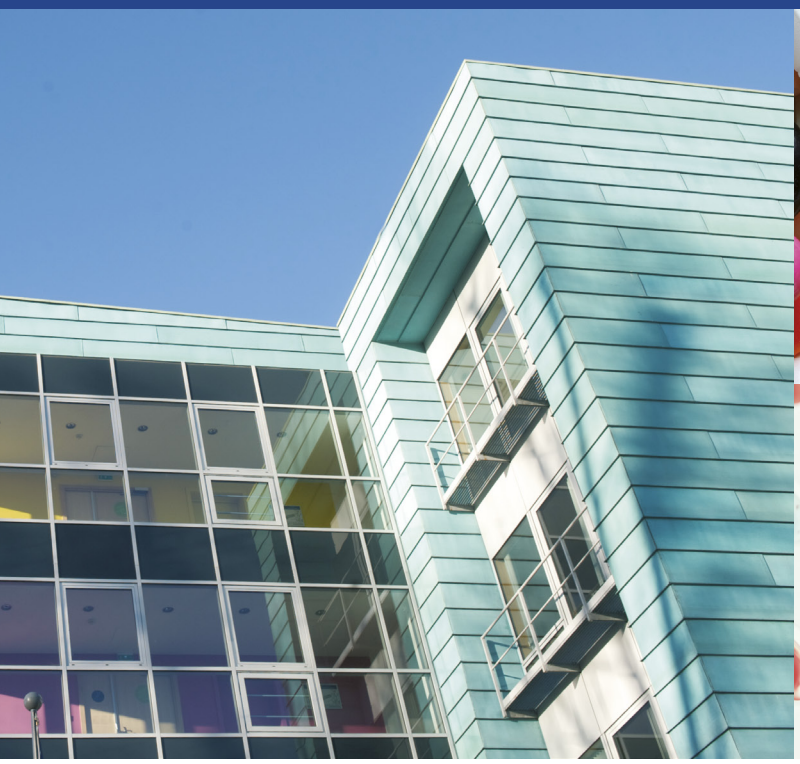
ANNUAL REPORT 2013



edqm
European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé

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ANNUAL REPORT 2013

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

Council of Europe, EDQM

French edition

Rapport annuel 2013

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Photos
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Layout and cover design:
Documents and publications production Department (SPDP), Council of Europe

Published by the Council of Europe
F-67075 Strasbourg Cedex
www.coe.int

Printed at the Council of Europe

Contents

FOREWORD	**5**
THE EDQM AT A GLANCE: VALUES, AIMS, ACTIVITIES	7
CORE ACTIVITIES	**9**
The European Pharmacopoeia	9
Pharmaceutical Reference Standards	16
Certification of suitability to the Ph. Eur. monographs	18
The European Network of Official Medicines Control Laboratories (OMCL Network)	20
Blood Transfusion	27
Organ, Tissue and Cell Transplantation	31
Pharmaceuticals and Pharmaceutical Care	35
Anti-counterfeiting Activities	36
Cosmetics and Food Contact Materials	39
LIST OF COMMITTEES COORDINATED BY THE EDQM	**41**

Foreword

by Susanne Keitel, Director

As every year, the annual report provides an opportunity to review the activities of the past 12 months, to reflect on developments and achievements.

For the EDQM, the year 2013 was a year of challenges and opportunities. The 8th edition of the European Pharmacopoeia (Ph. Eur.) was published in July 2013, covering more than 2500 monographs and general texts. The Ph. Eur. Commission elected a new chair, Dr Jean-Louis Robert, Luxembourg, in June 2013, and adopted its priorities for the next triennium. Ukraine became the 38th member of the Ph. Eur. in March 2013, and the Taiwan Food and Drug Administration (TFDA) was granted observer status in November, emphasising the global outreach of the activity. Overall, 30 new monographs were adopted and almost 200 texts revised, some of which to further facilitate the implementation of enhanced approaches to quality control in the context of the "quality by design"-principle or to promote the reduction, refinement and replacement of animal testing (3Rs). Developing standards and recommendations in the field of biopharmaceutical and advanced therapy products was also high on the Commission's agenda with, e.g., the creation of two new working parties dedicated to the elaboration of general texts and recommendations on raw materials for the production of cell and gene therapy products and kits or test methods for the detection and quantification of host cell-derived proteins. The Ph. Eur., represented by the EDQM, continued to play an active role in pharmacopoeial harmonisation beyond Europe, both in the Pharmacopoeial Discussion Group (PDG) and the WHO initiative related to the development of harmonised approaches towards monograph development ("Good Pharmacopoeial Practices").

The portfolio of reference standards necessary to apply the monographs of the Ph. Eur. was further extended to match developments related to new and revised monographs. In addition, international standards for antibiotics (ISA) and international chemical reference standards (ICRS) required for the application of the International Pharmacopoeia, the responsibility for whose establishment, monitoring and distribution the WHO has entrusted to the EDQM, were made available to users throughout the year.

While the number of new applications received in the Certification of suitability to the monographs of the Ph. Eur. (CEP) procedure slightly decreased compared to 2012, the number of requests for revisions increased. The international interest in the procedure was demonstrated by a visit from expert assessors from ANVISA, the Brazilian regulatory authority, who wished to be trained in the assessment and use of certificates of suitability. Requests from other non-European authorities have been received and respective study visits will continue to be organised in 2014/15. The added value of the CEP procedure for regulatory authorities continued to be discussed in the context of the International Generic Drug Regulators' Pilot (IGDRP), an informal work-sharing initiative which brings together regulators from different continents, e.g. Australia, Brazil, Canada, Chinese Taipei, EU, Singapore, South Africa and Switzerland.

The European Network of Official Medicines Control Laboratories (OMCL Network), the main goal of which is to share know-how, ensure access to state-of-the-art technology, and to work-share and mutually recognise test results based on commonly agreed procedures and guidelines, continued a number of activities initiated in the past few years, for example new programmes for testing falsified and other illegal medicines, the testing of unlicensed pharmaceutical preparations and quality control of active pharmaceutical ingredients on the European market as well as conducting collaborative studies in the field of gene therapy product testing and establishing guidance documents for stock-piled medicines. The activities of the Network, which are co-funded by the European Commission, are an essential contribution to ensuring the quality of medicines on the market while making best use of member States' resources. In the context of the Network's quality management programme, mutual joint audits and visits were carried out, a number of them in the context of requests for (associate) membership in the Network received from the OMCLs of the Former Yugoslav Republic of Macedonia, Belarus, Israel and Singapore. The increasing number of non-European countries requesting to join the OMCL Network demonstrates the interest and added value of this activity.

In the field of blood transfusion, the 17th edition of the *"Guide to the Preparation, Use and Quality Assurance of Blood Components"* was published, complemented by the *"Good Practices Guidelines for Blood Establishments and Hospital Blood Banks required to comply with EU Directive 2005/62/EC",* the drafting of which was co-funded by the European Commission. In the context of the Blood Quality Management Programme established in 2012, 4 Blood Mutual Joint Visits were carried out. The programme aims at proposing common tools enabling European blood establishments to develop, implement, assess, maintain and improve their Quality Management System on a harmonised basis. As regards activities related to organ, tissue and cell transplantation, the 5th edition of the *"Guide to the Quality and Safety of Organs for Transplantation"* and the 1st edition of the *"Guide to the Quality and Safety of Tissues and Cells for Human Application"* were published; in addition, a Council of Europe resolution *"on establishing procedures for the collection and dissemination of data on transplantation activities outside a domestic transplantation system"* was adopted by the Committee of Ministers.

Of the different activities related to pharmaceutical care, the launch of a project to develop additional pharmaceutical care indicators is most noteworthy. Results of this study, which includes outcome- and patient-oriented indicators covering healthcare delivery by professionals, are expected in 2014. Information provided through these indicators will be of practical use for policy-makers and professional associations in standard-setting. 2013 saw also the approval of a project to elaborate a harmonised "European Formulary for Paediatric Formulations" under the auspices of the European Committee for Pharmaceuticals and Pharmaceutical Care, in close collaboration with the Ph. Eur. Commission. The aim of this project is to review existing formulations for non-licensed paediatric medicines used in member States in accordance with current quality and safety requirements to provide adequate standards for medicines used in the treatment of the paediatric population for which no licensed alternative exists.

Anti-counterfeiting activities focussed predominantly on the promotion of the MEDICRIME convention and the "single points of contact" (SPOCs) network beyond Europe, the further development of eTACT, the EDQM's anti-counterfeiting traceability service for medicines and the API Fingerprint Programme, developed in close collaboration with the OMCL network.

Work to control the quality of cosmetic products continued through the European network of national official cosmetics control laboratories (OCCL), established in 2010 based on the successful model of the OMCL network. In the field of food packaging materials and articles for food contact, a resolution on *"metals and alloys used in food contact materials and articles"* was adopted by the Committee of Ministers.

As in previous years, the EDQM underwent a thorough audit by Afnor, the French certification body, to maintain its ISO 9001:2008 certification. In addition, following the successful audit, its scope was extended to cover the conduct of laboratory studies. In May 2013, the EDQM laboratory received the official ISO/IEC 17025/2005 accreditation from the Belgian accreditation body BELAC, based on an audit performed in December 2012. This certificate demonstrates that the laboratory operates an adequate quality management system, is technically competent and is able to generate technically valid results.

Overall, 2013 was another successful year for the EDQM and I would like to take the opportunity to sincerely thank the numerous experts appointed by the 37 member states of the Ph. Eur and its observers for their support and dedication. Their expertise and enthusiasm are crucial for the work of the Ph. Eur. Commission and its Groups of Experts and Working Parties, the Committees and Expert Groups in the areas of Blood Transfusion, Organ, Cell and Tissue Transplantation, Pharmaceuticals and Pharmaceutical Care, Consumer Health Protection, the OMCL Network and the Certification Scheme.

The EDQM at a glance:
Values, aims, activities

The European Directorate for the Quality of Medicines & HealthCare (EDQM): 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 continent, ensuring respect for its fundamental values: human rights, democracy and the 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, the Council of Europe works to find shared solutions to major problems such as terrorism, organised crime and corruption, cybercrime, bioethics and cloning, violence against children and women, protection of public health and trafficking in human beings. Cooperation between all member states is the only way to solve the major problems facing society today.

Our mission

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 on the Elaboration of a European Pharmacopoeia" and beyond;
- ensuring the application of these official standards to substances used for the production of medicines;
- coordinating a network of Official Medicines Control Laboratories (OMCLs) to collaborate and share expertise between member states and to effectively use limited resources;
- proposing ethical, safety and quality standards:
  - for the collection, preparation, storage, distribution and appropriate use of blood components in blood transfusion;
  - for the transplantation of organs, tissues and cells;

- collaborating with national, European and international organisations in efforts to combat counterfeiting/falsification of medical products and similar crimes;
- providing policies and model approaches for the safe use of medicines in Europe, including guidelines on pharmaceutical care;

  and by
- establishing standards and coordinating controls for cosmetics and food packaging.

Our evolution

The origins of the EDQM date back to 1964, when the Convention on the Elaboration of a European Pharmacopoeia was signed by eight member states of the Council of Europe with the vision of creating a common European Pharmacopoeia. The "European Pharmacopoeia Secretariat" was set up pursuant to Article 9 of the Convention, and over the years it has become a directorate of the Council of Europe, with successive name changes reflecting the new missions assigned to it. In 2013 the EDQM employed 300 staff and was structured in nine administrative entities.

Contributing to the protection of public health

The EDQM protects public health with quality standards for medicines and recommendations for their safe use. To protect occupational health and the environment, the EDQM avoids the use of substances of very high concern whenever possible (e.g. notably within the framework of the REACH programme and the ozone-depleting substances regulations).

In 2013 the EDQM reinforced risk mitigation measures where the distribution of hazardous substances is unavoidable by issuing all Safety Data Sheets in CLP (hazard pictograms and signal words) format and publishing them in 26 European languages for the substances considered hazardous.

Continual investment in sustaining EDQM's quality system

The EDQM is ISO-certified for a number of its activities. After a comprehensive three-day certification audit, AFNOR Certification (AFAQ), the French accreditation body, decided in December 2013 to renew and extend the scope of the EDQM's ISO 9001 certificate to the conducting of laboratory studies.

The EDQM is certified as meeting the requirements of ISO 9001: 2008 for the following activities:

- Evaluation of applications for certificates of suitability to the monographs of the European Pharmacopoeia (Ph. Eur.) and management of the inspection programme of manufacturing sites and associated brokers;
- Planning, implementation and coordination of post-marketing surveillance studies for medicinal products and management of related databases;
- Coordination of the elaboration and issuing of guidelines related to the OCABR procedure for the release of batches of human immunological medicinal products (blood and vaccine);
- Management of the elaboration, revision, correction and suppression of Ph. Eur. texts, their publication in printed and electronic format, as well as their distribution; and
- Conducting of laboratory studies.

The certification of compliance with ISO 9001:2008 recognises that the policies, practices and procedures of the organisation ensure consistent quality in the services and products provided to customers and stakeholders.

In April 2013, the EDQM laboratory received the official ISO/IEC 17025:2005 accreditation from the Belgian accreditation body BELAC. This certificate demonstrates that the EDQM laboratory operates a quality management system, is technically competent[1] and is able to generate technically valid results.

It covers all aspects of the laboratory management system, including sample preparation, analytical testing competence, documentation control, accommodation and environmental conditions, equipment, traceability and reporting.

With the extension of its ISO 9001 certification and the newly obtained ISO 17025 accreditation, customers and stakeholders can be confident that the EDQM is dedicated to maintaining the highest efficiency and response capacity in achieving its goal of total customer and stakeholder satisfaction.

1. Please refer to the Annex to the accreditation certificate available on the EDQM website for the complete list of accredited techniques.

Core activities

THE EUROPEAN PHARMACOPOEIA

What it is and how it works

The Ph. Eur. lays down quality standards for the manufacture and control of medicines in Europe and beyond. These quality standards – at the end of 2013 it covered some 2,240 monographs and 346 other texts – include excipients and active pharmaceutical ingredients (APIs) in both their original state and in the form of pharmaceutical preparations, and are legally binding for the 38 signatory parties to the Council of Europe's Convention on the Elaboration of a European Pharmacopoeia.[2]

Preparing the Ph. Eur. is the responsibility of the European Pharmacopoeia Commission ('the Commission'). The EDQM supports the Commission by providing the scientific secretariat; it is also responsible for establishing, producing, monitoring and distributing the reference standards needed when applying the monographs.

2. Signatory parties of the European Pharmacopoeia Convention: Austria, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Montenegro, Netherlands, Norway, Poland, Portugal, Romania, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, the former Yugoslav Republic of Macedonia, Turkey, Ukraine, United Kingdom and the European Union.

A continuous process to protect public health

All standards of the Ph. Eur. – elaborated or revised by the 20 groups of experts and by the ad hoc working parties – are adopted by consensus by the Commission. Once adopted, standards become mandatory on the same date in all member states. 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 parties to the Convention.

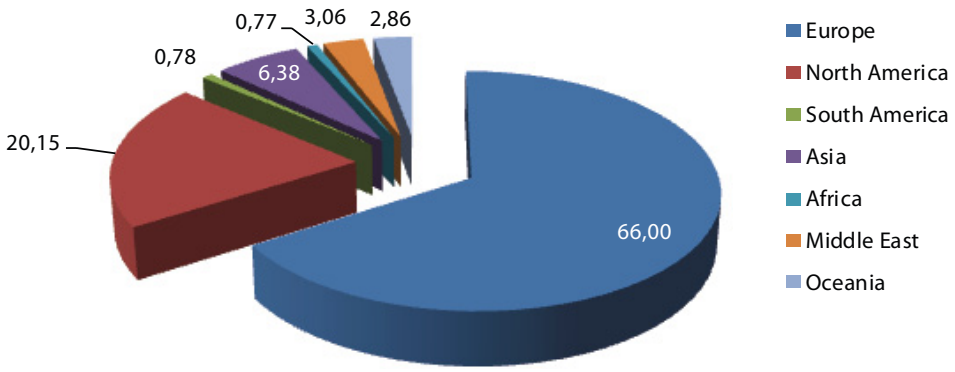
The work programme (elaboration of new monographs or general chapters, or revision of existing ones) is decided by the Commission at its three annual sessions. In general, whenever two member states express a wish to elaborate a text, the Commission adds the item to the work programme. Changes to the work programme are published on the EDQM website and in Pharmeuropa Online, which is freely accessible (see page 13).

Importance of the Ph. Eur. beyond Europe

Globalisation and expansion in international trade are creating a growing need to develop global quality standards for medicines. Standards are a vital instrument for marketing authorisations, market surveillance and free movement and trade in medicines between a number of different regions and countries.

It is therefore no surprise that the Ph. Eur. is also widely used internationally. Some non-European countries (e.g. Australia, Canada) refer to the Ph. Eur. in their national legislation as one of their official pharmacopoeias. Observers from non-member states and international organisations participate in the sessions of the Commission and in meetings of its groups of experts. In 2013 there were 26 observers (including 24 countries).

% subscriptions to the Ph. Eur. by geographical zone



Key facts and figures

Wider participation

Ukraine became the 38th member of the Ph. Eur. on 18 March 2013, when the Convention on the Elaboration of a European Pharmacopoeia came into force in that country. This ratification shows the desire of the Ukrainian authorities to participate in the development of European standards for the quality of medicines and to strengthen their collaboration with European countries in the field of medicines and healthcare. It also demonstrates the importance of the work of the Commission at international level.

At its November session, the Commission also granted observer status to the Taiwan Food and Drug Administration (TFDA). This status will allow the TFDA to participate in the scientific work of the Commission, to benefit from European experience in the field of medicinal products for human and veterinary use, to exchange with experts from European licensing authorities and inspectorates and to share the work on the development of international quality standards for medicines and the methods of analysis used.

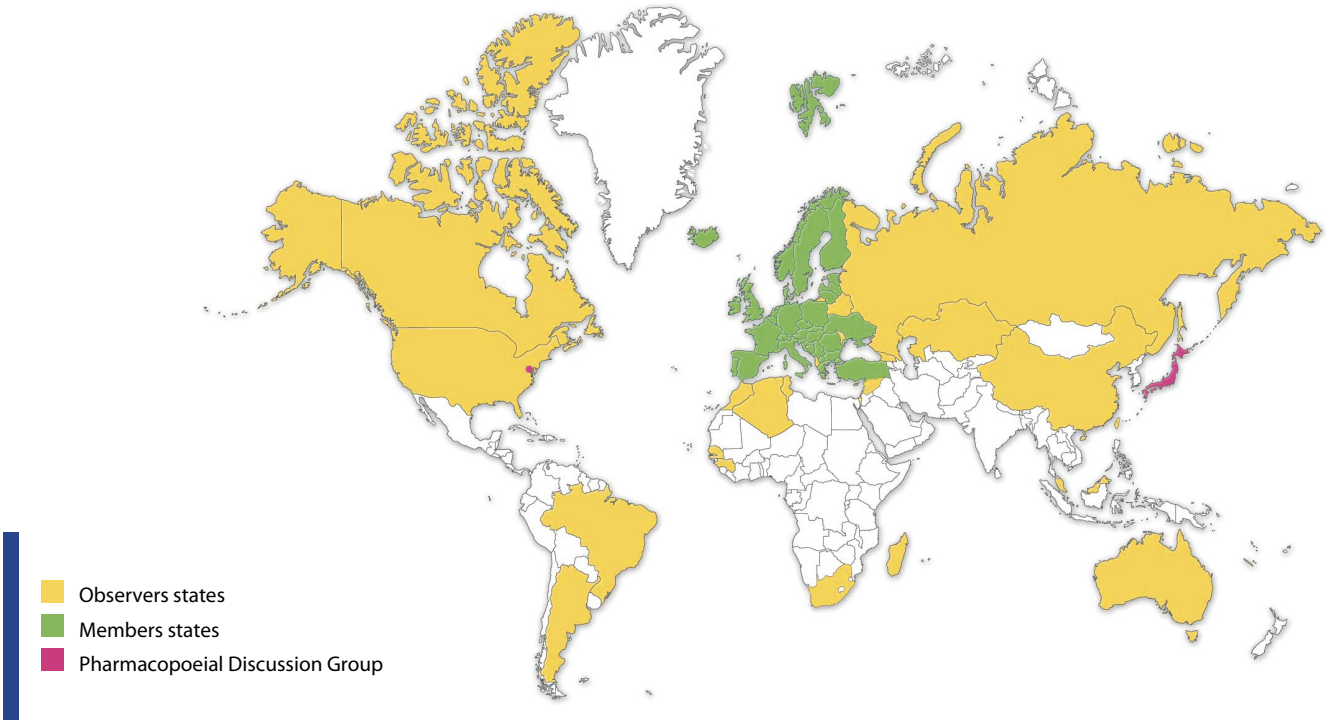
A new Chair and a new presidium elected

During its 145th session (held in March), the Commission elected Dr Jean Louis Robert as Chair for a term from June 2013 to June 2016. He becomes the 17th Chair of the European Pharmacopeia Commission since its establishment in 1964. Following the election of the new Chair, the Commission elected the first Vice-chair, Dr Tobias Gosdschan (Switzerland), and the second Vice-chair, Mr Erik Wolthers (Denmark), at its 146th session. The Presidium, which consists of the Chair and the two Vice-chairs, assisted by the Director of the EDQM and the Secretary to the Commission, supports the Commission in defining criteria for prioritising its work and in identifying a set of priorities for the next three years.

Decisions taken during the three 2013 sessions of the Commission

30 new monographs adopted

- Monographs on five active substances still under patent protection, elaborated in close collaboration with regulators and the respective innovators (P4 procedure): *Capecitabine* (2762), *Aripiprazole* (2617), *Ziprasidone mesilate trihydrate* (2649), *Vardenafil hydrochloride trihydrate* (2782) and *Human coagulation factor IX (rDNA)* (2522)



- 25 other new monographs: *Amomum fruit* (2554), *Round amomum fruit (2555), Dioscorea rhizome* (2473), *Macrogols, high-molecular-mass* (2444), *2,4-Dichlorobenzyl alcohol* (2410), *Chlormadinone acetate (2702), Quetiapine fumarate* (2541), *Brimonidine tartrate* (2760), *Esomeprazole magnesium dihydrate* (2787), *Valaciclovir hydrochloride, hydrated* (2751), *Diphtheria, tetanus and pertussis (acellular, component) vaccine (adsorbed, reduced antigen(s) content)* (2764), *Magnesium phosphoricum for homoeopathic preparations* (2505), *Agaricus phalloides for homoeopathic preparations* (2290), *Agnus castus fruit dry extract* (2309), *Glucosamine sulfate potassium chloride* (2708), *Homoeopathic pillules, coated (2786), Human normal immunoglobulin for subcutaneous administration* (2788), *Ignatia for homoeopathic preparations* (2513), *Meldonium dihydrate (2624), Methane* (2413), *Nettle root* (2538), *Nux vomica for homoeopathic preparations* (2514), *Pullulan* (2603), *Sulfadimethoxine* (2741) *and Sulfadimethoxine sodium for veterinary use* (2745).

2 new general chapters

- A new general chapter on *"Names of herbal drugs used in traditional Chinese medicine"* (5.22); Chinese names (in pinyin and sinograms) of the herbal drugs that are the subject of a monograph will be published for transparency in this information chapter. This chapter will be supplemented each time a new monograph on a herbal drug used in traditional Chinese medicine is adopted.
- A new general chapter on *"Carrier proteins for the production of conjugated polysaccharide vaccines for human use"* (5.2.11).

198 revised texts

A total of 184 monographs and 14 general chapters were revised, including:

- A revised version of chapter *"Pharmacopoeial harmonisation"* (5.8). This chapter was updated to include the harmonisation status of monographs in order to provide information to users on the degree of harmonisation reached between the Ph. Eur., the United States Pharmacopoeia (USP) and the Japanese Pharmacopoeia (JP) for the monographs listed in this chapter.
- A revised version of the *General Notices,* which takes note of the finalised European Medicine Agency (EMA) Guideline on Real-Time Release Testing and is aimed at encouraging the use of enhanced approaches to quality control utilising process analytical technology (PAT) and/or real-time release testing (including parametric release) strategies. Regarding the 3Rs concept (reduction, refinement and replacement of animal testing), new provisions for additional systems monitoring the consistency of production with the intention to reduce (and ultimately replace) animal testing have also been added.

General matters and policies

Developments and priorities in 2013

In order to remain useful and state-of-the-art, a pharmacopoeia needs to be constantly updated. Revisions take account of scientific and technical advances, legal and regulatory developments, the increasing demand for generic and biosimilar products, new risks to public health and the globalisation of trade and commerce. Current developments of the Ph. Eur. include:

- Continuous efforts in the field of impurities. EDQM actively contributed as an observer to the development of the ICH Q3D Guideline for Elemental Impurities, the draft of which reached Step 2b in July 2013 and is now in its consultation period (Step 3). This is expected to be finalised and approved during 2014. At the same time, the Ph. Eur. general chapter on *Metal catalyst or metal reagent residues* (5.20) and the chapter on *Heavy metals* (2.4.8.) are undergoing extensive revision.
- Modernisation of quality standards: the review and revision of existing texts to take into account needs arising from Process Analytical Technology (PAT), Real-time release testing (RTRT) or Quality by Design (QbD) concepts.
- Drafting and revision of general chapters in the field of chemometrics, ie modelling of analytical data (e.g. multivariate data analysis, data mining, chemical imaging etc.) and of measurement techniques relying extensively on analytical data modelling (NIR, RAMAN) or other vibrational spectroscopies.
- Review and revision of the monograph on *Water for injections* (WFI) (169) to consider allowing non-distillation technologies for the production of water for injections in addition to distillation.
- Evaluation of the pilot phase on Finished Product monographs.
- Extension of the P4Bio pilot phase for biological substances still under patent protection to cover additional types of products.
- Establishment of finished product monographs for biopharmaceutical substances, where appropriate and considering quality characteristics as well as clinical properties of the products.
- Elaboration of a general text on raw materials for the production of cellular and gene transfer products including antibodies, basal media (for cell culture), serum/serum replacements, growth factors and cytokines.
- Elaboration of a recommendation with regard to the development, validation and use of in-house or commercial kits or test methods for the detection and quantification of host cell-derived proteins.
- Continuous revision of pharmacopoeial texts to implement the 3Rs concept (replacement, refinement and reduction of animal testing) in line with EU Directive 2010/63/EU of 22 September 2010 on the protection of animals used for scientific purposes

Achievements of the Biological Standardisation Programme (BSP)

The BSP, a joint effort with the EU Commission, pursues the following goals in the area of standardisation of biologicals: establishing biological reference materials; developing and validating new analytical methods; and validating alternative methods based on the 3Rs concept.

Since the start of the programme in 1992, 131 BSP projects have been initiated. In 2013, 21 projects were pursued in different fields:

- Vaccines for human use: 6 projects
- Vaccines for veterinary use: 3 projects
- Plasma-derived products: 9 projects
- Biotechnology products: 3 projects

Five projects – all in the field of vaccines for human and veterinary use – were devoted to establishing alternatives to animal experiments, one project to developing a new or improved assay and 15 projects to establishing reference materials for biologicals.

This led to the establishment of one new reference standard (for hepatitis B immunoglobulin) and four reference standard replacement batches (for oral poliomyelitis vaccine, prekallikrein in human albumin, immunoglobulin for electrophoresis and heparin sodium) *(see page 17)*. Ten projects were under way in 2013 to establish replacement batches for existing reference standards. All of these projects were necessitated by low stocks; there was no case of the use of a reference standard having to be stopped owing to quality issues.

The strong efforts to apply the 3Rs concept to the field of quality control of biologicals continued in 2013. The efforts of the EDQM and the BSP in particular to elaborate, validate and implement 3R methods are widely acknowledged. A new project was started up to replace the Minimal Lethal Dose (MLD) and the Total Combining Power (TCP) antigenicity test in mice required by the Ph. Eur. for clostridium septicum vaccines for veterinary use in the context of the potency assay. This project is being run jointly by the EDQM and the European Partnership for Alternative Approaches to Animal Testing (EPAA) – a high-level initiative by the EU Commission and industry. If the study has a successful outcome, this approach could also be used for other clostridial vaccines.

In another project aimed at replacing the histamine sensitisation test (used for testing for the presence of residual pertussis toxin in acellular pertussis vaccines), the BSP is working with an international group of scientists from Europe and North America representing governmental laboratories as well as vaccine manufacturers. This group is scrutinising several potential replacement tests with the goal of selecting the best candidate for further validation and inclusion in the compendial texts. First results are expected in 2014.

International harmonisation and the Pharmacopoeial Discussion Group

Two meetings of the Pharmacopoeial Discussion Group (PDG) – comprising the Ph. Eur., the Japanese Pharmacopoeia (JP) and the United States Pharmacopoeia (USP) as members and the World Health Organization (WHO) as an observer – were held in 2013; one was hosted by the EDQM in Strasbourg (France) in June, and the other by the JP in Tokyo (Japan) in November.

Currently, 28 of the 35 General Chapters and 45 of the 62 excipient monographs on the work programme have been harmonised. Sign-offs at these meetings included the two new excipient monographs, *Isomalt* (1531) and *Hydroxypropylcellulose* (337) as well as a revised general chapter "*Bulk density and tapped density of powders*" (2.9.34). Excipient sign-offs included revisions to the monographs on *Sodium Chloride* (193), *Rice Starch* (349), *Saccharin* (947) and *Sodium starch glycolate (types A and B)* (0983-0984). There was in-depth discussion on 20 additional items currently on the work programme with a view to resolving outstanding issues.

The PDG completed its work activities in relation to the ICH Q4B Annex for Uniformity of Dosage Units by signing off on a correction to clearly identify local European Pharmacopoeia text pertaining to semi-solid products and the possibility of using Mass Variation testing, based on validation data. This enabled the ICH Q4B Expert Working Group (EWG) to complete its timely sign-off to the Q4B Annex.

Further harmonisation initiatives

The Ph. Eur. is also actively involved in a number of other international harmonisation initiatives, such as the WHO initiative to draft "Good Pharmacopoeial Practices", which may serve as a basis for future work-sharing and collaboration between the pharmacopoeias of the world.

The Second International Meeting of World Pharmacopoeias, a meeting to which all the pharmacopoeias and pharmacopoeial secretariats known to the WHO were invited, took place in April 2013 in New Delhi (India) under the auspices of the WHO, with the aim of bringing together the different pharmacopoeias and discussing potential ways to strengthen collaboration and harmonisation, including the elaboration of "Good Pharmacopoeial Practices".

Publications, databases and websites

The 8th Edition of the European Pharmacopoeia including its 2013 updates (8.1 and 8.2) contains 2,240 monographs, including general standards that apply to groups of ingredients or dosage forms, and 346 general texts including methods of analysis.

To further facilitate access to the texts, an additional version adapted for tablet computers was made available online. This version is a complement to the online version and allows optimised access for smartphones and tablet computers.

Publication of draft versions of monographs in Pharmeuropa Online has made it possible for a large number of interested parties to consult these texts. Pharmeuropa, the Ph. Eur. forum, is paperless and freely available online in order to optimise interaction between the Commission and its stakeholders, to allow users to have more time to comment on drafts, and to ensure greater access for stakeholders worldwide. Texts are published on an ongoing basis, but the principle of four comment deadlines per year has remained unchanged, as have channels and procedures for providing comments to published draft texts.

A new EDQM Store was launched in May for the sale of publications online, which allows better integration with the EDQM Enterprise Resource Planning (ERP) system. More than 4,500 customer accounts were created and about 6,000 orders were received through the new online store in 2013.

Communication with partners and stakeholders

The Ph. Eur. is an integral part of the regulatory control system for the quality of medicines. To remain useful it has to be adapted to the needs of its users, notably the experts dealing with applications for marketing authorisation (prepared by the manufacturers and assessed by the competent authorities). Unlike licensing dossiers, which are prepared and assessed for an individual product, the Ph. Eur. is the indispensable communication and standardisation tool that allows a uniform standard to be applied. This tool continues to serve its users only if they make their opinions or needs for adaptation known – therefore, collaboration with competent authorities and with manufacturers and industries is crucial.

Cooperation with national and European regulatory authorities

The Commission works in close collaboration with national competent authorities and the European Medicines Agency (EMA). This cooperation is crucial to ensuring continued consistency between the approaches of licensing authorities and the Ph. Eur. Hence, EMA scientific guidelines and Ph. Eur. monographs and chapters are complementary instruments for ensuring the quality of medicinal products:

- The Ph. Eur. sets legally binding standardised specifications for pharmaceutical preparations, their constituents and containers.
- EMA guidelines provide advice on the best or most appropriate way to fulfil legal obligations.

Members of EMA working groups (ie for which the EMA is providing the Secretariat) or of the EMA Secretariat itself are observers to some of the Commission's groups of experts and working parties.

Likewise, the EDQM has observer status with a number of EMA bodies, e.g. the Committee for Advanced Therapies (CAT), the Herbal Medicinal Products Committee (HMPC), the joint CHMP/CVMP Quality Working Party (QWP), the Biologics Working Party (BWP) and the Immunologicals Working Party (IWP).

In addition, representatives of national authorities are members of the Ph. Eur. Commission and its groups.

Specific collaboration with EMA

The monograph on *Water for Injections* (169): A revision process has been initiated for the Commission to consider allowing non-distillation technologies for the production of *Water for Injections* in addition to distillation. The revision process is being conducted in close collaboration with the GMP/GDP Inspectors Working Group and the Joint CHMP/CVMP QWP of the European Medicines Agency.

Raw materials used in the production of cell-based and gene therapy products: Currently, a large number of these raw materials are only available in research or *in-vitro* grades, and information on the exact composition or traceability is often not readily available. While only a limited number of such advanced therapy products are authorised in Europe at present, many more are under development. Harmonised quality standards for the raw materials used in their production will facilitate their development and are essential to ensuring their quality and safety.

National authorities and the EMA are also participating in the work of the Ph. Eur. by submitting requests for revisions and reviewing draft texts published in Pharmeuropa Online.

Communication with National Pharmacopoeia Authorities (NPAs)

The process of monograph development is undertaken mainly at European level, with member states contributing resources to this collaborative process rather than developing national standards. This results in a substantial saving of resources and there is no subsequent need to harmonise national positions.

The EDQM organises an annual meeting of Secretaries of NPAs to facilitate and coordinate activities of common interest and to provide an informal forum for exchanging information. The 2013 annual meeting of the NPAs of Ph. Eur. member states took place in Oslo (Norway) in April 2013, hosted by the Norwegian Medicines Agency (Statens legemiddelverk, NoMA). Twenty-three of the 37 member states participated in this event. The participating NPAs held in-depth discussion on the terms of reference of all Ph. Eur. groups. They shared best practices for identifying and nominating experts and regarding how the work of these groups is followed by NPAs generally. The NPAs also discussed the Ph. Eur. position on the WHO's "Good Pharmacopoeial Practices" initiative.

Cooperation with manufacturers and industry

Involvement of manufacturers and industry in the elaboration or revision of Ph. Eur. texts is essential to ensure their relevance. Upon nomination by NPAs, representatives of manufacturers and industry can be members of the Groups of Experts and Working Parties; they can also be members of national delegations to the Commission.

Another way to participate in the work of the Ph. Eur. is by submitting draft texts, requests for revision (e.g. impurity profile) providing data, samples etc. and/or by commenting on draft texts published in Pharmeuropa Online.

In addition, the EDQM holds annual bilateral meetings with Industry associations to promote exchange on all aspects related to the work of the EDQM. In 2013, consultations/meetings were organised with AESGP, APIC/CEFIC and EFPIA.

The EDQM also continues to collaborate and participate in a number of WHO meetings and consultations including; the International Nonproprietary Names (INN), the Expert Committee on Biological Standardisation (ECBS), and the Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP).

Events

2013 was dedicated to promoting the new 8th Edition of European Pharmacopoeia.

The EDQM organised two training sessions on the Ph. Eur. 8th Edition, in July in Strasbourg (France) and in December in Vienna (Austria). The programme was designed to enable participants to expand their knowledge and familiarise themselves with the work and procedures of the Ph. Eur..

In February 2013, the EDQM organised a symposium on Bluetongue Vaccines (BTV). The aim of this symposium was to reflect on the lessons learned from past experiences, the challenges that still remain and the desirability and feasibility of drafting a monograph for BTV inactivated vaccines. The symposium gave the participants a good overview of the complexity of the disease and an update on the latest scientific and regulatory developments.

In April 2013, the EDQM, with the support of the EMA, held a symposium on raw materials used in the production of cell-based and gene therapy products. The symposium discussed the quality standards needed for such materials and focused on the availability of suitable information on their quality. The outcome of this symposium was also crucial for the working party in charge of drafting such a chapter to better understand the needs and constraints of users.

In November 2013, the EDQM and the State Administration of Traditional Chinese Medicine of the People's Republic of China (SATCM) jointly organised a symposium on Traditional Chinese Medicines (TCMs) in Strasbourg, France. Recognising the growing importance of TCMs worldwide, the aim of the symposium was to intensify the collaboration and exchanges between experts from Europe and China and to receive feedback from stakeholders on the use of Ph. Eur. TCM monographs.

Later in November 2013, the EMA, with the support of the EDQM, held a workshop on the characterisation of new clotting factor concentrates. The workshop discussed potency assays used for labelling and testing of post-infusion samples for new clotting factor VIII and IX concentrates, which will be used to treat Haemophilia A1 and B2. At present, a number of clotting factor products are authorised in Europe. However, many new-generation recombinant products are in the late stages of development and it was felt that a more harmonised approach to assigning potency to these clotting factor concentrates was required.

Official visits

In June 2013, the EDQM met with a delegation from the Taiwan Food and Drug Administration (TFDA). The visit focused on the different activities of the EDQM, their impact and achievements, and the possibilities for future cooperation between the two organisations. In December 2013, the Commission granted observer status to the TFDA.

In September 2013, the EDQM met with the Chinese National Institutes for Food and Drug Control (NIFDC). Topics discussed included an overview of Ph. Eur. activities in the field of TCMs and reference standards and ways to further strengthen collaboration in the area of quality control and standardisation of medicines. The EDQM's laboratory and reference standards production facilities were also visited.

PHARMACEUTICAL REFERENCE STANDARDS

Why have reference standards?

Official reference standards (RSs) are an essential component of most texts of the Ph. Eur. They include chemical reference substances (CRSs), herbal reference standards (HRSs), biological reference preparations (BRPs) and reference spectra. They are officially adopted by the Commission and are the sole authority in case of arbitration. The current Ph. Eur. RS catalogue consists of almost 2,600 articles, which are made available by the EDQM.

Management of the portfolio includes adding new RSs relating to new or revised monographs and texts to the catalogue. It also includes the replacement of existing batches when the corresponding stock is running low. However, establishing RS is only one of the activities. The lifecycle management of RSs encompasses a variety of other activities, such as procurement of candidate materials, classification, characterisation, manufacturing, labelling, quality control, release, storage, distribution and monitoring.

Responsibility for WHO standards

In May 2006 the EDQM took over responsibility for the establishment, storage and distribution of WHO International Standards for Antibiotics (ISAs). ISAs are essential for the standardisation and quality control of antibiotic drug substances and pharmaceutical drug products. They are supplied for use in microbiological assays performed for quality control.

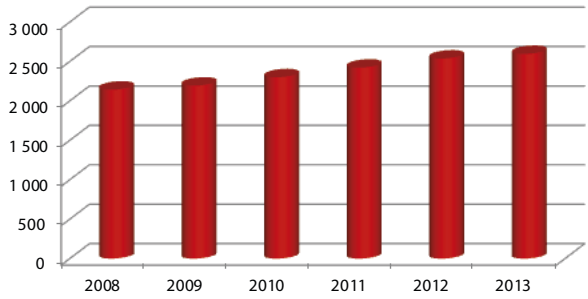
Since 2010, the EDQM has also been responsible for the establishment, monitoring and distribution of the WHO International Chemical Reference Substances (ICRSs); these RSs are prescribed by the International Pharmacopoeia, which is published by the WHO and used worldwide.

Key facts and figures

Reference standards for the Ph. Eur.

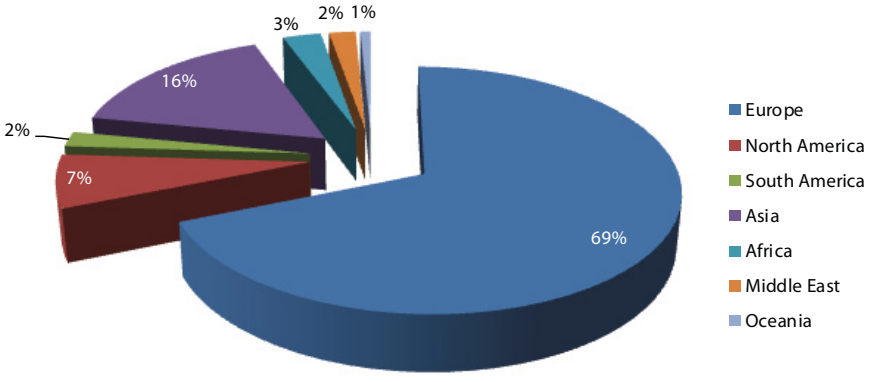
The Ph. Eur. catalogue, at the end of 2013, included 2,569 reference standards.

Growth of the CRS portfolio



The Ph. Eur. RSs are widely used internationally as a result of the globalisation of pharmaceutical trade. In 2013, the Ph. Eur. RSs were distributed in 106 countries – a far broader geographical scope than the countries that have ratified the European Pharmacopoeia Convention.

Ph. Eur. vials distributed by geographical area



New RSs and BRPs

In 2013, the Commission adopted 80 batches of new RSs (including a reference material for equipment verification) and 220 replacement batches; 44 assay RSs have been established, 18 of which required a collaborative study.

The international collaborative studies performed by the BSP in 2013 led to the adoption of five BRPs by the Commission (*see page 12*):

- Four replacement batches: Oral Poliomyelitis Vaccine BRP (batch 4), Prekallikrein Activator in Albumin BRP (batch 4), Immunoglobulin for electrophoresis BRP (batch 3) and Heparin Sodium BRP (batch 4).

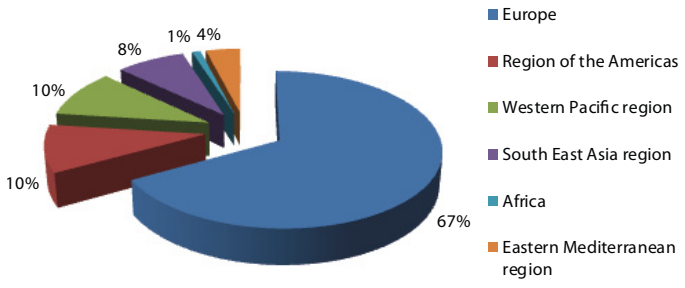
  In case of the Heparin Sodium BRP (batch 4), the current BRP batch 3 which was calibrated for the sheep blood clotting assay according to the current version of chapter 2.7.5. of the Ph. Eur. was re-calibrated for use in the more specific anti-IIa/anti-Xa assays. This new test will replace the clotting assay in chapter 2.7.5. as of supplement 8.3. of the Ph. Eur.
- One new BRP: Human Hepatitis B Immunoglobulin (batch 1), which will be used for the assay of human hepatitis B immunoglobulin preparations by ELISA.

EDQM activities for the WHO

International Chemical Reference Standards (ICRSs)

A total of 13 establishment reports were adopted by the ICRS Board: Biperiden HCl ICRS 1; Cytarabine ICRS 1; Timolol maleate ICRS 1; Valproic acid ICRS 1; Amiloride HCl ICRS 1; Dextromethorphan hydrobromide ICRS 1; Quinidine sulfate ICRS 1; Pentamidine isetionate ICRS 1; Metoclopramide hydrochloride ICRS 1; Noscapine ICRS 1; Salbutamol ICRS 1; Iopanoic acid ICRS 1; and Tiabendazole ICRS 1.

% of ICRS vials ordered/distributed by geographical zone



International Standards for Antibiotics (ISA)

In 2013, a project was run with a view to replacing the current IS for Bleomycin. Results will be submitted to the WHO Expert Committee on Biological Standardisation (ECBS) for the meeting in October 2014.

General matters and policies

The EDQM has added Nuclear Magnetic Resonance (NMR) to its analytical competencies. NMR is a powerful technique for characterising and analysing substances for pharmaceutical use, whether small molecules or large and complex ones. The NMR capacity will enable the EDQM to better characterise its RSs and better contribute to the elaboration of Ph. Eur. Texts.

Special thanks are due to the Medical Products Agency (MPA) in Sweden for their invaluable contribution to this achievement; another example of the fruitful interaction between National Authorities and EDQM.

Publications, databases and websites

In 2013 the EDQM launched a project to publish leaflets for all Ph. Eur. RSs in order to provide users with more information, e.g. monograph references, handling instructions, storage conditions and – when applicable – adopting European Regulation (EC) No 1272/2008 for hazard pictograms and signal words (CLP).

ACITRETIN CRS
Sicherheitsdatenblatt
Sicherheitsdatenblatt gemäß Verordnung (EG) Nr. 1907/2006 (REACH)
Ausgabedatum: 27/06/2013 Überarbeitungsdatum: 27/06/2013 Ersetzt: 25/1

ABSCHNITT 1: Bezeichnung des Stoffs bzw. des Gemischs und des Unternehmens
1.1. Produktidentifikator
Produktform : Stoff
Handelsname : ACITRETIN CRS
EG Nr : 259-474-4
CAS-Nr : 55079-83-9
Produktcode : A0225000
Andere Bezeichnungen : RTECS No : RA8460000
1.2. Relevante identifizierte Verwendungen des Stoffs oder Gemischs und Verwendungen, von denen abg
1.2.1. Relevante identifizierte Verwendungen
Hauptverwendungskategorie : Das Produkt ist für Forschung, Analyse und wissenschaftliche Aus
Verwendung des Stoffes/des Gemischs : Nur für den gewerblichen Gebrauch
Funktions- oder Verwendungskategorie : Laborchemikalien
1.2.2. Verwendungen, von denen abgeraten wird
Keine weiteren Informationen vorhanden
1.3. Einzelheiten zum Lieferanten, der das Sicherheitsdatenblatt bereitstellt
European Directorate for the Quality of Medicines & Healthcare
EDQM, Council of Europe
F-67081 Strasbourg
T +33(0)388412035 - F +33(0)388412771
1.4. Notrufnummer
Notrufnummer : +44(0)1235239670
ABSCHNITT 2: Mögliche Gefahren
2.1. Einstufung des Stoffs oder Gemischs
Einstufung gemäß Verordnung (EG) Nr. 1272/2008 [CLP]
Skin Irrit. 2 H315
Eye Irrit. 2 H319

To prevent exposure to hazardous chemicals necessary for ensuring the quality of medicines, the EDQM published translations of standard safety datasheets for Ph. Eur. and WHO reference standards at www.publichem.com/edqm in 2013.

Communication with partners and stakeholders

Some RSs (generally for assay/potency) are established through a collaborative study involving several laboratories. Continuous collaboration with national laboratories and centres of excellence is fundamental for collaborative studies. A network of some 30 national laboratories is in place and serves to carry out these studies.

Exchange with key non-European authorities takes place regularly. A staff member of the EDQM Laboratory Department (DLab) has been appointed member of the Reference Standards Committee of the Chinese National Institute for Food and Drug Control (NIFDC) for the period 2013-2016.

Events

DLab staff contributed to the two training sessions for the users of the Ph. Eur., one in Strasbourg (France) and the other in Vienna (Austria).

An EDQM DLab staff member actively participated in the 8th NIFDC Reference Standard Committee meeting in Beijing (China) in September 2013 as a Committee member. This provided an opportunity to exchange information on how pharmacopoeia RSs are established, paving the way for future collaboration in this area.

An EDQM DLab staff member attended a conference on "State regulations in the area of drugs and medical devices circulation" in Moscow (Russia) in October 2013 and presented the enzyme reference standards of the Ph. Eur.

Official visits

In July 2013, the EDQM met with Thailand's Ministry of Public Health to discuss topics related to the establishment, production and monitoring of RSs. The aim of the meeting was not only to share technical know-how and knowledge but also to strengthen relations between the two organisations. The EDQM's laboratory and RS production facilities were also visited.

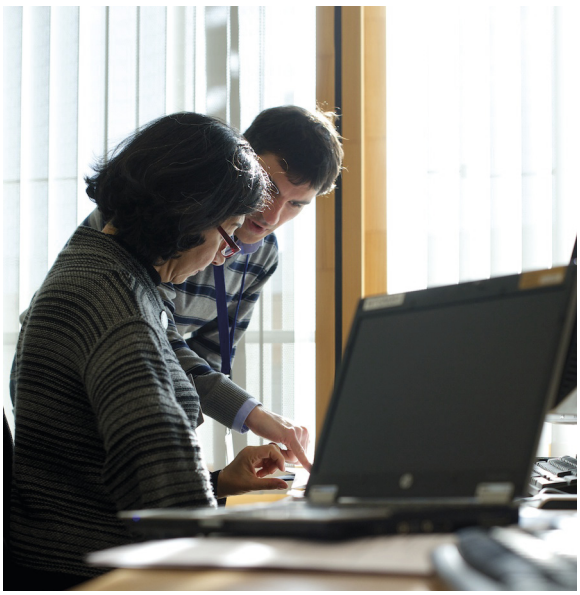
CERTIFICATION OF SUITABILITY TO THE PH. EUR. MONOGRAPHS

Why certification is more important than ever

As the world's economy continues to evolve – with some markets expanding and others declining, and a growing emphasis on the free circulation of goods and services, including medicinal products – manufacturing processes and production are increasingly relocated outside of Europe. This creates new challenges for national and European authorities in terms of closely monitoring and controlling the quality of substances used in the manufacture of medicines.

The Certification of Suitability (CEP) procedure carried out by the EDQM aims to evaluate and validate the capacity of Ph. Eur. standards to control the quality of substances used in the production of medicinal products. The procedure therefore centralises the evaluation of data for the benefit of regulatory authorities and industry and contributes to keeping the relevant Ph. Eur. monographs up to date.

The EDQM also carries out inspections of manufacturing and/or distribution sites of active substances covered by CEPs, to ensure that Good Manufacturing Practices (GMPs) are complied with and that the information supplied under the certification procedure is accurate.



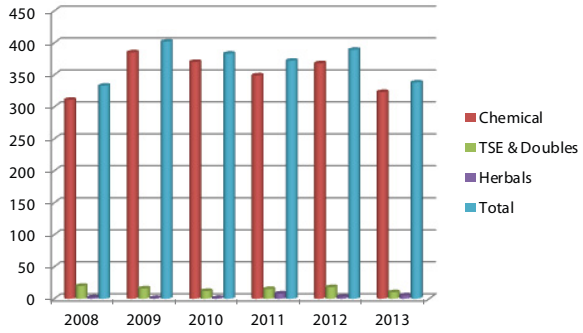
Key facts and figures

The number of new applications in 2013 fell by about 10 per cent compared to the previous year (338 dossiers received), while the number of requests for revision rose by some 15 per cent (1,390 requests).

307 new certificates and 1,142 revised certificates were issued in 2013. There are currently more than 3,700 valid CEPs, covering chemical purity, the risk of transmissible spongiform encephalopathy (TSE) and herbal drug preparations. Overall, 90 per cent of new dossiers and 75 per cent of requests for revision were treated within official timelines.

In 2013, there were significant developments in the area of herbal drugs and the evaluation of herbal drug preparations. Six new CEPs for these products were issued this year, bringing the total to 12, and some policies were also revised (see below).

Number of new CEP applications received



Within the framework of the EDQM inspection programme, 34 manufacturing sites – located mostly in Asia – were inspected with the participation of inspectors from national supervisory authorities. In addition, information on GMP compliance of 31 other sites was obtained by exchanging data with inspectorates from member states and international partners. The rate of non-compliance by sites inspected by EDQM in 2013 was high (38 per cent or 13 sites), once again demonstrating the adequacy of the risk-assessment tools to select the sites to be inspected, but also showing the lack of sustainability of GMPs for some companies which are re-inspected after one or two years.

General matters and policies

The Certification Division revised important policy documents in 2013, such as:

- Content of the dossier for herbal drugs and herbal drug preparations;
- Guideline on requirements for revision/renewal of CEP applications and the related documents;
- Guidance for electronic and paper submissions.

Also, following a request from EU regulators, information reported on CEPs regarding manufacturing sites was extended in July 2013 to manufacturers of intermediates.

At the end of 2013, Dr Marianne Ek (from Sweden, former chair of the Commission) was elected chair of the Steering Committee of the Certification procedure for a 3-year term of office, replacing Dr Mike Morris.

Following a decision by the Certification Steering Committee, a 3-person Technical Advisory Board (TAB) for herbal drugs and herbal drug preparations was created in 2013 and met for the first time in November. The TAB for chemical purity assessment met 3 times in 2013.

Communication with partners and stakeholders

The Certification Division was involved in a number of international platforms of collaboration, such as the International Generic Drugs Regulatory Pilot (IGDRP), the international API inspection programme, PIC/S work and the ICH Q7 Q&A Implementation Working Group.

As part of its collaboration with the WHO and USFDA, 4 joint inspections were carried out in 2013 with the WHO and the USFDA.

The Certification procedure also features in the EDQM's annual meetings with industry associations to promote exchange on all aspects related to the work of the EDQM. In 2013 the Certification Division participated in consultations/meetings with APIC/CEFIC and EFPIA.

Events

The Certification Division (DCEP) took part in several international events and exhibitions throughout 2013.

DCEP staff contributed to the two training sessions on the Ph. Eur. 8th Edition organised in 2013. The second day of both sessions was dedicated to the Certification procedure, sharing advice on preparing an application, revisions and the inspection programme.

On 7 November, the EDQM organised a live webinar on "How to prepare for an inspection". The presentations focused on understanding the EDQM's expectations, preparing and managing the inspection, gathering evidence of compliance and an overview of what the inspectors look for. It also addressed what happens after an inspection, the possible outcomes and their consequences. A majority of the participants were from Asia and the webinar concluded with a lively Q&A session.

Once again, the Certification Division was represented at three CPhI pharmaceutical exhibitions (in Shanghai, Frankfurt and Mumbai) and organised several face-to-face meetings with CEP holders. The aim of these meetings was to inform applicants of the practical aspects of the procedure and to assist them by clarifying misunderstandings and contributing towards resolving any difficulties they may be experiencing. There was a strong response to and interest in these personalised meetings and specific documentation was distributed to visitors to promote the procedure.

The EDQM's Certification Division and the Chamber of Commerce for Import and Export of Medicines and Health Products (CCCMHPIE) jointly organised a symposium in Shanghai (China) in June 2013. The audience was mainly from industry and the aim was to provide up-to-date information on the requirements of the Certification procedure for applicants in China. The WHO also gave a presentation on its prequalification of active pharmaceutical ingredients (APIs) programme.

Official visits

In 2013, the EDQM's Certification Division welcomed officials from Brazil's Agência Nacional de Vigilância Sanitária (ANVISA). The meeting discussed ways to strengthen the exchange of information regarding the evaluation of the quality of pharmaceutical substances and inspection results of manufacturing sites.

THE EUROPEAN NETWORK OF OFFICIAL MEDICINES CONTROL LABORATORIES (OMCL NETWORK)

Why a European network?

In 1994, the Commission of the European Union and the Council of Europe took the positive step of creating a Network of Official Medicines Control Laboratories (OMCLs), a measure taken to prevent substandard medicinal products from reaching patients and thus compromising the effectiveness of their treatment.

Coordinated by the EDQM since 1995, the OMCL Network supports regulatory authorities in controlling the quality of medicinal products for human and veterinary use that are available on the market. Operating independently from manufacturers and thus without any conflict of interest, the 67 OMCLs that are currently part of the Network[3] test these products and facilitate the exchange of knowledge between regulatory authorities in Europe.

This collaboration at European level offers several advantages: the sharing of know-how within a pool of experts, access to state-of-the-art technology and selective analytical methods, work sharing and mutual recognition of test results based on commonly agreed procedures and guidelines. This process also allows competent national authorities to avoid duplication of efforts and therefore to save resources and costs in the testing of medicinal products.

In recent years, a number of initiatives have been launched in addition to the Network's core activities: new programmes for testing falsified and other illegal medicines, the testing of unlicensed pharmaceutical preparations and quality control of active pharmaceutical ingredients (APIs) on the European market. Collaborative studies in the field of gene therapy product testing have also been carried out. Finally, guidance documents for OMCLs for the monitoring of stockpiled medicines have been established by dedicated working groups.

Quality Management Programme

The Quality Management (QM) Programme of the OMCL Network aims to forge a common approach for OMCLs to implement, maintain, assess and improve their quality management systems on a harmonised basis. It also provides assistance to OMCLs keen to increase their technical competence through training visits to other OMCLs and specific training courses organised by the EDQM. The QM Programme is continuously expanding, thanks to the strong commitment of OMCLs to high standards and to the valuable contribution of the Network's experts.

Mutual Joint Audits/Visits (MJAs/MJVs)

During 2013, 13 MJAs were carried out on OMCL sites, two of which were performed as joint audits together with the respective National Accreditation body. Some of these MJAs were initial audits, a prerequisite for the laboratories to become full or associate members of the OMCL Network, as is the case for the OMCLs of the Former Yugoslav Republic of Macedonia, Belarus, Israel and Singapore. It is an encouraging development that an increasing number of non-European countries are willing to join the OMCL

3. The General European Network of Official Medicines Control Laboratories (GEON) is open to the 37 member countries of the European Pharmacopoeia Convention as well as to the 26 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. and specific OMCL Network guidelines as common standard, implementation of the ISO/IEC 17025 standard).

Network and ask for audits of their OMCLs. Since the beginning of the QM Programme in December 1997, 107 MJAs, 50 MJVs, 2 Tutorials and 18 Training Visits have been carried out in the OMCL Network.

OMCL Network QM Guidelines

In 2013 a new guideline for "*Qualification of Balances*" was adopted by the OMCL Network. In addition, a recommendation document for the "*Qualification of Analytical Columns*" was elaborated by a working group of the OMCL Network. As of 2013, the recommendation documents can now also be consulted on the EDQM website under "*Control of Medicines*", "*Quality Management programme*".

Cooperation with the European Cooperation for Accreditation (EA)

The EDQM has taken steps to establish a relationship with the European cooperation for Accreditation (EA), with the aim of evaluating the possibility of future cooperation between the EDQM and the EA, such as exchange of know-how, joint audits of National Accreditation bodies and EDQM/MJA-auditors and mutual participation in meetings as observers. In 2013 the EDQM was accepted as a "Recognised Stakeholder" of the EA.

Training Courses/workshops

In March 2013, the EDQM organised the latest in a series of workshops for QM auditors, which help to exchange experience and to harmonise requirements during audits performed in the OMCL Network.

General OMCL Network activities

API Working Group

There has been a need for increased control of Active Pharmaceutical Ingredients as a consequence of the globalisation of the manufacturing and trading of active ingredients. The implementation in the EU of the so-called "Falsified Medicines Directive" (2011/62/EU) in 2013 was an important measure, requiring involvement of OMCLs in the monitoring of APIs on the European market.

The major objective of the API Working Group is to foster collaboration between OMCLs in the control of the quality of APIs on the European market, and to raise awareness of the valuable contribution that OMCLs make in this field. Specific goals include: improving the sharing of information between OMCLs with respect to API testing; elaborating better selection criteria for the testing of critical APIs; randomising the sampling of APIs as much as possible; and fostering market surveillance studies on APIs through scientific discussions and, where necessary, training.

Two meetings of the working group took place in 2013. One major point of discussion was the establishment of an API testing database, which became operative in February 2013 and now allows better information-sharing on API testing activities in the network.

After the API fingerprint project was reoriented with the goal of increasing the role of the OMCLs in the programme, a pilot Market Surveillance Study (MSS) on selected groups of APIs was conducted in 2013 (*for further details on the API fingerprint project, see page 37*).

An EDQM webpage dedicated to the work of the API Working Group was launched in early 2013. The content is reviewed regularly and updated; the next version of the webpage will appear in early 2014.

Finally, discussions on API risk factors resumed in 2013 in the OMCL Network. This will provide feedback to a newly-established Heads of Medicines Agencies (HMA) working group led by the Irish Medicines Board (IMB), which will continue the work of developing a global approach to risk-based selection of medicines for testing.

Counterfeit/Illegal Medicines Working Group

Another crucial element in the OMCL Network's activities is its contribution to the EDQM's efforts to combat the counterfeiting of medical products and similar crimes. A Counterfeit/Illegal Medicines Working Group was established following the first "Counterfeit Symposium for OMCLs" in 2011.

This expert group met twice in 2013. One focus of the meetings was to analyse the lessons learned from the first MSS on Suspected Illegal Products (MSSIP) targeting dietary supplements with supportive slimming effect, and to monitor a second MSSIP on dietary supplements advertised as sexual potency enhancers in 2013 (*see also "General studies on market surveillance" page 24*).

Two new technical training sessions for OMCL members were organised jointly by the EDQM and the Dutch and Austrian OMCLs respectively, in Bilthoven (The Netherlands) in June 2013 and in Vienna (Austria) in December 2013. While the Bilthoven session focused on vibrational spectrometry (Near Infra-Red (NIR) and RAMAN), the participants in the Vienna session were introduced to screening methods employing GC-MS and UPLC-MS technologies which had been developed in the Austrian OMCL. Additional training sessions in Vienna and Montpellier (France) are planned in 2014.

The Counterfeit/Illegal Medicines Working Group worked intensively in 2013 on a harmonised approach for reporting on the testing of illegal medicines in the network. Since 2012, a global activity report on illegal medicines testing in the GEON has been sent to the EU Commission on an annual basis.

The Working Group also assisted the Secretariat in establishing the Know-X database, which will collate information about illegal medicines confiscated by customs or police and dealt with by health authorities or tested in OMCLs (*see page 37 for more details on this and other anti-counterfeit activities coordinated by the EDQM*). The database was developed in 2013 and tested by selected OMCL users in the second half of the year. It is planned to launch the database in the first half of 2014. This new IT tool should help to promote communication between the different partners involved in the fight against falsified medicines (customs, police, health authorities and OMCLs).

Standardised test reports on illegal medicines have been collected by the EDQM since 2006 on a common data platform, with controlled access restricted to members of the network. The existing individual reports (numbering more than 1,300) will be migrated into the new Know-X database.

One Suspicious Unknown Product (SUP006) study was carried out in 2013. Each of the 19 participating laboratories received 4 identical unidentified tablets, including thiocolchicoside, which had been taken from the legal market. They were requested to identify and quantify the active pharmaceutical ingredient in the tablets using the method(s) of their choice. 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.

Preparatory work began in 2013 for a second "Counterfeit Symposium for OMCLs", with the support of the Working Group; the symposium will take place on 10-11 September 2014.

OMCL Testing Group on Unlicensed Pharmaceutical Preparations

The major objectives of this group are to provide guidance on sampling strategies, the selection of testing methods and setting specifications, where needed, and to raise awareness of the significant contribution of OMCLs to controlling the quality of unlicensed pharmaceutical preparations. At the group's second meeting (November 2013), the results of the MSS on unlicensed pharmaceutical preparations for paediatric use (capsules and suppositories) were presented and discussed. A second MSS on unlicensed pharmaceutical preparations for cutaneous application (solutions and ointments containing any type of API) was agreed upon, and results are to be reported by autumn 2015.

Gene Therapy Products (GTP) Working Group

The OMCL GTP Working Group was set up in 2008 to prepare the OMCLs for their role in monitoring the quality of GTPs. The goal of this Working Group is to foster collaboration between OMCLs working in the field of GTPs, in order to save time and resources through sharing knowledge and technologies. Currently 11 OMCLs are active members of the Working Group.

Work on current studies continued in 2013, in particular on full validation of the ELISA method for determining physical particle titres. An additional collaborative study on determining the infectious titre of adeno- associated virus (AAV) preparations

was also initiated. The additional work performed on the capillary electrophoresis (CE) method for the determination of DNA concentration and topology was taken forward; a manuscript summarising these results will be published in 2014.

The 5th meeting of the group in November 2013 at the Swiss OMCL in Bern included a session open to manufacturers; they showed great interest in the work performed by the Working Group and reiterated their strong commitment to supporting its activities.

18th Annual Meeting of the GEON

The EDQM held its 18th Annual Meeting of the OMCL Network in Helsinki in June 2013. This conference was organised with the help of the Finnish Medicines Agency (FIMEA) and co-sponsored by the Finnish Food Safety Authority (EVIRA) and FIMEA. The meeting brought together over 220 health experts from 35 countries, representing 55 OMCLs, to exchange experience and discuss topics of common interest for the coordination and harmonisation of their efforts to protect patient and animal health in Europe. For the first time, participants from Ukraine and the Former Yugoslav Republic of Macedonia joined the meeting as full members of the Network. The meeting was dedicated to Mr Jean-Marc Spieser, one of the founding fathers of the OMCL Network, who passed away on 1 April 2013.

In seven individual sessions, results were presented and discussions held on laboratory control of active ingredients, pharmaceuticals, falsified and other illegal medicines, unlicensed pharmaceutical preparations, biological products and the official control authority batch release (OCABR) of human vaccines, human blood and plasma derivatives and immunological veterinary medicinal products.

OMCL Network Annual Meeting – General Session

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

- The plenum approved the proposals to further amend the core document and Annex 1 of the GEON Terms of Reference. The following new aspects would be introduced into the document: public relation activities of the Network; where applicable, closer collaboration between sub-groups/networks of the GEON; clarification of the term "data sharing"; addition of a new chapter dealing with the role of OMCLs and the GEON. Furthermore, the former internal document "*Application for New Membership to the GEON*" was endorsed by the plenum to become Annex 6 of the GEON Terms of Reference.
- It was decided to carry out further work on the "*Mutual Joint Audits for OMCLs accredited against ISO/IEC 17025*" position paper of the GEON Advisory Group, to turn it into a Network document and place it in the public domain. The concept of joint audits of National Accreditation Bodies and the EDQM/OMCL network is promoted in this document, which also highlights enhanced cooperation between the MJA programme of the Network and the EA for the mutual recognition and joint conducting of laboratory audits.
- In accordance with the rules of the Network, an election was held to replace four of the eight GEON Advisory Group members.
- The public relations activities of the Network were the focus of a special session, which adopted a position paper entitled "*Publicising the work of OMCLs and the GEON*". Several OMCL representatives also shared their experience of PR work at national level. The importance of internal PR was acknowledged by the OMCLs, and the GEON Advisory Group was requested to elaborate further on this topic.
- Other subjects addressed included the difficulties for OMCLs in fulfilling the new requirements of the revised Directive 2010/63/EC on the protection of animals used for scientific purposes, and new types of market surveillance studies currently running in the network, (e.g. on medical devices, illegal medicines, unlicensed pharmaceutical preparations etc.). These items will be followed up in the competent GEON subgroups and OMCL working/advisory groups.

Proficiency Testing Scheme (PTS) studies

PTS studies have become a regular programme within the OMCL Network. In 2013, five studies were organised in the physico-chemical field, with an average participation of 46 national control laboratories and 40 other pharmaceutical control laboratories from the private sector, industry and hospitals. In the biological area, 4 studies were organised, involving an average of 22 laboratories (10 OMCLs and 12 laboratories from the private sector).

In 2013, the last two studies under the 5th PTS agreement with the WHO were finalised: a study on dissolution testing and a study on content determination by titration. On average, 50 governmental control laboratories from the six different WHO world regions (Africa, Americas, Eastern Mediterranean, Europe, South-East Asia and Western Pacific) participated in these studies.

General studies on market surveillance

Market Surveillance Studies (MSSs) 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. In 2013, no classic MSSs were organised.

Instead, several "atypical" MSSs were initiated in 2013, including an MSS on "Eye Drops and Nasal Preparations registered as Medical Devices" and an MSS on "Heparin and Low Molecular Mass Heparin APIs and Finished Products". A new MSS on Suspected Illegal Products (MSSIP) on "Dietary Supplements advertised as Sexual Potency Enhancers" was also launched. Results for all these studies are expected to be available early in 2014.

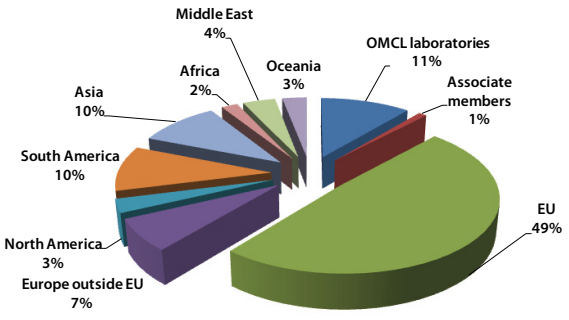
The first MSSIP on "Slimming Dietary Supplements" was finalised in 2013. Twenty-one OMCLs sent results for about 370 batch samples taken from the legal and the illegal supply chains. Almost half of the samples analysed (47 per cent) were reported to contain undeclared APIs.

CombiStats™

In March 2013 a major new version of the CombiStats™ software was released. This computer programme for the statistical evaluation of biological dilution assays in accordance with Chapter 5.3 of the Ph. Eur. was first made available in 1999 to laboratories of the OMCL network; as of November 2005, non-OMCL laboratories may also obtain a user licence. The newly-released version 5.0 introduces possibilities such as equivalence testing, robust regression, password protection of datasheets, 5-parameter asymmetric sigmoid curves, and more. The electronic user manual has also been made available in printed format and can be ordered from the EDQM Store.

Two training courses were organised in March and October 2013 and were open also to industry and private sector participants.

CombiStats™ licenses per region



The number of users has steadily increased since its public release. By December 2013, 11 per cent of licences were issued to OMCL laboratories in 25 countries and 89 per cent to non-OMCL users in 43 countries. The pie-chart 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 Algeria, Argentina, Australia, Bangladesh, Brazil, Canada, China, Egypt, India, Indonesia, Israel, Japan, Peru, South Africa, South Korea, Thailand, Tunisia, Uruguay and the USA. CombiStats™ has thus evolved into a common internationally agreed reference in its domain and contributes to mutual recognition of data and results by all interested parties.

EU/EEA-specific activities

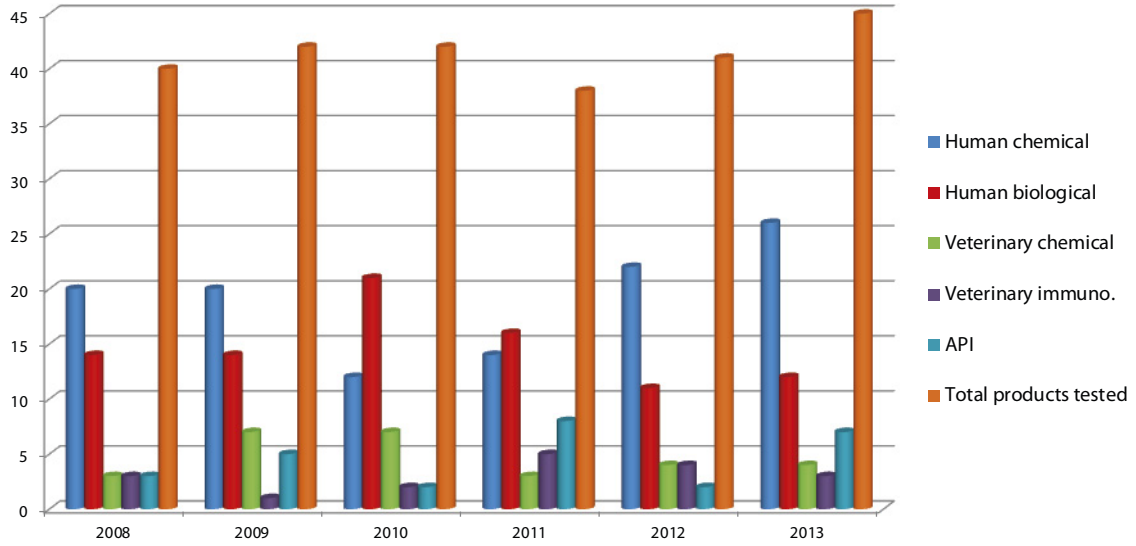
Market Surveillance for Products with a Centralised Marketing Authorisation (CAPs)

Since 1995, the EU Commission has being granting EU-wide marketing authorisations for new medicines for both human and veterinary use, known as Centrally Authorised Products (CAPs). Since these products may be marketed in all EU and European Economic Area (EEA) member states, a coordinated approach to controlling the quality of these products is necessary. In June 1999, a contract governing an annual CAP Sampling & Testing Programme was signed by the EMA and the EDQM. The EMA is the sponsor of the programme and has overall responsibility for it, while the EDQM coordinates the sampling and testing operations. The EDQM's duties include reporting the results of the testing programme and proposing follow-up actions, if necessary, to the EMA. National inspection services gather sample products from the market, and members of the EU/EEA OMCL Network test them. The list of products to be included in the annual programme is prepared by the EMA Secretariat in collaboration with the EMA Scientific Committees, using a risk-based approach tool.

The programme for sampling and testing of Centrally Authorised Products (CAP) was successfully continued in 2013, entering its fifteenth consecutive year.

The 2013 work programme included 38 medicinal products for human use (12 biologicals and 26 chemical products) and 7 medicinal products for veterinary use (3 immunobiological products and 4 chemical products). Two ad-hoc tests were performed according to the recommendations of the Rapporteur. In addition to the finished dosage form, testing of active substances (API) was performed for 7 products. The total number of products (45) corresponds to the optimal range considering the operational capacities of the OMCL Network.

Number of products tested in the CAP Programme 2008-2013



Thirty-four OMCLs were involved in the 74 testing operations of the 2013 CAP Programme. The controls showed that a majority of the products tested were of the expected quality and the results complied with the authorised specifications for almost all products. One confirmed out-of-specification result was reported to the EMA. The EMA will handle the follow-up to these observations.

A CAP standard procedure for handling future CAP Generics programmes was drafted in 2012 based on the experiences acquired with the 2011 Clopidogrel generics trial programme. The document "*General Procedure for Sampling and Testing of Generic Centrally Authorised Products*" (PA/PH/CAP (12) 32 9R) was fine-tuned in 2013 and released after adoption by the OMCL Network in December 2013. The procedure is available on the EDQM website. Additional information on the CAP programme can be found on the EDQM site as well as on the EMA website.

In December 2013, the EDQM's coordination activities with respect to the CAP Sampling and Testing Programme successfully underwent an ISO9001 re-audit conducted by AFNOR Certification.

Mutual Recognition Procedure (MRP)/ Decentralised Procedure (DCP) post-marketing surveillance scheme

The MRP/DCP post-marketing surveillance scheme was initiated on a voluntary basis by members of the OMCL Network from the EEA member states and the EDQM in late 2000 and has been further developed since then. By avoiding duplicate testing of the same product in different member states, the scheme provides a coordinated and cost-saving approach to post-marketing surveillance.

In 2013 the 9th regular programme for the market surveillance of medicinal products authorised in the EEA via the MRP or DCP procedure was conducted. Some 800 product testing projects were allocated to the 2013 programme, which is comparable to the previous year's figures. The 2013 test reports came from 19 different OMCLs.

Around 15 per cent of samples tested in the programme originate from a member state or an OMCL that is not involved in the testing (about 10 per cent in 2012). This demonstrates the added value of the surveillance scheme with respect to work-sharing and the increasing efforts of the OMCLs to include samples from other member states in their national testing programmes. In about 2 per cent of the tested materials, findings regarding regulatory issues could be identified, (e.g. insufficient details of test method, wrong calculation formula used in the SOP), and in 2 per cent of the cases one or more out-of-specification results were reported. Some 12 per cent of the tested products were for veterinary use; this ratio is higher than in former years. Approximately 2 per cent of tested samples were biologicals, which reflects the general distribution of product types registered via these European procedures. Since 2012 more DCP products than MRP products have been included in the annual programme.

The internal database used for the planning, sampling and reporting of MRP/DCP product testing activities within the Network was further developed – a new version of the database was launched in February 2013. Since then, API test reports have been registered in a separate module of the database, allowing the reporting of API testing activities independently from registered MRP or DCP products. The database was updated a second time in October 2013. In total, 22 database amendments were implemented in 2013, affecting both the MRP-/DCP-product and API modules. These were initiated both by OMCL users of the system and by the EDQM Secretariat.

In late 2013, database access was granted to a number of non-EU OMCLs, including laboratories from Bosnia & Herzegovina, Serbia, Switzerland, the Former Yugoslav Republic of Macedonia and Ukraine. Access for non-EU countries is restricted to the API module. Three training courses were organised in 2013 for new users from non-EU countries and for core OMCL database users.

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 concept of "repetition" and the fact that the MRP-/DCP-product and API test reports are now handled in separate modules of the database. The latest document version was posted on the EDQM website in August 2013. A new document, "*History, results, and benefits of the post-marketing surveillance scheme for the testing of mutual recognition/decentralised procedure products*", was published on the EDQM website in July 2013. This document underlines the added value of the MRP/DCP product testing scheme by providing some global figures.

In December 2013, ISO 9001-compliance of the EDQM's coordination activities with respect to the MRP/DCP product market surveillance scheme was re-certified by AFNOR Certification.

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

The human OCABR network is a specialised group of OMCLs within the GEON. The primary goal of this network is harmonised application of Article 114 of EU Directive 2001/83/EC, as amended, to foster the mandated mutual recognition of batch release for human vaccines and medicinal products derived from human blood and plasma. Close collaboration and exchange of information through meetings and by correspondence as well as the elaboration and maintenance of common guidelines provides a dynamic environment for cooperation and work-sharing. Network members are dedicated to supporting public health by providing expert surveillance of the quality of vaccines and blood-derived medicinal products on the EU market using a system that is also widely recognised outside the EU. A new improvement of the confidential OCABR database was completed in 2013. The database facilitates real-time reporting of batch release status. In 2013, approximately 9,000 final batches of vaccine and human blood derived products and more than 8,600 plasma pools underwent OCABR procedures within the Network.

The 18th Annual Meeting of the OMCL Network included parallel sessions for blood and vaccine issues and a joint session to address common points of interest. The joint OCABR session was attended by almost 90 participants from 28 member states. Participants reviewed activities from the past year and determined strategies for the coming period. 2013 saw the participation of 3 new partners: Croatia participated for the first time as a full member thanks to its accession to the EU in 2013; Israel participated in the joint session and the parallel session for vaccines, following the finalisation of the Agreement on Conformity Assessment and Acceptance of industrial products (ACAA); and Canada participated as an observer in the blood, vaccine and joint sessions based on the Memorandum of Understanding concerning exchange of information on OCABR-like activity signed between the Biologics and Genetic Therapies Directorate, Health Canada and the EU OCABR network in 2012.

In the plenary session there was a focus on the reduction, refinement and replacement of animal use (3Rs) for the quality control of biologicals and OCABR testing. The results of a survey on the state of implementation of Directive 2010/63/EU among OCABR OMCLs and involved manufacturers (and in particular, elements related to Articles 13 and 38) were presented. The Network also adopted a revision to the EU Administrative Procedure for OCABR, to include a statement in the principles of the procedure noting the obligation to apply the 3Rs when performing OCABR, in order to highlight the Network's longstanding commitment to this concept.

Other meetings throughout the year included those between the OCABR Advisory Group and the vaccine manufacturers' association and the blood manufacturers' association respectively to exchange views on OCABR practice, address issues of common importance and foster a good working relationship. The annual workshop on testing oral poliomyelitis vaccine bulks – participants included representatives of OMCLs, the relevant manufacturers and the WHO – proved fruitful and interesting and offered the opportunity to verify harmonisation of this critical technique.

One new and 15 revised guidelines for vaccines and 1 revised guideline for blood-derived products were finalised in 2013. A number of other internal guidelines were also finalised. All adopted product-specific guidelines and administrative procedures are now available exclusively from the EDQM website.

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

The Veterinary Batch Release Network (VBRN) involves a subset of specialised OMCLs and competent authorities focusing on the independent control of immunological veterinary medicinal products (according to Articles 81 and 82 of EU Directive 2001/82/EC, as amended).

At the 18th Annual Meeting of the OMCL Network, 25 participants from 16 member states took part in the VBRN session, where annual reports of the activities of the different member states were presented. Progress continues in the harmonised application of the provisions of the EU Directive for veterinary medicines. Important areas of focus included the improvement of participation of all member states in reporting and discussion, through use of a new reporting tool. Issues related to the 3Rs were highlighted in the context of method validation and maintenance of competence; the VBRN has taken the lead in this area by drafting two guidance documents for the OMCL Network. Positive results were also reported concerning efforts aimed at making stakeholders such as the Heads of Medicines Agencies and the EU Commission acknowledge the importance of testing and the need for resources for control of IVMPs. As part of its work programme, the VBRN has begun to reflect on how to ensure that the shortlist of products eligible for OCABR is updated to reflect the current state of the art in IVMP production in the EU, as mandated by the EU Commission in its Recommendations document on batch release for IVMPs and endorsed by the Veterinary Pharmaceutical Committee on 20 March 2007.

The VBRN Advisory Group met with manufacturers of IVMPs in March 2013 to discuss items of common interest. The plenary session of the Annual Meeting gave an opportunity to pass on the information exchanged in the March meeting to the wider Network.

All adopted administrative procedures and product-specific guidelines, as well as protocol templates, can be downloaded from the EDQM website.

BLOOD TRANSFUSION

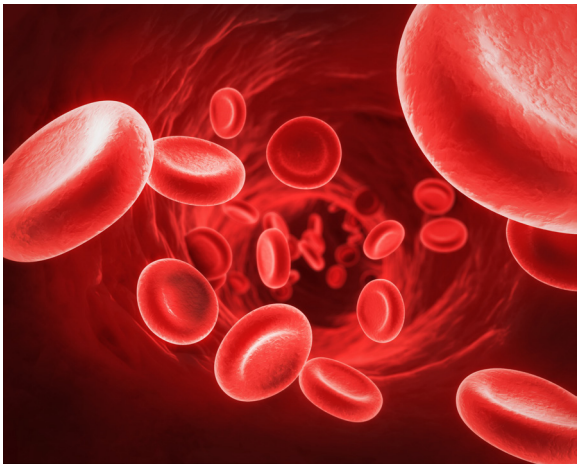
60 years of pioneering blood safety

The Council of Europe has been actively contributing to the safety and quality of blood and blood products in Europe and beyond for sixty years. Since the beginning, the guiding principles have been to promote voluntary and non-remunerated donation, to achieve self-sufficiency and to protect both the donors and the recipients of labile blood components by actively implementing high quality and ethical standards.

Responsibility for the scientific secretariat of the Council of Europe's activities in the field of blood transfusion was transferred to the EDQM in 2007. The European Committee on Blood Transfusion (CD-P-TS) was also created at that time, charged with steering and coordinating the Council of Europe's activities in the area of blood transfusion and overseeing the work of its expert groups.

The CD-P-TS currently consists of 61 representatives (48 members and 13 observers), drawn from Council of Europe member states and signatories of the Convention on the Elaboration of a European Pharmacopoeia, as well as observers such as the EU Commission, the WHO and Council of Europe Committees on bioethics and European public health. Both members and observers are represented in the CD-P-TS expert groups.

The CD-P-TS held a bureau meeting involving the chair, vice-chair and the chairs of the different expert groups in June and a plenary session at the EDQM premises in November 2013.



Key facts and figures

Collaboration between 33 member states provided the foundation for activities in the area of blood transfusion in 2013.

- At the policy level, a resolution on risk behaviours having an impact on blood donor management and transfusion safety was adopted by the Council of Europe's Committee of Ministers.
- Inter-institutional cooperation with the EU Commission (under Agreement 2011 51 01) continued through a European Programme of External Quality Assessments, with voluntary participation of blood establishments in Blood Proficiency Testing Scheme (B-PTS) studies.

  The B-PTS is a form of external assessment of quality control management systems that uses inter-laboratory comparisons to determine the performance of blood transfusion screening laboratories responsible for testing individual blood donations. This scheme supplements each laboratory's own internal quality control procedures by providing an external measure of their testing capabilities. Since 2010, 13 B-PTS studies were organised, covering the following fields:
  - Nucleic acid amplification techniques (Hepatitis C (HCV), Hepatitis B, Human Immunodeficiency (HIV) viruses);
  - Serology (Hepatitis B surface antigen (HBsAg), HIV antibodies, HCV antibodies); and
  - Immunohaematology (ABO, Rhesus, Kell, extended phenotyping and irregular antibodies).
- The B-PTS activity has been well received by blood establishments, resulting in increased interest in participation in the scheme. Four B-PTS studies were run in 2013, and the average number of participating laboratories per study increased by 30 per cent.
- Four Blood Mutual Joint Visits (B-MJVs) were also conducted in 2013.

General matters and policies

Risk behaviours having an impact on blood donor management and transfusion safety (TS057)

The EDQM project "*Risk behaviours having an impact on blood donor management and transfusion safety*", which started in February 2010 with the notable participation of the EMA, ECDC (European Centre for Disease Prevention and Control), EBA (European Blood Alliance), USFDA, Health Canada, Australia's TGA and the WHO, was completed. The findings of the working group provided the basis for a number of proposals regarding donor deferral rules, which were adopted in March 2013 by the Council of Europe's Committee of Ministers in the form of Resolution CM/Res(2013)3 "*on sexual behaviours of blood donors that have an impact on transfusion safety*", plus a technical memorandum (both documents are published on the EDQM website).

Blood Quality Management Programme

The Blood Quality Management (B-QM) programme was set up by the EDQM in 2012, with the aim of proposing common tools enabling European blood establishments (BE) to develop, implement, assess, maintain and improve their Quality Management System (QMS) on a harmonised basis. The programme started with a 2-year pilot phase, during which 6 Blood Mutual Joint Visits (B-MJVs) were carried out, 4 of these in 2013.

An increasing number of European countries and BEs are willing to participate in the B-QM programme, given that no such programme existed before. With the strong support of the CD-P-TS, the B-QM programme will be further expanded in 2014 by offering the following schemes:

- Training Visits (TV): on-site visit and training for BE staff on technical and QMS topics. Tailor-made training based on the situation observed;
- Blood Mutual Joint Visits (B-MJV): scrutiny of the QMS under development at the BE and provision of recommendations for improvement and/or advice on the implementation of the QMS; observation of the level of implementation of the minimum standards of the Guide (*see next Section*) as well as other standards used in the BE;
- Blood Mutual Joint Audit (B-MJA): check on compliance of the implemented QMS with the Guide as well as relevant guidelines and standards used in the BE. After the B-MJA, the BE is provided with an attestation, stating whether or not the BE is compliant with the standards in place in the BE.
- These schemes are carried out by auditors from European BEs, who share their experience during the TV/B-MJV/B-MJA.

There are plans to develop a Quality Management book in addition to other on-site tools in 2014.

Publications, databases and websites

Guide to the Preparation, Use and Quality Assurance of Blood Components – 17th Edition

The 17th Edition of the "*Guide to the Preparation, Use and Quality Assurance of Blood Components*" was published in the two official languages of the Council of Europe, English and French. A complementary eBook-version was made available to purchasers of the printed edition.

A dedicated expert working group of the CD-P-TS – consisting of members from Europe, Australia, New Zealand and the US – has the task of updating the Guide to reflect the latest scientific developments, with a revised edition scheduled for publication every two years. The Guide defines common harmonised quality and safety standards for the collection, preparation and distribution of blood components, based on voluntary, non-remunerated donation. It also outlines common standards for quality systems to be implemented in BEs and hospital blood banks.

Good Practices Guidelines/Elements of quality systems (TS066)

The "*Good Practice Guidelines for Blood Establishments and Hospital Blood Banks required to comply with EU Directive 2005/62/EC*" were published on the EDQM webpage to boost distribution among stakeholders.

The document was prepared by the TS066 Working Group as an ad hoc cooperation between the Council of Europe/EDQM and the EU Commission as part of Grant Agreement No 2010 53 05, and adopted by the CD-P-TS in November 2013. The guidelines serve as a harmonised reference standard during compliance assessment of quality systems in BEs performed either by national inspectors in the EU member states and/or auditors in Blood Mutual Joint Visits/Audits (B-MJV/B-MJA), which are also open to non-EU member states.

The Good Practice Guidelines will become an integral part (Appendix 1) of the 18th Edition of the "*Guide to the Preparation, Use and Quality Assurance of Blood Components*", to be published in 2015. Ultimately, they could become part of European Union law.

Communication with partners and stakeholders

EU Commission/DG-SANCO

In April and October 2013, the EDQM attended the EU Commission meetings of the competent authorities on blood components in Brussels, as an observer. In addition to the agreements for ad hoc cooperation (Grant Agreements No 2010 53 05 and No 2011 51 01), collaboration with the EU Commission allows exchanges such as that of the data collected in Council of Europe member states during the annual survey; *"Report on the Collection, Testing and Use of Blood and Blood Components in Europe", (2010)*. These data will be used by the EU Commission's Directorate General for Health and Consumer Affairs (DG SANCO) to develop a report on the "*Landscape of blood and blood components and plasma derivatives in Europe*", to provide a basis for assessing the need to revise the European Directives covering blood and blood components.

Pharmaceutical Inspection Co-operation Scheme (PIC/S)

The EDQM is a partner in the Pharmaceutical Inspection Co-operation Scheme (PIC/S) and participated in the "20th PIC/S Expert Circle on Human Blood, Tissues and Cells" organised by the Taiwan Food and Drug Administration (TFDA) in September 2013 in Taipei City. The meeting brought together experts, inspectors and regulators from around the world in the context of the scheduled revision of the "*PIC/S GMP Guide for Blood Establishments*". The EDQM gave a keynote lecture on the Council of Europe/EDQM activities in this field, with a particular focus on the "Interim Elements of Good Practice Guidelines for Blood Establishments and Hospital Blood Banks" (which have since been superseded by the Good Practice Guidelines).

World Health Organization (WHO)

At the WHO's invitation, the EDQM gave a presentation at the High-level Policy Makers Forum organised in collaboration with the Italian Ministry of Health and the Japanese Ministry of Health and Welfare in Rome in October 2013. The meeting was convened to address the topic of achieving self-sufficiency in blood components and blood products based on voluntary, non-remunerated donation. This was a good opportunity to promote the visibility of

the CD-P-TS and the EDQM's activities in the field of blood components and blood products to an audience consisting of policy-makers mostly from outside Europe.

International Society of Blood Transfusion (ISBT)

The EDQM participates regularly in the annual conferences of the ISBT, an international society of about 1,400 professionals operating worldwide in the field of blood transfusion. In 2013, the ISBT held conferences in Amsterdam (The Netherlands) in June and in Kuala Lumpur (Malaysia) in November (*see "Events" in this Chapter*). The EDQM was granted observer status with the ISBT's Board of Directors, enabling it to promote the Council of Europe's core values globally.

IPFA/PEI 20th International Workshop on Surveillance and Screening of Blood-Borne Pathogens and 24th Standardisation of Genome Amplification Techniques (SOGAT) Meeting

The EDQM participates in the IPFA/PEI and SOGAT annual workshops, which in 2013 took place in Helsinki (Finland) and Ljubljana (Slovenia) respectively. Participation in these conferences allows the activities undertaken by the CD-P-TS and the EDQM in the field of safety of blood donations to be promoted and shared.

Competent Authority Training of Inspections in Europe (CATIE)

The overall objective of the CATIE project is to set up a training programme for regulatory inspectors in the EU in according with Article 8 of Directive 2002/98/EC, which sets standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components. The EDQM was invited to participate as an observer at one of the annual CATIE courses, held in Malta in April 2013.

Events

In 2013, the EDQM was invited to be a partner in the global annual celebration of World Blood Donor Day (WBDD). This year's campaign saw the 10th Anniversary hosted in Paris, in conjunction with the French national blood service (Etablissement français du sang - EFS). The focus for the 14 June celebration was 'blood donation is a gift that saves lives' and the slogan was "Give the gift of life: donate blood".

As an official partner of the event, the EDQM developed a number of promotional items and also provided electronic material to the Council of Europe member states, allowing each member state to have material in their own national language. As part of the promotional campaign, social media channels were used to encourage discussion and debate on blood donation; with the use of the Thunderclap platform, the messages were spread throughout Twitter and Facebook, helping to reach a wide target audience.

The EDQM also organised two blood donor sessions which were open to Council of Europe staff and their families.

Symposia

In partnership with the Paul-Ehrlich-Institut (PEI) and the Ludwig-Maximilian-University (LMU), a technical symposium on the "Optimal use of clotting factors and immunoglobulins" was held in Kreuth (Germany) in April 2013. Leading experts shared their knowledge and professional views on the latest scientific information and data available on the use of these products in Europe. Included in the programme were two subject-specific workshops which allowed the participants to debate in greater detail matters related to best practices and recommendations, new therapies and indications as well as supply and safety.

International Fairs & Exhibitions

The EDQM once again participated in the Congress of the International Society of Blood Transfusion (ISBT), which in 2013 was held in Amsterdam (The Netherlands) in June. The event attracted healthcare professionals in the fields of blood transfusion, immunology and virology from across Europe. Visitors to the EDQM stand were able to collect information on the EDQM's activities in this area. It was also an ideal opportunity to present the latest 17th Edition of the Guide and the EDQM's Blood-PTS Scheme and to arrange face-to-face meetings with a wide range of specialists and organisations.

EU Commission Press Conference on Transplantation and Blood Transfusion

The EDQM was invited to a two-day press event organised by the EU Commission in Madrid in June. The aim was to present European projects contributing to the improvement of transplantation and blood transfusion practices in Europe to a panel of European journalists. The EDQM gave a presentation and exhibited a poster on the European standards for the quality and safety of blood transfusion developed by the Council of Europe.[4]

4. For the full agenda of the event, see http://ec.europa.eu/eahc/news/news244.html.

ORGAN, TISSUE AND CELL TRANSPLANTATION

Medical progress based on strict quality and safety standards

The Council of Europe's work in contributing actively to the implementation of high standards for the protection of public health and for the promotion of human rights and dignity extends to the area of organ, tissue and cell transplantation.

The European Committee on Organ Transplantation (CD-P-TO) is the steering committee in charge of transplantation activities at the EDQM. It actively promotes the non-commercialisation of organ, cell and tissue donation, the fight against trafficking and the development of ethical, quality and safety standards in the field of transplantation. This Committee is composed of internationally-recognised experts from Council of Europe member states, observer countries, the EU Commission, the WHO, representatives from the Council of Europe's Committee on Bioethics (DH-BIO) and several non-governmental organisations.

Key facts and figures

Priority areas of the CD-P-TO work programme yielded the following results during 2013:

- Release in September of the 5th Edition of the "*Guide to the Quality and Safety of Organs for Transplantation*" (*see page 33*);
- Publication in October of the 1st Edition of the "*Guide to the Quality and Safety of Tissues and Cells for Human Application*" (*see page 33*);
- Resolution CM/Res(2013)55 on "*establishing procedures for the collection and dissemination of data on transplantation activities outside a domestic transplantation system*" was adopted by the Committee of Ministers in December (*see page 33*).

General matters and policies

Quality and Safety of Organs, Tissues and Cells for Transplantation

After the publication of the 5th Edition of the "*Guide to the Quality and Safety of Organs for Transplantation*" in September, Working Group TO057 was constituted for the elaboration of the 6th Edition. Seventeen experts were appointed to participate in this Working Group. The European Donation & Transplant Coordination Organisation (EDTCO) and the EU Commission actively participate in the drafting process. The first meeting of the Working Group was held in November 2013 in Strasbourg (France). The 6th Edition of the Guide will be published in 2016 and every 2 years thereafter.

Following the publication of the 1st Edition of the "*Guide to the Quality and Safety of Tissues and Cells for Human Application*" in October, two working groups have been appointed to work on the elaboration of the 2nd Edition: TO055, to update the existing general and tissue-specific content of the Guide, and TO056, to elaborate the new chapter(s) on Assisted Reproductive Technologies (ART). A total of 21 and 15 experts were appointed to participate in TO055 and TO056, respectively. The European Association of Tissue Banks (EATB), the American Association of Tissue Banks (AATB), the European Society of Human Reproduction and Embryology (ESHRE) and the EU Commission actively participate in the drafting process. The first meeting of these working groups took place on 24-26 September 2013 in Strasbourg. The 2nd Edition of the Guide will be published in 2015 and every 2 years thereafter.

The ad hoc Grant Agreement 2012 51 01 between the EU Commission and the EDQM, entitled "*Dissemination of best practices in organ donation/ transplantation*" and signed in October 2013, is aimed at elaborating and disseminating common European quality and safety standards for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells. These standards will be published in the 2nd Edition of the "*Guide to the Quality and Safety of Tissues and Cells for Human Application*".

Although many countries with established transplant programmes have improved their deceased donation rates during recent years, none can cover the true need for kidneys from this source, even after developing deceased donation to its maximum therapeutic potential. Considering that live kidney donation is a safe procedure – if performed according to recognised international standards – in terms of donor evaluation, selection and donor care, Resolution CM/Res(2013)56 "*on the development and optimisation of live kidney donation programmes*" was adopted by the Committee of Ministers in 2013. This Resolution recommends that member states develop and optimise programmes for kidney donation from live donors based on recognised ethical and professional standards as a better way to pursue self-sufficiency in transplantation. The development and optimisation of such programmes will increase the supply of kidneys for transplantation by optimising the utilisation of organs, ultimately improving quality of life and life expectancy for patients with end-stage kidney disease.

Additionally, a draft Resolution "*on establishing national/supranational living donor registries/ databases*" is being drawn up.

The Council of Europe has been studying the issue of cord blood donation for a number of years and has always been concerned about the proliferation of private cord blood banks dedicated to the collection and storage of cord blood for autologous use. A survey to address compliance among the member states to Council of Europe Recommendation Rec(2004)8 of the Committee of Ministers "*on autologous cord blood banks*" was conducted and the results, published in the *Newsletter Transplant* 2013, proved very worrisome. As a result, the CD-P-TO started working on the elaboration of a brochure providing unbiased information to families on cord blood banking, describing what stem cells are, their uses, options for cord blood donation, allogeneic vs. autologous use, medical indications, etc.

International Collaboration Efforts

In July 2011, the Council of Europe launched a three-year collaborative project, The Black Sea Area (BSA) Project aimed at battling organ shortages and improving access to transplant health services in the Council of Europe BSA 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 an effective legislative framework, the establishment of national transplant authorities and programmes and infrastructure, and the analysis of the clinical practices for the donation-transplantation process inside hospitals in those countries with already-existing transplant programmes.

During 2013, a number of activities were undertaken to ensure the progress of this project, including meetings with other international initiatives aimed at exploring possible ways of collaboration and site visits to countries willing to receive international help to improve their donation/transplantation systems.

Fight against Human Trafficking for the Purpose of Organ Removal and Trafficking in Human Organs

The existence of worldwide human trafficking for the purpose of organ removal (HTOR) and the trafficking in human organs (THO) for the purposes of transplantation are well-established facts. On a global level, it is estimated that up to 5-10 per cent of kidney transplants performed annually are the result of trafficking (3,400 to 6,800 kidneys per year, which may still be an underestimate). Currently, several legal instruments address the problem of HTOR but there are important loopholes related to THO not linked to human trafficking, despite the grave safety and ethical concerns associated with this practice.

The new draft Convention against Trafficking in Human Organs, elaborated by the Committee of Experts on Trafficking in Human Organs (PC-TO), of which the CD-P-TO was part, will be the first in the world to provide a definition of THO, criminalise it, protect the rights of the victims, facilitate national and international cooperation and provide a monitoring mechanism to ensure the effective implementation of its provisions. In 2013, the drafting of this new Convention was completed and the final draft text was transmitted to the Parliamentary Assembly for opinion. It is expected that the draft Convention will be adopted by the Committee of Ministers in early 2014.

In order to reinforce the fight against HTOR and THO, in 2013 closer links were forged with other international committees, bodies and organisations, such as the Declaration of Istanbul Custodian Group, the Council of Europe Group of Experts on Action against Trafficking in Human Beings (GRETA) and the United Nations Office on Drugs and Crime (UNODC).

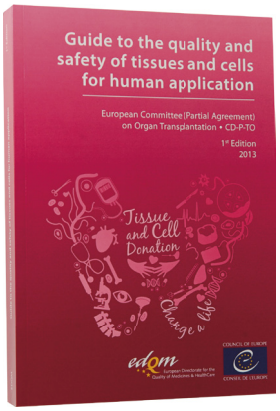
Finally, Resolution CM/Res(2013)55 on "*establishing procedures for the collection and dissemination of data on transplantation activities outside a domestic transplantation system*" was adopted by the Committee of Ministers. This Resolution recommends that member states designate a contact person in charge of regular collection of data on patients going abroad to be transplanted with an organ retrieved as a result of illicit transplantation procedures, performed outside the framework of a domestic transplantation system, and that they develop and implement an appropriate tool for such data collection.

Publications, databases and websites

The 5th Edition of the "*Guide to the Quality and Safety of Organs for Transplantation*" was published in September 2013. This guide has become the most important reference in Europe for professionals identifying organ donors, transplant coordinators managing the donation process and transplant physicians responsible for organ allocation and utilisation. Regular revision ensures that the Guide reflects recent advances in the field.

The 1st Edition of the "*Guide to the quality and safety of tissues and cells for human application*", providing the most up-to-date information for all professionals involved in donation, banking, transplantation and other clinical applications of tissues and cells, was published in October 2013. It is the first of its kind to define detailed ethical and technical guidance for tissues and cells in Europe.

Both guides were also published in PDF and eBook-format and made available free of charge to purchasers of the printed version.



Finally, the *Newsletter Transplant* 2013, providing international figures on organ donation and transplantation for the year 2012, was published.

Communication with partners and stakeholders

In March and September 2013, the EDQM attended, in an observer capacity, the Meeting of the EU Competent Authorities for Organs in Brussels (Belgium), and in June and December 2013 the Meeting of the EU Competent Authorities for Tissues and Cells in Brussels (Belgium). The EDQM was invited to participate in a press event on transplantation and blood donation in June 2013 in Madrid, organised by the EU Commission (*see page 30*).

In February 2013, the EDQM attended the Final Conference of the EU-funded project SoHO V&S in Selsdon Park, Surrey (UK) and, in October, the interim meeting of the EU-funded project ACCORD in Madrid (Spain).

In April 2013, the EDQM attended the Anniversary Meeting of the Declaration of Istanbul in Doha, Qatar.

In July 2013, representatives of the South Eastern European Health Network (SEEHN), the Mediterranean Network (MN), the EU Commission and EDQM/Council of Europe met in Zagreb (Croatia) to discuss possible avenues for future collaboration and possible existing overlaps between different initiatives, aimed at developing and optimising transplantation systems in countries with low or non-existent donation rates.

A site visit to Ukraine took place in October 2013, involving meetings with Ministry of Health officials, responsible personnel at the National Transplant Agency and directors and doctors at several hospitals with the potential to establish donation and transplantation programmes.

In December 2013, the EDQM attended the Expert Group Meeting on Trafficking in Persons for the Removal of Organs organised by the UNODC in Vienna (Austria).

During 2013, the EDQM was invited to participate and give presentations at the annual congresses of the European Group for Blood and Marrow Transplantation (EMBT) in London (UK), the European Society for Organ Transplantation (ESOT) in Vienna (Austria) and the EATB in Brussels (Belgium).

Events

A Council of Europe initiative launched in 1998, the European Day for Organ Donation and Transplantation (EODD) aims to promote organ donation and transplantation in the Council of Europe member states. It is also an opportunity to honour all organ donors and their families and to thank transplantation professionals throughout Europe, whose hard work helps save lives and improve the quality of life of many people. Each year a different member state is selected to host the event, and the 15th EODD was hosted by Belgium.

The Belgian authority, the Federal Public Service (FPS) for Health, Food Chain Safety and Environment, hosted the celebration day on 12 October, with the main event taking place in Brussels. A number of events were organised in the capital and throughout Belgium, including the famed Manneken Pis being clothed in a new outfit carrying the messages of the EODD and a musical concert at the Cathédrale des Saints Michel et Gudule attended by Princess Astrid of Belgium. In addition to the main celebration day in Brussels, there were also a number of other simultaneous celebrations throughout Council of Europe member states.

The EDQM was also very active in the promotion of the Day and produced a number of video trailers that were made available on social media channels such as Twitter, Facebook and YouTube. The EDQM also developed an interactive map providing links to European organ donation and transplantation websites.

The overall campaign was a huge success, receiving great media attention through TV, radio and print media coverage. The European campaign generated global attention, with news articles appearing as far away as New Zealand and Australia.

Workshops

In October 2013, the EDQM gave a presentation on EODD at the Fourth Journalist Workshop on *"Organ Donation and Transplantation"*. The workshop was organised by the EU Commission's DG SANCO in Brussels (Belgium).

Despite countless media campaigns, organ donation rates vary widely in Europe, with only a few countries succeeding in significantly increasing the number of donors. The purpose of this media workshop was twofold: firstly and more broadly, to give journalists an overview of the situation and the most noteworthy laws and regulations of the current system, and secondly, to address the role and impact of the media in this field, (e.g. health communication, managing adverse publicity and the growing role of social media). The programme also included testimonials from recipients and their families, people whose feelings and experiences are at the heart of the subject.

PHARMACEUTICALS AND PHARMACEUTICAL CARE

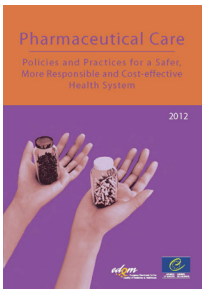
Optimal use of Pharmaceuticals for the purpose of improving patients' quality of life

Public authorities and the manufacturing and distribution sectors devote heavy resources to the quality, safety and efficacy of medicines. However, the safe and appropriate use of medicines is also important in terms of achieving the best possible medication outcome for 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 in Hepler and Strand*[5]).

The activities described below are overseen by the European Committee on Pharmaceuticals and Pharmaceutical Care (CD-P-PH) and are carried out by Committees of Experts. They are aimed at developing and promoting best practices in pharmaceutical care and the classification of medicines into prescription and non-prescription medicines.

Key Facts and figures

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.



Based on earlier work, detailed testing protocols were developed in 2013 in areas where quality assessment is of key importance for the quality of pharmaceutical care in Europe:

- adherence to nationally agreed clinical practice guidelines for antibiotics;
- monitoring of therapeutic plans and medicine safety by prescribers and pharmacists through linking information about patients' medical conditions and therapy in anticoagulant and antibiotic therapy;
- structured pharmacist-patient consultations (long-term medical therapy; patients needing more medicines and suffering from more than one disease at a time) via "My CheckList";
- implementation of the pharmaceutical care philosophy and working methods in Europe.

5. Hepler, D.D. & Strand, L.M, Opportunities and responsibilities in pharmaceutical care, *Am J Hosp Pharm.* 1990 Mar; 47(3):533-43.

The studies were initiated in 2013, with results expected in 2014. 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 use for policy-makers and professional associations in standard-setting.

General matters and policies

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 approved a project and established an ad hoc group of experts that will draft guidelines on the criteria for the elaboration, re-evaluation and maintenance of paediatric pharmacy-preparations. These guidelines are intended to provide the basis for a future harmonised "European Formulary for Paediatric Formulations", which will be established based on existing national formulations in cooperation between the European Pharmacopoeia Commission and the CD-P-PH.

Promoting the implementation of 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*" drafted by the CD-P-PH/PC Committee of Experts, key elements for specific guidance have been drafted in 2013 in the following areas:

- the dispensing of a patient's medication required to cover a certain period of time by machines which deliver the required units of different medicines in one container or pouch (ie automated dose dispensing systems). The guidance will facilitate that automated dose dispensing takes place when appropriate for the type of patient, their clinical needs and the supportive care that is available to them, for the type of medicine and for the care setting;
- general quality and safety norms for bringing medicines to the strength required for administration through adding a liquid (reconstitution).

The Committee of Experts on the Classification of Medicines as Regards their Supply (CD-P-PH/PHO) establishes and promotes good classification practices. Its work is centred on patient safety and the accessibility of medicines in Europe. It issues annual recommendations to health authorities for the classification of medicines into prescription and non-prescription medicines, as this is currently not harmonised in Europe.

Publications, databases and websites

The annual update leading to the 2013 classification recommendations was concluded and is available on the EDQM website[6]. Furthermore, the review of the classification of medicines for treatment of skin infections and other diseases affecting the skin was finalised in 2013 and will be published in 2014 on the EDQM website.

Throughout 2013, the web published database (MELCLASS), which presents the classification status of medicines in the member states, was continually updated. (www.edqm.eu/melclass).

Communication with partners and stakeholders

In 2013, relevant associations such as the European Association of Hospital Pharmacists (EAHP), the International Pharmacists Federation (FIP) and the EuroPharm Forum provided scientific and public health-oriented input to the "Indicators" and "Reconstitution" work streams. A meeting with the Association of the European Self-Medication Industry (AESGP) took place to discuss progress in the classification of medicines.

6. See Revisions of the appendices of Resolution ResAP(2007)1 "*on the classification of medicines as regards their supply*" and Database on the classification of medicines at http://www.edqm.eu/melclass/.

Events

The quality of pharmaceutical care indicators project was presented at the Symposium for Senior Pharmaceutical Policy-Makers "*Achieving Responsible Use of Medicines – Real Patients, Real Policy, What Really Works?*", held in August 2013 in Dublin (Ireland). It is expected to mobilise stronger political will to develop pharmaceutical care indicators.

ANTI-COUNTERFEITING ACTIVITIES

Combating crime to protect public health

During 2013, the EDQM continued to develop its comprehensive anti-counterfeiting strategy at different levels. This is essential to ensure that the Public Health mission of the EDQM in the area of the quality of medicines and healthcare is not undermined by criminals and rogue actors operating in unregulated areas as well as in the legal supply chain.

Targeted programmes and projects

MEDICRIME: risk management and prevention

Public health needs to be protected from falsified/counterfeit medicines and similar crimes threatening health. These crimes firstly pose a major threat to patients, who are particularly vulnerable, and also compromise the integrity of healthcare systems, public security and people's welfare.

The CD-P-PH Steering Committee and the Committee of Experts on minimising public health risks posed by counterfeit medical products and similar crimes (CD-P-PH/CMED) are constantly developing and promoting best practices in the protection of public health from counterfeit and other illegal medicines. Their work programme comprises multi-sectorial prevention and risk management strategies, support for the implementation of relevant legislation, transfer of know-how, specific policy proposals and practical tools. The Council of Europe's MEDICRIME Convention provides states with a powerful legal framework to prevent and combat counterfeiting of medical products and similar crimes. It introduces common standards for effective legislation, prevention, prosecution of criminals and protection of victims. Having been involved in the Convention's development and adoption process from the outset, both the CD-P-PH and the CD-P-PH/CMED contributed signifi-cantly in 2013 to the promotion of the signature and ratification of the MEDICRIME Convention. As of December 2013, 23 states have signed the MEDICRIME Convention, including three states outside Europe. Two European states have legally implemented ("ratified") the Convention in their domestic legislation.

In 2013, the CD-P-PH/CMED assisted in the development of a database (named "Know-X") for storing comprehensive information on medicrime cases once the investigation of the case is completed. Know-X is intended to host chemical analytical information as well as risk management and prevention information related to medicrime cases. Therefore, its development benefits from cooperation with the OMCL working group on counterfeit medicines (*see page 21*). In addition to its value for OMCLs, the database will speed up action by health and law enforcement authorities on suspect medicines and support the signatory states of the MEDICRIME Convention in terms of trend monitoring and follow-up. Know-X will be operational in 2014.

The concept of a network of single points of contact (SPOCs) for medicrime, based on the Council of Europe model and inspired by the Convention's specific provisions, was strongly supported at a workshop on 22-23 May 2013 in Seoul (Korea) for authorities and stakeholders in the Asian-Pacific Economic Cooperation (APEC) region in the context of the APEC Life Science Innovation Forum (LSIF). This opened the door to better international cooperation among states at international level and proved the model's utility and acceptance. The EDQM had drafted the concept with a view to supporting a harmonised approach towards networking among SPOCs in the APEC region; a third of the APEC members hold observer status with the Council of Europe or the European Pharmacopoeia Commission.

In 2013, a pilot study aiming to evaluate an approach for screening health damage caused by medicrime was carried out among healthcare establishments in five countries and four hundred patients.

eTACT: anti-counterfeiting traceability service for medicines

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 is intended to provide a system that can be used by authorities and stakeholders (ie manufacturers, distributors, healthcare professionals and patients) across the entire medicines supply chain, from the 37 member states of the Ph. Eur. Pharmacopoeia Convention 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 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 public 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 coordination with regulatory authorities and to prevent the misuse of data.

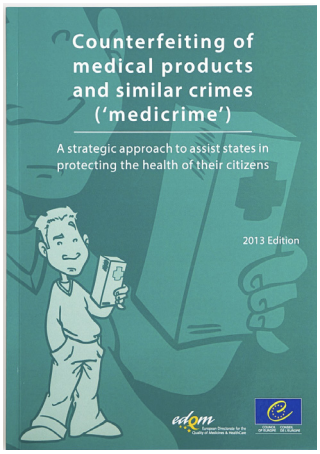
In 2013, the comments gathered from all over Europe during eTACT workshops were included in the User and Business Requirements document for the future eTACT service to prepare for its flexible integration in the future global landscape for pharmaceutical traceability. This is also ensured by the use of globally recognised interoperability standards. Interfacing with national, EU, European and global initiatives in this area will be vital for the deployment of cost-effective systems in the legal medicines supply chains over the coming years. Furthermore, the governance of the future eTACT service was discussed with authorities from Ph. Eur. member states, patients associations and operators of the supply chain.

API Fingerprint Programme

After a first phase focusing on specific methods for specific sources of Active Pharmaceutical Ingredients (APIs) at risk of being counterfeited, the project was reoriented to base the selection of target APIs on a risks analysis by the Official Medicines Control Laboratories (*see page 21*). A pilot Market Surveillance Study (MSS) on selected groups of APIs (macrolide antibiotics and statins) was conducted in 2013. It was decided to focus initially on testing for residual solvents by GC-MS, keeping the option open to perform additional testing at a later stage. The aim is to determine the authenticity of the same API from different sources and to be able to make a distinction between all of them. The introduction of chemometric methods will become necessary and scientific discussions on this topic have been stepped up among OMCLs within the framework of the project. This will require close collaboration and work sharing. The possible need for specific training was also addressed in this connection.

Publications, databases and websites

The 76-page booklet "*Counterfeiting of medical products and similar crimes (Medicrime). A strategic approach to assist states in protecting the health of their citizens*" was published in English and French. It presents approaches for aligned cooperation among authorities and stakeholders in the manufacturing and distribution chain of medical products, and takes account of earlier research on a grid for specific actions and cooperation for authorities.



Communication with partners and stakeholders

The Secretariat and delegations of the Committee of Experts CD-P-PH/CMED promoted the MEDICRIME Convention and related activities at an event organised by the United Nations Office for Drugs and Crime (UNODC) in February 2013. They also contributed to a training seminar for competent health and law enforcement authorities in Asia hosted by the Singapore health authorities, in the context of the APEC, in April 2013.

As a follow-up, the EDQM has significantly contributed to the APEC project on Global Medical Product Integrity and Supply Chain Security, by leading the working group on the previously mentioned Single Point of Contact (SPOC) and by contributing to the working group on Track and Trace Systems.

The eTACT project team met manufacturers of pharmacy Point-of-Sale (POS) systems during a technical workshop in Strasbourg (France) in March 2013; this was organised to fine-tune the specific business processes and constraints of POS systems to be interfaced with future traceability systems deployed in the legal supply chain, and in particular at pharmacy level. The workshop was based on the current live demo eTACT system used by EDQM to test the functionalities of the future eTACT system. The observations collected during the workshop helped the EDQM to increase the flexibility and inter-operability of the future eTACT system.

Events

In October 2013, the EDQM, in cooperation with the Criminal Law Division of the Council of Europe's Directorate General of Human Rights and Rule of Law, organised an international conference on 'Counterfeiting of medical products and similar crimes: how to combat these crimes and protect public health at global level' at its premises in Strasbourg (France). For the first time, 70 senior officials from health and law enforcement authorities from Africa, Asia, America and Europe discussed together the best approaches to fighting medicrime, including avenues for future collaboration in the legal and public health fields so that the MEDICRIME Convention can be ratified by as many countries as possible worldwide.

The conference programme was specifically designed for the observer states of the Council of Europe and Ph. Eur. Commission with a focus on the practical issues surrounding the implementation of the Convention, the different legal systems and procedures that exist and the lessons learnt from states that have already signed or ratified it. There were also plenty of opportunities for networking and dialogue and it provided an ideal platform for the development of international relations among the states. The CD-P-PH and the CD-P-PH/CMED contributed significantly to the programme and conclusions of this conference.

The two-day event also included a press briefing to update the media on the status of the Convention and to inform them of the EDQM's role in combating the counterfeiting of medical products and similar crimes.

The EDQM was invited to participate in the *5eme Journées Médicales Guinée et Région Rhône-Alpes*, held in May 2013 in Conakry (Guinea). The meeting was organised by the Ministry of Health & Public Hygiene, the Facility of Medicine, Pharmacy and Odonto-Stomatology and *France-Guinée Coopération*. The aim was to inform delegates in order to promote awareness and understanding of the MEDICRIME Convention.

Within the framework of the CD-P-PH/CMED-supported training platform for customs, police and health officials to combat medicrime, the EDQM organised:

- a regional training session for officials from Estonia, Finland, Lithuania, Latvia, the Russian Federation and Sweden in May 2013, together with the Health Care Inspectorate of Latvia;
- a regional training session for officials from Angola, the Democratic Republic of Congo, the Republic of Congo and Zambia in November 2013, together with the Ministry of Health, Directorate of Pharmacy and Medicines, Democratic Republic of Congo. This was the first training session for Single Points of Contact (SPOCs) under the MEDICRIME Convention in a region outside Europe.

And finally, a regional conference was organised in November 2013 together with the Criminal Law Division of the Directorate General Human Rights and Rule of Law (DGI) of the Council of Europe. It took place in Madrid, Spain, one of the two countries with Ukraine having ratified the MEDICRIME Convention. The objective of the Conference, which was opened in the presence of the Spanish Ministers of Justice and Health was to promote the practical implementation of the Convention. The audience included officials responsible for policy-making, representatives of judicial, health and enforcement authorities, including the Spanish ministers of Justice and Health, as well as state prosecutors, heads of police and customs agencies, head of medicines agencies and members of relevant international and European institutions and organisations. In total 14 countries were represented.

COSMETICS AND FOOD CONTACT MATERIALS

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 come into contact with food.

The work programme is 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 34 member states and 3 observers to the European Pharmacopoeia Convention follow or contribute actively to the work. The EU Commission (DG SANCO), its Joint Research Centre (JRC) and the European Food Safety Authority are able to send representatives to the meetings of this Committee and its subordinate expert groups.

In the field of cosmetics, the focus of the work is on the new European network of Official Cosmetics Control Laboratories (OCCLs). So far, more than 30 official laboratories participate in regular network activities, including laboratories in 16 Member States of the European Union. Concerning food packaging, quality and safety requirements for non-plastic materials are being harmonised and test methods are being developed and kept up-to-date.

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 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 more than 30 control 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 DG SANCO and the 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 finalised in 2014), 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 intended for use on or by children and product compliance with EU regulations has been tested in an MSS started in 2012 (to be finalised in 2014). Shampoos, skin creams, bath lotions and several other product types will be tested for their compliance with relevant European or national regulations.

Proficiency Testing Scheme (PTS) studies are carried out to verify the laboratory performance concerning the testing of specific cosmetic ingredients and to ensure that test results are comparable in Europe. In 2013, the range of products involved in these studies included fragrances and hair dyes. The amounts of *allergenic substances* (restricted by European regulations) and of *phthalates* (prohibited) were determined in fragrances, while hair dyes were tested for their content of the cosmetic ingredient *p-phenylenediamine* (restricted).

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 are addressed by Council of Europe Resolution CM/ResAP (2012) 1, which was adopted and published in 2012 ("*Safe Cosmetics for Young Children*", 1st Edition).

A Spanish version is now available online from the Agencia Española de Medicamentos y Productos Sanitarios (AEMPS).

Tattoos and permanent make-up

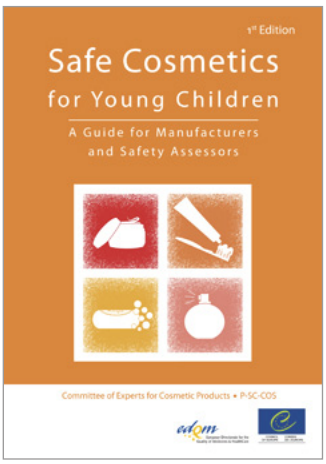
To implement the recommendations of Council of Europe Resolution AP (2008) 1 "*on tattoos and permanent make-up*", the compilation of safety and documentation requirements for tattoos and permanent make-up is under preparation. This document is expected to be finalised and published in 2014.

Packaging materials and articles for food contact

Resolution CM/Res(2013)9 "*on metals and alloys used in food contact materials and articles*" was adopted in June 2013. This Resolution has been published together with quality requirements for materials such as aluminium foil, kitchen utensils, coffee machines etc. where no EU regulation exists. Council of Europe member states agreed on Specific Release Limits (SRLs) for metal ions that are released from materials and may be transferred from packaging or containers to food.

For example, aluminium release should not exceed 5 mg/kg (measured in food or food simulants), nickel release should not exceed 0.14 mg/kg, and lead should not be released in amounts greater than 0.010 mg/kg. Detailed instructions on how to perform laboratory testing are described in the new Technical Guide. Transitional measures have been recommended to national food authorities.

Furthermore, the P-SC-EMB Committee of Experts decided to completely 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 2014.



List of committees coordinated by the EDQM

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 2013, its membership now comprises 38 signatory parties to the Convention (37 states and the European Union). The 26 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 medicines on 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 2013, 2,240 quality standards and 346 general texts including methods of analysis 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 8th 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-funded by the European commission and 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)

Since 2007, the EDQM has been responsible for the scientific secretariat of the Council of Europe's activities in the field of blood transfusion, with the European Commission also co-funding a number of activities.

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*".

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 Similar 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. 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 (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.

PREMS 09914– PRDD-14-08

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It comprises 47 member states, 28 of which
are members of the European Union.
All Council of Europe member states have signed up to
the European Convention on Human Rights, a treaty designed
to protect human rights, democracy and the rule of law.
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the implementation of the Convention in the member states.

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