

# European Directorate for the Quality of Medicines (EDQM) Annual Report of Activities - 2006

The activities of European Directorate for the Quality of Medicines are described in terms of its 3 main areas of responsibility:

1. the European Pharmacopoeia, including publication and communications activities, and international relations
  - 1.1. European Pharmacopoeia Department
  - 1.2. Communications and Public Relations
  - 1.3. Provision of reference substances and preparations
  - 1.4. Preparation and dispatching of samples
  - 1.5. Biological Standardisation Programme
2. the procedure for Certification of Suitability,
3. the European network of Official Medicines Control Laboratories (OMCLs).

In 2006, pharmacopoeia authorities and licensing authorities all over the world showed growing interest in the work of the European Pharmacopoeia, Certification of Suitability and the network of Official Medicines Control Laboratories.

## 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, "The Former Yugoslav Republic of Macedonia", 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, Turkey and the United Kingdom.

There are 3 new observer states at the European Pharmacopoeia Commission: Kazakhstan, the Russian Federation and Belarus, bringing the total number to 20, namely: the World Health Organization (WHO) plus 6 European countries (Albania, Georgia, Kazakhstan, the Russian Federation, Belarus and Ukraine) and 13 non-European countries [Algeria, Australia, Brazil, Canada, China, Israel, Madagascar, Malaysia, Morocco, Senegal, Syria, Tunisia and the United States (FDA)].

### 1.1 EUROPEAN PHARMACOPOEIA DEPARTMENT

#### GENERAL ACTIVITIES

The European Pharmacopoeia Commission continued its work on the preparation of the supplements of the 5<sup>th</sup> Edition, which entered into force on 1<sup>st</sup> January 2005.

Three supplements (5.6, 5.7 and 5.8) were published in 2006 with implementation on the 1<sup>st</sup> January 2007, 1<sup>st</sup> April 2007 and 1<sup>st</sup> July 2007, respectively.

At its 3 Sessions in March, June and November 2006, the European Pharmacopoeia Commission adopted 236 monographs (new and revised). Procedure IV set up for new products and based on collaboration with the manufacturers and national control laboratories continued to yield encouraging results: 7 monographs were adopted. This procedure has now been adopted as a standard procedure. The number of documents produced (new and revised) increased slightly: 3308 in 2006 (compared to 3025 in 2005). A new chapter on methods of preparation of homoeopathic stocks and potentiation was adopted and a new working party was set up to elaborate new methods of production. The European Pharmacopoeia extended its work on biological standardisation to new areas: a new chapter on viral safety was adopted and a number of general monographs now refer to this chapter. 2 new monographs on salmonella vaccines (inactivated) for chickens were adopted; these 2 veterinary vaccine monographs are primarily aimed at protecting consumers of hens' eggs from salmonella. Finally, the chapter on mycoplasmas was modified to include nucleic acid amplification as a detection technique.

In 22 existing monographs on active substances, the test for Related substances by TLC has been replaced by a modern HPLC test in order to align the monographs with the requirements for new chemical entities.

A specific work programme for the elaboration of monographs on herbal drugs used in Traditional Chinese Medicines has begun and the first 3 monographs were adopted.

230 days in total were devoted to meetings in 2006. This includes the 3 plenary sessions of the Commission and the corresponding preparatory meetings, the meetings of the Groups of Experts and those of the *ad hoc* Working Parties (115). This total also includes the participation of members of the Secretariat in various other meetings: meetings of the Pharmaceutical Committee (Brussels) on medicines for human and veterinary use, meetings of the various working parties of the Committee for Medicinal Products for Human Use (CHMP) and of the Committee for Medicinal Products for Veterinary Use (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). In addition, the EMEA/EDQM meeting of the chairs of these groups (chair of the CHMP and chair of the European Pharmacopoeia Commission) with the participation of the heads of the scientific services of the

EMEA/EDQM, gave an overview of the subjects of mutual interest and projects that could be set up in the future. 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 ICH Quality Expert Working group (Q4B EWG), 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 Pharmacopoeial Discussion Group [European Pharmacopoeia (Ph. Eur.), Japanese Pharmacopoeia (JP) and United States Pharmacopoeia (USP)] met in Yokohama (Japan) on the 5<sup>th</sup>-8<sup>th</sup> June 2006 and in Chicago (United States) on the 22<sup>nd</sup>-26<sup>th</sup> October 2006 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 by PDG:*

3 new monographs signed off: Hypromellose phthalate, Rice starch and Povidone.

#### *Regulatory acceptance of pharmacopoeial interchangeability*

To facilitate this recognition, the ICH Steering Committee has set up an Expert Working Group: ICH-Q4B. As the 3 pharmacopoeias are made legally binding by the respective legislations, the regulatory authorities have to set up a common procedure to allow official recognition of the 3 pharmacopoeias for texts considered to be harmonised and therefore interchangeable; the authorities must also deliver a clear message to the industries in the 3 regions with a common date for entry into force. The text defining the role of the PDG and the various stages leading to international harmonisation has been revised to reflect the interaction with the ICH-Q4B EWG.

2 joint meetings between the PDG and the Q4B EWG were held on the 8<sup>th</sup> June 2006 and 26<sup>th</sup> October 2006 to discuss the regulatory acceptance of harmonised monographs and general chapters, particularly those covered by the ICH Q6A guideline; the document detailing the roles and responsibilities of the PDG and Q4B EWG was discussed with further refinement necessary; 5 packages for harmonised general chapters were submitted by the PDG to the Q4B EWG: dissolution, extractable volume, particulate matter in parenterals, residue on ignition/sulphated ash and the sterility test.

Examination of the test for residue on ignition/sulphated ash was completed by the Q4B EWG, and tests, analytical procedures, and acceptance criteria of the three pharmacopoeias will be recognised as interchangeable by the regulatory authorities in the 3 regions once the harmonised text has been published and implemented in all 3 regions. The PDG will reply in 2007 to the Q4B EWG on the determination of particulate contamination, for which harmonisation is expected following the USP's proposal for revision of its text. The USP has revised its text on the test for extractable volume and the PDG is

waiting for the Q4B EWG's conclusions on this subject. The dissolution test was discussed at the 24 October 2006 meeting and the Q4B EWG prepared a report listing a number of aspects that had to be resolved in order to achieve regulatory interchangeability. The remaining issues for regulatory interchangeability of the test for sterility have been resolved, with each Pharmacopoeia agreeing to move towards harmonisation at the expense of its local concerns. Finally, documentation packages on the PDG-harmonised tests for disintegration and uniformity of dosage units are being prepared and will be submitted to the Q4B EWG. This is also the case for chapters on microbial count methods, tests for specified micro-organisms and acceptance criteria for pharmaceutical preparations.

#### *Relations with industry associations:*

A meeting with pharmaceutical industry associations was held on 6 June 2006 to exchange information on progress with the current work programme and future harmonisation needs. Industry associations were encouraged to play an active role in the harmonisation process as important stakeholders.

Excipients producers: 2 meetings were held with Tri-PEC (IPEC Americas, IPEC Europe, Japanese Pharmaceutical Excipients Council) on 8 June and 26 October 2006 to discuss the work programme on harmonisation of excipient monographs. Current issues include functionality-related characteristics, use of additives and processing aids in excipients, analysis of povidone/crospovidone and cellulose derivatives, and the future of harmonisation.

#### STANDARD TERMS

Since 2006, it has been the responsibility of the national authorities to introduce the translations of standard terms into the specialised database, on the EDQM Internet site. These terms are now available in 27 languages; the addition of Chinese is currently being worked on.

#### TRANSLATIONS AND PUBLICATIONS

The European Pharmacopoeia is published in both official languages of the Council of Europe; a Spanish version is also available, but for now only on the Internet. A paper version is planned for the 6<sup>th</sup> edition. In 2006, 206 texts were translated from English to French (equivalent to 1333 pages with 300 words per page) and 244 from French to English (equivalent to 826 pages with 300 words per page).

In the area of publications, the year 2006 issues of *Pharmeuropa* comprised a total of 722 pages in French and 696 pages in English, *Pharmeuropa Bio* (issues in English only) comprised 88 pages, and the 5<sup>th</sup> Edition of the European Pharmacopoeia comprised 5770 pages in French and 5440 in English. The 3 supplements for 2006 of the 5<sup>th</sup> Edition comprised 1128 pages in French and 1070 in English.

The 5<sup>th</sup> edition consists of 1985 monographs, 307 general texts and 2356 descriptions of reagents, and is published in both electronic and book form.

A "Certificate of Authenticity" for the EDQM publications has been developed to protect against unauthorised copying. This certificate contains open and hidden

security features. In addition each certificate contains a unique "EDQM Publication ID", which serves for registration of the electronic versions and allows users to verify their genuine EDQM publication using an online registration.

The cumulative electronic edition of the European Pharmacopoeia is 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 and the KNOWLEDGE database. The *online* version uses an improved interface with some added features such as showing the number of hits in the table of contents and an improved hitlist presentation. All 3 electronic formats contain printable PDF files of the texts which are identical to those of the paper version.

*Pharmeuropa* (including *Pharmeuropa Bio* and *Pharmeuropa Scientific Notes*) is now also 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 18 (2006). The necessary access code can be generated using the information from the Certificate of Authenticity on the inside front cover of *Pharmeuropa* 18.1.

Access to the online version of Standard Terms has now been 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 on the Certificate of Authenticity on the inside front cover.

## 1.2 COMMUNICATIONS AND PUBLIC RELATIONS

The EDQM continued its general policy of communications with its partners, giving priority in 2006 to reinforcing its Internet site 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 products.

In its international relations, the EDQM strived to consult all its partners by meeting 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 users about EDQM products and services.

The number of visitors and visits to the EDQM Internet site continued to increase, in November 2006 reaching over 16 000 visitors and 47 000 visits for that month.

A number of features were introduced in 2006 which were greatly appreciated by users.

- A new electronic version of the list of Standard Terms, which is available on subscription and accessed via the Internet site.

- The *Frequently Asked Questions* (FAQ) page was updated for all of the activities of the EDQM. New questions and answers were included and user feedback was used to revise answers.
- The new online HELPDESK service, accessed via the Internet site of the EDQM, has been fully operational since April 2006 and covers all the EDQM's areas of activities. It has received 7000 questions since this date. If all types of questions are considered, the average time for the EDQM to reply to a question is 3 days. However, technical questions on European Pharmacopoeia texts may require more time, especially if the group of experts has to be consulted or if a laboratory study has to be carried out.
- The KNOWLEDGE database continues to be the central repository of technical and regulatory information for the texts of the European Pharmacopoeia. This database now provides information on the history of revisions of European Pharmacopoeia texts.
- The PHARMACEUTICAL REFERENCE SUBSTANCES database has also been considerably reinforced and can now be used to obtain new information on reference substances or reference preparations: the origin of the substance, information on the validity of the batches, a list of new substances available etc. It became accessible on line during the year.

It should also be noted that EDQM Internet sites changed domain names in 2006 and have become: <http://www.edqm.eu> and <https://www.edqm.eu/store>, respectively.

### Organisation of symposia on current issues

*Symposium on New impurities control: setting specifications for antibiotics and synthetic peptides, September 2006, Strasbourg, France*

The main aims of this international symposium were:

- to discuss a technical and scientific approach to cover new aspects of Quality and Safety for the 2 classes of products: antibiotics and synthetic peptides; this approach will then be used in the elaboration and revision of European Pharmacopoeia monographs,
- to take into consideration the views and expectations of all parties involved, such as European authorities and national authorities, manufacturers, inspectors and assessors from all over the world, when revising existing European regulations.

Round-table discussions took place at the end of each session and these were aimed at exploring the 2 topics further and to open up the debate in order to share scientific knowledge and expertise.

This symposium was attended by 135 participants from 30 different countries.

A regulatory debriefing session was also held after the plenary symposium with a view to reviewing the proposals and feedback received. The EDQM is responsible for writing a report summarising the discussions and circulating it to the relevant European bodies and to the European Pharmacopoeia Commission.

*Symposium on New microbiology chapters of the European Pharmacopoeia, October 2006, Strasbourg, France*

The main aims of this international symposium were:

- to present and to explain the changes and new features in the harmonised chapters and to analyse their impact for users;
- to help professionals to manage the transition period (2007-2010) intended to allow adaptation to the new chapters for the wide range of products affected;
- to present the new general chapter on alternative methods and its role in facilitating the introduction of modern techniques, taking into account the viewpoints of regulatory authorities and industry.

Discussions and Round-table discussions took place at the end of each presentation and session. These were aimed at answering the questions of the audience and explaining the rationale behind innovations and changes in order to share scientific knowledge and expertise.

This symposium was attended by almost 190 participants from 28 different countries.

*International symposium on Requirements for production and control of avian influenza vaccines, October 2006, Strasbourg, France*

The main aims of this symposium were the following:

- to discuss within existing regulations if it is necessary to regulate avian influenza vaccines via the European Pharmacopoeia so that their quality will be controlled and assured in the same way throughout Europe as a number of new avian influenza vaccines are in the process of obtaining or have already received their marketing authorisation;
- to take into consideration the views and expectations of all parties involved, such as European authorities and national authorities, manufacturers, inspectors and assessors from all over the world;
- to discuss future regulatory provisions, in particular those regarding the demonstration of immunogenicity and routine potency testing.

Round-table discussions took place at the end of each session which were aimed at further exploring all the issues concerning production and quality control further and to open up the debate in order to share scientific knowledge and expertise.

This symposium brought together 80 scientific experts from 18 countries, representatives of vaccine manufacturers and of European national control laboratories to exchange their points of view and their experiences so that they could find answers to these questions.

The conclusions of the symposia are published on the Internet site of the EDQM (<http://www.edqm.eu>).

**Training sessions / presentation of the missions of the EDQM**

*The EDQM organised 3 training sessions in 2006, in London (March 2006), Chicago (April 2006) and Dublin (November 2006).*

The session in the United States was organised at the request and with the support of the Midwest Compensial

Group (MWCG) and was attended by over 60 participants from the major pharmaceutical companies in this region. The programme for this training session had been tailored to the needs of the participants, who rated it very highly in their evaluations.

*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: Mumbai (India) with the association of Indian generics producers, IDMA (150 persons, January 2006), Shanghai (China) with the Chinese Pharmaceutical Association CPA (80 persons, June 2006) and Sao Paulo (Brazil) with the Brazilian authorities (150 persons, October 2006). A session was also organised in Rabat (Morocco) by the Moroccan Health Ministry (150 persons, September 2006).

A training session was also held in Strasbourg (September 2006) for quality auditors in the European Network of official medicines control laboratories (OMCL). This very specific session was attended by 25 participants from 13 countries.

**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 (February 2006)*

*Brazilian and United States delegations (March and June 2006)*

Following the March and June 2006 sessions of the European Pharmacopoeia Commission, the EDQM was visited by delegations from the Food and Drug Administration of the United States and Brazil. These visits were part of the follow up to observer status at the Commission being granted to these countries and discussions took place on future programmes for collaboration.

*Visits from German farmers and Dutch nurses (May 2006)*

The EDQM welcomed 2 groups of visitors in May 2006. The 1<sup>st</sup> group consisted of 40 German farmers who attended a presentation on EDQM activities specifically related to their work (veterinary vaccines in particular). The 2<sup>nd</sup> group, consisting of Dutch nurses, attended a presentation that gave a broader view of EDQM activities for the protection of public health.

**Exhibition on the European Pharmacopoeia for the general public**

Since 2004, the EDQM has been making available to those who request it a travelling exhibition entitled "Find out about the European Pharmacopoeia and Medicines" which can be used as an educational tool during a particular event. This exhibition consists of panels which explain what a pharmacopoeia is and how it guarantees the quality of our medicines; there are also panels describing all the activities of the EDQM in its European and global environment.

This exhibition was presented in various places and to various audiences in 2006:

*June 2006, Bonn, Germany*

In conjunction with the annual meeting of national pharmacopoeia secretariats, the English version of the exhibition was shown to staff of the BfArM (Bundesinstitut für Arzneimittel und Medizinprodukte). The exhibition helped explain the programme for European co-operation in the area of quality control of medicines, a programme in which the German authorities are very active participants.

*June 2006, Hospices civils de Lyon, France*

The French version of the exhibition was presented to the general public as part of an event entitled "les Promenades Pharmaceutiques", for 2 weeks in the "Grand dôme des hospices civils" of the Hôtel Dieu hospital.

*October 2006, construction site of the new EDQM building, Strasbourg, France.*

**International relations**

**Relations with partner European authorities and other international organisations**

*Relations with the Commission of the European Communities*

Representatives of the EDQM participated in a joint meeting with representatives of the Commission of the European Communities. One of the objectives was to discuss the need for a future European procedure to guarantee the quality, efficacy and safety of veterinary vaccines (*July 2006, Brussels, Belgium*). Exchanges also took place during other meetings in 2006.

*Relations with the European Medicines Agency (EMA)*

In addition to the yearly consultation meeting between the two institutions, co-ordination and co-operation activities with the agency continued throughout the year. EDQM representatives participated as observers in all the working parties, notably the Biotechnology, Quality, Herbal Medicinal Plants, Inspection and Immunological working parties. Representatives of the agency were also invited to participate in symposia organised by the EDQM in areas of common interest to both institutions.

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 Committees on Biological Standardisation (ECBS) and on Reference Standards. 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 has been designated as a WHO collaborating centre for International Standards for Antibiotics (ISA). In this context, the EDQM presented its first study on an antibiotic; this study and the corresponding international standard were approved by the Committee.

The EDQM and the WHO also met in July 2006 in Strasbourg (France). This specific meeting was aimed at the elaboration of a manual for WHO reference laboratories that would describe methods to be set up for the quality control of diphtheria, tetanus and pertussis vaccines including alternative serological methods.

The EDQM also participated in the first meeting of the WHO International Medical Products Anti-Counterfeiting Taskforce (IMPACT) in November 2006 in Bonn (Germany). This meeting was organised to set up this taskforce, which will establish an action plan to fight counterfeit medicines.

*Relations with the World Organisation for Animal Health (OIE)*

The EDQM has developed regular contacts with this organisation which plays a similar role to the WHO but for animal health. Representatives of the EDQM thus participated in meetings of OIE working groups in 2006, in particular those of working groups on laboratory diagnosis of diseases (epizooties, surveillance programme) and those on the standards used for the control of veterinary vaccines. The EDQM was also invited to the organisation's annual meeting in December 2006 and took this opportunity to describe its experience in setting up the European network of OMCLs and presented its results.

*Relations with the World Antidoping Agency (WADA)*

The World Antidoping Agency (WADA) is the independent international organisation created in 1999 to promote, co-ordinate and supervise the fight against all forms of doping in sport. WADA concentrates its efforts in several areas of activities, notably out-of-competition testing (with no advance notice) in collaboration with its partners, to supplement antidoping efforts by the partners.

A representative of the EDQM laboratory was named as an independent expert working with the WADA Laboratory Committee, and participated in the working meetings (March, June, September and November 2006). This Committee is responsible for the accreditation and proficiency testing of independent antidoping testing laboratories. The EDQM has recognised expertise in the area of proficiency testing of laboratories and statistical analysis. The EDQM therefore collaborated with this Committee in these specific technical areas.

**Meetings and consultations with partner authorities**

*Annual meeting of the European Network of Official Medicines Control Laboratories (OMCLs), (May 2006, Limassol, Cyprus)*

At the invitation of the EDQM, 180 participants from 32 countries attended the annual meeting of the European network of OMCLs (see chapter 3 for more details).

*Relations with the Heads of Medicines Agencies (HMA) group*

Representatives of the EDQM participated in the meetings of this group in 2006 and presented the activities of the EDQM to reinforce co-operation and synergy between the various partners in Europe.

*Relations with the secretariats of national pharmacopoeias (May 2006, Bonn, Germany)*

The annual meeting of the national secretariats of pharmacopoeias was attended by 24 participants representing 21 national authorities. The meeting had been organised at the BfArM (Bundesinstitut für Arzneimittel und Medizinprodukte), the German agency in charge of marketing authorisations and control of medicines for human use.

*Relations with the United States Pharmacopeia (USP) (April 2006, Rockville and Washington, United States; July 2006, London, United Kingdom; December 2006, Strasbourg, France)*

The EDQM had several meetings with the United States Pharmacopeia: in April a representative of the EDQM was invited to USP headquarters to exchange views and technical experience on various subjects of common interest. This representative also attended an international conference on the establishment of herbal reference standards and presented the point of view of the European Pharmacopoeia.

In July 2006, in London (United Kingdom): a tripartite meeting brought together representatives of the EDQM, the USP and a British control laboratory (NIBSC) to discuss a project for reinforced co-operation between these 3 organisations and a possible partnership to develop common reference centres for various major European organisations.

Finally a discussion meeting was organised in Strasbourg in December 2006.

*Relations with the Brazilian authorities (October 2006, Sao Paulo, Brazil)*

At the invitation of the Brazilian authorities responsible for the quality control of medicines (ANVISA, Brazilian Pharmacopoeia), a multidisciplinary team from the EDQM participated in several meetings and visits to explain the activities of the EDQM more extensively. This initiative followed the granting of observer status at the European Pharmacopoeia Commission to Brazil. The possibility of reinforced co-operation between Brazil and EDQM was also discussed. The protocol for a co-operation agreement was signed during this visit.

*Relations with the Canadian authorities (November 2006, Ottawa, Canada)*

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.

In this context, exchanges of staff and information on this procedure concerning active substances used in medicines for human use have already taken place. An additional step was taken in November 2006 when a representative of the EDQM was invited to discuss the progress made on official recognition of certificates of suitability by the Canadian authorities. The terms of an agreement for future co-operation between these two organisations were also discussed.

*Relations with the Chinese authorities (June 2006)*

A team from the EDQM was received by the Chinese authorities in charge of quality control of medicines at

the national (Beijing) and provincial (Shanghai) levels as laid down in the mutual agreements that have been signed or which are being finalised.

*Relations with the Indian authorities (January and November 2006)*

An official meeting with the Indian Pharmacopoeia (IPC) was held in January 2006 during the training session in Mumbai; these exchanges continued during the year, in particular in November 2006 in Basel as part of the first Indo-European forum, which brought together representatives of the Indian authorities and of industry.

*Relations with the Russian authorities (September and October 2006)*

As part of the preparation for an international conference on the fight against counterfeit medicines, the EDQM met the Russian authorities in September 2006 to present the activities of the European Pharmacopoeia and the European network of Official Medicines Control Laboratories. This meeting was also useful since the Russian authorities had recently been granted observer status at the European Pharmacopoeia Commission.

At the same time as the international conference in October 2006, an additional meeting was held to discuss an action plan for future collaboration with the Russian authorities.

*Relations with the Argentine authorities (October 2006)*

During its visit to attend a prominent pharmaceutical exhibition in Buenos Aires, a delegation from the EDQM had been invited by the Argentine authorities (Argentine Pharmacopoeia and ANMAT Administracion nacional de medicamentos, alimentos y tecnologia medica) to present its activities. During these 2 meetings, subjects of common interest and possible partnerships were identified for coming months.

*Relations with Mozambique (August 2006)*

An audit of the National Control Laboratory had been organised in collaboration with the WHO to evaluate existing resources and to help define future needs and areas for co-operation.

**Annual consultations of partner associations**

*EFPIA (European Federation of Pharmaceutical Industries Associations), EVM (European Vaccines 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/APIIC (Active Pharmaceutical Ingredients Committee),*

A representative of the EDQM was invited to the annual meeting of the Committee; this meeting was held in Prague (Czech Republic) in October 2006, to present public health activities in the area of quality control of active substances for pharmaceutical use and to discuss

the implementation of a specific action plan, in particular in the fight against counterfeit medicines.

*PICS (Association of pharmacist-inspectors)*

The Chair of the association was received at the EDQM in November 2006 as part of the regular consultations organised with this association.

**Professional exhibitions in the pharmaceutical world**

Various professional exhibitions provided an opportunity to meet users of the European Pharmacopoeia from Latin America and Asia. Each time, the EDQM presented the 5<sup>th</sup> Edition, its publications and services to visitors through stands and sometimes presentations in satellite symposia.

The EDQM therefore participated in the following:

*6th CPhI, June 2006, Shanghai, China*

The EDQM participated in the Congress of Pharmaceutical Ingredients (CPhI) fair/exhibition for the 4<sup>th</sup> consecutive year. It was attended by nearly 10 000 visitors in 2006. The EDQM stand received many visits by participants (850 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. The brochures and catalogues were translated into Chinese to facilitate understanding.

*4<sup>th</sup> ETIF, October 2006, Buenos Aires, Argentina*

A stand and a conference had been organised during this exhibition aimed at producers of raw materials for pharmaceutical use from Argentina and other South American countries. The EDQM's stand was visited by over 350 participants, for whom documents in Spanish had been prepared and were distributed. This participation helped promote the publication of an electronic version of the publication of the European Pharmacopoeia in Castilian.

*1st Indian CPhI, December 2006, Mumbai, India*

This was the first time this event was organised and it was a great success since it was combined with another major Indian pharmaceutical event, the Indian Pharmaceutical Congress (IPC). Over 10 000 visitors attended this event and the EDQM stand received 850 visitors in 3 days. Although most of the participants were Indian, other countries were also involved in this event. The local distributors of EDQM publications had been invited to the stand and the presence of the EDQM at this conference had been 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 wished to apply for a certificate.

**1.3 PROVISION OF REFERENCE SUBSTANCES AND PREPARATIONS**

154 new chemical reference substances (or spectra) and biological reference preparations (including 14 for plants) were adopted in 2006, bringing the number

of substances available to users of the European Pharmacopoeia to 1898. Extensive collaborative studies were required for 52 of these substances (including 12 for plants) to determine the content of the substances used in the assays. In addition, 112 reference substances were replaced and the European Pharmacopoeia laboratory regularly monitored 452 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: 184 564 vials in 2006 (152 983 vials in 2005) and the number of orders increased from 20 535 to 24 094. Taking bulk substances selected by the European Pharmacopoeia Commission for use as reference substances, the Production Unit of the EDQM prepared 549 batches (filling 337 592 vials) and 5 batches by lyophilisation, filling 65 552 vials.

**1.4 PREPARATION AND DISTRIBUTION OF SAMPLES**

2895 (2773 in 2005) new samples were received by the EDQM in 2006. The total number of samples in stock was 21 173. 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 3186 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 monographs. In addition, 5730 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 Biological Standardisation and OMCL Network (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 European Pharmacopoeia 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 Medicine (USA).

Since its start in 1992, 96 BSP projects were initiated and 90 BRPs or replacement batches have been established.

In the year 2006, the following projects were pursued:

*In the field of vaccines for human use:*

- Validation of alternatives to Auszyme ELISA kits for the *in vitro* potency assay of the rDNA hepatitis B vaccine

- Validation of a serological method for potency assay of acellular pertussis vaccine
- Standardisation of the assay for residual pertussis toxin
- 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 vaccines for veterinary use*

- Establishment of mycoplasma reference strains BRPs
- Establishment of a new type of *equine influenza antiserum BRP*

*In the field of blood and plasma products*

- Establishment of BRP for assay of SD-plasma and fibrin sealant kits
- Establishment of *human coagulation factor VII concentrate BRP*
- Validation of an *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 BRP replacement batch for determination of pre-kallikrein titres in human albumin

*In the field of biotechnology products*

- Establishment of *somatropin CRS batch 2* and *somatropin/desamidomatropin resolution mixture CRS batch 1*
- Establishment of *heparin sodium BRP batch 3*
- Establishment of an HPLC assay for interferon alfa-2
- Establishment of *low molecular mass heparin for calibration BRP batch 2*
- Establishment of *erythropoietin BRP batch 3*
- Establishment of BRPs and ELISA assays for two major recombinant allergens (Bet v 1, Phl p 5a)
- Establishment of *C-GSF (filgrastim) BRP*

The studies led to the adoption of the following reference preparations by the Ph. Eur. Commission in 2006:

- 5 low-passage mycoplasma reference strains:
  - *Acholeplasma laidlawii BRP batch 1*
  - *Mycoplasma fermentans BRP batch 1*
  - *Mycoplasma hyorhinis BRP batch 1*
  - *Mycoplasma orale BRP batch 1*
  - *Mycoplasma synoviae BRP batch 1*

- *Equine influenza subtype 2 American-like strain A/eq/South Africa/4/03 horse antiserum BRP batch 1*
- *Heparin sodium BRP batch 3*
- *Somatropin CRS batch 2*
- *Somatropin/desamidomatropin resolution mixture CRS batch 1*
- *Human coagulation factor VII concentrate BRP batch 1*

The full reports on the concluded collaborative studies were published/will be published in *Pharmeuropa Bio 2006-1* (end of November 2006) and 2007-1, respectively.

A great success in 2006 was the establishment of the five low-passage mycoplasma reference strains for use in the Ph. Eur. culture method (2.6.7.) and potentially in the future for PCR purposes. This is the first time that such reference strains were made available by an official source. The reference strains will be provided globally in the context of international harmonisation efforts (VICH).

In the field of vaccines for human use, a project was run that aimed at a better standardisation of the serological methods used for clinical evaluation of influenza vaccines during the annual licensing procedure according to the CHMP guidelines; this has been requested by the CHMP Biologics Working Party (BWP) of the EMEA. In the first part of the project that has been 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. It turned out that reproducibility of the HI test is not satisfactory for this purpose and that the CHMP criteria will need to be revised. The second part of the project aimed at improving the reproducibility will start in 2007.

The strong efforts to apply the 3R concept to the field of quality control of biologicals were continued. A meeting with all interested parties was held on the 5<sup>th</sup> April 2006 in Strasbourg to explore the acceptance by manufacturers and regulatory authorities of alternative methods for the potency assay of botulinum toxin. Currently the potency of such preparations is stated in in-house units based on an LD<sub>50</sub> assay. There is presently strong pressure in Europe and throughout the world from the highest political levels to reduce as far as possible the use of animals for the testing of botulinum toxin. It was concluded at the meeting that none of the currently investigated alternative tests is at a stage where it can be applied for routine batch release and at least one year will be needed to conclude their ongoing feasibility experiments. The situation will be monitored and if appropriate, a project will be initiated in order to validate an alternative assay.

Furthermore, three projects were pursued in 2006 in the context of the 3R concept: the 1<sup>st</sup> project aims at the replacement of the challenge assay for tetanus immunoglobulin by an *in vitro* assay; a 2<sup>nd</sup> one attempts to better standardise the assay for residual pertussis toxin and thus create the basis for a future project aimed at replacing the *in vivo* histamine challenge test by an *in vitro* assay; the 3<sup>rd</sup> project extends to acellular pertussis vaccine the previous projects on the development of

serological assays to replace *in vivo* challenge as the 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 enormously reduce the number of animals needed for these assays.

As in previous years, co-operation with international partners continued and projects to establish common standards were set up whenever possible with the ECBS. An example of this is the establishment of a standard for low molecular mass heparin for calibration. The project for the establishment of the BRPs for determination of anti-A and anti-B haemagglutinin titres in immunoglobulins will be run together with FDA/CBER.

#### **EDQM designated a WHO collaborative centre for international standards for antibiotics**

The EDQM was designated a WHO Collaborative Centre for the International Standards for Antibiotics (ISA). This decision had been taken at the 56<sup>th</sup> meeting of the WHO Expert Committee on Biological Standardisation (ECBS), which took place in Geneva in October 2005, and came into effect on 4 May 2006.

These standards are essential in the standardisation and quality control of antibiotic drug substance and pharmaceutical drug products. They are supplied for assays described in the specifications for quality control based on anti-microbiological activity measurements.

The EDQM took over responsibility for the establishment, storage and distribution of WHO ISA from the National Institute for Biological Standards and Control (NIBSC) on 4<sup>th</sup> May 2006. Batches that were held and distributed by NIBSC are now being distributed by the EDQM.

The EDQM will also organise international collaborative studies, to establish new or replacement standards where appropriate and required. In 2006 the collaborative study aimed at the establishment of a replacement batch for the current IS for nystatin, the stocks of which were exhausted, was organised and the establishment report was adopted by ECBS at its session in October 2006. In 2007, for three other substances for which the current IS lot is nearing exhaustion, studies will be initiated: amphotericin B, vancomycin and gramicidin.

For more comprehensive information on the availability of standards and for ordering information, please consult the EDQM website: [www.edqm.eu](http://www.edqm.eu).

#### **1.6. QUALITY MANAGEMENT SYSTEM**

The EDQM continued to set up 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.

## **2. CERTIFICATION OF SUITABILITY OF MONOGRAPHS OF THE EUROPEAN PHARMACOPOEIA**

322 new applications (including 19 for products with TSE risk) and 535 requests for revision were received, in addition to the regular updates following the

publication of revised monographs in the supplements of the European Pharmacopoeia. 938 (new or revised) certificates were granted after assessment.

In total, over 3000 applications have been received and 2200 certificates have been granted since the procedure became operational. These are regularly up-dated.

Requests for revision or renewal of certificates are processed according to a procedure that has been brought into line with the procedure for marketing authorisations of medicines. In particular, the deadlines for examination of dossiers have been shortened according to well-defined evaluation criteria based on the Community regulations classification.

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, 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 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, as amended).

The 3 Cs (consultation, co-ordination, co-operation) that characterise the procedure are implemented by a Steering Committee consisting of the Chairs of the European Pharmacopoeia Commission, the Joint CHMP /CVMP Quality Working Party, the CHMP Biotech Working Party, the CVMP Immunological Products Working Party, the Herbal Medicinal Products Working Party and the Inspection Working Party as well as representatives of the Commission of the European Communities, authorities of non-European Union member states of the European Pharmacopoeia, the EMEA and the EDQM. The Steering Committee met twice in 2006 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, and they elaborate or revise the technical documents needed for the procedure to function effectively.

Operated on the basis of a 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 raw materials for pharmaceutical use. 20 inspections with the participation of 13 inspectors from 8 different national agencies were carried out in 2006, mostly in China and India which represent 70 to 80% of the production of pharmaceutical raw materials used in the world.

The Certification division (DCEP) participated in several events (conferences, fairs-exhibitions, meetings with national delegations) in particular in India and China (see above) to improve its visibility and reinforce co-operation with its various partners (manufacturers and authorities). The efforts to enhance communications were also helped by the development of private consultations ('one-to-one meetings' proposed during these events, 'technical advice' on the premises of the EDQM); these consultations were very popular with our users.

### 3. NETWORK OF OFFICIAL MEDICINES CONTROL LABORATORIES (OMCLs)

The network of Official Medicines Control Laboratories (OMCLs) was established in 1995 on the initiative of the EDQM in close co-operation 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 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,
- *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, 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, human vaccines and veterinary immunobiologicals.

"Networking" means sharing of know-how within a pool of experts, work sharing as well as 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 and Mutual Joint Audits. Another contribution to "networking" are the annual meetings, which bring together representatives from the whole network to discuss and exchange viewpoints on topics of common interest, i.e. 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 EDQM and hosted by one of the members of the network on a rotating basis.

#### *Activities involving all OMCLs of the network*

##### *Annual meeting of the plenary network*

The 11<sup>th</sup> annual meeting of the OMCL Network was held on 9<sup>th</sup>-12<sup>th</sup> May 2006 in Limassol (Cyprus), hosted by the Cypriot OMCL "State General Laboratory" and opened by the Minister of Health of the Republic of Cyprus, Dr. Andreas Th. Gavrielides. 180 representatives from 32 countries took part in the meeting.

#### *Quality Management Systems*

The Quality Assurance (QA) programme of the OMCL Network, co-ordinated 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.

On the occasion of its 2006 Annual Meeting, the OMCLs of the Network decided to render public a number of key QA documents such as procedures, guidelines and policy papers. They are now available for download on the EDQM website ([http://www.edqm.eu/site/page\\_527.php](http://www.edqm.eu/site/page_527.php)) and illustrate the willingness of the OMCL Network to increase the transparency of their activities.

During the year 2006, the following activities were carried out within the OMCL Network as part of the QA programme:

- 5 Mutual Joint Audits (MJA): 3 of them in OMCLs testing human and veterinary medicines (1 chemical field, 2 chemical and biological) and 2 in OMCLs testing human medicines (biological).
- 2 Training Visits, focused on biological methods for the quality control of vaccines for veterinary use.

No Mutual Joint Visits or Tutorials were performed in 2006.

In total, since the beginning of the QA programme in December 1997, 35 MJA, 45 MJV, 2 Tutorials and 11 Training Visits have been carried out in the OMCL Network. 10 MJAs are already planned for 2007.

#### *Training courses for the OMCL Network*

In 2006, the EDQM organised 3 QA training courses:

- a technical training course for the biological field, open to all scientific/technical staff of the OMCLs, members of the OMCL Network and also associate members, took place in Strasbourg from 6 to 9 February, with 112 participants from 29 countries (among them 1 participant from South Africa, 1 from Thailand and 2 from the WHO headquarters),
- a training course for 35 new members of the pool of auditors of the OMCL Network participating in the MJA/MJV scheme was also carried out in 2006, split into two sessions (June and September), in order to limit the number of participants and thus to ensure an interactive participation.

#### *OMCL Network Quality Assurance Guidelines*

A new annex to the OMCL Network guideline "Qualification of equipment" was adopted at the OMCL Network annual meeting in May 2006, dealing with requirements for GC equipment qualification. 2 new annexes, focusing on the qualification of UV-Visible and IR spectrophotometers respectively, are under preparation by a group of experts with the aim of finalising these documents in early 2007 so that they can be submitted for approval during the next annual meeting of the OMCL Network in May 2007 in Prague.

#### *Collaboration with EA*

Discussions with representatives of the European co-operation for Accreditation (EA) concerning the

recognition of the contribution of OMCLs in setting up Quality Management Systems within their domain are ongoing. In 2005, the following guidelines/documents were approved by EA as recommendation documents to be used in the context of quality system audits of OMCLs and are now also available on the EA website:

- validation of analytical procedures,
- scope of accreditation of Official Medicines Control Laboratories,
- uncertainty of Measurement: Policy on the estimation and application of uncertainty in analytical measurement (compliance testing)

Where appropriate in the context of pharmaceuticals the EDQM/OMCL Network intends to present further guidelines for approval and use by the EA members.

#### *Proficiency Testing Scheme Studies (PTS)*

Over the years, the Proficiency Testing Scheme (PTS) studies have become a regular programme within the Network. In 2006, six studies were organised in the physico-chemical field, with an average participation of 39 national control laboratories and 26 other pharmaceutical control laboratories, private sector industry and hospitals, while in the biological area 4 studies were organised, involving an average of 24 laboratories.

The 3<sup>rd</sup> PTS agreement with WHO covering the period of July 2004 to June 2006 has been fulfilled. On average 34 governmental control laboratories belonging to 6 different regions of the world (Africa, Americas, Eastern Mediterranean, Europe, South-East Asia and Western Pacific) participated in each of the 4 studies, two of which were finalised in 2006. The final report of this 3<sup>rd</sup> agreement was delivered to the WHO and discussed and approved on the occasion of the QA/WHO meeting held in October 2006 in Geneva.

In addition, the EDQM coordinated a special ASEAN (Association of Southeast Asian Nations) training programme for PTS sponsored by the EU and involving central and regional Official Control Laboratories from 9 countries of South East Asia (Brunei Darussalam, Cambodia, Indonesia, Malaysia, Laos, Philippines, Singapore, Thailand and Vietnam). The programme, covering 6 different physico-chemical studies, was conducted in 2005 and finalised in 2006.

#### *General studies on market surveillance (MSS)*

Market Surveillance Studies (MSS) aimed at screening the quality of products commercialised in countries of the Network were carried out for the following products in 2006: erythromycin liquid preparations and erythromycin ester preparations as well as trimethoprim (raw material (API) and tablets). An MSS on diclofenac retard preparations was also initiated. An average of 15 OMCLs participated in each of the studies.

2 additional studies were finalised in 2006: the MSS on equisetum stem adulterations and the MSS on cadmium in herbal drugs.

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

#### *Collaborative study on GC-EI-MS*

The collaborative study on GC-EI-MS (gas chromatography - electron impact - mass spectrometry) on an "unknown" sample sourced on the illicit market, which had been initiated in 2005 was also finalised during 2006.

#### *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 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 license. Together with the public release of the software an official website has been launched at [www.edqm.eu/combistats](http://www.edqm.eu/combistats) on which an online manual, tutorial, examples and background information can be found. A free demonstration version can also be downloaded.

In 2006 a total of 77 licenses have been issued, 35 of which to OMCL laboratories in 24 countries and 42 to non-OMCL users in 19 countries. As of 31 December 2006, CombiStats is used in 18 countries of the EU and in 15 countries outside the EU, including countries such as Argentina, Australia, Canada, India, Japan, South-Korea, USA and South-Africa. CombiStats has thus developed into an internationally agreed common 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*

All 25 EU Member States were invited to take part in the traditional confidential exchange of information on issues related specifically to OCABR in different dedicated sessions during the annual meeting. Representatives from 23 of the Member States attended this meeting. In anticipation of the accession of Bulgaria and Romania in 2007 and in an effort to facilitate their integration, representatives from these countries were accepted as observers. As in previous years, EEA Member States and Switzerland, a Mutual Recognition Agreement (MRA) partner, also participated in the annual meeting.

For the 2<sup>nd</sup> consecutive year an important workshop was held at the National Institute for Biological Standards and Control (UK) on the batch release of oral poliomyelitis vaccines (OPV). On 18-19 September 2006, 12 participants from 5 Member States and observers from EDQM and WHO participated in this hands-on workshop to develop and maintain experience in the new transgenic mouse neurovirulence assay which will replace the neurovirulence assay in monkeys, and to refine guidelines for the implementation of training and testing procedures at OMCLs.

### *Human Biologicals*

At the annual meeting, a review of OMCL batch release activities since 2005 for both blood and vaccines and special scientific presentations were given. An issue of concern was the implication of the access to information policies valid throughout the EU on the exchange of OCABR specific sensitive information. Following the meeting a survey of policies in the different Member States was carried out and the results were shared with the network members and Heads of Medicines Agencies for relevant follow-up action. Interest in work-sharing and possible subcontract testing between OMCLs for OCABR continued in 2006. A survey on possible fee structures for sub-contract arrangements, based on a position paper adopted at the annual meeting, was carried out in the network. A model template for a sub-contract agreement to be used in the context of OCABR has also been adopted to facilitate the establishment of such arrangements.

Once again, information exchange proved to be a priority issue. Use of the restricted access extranet site maintained by EDQM and dedicated to human biological OCABR issues (OCABRnet) continued to be an important tool. Significant progress was made in the development of an online, real-time database of batches having undergone OCABR. A cahier des charges for the system development was finalised in 2006 and a considerable development of the system is anticipated for 2007.

### *Common procedures for batch release of human biologicals*

A major revision of the annual report format (Annex V of the Administrative Procedure) was adopted to facilitate a harmonised approach and maximise the information shared. An editorial revision to Annex IV, the Marketing Information Form, was also adopted for clarification. A position paper highlighting concerns over issues related to parallel import and parallel distribution of biological medicinal products was adopted and has been forwarded to the EU Commission. A position paper on submission of batch protocols by electronic means was adopted for presentation to the manufacturers' associations to facilitate development of more rapid and efficient exchange of critical information for batch release.

### *Blood products and plasma derivatives*

The existing guidelines for the blood and plasma derivatives were found to be perfectly sufficient and no new revisions or additions were required in 2006.

### *Human Vaccines*

The following new internal procedures/position papers were adopted in 2006:

- Standard Operating Procedure for OMCL performing observation of the transgenic mouse test for OPV bulks
- Guideline for training requirements for OMCL readers performing observation of the transgenic mouse test for OPV bulks

A strategy for independent testing of OPV bulks was endorsed and has been circulated to involved manufacturers for comments and further development.

3 new guidelines were adopted in 2006:

- Influenza Vaccine (Surface Antigen Inactivated, Virosome),
- Measles, Mumps, Rubella and Varicella Combined Vaccine,
- Rotavirus Vaccine

The following new guideline was approved for external consultation:

- Recombinant Human Papillomavirus virus-like particle vaccine

In addition, 12 existing guidelines were revised to bring them up to date with the state of the art methodology and European Pharmacopoeia monograph requirements.

All adopted guidelines and administrative procedures are available in a booklet published by the EDQM at the end of December 2006. They are also available for download on the EDQM website ([http://www.edqm.eu/site/page\\_611.php](http://www.edqm.eu/site/page_611.php)).

A working group has been established, dedicated to the pandemic influenza preparedness initiative. The goal of the group is to exchange practical experience with new methods and procedures for the potential batch release of these products in an emergency situation.

### *Immunological Veterinary Medicinal Products (IVMPs)*

Exceptionally in 2006, the annual meeting for Competent Authorities (CA) and OMCLs involved in control of veterinary immunological products took place in November in Strasbourg. This was to allow time to acquire experience in a pilot phase of the new system of procedures and guidelines for application of articles 81 and 82 as implemented under the current legislation, which formally began in October 2005. The meeting consisted of confidential sessions involving Member States only as well as open sessions involving industry representatives. The meeting was also attended by representatives from the EU Commission.

2006 was a year of intense activity. In addition to the annual meeting, another plenary session open to all EU/EEA interested parties and industry representatives was organised by the EDQM in April 2006. This was complemented by 2 meetings (February and July) and a conference call (November) of a smaller working group consisting of representatives from competent authorities from 4 Member States and Switzerland, from IFAH Europe, from the EMEA, from the EDQM and from the EU Commission, and finally 2 meetings of a sub-working group on risk assessment. These meetings of the working group were held in Brussels under the auspices of the EU Commission with the goal of advancing the finalisation of additional elements required for application of the new Directive for Veterinary Medicine and contribute to an overall recommendation document to be presented to the Veterinary Pharmaceutical Committee.

As a result, the following procedures and guidelines have been developed for presentation to the Veterinary Pharmaceutical Committee for use endorsement in early 2007:

- A strategy for risk assessment of vaccines based on a semi-quantitative approach with a grading of risk according to pre-defined factors,

- Strategies for trend analysis to allow proposals of reduced frequency testing, and procedures to deal with discrepant results between the OMCL and the manufacturer. In addition, the 5 model templates for manufacturers' protocols have been revised based on practical experience obtained during the pilot phase and should be in place for the beginning of 2007.

All of the adopted administrative procedures and product specific guidelines and model templates are available on the EDQM website for download ([http://www.edqm.eu/site/page\\_634.php](http://www.edqm.eu/site/page_634.php)).

#### *Meeting with manufacturers' associations*

Each of the sub-networks for OCABR of biologicals held separate meetings in Strasbourg with the relevant manufacturers' association in the course of 2006 to allow for exchange and feedback and to ensure transparency and good will.

Representatives from the vaccine network met with members of the European Vaccine Manufacturers' (EVM) Association and other independent manufacturers on 31 October 2006. Representatives from the blood network met with representatives from the International Plasma Fractionation Association (IPFA) and the Plasma Protein Therapeutics Association (PPTA) on 10 November 2006. Representatives from the veterinary network for IVMPs met with representatives from IFAH – Europe on numerous occasions, as noted above.

#### *Meeting on human parvovirus B19 DNA NAT test kits*

Since 2005 the A6- and the V9 virus are officially classified as human parvovirus B19. PTS studies organised by the EDQM as well as scientific reports in the literature provided evidence that currently available test kits for detection of DNA from A6- and V9 virus by Nucleic Acid Amplification Techniques (NAT) are not satisfying and may give rise to discrepant results during the testing of plasma pools by manufacturers and OMCLs. The EDQM thus organised a meeting with representatives from all involved parties (OMCLs, manufacturers of plasma derivatives and of B19 NAT test kits, the EMEA) on 9 November 2006 in Strasbourg to explore potential solutions of the problem. One of the results of the meeting was to encourage WHO to establish an International Standard for A6 virus DNA for NAT testing and to encourage test kit manufacturers to provide NAT test kits which also detect A6 and V9 virus DNA.

#### *Market Surveillance for products with a centralised marketing authorisation*

The programme for sampling and testing of Centrally Authorised Products (CAP) was successfully continued in 2006 and entered its 8<sup>th</sup> consecutive year. Since its implementation, the programme has been continuously improved thanks to the close collaboration of all stakeholders:

- the EMEA which is the sponsor and has the overall responsibility for the programme,
- the EDQM which coordinates sampling and testing operations on the basis of the information provided by the Marketing Authorisation (MA) Holders

upon request from the EMEA and reports to EMEA the outcome of sampling and testing operations, especially the control results, with proposals for follow-up actions where necessary,

- the national inspection services of the designated Member States within the EEA which perform product sampling on the market,
- the OMCLs of the EU/EEA OMCL Network which perform analytical testing of products.

The CAP programme covers medicinal products for both human and veterinary use. In 2006 it included 32 products divided between 8 non-chemical products (biotech or veterinary immunological products) and 24 chemical/pharmaceutical products. In addition, testing was also carried out on the active substances of 8 of these products. These figures correspond to a decrease of 5% compared to the 2005 CAP programme and represent the lowest number of products tested in the CAP programme since it was initiated. However, this follows the trend seen with the number of MAs granted over the years. To avoid fluctuation in the number of products tested per year, the different partners of the programme decided in 2003 that a fixed number of products would be included in each yearly programme. The target of at least 40 products was considered to be appropriate. This number also allows the inclusion of products on an *ad hoc*-basis should specific issues emerge. Products to be included in the 2006 programme were selected by the EMEA expert committees from those authorised in 2003 (year n-3), thus guaranteeing that the selected products have indeed been launched and manufactured on a large scale. In addition, some products tested in previous years were included for re-testing.

Market samples were collected for each product in 3 EU/EEA countries in order to have an overview of the actual product quality of the distributed batches. Sampling took place mainly at wholesalers (74%) and for less than 10% in retail or hospital pharmacies, mainly because of the distribution scheme of centrally authorised products which are generally difficult to obtain in sufficient quantities at the very end of the distribution chain (pharmacies/hospital) without depleting the essential stock needed for patient care. Overall, 89 sampling operations were carried out by national inspection services in 24 EU/EEA countries. The market samples and non-commercially available standards and specific reagents provided by the manufacturers represented about 300 stock items. Initial storage, coding and dispatching to OMCLs for testing was dealt with by the EDQM.

Traditionally, testing was performed by 2 OMCLs, independently from the product manufacturers, for all non-chemical products. Since 2005 a new testing scheme has been applied for chemical products: In 2005 about one third of the chemical products were tested by a single OMCL, and this was continued, as planned, in 2006 with two thirds of the chemical products included in the programme. A second OMCL would be involved at a second stage only in case of questionable results linked to analytical or compliance issues. The gradual implementation of such a testing format will be completed in 2007 with all chemical products being

tested by one single OMCL (except for specific cases). Given this background, it is planned that the OMCLs that have successfully undergone external assessment of their Quality Assurance system and fulfil the requirements for market surveillance of medicinal products will progressively be given preference for participation in such CAP projects.

Overall, 30 OMCLs from 24 EU/EEA countries took part in the testing phase of the 2006 programme. In total, 54 testing operations were carried out.

For all products, individual product reports were compiled by the EDQM and distributed to all parties (EMEA, OMCL Network, involved sampling contact persons). All issues were thus reported to the EMEA and their scientific experts, proposing follow-up actions on the registration dossier and/or on analytical testing methods where necessary. In general, the MA holder obtains access to the reports via EMEA. A global report on the outcome of each programme is published on the EMEA website six to eight months after the completion of the yearly sampling and testing campaign.

The collaboration between all parties was facilitated by the extensive use of IT tools (EMEA Eudralink, EDQM CAPnet server) and 2 productive meetings at the EDQM. Thanks to the work of the Advisory Group of the CAP programme, 2 Quality Assurance documents were finalised including the very specific case where out-of-specification results are encountered including advice on how they should be handled to ensure the rapid delivery of a scientific conclusion to decision makers. The documents were adopted during the annual meeting of the EEA OMCLs involved in the CAP programme, which took place at the end of November/beginning of December 2006 in Paris at the *Agence Française de Sécurité Sanitaire des Produits de Santé* (AFSSAPS) premises. Participants emphasised that the implementation of a risk-based approach in the selection of products to be tested to optimise the use of OMCL resources should be carefully evaluated. The necessity to facilitate exchanges between the institutional partners (assessors, inspectors, OMCLs) involved in the products' management was also highlighted and this is in line with the global strategy under development by the Heads of Medicines Agencies.

#### *Post-marketing surveillance of products with a marketing authorisation according to the Mutual Recognition Procedure (MRP)*

In 2006 the second regular programme of post-marketing surveillance of MRP-products was performed after running a trial phase between 2000 and 2005. 16 OMCLs have actively participated in this year's programme and approximately 250 projects could be finalised.

At a breakout session of the MRP-testing group at the end of 2005, it was decided to meet at least once a year to discuss pending items and topics of general interest within the group, but also to present the individual testing plans and to establish a testing programme for the consecutive year.

In fact, in 2006, 2 meetings of the MRP-testing group took place concomitantly with other relevant annual meetings in order to save time and resources.

The most important steps taken during the last year were the following:

The general procedure "Co-operation in post-marketing surveillance of mutual recognition procedure products" was finalised by the group and is now available to the public on the EDQM homepage along with a short introduction to the "mission" of the MRP-testing programme.

The draft version of the future MRP computer application (MRP-product testing database) was introduced at the November meeting and is scheduled to become operational in the first half of 2007. This IT tool will allow a better co-ordination of the planning, sampling and reporting phase, but will also provide information about follow-up actions taken on the basis of test results. Reading access to the database will also be granted to the users of CTS (Communication and Tracking System), the regulators of national competent authorities.

The MRP 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 testing scheme.

For the selection of future annual test programmes it was decided to introduce a risk-based approach. For this purpose a trial phase group consisting of 7 volunteering OMCLs was set up at the end of 2006. The group will work with a risk-based model developed by the Dutch OMCL, and in a first step will rank products from a jointly established random list according to their pertinence of being tested. It is intended to use the experience gained from this "dry run" for the establishment of future MRP-testing programmes.

#### **4. EXTENSION OF EDQM ACTIVITIES**

The Council of Europe has decided to apply the EDQM's expertise in consultation and networking activities at the European and world level to 2 new areas of great importance:

- **Blood transfusion:** the work programme is based on 3 main principles:
  - no commercial use of products of human origin,
  - voluntary, non-remunerated donations,
  - protecting the health of donors and recipients.
- **Organ transplantation:** the work programme is based on the following principles:
  - guaranteeing human dignity,
  - striving to maintain and improve the protection of human rights and fundamental freedoms,
  - ensuring that there is no commercial use of products of human origin,
  - protecting donors as well as recipients.

#### **5. NEW EDQM BUILDING**

This new building is critical to the future development of the EDQM and will help it respond to new public health needs in Europe. Work on the building continued

throughout 2006 and the administrative part was finished in December 2006 so that all departments and divisions, except the Department of the Laboratory and the Division of Reference Standards and Samples,

were able to move from the Meinau building to the new building at the end of the year. The building is expected to be fully ready by March 2007.