advice held at the EDQM premises); these consultations were very much appreciated and sought-after by users as they provide applicants with the unique opportunity to obtain specific advice on the requirements for demonstrating the conformity of a substance with a monograph.

3. NETWORK OF OFFICIAL MEDICINES CONTROL LABORATORIES (OMCLs)

The network of Official Medicines Control Laboratories (OMCLs) was established in 1994 on the initiative of the EDQM in close co-operation with the Commission of the European Union. The network is open to all countries that have signed the European Pharmacopoeia Convention as well as to observers to the European Pharmacopoeia Commission, provided that the criteria of the network are fulfilled.

There are 2 levels of collaboration.

- *General activities* covering all areas of common interest and involving all member states of the network such as work in the field of Quality Assurance (QA), Proficiency Testing Scheme (PTS), Market Surveillance Studies (MSS) and common network strategies (risk-based approach for post-marketing sampling and testing, combating counterfeits and illegal medicines, establishment of centres of expertise, improvement of communication, etc.).
- *Activities restricted to the European Economic Area (EEA)*, in which a number of activities take place within the more restrictive regulatory framework for medicines in the EU/EEA, notably those connected to the Centralised Marketing Authorisation Procedure (CAP), the Mutual Recognition Procedure (MRP) / Decentralised Procedure (DCP) and the Official Control Authority Batch Release (OCABR) of blood and plasma derivatives, human vaccines and veterinary immunobiologicals.

'Networking' means sharing of know-how within a pool of experts, work sharing and mutual recognition of test results based on commonly agreed procedures, and consequently saving of resources and costs in the testing of medicinal products.

For this purpose the implementation and maintenance of harmonised Quality Management Systems (QMSs) (based on ISO/IEC 17025) among the Network members and the assessment of established systems, based on commonly agreed procedures, are required. Since 1997 several tools have been put in place to help OMCLs work towards these goals, such as Training Visits, Tutorials, Mutual Joint Visits (MJVs) and Mutual Joint Audits (MJAs).

Also making a contribution to networking are the annual meetings, which bring together representatives from the entire network to discuss and exchange viewpoints on topics of common interest, such as independent testing of medicines, to summarise the year's activities and decide on an action plan for the coming year. These meetings are organised by the EDQM and hosted by one of the members of the network on a rotating basis.

Finally, the establishment of an OMCL inventory database with restricted access for network members has been accomplished during 2007 to foster information exchange on competences and equipment available within the network.

ACTIVITIES INVOLVING ALL OMCLS OF THE NETWORK

Annual meeting of the plenary network

The 12th annual meeting of the OMCL Network was held on 7-11 May 2007 in Prague, Czech Republic, and was co-organised by the EDQM and the Czech OMCL for human medicines (State Institute for Drug Control, Laboratory Control Branch), as well as the local veterinary OMCL (Institute for State Control of Veterinary Biologicals and Medicines). 216 representatives from 33 countries, representing 51 control laboratories, attended 8 different specialised sessions, during which the quality control of medicines was discussed, in particular in the field of pharmaceuticals, and the official control authority batch release of biologicals.

In the General Session the policy document 'Factors for determining OMCL status within the European OMCL Network' was adopted by the plenum. This document will be annexed to the General European OMCL Network (GEON) Terms of Reference and further specifies the criteria for becoming a member of the network and the responsibilities of network members.

OMCL inventory database

One important measure to strengthen the communication within the Network is the provision of supportive information tools. The idea for establishing an OMCL inventory database is almost as old as the network itself. In 1998, the EDQM issued a CD-ROM including, besides basic information about the members of the Network (e.g. name, contact address, etc.), a list of techniques/test methods performed within each OMCL. For several reasons, among others being the rigidity of the records (with data being 'frozen' on a CD), the project was not followed up until 2004, when the network decided to work on a web-based OMCL inventory and competence database. This approach would allow information to be updated on an on-going basis.

Following 2 training sessions in March 2007 in Strasbourg and Vienna, the database was finally launched in July 2007. The initial set of data was entered by the EDQM Secretariat on the basis of questionnaires that had been issued 2 years earlier. Thereafter, each OMCL is responsible for the data administration with respect to its organisation. Access to the information is restricted to OMCLs of the Network, and several technical measures have been taken to guarantee data security and confidentiality.

Quality Management Systems

The Quality Assurance (QA) programme of the OMCL Network, coordinated by the EDQM, is aimed at proposing a common tool for OMCLs to implement, maintain, assess and improve their quality management systems in a harmonised way. It also provides assistance to OMCLs willing to increase their technical competence by means of training visits hosted by other OMCLs and specific training courses organised by the EDQM.

During 2007, 8 Mutual Joint Audits (MJAs) were carried out at OMCL sites: 5 in OMCLs testing human and veterinary medicines (2 in the chemical field, 3 chemical and biological), 1 in an OMCL testing veterinary medicines (chemical field), and 2 in OMCLs testing human medicines (chemical and biological field).

No Mutual Joint Visits (MJVs), Training Visits or Tutorials were performed.

In total, since the beginning of the QA programme 10 years ago, 43 MJAs, 45 MJVs, 2 Tutorials and 11 Training Visits have been carried out in the OMCL Network. 14 MJAs, 3 MJVs and 1 Training Visit are already planned for 2008.

Training courses for the OMCL Network

In 2007, the EDQM organised 2 QA training courses.

- Basic Training on Quality Assurance (25-26 September 2007), which took place at AGES-Akademie, Vienna, Austria, with 52 participants from 27 countries (40 participants from the OMCL Network and 12 participants sponsored by the WHO from regional laboratories in Armenia, Azerbaijan, Ethiopia, Ghana, Kenya, Russia, Sudan, Tanzania, Uganda, Ukraine and Yemen).
- Basic Training on Quality Assurance (27-28 November 2007), which took place at the Laboratoire National de Contrôle de Médicaments, Rabat, Morocco, with 68 participants from 17 countries (all sponsored by the WHO and coming from Algeria, Benin, Burkina Faso, Burundi, Cameroon, Ivory Coast, Democratic Republic of Congo, Guinea, Madagascar, Mali, Mauritania, Morocco, Niger, Senegal, Rwanda, Lebanon and Tunisia).

OMCL Network Quality Assurance Guidelines

2 new annexes to the OMCL Network guideline 'Qualification of equipment' were adopted at the OMCL Network annual meeting in May 2007, dealing with requirements for the qualification of UV-visible and IR spectrophotometers, respectively. A new annex, dedicated to the qualification of automatic titrators, will be submitted for approval at the next annual meeting of the OMCL Network in June 2008 in Strasbourg.

The preparation of other guidelines is foreseen on topics such as Validation of computerised systems, Safety/security measures in chemical and biological laboratories, and Management of expiry dates of reagents.

Several key QA documents and guidelines are available on the EDQM website (<http://www.edqm.eu>). These guidelines are also included in the latest version of the QA booklet of the OMCL Network 'Quality Assurance Documents for the OMCL Network' (published in November 2007).

Collaboration with the European co-operation for Accreditation (EA)

In October 2007, the European co-operation for Accreditation (EA) adopted the following OMCL guidelines as advisory documents, to be used by accreditation bodies when assessing Quality Management Systems at OMCL sites: Qualification of Equipment – Core Document; Annex 1: Qualification of HPLC equipment; Annex 2: Qualification of GC equipment; Annex 3: Qualification of UV-visible spectrophotometers; Annex 4: Qualification of IR spectrophotometers.

In addition, the 2 aides-memoires used by the auditors during MJAs/MJVs were also adopted: Standard aide-memoire for the MJA of OMCLs, and Aide-memoire for environmental conditions and treatment of biological models.

3 OMCL guidelines/policies were already adopted by the EA in 2005 as advisory documents: Validation of analytical procedures; Scope of accreditation of OMCLs; and Uncertainty of Measurement: Policy on the estimation and application of uncertainty in analytical measurement (compliance testing).

These guidelines can be downloaded from the EDQM website (<http://www.edqm.eu>) and from the EA website (<http://www.european-accreditation.org>).

Proficiency Testing Scheme studies

Over the years, the Proficiency Testing Scheme (PTS) studies have become a regular programme within the Network. In 2007, 5 studies were organised in the physico-chemical field, with an average participation of 42 national control laboratories and 29 other pharmaceutical control laboratories, private sector industry and hospitals, while in the biological area 2 studies were organised, involving an average of 25 laboratories (13 OMCLs and 12 laboratories from the private sector.)

The 4th PTS agreement with the WHO, covering the period from April 2007 to June 2009, was signed in March 2007. On average 50 governmental control laboratories belonging to 6 different world regions (Africa, Americas, Eastern Mediterranean, Europe, South-East Asia and Western Pacific) will participate in each of the 5 studies proposed in this 4th phase.

General studies on market surveillance

In 2007, Market Surveillance Studies (MSSs) that aimed at screening the quality of medicinal products commercialised on the European market were carried out for the following products: diclofenac retard preparations; procaine-containing aqueous solutions for injection; and essential oils (coriander, lavender and peppermint oil). Where pertinent, the results of these studies will support the revision of the relevant monographs and/or general chapters and methods of the Ph. Eur.

An average of 12 OMCLs participated in each of the studies. 2 additional studies, which had been initiated in 2006 (erythromycin liquid preparations and erythromycin ester preparations; and trimethoprim, raw material and tablets), were also finalised during 2007.

At the Annual Meeting of the OMCL Network in Prague,

the following MSSs were agreed upon: lisinopril tablets; intramammary suspensions containing amoxicillin, clavulanate and prednisolone; levothyroxine tablets; morphine oral retard products; and omeprazole and lansoprazole gastro-resistant tablets and capsules. The preparation of the protocols for these studies by the respective scientific advisors was initiated in 2007.

Collaborative study on radiopharmaceuticals

A first collaborative study on radiopharmaceutical preparations was initiated in 2007. A total of 13 laboratories (OMCLs and non-OMCLs) participated in this exercise, which consisted of the determination of the radiochemical purity of a Tc-99m-labelled compound by HPLC. The results became available at the end of 2007 and their statistical evaluation will take place early in 2008. The outcome of the study will be presented at the meeting of the relevant group of experts of the Ph. Eur. Commission in April 2008.

Analysis of suspicious unknown products

In 2007, a procedure to evaluate results from the analysis of suspicious unknown products was agreed and a trial phase on 'Performance Studies for Investigational Testing' was initiated. The testing phase of the first proposed study, involving 19 OMCLs, started in January 2008.

CombiStats

In 1999, the EDQM initiated the development of a computer programme for the statistical evaluation of biological dilution assays in accordance with Chapter 5.3 of the Ph. Eur. At that time, most laboratories of the OMCL network used their own in-house-developed software, which led to a strong demand for a common programme to harmonise the presentation of assay data and the analysis thereof. The lack of availability of suitable commercial software resulted in the development of 'CombiStats', which has been used to the general satisfaction of the network since 2000.

Initially the software was only available to OMCLs, but as of 1 November 2005, non-OMCL laboratories can also obtain a user licence. Together with the public release of the software, an official website has been launched at <http://www.combistats.eu>, on which an online manual, a tutorial, examples and background information can be found. A free demonstration version can also be downloaded. The software has been advertised in Pharmeuropa and flyers have been printed to make the software better known to potential users. An important update is currently under development and is expected for release in spring 2008.

In 2007, a total of 92 licences were issued, 38 of which were to OMCL laboratories in 22 countries and 54 to non-OMCL users in 23 countries. As of 31 December 2007, CombiStats is used in 18 countries of the EU and 14 countries outside the EU, including non-European countries such as Argentina, Australia, Canada, India, Japan, South Korea, Uruguay, USA and South Africa. CombiStats has thus evolved into a common internationally agreed reference in its domain and contributes to mutual recognition of data and results by all interested parties.

EU/EEA-SPECIFIC ACTIVITIES**Official Control Authority Batch Release (OCABR) of Biologicals for Human Use***Major highlights*

In the annual meeting of the OMCL in Prague, representatives from the 27 EU member states plus EEA member states and mutually recognised partner Switzerland were invited to take part in the annual plenary session for OCABR activity. More than 80 participants from 24 member states attended. A representative from the European Commission also took part in the OCABR common session involving representatives from both the blood and plasma derivatives field and the vaccine field. Separate parallel sessions were also held to focus on activities related to OCABR for human blood and plasma derivatives and human vaccines.

Following on from the discussions in 2006, a meeting was held on 26 March 2007 to exchange information and develop strategies on a practical level for the eventual OCABR of pandemic influenza vaccines. The meeting was attended by representatives from 9 OMCLs involved in the batch release of inter-pandemic influenza vaccines and/or those who have been contacted by manufacturers as potential batch releasers for pandemic vaccine. Representatives from the WHO also attended.

Another important meeting organised in August 2007 involved an exchange between OMCLs and a number of representatives from vaccine manufacturers as part of a reflection on ongoing and future strategies for replacing, reducing and refining (3Rs) the use of animals during OCABR. A follow-up meeting is planned for January 2008.

Representatives from the EDQM and a number of EU OMCLs involved in OCABR also took part in an initiative co-hosted by the WHO and Health Canada on 21-22 September 2007 to review aspects of official batch release on a global level. The meeting included authorities and manufacturers from around the world. The general consensus was that official batch release was an important tool that should be fostered through the preparation of specific guidance. A drafting group, including representatives from the EU OCABR network, will prepare an appropriate guidance document to be adopted by the WHO Expert Committee for Biological Standardisation.

Annual meeting summary

A review of activities since 2006 for batch release of both blood derivatives and vaccines and specific scientific presentations were given at the annual meeting. An issue of discussion in the common OCABR session was the need for a member state to have a marketing authorisation in their territory for a product in order to perform OCABR on batches of that product. Following the meeting a survey on current practice was carried out and results forwarded to the EU Commission for consideration. In another issue, it was proposed that a common policy was required on how to deal with OCABR certificates that have been issued in good faith, should the situation arise that the batch is later withdrawn from the market. A survey on current practice was carried out and the responses reviewed by the advisory group in their autumn meeting for further action.

Other issues of interest included the evolution and need for the involvement of EU OMCLs in the testing of human biologicals as part of the EU OMCL procedure for application of Article 58 of Council Regulation 726/2004. A teleconference was organised following the meeting with representatives of the WHO to further clarify the situation in order to allow progress in this area.

Another focus of activity was the attempt to increase awareness of the ongoing need to interact more effectively with other branches of the regulatory system. The EMEA has been contacted with examples of areas where technical input from OMCLs upstream of licensing would be beneficial. In a similar issue, better interaction with inspectors and the potential impact of PAT systems by manufacturers was highlighted and a meeting with relevant authorities is planned for 2008.

Progress on the development of a real-time database of batches having undergone OCABR has resulted in the choosing of a system developer after a tender competition. Development is expected to begin in January 2008 and a pilot version should be available by mid-2008.

Adopted Guidelines/Procedures

- *Common Procedures for OCABR*

A revision proposal to include a new annex VII (for procedural information on batches withdrawn during parallel testing), a related revision to annex VI and a revision to include a statement on the reason for batch rejection in annex IIe in the EC Administrative Procedure for Official Control Authority Batch Release were adopted.

- *Guidelines for Human Blood and Plasma Derivative Products*

3 revised product-specific guidelines were adopted, for:

- human immunoglobulins;
- human albumin;
- validation of NAT for quantification of B19 virus DNA in plasma pools; this guideline is presently under consideration with Ph. Eur. group of experts 6B for inclusion in a general chapter of the Ph. Eur.

- *Guidelines for Human Vaccines*

1 new-product specific guideline and 10 revised guidelines were adopted for:

New

- human papillomavirus (rDNA) vaccine;

Revised

- varicella/shingles vaccine;
- BCG vaccine;
- hepatitis A vaccine (inactivated, adsorbed);
- hepatitis A (viroosomal) vaccine;
- hepatitis B (rDNA) vaccine;
- influenza vaccine;
- influenza vaccine (surface antigen, inactivated, virosome);
- poliomyelitis vaccine (inactivated);
- tick-borne encephalitis (TBE) vaccine;
- control authority approval of poliomyelitis vaccine (oral) (OPV) - monovalent bulks;

In addition, a procedure to assure the independent testing of OPV monovalent bulks by the transgenic mouse neurovirulence test was adopted.

All adopted product-specific guidelines and administrative procedures are available in the book published by EDQM at the end of December 2007. They can also be downloaded in their entirety from the EDQM website (http://www.edqm.eu/site/Human_Biologicals_OCABR-611.html).

• *Official Control Authority Batch Release (OCABR) of Immunological Veterinary Medicinal Products (IVMPs)*

The following procedures and guidelines, developed through the course of 2006/7 by the IVMP OCABR network in co-operation with the EU Commission and with industry consultation, were adopted by the Veterinary Pharmaceutical Committee in their session of 20 March 2007:

- the procedure for application of Article 81 (Official Batch Protocol Review (OBPR));
- the procedure for application of Article 82 (Official Control Authority Batch Release (OCABR));
- 15 product-specific guidelines for products on a shortlist for OCABR as determined through risk assessment;
- 5 model templates for manufacturers' protocols to be submitted for OCABR and OBPR.

All the adopted documents can be downloaded from the EDQM website (http://www.edqm.eu/site/Veterinary_Biologicals_OCABROBPR-634.html)

A recommendation document from the EU Commission developed with input from the network and industry was also adopted by the Veterinary Pharmaceutical Committee in March 2007. It highlights strategies for risk-based assessment for application of OCABR and trend-analysis strategies to be used for test-reduction proposals, as well as guidance on dealing with out-of-specification results. This document can be obtained from the EU Commission website (http://ec.europa.eu/enterprise/pharmaceuticals/index_en.htm).

These documents are now in force and replace the former system. An implementation phase is underway with the first accounting to take place at the annual meeting in June 2008.

As the annual meeting of 2006 took place in November in order to accommodate the pilot phase, the annual meeting in 2007 focused on scientific issues only. Of key importance was a review of the current practice for potency testing of inactivated rabies vaccines for veterinary use, which was dealt with in a dedicated session. The difficulties linked to validation of this assay and the need to reduce animal use were highlighted. A working group has been formed with the goal to optimise the current assay and investigate possible alternatives.

As OCABR is a may clause, and OBPR is a voluntary procedure applied through goodwill and mutual understanding, a survey was performed in the 4th quarter of 2007 to determine the state of application of both article 81 and article 82 in the different member states. Results were communicated to the EU Commission and the manufacturers' associations.

Market surveillance for products with a centralised marketing authorisation

The programme for sampling and testing of Centrally Authorised Products (CAPs) was successfully continued in 2007 and entered its 9th consecutive year. Since its implementation the programme has been continuously improved thanks to the collaboration between all stakeholders:

- the European Medicines Agency (EMA), which is the sponsor and has overall responsibility for the programme;
- the EDQM, which co-ordinates the sampling and testing operations on the basis of the information provided by the marketing-authorisation (MA) holders upon request from the EMA, and reports to the EMA the outcome of the sampling and testing operations with proposals for follow-up actions where necessary;
- the national inspection services, who perform product sampling on the market;
- the OMCLs of the EU/EEA OMCL Network, who perform analytical testing of products.

The CAP programme covers medicinal products for both human and veterinary use. In 2007, it covered a total of 40 medicinal products, corresponding to 35 medicinal products for human use (11 biologicals (formerly list A products) and 24 chemical/pharmaceutical/radiopharmaceutical products (formerly list B products)), as well as 5 medicinal products for veterinary use (3 immunobiological and 2 chemical products). In 2007 the programme included the examination of the active substances (APIs) of 3 different products. This makes 2007 the sampling and testing programme with the lowest number of active substances tested since 2002. With regard to the total number of medicinal products included in the programme, an increase of 25 per cent compared to the 2006 CAP programme could be observed. This brings the CAP 2007 programme back into the usual range of number of products tested each year and indicates that, for some reason, the CAP 2006 programme was an exception with only 33 products tested. It also implements the agreement established between the EMA and the EDQM stating that the number of products included in the yearly programmes would be fixed at at least 40 as of 2007. Products to be included in the 2007 programme were selected by EMA expert committees from those authorised in 2004 (year n-3), thus guaranteeing that the selected products have been launched and manufactured on a large scale. In addition to these products, the list was complemented with 9 products from a reserve list, which had been drawn up in collaboration with the OMCLs.

Further to a general batch recall initiated in December 2006, one veterinary immunobiological product could not be tested as no more samples could be found on the EU/EEA markets. The manufacturer did not foresee the reintroduction of this medicinal product on the market in 2007, and this product was therefore withdrawn from the 2007 CAP programme in August 2007.

In accordance with the procedure PA/PH/CAP (05) 96 DEF 'Procedure for ad-hoc testing of centrally authorised products', one product that applied for an MA was added to the 2007 programme in January 2007 upon request

from the CHMP. The purpose of this pre-authorisation testing was to assess the suitability of 2 analytical methods described in the marketing authorisation file during the evaluation period as support to the assessors.

In general, market samples were collected in 3 EU/EEA countries for each product in order to have an overview of the actual product quality of distributed batches. This sampling pattern was customised for products with a low volume of distribution such as orphan medicines, and for products where different dosage strengths were investigated. Overall, 116 sampling operations have been carried out by national inspection services in 27 EU/EEA member states. The proportion of samples drawn from hospitals and pharmacies has significantly increased since 2006 to approximately 16 per cent of the total sampling operations, to the detriment of sampling operations carried out at wholesalers. The application of the new 1-OMCL-only testing scheme for all chemical products tested in the 2007 programme (see below) may have contributed to this positive trend by reducing the overall number of pharmaceutical units to be sampled for *chemical products*. Even though more than 80 per cent of the samples still originate from MA holder warehouses or wholesalers, the trend towards sampling further down the distribution chain that seems to emerge from this data should be regarded as a promising first step. Market samples, non-commercially available standards and specific reagents provided by the manufacturers represented approximately 400 items. Collection of these materials, storage, coding and dispatching to OMCLs for testing was dealt with by the EDQM.

As planned, the new testing scheme for chemical products, gradually introduced since 2005, was applied to all chemical products for the first time during the 2007 programme. All chemical products were tested by a single OMCL, with the possibility of involving a 2nd OMCL at a 2nd stage only in the case of analytical or compliance issues. The reduction in the number of OMCLs involved in the testing operations on chemical products resulted in a reduction in the number of pharmaceutical units required to perform this testing campaign; this allows for a higher proportion of sampling operations in hospitals and pharmacies and such an increase was actually observed in 2007. Testing of *non-chemical products* continues to be performed by 2 OMCLs in parallel.

On the whole, 29 OMCLs from 24 EU/EEA countries took part in the 2007 programme, which consisted of a total of 58 testing operations. In 2007, only one product did not meet the registered specifications: concerns regarding the suitability of the analytical method used by the MA holder for routine investigation of the pH of a solution for injection were brought up by out-of-specification results obtained during the testing. This finding was not considered a threat to public health and no recall was initiated. Nevertheless, the issue was reported to the EMEA who initiated appropriate follow-up actions.

All other products tested complied with their authorised specifications; for some of them minor issues, mainly related to the quality of the analytical documentation (MA dossier and/or standard operating procedures (SOPs) for quality control (QC)), were reported. Difficulties were also encountered during method setting-up, e.g. for automated methods or unusual techniques. In 2 particular cases (such as for specific testing methods

involving bioassay on cell line) and to overcome these difficulties, specific training visits, in collaboration with the MA holder, were organised.

For all products, individual product reports were issued by the EDQM and distributed to all parties (EMEA, OMCL Network, involved sampling contacts). All issues were thus reported to the EMEA and their scientific experts, together with the proposals for necessary follow-up actions on the registration dossier and/or on analytical testing methods. The individual product reports are distributed to the MA holder via the EMEA. In general, AMM holders have access to reports via the EMEA. A global report on the results of each annual programme is published on the EMEA website 6 to 8 months after the end of the annual sampling and control campaign.

The collaboration between all parties was facilitated by the extensive use of IT tools (EMEA Eudralink, EDQM extranet CAPnet) and 2 productive meetings at the EDQM. Thanks to the work of the Advisory Group of the CAP programme, a revised version of the general procedure describing the course of a yearly programme was adopted during the 2007 CAP Annual meeting, which took place in December 2007 in Strasbourg. A risk-based approach for the selection of products to be tested is currently being established in collaboration with the EMEA and the OMCL Network, with the objective to replace the 'n-3' rule for inclusion of centrally authorised products in a yearly programme. Discussions about harmonisation of the selection of parameters to be tested for each product have also been initiated in 2007 within the CAP Advisory Group. These discussions will continue in 2008 and are expected to result in the drafting of a document intended to help assessors select the different parameters to be investigated.

Post-marketing surveillance of products with a marketing authorisation according to the Mutual Recognition Procedure (MRP) and the Decentralised Procedure (DCP)

In 2007 the 3rd regular programme of post-marketing surveillance of MRP products was performed. During this year, for the first time, the OMCLs were also encouraged to consider DCP products in their individual testing plans. By the end of 2007, about 10 per cent of medicines out of the pool of former MRPs were authorised via this new community procedure. 15 OMCLs have actively participated in the 2007 programme and approximately 330 projects (compared to 250 in 2006) could be finalised. It was also noted that more samples were exchanged between the participants than in previous years, which allowed the coverage of a broader range of batches per project.

In 2007, 2 meetings of the MRP/DCP testing group took place during the annual OMCL and CAP meetings, respectively, in order to save time and resources.

The Most important step taken during the previous year was the launch of Version 1.0 of the MRP/DCP-product testing database in July. This IT tool allows a better co-ordination of the planning, sampling and reporting phase, but also provides a platform for information exchange about follow-up actions taken on the basis of test results. This piece of information had not previously been considered in the programme. In a next step it is planned to grant reading access to the

users of the Communication and Tracking System (CTS), the regulators of national competent authorities. This database project is one of the contributions to a closer collaboration of the OMCL Network and the EDQM with the owners of the CTS, the Heads of Medicines Agencies, who have expressed their interest in the MRP/DCP testing scheme.

In order to make the OMCL users familiar with the new computer application, a specific training course for OMCL database administrators was organised by the EDQM on the occasion of the annual meeting of the General OMCL Network in Prague. In future meetings a sufficient time slot will be reserved for discussing the use and improvement of this IT tool.

For the establishment of future annual programmes, it was decided to introduce principles of risk assessment in the selection process of test products. During 2007 a trial phase group consisting of 7 volunteering OMCLs enhanced a risk-based model originally developed by the Dutch OMCL after ranking in a 'test run' products from a jointly established random list employing the original model. It is intended to use the model as a selection tool for the planning of other network activities (CAP programme) and national testing campaigns.

4. HEALTH CARE ACTIVITIES

Blood Transfusion (TS) and Organ Transplantation (TO)

Within the context of intergovernmental co-operation in the field of health, the Council of Europe has consistently selected ethical problems for study. One of the most important ethical issues relates to the non-commercialisation of human substances, i.e. blood, organs and tissues.

With regard to blood transfusion, co-operation among member states started back in the 1950s. From the outset, the activities were inspired by the following guiding principles: promotion of voluntary, non-remunerated blood donation; mutual assistance of member states (e.g. in the exchange of blood typing reagents); optimal use of blood and blood products; and protection of the donor and the recipient.

Later, activities in the field of organ transplantation were initiated according to the leading principles of ensuring the dignity of the human being, maintaining and promoting human rights and fundamental freedom, non-commercialisation of substances of human origin and protection of donors and recipients.

Around its first agreements in the 1950s and the 1970s, the Council of Europe has established pan-European programmes on blood transfusion and transplantation. Since February 2007, these programmes are run under the aegis of 2 new Steering Committees (the European Committee (Partial Agreement) on Blood Transfusion (CD-P-TS) and the European Committee (Partial Agreement) on Organ Transplantation (CD-P-TO)), which were created by the Council of Europe under the charge of the EDQM.

Meetings, events, communication

In 2007, each of the committees met twice to elaborate their respective work programmes and to initiate

activities. Financial assistance was granted to support the participation of a number of delegates from Eastern Europe at these plenary meetings.

A blood collection on the new EDQM premises was organised in collaboration with the Strasbourg Section of the Etablissement Français du Sang (EFS) and with the Amicale of the Council of Europe, in support of World Blood Donor Day.

The 9th European Organ Donation and Transplantation Day was hosted for the first time by a patient association, the Irish Kidney Association, and was organised on 13 October 2007 in Dun Laoghaire (Dublin, Ireland).

A 'Healthcare' section was included on the EDQM public website.

Projects and publications

A subordinate working group was created and a public enquiry performed to enable the update of the 13th edition of the Council of Europe 'Guide to the preparation, use and quality assurance of blood components'. The new edition was published in English and in French in January 2008.

The follow up of the reporting by Council of Europe member states on the collection, testing and use of blood components was organised, and the 2004 survey was completed and published. Reports on the 2005 and 2006 surveys and on trend analysis on data from the years 2001-2006 are currently under preparation.

2 Recommendations to member states on 'The background, functions and responsibilities of a National Transplant Organisation (NTO)' and on 'Quality improvement programmes for organ donation' (see <http://www.edqm.eu/site/Recommendations-74.html>) that were adopted by the Committee of Ministers on 6 November 2006 were published in the 2007 issue of 'Transplant Newsletter' together with the international figures on organ donation and transplantation.

International surveys on critical issues (e.g. transplant tourism) and drafting of state-of-the-art position papers (e.g. on international organ exchanges) were initiated.

Resolutions

3 draft Resolutions were elaborated in collaboration with the Bioethics Committee of the Council of Europe (CDBI) on donor responsibility and limitation of donation of blood and components, living donor kidney transplantation and living donor liver transplantation. They will be submitted to the Committee of Ministers for adoption in 2008.

5. EXTENSION OF EDQM ACTIVITIES

The Council of Europe has decided to carry forward the activities related to pharmaceuticals, hitherto carried out in the framework of the Partial Agreement in the Social and Public Health Field, within the EDQM as of 1 January 2008.

The above-mentioned programme of activities covers areas of great relevance for the quality of healthcare and healthcare practice in Europe, in particular:

- patient-oriented, intergovernmental co-operation as regards pharmaceutical practice, focusing on the safe and effective use of medicines in society;

- model approaches for risk management, prevention and improved co-operation among public and private sectors in the field of public health protection from counterfeit medicines and related crimes;
- the harmonisation of provisions and practice as regards the legal classification of medicines as prescription and non-prescription medicines, with a view to patient safety, the accessibility of medicines and responsible management of healthcare expenditure.

The activities will be continued within the framework of the EDQM, Department of Biological Standardisation, OMCL Network & HealthCare (DBO)

6. NEW EDQM BUILDING

The new building was critical for the future development of the EDQM and will help it to respond to new public health needs in Europe. Starting in 2004, work was completed in March 2007 with the move of the Laboratory department and the Division for reference standards and samples.

The building offers new meeting rooms, including a specific room for the sessions of the European Pharmacopoeia Commission, new analytical laboratories, and dedicated facilities for reference standards production, storage and shipment.

It has been built and operates according to the French HQE ('High Environmental Quality') standard.