

European Directorate for the Quality of Medicines (EDQM) Annual report of activities - 2000

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

After Hungary signed the European Pharmacopoeia Convention in June 1999, the number of parties to the Convention increased to 28, namely the European Union and the following countries: Austria, Belgium, Bosnia and 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 and the United Kingdom.

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

At its three Sessions in March, June and November 2000, the European Pharmacopoeia Commission adopted 264 monographs, of which 175 were revisions and 89 were new texts; 7 of these monographs were produced during the year according to the rapid implementation procedure. The Commission also adopted 33 chapters and general methods, of which 18 were revisions and 15 were new texts. One of these chapters was rapidly implemented, 5.2.8 TSE risk. Overall, 297 texts were adopted (193 revised texts). The number of monographs prepared by the procedure for adaptation of national monographs or procedure III decreased (20 in 2000 compared with 29 in 1999). The number of documents produced (new, revised) is slightly higher (2650 compared with 2436 in 1999). The new monographs can be broken down as follows: 183 on inorganic or organic

products, 9 on vaccines, 24 on biologicals, 28 on herbal drugs or preparations, 4 on dosage forms, 4 on homoeopathic preparations and 3 on radiopharmaceutical preparations. Of the new chapters, special mention should be given to the following texts, which were prepared and harmonised with the USP and the Japanese Pharmacopoeia; test for bacterial endotoxins, test for sulphated ash, test for extractable volume for parenteral preparations.

The rapidly implemented texts comprised urgent revisions such as the following monographs:

- products with risk of transmitting agents of animal spongiform encephalopathies;
- methylthioninium chloride to improve the quality of specifications and extend the scope to parenteral use;
- haemophilus Type B Conjugate vaccine, revised after the requirements of the WHO were updated and to limit the use of animals to those that are necessary to guarantee the quality of the vaccine;
- magnesium sulphate heptahydrate to modify the name to avoid confusion between the various hydrates of this substance.

A total of 248 days of meetings were held in 2000. This includes the three plenary sessions of the Commission and the corresponding preparatory meetings, the meetings of the Groups of Experts (51) and those of the *ad hoc* Working Parties (6). 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) and the meeting with CEN. 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:

Revision programme for the preparation of the 4th Edition

The Commission continued its revision of the texts of the 3rd Edition, progressively adapting them whenever possible to the new version of the Technical Guide for the Elaboration of Monographs (published in 2000) and to the new chapter on separation techniques. In addition, it should be pointed out that the style of new monographs has been simplified to make the European Pharmacopoeia easier to use and to harmonise the presentations of the English and French versions. However, it will not be possible to adapt all 1500 existing monographs of the 3rd Edition to the new style in time for the release of the 4th Edition, planned for the beginning of the summer of 2001. Both styles will therefore co-exist in the European Pharmacopoeia during a transitional period.

Standard Terms

The lists published in 1998 continued to be updated constantly. The terms cover pharmaceutical forms, routes of administration and containers for medicines for human and veterinary use. These terms are used in the Summary of Product Characteristics (SPC) for marketing authorisations in accordance with Guideline 3/3593/31 of the Committee for Proprietary Medicinal Products and the Notice to Applicants revised by the European Pharmacopoeia Commission. The revised version published at the beginning of the year 2000 includes translations into 21 European languages. The previous edition included translations into 16 European languages: English, Croatian, Danish, Dutch, Finnish, French, German, Greek, Italian, Norwegian, Portuguese, Slovak, Slovene, Spanish, Swedish and Turkish. These lists have been enriched by the addition of translations into Bulgarian, Hungarian, Icelandic, Polish and Czech.

Communications and public relations

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

- **Mycoplasma testing: towards a new technique for the identification and detection of strains, Paris (France), 13-14 March 2000.** One of the topics of discussion was the use of the PCR technique (polymerase chain reaction). Data was presented to show the usefulness of PCR either alone or in conjunction with the methods that are now used (culture, DNA staining). The current European Pharmacopoeia method, which makes use of culture techniques and DNA staining, will be supplemented by the PCR technique. The requirements concerning mycoplasmas in monographs on vaccines will therefore be revised, and the tests will possibly be simplified and shortened. This symposium, which is of great importance for the elaboration of a common

European monograph and for a future harmonised approach within the framework of VICH was attended by 60 persons from 14 countries (including Australia, United States and Japan). Through this action the EDQM hopes both to promote continued progress in international harmonisation and to facilitate free movement of medicines for human and veterinary use while guaranteeing public health.

- **Tetanus vaccines for human use, Strasbourg (France), 22-23 June 2000 (meeting co-organised with the WHO).** It was important to survey the recent development in the field of quality control of tetanus vaccines and to examine the progress made for their potency determination. Serological potency models using ELISA and TOBI techniques were the centre of interest. Data was presented to show the usefulness of these methods either alone or in conjunction with the methods that are now used. The current European Pharmacopoeia and WHO potency test involves tests in animals and a more acceptable method for routine testing of tetanus vaccines has long been sought. Discussions were held on common approaches on how to perform quality controls of these vaccines in the future based on alternative methods for demonstration of batch consistency. In this context issues related to standards were addressed and the need for having a harmonised approach based on International Units of biological activities was expressed. A draft proposal describing a harmonised approach for use in monitoring consistency of production batches was also considered and will be submitted to the appropriate groups of experts.
 - **Herbal Medicinal Products: Quality Evaluation – Contribution of the European Pharmacopoeia, Nice (France), 16-17 November 2000.** The main objective of the symposium was to gather information for the future direction of work on development of European Pharmacopoeia monographs. This involved sharing points of view and experience with the principal users and examining the current situation as regards the quality of herbal drugs used in the pharmaceutical industry. After two days of exchanges and lively discussion, four main ideas for future development became apparent:
 - the need to pursue the elaboration of monographs of the European Pharmacopoeia on herbal drugs and extracts;
 - standardisation of terminology;
 - strengthening communications between the various partners;
 - improving the transparency of the monographs and adapting them, where necessary, to the needs of all users, particularly to facilitate the evaluation of licensing dossiers and avoid duplication of work.
- The success of this symposium showed the dynamism of international activity in the area of the

quality of medicines and highlighted the co-operation between the Council of Europe and the European Union and the complementarity of the activities of the two organisations

The EDQM also continued to develop its INTERNET SITE. This site facilitates contacts with the 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 Directorate, 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

101 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 1297. Extensive collaborative studies were required for 24 of these substances to determine the content of the substances used in the assays. In addition, 65 substances were replaced and the European Pharmacopoeia laboratory regularly monitored 128 substances and carried out quality control tests during the production of 347 batches. The number of chemical reference substances and biological reference preparations distributed to users continued to climb: 70 367 in 2000 (49 254 in 1999) and the number of orders increased from 8717 to 10 571. From bulk substances selected by the European Pharmacopoeia Commission for use as reference substances, the Production Unit of the EDQM prepared 347 batches (filling more than 63 000 vials) and 13 batches by lyophilisation, filling 14 000 vials.

Preparation and distribution of samples

During the year, 1898 (1639 in 1999) new samples were received by the EDQM. The total number of samples in stock was 10 760. Nearly 140 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 1692 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 5781 samples were prepared for distribution to the various experts of the European Directorate for the Quality of Medicines (for the elaboration of monographs and the organisation of collaborative studies, market surveillance studies, biological standardisation projects).

Biological standardisation

The Biological Standardisation Programme (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 titration methods,
- validation of alternative methods to reduce, refine or replace the use of 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 polio 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 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 polio 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 in 2000 of the following:

- hepatitis A vaccine (3 product specific reference preparations),
- oral polio vaccine, batch 2,
- tetanus guinea pig antiserum, for the serological assay of tetanus vaccine for human use,
- tetanus guinea 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 Ph. Eur.

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.

In 2000, 421 new applications (including 230 for products with TSE risk) and 55 requests for revision were received. 176 new certificates were granted or revised (139 for chemical products and 37 for products with TSE risk).

In total, 590 certificates have been granted and 226 revisions have been carried out 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 2000 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, a technical advisory board has been set up which consists of expert rapporteurs who participate in the evaluation of dossiers. This board deals with any technical or scientific questions raised by the rapporteurs. To facilitate the assessment of dossiers on fermentation products, a guideline has been elaborated which has been distributed to the industry and assessors of the CPMP/CVMP for comments.

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 2000, 353 texts were translated from English to French and 237 from French to English.

In the area of publications, the year 2000 issues of *Pharmeuropa* comprised a total of 734 pages in French and 719 pages in English, *Pharmeuropa Bio* (issues only in English) comprised 225 pages, and the cumulative supplement 2001 of the 3rd edition of the European Pharmacopoeia comprised 1770 pages in French and 1705 in English.

The CD-ROM 2001 has been improved with the use of new software. This CD-ROM makes it possible to view all 1550 monographs, 285 general methods of analysis and 1585 reagents, as well as the catalogue of reference substances and 1100 safety data sheets that correspond to these reference substances. The CD-ROM format has the following convenient features: hierarchic table of contents, subject index and keyword search. Hyperlinks in the text of a monograph give access to information on general methods, reagents and reference substances used in the monograph. A click on a hyperlink opens a new screen automatically without closing the screen that is currently being used.

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 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. This year representatives from 31 countries met for 3 days in Lisbon.

Work in the area of quality assurance systems has intensified, with 15 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 35 national laboratories on average while in the biological area 3 studies were organised, involving 14 national laboratories on average.

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

- salbutamol pressurised metered-dose preparations for inhalation,
- dihydrostreptomycin sulphate in veterinary suspensions for injection,
- nifedipine retard oral preparations,

- Trimethoprim impurities in raw materials and tablets,
- doxycyclines in oral preparations for human and veterinary use.

Activities restricted to the European Economic Area

These were the following.

- Batch release control for vaccines and blood products. The programme for the preparation of guidelines for each type of vaccine or blood product continued. Two working parties were set up (which met 4 times) and 22 guidelines were adopted (1 for the general procedure, 4 for blood products, 17 for vaccines) available as a booklet and on the EDQM Internet site. Eighteen new guidelines were prepared. These are now being finalised after consultation. Three guidelines on general procedures were also prepared.

The network held its annual meeting both for vaccines and blood products, during which views were exchanged with the industries concerned (EFPIA/EVM; EAPPI, PPTA, EPFA). An Advisory Working Party was set up and it met twice this year.

- Surveillance of products having received a marketing authorisation for countries in the European Union in accordance with the decision of the Pharmaceutical Committee to set up a pilot phase for sampling and testing of centrally authorised medicinal products.

After a contract was signed in June 1999 between the EMEA and the EDQM, a programme was implemented in 1999 and 2000 for the surveillance of 35 medicines that had received a Community marketing authorisation in 1996 and 1997.

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 2000, the EDQM processed 264 batches of substances and reagents representing 4914 samples which were distributed to the various national official control laboratories for study according to well established protocols derived from marketing authorisation dossiers.