

# EUROPEAN DIRECTORATE FOR THE QUALITY OF MEDICINES

## ANNUAL REPORT OF ACTIVITIES - 2001

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

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

### I. THE EUROPEAN PHARMACOPOEIA

#### Parties to the Convention and observers

The European Pharmacopoeia Convention has been signed by 29 parties: the European Union and the following countries: Austria, Belgium, Bosnia-Herzegovina, Croatia, Cyprus, the Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Grand-Duchy of Luxembourg, The Netherlands, Norway, Portugal, Slovakia, Slovenia, Spain, Sweden, Switzerland, "The Former Yugoslav Republic of Macedonia", Turkey, the United Kingdom, Yugoslavia. In addition, the accession of Estonia was announced for early 2002.

The number of observers increased by one state to 18 after Malta's application was approved, namely the WHO, 9 European states (Albania, Bulgaria, Estonia, Latvia, Lithuania, Malta, Poland, Romania, Ukraine) and 8 non-European states (Algeria, Australia, Canada, China, Malaysia, Morocco, Tunisia and Syria).

#### General activities

The European Pharmacopoeia Commission continued to work on the preparation of the 4<sup>th</sup> Edition; the initial volume was published in autumn 2001 and entered into force on 1 January 2002.

The European Pharmacopoeia Commission elected Professor H. G. Kristensen of the Royal Danish School of Pharmacy in Copenhagen as Chair for a term running from June 2001 to June 2004. Professor Kristensen thus becomes the 13<sup>th</sup> Chair of the European Pharmacopoeia Commission since 1964, succeeding Professor Calam who chaired the Commission for the last three years. Two new vice-Chairs were elected in June 2001 for three years: Dr. D. de Kaste (OMCL, The Netherlands) and Professor L. Turakka (OMCL Director; Finland).

At its three Sessions in March, June and November 2001, the European Pharmacopoeia Commission adopted 246 monographs, of which 165 were revisions and 81 were new texts. The Commission also adopted 16 chapters and general methods, of which 14 were revisions and 2 were new texts. Overall, 262 texts were adopted (179 revised texts). The number of monographs prepared by the procedure for adaptation of national monographs or procedure III decreased (14 in 2001 compared with 20 in 2000). The number of documents produced (new, revised) is slightly higher (3050 compared with 2650 in 2000). The new monographs can be broken down as follows: 39 on inorganic or organic products, 12 on vaccines, 3 on biologicals, 20 on herbal drugs or preparations, 1 on a dosage form, 3 on homoeopathic preparations and 3 on radiopharmaceutical preparations.

A total of 290 days was devoted to meetings in 2001. This includes the three plenary sessions of the Commission and the corresponding preparatory meetings, the meetings of the Groups of Experts (105) and those of the *ad hoc* Working Parties (15). This total also includes the participation of members of the Secretariat in various other meetings: meetings of the Pharmaceutical Committee (Brussels) on medicines for human and veterinary use, meetings of the various working parties of the Committee for Proprietary Medicinal Products and of the Committee For Veterinary Medicinal Products of the EMEA (nearly 20 meetings such as those of the Quality working party, Biotech working party, Veterinary Immunological working party, Inspectors working party and Herbal Medicinal Products working party). Members of the Secretariat also attended meetings of the Pharmacopoeial Discussion Group for International Harmonisation with Japan and the United States, preparatory meetings of the Quality Working Party for ICH 5, meetings of VICH working parties and meetings to organise and take part in international scientific conferences and congresses.

The following activities are particularly noteworthy.

#### The 4<sup>th</sup> Edition

The 4<sup>th</sup> Edition was published in September 2001 and its first supplement in October 2001; the second was planned for January 2002. Henceforth, three new supplements will be published each year, following each session of the Commission.

Each new edition has provided the opportunity to revise and supplement the texts, and this 4<sup>th</sup> Edition is no exception. Both form and content have undergone changes:

### Form

- Presentation and style: while the European Pharmacopoeia continues to be published as a bound book, differences from the previous version are apparent as soon as it is opened and these correspond to suggestions received during the user satisfaction survey:
  - the use of thinner paper made it possible to publish all the texts in a single volume even though the number of texts is constantly increasing (about 1700 monographs and several hundred general methods); the binding has been reinforced so that the book can withstand daily use better than the previous edition;
  - the organisation of the texts into chapters has been slightly modified, to make the Pharmacopoeia easier to use and also to make it easier to find information in certain specific areas. This new organisation is described at the beginning of the book. The general chapters come first followed by the monographs, grouped into separate sections:
    - General monographs
    - Dosage forms
    - Vaccines for human use
    - Vaccines for veterinary use
    - Immunosera for human use
    - Immunosera for veterinary use
    - Radiopharmaceutical preparations
    - Sutures for human use
    - Sutures for veterinary use
    - Homoeopathic preparations.
- Cross-references between general monographs and specific monographs have almost all been deleted; these could not be exhaustive and had to be adapted to each substance. Instead, there is a running footer directing the reader to the list of relevant general monographs.
- The simplified style already used for some of the monographs in the 3<sup>rd</sup> Edition has been extended in the 4<sup>th</sup> Edition.
- The degree of hydration will now be given systematically in new monographs.

### Content

- The scope of the general monographs has been extended to all classes of pharmaceutical substances and preparations. A new general monograph on *Substances for pharmaceutical use (2034)* has also been elaborated; it incorporates the concepts of the European Union guidelines on limiting impurities and on residual

solvents. As a result, information does not have to be repeated in several specific monographs and, especially, the same approach can be used in similar situations, so that the user is free to adapt the relevant purity and quality tests so that they are appropriate for the origin or method of manufacture of the product. The user then chooses purity tests from the general monographs and refers to these tests in the marketing authorisation dossier or in the application for Certification of suitability of monographs of the European Pharmacopoeia.

- International harmonisation with the Pharmacopoeias of the United States and Japan has resulted in the following:
  - the introduction into the General Notices of the concept of “interchangeable methods” among the three Pharmacopoeias;
  - the addition of a new chapter (5.8); it provides detailed information on the status of harmonised texts. In addition, each harmonised general chapter will include an introductory statement on the interchangeability of the texts of the three pharmacopoeias with a precise reference to the edition or supplement concerned.
- After numerous discussions and exchanges with the national licensing authorities on homoeopathic preparations, the Commission finally decided to keep only one official Latin title despite the existence of many different traditional titles. However, a table with no official status listing the synonyms of the titles used in homoeopathy in different European countries was published in the July 2001 issue of *Pharmeuropa* (Vol. 13, No. 3, p. 463); this table should facilitate the transition, which is the responsibility of the national authorities.

### Standard terms

The list continued to be updated by adding terms for new dosage forms used in applications for marketing authorisation. Revisions made between publications of the list are published in an issue of *Pharmeuropa*. This was done this year: *Pharmeuropa* 13.3, July 2001, p. 455.

### Communication and public relations

The European Pharmacopoeia Commission reinforced its communications activities by organising international scientific conferences or seminars on the following subjects.

- **Workshop on “Certification for TSE risk products”, Strasbourg (France), 11 January 2001**

173 professionals in the area of the quality of medicines from 22 European countries and also from India and the United States, participated in this conference whose objectives were particularly important:

- reviewing, for the first time, the new extension of the scope of the procedure to products with a risk of TSE (transmissible spongiform encephalopathies) such as gelatin, tallow derivatives, foetal serum, culture media components and some active ingredients;
  - sharing points of view and experience with the principal users;
  - and examining the current situation as regards the quality and safety of raw materials used in the pharmaceutical industry to ensure medicines on the market are of the highest quality for protection of Public Health.
- **Conference on “Current developments in pharmaceutical analysis”, Cannes Mandelieu (France), 8-9 February 2001**
- 268 professionals working in the area of the quality of medicines from 34 European countries and also from Canada, the United States, Malaysia, Israel, Russia and Ukraine were brought together to study recent scientific and technological developments in pharmaceutical analysis.
- A variety of themes were dealt with:
- the theoretical and practical basis for establishing quality specifications for medicines;
  - new techniques now finding a place in pharmaceutical analysis: chromatographic and electrophoretic techniques for enantiomeric purity, near infrared and Raman spectrometry for material analysis;
  - in-process testing and parametric release as alternatives to finished product testing;
  - future needs for monographs on excipients;
  - the place of reference substances and methods for their establishment;
  - separation techniques, validation, equipment qualification and performance testing.
- **Symposium on “Pestivirus contamination of bovine sera”, Paris (France), 29-30 March 2001**
- 108 persons from 17 countries (including Canada, Egypt, United States and Japan) participated in this symposium which was of great importance for the world-wide harmonisation of the licensing dossiers.
- The current knowledge of pestivirus infection of animals and the potential contamination of materials derived from infected animals, especially bovine sera, as well as the methods to avoid, detect and reduce contamination were critically reviewed.
- Regarding preventive measures, it was emphasised that vaccination of animals, especially cattle, prevents spreading of pestivirus infection. The draft European Pharmacopoeia monograph on the vaccine against Bovine Viral Diarrhoea (BVD, caused by one of the strains of pestivirus) was discussed and was seen as an important step towards prevention of BVD infection.
- **Conference on “Certification of suitability of monographs of the European Pharmacopoeia. New developments of the procedure – How to apply for a CEP”, Athens (Greece), 8-9 November 2001**
- 250 professionals concerned by the quality of medicines from 33 countries including Australia, Canada, Egypt, China and United States participated in the conference. Several ideas for future development had become apparent, notably:
- adapting the procedure as soon as possible to make the CTD (Common Technical Document adopted by ICH) format acceptable.
  - considering the greater use of general monographs, to extend the scope of the procedure to substances not covered by a specific monograph (as done for TSE products)
- **Conference on “Quality control of equine influenza vaccines”, Budapest (Hungary), 10-11 December 2001**
- The European Directorate for the Quality of Medicines of the Council of Europe (EDQM) has organised, in collaboration with the Office International des Epizooties (OIE), this scientific symposium on the quality control of equine influenza vaccines. This symposium brought together 50 representatives from 16 countries (Europe, US, Canada and South Africa), from academia, national and supra-national licensing authorities, vaccine manufacturers and epidemiological/diagnostic centres.
- The current epidemiological situation and the licensing requirements in Europe and the Americas as well as the recommendations stipulated by the OIE were presented during these two days of exchanges and lively discussions. Issues related to the standardisation and quality control of equine influenza vaccines were critically reviewed and the contribution of the current standards to efficacy and batch consistency of the vaccines were discussed. Finally the future perspectives and challenges in the development and quality control of the vaccines were addressed.
- **Workshop on Impurities, Strasbourg (France), 19-20 December 2001**
- This workshop was attended by 70 participants representing the national and European licensing

authorities, national control laboratories, Inspections, national pharmacopoeia experts, manufacturers from the pharmaceutical industries and their suppliers. It was aimed at determining the needs for identification and control of impurities in the context of world trade. The conclusions of the workshop will help improve the elaboration of monographs and facilitate their use thus improving the protection of consumers.

The EDQM also continued to develop its Internet site. This site facilitates contacts with users and regularly provides information on the opinions of the Commission, in particular the list of decisions taken at each of its sessions in March, June and November, namely the list of adopted monographs, the list of adopted reference substances, the corresponding safety data sheets, and the main decisions on general policies. Users can also consult new or revised *monographs that have been rapidly implemented*, the list of employment opportunities in the EDQM, the list of certificates of suitability of monographs of the European Pharmacopoeia and full information on how the certification procedure works.

### Providing reference substances and preparations

127 new chemical reference substances (or spectra) and biological reference preparations were adopted during the year, bringing the number of substances available to users of the European Pharmacopoeia to 1414. Extensive collaborative studies were required for 36 of these substances to determine the content of the substances used in the assays. In addition, 67 substances were replaced and the European Pharmacopoeia laboratory regularly monitored 164 substances and carried out quality control tests during the production of 432 batches. The number of chemical reference substances and biological reference preparations distributed to users continued to climb: 82 086 in 2001 (70 367 in 2000) and the number of orders increased from 10 571 to 12 149. Taking bulk substances selected by the European Pharmacopoeia Commission for use as reference substances, the Production Unit of the EDQM prepared 426 batches (filling 93 448 vials) and 6 batches by lyophilisation, filling 8103 vials.

### Preparation and distribution of samples

2125 (1898 in 2000) new samples were received by the EDQM in 2001. The total number of samples in stock was 14 890. 141 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 1555 samples for these laboratory studies to check the quality of the substances available on the market (multisource substances for the adaptation of national monographs procedure) or to check the robustness of national

monographs proposed as draft European monographs. In addition, nearly 7939 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, biological standardisation projects).

### Biological standardisation

The Biological Standardisation Programme (Division IV) continued its work in the three following areas of activity:

- establishment of common European standards, which were available in sufficient quantities so that Official Medicines Control Laboratories and manufacturers could use them as working standards,
- establishment of validated and standardised potency assay methods,
- validation of alternative methods to reduce, refine or replace the use of laboratory animals during experimentation.

The details of the studies will be published in the Biological Pharmeuropa issues (2 per year). Specific actions were taken in the following areas:

- validation of an immunogenicity assay as potency assay for inactivated poliomyelitis vaccine (IPV),
- establishment of 3 product-specific hepatitis A vaccine BRPs (types A, B, C),
- validation of serological methods as potency assay for tetanus vaccine for human use (Phase III),
- establishment of tetanus vaccine (human use) BRP batch 2 and WHO 3rd IS,
- establishment of guinea pig tetanus antiserum BRP for serological potency assay of tetanus vaccine for human use,
- validation of a serological method for potency assay of diphtheria vaccine,
- establishment of *Bordetella pertussis* mouse antiserum BRP for serological potency assay of acellular pertussis vaccine,
- establishment of pertussis toxin BRP for test for absence of residual toxin in acellular pertussis vaccine,
- establishment of oral poliomyelitis vaccine (OPV) BRP batch 2,
- establishment of guinea pig and rabbit antiserum BRPs for serological potency assay of tetanus vaccine for veterinary use,
- establishment of rabbit *Clostridia* antiserum BRP for serological potency assay of clostridia vaccine for veterinary use,

- establishment of ELISA coating antigen BRP for serological potency assay of swine erysipelas vaccine,
- reporting phase for antiserum BRPs for potency assays of equine influenza vaccine,
- establishment of rabies vaccine for veterinary use BRP batch 3,
- establishment of mycoplasma reference strains BRP,
- establishment of human coagulation factor VIII concentrate BRP batch 3,
- establishment of human immunoglobulin BRP batch 2,
- establishment of an HPLC assay for interferon alfa2.

The studies led to the adoption of:

- hepatitis A vaccine (3 product-specific reference preparations),
- oral poliomyelitis vaccine, batch 2,
- tetanus guinea pig antiserum, for the serological assay of tetanus vaccine for human use,
- tetanus guinea pig and rabbit antiserum, for the serological assay of tetanus vaccine for veterinary use,
- *Bordetella pertussis* mouse antiserum, for the serological assay of acellular pertussis vaccine,
- Clostridia rabbit antiserum, for the serological assay of clostridial vaccines for veterinary use,
- rabies vaccine for veterinary use, batch 3.

### **Certification of suitability of monographs of the European Pharmacopoeia**

The extension of the procedure to products with risk of transmitting agents of animal spongiform encephalopathies (Resolution AP-CSP (99) 5 implemented on 1 January 2000) doubled the workload of the unit.

454 new applications (including 239 for products with TSE risk) and 123 requests for revision were received. 522 certificates (new or revised) were granted (245 for chemical products and 277 for products with TSE risk).

In total, 885 certificates have been granted since the procedure became operational.

#### *Creation of a Steering Committee*

The procedure illustrates the exemplary collaboration between the partners, namely the working parties of the CPMP, CVMP, and the European Pharmacopoeia Commission, which while consulting Industry (EFPIA, AESGP, CEFIC, FEDESA, EGEA, EAPPI, IPEC), worked together to find practical solutions to improve quality assurance without complicating the

administrative procedures for evaluation. The licensing authorities have clearly expressed their preference for the certification procedure when there is a European Pharmacopoeia monograph (Guideline on Requirements in relation to active substances and implementation of revised directives 75/318/EEC and 81/852/EEC).

To better apply the 3 Cs (consultation, co-ordination, co-operation) that characterise the procedure, a Steering Committee consisting of the Chairs of the European Pharmacopoeia Commission, the Joint CPMP/CVMP Quality Working Party, the CPMP Biotech Working Party and CVMP Veterinary Immunology Working Party and representatives of the Commission of the European Communities, the EMEA and the EDQM. The Steering Committee met 4 times in 2001 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. To facilitate and harmonise the assessment of dossiers on fermentation products, a standard operating procedure was elaborated after discussions with the industry and assessors of the CPMP/CVMP.

### **Translations and publications**

It should be noted that the European Pharmacopoeia is published in both official languages of the Council of Europe, namely English and French. The EDQM therefore has its own specialised translation service. In 2001, 305 texts were translated from English to French and 235 from French to English.

In the area of publications, the year 2001 issues of *Pharmeuropa* comprised a total of 809 pages in French and 787 pages in English, *Pharmeuropa Bio* (issues in English only) comprised 180 pages, and the 4<sup>th</sup> Edition of the European Pharmacopoeia comprised 2623 pages in French and 2416 in English. The two supplements published in 2001 of the 4<sup>th</sup> Edition comprise 510 pages in French and 470 in English.

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

An "online" electronic version was launched with the 4<sup>th</sup> Edition; it is available in three versions: a

single-user version, an intranet version and an Internet version. All the versions use a Web browser interface to present the information. A demo version of the Internet version can be found at <http://online.pheur.org/demo.htm>.

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

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

There are two levels of collaboration:

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

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

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

### General co-operation between official control laboratories

An annual meeting of the plenary network brings together the various participants and allows them to summarise the year's activities and decide on an action plan for the coming year. It is organised by one of the members of the network on a rotating basis so that the partners get to know each other better and interact more. The sixth annual meeting was attended by 137 representatives from 54 laboratories from 30 countries and was held on 23-27 April 2001 in Uppsala (Sweden). A representative of the EMEA was also present for direct contact with this Agency.

Work in the area of quality assurance systems has intensified, with meetings being organised, the meeting of the plenary group (36 participants from 23 countries) plus the meetings of the working parties. This resulted in the adoption of a programme to harmonise the quality assurance policies of all the members of the network and a specific programme for interlaboratory audits. Two European courses were set up to provide specific training in quality audit techniques for experts from OMCLs.

Proficiency Testing Studies (PTS) are now being carried out regularly and this year 5 studies were organised in the physico-chemical area with the participation of 30 national laboratories on average while in the biological area 7 studies were organised, involving 12 national laboratories on average.

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

- erythromycin base and salts,
- valerian root.

### Activities restricted to the European Economic Area.

These were the following.

#### I - Official batch release of biologicals

For the first time the annual meetings for batch release of blood and plasma derivatives and vaccines were held in conjunction with the annual meeting for the OMCL general network. The meeting took place in Uppsala, Sweden on 23-27 April 2001. This successful meeting included not only the traditional confidential exchange of information between OMCLs involved in batch release on issues related specifically to batch release but also the opportunity to interact with colleagues in a broader context for the mutual exchange of expertise and experience on common issues.

Review of OMCL batch release activities from 2000 for both blood and vaccines and specific scientific presentations highlighted:

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

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

Proposed revisions to annexes III and IV of the Administrative Procedure for Batch Release of Biologicals were adopted.

In addition the following 3 new internal procedures were adopted:

- Technical procedure for agreement to reduce *in vivo* potency testing by OMCLs during batch release;
- Procedure for official control authority batch release of centrally authorised immunological medicinal products and medicinal products derived from human blood and plasma;
- Procedure for implementation of technical documents for the official control authority batch release network.

#### *Blood products and plasma derivatives*

The meeting of the network for batch release of human blood and plasma derivatives took place on 23 April 2001.

Four (1 new and 3 revised) product-specific guidelines were adopted. These guidelines can be found in a booklet published by the EDQM and on the EDQM web site

#### *Human Vaccines*

The meeting of the network for batch release of human vaccines took place on 26-27 April 2001.

Thirty-two (15 new and 17 revised) product-specific guidelines were adopted. These guidelines can be found in a booklet published by the EDQM and on the EDQM web site.

Two guidelines were approved for consultation:

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

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

The member states still used widely different approaches in this area. At a general meeting of

OMCLs involved in evaluation of IVMPs, which was held in Strasbourg on 23 October 2001, the means to improve harmonisation and transparency of the official control authority batch release system (OCABR) in the EU/EEA as implemented according to the current legislation, was discussed. Proposals for action to improve mutual recognition included development of product-specific guidelines. A revision of the administrative procedure for OCABR of IVMPs was also undertaken.

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

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

For these medicines, the network decided in its procedure that sampling from three different countries on average would be sufficiently representative of the European Union market. Samples are collected in principle throughout the medicines distribution system (wholesalers, community or hospital pharmacies) by national inspectors. Samples of each product are sent to the EDQM, which distributes them to two national control laboratories which carry out the required laboratory tests at the same time. The analyses and results are collected by the EDQM. A report is established and sent to the EMEA for any follow up that might be needed.

In 2001, the EDQM processed 28 medicines representing 150 samples which were distributed to the various national official control laboratories for study according to well established protocols derived from marketing authorisation dossiers. The results that had been sent to the CPMP or CPVP (EMEA) were used to make sure that the quality of these substances was good and to check the reproducibility of the methods of analysis.