

Foreword



As every year, the annual report provides an opportunity to review the activities of the past 12 months, to reflect on developments and achievements. The work to further strengthen the standards of the European Pharmacopoeia (Ph. Eur.), both in the form of pharmacopoeial texts and related reference standards, continued to be a major focus of the EDQM in 2012.

The P4 procedure, a procedure dedicated to substances still under patent and for which monographs are elaborated in close collaboration with regulators and the respective innovator companies, again demonstrated its usefulness. Up to the end of the year, a total of 64 monographs covering both chemically-defined and biological substances have been adopted, five of which were finalised in 2012. The Ph. Eur. Commission continued its work on facilitating the implementation of the new quality paradigm in the development and production of medicines by adopting an optional general chapter Demonstration of uniformity of dosage units using large sample sizes (2.9.47). The Commission also identified the need to further investigate the feasibility of specific finished product monographs and initiated a pilot project on such monographs. The Finished Product Monograph Working Party is solely composed of representatives from competent authorities and it will draft a concept for a multi-source product and, in close collaboration with the innovator, for a product still under data protection. An evaluation of these activities is scheduled for 2014. In the field of veterinary medicines, about 80 vaccine-specific monographs were revised to align them with two recently adopted VICH guidelines. The activities of the Ph. Eur. Commission and the Biological Standardisation Programme related to the 3Rs (replacement, reduction and refinement of tests in animals) showed further progress, which have been widely acknowledged by all stakeholders.

At an international level, the Ph. Eur. continued the collaboration with its sister Japanese and United States pharmacopoeias in the framework of the Pharmacopoeial Discussion Group (PDG). The Ph. Eur. also very much supported an initiative of the World Health Organization (WHO) for global pharmacopoeial harmonisation. In this context, a decision was taken by the pharmacopoeias of the world to agree on harmonised policies and procedures related to, for example, monograph development, interactions with stakeholders and collaboration among pharmacopoeias. The Secretariat to the Ph. Eur. Commission volunteered to actively contribute to the compilation of this document, currently known under its working title "Good Pharmacopoeial Practices", to ensure that the different pharmacopoeias throughout Europe speak with one voice.

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The 'Certification of suitability to the monographs of the European Pharmacopoeia' (CEP) procedure celebrated the 20th anniversary of a two-year pilot phase that was initiated in 1992. Stakeholders from industry and competent authorities from different continents expressed their appreciation of the activities in the field and underlined the added value of the procedure as it helps competent authorities to make the best use of scarce resources, while facilitating marketing authorisation procedures for the industry. The outcome of GMP inspections of API manufacturing sites covered by CEPs conducted in 2012 emphasised the need for on-site inspections and, yet again, demonstrated the usefulness of the triggers developed in the context of a risk-based selection of manufacturing sites at a European level. Furthermore, it highlighted the need for more frequent verification of sustained GMP compliance.

In addition to their "routine" activities such as maintenance of the common quality system, carrying out proficiency testing scheme studies, market surveillance and official control authority batch release testing, the European Network of Official Medicines Control Laboratories made a number of contributions of additional value in other areas, e.g. in the fight against counterfeit/illegal API and medicinal products and the testing of unlicensed pharmaceutical preparations and gene therapy products.

In terms of blood transfusion activities, the finalisation of the 17th Edition of the "Guide for the preparation, use and quality assurance of blood components", which will be published in mid-2013, constituted a key milestone. The preparation of the 5th Edition of the "Guide to Safety and Quality of Organs for Transplantation" was also finalised, compiling guidance on the different aspects of the organ donation and transplantation process, from donor risk assessment to disease transmission.

In the field of pharmaceutical care, the report on "Policies and practices for a safer, more responsible and cost-effective health system" was published and it was referred to in the context of the Dutch Ministers Summit on "The benefits of responsible use of medicines: setting policies for better and cost-effective healthcare".

In the fight against falsified/counterfeit medicines, a lot of activities focussed on further promoting the Council of Europe's MEDICRIME Convention which, by the end of the year, had been signed by 22 states and ratified by one. The Convention will become operational when it has been ratified by five states. The EDQM also further developed eTACT, its proposed mass-serialisation service for medicines, by collecting important feed-back from all stakeholders throughout the supply chain. Features of this project that are of special importance to the EDQM include its envisaged public governance, inter-operability with existing national systems, flexibility and the empowerment of patients to verify the authenticity of their own medication.

The European Network of Official Cosmetics Control Laboratories continued its market surveillance study on decorative cosmetics and started an additional study on cosmetic products intended for use on or by children. A resolution on safety criteria for cosmetic products intended for infants was adopted by the Council of Europe Committee of Ministers in April 2012. In the area of packaging material for food, a new resolution on metals and alloys used in food contact materials has been drafted, which will supersede the corresponding guidelines published ten years ago. Its adoption is planned for 2013.

Finally, the EDQM is proud that its ISO 9001 certification has been extended. The audit performed by Afnor, the French certification body, not only covered the activities that had already been certified in previous years (certification of suitability activities, post-marketing surveillance studies conducted under the auspices of the EDQM, and the activities related to the OCABR procedure for the official control authorities release of batches of human immunological medicinal products, i.e. both blood products and vaccines) but, for the first time, it also covered the monograph process. Hence, the elaboration, revision, correction and suppression of pharmacopoeial texts, their publication in printed and electronic format, and their distribution, are now also ISO 9001 certified.

In addition, Belac, the Belgian accreditation body, conducted a thorough ISO/IEC 17025:2005 audit of the EDQM laboratory in December 2012. The granting of a corresponding certificate is awaited in the beginning of 2013.

Overall, 2012 was another challenging and successful year for the EDQM. The importance of its activities for the protection of public health in Europe and beyond has been acknowledged by the decision of the Ukraine to ratify the Convention on the elaboration of a European Pharmacopoeia in December 2012 and the requests for observer status from the Republic of Guinea and Singapore, granted in 2012. However, the achievements in 2012 would not have been possible without the support and dedication of the numerous experts appointed by the now 37 signatory states to the Convention. Their expertise and enthusiasm are crucial for the work of the European Pharmacopoeia Commission and its Groups of Experts and Working Parties, the Committees and Expert Groups in the areas of Blood Transfusion, Organ Transplantation, Pharmaceuticals and Pharmaceutical Care, Consumer Health Protection, the OMCL Network and the Certification Scheme. I would like to take this opportunity to express our sincere gratitude to all of them.

Susanne Keitel
Director



THE EDQM AT A GLANCE: values, aims, activities

■ The European Directorate for the Quality of Medicines & HealthCare: a Directorate of the Council of Europe

The primary aim of the Council of Europe is to create a common democratic and legal area throughout the whole of the continent, ensuring respect for its fundamental values: human rights, democracy and the rule of law.

Human Rights... Democracy... Rule of Law

These values are the foundations of a tolerant and civilised society and indispensable for European stability, economic growth and social cohesion. On the basis of these fundamental values, we try to find shared solutions to major problems such as terrorism, organised crime and corruption, cybercrime, bioethics and cloning, violence against children and women, and trafficking in human beings. Co-operation between all member states is the only way to solve the major problems facing society today.

Objectives

- to protect human rights, pluralist democracy and the rule of law.
- to promote awareness and encourage the development of Europe's cultural identity and diversity.
- to find common solutions to the challenges facing European society.
- to consolidate democratic stability in Europe by backing political, legislative and constitutional reform.

■ The mission of the EDQM

The mission of the EDQM is to contribute to the basic human right of access to good quality medicines and healthcare, and to promote and protect human and animal health by:

- establishing and providing official standards which apply to the manufacture and quality control of medicines in all the signatory states of the Convention for the elaboration of a European Pharmacopoeia and beyond.
- ensuring the application of these official standards to substances used for the production of medicines.
- co-ordinating a network of Official Medicines Control Laboratories to collaborate and share expertise between member states and effectively use limited resources.

- establishing quality standards and promoting ethical practices:
 - for the collection, preparation, storage and use of blood components concerning transfusion medicine.
 - for organ transplantation including tissues and cells.
- collaborating with national and international organisations in efforts to eliminate illegal and counterfeit medicinal and medical products.
- providing policies and model approaches for the safe use of medicines in Europe, including guidelines on pharmaceutical care.
- establishing standards and co-ordinating controls for cosmetics and food packaging.



The European Directorate for the Quality of Medicines & HealthCare (EDQM)

The EDQM, whose origins date back to 1964, has over the years become a directorate of the Council of Europe. In 2011, the EDQM employed 240 full-time staff members and was structured into nine administrative entities.

It was set up by virtue of article 9 of the Convention on the Elaboration of a European Pharmacopoeia, which was signed by eight member states of the Council of Europe in 1964 with the vision of creating a common European Pharmacopoeia. Known for many years as the “European Pharmacopoeia Secretariat”, this administrative entity of the Council of Europe has undergone successive name changes, each time to reflect the new missions assigned to it.



1. CORE ACTIVITIES

1.1 The European Pharmacopoeia (Ph. Eur.)

Purpose

The purpose of the European Pharmacopoeia (Ph. Eur.) is to promote public health by the provision of recognised standards ensuring the quality of medicines. Their existence ensures the quality of medicinal products and components, and facilitates their free movement throughout Europe. Ph. Eur. monographs and texts are designed to be appropriate to the needs of regulatory authorities, manufacturers of starting materials and medicinal products and those engaged in the quality control of medicinal products and their constituents.

The Ph. Eur. is governed by the Ph. Eur. Commission which supervises the work of the more than 70 working parties and groups of experts. The Commission is composed of delegations of the 38 signatory parties and 24 observers to the Convention on the Elaboration of a European Pharmacopoeia.

The European Pharmacopoeia is widely used internationally. The Commission works closely with all users of the Pharmacopoeia in order to better satisfy their needs and facilitate their co-operation.

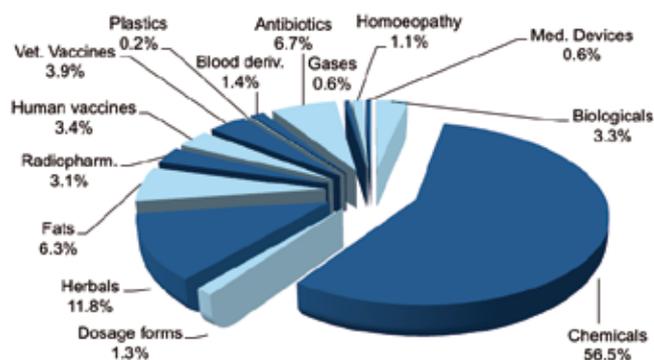
An official reference to serve public health

Ph. Eur. quality standards are not only part of the requirements for marketing authorisation for a medicinal product, but are legally-binding throughout the entire life-cycle of the product. They guarantee a single common quality standard for medicines throughout Europe.

All producers of medicines and/or substances for pharmaceutical use must, therefore, apply these quality standards in order to market their products in the signatory states of the Convention.

A large scope to cover all public health issues

In its current version, the Ph. Eur. contains 2224 monographs, including general standards that apply to groups of ingredients or dosage forms, and 345 general texts including methods of analysis. As shown below, its scope extends far beyond "classical" chemically-defined medicines:



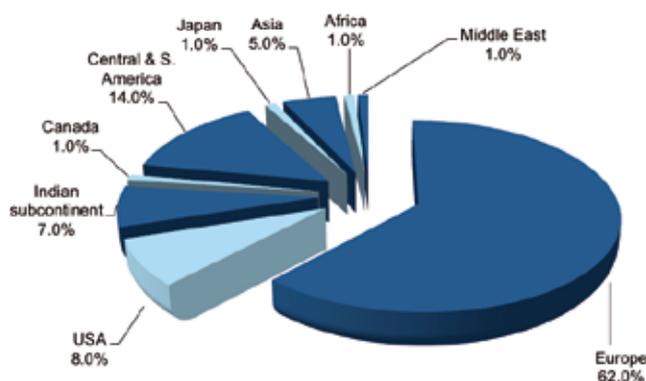
*2011 Data

Officially adopted and implemented by all member states

All standards of the Ph. Eur. are adopted by consensus by the Ph. Eur. Commission. Once adopted, standards become mandatory on the same date in all member states.

The 24 observers from all continents (*Albania, Algeria, Argentina, Armenia, Australia, Belarus, Brazil, Canada, China, Georgia, Israel, Kazakhstan, Madagascar, Malaysia, Moldova, Morocco, Republic of Guinea, Russian Federation, Senegal, Singapore, Syria, Tunisia, United States of America and the World Health Organization (WHO)*) are welcome to participate in the deliberations of the Commission and its Groups of Experts and Working Parties.

% of subscriptions to the Eur. Ph. by geographical zone



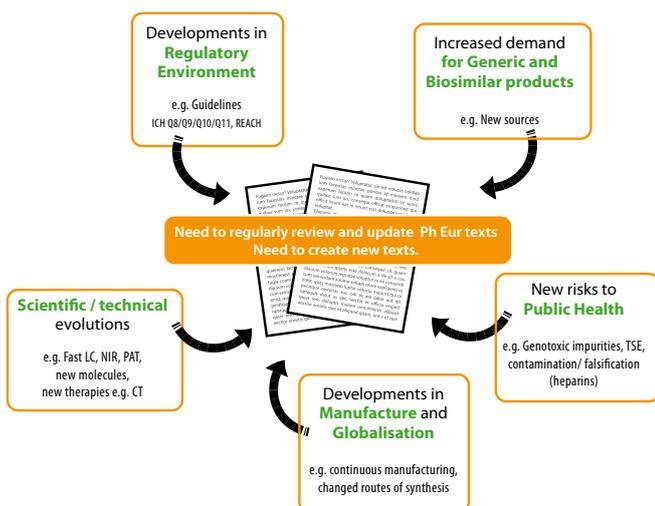
*2011 Data

An on-going process to add to and revise existing quality standards

The Ph. Eur. is maintained by the European Pharmacopoeia Department, composed of scientific officers who act as Secretaries to the groups of experts and working parties that establish the texts of the Ph. Eur. More than 800 experts from all over Europe contribute their expertise and knowledge to the drafting process. As shown in the following figure, there is a continuous need to update monographs, taking account of new developments and requirements arising for scientific, regulatory or other reasons.

Translators in the European Pharmacopoeia Department ensure that the Ph. Eur. is translated into English and French, the two official languages of the Council of Europe. It is also translated into Spanish in co-operation with the Spanish authorities. Translations into other national languages of member states of the Convention, e.g. German, Hungarian and Polish, are performed under the responsibility of the individual member states.

How quality standards are regularly reviewed and revised to remain state-of-the-art



Stakeholder Consultations

To optimise the interaction between the European Pharmacopoeia Commission and its users and to allow users to have more time to comment on drafts and ensure broader access to stakeholders worldwide, Pharmeuropa, the European Pharmacopoeia forum, is now paperless and freely available online.

Texts are published on an on-going basis, but the principle of four issues per year and the four comment deadlines have remained unchanged, as have channels and procedures for providing comments to published draft texts. (see chapter 2.2 Information Technology and Publications activities page 32).

Exchanges and discussions with National Pharmacopoeia Authorities (NPA) members of the European Pharmacopoeia Convention

The annual meeting of the National Pharmacopoeia Authorities of the European Pharmacopoeia member states took place in Bern (Switzerland) in May 2012. The meeting was hosted by Swissmedic, the Swiss Agency for Therapeutic Products. Twenty-one of the thirty-six member states of the Convention on the elaboration of a European Pharmacopoeia participated in this event.

Topics discussed included:

- the mid- and long-term strategy of the European Pharmacopoeia in the field of biological and chemically-defined products.

- follow-up to the actions proposed and decided upon following the conference “European Formulary on Paediatric Formulations” organised by the EDQM in November 2011. The NPAs greatly welcomed and fully supported the proposal to elaborate such a European Formulary.
- the potential need for further action on the Second identification testing section in individual monographs as regards its scope, requirements and maintenance. Those discussions triggered the decision to create a Second Identification Test Working Party as endorsed by the Commission in June 2012. The first objective of this Working Party will be to prepare a guidance document defining the criteria for inclusion of a second series of identification tests in individual monographs, solely intended to be carried out in pharmacies. This will also include a review of the methods and instrumentation available in pharmacies for this purpose.

International Harmonisation and Pharmacopoeial Discussion Group

Globalisation and expansion in international trade present a growing need to develop global quality standards for medicines. Standards are a vital instrument for marketing authorisation, market surveillance, and free movement and trade of medicines among regions and countries.

The European Pharmacopoeia is engaged in a process of harmonisation of general methods and excipient monographs with the Japanese Pharmacopoeia and the United States Pharmacopoeia, within an informal structure referred to as the Pharmacopoeial Discussion Group (PDG). Information on the status of harmonised texts is given in general chapter *Pharmacopoeial harmonisation* (5.8) of the Ph. Eur. and on the International harmonisation page of the EDQM website.

The PDG considers proposals made by national associations of manufacturers of pharmaceutical products and excipients in order to select general methods of analysis and excipient monographs for addition to its work programme.

At present, 28 of the 35 General Chapters and 43 of the 62 excipient monographs of the current work programme have been harmonised.

Monographs on Finished Products

Up to the 8th Edition, monographs on Finished Products have not been elaborated, with a few exceptions, e.g. those on immunosera for human use, immunosera for veterinary use, some biological preparations such as insulin preparations, radiopharmaceutical preparations, vaccines for human use and vaccines for veterinary use.

Harmonisation and standardisation for Finished Products throughout the Ph. Eur. member states have so far been dealt with via the drafting of general dosage form monographs, which set out elements common to all preparations within



the scope of the monograph, and via the development of standard test methods used for testing of Finished Products. The inclusion of these general monographs and methods in the European Pharmacopoeia gives a common basis for competent authorities and manufacturers in the preparation and evaluation of applications for marketing authorisation. A general monograph on *Pharmaceutical preparations* (2619) was also adopted in 2012. This monograph is intended to be a reference source of standards in the European Pharmacopoeia on active substances, excipients and dosage forms, which are to be applied in the manufacture/preparation of pharmaceuticals, but not a guide on how to manufacture them as there is already specific guidance available covering methods of manufacture and associated controls.

However, the Commission, in its 144th session, decided to revisit its policy and initiate a pilot phase on Finished Product monographs. The purpose of this pilot project is to conduct a feasibility study on two draft finished product monographs containing chemically-defined active substances (one single-source and one multi-source product) allocated to a dedicated Working Party by the Commission. At the end of the pilot phase, the Commission will decide whether or not to routinely develop finished product monographs.

P4 procedure: A success story!

The P4 procedure applies to substances for which only a single manufacturer has been identified. It is usually applied to substances still under patent protection with a high interest for future generics. The monograph draft is based on substances used in medicinal products that have been authorised by the competent authorities of Parties to the European Pharmacopoeia Convention, normally in the EU.

Already, 61 P4 and P4Bio monographs (including five monographs adopted in 2012, *i.e.* *Ciclesonide* (2703), *Pemetrexed disodium heptahydrate* (2637), *Atomoxetine hydrochloride* (2640), *Dutasteride* (2641) and *Human coagulation factor VIIIa (rDNA)* (2534)) have been adopted by the Ph. Eur. Commission.

Ph. Eur. and Quality by Design (QbD)

A Process Analytical Technology (PAT) Working Party has been created to keep pace with the technical advances in the field of QbD/PAT and is working in close collaboration with the European Medicines Agency (EMA) PAT Working Group. One of the key objectives of the creation or revision of general texts on issues related to PAT in the Ph. Eur. is to facilitate and foster the application of enhanced control strategies, including PAT and real time release.

As an outcome of the work of the Ph. Eur. PAT Working Party, the alternative optional Chapter *Demonstration of Uniformity of Dosage Units using large sample sizes* (2.9.47) has been elaborated and was adopted by the Ph. Eur. Commission in 2012. This chapter can be utilised by applicants, for example, when increased information from non-destructive

NIR process controls is available, and could therefore be used to replace conventional testing of uniformity of dosage units. The members of this Working Party also revised the chapter *NIR Infrared Spectroscopy* (2.2.40) to introduce PAT-related concepts such as in-line and on-line measurements. This chapter was prepared in close consultation with the EMA CVMP/CHMP Quality Working Party and will be complemented by the revised EMA “*Guideline on the use of near infrared spectroscopy by the pharmaceutical industry and the data requirements for new submissions and variations*” (finalisation expected in 2013). Currently, the PAT Working Party is reviewing the chapter on *Raman spectrometry* (2.2.48).

Reflections on the need for new general chapters, *e.g.* NIR-imaging, tera hertz spectroscopy and acoustics are also on-going.

The NIR Working Party is currently drafting a general chapter on *Chemometric methods applied to analytical data* (5.21).

Heavy Metals

Following the adoption of the European Medicines Agency (EMA) “*Guideline on the specification limits for residues of metal catalysts or metal reagents*”, the Ph. Eur. Commission decided to elaborate a new chapter on *Metal catalyst or metal reagent residues* (5.20), which is a reproduction of the EMA guideline. To support users in its implementation, a method for the *Determination of metal catalysts or metal reagent residues* (2.4.20) has also been elaborated. The methodology described in the latter chapter describes the general approach for the determination of metal catalysts or metal reagent residues in substances for pharmaceutical use and can be applied where possible. Both documents have been adopted by the Ph. Eur. Commission and published in the Ph. Eur.

Once the ICH Q3D Guideline for Metal Impurities has been adopted, it is envisaged to replace the current EMA “*Guideline on the specification limits for residues of metal catalysts or metal reagents*”. As a consequence, the Ph. Eur. Chapter on *Metal catalyst or metal reagent residues* (5.20) will be revised and updated accordingly and method 2.4.20 will also be reviewed and revised if needed.

Achievements of the Ph. Eur. Commission for the 3Rs

During its 142nd Session, the European Pharmacopoeia Commission decided to harmonise the European Pharmacopoeia texts for veterinary vaccines and, in doing so, improve their consistency. This was the culmination of several years of extensive and ambitious work that started under the framework of the harmonisation with *VICH Guidelines (GL) 41 (test for reversion to virulence)* and *44 (developmental safety tests)*, that came into force in 2008 and 2009. It involved work on around 80 Ph. Eur. vaccine-specific monographs, the general monograph on *Vaccines for veterinary use* (0062) and two general chapters (*Evaluation of safety of veterinary vaccines and immunosera* (5.2.6) and *Evaluation of safety of*

each batch of immunosera for veterinary use (55.2.9)), all of which were published in *Pharmeuropa* 23.1 for public enquiry.

Beyond VICH harmonisation and to ensure consistency with European regulations, the European Pharmacopoeia harmonised all the monographs, including monographs for vaccines intended for species that were outside the scope of the VICH Guidelines. As a consequence, the safety tests and the tests for increased virulence performed during development of the vaccines were harmonised and this will greatly reduce the number of animals used for testing.



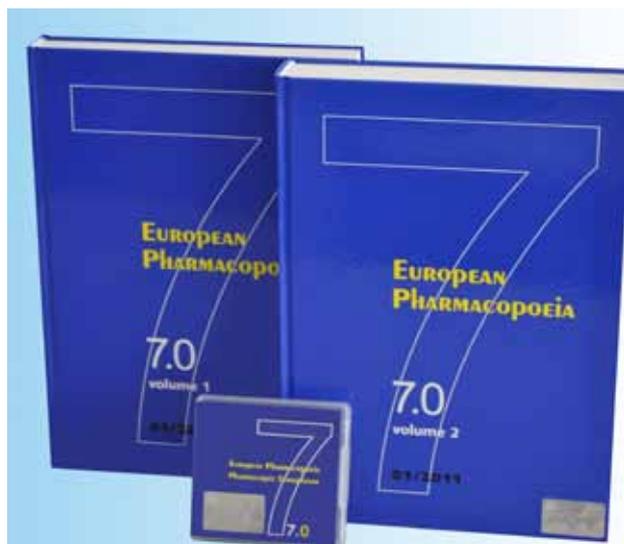
The general monograph on *Vaccines for veterinary use (0062)* was revised to delete the TABST (*target animal batch safety test*), except in “particular circumstances” to cover the need to perform, on an ad hoc basis, further testing and safety tests in particular.

In the interest of the 3Rs (Refinement, Reduction and Replacement of animal experiments), the European Pharmacopoeia Commission also adopted the deletion of the TABST from the European Pharmacopoeia for all veterinary vaccines. The deletion of the TABST goes a step further than the option, available since 2004, of waiving use of the TABST for established vaccines.

Also in the context of the 3Rs, the monograph on *Rabies vaccine (inactivated) for veterinary use (0451)* was revised to include further details on the serological assay to be used whenever possible as a less stressful alternative to the challenge potency assay using live animals.

During the 143rd Session and following the adoption of the general chapter *Residual pertussis toxin and irreversibility of pertussis toxoid (2.6.33)*, nine revised monographs on vaccines to reference this new general chapter were adopted. The protocol described in the chapter, which is an outcome of a study from the Biological Standardisation Programme (BSP), will facilitate standardisation of the method and therefore reduce the unnecessary use of animals.

As a result, there is currently no use of animals in testing of medicinal products derived from human blood and plasma at the European Pharmacopoeia level. For human and veterinary vaccines, in many cases *in vivo* testing has been replaced by



in vitro methods. For the remaining *in vivo* assays, different strategies are used to promote reduction and refinement, e.g. serology assays or single dilution assays for diphtheria, tetanus, acellular pertussis and rabies (veterinary/human) vaccines.

These decisions are fully in line with the EDQM’s mission to promote and protect human and animal health, and with the EDQM’s commitment to the 3Rs principles.

In view of the implementation on 1 January 2013 of Directive 2010/63/EU of the European Parliament and of the Council on the protection of animals used for scientific purposes, at its 144th Session the European Pharmacopoeia Commission made an evaluation of the texts of the Pharmacopoeia that recommend alternatives to animal tests, aiming to make this information available to users.

Key figures for 2012:

During its three sessions, the Commission adopted:

43 new monographs, including:

- Chemicals and Biological: Five monographs [*Ciclesonide (2703)*, *Pemetrexed disodium heptahydrate (2637)*, *Atomoxetine hydrochloride (2640)*, *Dutasteride (2641)* and *Human coagulation factor VIIa (rDNA) (2534)*] elaborated under the P4 or P4Bio procedures and 12 monographs on *Atovaquone (2192)*, *Oxcarbazepine (2577)*, *Starch, hydroxypropyl, pregelatinised (2645)*, *Follitropin (2285)*, *Follitropin concentrated solution (2286)*, *Alimemazine hemitartrate (2650)*, *Desloratadine (2570)*, *Diacerein (2409)*, *Abacavir sulfate (2589)*, *Anastrozole (2406)*, *Risedronate sodium (2572)* and *Rivastigmine hydrogen tartrate (2630)*, all elaborated under the usual procedure.
- *Pharmaceutical preparations (2619)*: one general monograph that is intended to be a reference source of standards in the European Pharmacopoeia on active substances, excipients and dosage forms that can be applied in the preparation/manufacture of pharmaceuticals.



- Herbal drugs, herbal drug preparations and herbal drugs used in Traditional Chinese Medicines: 14 monographs on *Clematis armandii stem* (2463), *Magnolia officinalis flower* (2568), *Salvia miltiorrhiza root* (2663), *Blackcurrant leaf* (2528), *Saw palmetto extract* (2579), *Fraxinus rhynchophylla bark* (2452), *Sophora flower* (2639), *Eclipta prostrata herb* (2564), *Eucommia bark* (2412), *Mandarin epicarp and mesocarp* (2430), *Fleeceflower root* (2433), *Capsicum soft extract, standardised* (2529), *Turmeric rhizome* (2543) and *Belamcanda chinensis rhizome* (2561).
- Vaccines: five monographs on *Salmonella enteritidis vaccine (live, oral) for chickens* (2520), *Salmonella typhimurium vaccine (live, oral) for chickens* (2521), *Turkey infectious rhinotracheitis vaccine (live)* (2461), *Bordetella bronchiseptica vaccine (live) for dogs* (2525) and *Yersiniosis vaccine (inactivated) for salmonids* (1950).
- Radioactive compounds: three monographs on *Gallium (68Ga) chloride solution for radiolabelling* (2464), *Alovedine (18F) injection* (2460) and *Fluoromisonidazole (18F) injection* (2459) and one monograph on a precursor for a radiopharmaceutical preparation, *Succimer for radiopharmaceutical preparations* (2545).
- One monograph on a propellant gas, *Norflurane* (2257), and one general monograph on *Veterinary semi-solid preparations for oral use* (2638).

5 new General Chapters including:

- One method of analysis on *Absence of residual pertussis toxin and irreversibility of pertussis toxoid* (2.6.33).
- One method of analysis of *Radioactive compounds: Detection and measurement of radioactivity* (2.2.66).

254 revised texts, amongst them:

- General monograph on *Substances for pharmaceutical use* (2034): a revised version of this general monograph in which the *Production and Related Substances* sections

have been updated following the elaboration of general methods for the determination of *Methyl, ethyl and isopropyl methanesulfonate in methanesulfonic acid* (2.5.37) and in *active substances* (2.5.38) has been adopted. This revision of the general monograph *Substances for pharmaceutical use* (2034) and the adoption of the three general methods for the determination of methyl, ethyl and isopropyl methanesulfonates triggered the revision of the production section of 11 monographs of active substance mesilate salts.

- General chapter on *Near-infrared spectrophotometry* (2.2.40).
- Chapter on *Pharmacopoeial harmonisation* (5.8). In order to provide more transparency as regards the degree of harmonisation achieved within the Pharmacopoeial Discussion Group (PDG) and to support users, the non-harmonised attributes/provisions will be placed between black diamonds (◈◈) in the corresponding Ph. Eur. texts, while the local requirements will be placed between white diamonds (◊◊).

Achievements of the Biological Standardisation Programme

The Biological Standardisation Programme (BSP), a joint effort with the EU Commission, pursues the following goals in the area of standardisation of biologicals: establishment of biological reference materials, development and validation of new analytical methods and validation of alternative methods based on the 3Rs concept.

To this end, collaborative studies are performed involving all interested partners, e.g. Official Medicines Control Laboratories (OMCLs) and manufacturers. Whenever possible, such studies are run jointly with the WHO in order to economise the resources of participating laboratories. Since the start of the programme in 1992, 117 BSP projects have been initiated. In 2012, 16 projects were pursued in different fields:

- Vaccines for human use: 5 projects
- Vaccines for veterinary use: 1 project
- Plasma-derived products: 5 projects
- Biotechnology products: 5 projects

Five projects were devoted to the establishment of alternatives to animal experiments, 2 to the development of new or improved assays and 11 projects concerned the establishment of reference materials for biologicals (2 projects entailed both the development of new assay methods and the establishment of reference materials).

This led to the establishment of 2 reference standard replacement batches (for somatropin and endotoxin), 2 new reference standards for major recombinant allergens (for Bet v 1 and Phl p 5a) and 3 new Biological Reference Reagents (BRRs) for the assay of hepatitis A vaccine (see chapter 1.2 Pharmaceutical Reference Standards page 14). The project for the establishment of the endotoxin standard was run jointly with the WHO and USP. The resulting standards for the Ph. Eur., WHO and USP were prepared from the same starting material and have identical assigned values.

The reference standards for the major recombinant allergens Bet v 1 (from birch pollen) and Phl p 5a (from Timothy grass pollen) represent the first ever standards of this kind and are unique in the world. They will greatly help to improve the standardisation of extracts produced from these two allergens; such extracts are widely used for the desensitisation of patients suffering from allergies.

The strong efforts to apply the 3Rs concept to the field of quality control of biologicals were continued in 2012. About

one third of the BSP projects were devoted to the validation of alternatives to animal experiments. One project aimed at the validation of an *in vitro* assay method for the assessment of the potency of hepatitis A vaccines was concluded. In addition, two new projects were started to replace animal tests which are still part of the Ph. Eur.: the histamine sensitisation test, used for testing for the presence of residual pertussis toxin in acellular pertussis vaccines; and the NIH test, a direct challenge assay used for determination of the potency of rabies vaccines. In a previous BSP project, the NIH test was successfully replaced for batch release of rabies vaccines (inactivated) for veterinary use by a serological assay. The purpose of the new BSP project is the complete replacement of the NIH test, which is still used for the calibration of reference materials and for stability testing of rabies vaccines.

The establishment of the BRRs needed for the performance of alternative methods can also be subsumed under the 3Rs efforts of the BSP. Without such specific reagents, which are in most cases not commercially available, the 3Rs methods cannot be applied.

The efforts of the EDQM, and in particular the BSP, to elaborate, validate and implement 3R methods are widely acknowledged; for instance, by the European Partnership for Alternative Approaches to Animal Testing (EPAA) - a high level initiative of the EU Commission and industry. Consequently, the EDQM is represented on the Steering Committee of the EPAA Vaccine project, as well as on the Technical Committee and future EPAA studies will be run by the BSP.



1.2 Pharmaceutical Reference Standards

■ Reference Standards for the European Pharmacopoeia (Ph. Eur.)

Why have reference standards?

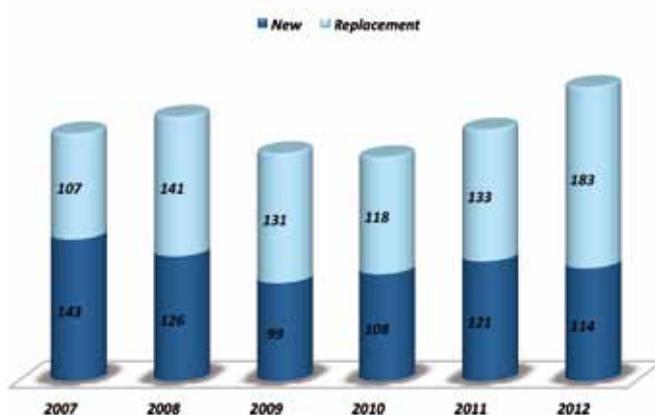
Most of the tests and assays described in the Ph. Eur. prescribe the use of official Ph. Eur. reference standards, *i.e.* carefully characterised specimens of substances intended for quality control.

Ph. Eur. reference standards are established by the EDQM and adopted by the Ph. Eur. Commission.

Chemical Reference Standards (CRS)

In 2012, 297 CRS were established, including 75 assay standards and 73 mixtures. An overview of the establishment of CRS in the period 2007-2012 is given below.

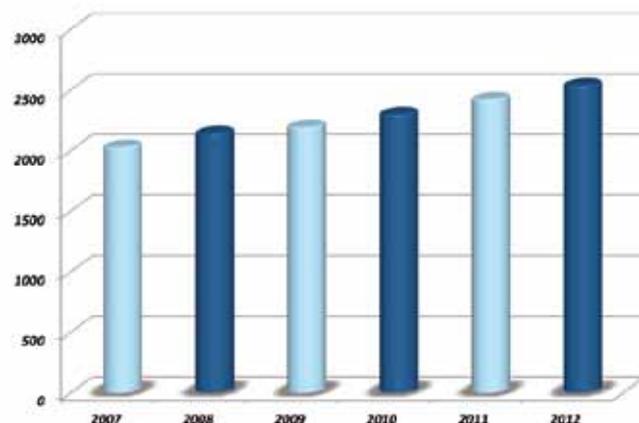
Establishment of CRS



Portfolio

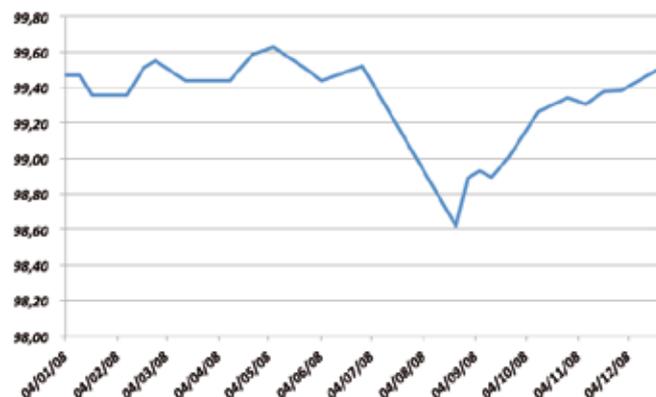
The portfolio now consists of 2537 items and is continuously monitored for fitness-for-purpose; 490 batches were examined in 2012.

Growth of the CRS portfolio

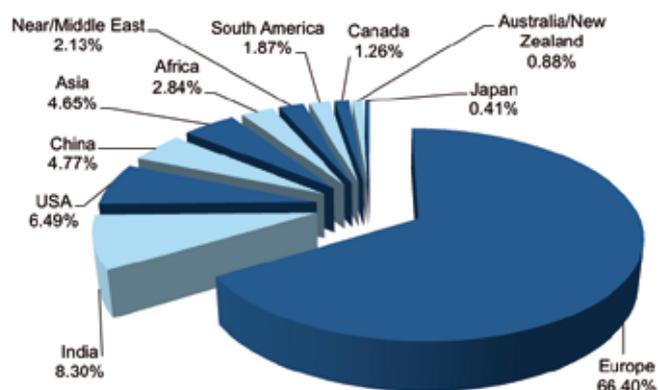


Careful planning and co-ordination of the inter-departmental activities facilitated the achievement of the objective to have at least 98% of the portfolio available to users at all times.

Availability of the CRS portfolio in 2012

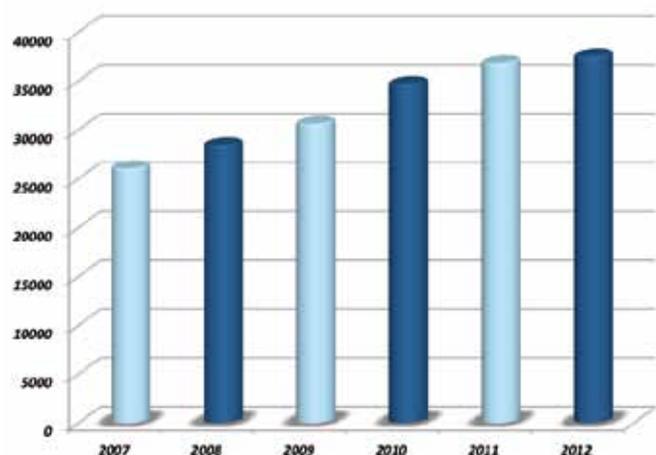


% of Ph. Eur. vials ordered/distributed by world area in 2012



Countries and regions outside of the European geographical zone account for more than a third of all distributed Ph. Eur. vials.

Growth in the number of orders processed/parcels distributed for Ph. Eur. reference standards for 2012



Biological Reference Materials

In 2012, the international collaborative studies performed by the Biological Standardisation Programme led to the adoption of four Biological Reference Preparations (BRPs)/Chemical Reference Standards (CRSs) by the European Pharmacopoeia Commission (see chapter 1.1 The European Pharmacopoeia page 11):

- Two replacement batches - Somatropin CRS (batch 3) and endotoxin BRP (batch 5).
- Two new CRSs, rBet v 1 and rPhl p 5a - both representing recombinant major allergens, for the assay of allergen extracts from birch (*Betula verrucosa*) and Timothy grass (*Pleum pratense*) pollen.

At the November session of the Ph. Eur. Commission, the proposal to establish a new class of reference materials, Ph. Eur. Biological Reference Reagents (BRRs), was approved. BRRs are materials that are established by the EDQM, have an official status (*i.e.* they are adopted by the Ph. Eur. Commission and referred to in the Ph. Eur.) and are necessary for performing certain tests of the Ph. Eur. (mostly assays), without being considered reference standards as such. BRRs are particularly needed when using alternative methods to animal experiments, such as ELISAs. BRRs will be distributed by the EDQM.

At the same session of the Ph. Eur. Commission, three BRRs for the ELISA of hepatitis A vaccines (coating reagent, primary detection antibody and secondary detection antibody) were adopted. The three BRRs will be used to replace the *in vivo* assay for hepatitis A vaccine preparations by an animal-free *in vitro* assay.

EDQM activities for the WHO

International Chemical Reference Standards (ICRS)

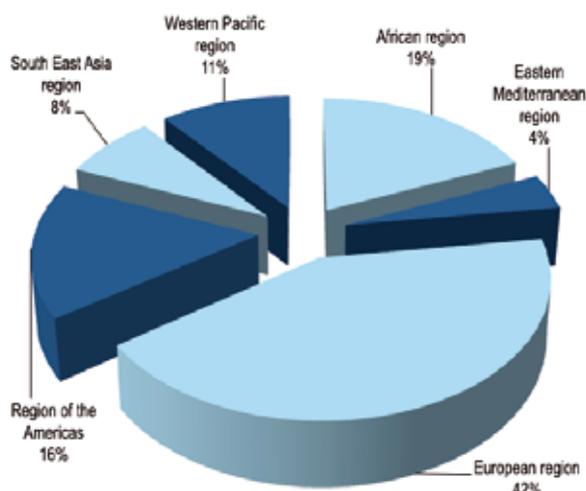
Since 2010, the EDQM is responsible for the establishment, monitoring and distribution of the WHO ICRS; reference standards that are prescribed by the International Pharmacopoeia, which is edited by the WHO and is used worldwide.

Seventeen ICRS establishment studies were completed in 2012: pyrimethamine ICRS 1, erythromycin ethylsuccinate ICRS 1, ciprofloxacin ICRS 1, pentamidine isetionate ICRS 1, proguanil hydrochloride reference spectrum, niridazole ICRS 1, azobenzene ICRS 1, atenolol ICRS 1, clofazimine ICRS 1, dacarbazine ICRS 1, gallamine triethiodide ICRS 1, glibenclamide ICRS 1, phenobarbital ICRS 1, salbutamol sulfate ICRS 1, spironolactone ICRS 1, tiabendazole ICRS 1 and verapamil hydrochloride ICRS 1. Twenty-four ICRS were monitored for fitness-for-purpose.

In addition, the analytical work to optimise the LC method for related substances of artemisinin was presented to the WHO Expert Committee, which decided to adopt the EDQM Laboratory's proposals and to change the monograph for artemisinin accordingly.



% of ICRS vials ordered/distributed by world area in 2012



International Standards for Antibiotics (ISA)

Since May 2006, the EDQM is responsible for the establishment, storage and distribution of ISA.

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

In 2011, the 2nd International Standard (IS) for Dihydrostreptomycin was established and work on the replacement of the current batches for Neomycin and Neomycin B began.



1.3 Laboratory Activities

The EDQM's Laboratory Department (DLab) consists of an Analytical Chemistry Division (ACD) and a Biology Section. In 2012, three important projects were pursued: full implementation of the LIMS, introduction of NMR and preparation for ISO 17025 accreditation. At the same time, DLab has contributed to the advancement and maintenance of European Pharmacopoeia (Ph. Eur.) standards, the Proficiency Testing Studies (PTS) and Market Surveillance Studies (MSS) programmes for the OMCL network and to the establishment of reference standards for the WHO.

Contributions to the permanent process of optimisation

Documentary standards: 97 scientific study reports were issued to support the various Ph. Eur. groups of experts. Ten P4 projects (including two P4Bio projects) were carried out. Sixteen studies were conducted to support the BSP programme.

Material standards: 297 CRS establishment reports were adopted by the Ph. Eur. Commission (see chapter 1.2 Pharmaceutical Reference Standards page 13).

Contributions to the PTS/MSS studies for the OMCL network

DLab has carried out scientific studies to support the PTS programme and the MSS programme of the OMCL network. (see chapter 1.5 OMCL Network page 18).

Collaboration with the WHO

DLab has also conducted scientific studies to support the WHO ICRS programme, linked to the International Pharmacopoeia and the ISA programme. (see chapter 1.2 Pharmaceutical Reference Standards page 13).

Continuous efforts to further improve efficiency and quality

- Maintaining, increasing and focussing on "core" activities.
- Increasing the output of the CRS monitoring programme.
- Ensuring ISO 17025 standards are adhered to.

Measures were taken to render the contribution of DLab sustainable in the medium-term by:

- introducing new techniques: a Nuclear Magnetic Resonance (NMR) instrument was installed in 2012.
- equipment renewal (UV detector, infrared spectrophotometer, headspace GC system).

1.4 Certification of Suitability to the Monographs of the European Pharmacopoeia

Purpose of the Certification procedure

The Certification of Suitability to the Monographs of the European Pharmacopoeia (CEP) procedure was established in 1994 and is aimed at:

- Ensuring that the quality of substances used in the production of medicines complies with Ph. Eur. standards and, hence, the requirements of the pharmaceutical legislation of the European Union and the member states of the Ph. Eur. Convention.
- Contributing to keeping the Ph. Eur. continuously up-to-date by assessing whether its quality standards still reflect the quality of substances on the market. Information on the different routes of synthesis and impurity profiles is used to constantly improve the quality of Ph. Eur. standards. This synergy with certification activities is of the utmost importance for the Ph. Eur., as it ensures that Ph. Eur. standards are up-to-date with respect to the products currently on the market.
- Facilitating at the European level the management of Marketing Authorisation Applications by a centralised assessment of the quality of substances for pharmaceutical use, thereby reducing the workload for authorities and Industry.

Which substances are covered by the Certification procedure?

Under the official procedure described in Resolution AP-CSP (07) I and referred to in European Union Directives 2001/83/EC and 2001/82/EC, as amended, and 2003/63/EC, manufacturers or suppliers of Active Pharmaceutical Ingredients (APIs) or excipients, or of herbal products used in the production or preparation of pharmaceutical products covered by a Ph. Eur. monograph or any substance with a risk of transmissible spongiform encephalopathy (TSE), can apply for a certificate of suitability.

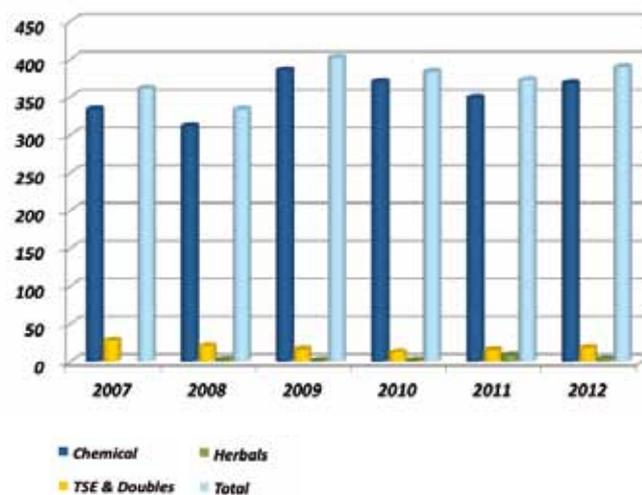
The EDQM inspection programme of Active Pharmaceutical Ingredient (API) manufacturers

Assessment of the quality documentation submitted to the EDQM for certification is complemented by an inspection programme. This inspection programme has been set up to verify compliance with both the CEP applications submitted to the EDQM and Good Manufacturing Practices (GMP, as laid down in Volume 4 of the Rules Governing Medicinal Products in the European Union) at the manufacturing/distribution sites covered by CEPs. The EDQM Certification Division is responsible for organising inspections and their follow-up, including taking any subsequent action regarding related CEPs or CEP applications and communicating with the authorities concerned. The annual inspection programme

is based on priorities recommended by the EMA/EU, and it is adopted by the Certification Steering Committee following consultation with the authorities in member states and the GMP/GDP Inspectors Working Group of the EMA.

Evaluation of CEP applications: key figures for 2012

Number of new applications received



Again in 2012, the Certification Division received an increased number of applications for CEPs compared with previous years. In 2012, 389 new applications and about 1200 requests for revision were received. The figures were published on a monthly basis on the EDQM website.

In 2012, 260 new and 950 revised CEPs were granted. In addition, an increasing number of requests for revision were approved without issuing a revised CEP (520), in line with the policy applied to notifications or minor revisions not affecting the quality of the final substance or the content of the CEP. The requests for revision received were complemented by the necessary updates to CEP applications when revised monographs were published in the supplements of the Ph. Eur.

Throughout 2012, more than 82% of new applications and revisions were treated within the official timelines.

There are currently more than 3500 valid CEPs, covering chemical purity, TSE risk and herbal drug preparations.

EDQM inspections: key figures for 2012

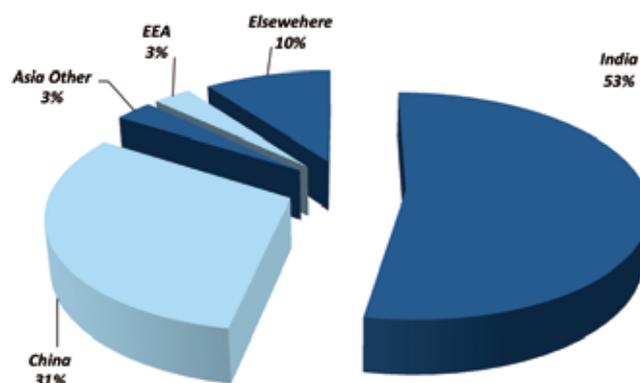
In 2012, 32 on-site inspections were performed, mainly in Asia, with the participation of inspectors from different national agencies. Three sites refused to be inspected following the announcement of an inspection (leading to immediate suspension of the relevant CEPs). Another 25 sites were covered by sharing information with inspectorates of member states and partners. From the inspections carried out, 13 companies were found to be non-compliant with



GMP, which led to the suspension or withdrawal of CEPs or closure of CEP applications. These figures again demonstrate the adequacy of the triggers applied in the risk-based selection of sites to be inspected. In addition, in 2012, on-site inspections included a high rate of re-inspections (>50%). Overall, about 60% of companies subjected to a re-inspection by the EDQM were found to be non-compliant. This evidenced a lack of commitment to sustaining GMP by a number of companies.

Since the beginning of the programme, the EDQM has performed 283 inspections and re-inspections. Of these, 229 were carried out outside the European Economic Area (EEA). Since 2003, the vast majority of the inspected sites have been outside the EEA.

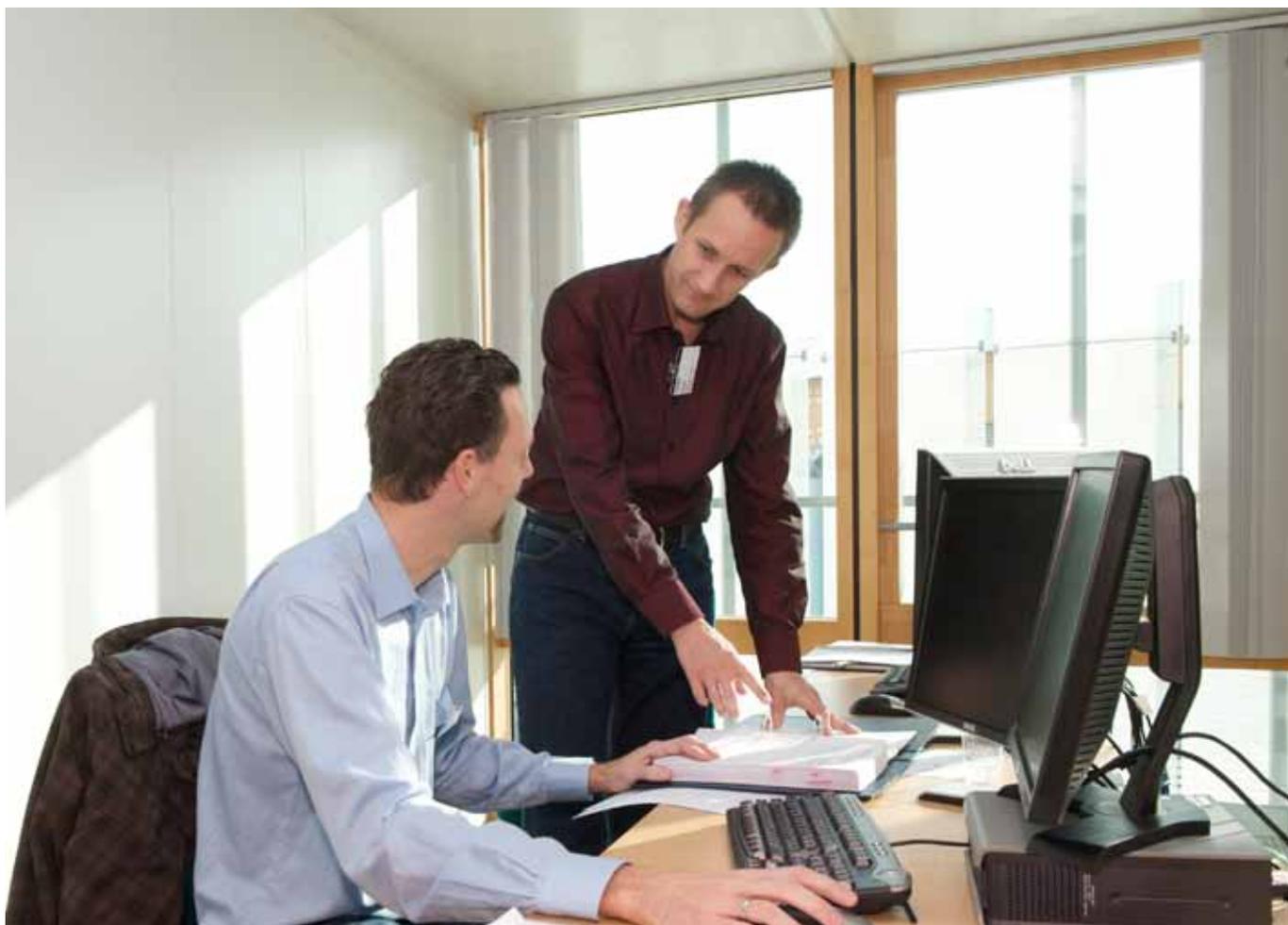
Locations of inspected sites in 2012



International API inspection programme:

Since 2008, the EDQM has been involved in the international API inspection programme, initiated by the EMA. This programme involves inspection authorities from the US, Australia, the WHO (since 2012) and individual European countries, as well as the EDQM. It is aimed at optimising resources through the exchange of information (inspection planning and reports) and the performance of joint inspections for API manufacturing sites of common interest. Besides

the exchange of inspection reports and other information on a routine basis, a joint inspection by the United States Food and Drug Administration (USFDA) and the EDQM was carried out in 2012 on a manufacturing site located in India. In addition, the EDQM has actively contributed to Pharmaceutical Inspection Cooperation Scheme (PIC/s) activities.





1.5 OMCL Network

Introduction

The General European Network of Official Medicines Control Laboratories (GEON), which was created on 26 May 1994 following a decision by the Commission of the European Union (EU) and the Council of Europe (CoE), is open to all countries that have signed the European Pharmacopoeia Convention as well as to observers of the European Pharmacopoeia Commission, provided that the criteria of the network are fulfilled (e.g. independence, public funding, implementation of the Ph. Eur. as common standard, implementation of the ISO/IEC 17025 standard in the laboratory). Since 1995, the EDQM is the co-ordinator of this Network and is responsible for its organisation and further development. The EDQM's co-ordinating activities in this field have been ISO 9001 certified by AFNOR, the French accreditation body, since 2010.

In the context of the OMCLs, the term 'networking' means sharing of know-how within a pool of experts, work-sharing and mutual recognition of test results based on commonly agreed procedures and, consequently, saving of resources and costs in the testing of medicinal products. For the competent national authorities, this also means avoidance of duplication of work and accession to state-of-the-art technology and selective analytical procedures.

Besides the core activities of the network, over recent years a number of additional initiatives have been launched, and new programmes have been established in particular in the fields of falsified medicines testing, monitoring of stockpiled medicines,

testing of unlicensed pharmaceutical preparations and quality control of active pharmaceutical ingredients (APIs) on the European market.

Since July 2012, rules for maintenance of membership to the Network have been in force, which regulate the obligations of Network members and the monitoring of these commitments. Three types of memberships to the GEON are possible: full, associated and limited membership. The list of members is published on the EDQM website.

Quality Management (QM) Systems

The following activities, co-ordinated by the EDQM, were carried out in 2012 within the framework of the QM programme of the OMCL Network.

Mutual Joint Audits and Mutual Joint Visits

During 2012, eleven Mutual Joint Audits (MJAs) and one Mutual Joint Visit (MJV) were carried out at OMCL sites. Two of the MJAs were performed together with the corresponding National Accreditation Bodies (NABs).

Training activities for the OMCL

In 2012, three training visits were organised by the EDQM to provide training on physico-chemical and biological laboratory methods. In addition, a workshop for technical auditors was held on the EDQM's premises, the objective of which was to share experience, inform about new QM Guidelines and to harmonise requirements during audits.



Co-operation with EA

On the initiative of the EDQM, in 2012 contacts with the European Co-operation for Accreditation (EA) were re-established with the objective of performing common audits between the EDQM/MJA and the NABs. The long-term perspective of this initiative is the mutual recognition of audit results.

OMCL Network Quality Management Guidelines

The following new OMCL Guidelines were adopted by correspondence and confirmed at the Annual Meeting in June 2012: *“Management of Reagents”*, PA/PH/OMCL (11) 157 5R and *“Handling and Use of Reference Standards in the OMCL Network”*, PA/PH/OMCL (11) 204 3R. The guideline *“Qualification of Automatic Titrators”* has been revised and the new version, PA/PH/OMCL (07) 108 4R came into force on 1 May, 2012.

The existing guideline *“Evaluation and Reporting of Results”* is currently under review. New guidelines for *“Qualification of Balances”* and *“Qualification of Analytical Columns”* are under elaboration and it is planned to elaborate a new guideline on *“Calibration of pH-meters”* in 2013, which shall be used as the basis for the revision of the Ph. Eur. General Chapter *Potentiometric determination of pH* (2.2.3).

At the Annual Meeting of the OMCL Network in Copenhagen, it was decided to no longer publish the Quality Management book. Instead, the current versions of the different QM Guidelines can be found on the EDQM website, together with other key Quality Assurance (QA) documents.

API Working Group

The major objective of the API Working Group is to raise awareness of the valuable contributions that OMCLs make in the control of the quality of drug substances on the European market. The tightening of the control of APIs is also a focus of the European National Competent Authorities and the EMA, and it was also highlighted at the International Summit of Heads of Medicines Regulatory Agencies in 2008. Control of APIs is necessary, given the globalisation of the manufacturing and trading of active ingredients. The implementation of new provisions of EU legislation (Directive 2011/62/EU, the so-called “Falsified Medicines Directive”) in 2013 is another measure that, in the future, will require greater involvement of OMCLs in the monitoring of APIs on the European market.

In 2012, two meetings of the Group took place that led to the finalisation of a common network document *“API Surveillance – Position Paper for OMCLs”*, in which the contributions of the OMCL Network in the surveillance of active ingredients on the European market are outlined. Currently, a page on the EDQM website dedicated to the work of the API Working Group is under preparation. The position paper will be published on this webpage. An additional focus of the meetings in 2012 was the discussion on re-orienting the API fingerprint project. This project, which aims at determining the

authenticity and source of active pharmaceutical ingredients by different measures (e.g. “fingerprint” techniques, chemometric analysis) had been run over the last two years in a pilot phase in collaboration with API manufacturers. The goal of the re-orientation was to increase the role of the OMCLs in the programme. A pilot Market Surveillance Study (MSS) on a selected group of APIs is planned in 2013.

Counterfeit/Illegal Medicines Working Group

The Counterfeit/Illegal Medicines Working Group, which was established following the first “Counterfeit Symposium for OMCLs”, met twice in 2012. The focus of the meetings was the preparation and implementation of a first MSS on suspected illegal products (MSSIP) targeting dietary supplements with a supportive slimming effect. A second similar MSS is planned for 2013. Another achievement of the Group was the organisation of a first technical training session for OMCL members, which was organised jointly by the Polish OMCL and the EDQM in Warsaw on 4-5 October 2012. The positive feedback received from the participants of this training session led to the decision to continue with a second complementary event in 2013.

The Group also forms the scientific body for other network activities in the field of falsified medicines testing. This includes the harmonisation of testing reports on counterfeit and illegal medicines which, since 2006, have been collected on a common data platform with controlled access that is restricted to members of the Network. In the coming years, it is planned to intensify sharing of expertise within the Network and to also extend communication to other partners involved in the fight against falsified medicines (customs, police and health authorities).

In addition, one Suspicious Unknown Product (SUP) study was carried out in 2012. Two unknown samples were provided for identification (APIs: JWH-081 and butylone) and results were received from 20 participants. This programme is organised by the EDQM and aims to evaluate whether OMCLs of the Network are able to identify (and where possible quantify) unknown APIs in a selected sample.

The activities of the Group are described in detail on the EDQM website, which also provides links to websites of national authorities active in the field.

OMCL Testing Group on Unlicensed Pharmaceutical Preparations

The major objectives of this Group are to raise awareness of the significant contributions of the OMCLs to the control of the quality of unlicensed pharmaceutical preparations and to provide guidance on sampling strategies, the selection of testing methods and setting specifications, where needed. The results of the MSS focused on unlicensed pharmaceutical preparations for paediatric use (capsules and suppositories), agreed upon at the first meeting of the Group in December 2011, will be available in the 4th quarter of 2013.

Stockpiled Biologicals Working Group

After the elaboration of a first technical guideline in 2009 outlining the contributions of OMCLs in the monitoring of stockpiled medicines (the respective document *PA/PH/OMCL (09) 94.3R* was published on the EDQM website), a Working Group was constituted in summer 2011 following a decision made during the Annual Meeting of the OMCL Network in Düsseldorf. The goal of this Working Group was to adapt the document on stockpiled medicines to the particularities of biological products in national stocks (vaccines and antisera). The revised document was adopted at the Annual Meeting of the OMCL Network in June 2012 and was published on the EDQM website. With the implementation of the updated guideline, it was decided to discontinue the regular meetings of this Working Group until a need arises.

Gene Therapy Products (GTP) Working Group

The OMCL GTP Working Group was set up in 2008 in order to prepare the OMCLs for their role in the surveillance of the quality of GTP. The goal of this Working Group is to foster collaboration between OMCLs working in the field of GTP to save time and resources by sharing knowledge and technologies. In 2012, three additional members joined the Working Group: the Austrian, Belgian and Canadian OMCLs.

During the 4th meeting of the Group in December 2012, the work programme was reviewed.

In 2012, three collaborative studies were started on adeno-associated viruses (AAVs), with the aim of validating the transferability of the following methods: determination of particles physical titre by ELISA, determination of viral genome titre by quantitative polymerase chain reaction (qPCR) and purity by polyacrylamide gel electrophoresis. The ELISA study was completed and it will be published in 2013 in *Pharmeuropa Bio* and *Scientific Notes*. Additional work has also been performed on a capillary electrophoresis (CE) method for the determination of DNA concentration and topology. The next meeting of the OMCL GTP Working Group is envisaged for the autumn in 2013 at the Swiss OMCL (Swissmedic) in Bern.

17th Annual Meeting of the General European Network of Official Medicines Control Laboratories (GEON)

The 17th Annual Meeting of the OMCL Network was held in Copenhagen from 11 to 15 June 2012. It was organised with the help and support of the Danish Health and Medicines Authority during the Danish EU Presidency; 220 experts from 34 countries, representing 48 institutions, gathered to exchange experience and to discuss topics of common interest for the co-ordination and harmonisation of their efforts to protect patient and animal health in Europe.

In eight individual sessions, expert discussions were held on laboratory control of active ingredients, pharmaceuticals,

biotechnology products and the official control authority batch release of human vaccines, human blood and plasma derivatives and immunological veterinary medicinal products. In addition, the Counterfeit/Illegal Medicines Working Group convened for the first time under the auspices of the Annual Meeting of the Network.

OMCL Annual Meeting – General Session/Policy documents

During the General Session of the Annual Meeting, which was open to full, associated and limited members of the Network, the following topics were addressed:

- A new procedure for the maintenance of membership in the OMCL Network was adopted by the plenum. This document, which was published on the EDQM website as Annex 5 of the Terms of Reference of the GEON, introduced a number of monitoring mechanisms for Network members and allowed the suspension or limitation of membership.
- The implementation of the membership procedure had an impact on a number of key policy Network documents; mainly the GEON Terms of Reference and some of its Annexes, which were revised accordingly. The updates were published on the EDQM website after the meeting.
- An internal crisis management procedure for OMCLs, which should enable the OMCL Network to react efficiently to situations where patient health is at risk due to quality issues with medicines, was introduced and discussed and has since been finalised and adopted by the Network.
- Other key topics discussed were the enlargement of the Network's efforts to contribute to the market surveillance of active ingredients and, related to this issue, the need to increase collaboration with other stakeholders (in particular, the quality assessors and GMP inspectors of the European National Competent Authorities).
- Special focus topics of the meeting were the contributions from OMCLs to the quality control of radiopharmaceuticals, cosmetics and medical devices. In these areas, the added-value of laboratory testing was impressively demonstrated.

Proficiency Testing Scheme studies (PTS)

Over the years, PTS studies have become a regular programme within the OMCL Network. In 2012, five studies were organised in the physico-chemical field, with an average participation of 42 national control laboratories and 31 other pharmaceutical control laboratories from the private sector, industry and hospitals. In the biological area, four studies were organised, involving an average of 21 laboratories (10 OMCLs and 11 laboratories from the private sector).

In 2012, two new studies from the 5th PTS agreement with the WHO were organised; a study on dissolution testing and a study on assay determination by liquid chromatography.

On average, 60 governmental control laboratories from the six different WHO world regions (Africa, Americas, Eastern Mediterranean, Europe, South-East Asia and Western Pacific) participate in these studies.

General studies on market surveillance

In 2012, Market Surveillance Studies (MSSs) aimed at screening the quality of medicinal products on the European market were finalised for oral acetylsalicylic acid products, clopidogrel API and tablets, as well as APIs and medicines presented as mesilate salts. Such testing campaigns provide an overall picture of the quality of products available on the European market for a given class of products. Where pertinent, the results of these studies also support the revision of the relevant monographs and/or general chapters and methods of the Ph. Eur., as well as directing specific actions by licensing and supervision authorities.

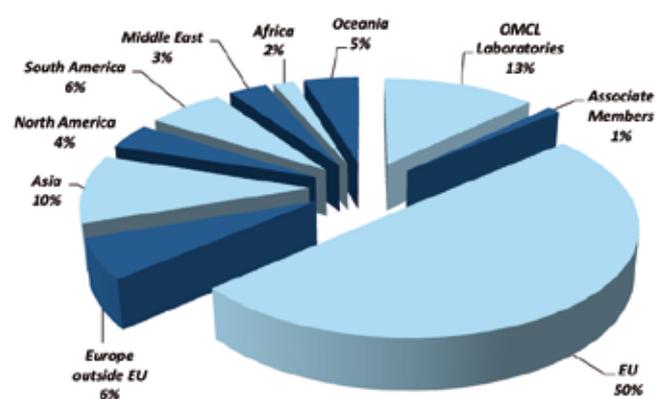
One “atypical” MSS was also initiated in 2012. For more details see the section above on the Counterfeit/Illegal Medicines Working Group. (see chapter 1.7 Pharmaceutical Care and Anti-Counterfeit Activities page 27).

CombiStats

In 1999, the EDQM initiated the development of a computer program for the statistical evaluation of biological dilution assays in accordance with chapter 5.3 of the Ph. Eur. At that time, most laboratories of the OMCL Network used their own software developed in-house, which led to a strong demand for a common program 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 November 2005, non-OMCL laboratories could also obtain a user licence. The number of users has steadily increased since its public release.

Two training courses were organised in March and November 2012, which were open to industry and private sector participants. Version 5.0 has been in development since 2012 and it is scheduled for release in early 2013.

CombiStats™ licences per region (in %)



By December 2012, 14% of the licences were issued to OMCL laboratories in 24 countries and 86% to non-OMCL users in 40 countries. The pie-chart below shows that roughly half of the non-OMCL licences were issued within the EU and the other half in the rest of the world, including non-European countries such as Argentina, Australia, Brazil, Canada, China, Egypt, India, Indonesia, Israel, Japan, Malaysia, Mexico, South Africa, South Korea, Syria, Taiwan, Tunisia, Uruguay and the USA. Thus, CombiStats™ has evolved into a common internationally-accepted reference in its domain and contributes to mutual recognition of data and results by all interested parties.

EU/EEA-specific Activities

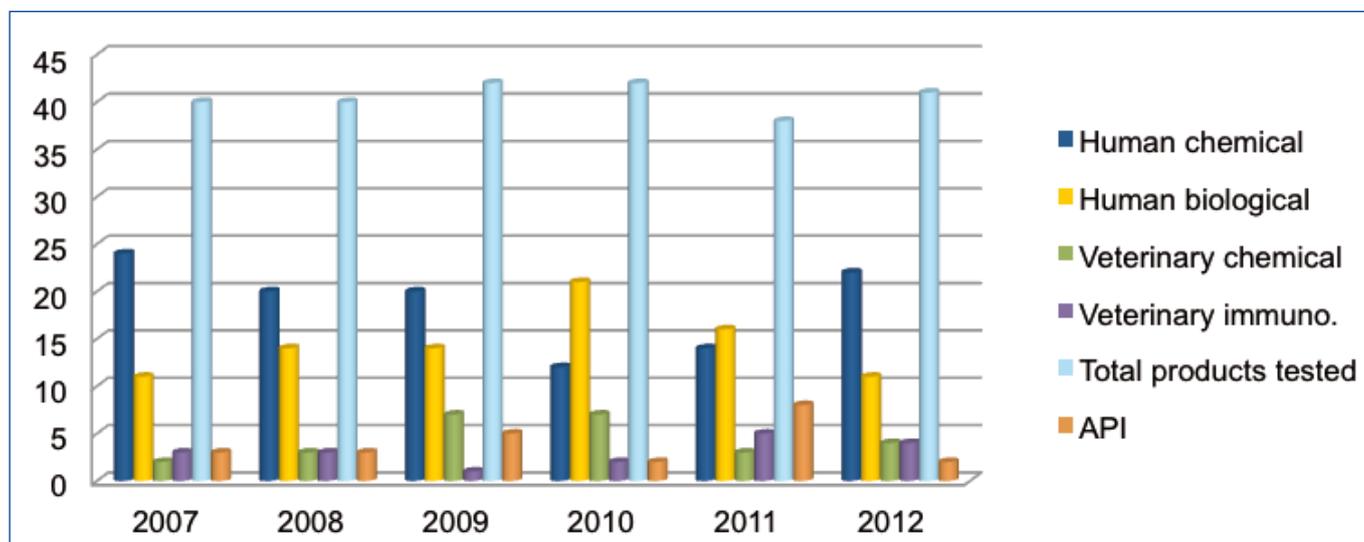


Market Surveillance for products with a centralised marketing authorisation (CAP)

The programme for sampling and testing of Centrally Authorised Products (CAP) was successfully continued in 2012 and entered its 14th consecutive year. The CAP programme is run on the basis of a contract between the European Medicines Agency (EMA), which is the sponsor and has overall responsibility, and the EDQM, which co-ordinates the sampling and testing operations using the information provided by the Marketing Authorisation Holders upon request from the EMA. It covers medicinal products for both human and veterinary use.

The 2012 work programme included 33 medicinal products for human use (11 biologicals and 22 chemical products) and 8 medicinal products for veterinary use (4 immunobiological products and 4 chemical products). In addition to the finished dosage form, testing of active substances (API) was performed for two products. The total number of products (41) corresponds to the optimal range, considering the operational capacities of the OMCL Network.

Number of products tested in the CAP Programme 2007-2012



A CAP standard procedure for handling future CAP Generics testing programmes was drafted based on the experience acquired with the 2011 Clopidogrel generics trial programme. This procedure is an adaptation of the current CAP sampling and testing procedure.

The co-ordination activities of the EDQM with respect to the CAP sampling and testing programme have been ISO9001 certified since 2010. A yearly follow-up audit was successfully passed in December 2012.

Mutual Recognition Procedure (MRP)/Decentralised Procedure (DCP) product testing programme

The MRP/DCP product market surveillance scheme was initiated on a voluntary basis by members of the OMCL Network from the European Economic Area (EEA) Member States and the EDQM at the end of 2000 and has been further developed since then. By avoiding duplicate testing of the same product in different member states, the scheme provides a co-ordinated and cost-efficient approach to post-marketing surveillance.

In 2012, the 8th regular programme for the market surveillance of medicinal products authorised in the EEA via the MRP or DCP procedure was conducted. More than 800 product testing projects were allocated to the 2012 programme, which was higher than the numbers in the last three years. The number of participants has stabilised over recent years to around 25 OMCLs per programme.

Around 10% of samples tested in the programme originated from a member state or OMCL that was not involved in the testing. This demonstrates the added-value of the surveillance scheme with respect to work-sharing. In about 3% of the tested materials, findings of a regulatory nature were identified (e.g. insufficient details of the test method, wrong calculation formula used in the SOP, etc.) and, in 2% of the cases, one or more out-of-specification results were

reported. This demonstrates the good quality of medicines on the European market. Approximately 5% of the products were for veterinary use and about 3% were biologicals, which reflect the general distribution of product types registered via these procedures. In 2012, for the first time, more DCP than MRP products were included in the surveillance scheme.

The general procedure “Co-operation in post-marketing surveillance of Mutual Recognition/Decentralised Procedure Products” (PA/PH/OMCL (06) 116) was amended with respect to the section describing follow-up actions in the case of findings. The latest version was posted on the EDQM website in September 2012.

The internal database used for planning, sampling and reporting of MRP/DCP product testing activities within the Network was further developed in 2012. A total of 11 database amendments were implemented; initiated both by the OMCL users of the system and the EDQM Secretariat. The database has been enlarged to allow for the reporting of API testing activities independently from the marketing authorisation type of the corresponding drug product. In addition, a refreshment training course for core OMCL database users was organised in November 2012, which included for the first time a representative from the accession country of Croatia.

In December 2012, the co-ordination activities of the EDQM with respect to the MRP/DCP product market surveillance scheme successfully underwent a re-audit for ISO 9001 certification.

Official Control Authority Batch Release (OCABR) of Biologicals for Human Use

The OCABR Network involves a subset of OMCLs focused on the harmonised application of Article 114 of EU Directive 2001/83/EC, as amended. The goal of the Network is to foster the mutual recognition of lot release as

mandated by the Directive. Regular exchange of information through correspondence and meetings, and elaboration and maintenance of common guidelines are important aspects of the Network's activities. Close interaction between the Network members provides excellent opportunities for work-sharing. The activities of the Network's members and their dynamic co-operation is driven by the desire to provide good quality, widely-recognised surveillance of the quality of vaccines and blood-derived medicinal products on the EU market and beyond and to reduce, replace and refine the use of animals in testing.

The annual meeting in Copenhagen, June 2012, included parallel sessions for blood and vaccine issues, and a joint session to address common points of interest. This joint session was attended by almost 80 participants from 24 member states. Participants reviewed activities from the past year and determined strategies for the coming period. In 2012, representatives from Croatia also attended the meeting as observers in anticipation of their accession to the EU in 2013.

At the OCABR plenary session, elections were held for 3 of the 6 posts in the Advisory Group. This Group now comprises representatives from Germany, The Netherlands and Italy for the blood section and from France, Belgium and the UK for the section on vaccines. In addition, the final elements were put in place for a Memorandum of Understanding (MoU) with the Biologics and Genetic Therapies Directorate, Health Canada in order to foster co-operative activities in the field of batch release. The MoU was subsequently signed by both parties in July 2012, opening the door to even greater international collaboration with the Canadian colleagues.

A number of internal guidelines and procedures related to network functioning were also revised. The Group continues to develop means to promote their contribution to the surveillance of biological medicinal products and to highlight the importance of feedback from these activities to other branches of the regulatory system, such as product assessment for licensing and inspections.

Other meetings were held throughout the year on specific topics and included a highly appreciated training session on OCABR for blood-derived medicinal products (which was attended by more than 30 participants from OMCLs, manufacturers and regulatory authorities). In addition, the yearly workshop on testing oral poliomyelitis vaccine bulks again included participants from relevant manufacturers in addition to the OMCL participants and it proved fruitful and interesting. A meeting of a special Working Group to identify viable strategies for demonstrating proficiency to external auditors when PTS studies are not available was also held.

An evolution of the OCABR database to refine and improve functioning was agreed upon at the annual meeting in 2011 and was completed in early 2012 and is now running smoothly. Additional updates are envisaged for 2013.

In order to improve accessibility to the public, all adopted product-specific guidelines and administrative procedures are now available exclusively from the EDQM website following a decision taken by the OCABR Network at the annual meeting. New and revised guidelines will be placed on the website within one month of their date of entry into force.



Official Control Authority Batch Release (OCABR) of Immunological Veterinary Medicinal Products (IVMPs) – Veterinary Batch Release Network (VBRN)

At the annual meeting in Copenhagen, 25 participants from 18 member states took part in the VBRN session. Elections were held for 2 of the 4 posts in the Advisory Group. The Advisory Group is now comprised of representatives from Germany, Hungary, Switzerland and the UK. As usual, annual reports of the activities of the different member states were presented. Progress in the harmonised application of Article 81 and Article 82 of EU Directive 2001/82/EU, as amended, for veterinary medicines was noted. As mandated by the EU Commission in its recommendation document on batch release for IVMPs and as endorsed by the Veterinary Pharmaceutical Committee 20/03/2007, the VBRN has made advances in the development of a number of common guidelines for the application of OCABR. A risk assessment table to help in judging the need for OCABR was adopted, as was a procedure on applying for temporary OCABR for products not on the restricted list when specific circumstances

arise. A general procedure for revising the restricted list of products eligible for OCABR was approved at the annual meeting and it was subsequently adopted after external review. It will come into force on 1 January 2013. The VBRN Advisory Group also continued to interact with the Heads of Medicines Agency (HMA) in order to highlight the need for resources in the field of IVMPs testing. This was manifested through a presentation in the veterinary session of the HMA meeting in October 2012.

The VBRN Advisory Group met with members of the manufacturers' association IFAH-Europe in February 2012 to discuss items of common interest. The plenary session of the annual meeting was an opportunity to pass on the information exchanged between them to the wider network.

All adopted administrative procedures and product-specific guidelines, as well as protocol templates, can be downloaded from the EDQM website. New and revised guidelines will be placed on the website within one month of their date of entry into force.

1.6 Blood Transfusion and Organ Transplantation



Blood transfusion activities

The European Committee on Blood Transfusion (CD-P-TS) held two meetings at the EDQM in March and November 2012. Preparation continued for the 17th Edition of the “*Guide for the preparation, use and quality assurance of blood components*”, which represents a key milestone in defining the standards for blood transfusion services. As this guide forms the basis for many national regulators in Europe and beyond, a joint Council of Europe/European Union working group was established in 2012 (including experts from blood services, control authorities and inspectorates), which aimed at revising the chapter on quality systems in blood establishments and supporting the experts of the working group in charge of the revision of the guide. The working group will continue its work in 2013, with the aim of addressing the relevant GMP issues in the blood guide.

Co-operation with the EU also allowed the commencement of the elaboration of common guidelines for Quality Management Systems (QMS) in blood establishments (‘Best Practice’ guidelines), which will become an integral part of the Council of Europe’s “*Guide for the preparation, use and quality assurance of blood components*” in its forthcoming editions.

Reporting of data on the collection, testing and use of blood components from European countries and from other regions of the world until the year 2010 has now been completed. The annual reports for 2009 and 2010, and a trend analysis on data collected from 2001 to 2008, are in press.

A pilot phase of a survey on quality indicators for optimal clinical use of blood was completed by the end of 2012.

The *ad hoc* working group on Blood Supply Management (working on issues related to the constant shortages in blood and blood components and the subsequent limitation in transfusion therapies, as well as the heterogeneous levels of donation in respective countries) has validated a self-assessment questionnaire in a pilot study in the blood banks of four countries and set up an online questionnaire that was answered by 39 countries. The results of the enquiry and good practices for Blood Supply Management were presented at a scientific symposium in Strasbourg on October 2012.

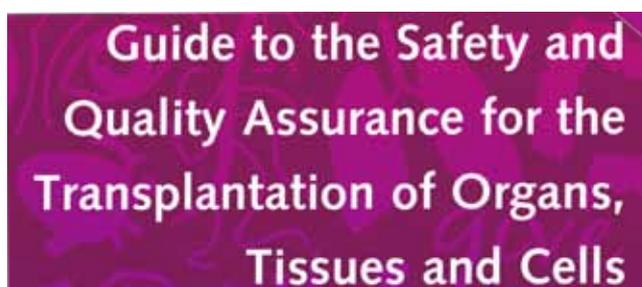
The project on “*Risk behaviours having an impact on blood donor management and transfusion safety*”, which started in February

2010 with the notable participation of the EU, EMA, ECDC (European Centre for Disease Prevention and Control), EBA (European Blood Alliance), USFDA, Health Canada, TGA and WHO, was completed. The group analysed existing data from epidemiological and risk modeling studies and surveillance programmes, and the implications of moving away from the permanent donor deferral criteria currently applied in relation to risk behaviours. The work was performed in close co-operation with other Council of Europe Steering Committees and expert groups (bioethics, transplantation and blood-derived medicinal products). A draft resolution and a technical memorandum were adopted by the CD-P-TS and submitted to the Committee of Ministers of the Council of Europe.

Inter-institutional co-operation with the EU facilitated the continuity of a European Programme of External Quality Assessments, with the voluntary participation of blood establishments in Proficiency Testing Scheme studies (B-PTS).

The B-PTS activity aims at assessing the performance of laboratories with regard to screening tests used for the qualification of individual blood donations. Since 2010, nine B-PTS studies have been organised for testing of nucleic acid amplification techniques (2 studies on Hepatitis C (HCV) and 2 studies on Human Immunodeficiency (HIV) viruses), serology (2 studies on Hepatitis B surface antigen (HBsAg) and 1 study on HIV antibodies) and immunohaematology (2 studies on ABO grouping and Rhesus phenotyping). The B-PTS activity is being well-received by blood establishments, resulting in an increased interest in participating in the scheme. Steps have been taken to continue the External Quality Assessment schemes.

The B-PTS programme has been complemented since 2012 by a pilot phase programme of peer visits/audits in European blood establishments, called Blood Mutual Joint Visit/Blood Mutual Joint Audits (B-MJV-B-MJA). This pilot programme will support implementation of Quality Management Systems in blood establishments in the forthcoming years.



Organ, Tissue and Cell Transplantation

The CD-P-TO continued the elaboration of:

- the “*Guide to Safety and Quality Assurance for the Transplantation of Organs*” (5th Edition), which deals with different aspects of the organ donation and transplantation process, from donor risk assessment to disease transmission,

and is a collation of information to provide transplant professionals with a useful overview of the most recent advancements in the field.

- the new “*Guide to the Quality and Safety of Tissues and Cells for Human Application*” (1st Edition), which provides sound information and guidance for all professionals involved in donation, banking, release, distribution and transplantation of tissues and cells, and inspection of the associated establishments. The combination of all these standards in one volume will help optimise the quality and minimise the risks of these complex procedures, which will ultimately help improve the rate of successful tissue and cell clinical applications.

Both guides will undergo a public consultation in early 2013 and become available in the summer of 2013.

The 2nd Edition of the publication containing all the Council of Europe Conventions, Resolutions, Recommendations and several relevant reports on safety, quality and ethical matters concerning procurement, storage and transplantation of organs, tissues and cells was published. (see chapter 2.2 Information Technology and Publications Activities page 32)

Newsletter Transplant, which gives international figures on organ donation and transplantation for 2011, was published in September 2012.

As part of its activities for the promotion of the non-commercialisation of organ donation and the fight against organ, tissue and cell trafficking, the CD-P-TO, together with the European Committee on Crime Problems (CDPC) and the Committee on Bioethics (DH-BIO) from the Council of Europe, was involved in the elaboration of a new criminal law convention to fight organ trafficking. The drafting process concluded in December 2012 and the final text will be submitted to the Committee of Ministers of the Council of Europe for formal adoption at the beginning of 2013.

In July 2011, the Council of Europe launched a three-year collaborative project that aims to battle organ shortages and to improve access to transplant health services in the Council of Europe Black Sea Area member states (Armenia, Azerbaijan, Bulgaria, Georgia, Moldova, Romania, Russian Federation, Turkey and Ukraine) through the development of safe and ethical donation and transplantation programmes. Efforts have been mainly directed towards the development of effective legislative frameworks, the establishment of national transplant authorities and national transplant programmes and infrastructures, and the analysis of the clinical practices for donation-transplantation activities inside hospitals in those countries with existing transplant programmes. An Advisory Board of experts from countries with established transplant systems has been following and supporting the progress of this new project. In May 2012, all the participants in this project met in Strasbourg, which was attended by the Permanent Representatives at the Council of Europe of Armenia, Azerbaijan, Georgia, Romania, Russian Federation, Turkey and Ukraine.

Due to continuous globalisation and the right to free patient movement, there is an increasing likelihood that a patient will try to register simultaneously for the same type of organ on

the waiting lists of different organ exchange organisations, regardless of their nation of origin or residence. The CD-P-TO, in collaboration with the Council of Europe Committee on Bioethics (DH-BIO), has been studying whether this multiple listing creates a situation of unequal access to transplantation based on an individuals’ means and resources and prevents the appropriate clinical monitoring of patients during the waiting period.

This movement of citizens across jurisdictional borders is expected to become increasingly common and, hence, the possibility of persons dying in conditions suitable for donation or needing transplantations outside of their countries of residence is likely to grow. Therefore, the CD-P-TO analysed the current approaches in the member states for obtaining consent to proceed with deceased organ donation from a legal and/or practical perspective, with a specific emphasis on cases when the deceased is a non-resident. The CD-P-TO also studied the transplantation practices for non-residents in member states, especially with regard to access to waiting lists, transplantation (including from living donors), allocation and health and social assistance. Some of these results were made available in Newsletter Transplant 2012.

Countries continue to work on optimising their deceased donation programmes and their deceased donation rates, which have improved considerably in recent years. However, no country manages to cover their needs through organs from deceased donors alone. Most transplant centres within Europe have a waiting list that greatly outnumbers available organs. Waiting times may be up to eight years and many patients deteriorate and even die while waiting for an organ. Given that transplantation of kidneys from living donors has become an efficient and life-saving procedure, the CD-P-TO has worked on the elaboration of a common strategy to safely increase living donation programmes throughout Europe, while ensuring the health and safety of the living donors and taking into consideration all the legal, sociological and psychological aspects of living organ donation. As a result, two draft Resolutions on “*Utilisation of kidneys from living donors for transplantation*” and on “*Establishing national/supranational living donor registries/databases*” have been elaborated and will be submitted to the Committee of Ministers for consideration in 2013.

The Council of Europe has been studying the issue of cord blood donation for a number of years and has always been concerned by the proliferation of private cord blood banks dedicated to the collection and storage of cord blood for autologous use. Recommendation Rec(2004)8 of the Committee of Ministers to member states on autologous cord blood banks and its Explanatory Memorandum recommends that member states only allow the establishment and operation of cord blood banks on the basis of altruistic and voluntary cord blood donation. More generally, it recommends that the promotion of cord blood donation for autologous use and the establishment of cord blood banks for autologous use should not be supported by member states or their health services. Following up on this Recommendation, the CD-P-TO elaborated and disseminated a questionnaire to address the situation on autologous cord blood banks throughout Europe.

1.7 Pharmaceutical Care and Anti-Counterfeiting Activities

The activities described below (except for the “eTACT” system and the “fingerprint” database) are overseen by the European Committee on Pharmaceuticals and Pharmaceutical Care (CD-P-PH) and are carried out by committees of experts. They aim at developing and promoting best practices in pharmaceutical care, and the protection of public health from counterfeit and other illegal medicines (“similar crimes”).

Safe and appropriate use of medicines

Public authorities and the manufacturing and distribution sector devote many resources to the quality, safety and efficacy of medicines. The safe and appropriate use of medicines is as important as product quality for the best possible medication outcome in an individual patient. Pharmaceutical care is understood as a quality concept and working method for the responsible provision of medicine therapy for definite outcomes in the interest of patients’ quality of life (see definition Hepler and Strand¹). The Committee of Experts on quality and safety standards in pharmaceutical practices and pharmaceutical care (CD-P-PH/PC) has developed additional scientific indicators for measuring the quality of pharmaceutical care in Europe. The indicators cover healthcare delivery by professionals such as doctors, pharmacists and nurses, and are outcome- and patient-oriented. The information provided through these indicators will be of practical utility for policy-makers and professional associations in standard-setting.



Studies piloting a series of generally-applicable and specific indicators for the quality of knowledge and implementation of pharmaceutical care and the co-management of therapeutic plans by patients and health professionals are on-going in several countries and are presented in a report “*Pharmaceutical care. Policies and Practices for a Safer,*

More Responsible and Cost-effective Health System (2012)”. These pilot studies are being carried out by eight academic institutions in Europe. The above report recommends that governments implement pharmaceutical care in their national health care systems using basic indicators and strengthen patient participation. The report was presented at the Dutch Ministers Summit “*The responsible use of medicines, setting policies for better and cost-effective healthcare*” on 3 October 2012. The participants at the summit considered the report as stimulating and policy-driven.

1. Hepler, D.D. & Strand, L.M, Opportunities and Responsibilities in Pharmaceutical Care, Am.J.Pharm.Educ.,53, 7S-15S(1989).

As medicines prepared by industry do not always cover all the health needs of patients, the preparation of medicines in pharmacies is important. The CD-P-PH/PC drafted the Council of Europe Committee of Ministers *Resolution CM/ResAP (2011)1 on quality and safety assurance requirements for medicinal products prepared in pharmacies for the special needs of patients*. In the framework of the promotional strategy to implement this Resolution, two web-based seminars targeted to competent authorities (June 2012) and pharmacist associations (November 2012) were conducted.

Responding to the growing demand in Europe for foreign traditional medicines, including Traditional Chinese Medicine (TCM), the CD-P-PH/PC pursued its strategic approach to ensure safe TCM practices in Europe. A pilot study was carried out among patients and consumers to validate information about TCM practices in Europe to assist them in their choices of healthcare and in communicating with healthcare providers. Furthermore, a concept for an education/training curriculum for therapists and pharmacists in Europe was studied.

The Committee of Experts on the classification of medicines as regards their supply (CD-P-PH/PHO) annually issues recommendations to health authorities for the classification of medicines into prescription and non-prescription medicines, as this is currently not harmonised in Europe. Its work promotes patient safety and the accessibility of medicines in Europe. A discussion of the annual revision of the 2012 classification recommendations was completed and will be published in 2013 on the EDQM’s dedicated webpage <http://www.edqm.eu/melclass/>.

Public health protection from counterfeit or other illegal medicines threatening health

The Steering Committee and the Committee of Experts on minimising public health risks posed by counterfeit medical products and similar crimes (CD-P-PH/CMED) accomplish their work programme through multi-sectorial prevention and risk management strategies, such as by providing support to the implementation of relevant legislation, transfer of know-how, specific policy proposals and practical tools. Having been involved in the development and adoption process of the Council of Europe MEDICRIME Convention from the outset, these bodies were entrusted with contributing to the follow-up mechanisms of the Convention as soon as it came into force.

Twenty-two states have signed and one state has ratified the MEDICRIME convention as of January 2013.

On 16 May 2012, a conference on “*Combating falsified medical products and similar crimes through legal instruments and practical measures*” was hosted and co-organised in Copenhagen by the Council of Europe and under the Danish Presidency of the Council of the European Union. The conference was attended by officials and experts of member and non-member states of the Council of Europe and the European Pharmacopoeia Convention. The conference developed a strategic approach to support the implementation



of the two complementary legal instruments: the Council of Europe MEDICRIME Convention and EU Directive 2011/62/EU on “Falsified Medicines”. The CD-P-PH and CD-P-PH/CMED contributed significantly to the programme of this conference and to the practical suggestions for states appended to the conference conclusions.

In the framework of the EDQM-supported training platform to combat medicrime, the CD-P-PH/CMED co-organised:

- with the Medicines and Healthcare Products Regulatory Authority (MHRA) of the United Kingdom, a regional training session for officials from Bulgaria, Hungary, Poland, Romania, the Slovak Republic and Turkey on 27-29 March 2012.
- with the health authorities of Armenia, a regional training session for officials from Armenia, Belarus, Georgia, Moldova, Russian Federation and Ukraine on 7-8 November 2012.
- with the Drug Regulatory authorities of Croatia, a regional training session for officials from Albania, Bosnia-Herzegovina, Croatia, Greece, Montenegro, Serbia, Slovenia and The Former Yugoslav Republic of Macedonia on 4-5 December 2012 providing, for the first time, specific training on networking between Single Points of Contact (SPOCs).

Through expert meetings, held on 29 October to 2 November 2012, CD-P-PH/CMED also developed and tested a basic, generally-applicable model approach for West African authorities who wish to analyse legislation, structures and processes to better fight medicrime and protect public health.

The Proceedings of the Expert Workshop “Communication about the risks posed by Counterfeit Medical Products and Similar Crimes” were published, with the significant support of the Italian Medicines Agency (AIFA) in the publication, drafting and production processes.

The Committee of Experts finalised a study protocol that will be piloted in 2013 for an approach to better identify and follow-up on signals of health damage to patients and consumers from counterfeit medical products and similar crimes.



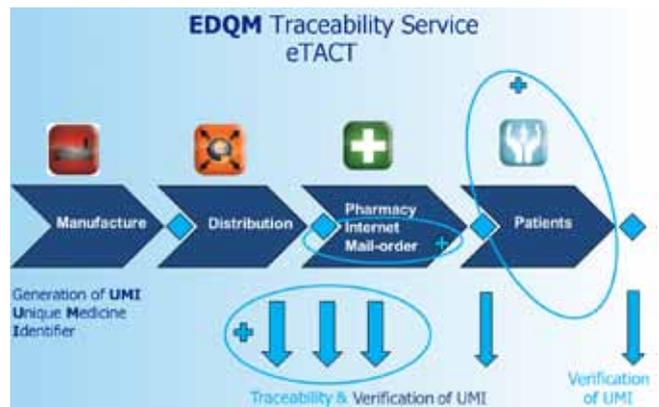
As part of its holistic anti-counterfeiting strategy, the Council of Europe/EDQM has further developed the project for an anti-counterfeiting traceability service for medicines. The eTACT service aims at providing a traceability and mass-serialisation system that can be used by authorities and stakeholders (*i.e.* manufacturers, distributors, healthcare professionals and patients) from across the entire medicines' supply-chain, from the 37 member states of the European Pharmacopoeia and beyond.

The eTACT service will help combat counterfeiting using a harmonised approach throughout participating countries. It will be a flexible system that will improve the control of the supply chain.

Allowing patients to verify the authenticity of their medication is a unique feature of the EDQM's project that will significantly contribute to the strengthening of the public's confidence in the legal supply chain, irrespective of the distribution route. Public governance of such a system is vital to ensure effective and proper project development in co-ordination with regulatory authorities and to prevent the misuse of data, *e.g.* commercial data.

In 2012, the eTACT IT system was presented to numerous authorities and stakeholders in order to gather comments from all over Europe. This will now allow the EDQM to elaborate a robust user and business requirements document for a real-scale service, to be implemented in line with upcoming national and regional requirements for the traceability of pharmaceuticals in Europe.

Progress has also been made with regards to functionality of the system and harmonised stakeholder governance and traceability, thus providing authorities and patients with a high performance tool.



API “Fingerprints” repository

The EDQM has further developed a project for the establishment of a repository of “fingerprints” or signatures of active pharmaceutical ingredients (APIs) used for the manufacture of medicines. For this purpose, the EDQM has collaborated with a dedicated task force of the OMCL Network. (see chapter 1.5 OMCL Network page 18).

In 2012, as part of a pilot project, the OMCLs involved completed a number of studies, with analyses performed on various methods and samples provided by the companies that had joined the project. In 2013, the EDQM and the OMCL Network will move to a second phase of the project, taking advantage of the review of the first phase to widen the scope to more transversal analysis methods on a larger number of samples of target APIs.

1.8 Cosmetics and Packaging for Food and Medicines

Consumer Health Protection

Since 1 January 2009, the EDQM has been engaged in efforts to strengthen consumer health protection in Europe, with a focus on the safe use of cosmetics and packaging or other materials that are intended to be brought in contact with food or medicines.

The work programme was elaborated by the Consumer Health Protection Committee (CD-P-SC, Steering Committee), which is composed of representatives from national ministries acting in the field of public health. More than 200 experts from 35 member states and observers to the European Pharmacopoeia Convention follow or contribute actively to the work.

The focus of the work is on the new European network of Official Cosmetics Control Laboratories (OCCLs) and on the development of harmonised quality standards for packaging materials that are used for food and medicines.

Two subordinate Committees of Experts implement the work defined by the CD-P-SC: the Committee of Experts on Cosmetic Products (P-SC-COS) and the Committee of Experts on Packaging Materials for Food and Pharmaceutical Products (P-SC-EMB).



Cosmetics testing

The European network of national OCCLs was set up in 2010 with voluntary members to share testing competences and resources and to enhance quality management in each laboratory in accordance with international standards. Under the aegis of the EDQM, collaborative analytical studies and expert meetings are organised, with contributions from several or all participating laboratories. The long-standing experience with the network of Official Medicines Control Laboratories (OMCLs) has been an asset in the start-up phase. The OCCL network has established close contacts with the European Commission (DG SANCO) and the Joint Research Centre (JRC).

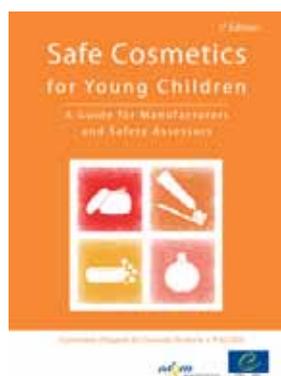
The main task of an OCCL is to check the quality of products on the market. As part of a market surveillance study (MSS) started in 2011 (to be continued up to the end of 2013), several countries are collecting samples of decorative cosmetics (make-up, eye-shadow, eye liner, lip gloss, etc.) to measure the content of certain metals that may give rise to health concerns, such as antimony, cadmium, chromium, lead, mercury and nickel. Traces of some of these metals may be unavoidable for technical reasons but, in most countries, maximum tolerable limits have not been set. Results from this study may be used to establish common guidance values for use by surveillance authorities.

The quality of cosmetic products that are intended to be used on or by children and product compliance with EU regulations has been tested in an MSS started in 2012 (to be continued in 2013). Shampoos, skin creams, bath lotions and several other product types will be tested for their compliance with relevant European or national regulations.

To verify the laboratory performance concerning testing of specific cosmetic ingredients and to ensure that test results are comparable in Europe, Proficiency Testing Scheme (PTS) studies are carried out. In 2012, the range of products included toothpaste, hair straighteners and depilatory creams. The amount of diethylene glycol was determined in toothpaste, while hair straighteners and depilatory creams were tested for their content of the cosmetic ingredient thioglycolic acid.

Sun protection products contain substances that filter or block UV light and many products indicate a so-called "sun protection factor, SPF". Effective market surveillance of these products includes a verification of the labelled SPF, for which suitable in vivo and in vitro methods are used. To review developments of analytical technology and surveillance activities in this field, a seminar on the topic was organised in April 2012, which was hosted by the CVUA in Karlsruhe (Germany). This seminar followed up on the topics presented in Montpellier (France) in 2011. Nineteen experts from 12 European countries participated and decided to harmonise approaches and to further develop methodologies.

Cosmetics for children under the age of three



Restrictions on cosmetics that are intended to be used on children up to the age of three is the subject of a new Council of Europe Resolution that was adopted on 14 March 2012 [CM/ResAP (2012) 1]. This Resolution and its supplementary guidance document for manufacturers and safety assessors were published in 2012 ("*Safe Cosmetics for Young Children*", 1st Edition).

(see 2.2 Information Technology and Publications Activities page 32).

Tattoos and permanent make-up

To implement the recommendations of Council of Europe Resolution AP (2008) 1 on tattoos and permanent make-up, the compilation of safety and documentation requirements for tattoos and permanent make-up is under preparation. This document is expected to be finalised and published in 2013.

Packaging for food and medicines



A new Resolution on metals and alloys used in food contact materials has been drafted, which refers to quality requirements for materials such as aluminium foil, kitchen utensils, coffee machines, etc. where no EU regulation exists. Council of Europe member states are recommended to apply Specific Release Limits (SRLs) for metal ions that are released from materials in contact with foodstuffs and transferred to food from packaging or containers. With the adoption of this Resolution, envisaged in 2013, these requirements will supersede the corresponding guidelines published in 2002 on metals and alloys used as food contact materials.

The upper limits for the release of metal ions have been agreed by the national experts of the P-SC-EMB. For example, nickel release should not exceed 0.14 mg/kg and lead should not be released in amounts greater than 0.010 mg/kg (concentrations measured in food). Detailed instructions on how to perform laboratory testing are described in a new Technical Guide that is planned for publication in 2013.

Furthermore, the Committee of Experts P-SC-EMB decided to entirely review the existing resolutions and technical documents that had been elaborated under the former Council of Europe Partial Agreement in the Social and Public Health Field (dissolved on 31 December 2008). The work has been assigned to rapporteurs who will prepare draft provisions for materials such as cork, ion exchange resins or paper and board. This work will be pursued in 2013.

Finally, a transversal project is aimed at limiting the use of inks and colourants for printed containers used for medicines or food. A positive list of safe substances will be compiled that can be consulted by manufacturers and surveillance authorities, and general quality criteria and analytical test methods will be developed.

2. SUPPORT ACTIVITIES

2.1 Quality Management System



The EDQM maintains and extends its ISO 9001 certification.

After a comprehensive four-day audit, Afnor Certification (AFAQ) prolonged the EDQM's ISO 9001 certificate and extended its scope to pharmacopoeial activities.

According to Afnor Certification, the EDQM is certified as meeting the requirements of ISO 9001:2008 for the following activities:

“Evaluation of applications (initial, revisions and renewals) for certificates of suitability to the monographs of the European Pharmacopoeia, granting of certificates, and management of the inspection programme of manufacturing sites and associated brokers.

- *Planning, implementation and coordination of post-marketing surveillance studies for medicinal products authorised by the centralised (CAP) and national (MSS studies) procedures;*
- *Management of the database related to post-marketing surveillance studies of medicinal products authorised by the mutual recognition (MRP) and decentralised (DCP) procedures and management of related interactions with users;*

- *Coordination of the elaboration and issuance of guidelines related to the OCABR procedure for the release of batches of human immunological medicinal products (blood and vaccine);*

according to the pharmaceutical legislation, notably directives 2001/82/EC and 2001/83/EC, as amended, and Regulation 726/2004 (EC) for the EU countries.

Management of the elaboration, revision, correction and suppression of European Pharmacopoeia texts, their publication in printed and electronic format, as well as their distribution”.

The EDQM laboratory (DLab) is audited by the Belgian Accreditation Body (BELAC).

In order to generate high quality data, DLab operates an ISO/IEC 17025:2005 Quality Management System. This system was extensively audited by an independent team of four experts from the Belgian Accreditation Body (BELAC) in December 2012. The ISO/IEC 17025:2005 accreditation certificate is expected to be delivered early in 2013.



2.2 Information Technology and Publications Activities

A website (www.edqm.eu) continuously progressing in terms of visits



A number of design, page layout and content changes to the EDQM website were undertaken in 2012. In July, the entire site was overhauled to better serve users and to reinforce the visual identity of the EDQM and the Council of Europe. The website attracted 80,157 visits and 32,774 visitors per month (statistics obtained using Google Analytics) in 2012, a slight increase compared to 2011.

Several new web pages were created (e.g. Consumer health protection, eTACT, Medicrime, Pharmaceutical care, Alternatives to Animal Testing) to promote and give more visibility to the work of the EDQM in these areas. Several other sections and pages were revised and modernised to give users more efficient access to the EDQM's resources. The news feeds were also improved to offer visitors RSS feeds based on themes.

An indispensable online user support service (HELPDESK)

The HELPDESK service is the first point of contact for information and support from the EDQM. It provides help with any technical or scientific questions concerning the various activities, products or services of the EDQM. The HELPDESK received 10,766 questions in 2012, which represents a slight rise of 1% in volume. The HELPDESK Frequently Asked Questions (FAQs) are updated regularly to cover all activities and to respond to changing user needs.

Enterprise Resource Planning (ERP)

The implementation of standard ERP software was continued in 2012 with the deployment of the sales and distribution process for the EDQM's publications and Customer Relationship Management (CRM) system. It will be pursued further in 2013 with a new webshop for both publications and reference standards. Work on encapsulating the production, sales and distribution of reference standards continues in 2013. This integration will further help to provide a better and more standardised service to the EDQM's customers.

Dynamic publication activities

The Publications Unit is responsible for the technical and administrative aspects of the publication of the European Pharmacopoeia, *Pharmeuropa*, *Pharmeuropa Bio* and Scientific Notes and other EDQM publications and technical guides.

Three supplements of the 7th Edition of the European Pharmacopoeia (7.6 to 7.8) were published in 2012, comprising 1,066 pages for the English version and 1,140 pages for the French version. The 7th Edition (including supplement 7.8) consists of 2,205 monographs (including those on dosage forms) and 344 general texts (including general monographs and methods of analysis).

The 1st Edition of "*Safe Cosmetics for Young Children*" was published in 2012, with an electronic version also available on the EDQM website. This guide was elaborated by the Committee of Experts on Cosmetic Products (P-SC-COS) and states that products must be safe for the health of infants and should only contain ingredients that are non-toxic. Thus, potent allergens or substances with endocrine-disrupting activity should not be present and preservatives should be used at their lowest effective concentrations. Detailed recommendations for baby creams and lotions were also agreed by experts in the field.

Support was also provided for the publication of other documents by the EDQM. In 2012, documents related to:

- Blood and blood components – "*Safety, Quality, Training and Ethical Matters Concerning Preparation, Use and Quality Assurance: Council of Europe Resolutions, Recommendations and Conventions*" (2012) - 1st Edition 
- Organs, Tissues and Cells – "*Safety, Quality and Ethical Matters Concerning Procurement, Storage and Transplantation. Council of Europe Conventions, Recommendations, Resolutions and Reports*" (2012) - 2nd Edition 
- Pharmaceutical Care – "*Policies and Practices for a Safer, More Responsible and Cost-effective Health System*" (2012)

were published in English. In addition, the Publications Unit contributed to the publication of the Organización Nacional de Trasplantes (ONT) - Newsletter Transplant.

An important role of the Publications Unit is to ensure a harmonised editorial style throughout all publications by proof-reading the texts to be published by scientific editors. Furthermore, the unit maintains lists of data needed for the publication work.

Publications on Blood Transfusion and Organ Transplantation published on new website (TOTS)

Publications on Blood Transfusion and Organ Transplantation are now published online. The site is available to subscribers at: <http://tots.edqm.eu/>.

Pharmeuropa online now with free access

The four issues of Pharmeuropa published in 2012 contained 159 texts for enquiry. One issue of Pharmeuropa Bio & Scientific Notes, containing 9 scientific articles in English, was published.



The online version became official in 2012 with the publication of Pharmeuropa 24.1 in the Texts for Comment database. The homepage provides links to public inquiries on draft European Pharmacopoeia texts or on matters of general policy, the latest official announcements on newly-adopted monographs, the latest news on Pharmacopoeial harmonisation, a readers' tribune and access to three databases:

- **Texts for comment** contains proposals for new and revised monographs and general texts that are intended for inclusion in the European Pharmacopoeia and are submitted for public comment.
- **Pharmeuropa Bio & Scientific Notes** contains all the news in the biological standardisation area and scientific articles linked to the work of the European Pharmacopoeia.
- **Pharmeuropa archives** contains past issues of Pharmeuropa.

It is possible to sign up for notifications to receive emails when draft comments for text are added to the site. Access to Pharmeuropa online is free. To receive full access to the content of the site, it is necessary to register. National authorities have privileged access to a commenting tool, making it possible for them to submit comments directly in the Texts for comment database. The site is available at: <http://pharmeuropa.edqm.eu/>.

Standard Terms

Since 1996, the EDQM has issued lists of Standard Terms, which provide harmonised vocabularies for dosage forms, routes of administration and packaging (including containers, closures and administration devices). The lists were originally drawn up in response to a request from the European Commission and cover medicines both for human

and for veterinary use. Standard Terms are used in the European Union Marketing Authorisation application form, the Summary of Product Characteristics (SmPC), product labelling and electronic communications.

Requests for new Standard Terms are submitted to the EDQM by national authorities, the EMA or the EU. These requests are assessed by the Standard Terms Working Party (STWP), which consists of experts elected by the European Pharmacopoeia Commission. The STWP meets 3 times annually to discuss the requests and to propose new terms and definitions or revise existing terms and definitions as necessary. Where possible, it also addresses requests electronically in order to reach decisions between meetings and, thereby, achieve more rapid resolutions. Any entirely new Standard Term concept that is agreed upon is sent to the Commission for adoption by correspondence before publication. Published terms are made available to national authorities in order to allow their experts to provide translations, which are submitted to the EDQM Secretariat for publication.

In 2012, the first Ukrainian translations were introduced to the database, bringing the total number of languages to 32 (Albanian, Bulgarian, Chinese, Croatian, Czech, Danish, Dutch, English, Estonian, Finnish, French, German, Greek, Hungarian, Icelandic, Italian, Kazakh, Latvian, Lithuanian, Macedonian, Maltese, Norwegian, Polish, Portuguese, Romanian, Serbian, Slovak, Slovenian, Spanish, Swedish, Turkish and Ukrainian).

By the end of 2012, the Standard Terms database held 771 unique terms, with 28 new terms having been added during the year, as well as many hundreds of translations submitted by the various national authorities.

2.3 Communication, Landmark events

Communication with stakeholders, partners and the general public

Communication plays a strategic role within the regulatory environment. The EDQM aims to disseminate important announcements, changes in policy, product releases and new collaborations by releasing regular press communications. In 2012, 21 press releases were issued and circulated via electronic mail to various media, authorities and partner associations all over the world. The impact of such press releases is regularly evaluated using online software, which measures the number of times files are downloaded, viewed and opened. This process is on-going and helps the EDQM to regularly monitor how the disseminated information is being received and used by journalists.

The EDQM's free, monthly E-Newsletter summarises the latest information, events and news, with links for retrieving this information from its website. The number of subscribers grew to over 12,600 and, along with the RSS feeds, new web content was quickly delivered to subscribers, with all major headlines summarised in a single email.

A year dedicated to consultations on topical subjects to allow feedback and better prepare users for quality challenges

Various events took place on technical and scientific subjects related to EDQM activities.

The EDQM organised a number of technical workshops in 2012

Two technical workshops were organised on the EDQM's anti-counterfeiting project, eTACT, and these were held in Strasbourg, France (January 2012) and in Sofia, Bulgaria (November 2012). During the open discussions, the EDQM gathered important and valuable feedback on the service from key stakeholders involved in the medicines supply-chain, regulatory authorities and patients' organisations. Their observations helped the EDQM to re-define the service so that it can be scaled up and deployed in the future and issues such as transparency, patient involvement and governance were debated. There was also a live demonstration of the IT tool to show its flexibility and interoperability with existing national systems in the medicines supply-chain.

A third workshop was organised on "Alternatives to the *Leptospirosis Potency Test*" in Strasbourg, France (January 2012), to share information and experiences on the recent advances that have been made in this area. The ideas put forward and outcomes were shared with the European Pharmacopoeia Commission.

International conferences and symposia

To commemorate the 20th anniversary of the Certification of Suitability to the Monographs of the European Pharmacopoeia Procedure, the EDQM organised an international conference in March 2012 in Larnaca, Cyprus. The conference was attended by over 150 delegates from 35 countries, representing all regions of the world. Topics discussed included the evolution of the Certification procedure, the major changes that had taken place over the last two decades, the use of Certificates (CEPs) and the inspections programme. Experts and representatives from regulatory authorities including Health Canada, the Therapeutic Goods Administration Australia (TGA) and the European Medicines Agency (EMA) shared their experiences and gave insights into the use of CEPs. There were also three parallel workshops and the feedback collected will help adapt the Certification procedure and its policies to better meet current demands.

In May 2012, a high-level international conference on the MEDICRIME Convention was organised in Copenhagen, Denmark, to promote awareness and the signature of the Convention and to highlight the importance of co-operation and networking between health, law enforcement and judicial authorities involved in the fight against falsified medical products and similar crimes. The conference was co-organised by the EDQM and the Danish Health and Medicines Authority under the Danish Presidency of the Council of the European Union. (see chapter 1.7 Pharmaceutical Care and Anti-Counterfeit Activities page 27).

The EDQM hosted a round-table discussion on "*Identifying falsified medicines: How best to protect European citizens?*" in Brussels, Belgium (June 2012). The event provided the EDQM with an opportunity to present the eTACT service to journalists, ambassadors from EU member states and patients' associations and it brought attention to discussions taking place at European level on the future architecture of the mass serialisation systems to be used in the legal medicines supply-chain to protect it from counterfeit/falsified medicines.

The 11th "*International Symposium on Pharmaceutical Reference Standards*", organised by the EDQM, was held in Strasbourg, France, in September 2012. This bi-annual event brought together 146 experts from 27 countries. The plenary sessions covered topics such as regulatory and logistical aspects, as well as the use and establishment of reference standards. Targeted breakout sessions were also included to specifically address reference standards for biologicals and the challenges for characterising small molecules. A poster session and a round-table discussion with the participation of representatives from authorities, pharmacopoeias and industry associations were also part of the programme.

Webinars

In 2012, the EDQM organised a total of seven webinars on a number of different topics. Interest in these web-based seminars has grown continuously and participants provided very positive feed-back. The technology has allowed the EDQM to offer training sessions on “hot topics” to a virtually unlimited number of people, anywhere in the world, instantly reaching a large audience.

The three webinars on the eTACT project and the two in the field of pharmaceutical care were tailored to a particular audience (national authorities, patient associations, hospital pharmacists) and on a specific subject matter (*Resolution CM/ResAP(2011)1 on quality and safety assurance requirements for medicinal products prepared in pharmacies for the special needs of patients*). This meant that the presentations and information given were pertinent, relevant and focused.

Given the vastness of the subject, two separate webinars were organised on reference standards in May. The first session covered the general concepts and the EDQM’s reference standards, while the second, organised in collaboration with the World Health Organization (WHO), concentrated on the reference standards of the International Pharmacopoeia and other working standards (in-house working standards).

All webinars were followed by a Q&A session among all the participants and copies of the slides and a recording were made available afterwards.

Training sessions – strengthening knowledge and sharing know-how

In 2012, four training sessions were organised on the European Pharmacopoeia (two in Strasbourg in May and July 2012, one

in Tel-Aviv, Israel in July 2012 and one in Lisbon, Portugal in December 2012).

The first session focussed on biological substances (peptides, human vaccines, blood and biotechnological products) and the programme was customised to meet the specific learning needs of the participants active in the field.

The others concentrated on chemical products and although the general format of the training was not changed, the programme was revised based upon participant’s feedback, training needs and changes in relevant trends and regulations. There were also plenty of panel discussions, case studies and workshops that provided opportunities for interaction with participants.

The training session in Tel-Aviv was organised on the initiative and with the support of the Israeli Institute for Standardization and Control of Pharmaceuticals of the Ministry of Health. As regards the training session organised in Lisbon, the EDQM received inestimable support from the Portuguese National Authority of Medicines and Health Products (INFARMED). Both Authorities not only provided logistical help and advice, but offered their meeting rooms and the assistance of their technical staff to the EDQM, for which the EDQM expresses its thanks.

International trade fairs and exhibitions

Attending international trade fairs and exhibitions is a great way for the EDQM to promote its activities, products and services to a specific audience or industry. Once again, the EDQM participated in the Congress of Pharmaceutical Ingredients (CPhI) that took place in Shanghai, China, in June 2012 and in Sao Paulo, Brazil in August 2012. The EDQM stand attracted a lot of attention and provided a unique



platform to meet with visitors, to network with existing and new clients and to develop relations with professionals in the industry. Brochures and leaflets with comprehensive up-to-date information on the EDQM's activities were distributed, many of which were available in Chinese. One-to-one technical consultations on the EDQM's Certification procedure were also organised and local distributors of EDQM publications assisted on the stands.

Partnerships at international level

To help national authorities and professionals worldwide, the EDQM co-organised and participated in a number of events; namely, in chronological order:

International collaboration of World Pharmacopoeias

The first "*International Meeting of World Pharmacopoeias*", a meeting of all the pharmacopoeias and pharmacopoeial secretariats known to the WHO, took place in February 2012 under the auspices of the WHO, with the aim of bringing the different pharmacopoeias together and discussing potential ways to strengthen collaboration and harmonisation.

The meeting was followed up by an open meeting with stakeholders, held under the auspices of the WHO and FIP, the International Pharmaceutical Federation, in October. This meeting, held over two days in Amsterdam, had the primary intention of gathering stakeholder's feedback on their needs regarding the harmonisation of world pharmacopoeias. A first draft structure for potential future Good Pharmacopoeial Practices (GPPs, a compilation of harmonised policies and approaches for monograph development) was set out by the WHO's Expert Committee on Specifications for Pharmaceutical Preparations, in order to show that it was taking concrete steps towards harmonisation between world pharmacopoeias.

Inter-governmental activities

The Asia Pacific Economic Cooperation (APEC) organised the "*Life Science Innovation Forum – Regulatory Harmonisation Steering Committee Meeting*" in Singapore in March, 2012. The EDQM was invited to share its holistic approach on the fight against counterfeit medicines. The focus of this APEC meeting was to promote an awareness of the need for high quality medicinal products and supply chain integrity on a global stage. A number of 'road maps' were set out by the participants, with the aim of achieving harmonisation in the field of drug safety in the near future. Participants in the meeting hailed mostly from APEC economies.

Other interesting worldwide collaborations

A workshop entitled "*Seminar on the impurities of pharmaceutical products*" was held in Casablanca, Morocco, on 27 March 2012. The EDQM participated by giving a presentation on Ph. Eur. reference standards.

In March 2012, the EDQM was invited by the Institute of

Medicines (IOM) to attend a meeting entitled "*Mitigating the Global Public Health Impacts of Counterfeit, Falsified, and Substandard Drugs*", in Washington, USA. The EDQM presented the Council of Europe's MEDICRIME Convention, which was well received by all those in attendance. Throughout the meeting, the need for international collaboration and harmonisation in the field of combatting counterfeit and falsified medicines was emphasised.

A "*Quality Control of Drugs and Medical Devices Conference*" was held in Moscow, Russian Federation, in April 2012. The EDQM participated by presenting its key activities in relation to the Ph. Eur., *i.e.* setting documentary standards and establishing material standards and its anti-counterfeiting activities. Overall, participants highlighted the need for an increase in collaboration and information exchange.

In May 2012, the EDQM participated in an API Workshop in Shanghai, China in the context of the Annual DIA China Meeting. The regulation of APIs, both globally and specifically in China, were the main focus of the presentations during this workshop, which was co-organised by the US Department of Commerce and SFDA. Administrative support from the DIA saw 100 participants in attendance, including representatives from industry, the SFDA and some local Chinese authorities. The involvement of the EDQM in this workshop also gave an opportunity to highlight and emphasise the EDQM's work in ensuring the quality of medicines through its certification activities (both in terms of assessment and inspection).

In June, the EDQM participated in a number of meetings in Shanghai, China during the CPhI China Congress. A half-day informative satellite meeting was organised for API manufacturers. The meeting was jointly organised with the World Health Organization (WHO), the Chinese State Food and Drug Administration (SFDA) and the China Centre for Pharmaceutical International Exchange (CCPIE). The programme was tailored to increasing manufacturers' understanding of the EDQM's Certification procedure and the inspections programme, as well as the WHO's API Prequalification Programme. Finally, a one day meeting was organised at the East China University of Science and Technology, School of Pharmacy, by the EDQM, WHO, SFDA and CCPIE to increase awareness on a wide range of topics and matters related to the quality of medicines, *e.g.* quality assurance, the WHO API Prequalification Programme, the Certification Procedure, and EDQM and USFDA inspections. The meeting was attended by around 75 participants, mainly from industry and universities.

The EDQM gave a plenary presentation on Ph. Eur. reference standards at the 13th "*Biological and Environmental Reference Material (BERM) Conference*", organised by the International Atomic Energy Agency (IAEA) in Vienna, Austria, in June 2012.

A "*Workshop on API Quality, GMP and Pharmacopoeias*" was jointly organised by the EU-China Trade Project and the China Chamber of Commerce for Import & Export of



Medicines & Health Products (CCCMHPIE) in Beijing, July 2012. This workshop provided a great deal of information regarding the new regulations of the EU Falsified Medicines Directive and their impact on exporting APIs from China into Europe. During the lively discussion, the EDQM's certification procedure and related inspections attracted a large number of questions.

A technical conference on “*Current Challenges in Global Regulatory Compliance - Quality of Pharmaceutical Ingredients*” was jointly organised by the EDQM, the World Health Organization (WHO) and the Indian Pharmaceutical Association (IPA). The EDQM's Certification procedure, including the inspection programme of API manufacturers, as well as the European Pharmacopoeia and international harmonisation, were all high on the agenda. Three pre-conference tutorials took place on preparing a new CEP, a revision application and an EDQM inspection and these were designed to provide a more in-depth understanding of the policies and procedures involved. The conference took place in Mumbai, India (September 2012), and it brought together around 90 representatives from a very broad cross-section of India's pharmaceutical industry.

In October 2012, a symposium on “*Pharmacopoeias and Reference Standards*” was organised by the Pharmaceutical Society of Korea in Seoul and a KFDA/EDQM/USP Joint Workshop on Pharmacopoeias and Reference Standards was held in Osong, Korea. The EDQM participated actively in both events by presenting its key activities relating to the Ph. Eur., *i.e.* setting documentary standards and establishing material standards.

Specific collaboration developed under the auspices of national authorities and the WHO

In September 2012 and in co-operation with the Partnership for Safe Medicines (PSM) and the World Health Organization (WHO), the Government of India invited the EDQM to participate in a “*Patient Safety and Drug Detection and Authentication Technology Workshop*” which took place in New Delhi, India. This workshop was a follow-up to the September 2011 APEC “*Drug Safety and Detection Technology*” seminar that took place in Beijing, China. It was organised into four technical sessions: “Challenges on Accessibility of Quality Medicines & Using Detection Technology”, “Regulatory Perspectives on Patient Safety”, “Detection Technologies as Part of a Larger Strategy for Drug Authentication Quality” and “Early Detection Technologies for Better Quality Medicines and Role of Serialization” and provided a great deal of information on the challenges faced by government and industries and how they intend to reverse the increasing trend of counterfeiting cases.

The 15th “*International Conference of Drug Regulatory Authorities (ICDRA)*”, aimed at promoting the exchange of information between drug regulators and developing collaborative approaches to issues of common concern, was held in Tallinn, Estonia in October 2012. The conference,

which is held every two years, was jointly organised by the Estonian Agency for Medicines and the World Health Organization (WHO). During the Pre-ICDRA programme, which was co-organised by the EDQM, the EDQM made presentations on issues relating to active pharmaceutical ingredients, *e.g.* the quality control of APIs, assessment of API documentation and the specific challenges for herbal medicines.

International collaboration on generic drug applications

In December 2012, the EDQM participated in discussions of the International Generic Drug Regulators Pilot Project (IGDRP) in Nanchang, China. The scope of the IGDRP is to investigate opportunities for work-sharing and mutual recognition in the field of generic applications. Acceptance of CEPs may help lessen the workload of regulators in the field of APIs. The EDQM also participated in the “*Third International Conference on Generic Drugs*” held at the same location. The sessions of this conference included an overview of the global generics regulatory environment, with presentations on certification from SFDA, Health Canada, the EDQM and the Polish Office for Registration of Medicinal Products, Medical Devices and Biocidal Products. The conference also included presentations on the technical requirements for generics in China, an update on FDA inspections in China and new developments in US regulatory requirements on generics and APIs, as well as a number of industry presentations on experiences in China and how to facilitate market access to the EU and the US for Chinese companies.

Promoting communication in blood transfusion activities

World Blood Donor Day was celebrated on 14 June 2012 and the theme chosen for the day was “Every blood donor is a hero”. The campaign aimed to encourage more people to voluntarily donate blood in order to maintain a safe and adequate supply. The global event was held in Seoul, Republic of Korea, hosted by the Korean Red Cross and the Ministry of Health and Welfare, Republic of Korea.

The EDQM made an interactive map available via its website, with links to European blood service websites. Visitors were able to connect and find out what festivities were being organised in their own country and how to get involved. A media kit was made available to all member states for use during their own local campaigns.

The EDQM participated in the 32nd “*International Congress of the International Society of Blood Transfusion (ISBT)*” in Cancun, Mexico (July 2012). The Congress attracted more than 2,400 delegates, most of whom were professionals involved in transfusion medicine activities. The EDQM continued the promotion of its “*Guide to the Preparation, Use and Quality Assurance of Blood Components*” (16th Edition 2010) and delegates were able to pick up information on on-going projects, Council of Europe recommendations and



resolutions, as well as the EDQM reports on the Collection, Testing and Use of Blood and Blood Components in Europe. Materials in Spanish were also prepared especially for the event.

In October 2012, the EDQM organised a symposium in Strasbourg, France, part of which was restricted to representatives from authorities and blood services, on “*Blood Supply Management*” (BSM). The programme covered topics such as the Council of Europe’s BSM project and survey, the different approaches to BSM being taken by different European blood services and an overview of some of the commercial software that is available and that can help manage the blood supply chain. The meeting concluded with a round-table discussion on good practices.

The EDQM also supported the Association Against Sickle-Cell Disease (DORYS) in the organisation of its 7th “*Congress on Sickle Cell Disease*”, which was held in Strasbourg, France (May 2012).

Organ transplantation activities

Since 1998, the Council of Europe organises a European Day for Organ Donation and Transplantation to promote organ donation and transplantation in its member states. It is hosted in a different member state each year, with the aim of raising awareness of the importance of organ donation and transplantation.

The EDQM celebrated the European Day of Organ Donation and Transplantation in Budapest, Hungary (October 2012). The day was organised by the Hungarian Transplantation Society and the EDQM’s information stand enabled the

general public to pick up information leaflets on organ donation in Hungarian. In addition to a Scientific Conference and a Press Conference, many outdoor activities were organised. An award-giving ceremony also took place to pay tribute to donors. The day ended with a ‘Donation Day Concert’ with well-known Hungarian artists.

Visits

The EDQM continued to open its doors to various groups of visitors, providing better knowledge and understanding of its work to the public.

2.4 International Collaboration

In an era of globalisation, international collaboration is of paramount importance for the EDQM to fulfil its mission of protecting public health. Harmonisation of standards, exchange of information and work-sharing are just a few examples of the EDQM's activities in working closely with its partners and stakeholders at an international level.

Bilateral meetings and visits

China

The productive co-operation with China continued with visits of delegations from the State Food and Drug Administration (SFDA), the National Institutes for Food and Drug Control (NIFDC) and the China Pharmaceutical International Exchange Centre (CCPIE) to the EDQM in January and November. The discussions focused on experience in the field of quality requirements for marketed drugs, quality monitoring and evaluation mechanisms for marketed drugs, handling of quality hazards and quality management systems. The EDQM's laboratory and reference standard production facilities were also visited.

Ukraine

In July of this year, the EDQM attended a celebratory event devoted to the 20th anniversary of the Ukrainian Scientific Pharmacopoeial Centre for Quality of Medicines. During the event held in Kharkov, the Head of State Administration reiterated the strong will and intention of the Ukrainian Government to sign the Ph. Eur. Convention and become a full Ph. Eur. member, which was completed on 17 December 2012.

Singapore

In June 2012, the Chief Executive Officer (CEO) of the Singapore Health Sciences Authority (HSA) made a courtesy visit with a delegation from HSA to discuss the work being conducted at the EDQM. Singapore is the 24th and most recent observer of the European Pharmacopoeia. Being responsible for the blood bank of Singapore and the regulation of health products, the HSA is very much interested in strengthening mutual collaboration with the EDQM in the areas of OMCLs, cosmetic laboratories and blood transfusions.

United States of America

The EDQM was visited by the US Food and Drug Administration's (FDA) Liaison Officer to the EMA in 2012, further developing the relationship between the two parties. The visit was conducted in order to present the work of the FDA and provide information on their interaction with the United States Pharmacopoeia (USP).

The World Health Organization (WHO)

In addition to its activities relating to International Chemical Reference Standards (ICRS) and International Standards for Antibiotics (ISA) described in chapter 1.2, the EDQM has supported the WHO's standard-setting activities by active contributions to the work of the Expert Committee on Specifications and the Expert Committee on Biological Standardisation.

Relations with the International Pharmaceutical Federation (FIP)

The "FIP Stakeholder Roundtables in conjunction with the Amsterdam Ministers' Summit", which looked at setting policies for better and more cost-effective healthcare, took place in Amsterdam in October 2012. Of a total of four round-table discussions that took place over 3 days, three were conducted before the Ministers' Summit with the aim of preparing suggestions for discussion. The fourth round-table discussion on the final day focussed on innovation.

Overall, the FIP Stakeholder Roundtables and the Ministers' Summit emphasised the importance and need for further action in the field of Pharmaceutical Care. The work of the EDQM/Council of Europe in the field was acknowledged throughout the conference and referred to in the conclusions. (see chapter 1.7 Pharmaceutical Care and Anti-Counterfeit Activities page 27).

International standards development

International Organization for Standardization (ISO)

For several years, the EDQM has been actively participating in the development of a group of five ISO standards that are intended to harmonise the Identification of Medicinal Products (IDMP) from a regulatory perspective. This work has been carried out by Working Group 6 of ISO Technical Committee 215. The EDQM has provided particular expertise in the preparation of ISO standard 11239, related to the preparation of controlled vocabularies for pharmaceutical dosage forms, routes of administration, units of presentation and packaging, and this included acting as the editor for the standard.

In October 2012, these five IDMP standards were published as official International Standards, marking a significant milestone in the IDMP project.

In addition to the work within ISO, the EDQM has been participating in the drafting of an IDMP implementation guide with the M5 expert working group of the International Conference on Harmonisation (of Technical Requirements for Registration of Pharmaceuticals for Human Use) (ICH), where the IDMP project first originated. Here, also, the EDQM acted as the editor for the module relating to ISO standard 11239.

Regular teleconferences were held throughout the year, as well as face-to-face meetings in the US and Japan, where collaboration was fostered between regulators and industry representatives from across the globe, in particular with the ICH members (Europe, US, Japan) and observers (Switzerland, Canada). A training session at the FDA premises in Washington, DC, took place in March 2012, during which speakers from the EDQM, the EMA and the US FDA provided progress reports on the development of standards and on the implementation guide for the benefit of attendees from regulatory agencies and industry across the US.

International Conference on Harmonization (ICH)

The existing (ICH) Q3A guideline classifies impurities as organic, inorganic, and residual solvents. Q3A and Q3B guidelines address the requirements for organic impurities, while Q3C addresses those for residual solvents. A new

guideline, Q3D, is under development to provide similar clarification for the requirements for metals, which are included in the ICH inorganic impurities classification. During 2012, the EDQM contributed to the development of a draft version of Q3D, which will undergo public enquiry during 2013 with a view to having a finalised guideline in 2014.

The extensive experience of the EDQM's inspectors in GMP inspections of API manufacturers was acknowledged by the invitation from the ICH steering committee to participate as an observer in the discussions of the ICH Q7 implementation working group

Conferences and workshops

Information on international conferences and workshops organised by the EDQM or in which the EDQM participated is provided in section 2.3 Communication and Landmark events page 34.

List of EDQM committees

THE EUROPEAN PHARMACOPOEIA COMMISSION

The Commission was set up in 1964 in accordance with the Convention on the Elaboration of a European Pharmacopoeia. Following the ratification of the Convention by the Ukraine in December 2012, its membership now comprises 38 signatory parties to the Convention (37 states and the European Union). The 24 observers from all over the world highlight the importance of the work of the European Pharmacopoeia Commission at international level. The Commission sets out the work programme and adopts the quality standards for all medicines and their components on the territories of member states. Nineteen permanent groups of experts and 54 “*ad hoc*” working parties established by the Commission carry out the Ph. Eur. work programme. By the end of 2012, 2,569 texts containing quality standards have been elaborated, adopted and implemented. These texts are constantly being revised to keep pace with technical and scientific progress in the development, production and quality control of medicines. The European Pharmacopoeia, which is now in its 7th Edition, is essential to the protection of public health. It is intended for professionals working in the area of medicines, who constantly refer to it.

THE BIOLOGICAL STANDARDISATION PROGRAMME (BSP) Steering Committee

The BSP focuses on the standardisation of the methods and tools for the quality control of biologicals by establishing reference standards and validating new methods; in particular, such methods where the use of animals is reduced, refined or replaced (3Rs initiative). These activities are supervised by the BSP Steering Committee.

NETWORK OF OFFICIAL MEDICINES CONTROL LABORATORIES (OMCL) Advisory Groups

About 35 countries have been participating in the activities of the OMCL Network since 1994; these activities are co-ordinated by the EDQM. The role of this Network is to ensure the consistent quality of medicines marketed in the member states and to contribute to the mutual recognition of the results of quality control testing of medicines by these states. Major decisions are taken by the annual plenary meetings of the OMCL Network. Advisory groups prepare and ensure the implementation of the annual work programme. There are two levels of collaboration within the network:

- general activities involving all of the member states of the Convention and the observer states. General activities cover work in the area of quality management systems, such as audits and proficiency testing studies (PTS), as well as market surveillance studies (MSS). These activities are prepared and followed by the General OMCL Advisory Group (AdGEON).

- activities restricted to the EU and the European Economic Area (EEA) concerning products with a centralised marketing authorisation (CAP), products authorised according to the mutual recognition or the decentralised procedure (MRP/DCP) and the Official Control Authority Batch Release (OCABR) system for biological products (human and veterinary). The latter activity also involves Switzerland. For the CAP and the OCABR activities, advisory groups ensure continuity of operations in the interval between the annual meetings of each specific network.

These activities involve European and national authorities. The OMCL Network also participates in investigations into fraudulent medicines.

CERTIFICATION OF SUITABILITY TO PH. EUR. MONOGRAPHS Steering Committee

The activities associated with the procedure for certification of suitability to Ph. Eur. monographs are guided by a Steering Committee and, currently, two Technical Advisory Boards (TAB). The Steering Committee is composed of representatives of European licensing authorities and inspectorates. It takes decisions on general policy, examines and comments on matters brought to its attention by the Technical Advisory Boards, adopts guidelines and the inspection programme and co-ordinates questions amongst the represented parties. It is also responsible for appointing assessors, as well as the members of the Technical Advisory Boards and their Chairs.

A network of about 80 assessors and 30 national inspectors participates in the work required for the evaluation of API quality dossiers and the inspection of manufacturing sites.

EUROPEAN COMMITTEE ON BLOOD TRANSFUSION (CD-P-TS)

This Steering Committee supervises the work of a number of individual projects and Working Groups, *e.g.* the European Database of Frozen Blood of Rare Groups, Blood Donor Management, and the *Ad-hoc* Working Groups on the “*Guide to the Preparation, Use and Quality Assurance of Blood Components*” and “*Risk behaviours having an impact on blood donor management*”.

EUROPEAN COMMITTEE ON ORGAN TRANSPLANTATION (CD-P-TO)

The Steering Committee focuses on elaborating and promoting the principle of non-commercialisation of organ donation, strengthening measures to avoid organ trafficking and elaborating high ethical, quality and safety standards in the field of organ transplantation. The members and observers of this Committee represent 41 countries from Europe and beyond. It supervises the activities of a number of individual projects on topics such as living donation, transplantation on

non-residents, multiple listing on transplantation waiting lists, autologous cord blood banks and co-operation of States from the Black Sea Area in organ transplantation.

EUROPEAN COMMITTEE ON PHARMACEUTICALS AND PHARMACEUTICAL CARE (CD-P-PH)

This Steering Committee supervises the programmes of activities of its subordinate committees:

- Committee of Experts on the Classification of Medicines as Regards their Supply (CD-P-PH/PHO).
- Committee of Experts on Quality and Safety Standards for Pharmaceutical Practices and Pharmaceutical Care (CD-P-PH/PC).
- Committee of Experts on Minimising Public Health Risks Posed by Counterfeiting of Medical Products and Related Crimes (CD-P-PH/CMED).

CONSUMER HEALTH PROTECTION COMMITTEE (CD-P-SC)

The CD-P-SC is responsible for managing the work programme and decision-making process in the areas of cosmetics and packaging for food and medicines. Health

authorities in the 31 European countries that signed the Convention on the Elaboration of a European Pharmacopoeia are eligible to contribute to the work, as well as four observers (Armenia, Georgia, Moldova and Singapore).

The Committee has two subordinate bodies that examine health-related issues and evaluate their risks, and they draft reports and recommendations for regulatory approaches:

- Committee of Experts on Packaging Materials for Food and Pharmaceutical Products (P-SC-EMB). The P-SC-EMB has working groups dedicated to release and migration testing of metals and alloys, paper and board and printing inks.
- Committee of Experts on Cosmetic Products (P-SC-COS). The P-SC-COS co-ordinates the work of the network of Official Cosmetics Control Laboratories (OCCL). Quality management, analytical methodology and mutual recognition are focus areas of this network. Proficiency studies and market surveillance studies are organised with the aim of improving the quality of cosmetic products on the market. To this end, the OCCL interacts with the national market surveillance authorities, the European Commission (EC) and the Joint Research Centre (JRC).

Besides cosmetics, the P-SC-COS also has a working group that addresses health issues related to tattoos and permanent make-up.



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