

Annual report of activities of the European Directorate for the Quality of Medicines (EDQM) - 1999

The European Directorate for the Quality of Medicines (previously the European Department for the Quality of Medicines) has two main areas of responsibility:

- 1) the European Pharmacopocia 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

Hungary signed the European Pharmacopoeia Convention on 9 June 1999 to become the 28th party to this Convention (Hungary previously had observer status at the Commission). It thus became a full member on 10 September 1999. It should be noted that the parties to the Convention are the European Union and the following countries: Austria, Belgium, Bosnia and Herzegovina, Croatia, Cyprus, the Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Grand-Duchy of Luxembourg, Norway, the Netherlands, Portugal, Slovakia, Slovenia, Spain, Sweden, Switzerland, "The Former Yugoslav Republic of Macedonia", Turkey and the United Kingdom.

The number of observers dropped from 17 to 16 with the change in Hungary's status. The current observers are: the WHO, Ukraine, Tunisia, Malaysia, Morocco, Estonia, Latvia, Lithuania, Albania, Poland, Romania, Bulgaria, China, Canada, Australia and Syria.

General activities

At its three Sessions in March, June and November 1999, the European Pharmacopocia Commission adopted 277 monographs, of which 175 were revisions and 102 were new texts; 26 of these monographs were produced in 1999 according to the rapid implementation procedure. The Commission also adopted 23 chapters and general methods, of which 12 were revisions and 11 were new texts. One of these chapters was a rapidly implemented text. Overall, 300 texts were adopted (187 revised texts). This number is markedly higher than in 1998 (258 texts), especially as regards the percentage of revised texts (187 versus 146 in 1998). The number of monographs prepared by the procedure for adaptation of national monographs or procedure III remained stable (29 in 1999 versus 24 in 1997 and 36 in 1996). The number of documents produced (new, revised) is slightly higher (2436 versus 2223 in 1998). The new monographs can be broken down as fol-

lows: 71 on inorganic or organic products, 4 on vaccines, 3 on biologicals, 19 on herbal drugs or preparations, 1 on a dosage form and 4 on radiopharmaceutical preparations. Of the new chapters, the following should be given special mention: Assay of total protein, which was prepared and harmonised with the USP and the Japanese Pharmacopocia; Validation of nucleic acid amplification techniques (NAT) for the detection of hepatitis C virus (HCV) RNA in plasma pools: guidelines; Minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products.

The rapidly implemented texts comprised urgent revisions such as the monographs on water (purified water and water for injection), on methylene blue as well as the adoption of new general monographs on production criteria whose implementation was requested by the licensing authorities (monograph on Products with Risk of Transmitting Agents of Animal Spongiform Encephalopathies).

A total of 300 days of meetings were held in 1999. These included three plenary sessions of the Commission and the corresponding preparatory meetings, the meetings of the Groups of Experts (60), of ad hoc Working Parties (14) and of Chairs of Groups of Experts. 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 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 4 (requiring about 25 days of meetings per person), 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 study of how to adapt the 4th Edition (publication planned for 2001) to the needs of users, especially the licensing authorities and the industries. The revisions of the Technical Guide for the Elaboration of Monographs and the Style Guide are now finished. These guides are to be published at the beginning of 2000. The Technical Guide includes the measures described in the ICH

guidelines as they pertain to the monographs. The chapter on separation methods has been entirely rewritten. As regards the Style Guide, the Commission decided to modify the style to make the European Pharmacopoeia easier to use and to harmonise the presentations of the English and French versions.

Standard Terms

The lists published in 1998 continued to be updated constantly. The terms included pharmaceutical forms, routes of administration and containers. 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. Translation into the various European languages continued. The next revised edition will be available in 21 European languages in early 2000.

Notification procedure

The previous summary of activities of the Commission (1998) mentioned the trial period approved by the European Pharmacopoeia Commission on the notification of work carried out at the national level. An evaluation of the results after two years of operation showed that the work of the national authorities was better co-ordinated and more transparent. The procedure has speeded up the preparation and adoption of certain types of monographs, especially herbal drugs. The Commission has decided to maintain the use of this procedure on a voluntary basis.

Communications and public relations

The EDQM continued to organise international scientific conferences or seminars on specific subjects. The conferences in 1999 were the following:

- “Biologicals beyond 2000: challenges for quality standards in an evolving field” which brought together over 200 participants from 28 countries. This conference was organised with representatives of the United States and Japanese pharmaceuticals as well as the licensing authorities of the FDA and the Japanese Health Ministry. It provided a forum for in-depth discussions on future methodologies and on areas of current research.
- “Certification of suitability: new aspects of the procedure”. Nearly 250 participants from 32 countries came to Berlin for this conference which set up a dialogue between assessors of certification dossiers, the licensing authorities and the manufacturers concerned.
- “Quality of water”: 70 participants from 17 countries attended this conference in Strasbourg where they concluded that it was necessary to have a grade of water between water for injection and purified water. A proposal was published in September 1999 (Pharmeuropa 11.3).

— “Alternatives to animal challenge testing in the batch control of leptospira vaccine for veterinary use”. This conference in Strasbourg was attended by over 50 participants from more than 15 countries. Focussed on potency and safety tests, it provided an overview of current knowledge of immunity to leptospira and concentrated on the need to assess and validate methods that are alternatives to the challenge test in hamsters.

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 main general policy decisions. 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

111 new chemical reference substances or biological reference preparations were adopted during the year, bringing the number of substances available to users of the European Pharmacopoeia to 1170. Extensive collaborative studies were required for 26 of these substances to determine the content of the substances used in the assays. In addition, 38 substances were replaced and the European Pharmacopoeia laboratory regularly monitored 255 substances and carried out quality control tests during the production of 363 batches. The number of chemical reference substances and biological reference preparations distributed to users continued to climb: 49 254 in 1999 (42 404 in 1998) whereas the number of orders increased from 7409 to 8717. From bulk substances selected by the European Pharmacopoeia Commission for use as reference substances, the Production Unit of the EDQM prepared 273 batches (filling more than 42 000 vials) and 90 batches by lyophilisation filling 37 500 vials.

Preparation and distribution of samples

During the year, 1639 new samples were received by the EDQM. The total number of samples in stock was 9175. Nearly one hundred 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 about 1600 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 2300 samples were prepared for distribution to the various experts of the European Pharmacopoeia for the elaboration of monographs and the organisation of collaborative studies (315 studies).

Biological standardisation

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

- establishment of common European standards, available in sufficient quantities so that Official Medicines Control Laboratories and manufacturers can 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:

- establishing biological reference preparations for diphtheria toxin, hepatitis A immunoglobulin, hepatitis C virus (test using nucleic acid amplification techniques), anti-rabies immunoglobulin, reference HCV-positive plasma for testing by nucleic acid amplification techniques (NAT), hepatitis A vaccines and in the veterinary area, establishing reference sera for equine influenza vaccine and swine erysipelas vaccine.
- standardising the titration method for the potency of inactivated polio vaccines.
- finalising correlation studies to develop ELISA and TOBI serological methods as alternatives to challenge tests in animals (the work will be covered during a special symposium in June 2000 (see announcement in the current issue)).

Work on other veterinary vaccines is nearing completion.

Certification of Suitability of monographs of the Ph. Eur.

This new procedure set up in 1994 continued to grow rapidly. 197 new applications and 58 requests for revision were received in 1999. 101 new certificates were granted or revised.

Extension of the procedure

During the year, the procedure was revised after extensive consultation with all the parties concerned (licensing authorities and industries). This revision involved broadening the scope of the procedure to cover products with risk of transmitting agents of animal spongiform encephalopathies. The revised procedure AP-CSP (99) 5 has the implementation date of 1 January 2000. It illustrates the exemplary collaboration between the partners, CPMP, CVMP, European Pharmacopoeia Commission and Industry, which during meetings with experts and with Industry (bringing together representatives of EFPIA, AESGP, CEFIC, FEDESA, EGEA, EAPPI, IPEC) worked together to find practical solutions to difficult problems in this area.

Implementation of GMP

As mentioned in the 1998 annual report, the procedure now requires manufacturers to declare in their application that the manufacture of their substance takes place in accordance with Good Manufacturing Practice (specifying which international guidelines are followed) and with the documents in their dossier. As part of a pilot phase continuing until Community directives in this area are adopted, the first inspections were carried out in 1999 by teams of inspectors from different national authorities.

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 1999, 388 texts were translated from English to French and 185 from French to English.

In the area of publications, the 1999 issues of *Pharmeuropa* comprised a total of 683 pages in French and 670 pages in English, *Pharmeuropa Bio* (issues only in English) comprised 173 pages, and the cumulative supplement 2000 of the 3rd Edition of the European Pharmacopoeia comprised 1406 pages in French and 1388 in English.

The proceedings of the scientific conference on water prepared by reverse-osmosis have been published. The proceedings of the other scientific conferences are planned to be published at the beginning of 2000. In addition, the OMCL newsletter prepared by the European network of control laboratories was published three times; it is distributed to about 500 laboratories.

The CD-ROM 2000 has been improved with the use of new software. This CD-ROM makes it possible to view all 1430 monographs, 260 general methods of analysis and 1380 reagents, as well as the catalogue of reference substances and 950 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 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 of medicines of 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

Henceforth 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 the meeting was attended by representatives from 30 countries for two and a half days in Copenhagen (see press release in *Pharmeuropa* 11.4).

Work in the area of quality assurance systems has intensified, with 8 meetings being organised, the plenary group plus the working parties (7 days of meetings). This resulted in the adoption of a harmonisation programme for the quality assurance policies of all the members of the network and a specific assistance and maintenance programme for quality assurance systems in the network, the adoption of 3 guidelines of general interest on validation of analytical procedures, evaluation and reporting of results and qualification of equipment.

Proficiency Testing Studies (PTS) are now being carried out regularly and this year 4 studies were organised in the physicochemical area with the participation of 30 national laboratories on average. These studies were extended to the biological area for the first time with the organisation of 4 studies 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 13 national laboratories on average:

- Diclofenac
- Tamoxifen
- Nifedipine

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: 5 working parties were set up and 19 guidelines were adopted (1 for the general procedure, 4 for blood products, 14 for vaccines) available as a booklet and on the EDQM Internet site; 4 new guidelines, which are currently undergoing consultation, were 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, 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.

A pilot phase initiated in 1998 and run jointly by the EMEA and the EDQM was completed; it involved 9 products. This pilot phase led to the adoption of an operational procedure and the signature of a contract in June 1999 between the EMEA and the EDQM that will govern a programme for the surveillance in 1999 and 2000 of 35 medicines that 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 followup that might be needed.

During the second half of 1999, the EDQM processed 62 batches of substances and reagents representing 227 samples which were distributed to the various national official control laboratories for study according to well-established protocols derived from marketing authorisation dossiers.