

# ANNUAL REPORT 2014

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



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### **French edition**

*Rapport annuel 2014*

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# Foreword

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*by Susanne Keitel, Director*



**2** 014 was a very special year for the EDQM: 50 years ago, the Convention on the Elaboration of a European Pharmacopoeia was adopted by the Council of Europe to create a European Pharmacopoeia (Ph. Eur.) which ensures the same quality of medicines for all European citizens. 2014 also marked the 50th anniversary of the creation of the Ph. Eur. Secretariat – today known as the EDQM – which is responsible for a vast portfolio of activities contributing to the protection of public health.

■ In 1964, eight pioneering countries laid the first stones of what has since become a true, united Europe in terms of the quality and control of medicines and healthcare. Ever since, national pharmacopoeias have worked together to build a European Pharmacopoeia. Now in its Eighth Edition and consisting of more than 2600 analytical standards, the Pharmacopoeia provides a pan-European setting for states to come together to find common ground and to pool resources and expertise.

■ Activities such as the Biological Standardisation Programme and the development of an efficient Network of Official Medicines Control Laboratories have been made possible thanks to this pan-European co-operation.

■ Today, the Ph. Eur. Commission adopts on average 200 texts every year, based on a unanimous vote of its 37 member states during its sessions. The strict requirements of the Ph. Eur. apply to all medicines, regardless of their origin, method of manufacture or type, and independent of whether they are intended to treat human or veterinary patients. Today, the Ph. Eur. is a reference well beyond the confines of our continent. Twenty-seven countries and organisations from all over the world, including WHO, have observer status and can participate in the work of the Ph. Eur. Commission and its more than 70 groups of experts and working parties.

■ However, in an era of globalisation, harmonisation of standards throughout Europe is not enough. This is why the Ph. Eur. has been heavily involved in pharmacopoeial harmonisation since 1989 when it set up the Pharmacopoeial Discussion Group (PDG) jointly with the Japanese and US pharmacopoeias, working together to reduce the costs of research and production of medicines by adopting standards applicable in all three regions of the International Conference on Harmonisation (ICH). In addition, the Ph. Eur. is active in a number of bilateral harmonisation initiatives worldwide and strongly supports the development of Good Pharmacopoeial Practices under the auspices of WHO. In this context, the EDQM hosted the International Meeting of World Pharmacopoeias in October 2014.

■ 2014 also marked the 20th anniversary of the European Network of Official Medicines Control Laboratories. Initially incepted to allow work-sharing and mutual recognition of test results between member states for market surveillance of authorised medicines and batch release of vaccines and blood products by the official control authority, the Network's activities have since been extended to include joint programmes for the detection of counterfeit and illegal medicines, testing of pharmaceutical preparations produced in community and hospital pharmacies and quality control of active pharmaceutical ingredients on the European market, to name but a few. In addition, members of the Network are also jointly preparing for future tasks, such as the testing of gene therapy products.

■ The Certification of suitability to the monographs of the European Pharmacopoeia procedure is another activity that celebrated its anniversary in 2014: 20 years ago, following a successful but informal two-year pilot phase, the procedure gained official recognition. Based on a resolution adopted by the Council of Europe's then Public Health Committee and enshrined in the pharmaceutical legislation of the European Union, the procedure assesses and validates the capacity of Ph. Eur. standards to control the quality of active pharmaceutical ingredients and excipients from a specific source. It provides the Ph. Eur. Commission with valuable information on the potential need to revise monographs. Certificates of suitability (CEPs) replace the substance part of the quality dossier in marketing authorisation applications and hence centralise the assessment of data for the benefit of both regulatory authorities and industry. Since 1999, the assessment of paper dossiers has also been complemented by risk-based GMP inspections of manufacturing sites. Since its creation 20 years ago, the procedure has been highly successful with over 6 000 applications received and CEPs accepted not only by the 37 member states of the Ph. Eur. Commission, but also in many countries beyond, including Australia, Canada, Brazil, Ghana, Saudi Arabia and South Africa, etc.

■ Since 2007, the EDQM has been entrusted with additional missions by the Council of Europe's Committee of Ministers, and is now also responsible for activities and programs in the field of blood transfusion, organ, tissue and cell transplantation, pharmaceuticals and pharmaceutical care, cosmetics and food contact materials.

■ While these examples show how the EDQM has evolved, come up with innovative solutions and acted effectively over the past 50 years, we nonetheless have to acknowledge that there are numerous challenges ahead of us. Protecting patients' health by ensuring the quality, efficacy and safety of medicines is a constant challenge. It involves keeping abreast of the latest scientific and therapeutic developments and ensuring optimum use of increasingly scarce resources. Together we will follow the course charted by our predecessors. The Ph. Eur., like all the other missions of the EDQM, is a success story, a perfect example of a European collaboration with a human dimension: it deals with issues that Europeans care about.

■ However, none of the EDQM's achievements would have been possible without the unwavering support of its member states and all those who have helped build the EDQM and taken part in its activities. In particular I would like to mention the experts from national and European authorities, universities, scientific institutes and industry who, through their expertise in a wide variety of scientific fields, have made such valuable contributions to our work. Of course I would also like to pay tribute to the EDQM staff who ensure the smooth running of all the committees and expert groups and provide a link between the past and the future of our organisation.

■ To another 50 successful years – santé!





# The EDQM at a glance

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## VALUES, AIMS AND ACTIVITIES

### **The European Directorate for the Quality of Medicines & HealthCare (EDQM): a Directorate of the Council of Europe**

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**T**he primary aim of the Council of Europe is to create a common democratic and legal area across the continent in which respect for its underlying values – human rights, democracy and the rule of law – is enforced.

— These core values form the foundations of a tolerant and civilised society and are essential for European stability, economic growth and social cohesion. They are the platform from which 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 women and children, protection of public health and trafficking in human beings. The solution to the major problems faced by society today lies in cooperation amongst all member states.

## Our mission

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— 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 publishing official standards for 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 that these official standards are applied to substances used to produce medicines;
- ▶ coordinating a network of Official Medicines Control Laboratories (OMCLs) between member states to pool expertise and rationalise limited resources;
- ▶ proposing ethical, safety and quality standards:
  - for the collection, preparation, storage, distribution and appropriate use of blood components for blood transfusions;
  - 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.

## Who are we?

■ The EDQM traces its roots back to 1964, when the Council of Europe adopted the Convention on the Elaboration of a European Pharmacopoeia with the aim of creating a common European Pharmacopoeia. The “European Pharmacopoeia Secretariat” was set up pursuant to Article 9 of the Convention and, over the years, has gradually emerged as a directorate of the Council of Europe in its own right, with successive name changes reflecting the new tasks assigned to it. In 2014 the EDQM employed 300 staff and was divided into nine administrative entities.

## Contributing to the protection of public health

■ The EDQM protects public health via 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 as part of the REACH programme and the ozone-depleting substances regulations).

■ In 2014 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 substances considered hazardous.

## Continual investment in sustaining EDQM’s quality management system

■ The EDQM is ISO-certified for a number of its activities. After a comprehensive three-day certification audit in December 2014, the French accreditation body, AFNOR Certification (AFAQ), decided to maintain its ISO 9001 certificate.

■ The EDQM has ISO 9001:2008 certification 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 for 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 publication of guidelines related to the Official Control Authority Batch Release procedure (OCABR) for batches of human biological medicinal products (blood and vaccine);
- ▶ Management of the elaboration, revision, correction and suppression of Ph. Eur. texts, their publication in printed and electronic format, and their distribution; and
- ▶ Carrying out laboratory studies.

■ Certification of compliance with ISO 9001:2008 requirements is proof that the policies, practices and procedures in force at the organisation ensure that the services and products provided to customers and stakeholders are of consistent quality.

■ In February 2014, the EDQM laboratory underwent a first ISO 17025:2005 standard follow-up audit conducted by the Belgian accreditation body BELAC. Certification was maintained for the most common techniques used in the laboratory. This certificate demonstrates that the EDQM laboratory operates a quality management system, is technically competent<sup>1</sup> 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, premises and environmental conditions, equipment, traceability and reporting.

■ With the maintenance of its ISO 9001 certification and its ISO 17025 accreditation, customers and stakeholders can be confident that the EDQM is dedicated to maintaining the highest efficiency and response capacity whilst working towards 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.

## THE 50TH ANNIVERSARY CELEBRATIONS

■ In 1964, eight pioneering countries laid the first stones of what has since become a true, united Europe in terms of quality and control of medicines and healthcare. 2014 is a triple milestone year since it marks not only the 50th anniversary of the Ph. Eur. but it is also 20th birthday of both the certification of suitability to the Ph. Eur. monographs procedure and the European Network of Official Medicines Control Laboratories.

### Official Visits

■ In February, the Deputy Secretary General of the Council of Europe, Ms Gabriella Battaini-Dragoni, was given a tour of the EDQM. The main purpose of her visit was to familiarise herself with the EDQM's activities and the challenges it faces in a global context. In an open exchange with the management team, she stated that she was particularly proud of the work being carried out by the European Pharmacopoeia and of its international reputation. She shared examples of the occasions when the EDQM was regularly mentioned for its work in the field of medicinal product quality control and in the fight against counterfeit medicines.

■ In April, the President of the Parliamentary Assembly of the Council of Europe (PACE), Ms Anne Brasseur, also visited the EDQM and its facilities. The President met with EDQM Director Susanne Keitel and was given an update on the work and activities of the Directorate, emphasising its close collaboration with the Council of Europe member states and with the different European institutions.

During her visit, Ms Brasseur was taken on a behind-the-scenes tour of the EDQM laboratory and its technical facilities.

■ Later that month, the EDQM met with a delegation from Rozdranadzor of the Russian Federation. This visit focused on the different activities of the EDQM, their impact and achievements, and the possibilities for future cooperation between the two organisations.

### International conference "50 Years of Leadership in the Quality of Medicines – Paving the Way for the Future"

■ In early October, nearly 300 delegates and experts from 45 countries gathered in Strasbourg for a three-day conference organised to mark the 50th anniversary of the EDQM and the Convention on the Elaboration of a European Pharmacopoeia.

■ The conference welcomed regulators and authorities from around the world, including the European Commission, the European Medicines Agency (EMA), Swissmedic and representatives from European Pharmacopoeia observer states such as Australia, Brazil, Canada and Singapore, World Health Organization (WHO), sister pharmacopoeias together with industry associations.

■ The conference was opened by Ms Gabriella Battaini-Dragoni, Deputy Secretary General of the Council of Europe, and Ms Anne Brasseur, President of the Parliamentary Assembly of the Council of Europe, both of whom expressed the organisation's appreciation for the invaluable contributions of the European Pharmacopoeia and the EDQM to protecting public health. In his address, the Chair of the Ph. Eur. Commission, Jean-Louis Robert, spoke of his aspirations for the Commission and thanked the delegations for their continued support and dedication.



■ The programme included several workshops whose feedback was presented to the Ph. Eur. Commission in November to allow any issues raised to be taken into consideration, especially during decision-making on future directions. This feedback is summarised below:

- ▶ *Experiences with European Pharmacopoeia monographs and expectations for the future:* the feedback on the use of Ph. Eur. monographs and general chapters was very positive. The Ph. Eur. was perceived as being close to its users and working hand-in-hand with its various stakeholders. Recommendations included ensuring the early availability of reference standards, provision of guidance on the cross validation of alternative methods, and the frequency of revisions to cover impurity profiles and new scientific and regulatory developments. The Ph. Eur. was also encouraged to pursue harmonisation/convergence with other pharmacopoeias.
- ▶ *Quality by Design (QbD):* the Ph. Eur. provides a framework for the application of QbD in its General Notices and a number of specific chapters. This workshop concentrated on its role within this new Quality Paradigm, more specifically the application of QbD to analytical methods and its potential impact on Ph. Eur. monographs. Ph. Eur. methods remain the reference for regulators, and more experience in the application of QbD was considered necessary. “Easier” methods should be dealt with first before attempting to tackle the more complex and examine the quality of analytical methods together with the quality of the product and its manufacturing process.
- ▶ *Finished product monographs (FPM):* this workshop was the ideal setting for participants to express their views on the Ph. Eur. Commission's decision to draw up monographs on chemically-defined finished products. The dissolution test was identified as a critical issue and the fact that this test needed to be discriminatory was highlighted. Participants also requested that the monographs be harmonised between the different pharmacopoeias and called for more information on the principles of elaboration or revision and for industry involvement in these discussions.
- ▶ *Impurities:* during this workshop, the new guidelines covering particular types of impurities, for instance, genotoxic or elemental impurities, and the analytical challenges involved in their determination, were discussed along with an implementation strategy. Ph. Eur. monographs provide a high degree of transparency, listing specified and unspecified impurities and the different impurities controlled by each method. Close collaboration with industry was considered crucial to obtaining all the necessary information on impurities as well as necessary samples. The importance of striking the right balance between regulatory requirements and industry practical feasibility was stressed and stakeholders expressed their need for support in the implementation of the new ICH guideline on elemental impurities (ICH Q3D).
- ▶ *Role of the OMCL Network:* participants received first-hand information on the OMCL's harmonised quality-system approach and the impact of independent testing by OMCLs in various (product) areas. Areas highlighted for further growth and development included collaboration between OMCLs, assessors and inspectors, post-marketing surveillance programme (PMSs) and market surveillance studies (MMSs).
- ▶ *Combatting Illegal Medicines:* the workshop addressed the different complementary facets of a holistic approach to combatting illegal practices in the pharmaceutical field. One area highlighted for concern was the quality and authenticity of dietary/food supplements and the need to reinforce legislation on medicines “disguised” as dietary/food supplements. The network approach taken by the Council of Europe/EDQM to the fight against counterfeit/illegal medicines, expressed through the MEDICRIME Convention and the Single Points of Contacts (SPOCs) model, was praised. Recommendations included fostering strategies to raise awareness and identify harm, providing state-of-the-art monographs, and developing new approaches, for example, a link to pharmacovigilance signals.

- ▶ *Pharmacopoeial harmonisation*: this workshop provided an insight into current pharmacopoeial harmonisation initiatives and discussed their opportunities and challenges. There was a call for more transparency on the harmonisation process and the need to prioritise the topics for harmonisation. Positive feedback was received on the bilateral prospective API harmonisation pilot and great interest expressed on whether this initiative would be continued and opened up to further APIs and excipients. Finally, participants also showed their support for the facilitation of global harmonisation of pharmacopoeial standards through the development of Global Pharmacopoeial Practices under the auspices of WHO.
- ▶ *Biologicals*: this workshop summarised the latest developments in the Ph. Eur. and discussed the specific challenges posed by the biotherapeutics of the future. Overall, there was support for the existing general chapters and general monographs on biologicals; however, attention was drawn to the need for flexibility and further harmonisation. The application of the P4 procedure was considered to be a two-phase process; as a starting point, an evaluation of users' needs and the elaboration of monographs on innovator products were considered necessary, followed, as more biosimilars emerged, by further evolution and standardisation of thinking. Close collaboration between pharmacopoeias, industry and regulators was also deemed important. The work of the Ph. Eur. on advanced therapy medicinal products (ATMPs) was believed useful, although product-specific monographs are far from being a reality today.
- ▶ *Certification*: participants received an update on the use of CEPs worldwide and of the related inspection programme. Discussions focused on how the procedure can best serve the needs of users, whether the competent authorities or industry. The transparency of the Certification procedures and the clear timelines were appreciated by users. The evolution of the procedures in line with developments in the international regulatory environment and the acceptance of CEPs by authorities outside its Member States were also encouraged. As regards API inspections, international cooperation was recommended with a view to further reducing the burden on manufacturers and to save resources while intensifying oversight of API manufacturers.

▶ *Herbals*: the workshop discussed new approaches in analytical testing of herbal drugs and preparations and related challenges in the detection of specific impurities/contaminants. The introduction of HPTLC for the quality control of herbals was raised but this needs further discussion with stakeholders. The extensive battery of tests described for dried herbal drugs was considered inappropriate for fresh herbal drugs. Instead, the participants recommended different levels of analytical requirements depending on the provenance of the fresh herbal drug and the methods by which it is processed into the herbal drug preparation. In addition, mandatory general tests for pesticides in essential oils and for arsenic in herbals drugs were considered unjustified.

■ The conference programme, presentations and a detailed summary of the recommendations are available for download on the EDQM website.

## Journalist Workshops

■ For the first time, the EDQM organised three bespoke media workshops (Strasbourg, Vienna and Brussels) for media professionals to give them a "close up and personal" insight into the work and role of the organisation. Depending on the audience, the workshops addressed topics that regularly get news coverage and maximum attention from the general public, such as counterfeit medicines, reimbursement of medical costs, generic medicines and the quality control of medicines.

■ With today's 24/7 news cycle and the unprecedented number of news resources available, the competition for audience attention is fierce. Hence, the ability to stand out from the crowd and deliver the latest news in the most captivating manner possible to garner coverage and visibility is of the utmost importance.

■ These workshops gave the EDQM the opportunity to build a more effective relationship with the different media, to identify which "stories" and topics appeal most, and poll what they already know about the organisation, what they are saying or thinking. It was the ideal occasion for the EDQM to develop direct connections with the press to improve coverage in the future.

■ Two of the venues were chosen to coincide with the country holding the Chairmanship of the Council of Europe and were organised with the support of the national regulatory agency (the Austrian Agency for Health and Food Safety - AGES and the Belgian Federal Agency for Medicines and Health Products - FAMHP).



## EDQM Exhibition

■ During the Council of Europe Parliamentary Assembly Session in June, the EDQM inaugurated its 50th Anniversary exhibition "The EDQM turns 50: to your good health!". On behalf of the Deputy Secretary General of the Council of Europe, Ms Gabriella Battaini-Dragoni, the Director General for Democracy of the Council of Europe, Ms Snežana Samardžić-Marković, unveiled the new exhibition which highlights the importance and the daily impact of the work conducted by the EDQM in the protection of public health. Permanent Representatives to the Council of Europe, vice-Presidents of Committees, members of the Sub-Committee on Public Health, together with EDQM and Council of Europe staff, gathered in the Lobby of the Chamber to view the exhibition which featured 11 panels covering three themes: the European Pharmacopoeia, the OMCLs Network and the Certification of Suitability to the Ph. Eur. procedure. Personal statements of Jean-Louis Robert (Chair of the Ph. Eur. Commission / Laboratoire national de santé (LNS), Luxembourg), Christa Wirthumer-Hoche (Austrian Agency for Health and Food Safety (AGES), Austria), Philippe Girard (Swissmedic, Switzerland) and Andrea Cseh Palos (National Institute of Pharmacy (NIP), Hungary), gave visitors the chance to experience the significance and diversity of the work being performed by the organisation through the eyes of different stakeholders. These expert testimonials show why cooperation, work and resource-sharing at a European level are so important.

■ The exhibition went on display in Bern (Swissmedic, May), Luxembourg (LNS, September) and Brussels (Federal Public Service Employment, Labour and Social Dialogue, November), and was also accompanied by a brochure and a video clip which can be viewed via the EDQM's website and on YouTube. Since September 2014, a trilingual version of the exhibition (English, French and German) is on display in front of the EDQM building.

## Other events in liaison with the City of Strasbourg

■ In April, the EDQM took part in the 10th edition of the "Dialogues de Strasbourg", a forum initiated by the City of Strasbourg and the Council of Europe, to encourage local citizens' involvement and interest in themes related to the work of the organisation. The theme chosen for the debate was "Counterfeit Medicines" and the event was opened by Ms Gabriella Battaini-Dragoni, Deputy Secretary General of the Council of Europe.

■ The EDQM also participated in the Europe Day and the "Strasbourg Road Races", both yearly highlights in Strasbourg's events calendar (May). The focus was on increasing public awareness of the organisation's role and its anniversary celebrations, with the distribution of promotional materials designed to provide general information on our everyday activities and respond to questions from the general public.



DIRECTION EUROPÉENNE DE LA QUALITÉ  
DU MÉDICAMENT & SOINS DE SANTÉ

L'edqm  
Santé!





# 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 2014, some 2,267 monographs and 349 other texts – mostly cover 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*.<sup>2</sup>

■ Preparing the Ph. Eur. is the responsibility of the European Pharmacopoeia Commission (“the Commission”). The European Pharmacopoeia Department assists the Commission by providing

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.

scientific secretariat support to its groups of experts and working parties with the assistance of other EDQM entities.

### A continuous process to protect public health

■ All standards of the Ph. Eur. – elaborated or revised by the groups of experts and 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 if they intend to market their products in the signatory states to the Convention.

■ The work programme (elaboration of new/revision of existing monographs or general chapters) is decided by the Commission during its three annual sessions. In general, whenever at least 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 accessible to the public (see *Section Publications of this Chapter, page 19*).



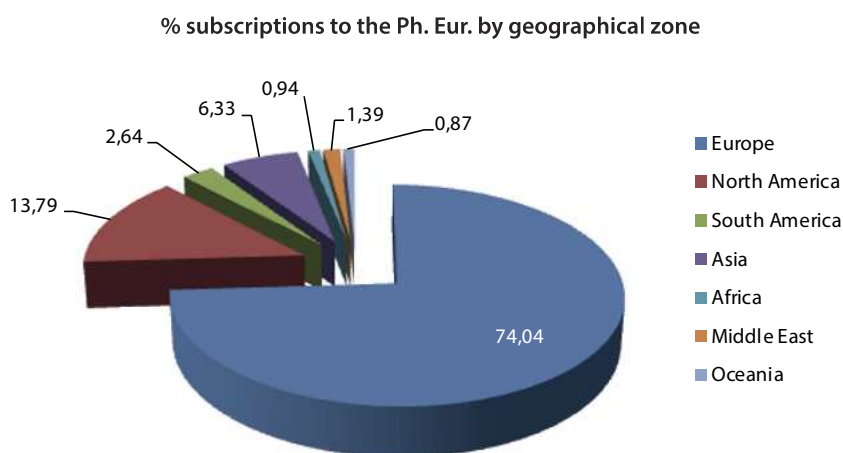
## Importance of the Ph. Eur. beyond Europe

Globalisation and expansion in international trade are creating a growing need for 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.

## Decisions taken during the three 2014 sessions of the Commission

### 26 new monographs adopted

- ▶ Monographs on two patent-protected active substances, elaborated in close collaboration with regulators and the respective innovators (P4 procedure): Imatinib mesilate (2736) and Rosuvastatin calcium (2631)



It is therefore no surprise that the Ph. Eur. is also widely used internationally. Some non-European countries (e.g. Australia, Canada) even 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 2014, there were 27 observers (including 25 countries with Azerbaijan being the latest to join the network).

## Key facts and figures

### Wide participation

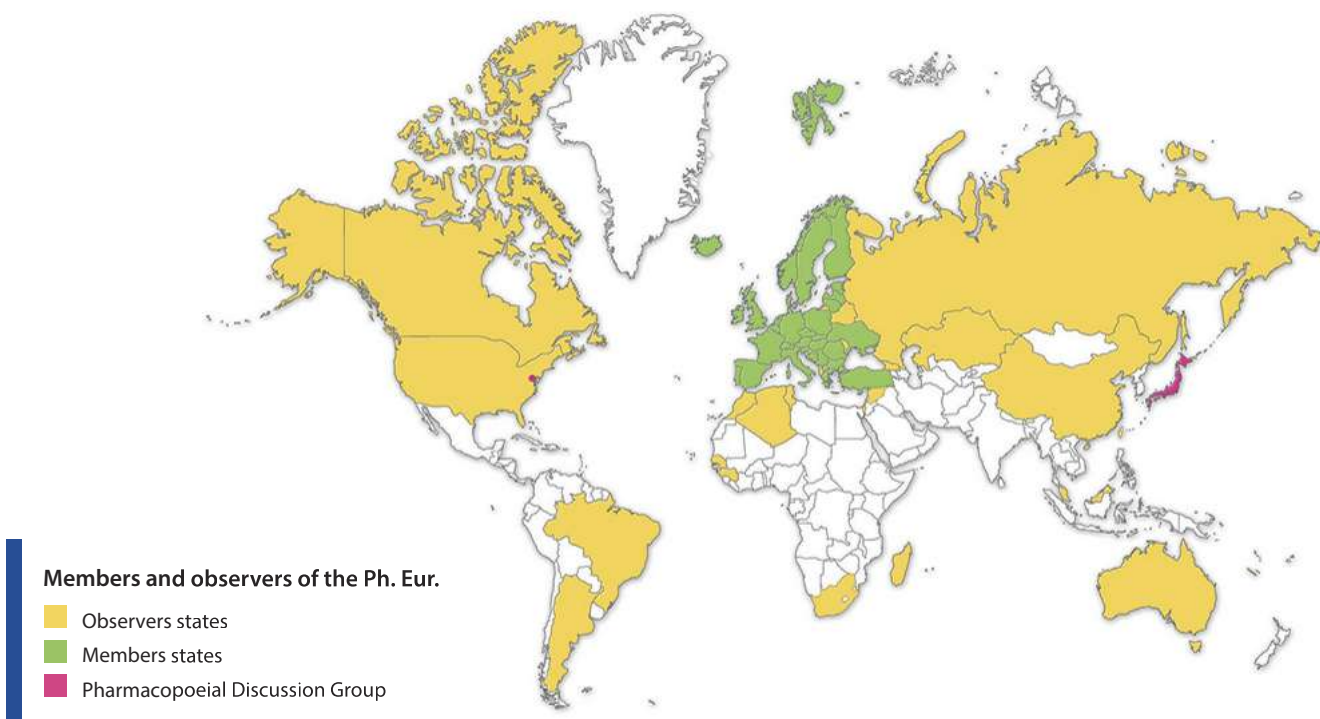
37 Member States and the European Union are signatory to the Convention on the Elaboration of a European Pharmacopoeia.

As an observer to the Ph. Eur. Commission, countries may take part in the scientific work of the European Pharmacopoeia Commission and its expert groups and working parties. Observers are welcome to attend Commission sessions and become involved in other EDQM activities for example in such diverse fields as the official medicines and cosmetic control laboratories, blood transfusion and organ transplantation, and combatting counterfeiting. Observer status also makes it easier to develop a mutually-beneficial relationship and share expertise on issues pertinent to the pharmaceutical and healthcare sector.

- ▶ 24 other new monographs: *Eplerenone* (2765), *Tizanidine hydrochloride* (2578), *Tolterodine tartrate* (2781), *Polyoxypropylene stearyl ether* (2602), *Zanamivir hydrate* (2611), *Lycii fructus* (2612), *Fluoroethyl-L-tyrosine (18F) injection* (2466), *Live attenuated intranasal influenza vaccine* (2772), *Macrogol isotridecyl ether* (2730), *Permethrin (25:75)* (1762), *Triclabendazole for veterinary use* (2609), *Anemarrhena asphodeloides rhizome* (2661), *Belladonna for homoeopathic preparations* (2489), *Copper tetramibi tetrafluoroborate for radiopharmaceutical preparations* (2547), *Exemestane* (2766), *Hamamelis bark* (2532), *Indigo plant leaf* (2727), *Nicorandil* (2332), *Petroleum rectificatum for homoeopathic preparations* (2683), *Pirfenidone* (2856), *Sodium selenite* (2740), *Solifenacin succinate* (2779), *Somatropin injection* (2370), *Staphysagria for homoeopathic preparations* (2289).

### 2 new general chapters

- ▶ Methyl, ethyl and isopropyl toluenesulfonate in active substances (2.5.40)
- ▶ Monographs on herbal drug extracts (5.23.). This information chapter will provide additional information and support for the interpretation of the general monograph Herbal drug extracts (0765).



## 191 revised texts

■ A total of 191 texts were revised, including:

- ▶ *Reference standards (5.12)*. This chapter has undergone a general overhaul to make sure that it reflects the state-of-the-art in pharmaceutical reference standards, and complies with the definitions and specifications of the corresponding ISO guides; Herbal Reference Standards (HRS), Biological Reference Preparations (BRP) and chemical reference substances for biologicals have also been added.
- ▶ The general monograph on *Herbal Drug Extracts (0765)* was extensively revised and now only covers herbal drug extracts. It gives more detailed explanations concerning the principles underlying the text and a glossary.
- ▶ 2014, saw the start of a campaign to eliminate mercury from reagents and equipment used in Ph. Eur. monographs. This has led to revision of several monographs and general chapters, such as distillation range, boiling point and potentiometric titration, to omit the use of calomel electrodes or mercury containing thermometers.

## Work programme highlights

■ In its 148th session, the Commission decided to launch a pilot phase for the writing of a product-specific monoclonal antibody (mAb) monograph using the multisource approach. The aim was to explore the possible elaboration of a number of general methodologies that could apply to a wide range of mAbs. Rationalisation of these methods enhances standardisation of different products already on the market but also those still in the development pipeline. By choosing a specific mAb, the Commission wished to test the robustness of such an approach.

■ In its 148th session, the Commission also approved the general principles for monographs on finished products containing chemically defined active substances (*for further details, see document available on the EDQM website*). The first draft of the finished products monograph on *Sitagliptin phosphate monohydrate tablets (2927)* was published in *Pharmeuropa online* for public consultation. This monograph was elaborated under the P4 procedure. Eight monographs on finished products containing chemically-defined active substances were added to the work programme of the group of experts for substances still under patent (P4), three at the 149th session and five at the 150th session.

■ In its 149th session, the Commission decided to add a general monograph on co-processed excipients on its work programme. Co-processed excipients consist of a combination of two or more excipients which are processed together in order to improve their properties without inducing a significant chemical change. A general monograph on co-processed excipients would define co-processed excipients in an appropriate manner. Common terminology would also help to prevent misuse of the term; in particular, clear distinction must be made between a simple physical mixture and a real co-processed excipient through the use of identification or Functionality Related Characteristics (FRC) tests. This general monograph could be used as guidance. It could also help to control the quality of co-processed excipients and their FRCs, but would not be used to control the quality of individual components of co-processed excipients.

■ During its 148th session, the Commission appointed the members of the Live Biotherapeutic Products Working Party (LBP). This group will be in charge of the elaboration of a monograph on Live Biotherapeutic Products, biological medicinal products that contain live micro-organisms such as bacteria or yeast. A LBP may be administered orally, vaginally or intravesically. A large number of LBPs are currently authorised on the European market and a need for harmonised quality criteria has been identified.

■ For a number of years, it has been widely agreed that too few medicines targeting the paediatric population are being developed and national formularies of unlicensed medicines (“off-label use”) for the treatment of children therefore continue to play an important role in paediatrics.

■ However, the different formularies available in Ph. Eur. member states are clearly not harmonised and monographs developed by some member states according to well-known and approved criteria may be of use to others.

■ The aim of the “PaedForm” project, which is run under the auspices of the European Committee on Pharmaceuticals and Pharmaceutical Care (CD-P-PH) in close cooperation with the Ph. Eur. Commission (*for further details on the CD-P-PH, see page 43*) is to improve access to suitable and age-appropriate medicines for children by culling acceptable unlicensed preparations from existing national formularies or individual existing formulations described by relevant national experts of the Ph. Eur. member states.

■ The members of the PaedForm Working Party (PaedF) of the Pharmacopoeia Commission were appointed during the 150th session of the Commission. This group will be responsible for the elaboration, and in the future, the revision of monographs on paediatric preparations according to criteria and guidelines

approved by the CD-P-PH. It will also be responsible for establishing and maintaining a Technical Guide for the elaboration and maintenance of monographs on paediatric preparations.

## Quality system

■ In December 2014, the EDQM’s activities related to the management of the elaboration, revision, correction and suppression of Ph. Eur. texts, their publication in printed and electronic format, and their distribution passed an ISO9001:2008 re-audit conducted by AFNOR Certification with flying colours.

## General matters and policies

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### Developments in 2014

■ A pharmacopoeia can only remain useful and state-of-the-art if it is continuously updated. Revisions take into account 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 impacting the Ph. Eur. include:

- ▶ *Implementation of the ICH Q3D guideline for elemental impurities:* the Commission and its Groups further discussed how this new guideline should be implemented in the Ph. Eur. A specific press release was issued in July 2014. The current chapter on Metal catalyst or metal reagent residues (5.20) reproducing the EMA Guideline on the specification limits for residues of metal catalysts or metal reagents (EMA/CHMP/SWP/4446/2000) will be revised and should reproduce the ICH Q3D guideline in the future, once the latter enters into force in Europe. As a consequence, the current chapter on Determination of metal catalyst and metal reagent residues (2.4.20.), which focuses on sample preparation and method suitability, will also be revised. Together with other general chapters related to elemental impurity analysis, it will be thoroughly reviewed to ensure that all comply with the latest requirements of the ICH Q3D guideline and the possibilities it offers. Last but not least, reference to the chapter on *Heavy metals* (2.4.8) will be deleted from each individual monograph for substances for pharmaceutical use for human and veterinary use. (*For further details see the press release on the EDQM’s website.*)
- ▶ *Bacterial endotoxins (BET):* at its 149th session, the Ph. Eur. Commission approved the Bacterial endotoxins Ph. Eur. policy for substances for pharmaceutical use. The policy was published in September 2014 on the EDQM website as well as in *Pharmeuropa online*.

According to this new policy, a test for bacterial endotoxins is not included in new monographs for substances for pharmaceutical use except where a specific method is to be described, for example if a specific sample preparation must be used or a specific method applied. If a test is included in the monograph, no limit is given for the test.

The requirements of the general monograph *Substances for pharmaceutical use (2034)* apply.

For existing monographs, BET specifications are kept in individual monographs for substances for pharmaceutical use. Existing limits remain in individual monographs to maintain the use of well-established limits.

In order for the policy to be applied, the following changes will be made to existing Ph. Eur. texts:

- General chapter *Guidelines for using the test for bacterial endotoxins (5.1.10)* will be expanded with further considerations regarding the setting up of limits.
- General monograph *Substances for pharmaceutical use (2034)* will be slightly reworded in order to take the above policy into account.

*More information can be found in the policy paper published on the EDQM website and in Pharmeuropa 26.4.*

- ▶ *General principles concerning finished product monographs:* the principles posted on the EDQM website must be read in conjunction with the Ph. Eur. General Notices, the relevant dosage form monograph and the general monograph on *Pharmaceutical Preparations (2619)*. The Ph. Eur. Commission will only elaborate monographs on products that have been authorised in at least one of the member states of the Ph. Eur. Convention and that contain an active substance for which a monograph has already been published in the Ph. Eur. or is on its work programme. As with other Ph. Eur. monographs, the elaboration and revision of finished product monographs will be subject to public consultation, and take into account current scientific knowledge and relevant medicinal products authorised at the time. The Ph. Eur. Commission has decided to start with the elaboration of single-source monographs on products that are potential future generics (for further details see the document published on the EDQM website).
- ▶ *Degree of hydration in the title of monographs on substances for pharmaceutical use:* the style guide of the Ph. Eur. has been revised and a new policy regarding precision of the degree of hydration in titles of monographs introduced.

When monographs refer to a hydrate form, whether well-defined or not, the corresponding degree of hydration must be indicated in the title, the chemical formula and the chemical name. When monographs cover both non-hydrates and hydrates, nothing is added to the title and the chemical name, but “xH<sub>2</sub>O” is stated in the chemical formula. These exceptions are clearly identified by adding the following sentence under Definition “It may be anhydrous or contain a variable quantity of water”. For non-hydrates, “anhydrous” is no longer specified in the title unless otherwise justified.

A proposal on implementation of this new policy will be published in Pharmeuropa 27.2 for comments. (More information can be found in the style guide available on the EDQM website).

- ▶ *General methods:* The European Pharmacopoeia currently contains more than 300 general chapters (methods and general texts). This collection of analytical tools has been compiled over many years in an attempt to keep up with the never ending quest for instrument and method innovation. As a result, while some essential texts are updated on a regular basis, others have been left unchanged: some require moderate revision whereas others need to be totally rewritten. Therefore, and in view of the extensive amount of work foreseeable, the Commission decided to seek a new revision strategy. A working party has therefore been created. This group will also be in charge of the definition and the prioritisation of the overall work program.

An initial inventory will be conducted to assess the texts and list their revision needs in order of priority. In the meantime, the group will be in charge of delegating or directly taking care of any revision process where an acute need has been identified or submitted. Ultimately the group is expected to make concrete proposals to the Commission, on the best way to tackle the revision needs of general methods.

This group will also be mandated to reflect on the content and degree of detail to be provided in general methods with a view to drafting a guide to the elaboration of general methods at a later stage. This guidance document could later be used as the basis for future revision and creation programs. The members of the groups were appointed during the 150th session of the Ph. Eur. Commission.

- ▶ *Second identification tests:* The members of the second identification test (SIT) working party elaborated a revision of a guidance document which was approved by the Commission at the 150th session. Following these activities, several monographs will be revised in 2015 in order to improve or delete second identification tests.



## Standard Terms

■ Since 1996, the EDQM has issued lists of Standard Terms, which provide harmonised vocabularies for dosage forms, routes of administration and packaging (including containers, closures and administration devices). The lists were originally drawn up in response to a request from the European Commission (EU), and cover medicines for both human and veterinary use. Standard Terms are used in the European Union Marketing Authorisation application form, the Summary of Product Characteristics (SmPC), product labelling, and electronic communications.

■ Requests for new Standard Terms are submitted to the EDQM by national authorities, the EMA or the EU, and are assessed by the Standard Terms Working Party (STWP), which consists of experts elected by the European Pharmacopoeia Commission. The STWP deals with most requests electronically so that decisions are reached as rapidly as possible, but it also meets face-to-face where necessary, usually at least once a year. Any entirely new Standard Term concept that is agreed upon is sent to the Commission for adoption by correspondence before publication. Published terms are made available to national authorities in order to allow their experts to provide translations, which are submitted to the EDQM secretariat for publication.

■ In November 2014 an entirely new version of the Standard Terms database was launched, after its structure, appearance and content were significantly overhauled. In keeping with international standard ISO 11239:2012, the structure of the database has been reorganised and considerable additional information has been added, in particular with respect to the characterisation and description of pharmaceutical dosage forms. Another considerable change is that access to the database is now free of charge, and within a month of its launch almost 2000 users had registered.

■ This revision was the ideal occasion to improve the existing search and browse features for an enhanced user experience; it also means that the Standard Terms database is now fit for use in a wider context, which is particularly important in view of the current development of a harmonised system for the identification of medicinal products (IDMP) across Europe, the USA and further afield. The IDMP project promises to fulfil a very important function in the electronic communication of medicinal product information, especially in a pharmacovigilance setting, and the new version of the Standard Terms database means that it is in an ideal position to continue providing its vital contribution to this project.

■ As of the end of 2014 a total of 32 languages were included in the Standard Terms database: Albanian, Bulgarian, Chinese, Croatian, Czech, Danish, Dutch, English, Estonian, Finnish, French, German,

Greek, Hungarian, Icelandic, Italian, Kazakh, Latvian, Lithuanian, Macedonian, Maltese, Norwegian, Polish, Portuguese, Romanian, Serbian, Slovak, Slovenian, Spanish, Swedish, Turkish and Ukrainian. It contained 860 unique Standard Terms (735 with “current” status) and over 25,000 translations.

## Achievements of the Biological Standardisation Programme (BSP)

■ The BSP is a joint EDQM-EU Commission initiative whose mandate is to establish biological reference materials, develop and validate new analytical methods, and validate alternative methods based on the 3Rs concept.

■ Since the programme’s launch in 1992, 139 BSP projects have been initiated. In 2014, 26 projects were pursued in different fields:

- ▶ Vaccines for human use: 6 projects
- ▶ Vaccines for veterinary use: 5 projects
- ▶ Plasma-derived products: 8 projects
- ▶ Biotechnology products: 7 projects

■ Six projects – all in the field of vaccines for human and veterinary use – focussed on establishing alternatives to animal experiments, three were devoted to developing or improving assays and the remaining 17 to establishing reference materials for biologicals.

■ This led to the establishment of one new reference standard (for physico-chemical testing of Erythropoietin) and three reference standard replacement batches (for assay of Erythropoietin, for Hepatitis A vaccine and for anti-D antibodies in intravenous immunoglobulin) (see *Chapter Pharmaceutical reference standards page 23 for more details*). In 2014, 13 projects were underway to establish replacement batches for existing reference standards, all prompted by low stocks; it was never necessary to stop using a reference standard owing to quality issues.

■ Commitment to applying the 3Rs concept to the field of quality control of biologicals continued in 2014. The EDQM’s efforts, through the BSP, to elaborate, validate and implement analytical methods following the 3Rs principle are widely acknowledged. The project on the replacement of animal tests for the determination of the Minimum 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 has reached the evaluation phase and results are expected in 2015.

■ A new project was launched to replace an animal test that is required by the Ph. Eur. monographs on Tetanus vaccines for both human and veterinary use. The aim is to demonstrate the absence of toxin and the irreversibility of toxoid. The proposed test consists of a very sensitive functional *in vitro* test (called BINACLE assay). A collaborative study will be run in 2015.

## 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 Pharmacopeia (USP) as members and the World Health Organization (WHO) as an observer – were held in 2014; one was hosted by the USP in Rockville (USA) in June, and the other by the EDQM in Strasbourg (France) in November.

Currently, 29 of the 36 General Chapters and 48 of the 62 excipient monographs on the work programme have been harmonised. These meetings saw the sign-off of three new excipient monographs, *Hydroxypropylcellulose, low substituted (2083)*, *Glucose Monohydrate/Anhydrous (178/177)*, and *Sodium lauryl sulfate (0098)*, and a new general chapter on *Thermal Analysis (2.2.34)* as well as a revised general chapter on *Polyacrylamide Gel Electrophoresis (2.2.31)*. Excipient sign-offs included revisions to the monograph on *Saccharin sodium (0787)*. 27 additional items currently on the work programme were also discussed in-depth with a view to resolving outstanding issues.

Following on from the discussion at its previous meeting, PDG members agreed on concrete actions to improve its working procedures and improve transparency to stakeholders. Highlights summarising the outcome of the June 2014 meeting will be made available on the websites of the three pharmacopoeias.

In light of the anticipated sign-off of the ICH Q3D guideline on elemental impurities, PDG members agreed to harmonise their general chapters on methods related to elemental impurities. They also agreed to add a general chapter on dynamic light scattering to the work programme, with the JP as the coordinating pharmacopoeia.

## 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 International Meeting of World Pharmacopoeias is organised under the auspices of WHO, with the aim of bringing together the different pharmacopoeias and discussing potential ways to strengthen collaboration and harmonisation, for example, via the elaboration of the aforementioned “Good Pharmacopoeial Practices”. Two meetings took place in 2014, one in April in London and the other in October in Strasbourg.

## Publications, databases and websites

The 8th Edition of the European Pharmacopoeia including its 2014 updates (8.3, 8.4 and 8.5) contains 2,267 monographs, including general standards that apply to groups of ingredients or dosage forms, and 349 general texts including methods of analysis.

A tablet version, which is complementary to the online version and allows optimised access for smartphones and tablet computers, continues to be supported.

Pharmeuropa, the Ph. Eur. forum is paperless and available online free of charge. The draft texts published for consultation in *Pharmeuropa online* are more easily and widely accessible to users. The objective is to optimise interaction between the Commission and its stakeholders, to give users 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 deadlines per year has remained unchanged, as have channels and procedures for sending comments on published draft texts. In 2014 *Pharmeuropa online* was accessed from 140 countries worldwide.

In November 2014 an entirely new version of the standard terms database was launched (*for further details on the Standard terms database, see page 18*).





## 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 must be adapted constantly to meet the needs of its end-users, notably the experts dealing with marketing authorisation applications (MAs) prepared by manufacturers and assessed by the competent authorities. Unlike MA dossiers, which are prepared and assessed for an individual product, the Ph. Eur. prescribes uniform and common standards applicable to numerous products and is therefore an essential tool for communication and standardisation. However, it continues to serve its users only if they express their opinions or revision requirements – hence, collaboration with competent authorities and with manufacturers and industries is crucial.

### Cooperation with national and European regulatory authorities

■ The Commission works closely 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.

■ Representatives of national authorities are members of the Ph. Eur. Commission and its 70 and more groups. National authorities and the EMA also take part in the work of the Ph. Eur. by submitting requests for revisions and reviewing draft texts published in *Pharmeuropa online*. Members of EMA working groups (i.e. for which the EMA provides 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).

### 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 dispenses with the need to harmonise national positions.

■ The EDQM organises an annual meeting of NPA Secretaries to facilitate and coordinate activities of common interest and to provide an informal forum for exchanging information. The 2014 annual meeting of the NPAs of Ph. Eur. member states took place in London (UK) in April 2014, hosted by the MHRA (Medicines and Healthcare Products Regulatory Agency). Twenty-three of the 37 member states participated in this event. The subjects discussed included current quality topics tabled at the European Medicines Agency's Joint CHMP/CVMP Quality Working Party that have a potential impact on the Ph. Eur., such as the use of co-crystals and other solid state forms of active substances in medicinal products and the quality of transdermal patches; this was also the occasion to exchange best practices ensuring good information-flow between the pharmacopoeias and regulators responsible for the quality of medicines. The importance of this continued collaboration with Health Authorities for the benefit of patients was stressed.

### Cooperation with manufacturers and industry associations

■ Ph. Eur. texts will only remain relevant if manufacturers and industry are involved in their elaboration or revision. If nominated by an NPA, representatives of manufacturers and industry can join the Groups of Experts and Working Parties; they may also be members of national delegations to the Commission.

■ Another way of taking part 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 exchanges on all aspects related to the work of the EDQM.

### Cooperation with WHO

■ The EDQM also continues to collaborate with WHO and take part in a number of joint meetings and consultations, including the International Non-proprietary Name (INN) programme, the Expert Committee on Biological Standardisation (ECBS), and the Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP).

## Events

■ The EDQM organised a number of webinars during the year.

In February, a repeat of the “Current developments in the field of the European Pharmacopoeia” was organised. The presentations focused on specific sections of the Ph. Eur. such as elemental impurities, implementation of PAT/QbD, biologicals and biotechnology products. The presentations were followed by a live Q&A session with the presenters.

In July and again in September, the EDQM organised several “live” webinar demonstrations of the new-look Extranet, designed to inform all the experts about the significant changes that had been made to the tool, what new and enhanced features had been added and how best to use it in their work for the Ph. Eur. Commission.

■ And several specific training sessions.

Two training sessions on the Ph. Eur. 8th Edition took place, in February and in July, both in Strasbourg (France). These were designed to help participants to build on their knowledge and familiarise themselves with the work and procedures of the Ph. Eur. The first session focused on biologicals (e.g. biotechnological products, peptides, human vaccines, blood products, cell and gene therapy products), while the second was devoted to chemical products.

In March, the EDQM organised a one-day training session for all Group of Experts Chairs, geared towards the newly elected incumbents. The aim was to provide these individuals with background information on the Ph. Eur. and share best practices as well as to highlight areas where the Secretariat can provide support. The training session was also open to observers.

Later in the year, the EDQM joined forces with the European Association of Nuclear Medicine (EANM) to give a training session on “Radiopharmaceuticals” in Strasbourg (France). In addition to covering Ph. Eur. fundamentals and general concepts, the programme explored topics such as SPECT and PET radiopharmaceutical preparations and chemical precursors for radiopharmaceutical preparations.

■ In September, the EDQM attended the Kazakhstan Forum of World Pharmacopoeias in Almaty, Kazakhstan, which was held on the occasion of the publication of the 3rd edition of the Kazakhstan Pharmacopoeia.



■ Later in September, the EDQM and the Indian Pharmaceutical Association (IPA) organised a joint technical conference on “Quality of Pharmaceutical Ingredients - Applying Learning to Practice”. The event coincided with the Platinum Jubilee Celebration of the IPA and attracted professionals working in the drugs and pharmaceutical sector from across the country. The programme covered European Pharmacopoeia topics such as finished product monographs and pharmacopoeial harmonisation.

■ From 6 to 8 October, nearly 300 delegates and experts from 45 countries gathered in Strasbourg (France) for a three-day conference organised to mark the 50th Anniversary of the EDQM and the Convention on the Elaboration of a European Pharmacopoeia.

Several interactive workshops were organised during the conference to encourage discussion and debate on specific themes of interest for the Ph. Eur., which included Experiences with European pharmacopoeia monographs and expectations for the future, QbD, Finished product monographs, impurities, pharmacopoeial harmonisation, biologicals and herbals. The recommendations will be presented to the European Pharmacopoeia Commission in November for further consideration. (*For further details on the Conference, see the Chapter on 50th Anniversary, page 9.*)

■ Immediately following the conference, the EDQM hosted the World Health Organization’s Fourth International Meeting of World Pharmacopoeias.

This meeting was opened by the Deputy Secretary General of the Council of Europe, Ms Gabriella Battaini-Dragoni, and the Coordinator for Quality and Safety of Medicines, Dr Lembit Rägo from the World Health Organization (WHO). It brought together pharmacopoeias from around the world and focussed on good pharmacopoeial practices and ways of harmonising pharmacopoeial standards on a global level.

■ In December, the EDQM took part in a training session in China (Beijing) co-organised by the EU-China Trade Project II (EUCTP II) and the China Chamber of Commerce for Import & Export of Medicines & Health Products (CCCMHPIE).

The EUCTP, working under the EU China trade dialogues, supports the Chinese government in developing, streamlining and harmonising its Quality Infrastructure (QI). The aim of the training session was to give delegates an update on European and Chinese Pharmacopoeias and their quality standards. The EDQM focused on the work of the European Pharmacopoeia and in particular on its working procedures, the elaboration of monographs (herbal drugs) and its work programme on traditional Chinese medicines (TCM). Various Q&A sessions then allowed delegates to raise specific issues and ask questions on subjects covered in the presentations.

Once again, the Certification Division attended CPhI China (Shanghai) and CPhI India (Mumbai). These pharmaceutical trade fairs provided a platform for the EDQM to showcase and promote the latest edition of the Ph. Eur. and meet customers face-to-face (see the chapter events under Certification of suitability to the Ph.Eur. monographs, page 26).

## Official visits

■ In August 2014, the EDQM met with the Chinese Pharmacopoeia (ChP) and the Chinese National Institute for Food and Drug Control (NIFDC). Topics discussed included future collaboration in the area of quality control and standardisation of medicines. On this occasion, the EDQM Director, Dr Susanne Keitel met with Dr ZHANG Wei, Secretary General of the ChP and Dr LI Bo, Director General NIFDC

## PHARMACEUTICAL REFERENCE STANDARDS

### Why have reference standards?

#### Ph. Eur. reference standards

■ Official reference standards (RSs) are established and monitored by the EDQM Laboratory. Their production and distribution are the remit of the Reference Standards Division (DRS). RS 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), biological reference reagents (BRRs) and reference spectra. They are officially adopted by the Ph. Eur. Commission and are the sole authority in case of arbitration. The current Ph. Eur. RS catalogue lists almost 2,600 items, which are made available by the EDQM.

■ Management of this extensive portfolio includes updating the catalogue with new RSs related to new or revised monographs and texts and replacing existing batches when the corresponding stock is running low. However, establishing RS batches is only one aspect of RS lifecycle management: other tasks include procuring candidate materials, and product classification, characterisation, manufacturing, labelling, quality control, release, storage, distribution and monitoring.



### Responsibility for WHO standards

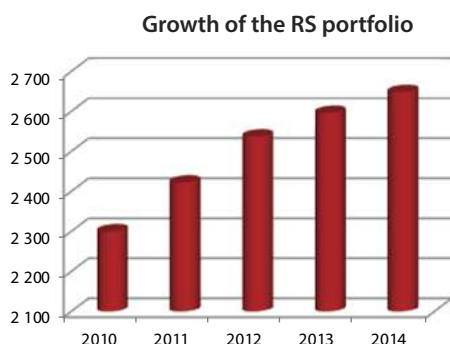
■ In May 2006 the EDQM took over responsibility for the establishment, storage and distribution of WHO International Standards for Antibiotics (ISAs). ISAs are essential for the standardisation and quality control of antibiotic drug substances and pharmaceutical drug products. They are supplied for use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

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

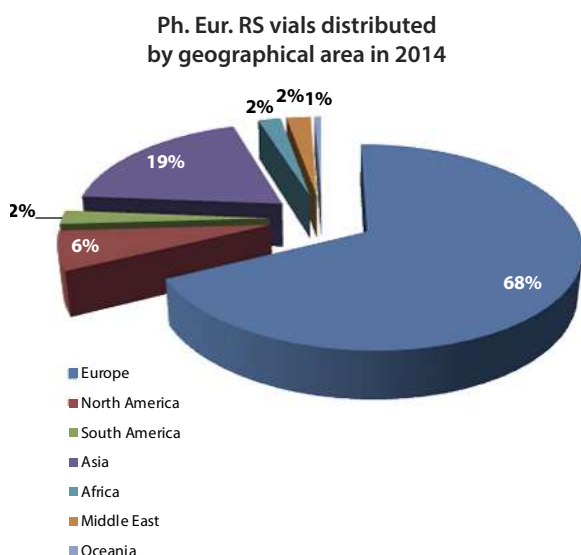
## Key facts and figures

### Reference standards for the Ph. Eur.

At the end of 2014, there were 2,648 reference standards in the Ph. Eur. catalogue.



Globalisation of the pharmaceutical industry means that Ph. Eur. RSs are widely used internationally: in 2014, Ph. Eur. RSs were distributed in 112 countries.



### New RSs adopted in 2014

In 2014, the Commission adopted 76 batches of new RSs and 172 replacement batches; 55 assay RSs have been established, 27 of which required a collaborative study.

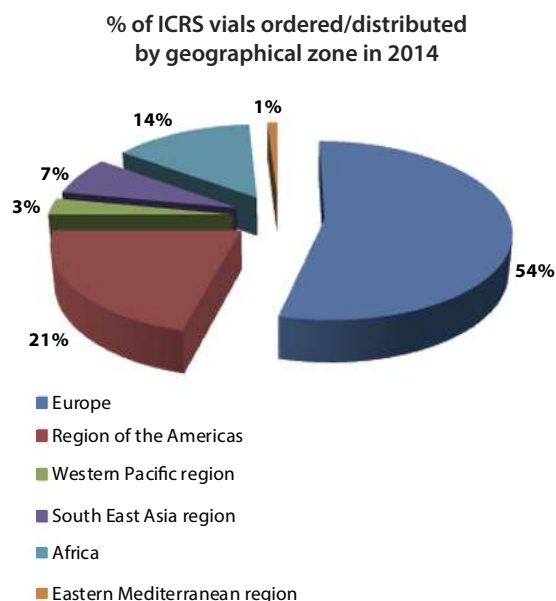
The international collaborative studies performed by the BSP in 2014 led to the adoption of four BRPs by the Commission (see Chapter European Pharmacopoeia page 18 for more details):

- ▶ Three replacement batches: Immunoglobulin panel for anti-D antibodies test BRP batch 2, Erythropoietin BRP batch 4, Hepatitis A vaccine (inactivated, non-adsorbed) BRP batches 2 and 3).
- ▶ One new CRS: Erythropoietin for physicochemical tests CRS batch 1.

### EDQM activities for WHO

#### International Chemical Reference Standards (ICRSs)

A total of 6 establishment reports were adopted by the ICRS Board: Tenofovir disoproxil fumarate ICRS 1; Efavirenz ICRS 2; Efavirenz impurity B ICRS 1; Alpha-artemether ICRS 1; Ritonavir ICRS 2 and Artemether ICRS 2.



#### International Standards for Antibiotics (ISA)

2014 saw a project launched with a view to replacing the current IS for Bleomycin. The 2nd IS for Bleomycin Complex A2/B2 was adopted by the WHO Expert Committee on Biological Standardisation (ECBS) at the meeting in October 2014. A new project for the establishment of the 4th IS for Streptomycin was also started in 2014. Results will be submitted to the ECBS for the meeting in October 2015.



## General matters and policies

The EDQM Laboratory now makes routine use of Nuclear Magnetic Resonance (NMR) for characterising and analysing substances for pharmaceutical use. NMR capacity will be further extended in the future to encompass quantitative use.

## Publications, databases and websites



In 2014, the EDQM published information leaflets for all Ph. Eur. RSs which provide users with additional useful information, e.g. monograph references, scientific information, storage conditions and – when applicable – hazard pictograms and signal words in CLP format as per European Regulation (EC) No. 1272/2008.

**INFORMATION LEAFLET Ph. Eur. Reference Standard**  
**Celecoxib impurity B CRS batch 2**

**1. Identification**  
Catalogue code: Y0001447      Unit Quantity: ca 10 mg

**2. Scientific Information**  
**2.1 Intended use**  
Reference Standard for laboratory tests as prescribed in the European Pharmacopoeia only.  
Established for use with the monograph(s): 2591.  
**2.2 Analytical information related to intended use, when applicable**  
**2.3 Uncertainty of the assigned value, when applicable**  
According to ISO Guide 34 and ISO Guide 35, for this Pharmacopoeial standard the uncertainty of the assigned value is not stated since it is considered to be negligible in relation to the defined limits of the method-specific assays for which the reference standard is used. Please also refer to Ph. Eur. chapter 5.12.  
**2.4 Validity**  
A statement on the validity of the batch (Batch Validity Statement) can be printed directly from the EDQM website (Reference Standards Database).  
**2.5 Instructions for use**  
Allow the closed container to equilibrate at ambient temperature before breaching to avoid uptake of moisture. Use "as is". Do not dry/desiccate before use. Once the container has been breached, stability of the contents cannot be guaranteed. It is for immediate use.

**3. Storage conditions**  
Store the original container at +5°C ± 3°C, protected from light. The container should not be opened until required for use.

**4. Safety**  
**CLP Hazard Classification**  
For laboratory use only. Handle in accordance with good occupational hygiene, safety and laboratory practices and take precautions to avoid exposure.

**Danger.**

For substances subject to GHS classification, the corresponding safety data sheet can be accessed via the EDQM website (Reference Standards Database) or is available upon request from the EDQM (Helpdesk-FAQ section).

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In addition, safety data sheets for Ph. Eur. and WHO RSs, including their translations in European languages, are now accessible directly from the EDQM website.

## Communication with partners and stakeholders

Some RSs (generally for assay/potency tests) 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 national laboratories has been set up and serves to carry out these studies: at the end of 2014, there were 32 laboratories in 23 different countries taking part in DLab studies.

Exchanges with key non-European authorities take place regularly. A member of the EDQM Laboratory paid a study visit to the Chinese National Institute for Food and Drug Control (NIFDC) in December 2014.

## Events

DLab staff contributed to the training session for Ph. Eur. users organised in Strasbourg which included specific presentations on reference standards.

## Official visits

In April, the EDQM met with the French Customs (*Douanes Françaises*) to explain the EDQM's activities and help customs representatives to better understand the numerous imports of chemical/biological products from all over the world controlled by their services.

In July, the EDQM met with the National Institute of Food and Drug Safety Evaluation from the Republic of Korea. The aim of the meeting was not just to share technical know-how and knowledge but also to strengthen relations between the two organisations.

## CERTIFICATION OF SUITABILITY TO THE PH. EUR. MONOGRAPHS



### Why certification is more important than ever

As the world's economy continues to evolve, extra-European production of pharmaceutical ingredients is becoming increasingly common. This creates new challenges for authorities as regards the monitoring and quality control of substances used in the manufacture of medicines.

The Certification of Suitability procedure has been set up by the EDQM to evaluate and validate the capacity of Ph. Eur. standards to control the quality of substances used in the production of medicinal products. To apply for a certificate (CEP), manufacturers must submit a dossier describing how their product is manufactured and quality controlled. The EDQM's decision to grant a CEP is based on the evaluation of the data in this dossier. The procedure 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 enforced and that the information supplied under the Certification procedure is accurate.

An increasing number of licensing authorities worldwide accept CEPs to support (fully or partially) the data related to the quality of APIs used in medicinal products.

### Key facts and figures

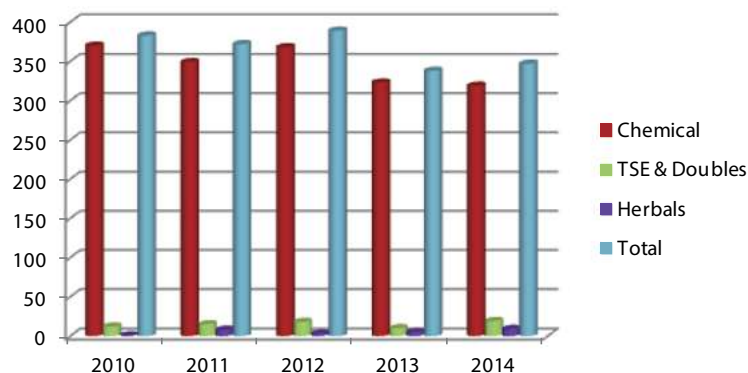
347 new applications were received in 2014, which is slightly up on the number received in 2013 (338 dossiers), while the number of requests for revision rose by some 15 per cent (1632 requests).

355 new certificates and 1374 revised certificates were issued in 2014. There are currently more than 3,800 valid CEPs, covering chemical purity, the risk of transmissible spongiform encephalopathy (TSE) and herbal drug preparations. Overall, more than 90 per cent of applications received were dealt with within official timelines.

The activity in the area of herbal drugs and herbal drug preparations increased slightly, with 9 new CEPs granted for these products this year, and an increasing number of new applications received.

As part 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 16 other sites was obtained by taking action on CEPs after the publication of a non-compliance statement by a EU/EEA supervisory authority and by exchanging data with inspectorates from member states and international partners. The rate of non-compliance for sites inspected by the EDQM in 2014 decreased significantly compared to the previous years (12%).

Number of new CEP applications received





## Quality System

■ In December 2014, the EDQM's activities as regards the 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 successfully underwent an ISO9001:2008 re-audit conducted by AFNOR Certification.

## General matters and policies

■ The Certification Division published a number of guidelines in 2014, including:

- ▶ Revised Terms of reference
- ▶ Policy for 2-round evaluation for CEP applications;
- ▶ Revision of the Guideline on requirements for revision/renewal of CEP applications and the related documents;
- ▶ Guideline on the Use of a CEP in a CEP application
- ▶ Revised policy on Suspension/cancellation of CEPs, closure of applications

■ In 2014, the Steering Committee met once, and the Technical Advisory Board for chemical purity evaluation met 3 times.

## Communication with partners and stakeholders

■ In 2014, the Steering Committee accepted a request from the Australian Therapeutics and Goods Administration (TGA) to take part in evaluation of CEP applications, and the first TGA assessor participating in the procedure was appointed.

■ In 2014, the Certification Division continued to be involved in a number of international platforms for collaboration, such as the International Generic Drugs Regulatory Pilot (IGDRP), the international API inspection programme, the Pharmaceutical Inspection Co-operation Scheme (PIC/S) and the ICH Q7 (Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients) Implementation Working Group.

■ EDQM has taken part in the meetings of the PIC/S committee of officials and takes part in PIC/S activities in the area of API inspections. In addition EDQM is included in the coordinating committee of the API expert circle, and has been involved in workshops for the 2014 API expert circle which took place in Rome.

■ As part of its collaboration with WHO and the American Food and Drug Administration (USFDA), 2 joint inspections were carried out in 2014.

■ The Certification procedure also features in the EDQM's annual meetings with industry associations as a means of promoting exchanges on the EDQM's work in general and getting feedback from stakeholders about the use of CEPs.

## Events

■ The Certification Division (DCEP) took part in several international events and exhibitions in the course of 2014.

■ In 2014, the EDQM organised a number of webinars. In September, a repeat of the 2013 webinar on "How to prepare for an inspection" took place. The presentations focused on understanding the EDQM's expectations, preparing and managing the inspection, gathering evidence of compliance and an overview of what 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.

■ Division staff also contributed to the training session on the Ph. Eur. 8th Edition organised in July. The second day's training programme was dedicated to the Certification procedure, giving practical details on how to prepare an application and revisions and providing an overview of the inspection programme.

■ In May, following the signature of a confidentiality agreement between the EDQM and the Taiwan Food and Drug Administration (TFDA), the two organisations jointly organised a symposium on the Ph. Eur. and the Certification procedure. The aim of the meeting was to equip local authorities, quality assurance and quality control professionals, manufacturers, and others in the pharmaceutical industry with the knowledge and know-how to promote and improve the quality of medicines. Following the meeting, Certification Division staff members were on hand to respond to specific queries on the procedure itself, and on the preparation of the different types of applications and inspections.

■ That same month, representatives of the EDQM's Certification Division took part in a workshop for officials of the Brazilian ANVISA in May 2014. This was followed by an international conference for Industry organised by ANVISA during which the policies for evaluation of dossiers, API starting materials, and the EDQM inspection programme were explained to the participants.

■ In September, the joint EDQM/IPA technical conference on "Quality of Pharmaceutical Ingredients – Applying Learning to Practice" also covered topics related to the certification of suitability procedure such as the requirements and assessment of CEP applications and inspections (*see the chapter European Pharmacopoeia page 21*).



■ In 2014, the EDQM also commemorated the 20th Anniversary of the official launch of the Certification of Suitability to the European Pharmacopoeia Monographs procedure, which had its own dedicated workshop during the October conference. Participants received an update on the use of CEPs worldwide and on how the procedure can best serve the needs of users (authorities and industry) (see the Chapter on 50th Anniversary page 11).

■ In November, the EDQM was invited to give a presentation on CEP application assessment policies at an international conference organised by the Serbian Medicines and Medical Devices Agency (ALIMS) to celebrate its 10th anniversary. The conference attracted officials from health authorities across the Balkans and was an excellent occasion for the EDQM to build new relations and discuss first-hand experiences.

■ Once again, the Certification Division attended CPhI China (Shanghai) and CPhI India (Mumbai). These pharmaceutical trade fairs provided a platform for the EDQM to showcase and promote the latest edition of the Ph. Eur. and meet customers face-to-face. In addition to providing information on the EDQM's activities, several pre-arranged meetings between exhibit visitors and Certification Division staff also took place. The aim was to inform applicants of the practical aspects of the procedure and to assist them by clarifying misunderstandings and finding solutions for any difficulties they may be experiencing.

## Official visits

■ In 2014, the EDQM's Certification Division welcomed officials from the Saudi Arabia Food and Drug Administration. This visit gave the Saudi FDA an insight into the CEP procedure for the evaluation of the quality of pharmaceutical substances and the inspection programme.

## 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 created a Network of Official Medicines Control Laboratories (OMCLs), a measure taken to prevent substandard medicinal products from reaching patients and compromising the efficacy of their treatment.

■ Coordinated by the EDQM since 1995, the OMCL Network supports regulatory authorities in controlling the quality of commercialised medicinal products for human and veterinary use. Operating independently of manufacturers and thus without any conflict of interest, the 69 OMCLs in the 40 Member States that are currently part of the Network<sup>3</sup> test these products and facilitate the exchange of knowledge between regulatory authorities in Europe.

■ This pan-European collaboration offers several advantages, not least the pooling of know-how by 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. It also means that national competent authorities do not duplicate their efforts, which saves time and resources and reduces the cost of testing medicinal products.

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 observer countries of the European Pharmacopoeia Commission, provided that the criteria of the network are fulfilled (eg independence, public funding, implementation of the Ph. Eur. and specific OMCL Network guidelines as common standard, implementation of the ISO/IEC 17025 standard).

■ In particular since 2008, a number of initiatives have been launched in addition to the Network's core activities, including 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.

■ At the international EDQM conference held to mark the 50th anniversary of the European Pharmacopoeia, a special workshop was dedicated to the achievements of the General European Network of Official Medicines Control Laboratories (GEON) to celebrate its 20th anniversary.

## Quality Management Programme

■ The OMCL Network's Quality Management (QM) Programme 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 hone their technical skills through training visits to other OMCLs and specific training courses organised by the EDQM. The QM Programme is continuously expanding, thanks to the unwavering commitment of OMCLs to high standards and to the invaluable contribution of the Network's experts.

## Mutual Joint Audits/Visits (MJAs/MJVs)

■ Mutual Joint Audits/Visits are designed to assess the compliance of OMCL quality management systems with the requirements of ISO/IEC 17025, the General European OMCL Network Quality Management Guidelines and the European Pharmacopoeia. In the course of 2014, 11 MJAs were carried out on OMCL sites, two of which were performed as joint audits together with the respective national accreditation body and one with WHO. Since the QM Programme was launched in December 1997, 118 MJAs, 50 MJVs, 2 Tutorials and 18 Training Visits have been carried out in the OMCL Network.

## OMCL Network QM Guidelines

■ The OMCL Network QM Guidelines are drafted by experts from the OMCL Network to provide support for laboratories in implementing the ISO/IEC 17025 requirements. In 2014, a new guideline for "Sub-contracting of tests" was adopted by the OMCL Network. Two guidelines for "Validation of analytical procedures" and "Evaluation and reporting of results" were revised and published. The guideline for "Calibration/qualification of pH meters" is currently

under revision and will be elaborated concurrently with the revision of General Chapter 2.2.3 "Potentiometric determination of pH" of the European Pharmacopoeia.

## Collaboration with the European Cooperation for Accreditation (EA)

■ The EDQM has begun to develop relations with the European Cooperation for Accreditation (EA), with the aim of evaluating the possibility of future cooperation between the two institutions, focussing on exchange of know-how, joint audits by 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. Two joint audits with the National Accreditation Bodies (NAB) were performed in 2013 and 2014 respectively. In 2014, a representative from the NAB was present on the first day of an MJA to witness the audit as stipulated in the MJA scheme. Cooperation between NABs and EDQM/MJA-auditors is scheduled to continue in 2015.

## Training Courses/workshops

■ The EDQM organised two training courses for new auditors in June and September 2014. This allowed the EDQM to add to the pool of auditors with the necessary expertise and qualifications to perform audits in the OMCL Network.

## Proficiency Testing Scheme (PTS) studies

■ The Proficiency Testing Scheme (PTS) organised by the EDQM provides laboratories with an objective means for assessing and demonstrating the reliability of their data. This is an important part of the external assessment of quality control management systems and helps build mutual trust between OMCLs which is vital in an effective common system for the quality control of medicines. In 2014, five studies were organised in the physico-chemical field, with an average of 43 national control laboratories and 34 other pharmaceutical control laboratories from the private sector, industry and hospitals taking part. The 2014 programme included studies on Potentiometric Titration, Relative Density, Dissolution Test, Liquid Chromatography and Atomic Absorption Spectrophotometry. Four biological studies were organised involving an average of 25 laboratories, i.e. Potency assay of human coagulation factor VIII, Hepatitis C virus detection by nucleic acid amplification techniques, parvovirus B19 detection by nucleic acid amplification techniques and Human albumin molecular size distribution (ongoing).

■ The laboratory work verifying the feasibility of the first two studies to be included in the 6th agreement with WHO, i.e. a PTS on Optical rotation and a PTS on Titration, was also carried out in 2014.



## General OMCL Network (GEON) activities

### General studies on market surveillance

■ Market Surveillance Studies (MSSs) provide a panoramic view of the quality of products available on the European market in a given therapeutic class. Where pertinent, the results of these studies may 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 2014, two classic MSSs were initiated: MSS046: Telmisartan APIs and Tablets and MSS047: Pramipexole APIs and Tablets.

■ The testing phase for two “atypical” MSSs, MSS045: “Eye Drops and Nasal Preparations registered as Medical Devices” and MSS045: “Heparin and Low Molecular Mass Heparin APIs and Finished Products”, was finalised in 2014. An MSS on Subdivision of Tablets was also agreed at the Annual Meeting of the GEON.

■ The second Market Surveillance Study on Illegal Products (MSSIP), focused on “Dietary Supplements advertised as Sexual Potency Enhancers”, was finalised in 2014. Twenty OMCLs sent results for about 520 batch samples taken from the legal and illegal supply chains (representing about 80% of the samples). Almost half of the samples analysed (49 per cent) were found to contain undeclared APIs. An MSSIP on Illegal Anabolics (MSSIP003), presented as a compilation of the results generated by the OMCLs in the time-period from 2012 until the middle of 2014, was also launched.

### API Working Group

■ Globalisation of the manufacture and trading of active ingredients has created a need for increased control of Active Pharmaceutical Ingredients (APIs). The implementation of the “Falsified Medicines Directive” (2011/62/EU) in the EU in 2013 was an important measure, requiring involvement of OMCLs in the monitoring of APIs on the European market.

■ The API Working Group was established in 2011 with the mandate of fostering collaboration between OMCLs controlling the quality of APIs on the European market and raising awareness of the valuable contribution that OMCLs make in this field. Specific goals include:

- ▶ Improving information sharing between OMCLs with respect to API testing – for this purpose an API testing database, a separate module of the MRP/DCP database, was developed and launched in February 2013;

- ▶ Supporting the development and maintenance of a general risk assessment tool for the planning of national market surveillance programmes with focus on critical APIs – here, the group works closely with the Heads of Medicines Agencies (HMA) Drafting Group for Risk-based Approach to Product Testing which has integrated this objective into its work programme;
- ▶ Randomising the sampling of APIs as much as possible – in this context closer collaboration with national inspectorates and customs authorities is sought;
- ▶ Fostering market surveillance studies on APIs through scientific discussions and, where necessary, training – two new “classical” API MSS on Pramipexol and Telmisartan were started in 2014 as “companion projects” to the 2014 CAP Generics Programme; in addition “chemometrics training for OMCLs” was organised at the premises of the EDQM in mid-2014.

■ The working group met twice in 2014. One major point was the discussion about the lessons learned from the pilot “Fingerprint” Market Surveillance Study (MSS) on statins and macrolide antibiotics which was the first study organised after reorientation of the API fingerprint project in 2013. Follow-up activities on this market surveillance study are scheduled for 2015 (*for further details on the API fingerprint project, see Chapter on Anti-counterfeiting activities page 44*).

### 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 2014. One focus of the meetings was to analyse the outcome and discuss follow-up of the second symposium for OMCLs on combatting counterfeits and other illegal medicines organised on 10-11 September 2014 in Strasbourg. More than 80 participants attended this two-day event, which was split into a multidisciplinary open day and a closed session restricted to members of the OMCL Network. During the open session, representatives from forensic and customs laboratories, national medicines and food authorities, enforcement groups and the European Commission shared their views on the problem of falsification of medicines, exchanged experiences with the OMCLs in the fight against falsified and illegal medicines and discussed means of improving collaboration. The restricted session gave the OMCL members an opportunity to present their work in the field of analysis of “illegal medicines” and to discuss technical issues encountered in the testing of unknown samples.

■ During their meetings the Counterfeit/Illegal Medicines Working Group also identified new topics for additional Market Surveillance Studies on Suspicious Illegal Products (MSSIP) for the coming years (*see also “General studies on market surveillance” page 29*).

■ Two new technical training sessions for OMCL members were organised jointly by the EDQM and the Austrian and French OMCL respectively, in Vienna (Austria) in January 2014 and in Montpellier (France) in November 2014. While the Vienna session focused on screening methods employing GC-MS and UPLC-MS technologies which had been developed in the Austrian OMCL, the participants in the Montpellier session were introduced to X-Ray Fluorescence Spectrometry and ICP-MS, Raman and NIR approaches, Image Analysis and Impurity profiles / API fingerprint techniques. Additional training sessions in Montpellier and Berne (Switzerland) are scheduled for 2015. In the latter session the spotlight will be on falsified biologicals during the hands-on training session.

■ Over the past years, the Working Group has also assisted the Secretariat in setting up the Know-X database, which was finally launched in March 2014 and collates information about illegal medicines confiscated by customs or police and either dealt with by health authorities or tested in OMCLs (*see page 45 for more details on this and other anti-counterfeit activities coordinated by the EDQM*). This new IT tool should foster communication between the different partners involved in the fight against falsified medicines (customs, police, health authorities and OMCLs). To date about 1,700 individual cases have been uploaded onto this new computer application.

■ One Suspicious Unknown Product (SUP007) study was carried out in 2014. Each of the 23 laboratories taking part received 3 identical unidentified tablets containing stanozolol obtained from the illegal supply chain. They were asked 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 is intended to evaluate whether OMCLs of the Network are able to identify (and where possible quantify) unknown APIs in a selected sample.

■ Finally, 2014 saw the Counterfeit/Illegal Medicines Working Group continue its work on a harmonised approach for reporting on the testing of illegal medicines in the Network. Since 2012, a general activity report on illegal medicines testing in the GEON has been sent to the EU Commission on an annual basis.

### **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 (UPP). As agreed by the Group in November 2013, a meeting was not held in 2014. An information document, outlining the position of the OMCL Network regarding the testing and the quality control of UPP, was finalised and presented at the Annual Meeting of the GEON. The results of a second market surveillance study, focussing on UPP for Cutaneous Application (solutions and ointments containing any type of API), should be available 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.

■ In 2014, the full validation of an ELISA method for the determination of physical particle titres was carried out. A paper describing the method in detail is soon to be published in *Pharmeuropa Bio and Scientific Notes*. The 6th Annual Meeting of the Working Group was hosted by the Institute for Public Health (Brussels, Belgium) in December 2014. During this session, the Working Group decided that additional work on viral genome titre and infectious genome titre of adeno-associated virus (AAV) preparations was necessary. In addition, collaborative studies on detection and quantification of residual host cell DNA, bacterial and mammal, will be initiated in 2015. The work programme was maintained as it stands since it appears to reflect current developments in the gene therapy field based on clinical trials and marketing authorisation applications.

## 19th Annual Meeting of the GEON

■ The EDQM held its 19th Annual Meeting of the OMCL Network in Interlaken in May 2014. The conference was co-organised and co-sponsored by SWISSMEDIC, the Swiss medicines agency. The meeting brought together 235 experts from 36 countries, representing a total of 60 OMCLs, to exchange experiences and discuss topics of common interest for the coordination and harmonisation of their efforts to protect patient and animal health in Europe. The Israeli Institute for Standardisation and Control of Pharmaceuticals, a newly associated member of the GEON, was present at the meeting for the first time. In 2014, the Singapore Pharmaceutical Laboratory, Applied Science Group of the Health Sciences Authority (HSA) also joined the Network as an associated member, but was not present at the meeting.

■ In nine 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 all members of the Network:

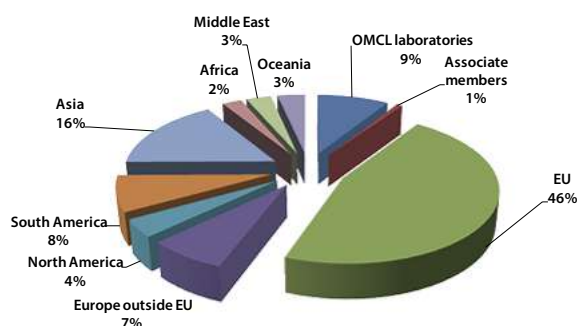
- ▶ The plenum proposed that the Advisory Group's 2014-2015 work programme should include future handling of OMCL status questionnaires and rules on the adoption of GEON documents as general topics. In addition, the group was requested to reconsider the subcontracting statement in the GEON Terms of Reference to bring it in line with the QMS guideline on subcontracting, which was scheduled for final adoption in June 2014.
- ▶ On basis of a GEON questionnaire launched in spring 2014, the decision was taken to add the QMS topics Management of records, Management of volumetric glassware and Uncertainty of measurement to AdG GEON work programme. For the first two of these topics it was agreed that recommendation documents should be elaborated in small working groups. The third item will be added to the agenda of the MJA auditors' workshop which is scheduled for 2015. In addition, the

general policy of organising, whenever feasible, joint audits by the EDQM/OMCL Network and a National Accreditation Body, was supported by the delegates.

- ▶ A new document concerning the conduct of "atypical" Market Surveillance studies was presented. These studies concern products that are typically not controlled using a common testing protocol (for example medical devices, dietary supplements, unlicensed pharmaceutical preparations etc.).
- ▶ For the first time, members of the three specific networks (EU/EEA CAP Network, OCABR Human Network and VBR Network) gave an oral report of their activities. Furthermore, representatives from the Counterfeit / Illegal Medicines Working Group, API Working Group, OMCL Testing Group on Unlicensed Pharmaceutical Preparations and Gene Therapy Product Working Group reported on their achievements during the past twelve months.
- ▶ The plenum also agreed to continue its efforts to raise awareness of the work done by OMCLs and the Network. In particular the need for internal public relations work was stressed.
- ▶ A special session was dedicated to the testing of medical devices (MDs) in OMCLs. In this part of the programme, a Network position paper was presented and examples of national testing campaigns as well as the results of the first GEON Market Surveillance Study on Medical Devices (focusing on eye drops and nasal preparations classified as Medical Devices) was presented. Finally, Erik Hansson, deputy head of Unit, Health Technology and Cosmetics, at DG Sanco (European Commission) presented an update on the new MD legislation.

## CombiStats™

CombiStats™ licenses per region





■ CombiStats™ is a computer programme for the statistical analysis of data generated by biological dilution assays in accordance with Chapter 5.3 of the Ph. Eur. It was first made available in 1999 to laboratories of the OMCL network but as of November 2005, non-OMCL laboratories can also obtain a user licence. The current version 5.0 was released in 2013 and introduced features 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.

■ One training course was organised in November 2014 which was also open to industry and private sector participants.

■ The number of users has steadily increased since public release of the software. By December 2014, 9% of the licences were issued to OMCL laboratories in 25 countries and 91% 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, Mexico, 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.

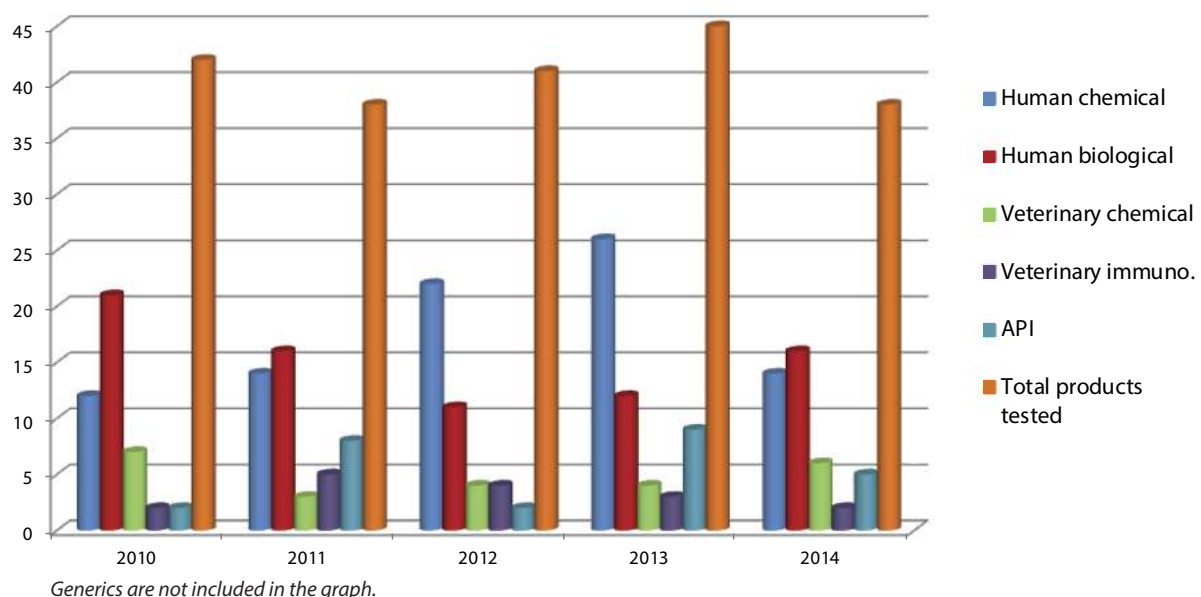
## EU/EEA-specific activities

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

■ Since 1995, the EU Commission has been 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 their quality control is necessary. In June 1999, a contract governing an annual CAP Sampling & Testing Programme was signed by the EMA and the EDQM. The EMA sponsors 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 which are then tested by members of the EU/EEA OMCL Network. The list of products to be included in the annual programme is prepared by the EMA Secretariat together with the EMA Scientific Committees, using a risk-based approach tool.

■ The programme for sampling and testing Centrally Authorised Products (CAP) was successfully pursued in 2014, entering its sixteenth consecutive year.

Number of products tested in the CAP Programme 2010-2014



■ In 2014, there were 30 medicinal products for human use (16 biologicals and 14 chemical products) and 8 medicinal products for veterinary use (2 immunobiological products and 6 chemical products) on the work programme. Active substance (API) testing was performed for 5 substances. One ad hoc test was performed on the recommendation of the Rapporteur.

■ In addition to the regular CAP programme, two generics programmes were conducted, during which 11 branded telmisartan or pramipexole products (generic medicinal products as well as the respective reference medicinal products) were tested.

■ Thirty-seven OMCLs were involved in the 97 testing operations of the 2014 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 out-of-specification result was confirmed and reported to the EMA. The EMA handles the follow-up for these observations.

■ Based on the experience acquired with the 2011 Clopidogrel generics trial programme, a CAP standard procedure was established; the document “*General Procedure for Sampling and Testing of Generic Centrally-Authorised Products*” (PA/PH/CAP (12) 32 10R) was fine-tuned in 2014 and released after adoption by the OMCL Network in December 2014. The procedure is available on the EDQM website. Additional information on the CAP programme can also be found on the EDQM site and on the EMA website.

■ In December 2014, 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 expanded since that time. 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. The OMCLs involved in the programme meet on a regular basis (twice a year) to evaluate the programme and discuss ways to optimise collaboration.

■ In 2014, the 10th regular programme for the market surveillance of medicinal products authorised in the EEA via the MRP or DCP procedure was carried out. Some 950 product testing projects were added to the 2014 programme, which is an increase over the previous year. The 2014 test reports came from 26 different OMCLs.

■ Around 10 per cent of samples tested in the programme originate from a member state or an OMCL that is not involved in the testing. This demonstrates the added value of the surveillance scheme with respect to work-sharing and the efforts of the OMCLs to include samples from other member states in their national testing programmes. In order to stress the importance of sample exchange for this testing scheme, the procedure entitled “*Co-operation in post-marketing surveillance of Mutual Recognition/Decentralised Procedure Products*” (PA/PH/OMCL (06) 116 14R) was updated accordingly in 2014. The latest document version was posted on the EDQM website in November 2014.

■ Regulatory issues were identified in about 3 per cent of the materials tested (e.g. insufficient details of test method, wrong calculation formula used in the SOP), with one or more out-of-specification results reported in a further 3 per cent of the cases. Some 4 per cent of the tested products were for veterinary use. Approximately 1 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 programmes.

■ The internal database used for the planning, sampling and reporting of MRP/DCP product testing activities within the Network was further developed, with two new versions of the database launched in January and March 2014. Since 2013, API test reports have been registered in a separate module of the database, allowing API testing activities to be reported independently from registered MRP- or DCP-products. In total, 17 database amendments were implemented in 2014, affecting both the MRP-/DCP-product and API modules. These were initiated both by OMCL users of the system and by the EDQM Secretariat.

■ The database currently holds more than 6100 MRP- and DCP-product testing records with contributions from 33 OMCLs. During the period 2002 to 2014, a participating member state testing one product received test results for an average 9 marketed products generated by other member states, which clearly demonstrates the advantages of the Network.

■ A task for the future will be to achieve, over time, a balance between the number of samples an OMCL sends for testing to another Network member and the number of samples the same OMCL accepts for testing from other Network members. The group also agreed to focus on the follow-up module of the database which provides feedback on actions that have been taken based on findings in OMCLs. So far, follow-up actions are reported in the module for one third of the findings only. In addition, the newly introduced features of the database (e.g. information on sampling location or on counterfeit testing activities) will be monitored over the next years.



■ In December 2014, 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.

■ The testing scheme is described in more detail on the EDQM website under <https://go.edqm.eu/postMSS>.

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

■ The human OCABR network is a specialised group of OMCLs within the GEON whose primary goal is to ensure harmonised application of Article 114 of EU Directive 2001/83/EC, as amended, to foster the 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 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. In 2014, over 9,000 final batches of vaccine and human blood derived products and more than 8,900 plasma pools were subject to OCABR procedures within the Network.

■ Roughly 80 participants from 26 member states took part in the 19th Annual Meeting of the OMCL Network which included parallel sessions for blood and vaccine issues and a joint session to address common points of interest. Participants reviewed activities from the past year and determined strategies for the coming period. The respective sessions on blood and vaccines included a focus on exchange of expertise to tackle scientific issues related to the testing of specific products.

■ Elections were held during the plenary session to renew the OCABR advisory group. The previous incumbents were re-elected resulting in a group composed of representatives from Belgium, Italy, France, Germany, the Netherlands and the United Kingdom.

■ The annual workshop on testing oral poliomyelitis vaccine bulks attended by representatives of OMCLs and the relevant manufacturers made it possible to harmonise practices related to this critical technique and proved to be a valuable experience for all.

■ The EU Administrative Procedure for OCABR, 5 revised guidelines for vaccines and 3 revised guidelines for blood-derived products were finalised in 2014. In addition the Human OCABR network worked together with the Veterinary Batch Release Network (VBRN) to elaborate and adopt 2 documents promoting the reduction, refinement and replacement of animal use (see below). All 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 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).

■ The 19th Annual Meeting of the OMCL Network saw 27 participants from 18 member states take part in the VBRN session, where annual reports of the activities of the different member states were presented. The VBRN advisory group was renewed following elections. The present incumbents were re-elected and the group now consists of representatives from Germany, Hungary, Switzerland and the United Kingdom.

■ Important focal points included finalisation of the new strategy 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 and work on a new strategy to allow reduced testing for specific products. Awareness was also raised about difficulties encountered with the correct application of official batch release procedures for products that enter the member states via parallel distribution or import channels.

■ A successful training workshop was held in Strasbourg in June for representatives from Competent Authorities, OMCLs and manufacturers of IVMPs. Topics covered included an overview of the EU system for batch release of IVMPs and a closed session for Competent Authorities and OMCLs on practical issues related to protocol review.



■ The VBRN took the lead in drafting two guidance documents for the OMCL Network related to the 3Rs in the context of method validation and maintenance of competence. Both were adopted in 2014 and are available on the EDQM website. In addition, revised versions of 2 product specific guidelines and 1 manufacturers' protocol template and the EU Administrative Procedure for Application of Article 82 for Official Control Authority Batch Release of IVMPs were finalised in 2014.

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

## Official visits

■ In December, a delegation from the Turkish Medicines and Medical Devices Agency (TMMDA) visited the EDQM. The aim of the visit was to give an overview of the work of the European Pharmacopoeia, the OMCL Network, its quality management system (MJA/MJV) and vaccine quality control testing.

## 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. From the very outset, the guiding principles have been to promote voluntary and non-remunerated donation, to achieve self-sufficiency and to protect both donors and recipients of labile blood components by actively enforcing 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, whose role is to steer and coordinate the Council of Europe's activities in the area of blood transfusion and oversee the work of its expert groups.

■ The CD-P-TS currently consists of 47 representatives (35 members and 12 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, WHO and the Council of Europe Committee on Bioethics. Both members and observers are represented in the CD-P-TS expert groups.

■ The CD-P-TS held a bureau meeting attended by its chair and vice-chair and the chairs of the different expert groups in June and a plenary session at the EDQM in November 2014.



### Key facts and figures

■ Collaboration between the 35 member states and the 12 observers provided the foundation for activities in the area of blood transfusion in 2014.

- ▶ Four B-PTS studies were run in 2014, and the average number of laboratories taking part per study rose by 30 per cent.
- ▶ Three Blood Training Visits (B-TV) and 2 Blood Mutual Joint Visits (B-MJVs) were conducted in 2014.

### General matters and policies

#### Risk behaviours having an impact on blood donor management and transfusion safety

■ The EDQM project "Risk behaviours having an impact on blood donor management and transfusion safety", was launched in February 2010 with the assistance of the EMA, ECDC (European Centre for Disease Prevention and Control), EBA (European Blood Alliance), USFDA, Health Canada, Australia's TGA and WHO. In 2013, a milestone was achieved with the adoption of Resolution CM/Res(2013)3 "on sexual behaviours of blood donors that have an impact on transfusion safety", together with a technical memorandum, by the Council of Europe's Committee of Ministers. The findings of the working group also provided the basis for a scientific publication in a peer-reviewed journal (R. Offergeld, *et al.*, *Vox Sanguinis* (2014) **107**,420-427) published in 2014.



■ Recommendation No. 5 of Resolution CM/Res(2013)3 calls for standardised, continuous data collection on the incidence and prevalence of sexually-transmitted infections in the general population, in blood donors and among individuals with risky sexual behaviours for use as a scientific basis for future amendments to donor deferral policy. A new working group was appointed by the CD-P-TS in 2014 to tackle these issues.

### Blood Proficiency Testing Scheme (B-PTS) Programme

■ Inter-institutional cooperation with the EU Commission (under Direct 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 evaluate 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, 17 B-PTS studies were organised, covering the following fields:

- ▶ Nucleic acid amplification techniques (Hepatitis C- (HCV), Hepatitis B-, Human Immunodeficiency (HIV) virus);
- ▶ Serology (Hepatitis B surface antigen (HBsAg), HIV antibodies, p24 antigen, 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 2014 and the average number of participating laboratories per study increased by 30 per cent.

### 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) under harmonised conditions. The programme started with a 2-year pilot phase, during which 6 Blood Mutual Joint Visits (B-MJVs) were carried out.

■ An increasing number of European countries and BEs are willing to participate in the B-QM programme, especially since such a programme did not previously exist. With the strong support of the CD-P-TS, the B-QM programme was further expanded in 2014 to include 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 to the Preparation, Use and Quality Assurance of Blood Components (*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 force in the BE.

■ These schemes are carried out by auditors from European BEs, who pool their experience for the purposes of the TV/B-MJV/B-MJA. In 2014, 3 Blood Training Visits (B-TV) and 2 Blood Mutual Joint Visits (B-MJVs) were conducted.

■ In addition, a guidance document on quality management in BEs is currently in development.

■ A key event in this programme is a training course on quality management dedicated to BEs which will take place in April 2015.



## Publications, databases and websites

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### Guide to the Preparation, Use and Quality Assurance of Blood Components – 18th Edition

■ A dedicated expert working group of the CD-P-TS – with members from Europe, Australia, New Zealand and the US – is entrusted with the task of updating the Guide to keep abreast of 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 by BEs and hospital blood banks. The Guide is also intended to make it easier to transcribe these common standards into national legislation.

■ The final draft version of the 18th Edition of the “Guide to the Preparation, Use and Quality Assurance of Blood Components” was approved by the CD-P-TS during its plenary session in November 2014 and will be published in 2015. A complementary eBook-version will be made available to purchasers of the printed edition.

### Good Practices Guidelines/Elements of quality systems

■ The “Good Practice Guidelines for Blood Establishments and Hospital Blood Banks required to comply with EU Directive 2005/62/EC” was elaborated as part of an ad hoc cooperation between the Council of Europe/EDQM and the EU Commission under the conditions of Direct Agreement 2010 53 05. The document was formally adopted by the CD-P-TS and is an integral part of the “Guide to the Preparation, Use and Quality Assurance of Blood Components” from the 18th Edition onward.

■ The Directorate General SANCO (DG SANCO) of the EU Commission is currently evaluating the possibility of giving these guidelines official status within EU legislation

### Optimal use of clotting factors and immunoglobulins

■ As an outcome of the Kreuth III symposium held in 2013, in November 2014, the CD-P-TS examined the preliminary drafts of two future Resolutions on principles for haemophilia and immunodeficiency therapies. Work on this will continue in 2015.

## Communication with partners and stakeholders

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### EU Commission/DG-SANCO

■ In April and November 2014, the EDQM attended, as an observer, the meetings of the competent authorities on blood components organised in Brussels by The Directorate General SANCO (DG SANCO) of the European Commission. In addition to the agreements on ad hoc cooperation (Direct Agreements 2010 53 05 and 2011 51 01), collaboration with the EU Commission allows exchanges of information, of which an excellent example is the data collected in Council of Europe member states during the annual surveys published as the “*Report on the Collection, Testing and Use of Blood and Blood Components in Europe*”. These data will be used by DG SANCO to elaborate a report on the “*Landscape of blood and blood components and plasma derivatives in Europe*”, which will be used to assess the need for revision of the European Directives on 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 the context of the scheduled revision of the “*PIC/S GMP Guide for Blood Establishments*”.

### World Health Organization (WHO)

■ As a follow up to the High-level Policy Makers Forum held in October 2013, the EDQM was invited to make a presentation at the side event organised by the Permanent Mission of Italy to the United Nations on the occasion of the World Health Assembly (WHA) which took place on May 19, 2014. With its audience of WHA delegates, the event provided an ideal opportunity to draw international attention to the work of the CD-P-TS and the EDQM in the fields of blood components and blood products, respectively.

## International Society of Blood Transfusion (ISBT)



■ The ISBT, an international scientific society of about 1,400 professionals operating worldwide in the field of blood transfusion, has granted the EDQM observer status with its Board of Directors. The EDQM can therefore promote the Council of Europe's core values in the field of blood transfusion on a global level. The EDQM participated in this year's Board of Directors meeting held during the annual conference in Seoul (South Korea) and also holds membership in two dedicated ISBT working parties; the Quality Working Party and the Code of Ethics Working Party.

### IPFA/PEI 20th International Workshop on Surveillance and Screening of Blood-Borne Pathogens

■ The EDQM regularly takes part in IPFA/PEI conferences which, in 2014, was held in Rome (Italy). Participation in these conferences showcases the activities of the CD-P-TS and the EDQM in the field of blood donation safety with respect to blood borne pathogen.

## Events

### World Blood Donor Day

■ As an official partner of the event, the EDQM issued a number of promotional items and also provided electronic material to the Council of Europe member states, translated into their local languages. As part of the promotional campaign, social media channels were used to encourage discussion and debate on blood donation. Tweets and Facebook posts made it possible to reach a wide target audience.

■ Every year, on 14 June, countries around the world celebrate World Blood Donor Day. This year's global event took place in Colombo (Sri Lanka) and the focus of the campaign was "Safe blood for saving mothers" since a timely supply of safe blood is essential need for the prevention of maternal mortality.

■ The EDQM joined forces with the French national blood service (Etablissement français du sang - EFS) and the German Red Cross (Deutsches Rotes Kreuz - DRK) in celebrations in Strasbourg (France). This cross-border initiative was a great success and demonstrated the importance of working together to motivate and recruit new blood donors. The EDQM manned an information stand where the general public was invited to find out more about blood donation and the activities of the organisation in this field. In addition to the promotional materials especially prepared for the event, the EDQM widely publicised the campaign via its website and social media channels such as Twitter and Facebook.

■ The EDQM also organised a blood donation session which was open to Council of Europe staff and their families.





### World Haemophilia Day Event

■ In 2013 the EDQM, the Paul-Ehrlich-Institut (Langen, Germany) and the Ludwig Maximilians University (Munich, Germany) organised a symposium on the “Optimal use of clotting factors and immunoglobulins” in Wildbad Kreuth (Germany), during which recommendations on the use of clotting factors and immunoglobulins were formulated.

■ In April, the European Haemophilia Consortium organised a meeting at the Paul-Ehrlich-Institut in Langen (Germany) to present the recommendations defining minimum standards for haemophilia care in Europe. The meeting took place a day before the World Haemophilia Day (WHD), an international commemoration day to increase awareness of haemophilia and to bring the needs of sufferers to the attention of the public at large.

### International Fairs & Exhibitions

■ The EDQM participated in the 33rd International Congress of the ISBT which was held in Seoul (Republic of Korea). The congress was organised jointly in conjunction with the 33rd Congress of KSBT and the 2014 Congress of the Korean Haematology Societies. The event attracted healthcare professionals working in blood transfusion and transfusion medicine from across the Asia region. Visitors were able to collect information on the EDQM's activities in this area, in particular on the latest Edition of the Guide, and learn more about the EDQM's Blood-PTS scheme.



### 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, WHO, members of the Council of Europe's Committee on Bioethics (DH-BIO) and several professional and non-profit organisations, such as the European Society for Organ Transplantation (ESOT), the European Association of Tissue Banks (EATB), the Transplantation Society (TTS) and the Donation & Transplantation Institute (DTI).



## Key facts and figures

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■ Some of the achievements of the CD-P-TO in the priority areas of its 2014 work programme include:

- ▶ Contribution to the adoption by the Committee of Ministers in July of the “*Convention against Trafficking in Human Organs*” and publication of the article “*A needed Convention against trafficking in human organs*” in the prestigious medical journal *The Lancet*.
- ▶ Publication of the article “*Concerted effort to promote donation and transplantation in Europe: the leading role of the Council of Europe and the CD-P-TO*” in the specialised journal *Organs, Tissues & Cells*.
- ▶ Release in September of the “*Newsletter Transplant 2014*”;
- ▶ Launch in December of the open consultation of the 2nd Edition of the “*Guide to the Quality and Safety of Tissues and Cells for Human Application*”.

## General matters and policies

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### Quality and Safety of Organs, Tissues and Cells for Transplantation

■ Subsequent to publication of the 5th Edition of the “*Guide to the Quality and Safety of Organs for Transplantation*” in September 2013, Working Group TO057 was established for the elaboration of the 6th Edition. Seventeen experts were appointed by the CD-P-TO to take part in this Working Group. The European Donation & Transplant Coordination Organisation (EDTCO) and the EU Commission play an active role in the drafting process. The 6th Edition of the Guide will be published in 2016 and every 2 years thereafter.

■ The 1st Edition of the “*Guide to the Quality and Safety of Tissues and Cells for Human Application*” was published in October 2013, and two working groups have been appointed by the CD-P-TO to work on the elaboration of the 2nd Edition: Group TO055, will focus on updating the existing general and tissue-specific content of the Guide, and TO056, will 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. In December 2014, upon completion of the drafting process, the open consultation for the 2nd Edition of the Guide was launched. This new edition will be published in 2015 and every 2 years thereafter.

■ The elaboration of the “*Guide to the Quality and Safety of Tissues and Cells for Human Application*” is partially funded by the EU Commission through the ad hoc Grant Agreement 2012 51 01 entitled “*Dissemination of best practices in organ donation/transplantation*”. This agreement is designed to promote the elaboration and dissemination of common European quality and safety standards for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells.

### International Collaboration Efforts

■ In July 2011, the Council of Europe launched The Black Sea Area (BSA) Project, a three-year collaborative initiative aimed at combatting 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 clinical practices for the donation-transplantation process inside hospitals in those countries with existing transplant programmes.

■ During this project, a number of activities were undertaken to ensure progress, 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.

■ This project terminated in July 2014 and a final report summarised all the findings and recommendations elaborated for each country. Future international collaborative efforts will be based on these invaluable data, ensuring the elaboration of tailored-made programmes suited to the specific needs of each country and current development of their donation and transplantation activities.

## 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 a conservative figure). Several legal instruments address the problem of HTOR but a number of practices have escaped prosecution due to the lack of consensus on what constitutes THO. Therefore, no harmonised legally-binding instruments existed for the criminalisation of THO and prosecution of perpetrators.

■ On 9 July 2014 the Convention against Trafficking in Human Organs was adopted by the Committee of Ministers. This Convention was elaborated by the Committee of Experts on Trafficking in Human Organs (PC-TO), in which the CD-P-TO took part. This international instrument is the first of its kind to provide a definition of THO, criminalise it, protect the rights of victims, facilitate national and international cooperation and provide a monitoring mechanism to ensure that its provisions are implemented effectively.

■ This Convention was praised in several articles in very influential medical journals, including The Lancet and the American Journal of Transplantation.

■ In his address during the open audience at Saint Peter's square on the occasion of the 16th European Day for Organ Donation & Transplantation (EODD) in Rome in October 2014, Pope Francis stated that "organ trafficking and commercialisation are immoral". His message was clear.

■ To step up the fight against HTOR and THO, 2014 forged closer links 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).

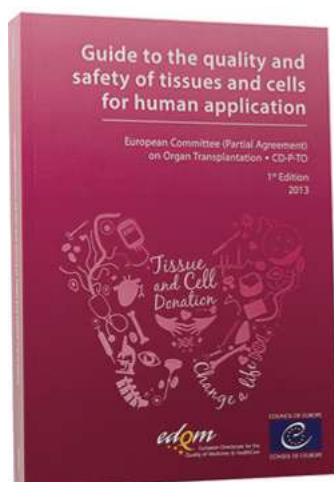
## Publications, databases and websites

■ The 5th Edition of the "Guide to the Quality and Safety of Organs for Transplantation" has become the gold standard reference textbook 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 remains up to date with recent advances in the field.

■ The same is becoming true for the 1st Edition of the "Guide to the quality and safety of tissues and cells for human application", which provides the most recently published information for all professionals involved in donation, banking, transplantation and other clinical applications of tissues and cells. This Guide is the first of its kind to provide detailed ethical and technical guidance for tissues and cells in Europe.

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

■ The *Newsletter Transplant* 2014, which provides international figures on organ, tissue and haematopoietic stem cell donation and transplantation, waiting lists and refusals to donate for the year 2013, was also published last year. This data collection and analysis exercise has been carried out by the Spanish transplantation authority Organización Nacional de Trasplantes (ONT) since 1996. The Newsletter presents compiled information from 69 countries, with variables included and analysed every year.



## Communication with partners and stakeholders

■ In February 2014, the EDQM was invited to participate in the World Health Organization (WHO) International Technical Consultation on Cell, Tissue and Organ Donation/Transplantation in the Western Pacific Region in Seoul (South Korea).

■ In March and September 2014, the EDQM attended the Meeting of the EU Competent Authorities for Organs in Brussels (Belgium) as an observer, and was also present at the Meeting of the EU Competent Authorities for Tissues and Cells in Brussels (Belgium) in June and December 2013.

■ In March 2014, students from Syracuse University visited the Council of Europe and attended a lecture on the work of the EDQM in donation and transplantation of organs, tissues and cells.

■ In April and October 2014 the CD-P-TO held its annual plenary meetings in Strasbourg (France) and Rome (Italy), respectively.

■ In May 2014, the EDQM was invited to take part in the Regional WHO meeting on Donation and Transplantation in Punta Cana (Dominican Republic).

■ Similarly, the expertise of the EDQM in donation after circulatory death (DCD) was shared at the 3<sup>rd</sup> International Workshop on DCD Donors in June 2014 in Barcelona (Spain).

■ During 2014, the EDQM was invited to present at the annual congress of the European Donation & Transplant Coordination Organisation (EDTCO) in October in Budapest (Hungary) and the International Conference on Living Donation High Quality Practices (LIDOBS) in November in Barcelona (Spain).

■ In November 2014, the EDQM was invited to the meeting of the Group of Experts on Action against Trafficking in Human Beings (GRETA) in Strasbourg (France), for an exchange of views. The objective of this meeting was to define the scope and identify the complementarities between the Council of Europe Convention on Action against Trafficking in Human Beings from 2005 and the new Convention against Trafficking in Human Organs.

■ In December 2014, experts from the CD-P-TO and the Secretariat attended a "horizon scanning" meeting organised by the Council of Europe Committee on Bioethics (DH-BIO) entitled "Prohibition of financial gain – What are the challenges?" The objective of the meeting was to obtain a clearer overview of possible problems encountered in relation to the principle laid down in Article 21 of the Convention on Human Rights and Biomedicine, including in the interpretation of what constitutes payment, or compensation for reasonable expenses or loss of income incurred by donors of organs, tissues and cells.

## Events

■ A Council of Europe initiative launched in 1998, the European Day for Organ Donation and Transplantation (EODD) promotes organ donation and transplantation in the Council of Europe member states. It is also an opportunity to honour organ donors and their families everywhere 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 16th EODD was hosted by Italy.

■ The Italian authority, the *Centro Nazionale Trapianti* (CNT), hosted the celebration day on 11 October, with the main event taking place in Rome. A number of other events were organised in the capital, including a public audience with Pope Francis in Saint Peter's square, fun and educational sessions on the subject of donation for children and adults, and a gala concert given by numerous well-known Italian artists. In addition to the main day in Rome, a number of other celebrations took place simultaneously throughout Council of Europe member States.



## PHARMACEUTICALS AND PHARMACEUTICAL CARE

### Optimal use of Medicines for the purpose of improving patients' quality of life

Public authorities and the manufacturing and distribution sectors devote a considerable amount of time, effort and money to the quality, safety and efficacy of medicines. The safe and appropriate use of medicines is paramount for achieving the best possible treatment outcome in individual patients. Pharmaceutical care is understood as a quality concept and working method for the responsible provision of drug therapy for definite outcomes that will improve patients' quality of life (see definition in Hepler and Strand<sup>4</sup>).

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.

### Key Facts and figures

The Committee of Experts on quality and safety standards in pharmaceutical practices and pharmaceutical care (CD-P-PH/PC) has made significant progress in the development of scientific indicators for the quality of pharmaceutical care.

Pilot studies were carried out in several European countries to validate indicators measuring the quality of pharmaceutical care in Europe. With a view to continuously improving health outcomes and patients' quality of life, the indicators cover the following key areas of the pharmaceutical care process:

- ▶ adherence to nationally agreed clinical practice guidelines for antibiotics;
- ▶ monitoring of therapeutic plans and drug safety by prescribers and pharmacists through linking information about patients' therapy and medical conditions in anticoagulant and antibiotic therapy;
- ▶ structured pharmacist-patient consultations (long-term medical therapy; polypharmacy and patients with more than one medical condition) via "My CheckList";

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

- ▶ implementation of the pharmaceutical care philosophy and working methods in Europe.

The studies initiated in 2013 were finalised in 2014. The indicators focus on healthcare delivery by professionals such as medical 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.

### Policy support

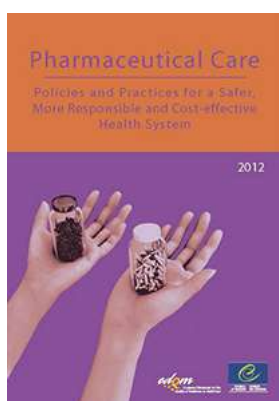
As medicines prepared by industry do not always cover all the health needs of patients, the preparation of medicines in pharmacies is important.

Under the aegis of the CD-P-PH, an ad hoc group of experts has begun developing guidelines and listing criteria for the elaboration, re-evaluation and maintenance of paediatric pharmacy-preparations. These guidelines will provide the basis for a future harmonised "European Formulary for Paediatric Formulations" (PaedForm), which will be established based on existing national formulations in cooperation between the European Pharmacopoeia Commission and the CD-P-PH (see the chapter on the European Pharmacopoeia, page 16).

In 2014, the CD-P-PH/PC commissioned a report about the best practices for automated dose dispensing (ADD) systems and their implementation in Europe as a means of promoting application 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". The observations from the report and further consultation with stakeholders in 2015 will be used to establish a guidance document ensuring that ADD takes place when appropriate for patients and their clinical needs and with the necessary supportive care

The CD-P-PH/PC also progressed towards a guidance document setting out general quality and safety standards for bringing medicinal products to the strength or dosage form required for administration by adding a liquid (reconstitution). A further consultation with relevant stakeholders on the draft guidance will take place in 2015.

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. Every year, it issues recommendations to health authorities for the classification of medicines into prescription and over-the-counter medicines, as this is currently not harmonised in Europe.





## ANTI-COUNTERFEITING ACTIVITIES

### Combating crime to protect public health

In 2014, the EDQM continued to develop its comprehensive anti-counterfeiting strategy at different levels, targeting Europe and the rest of the world through the European Pharmacopoeia Member States and observers. The EDQM thus supports authorities in the fight against criminals and “rogue” actors operating in both unregulated areas and the legal supply chain whose activities undermine the integrity and quality of legal medical products.

### Targeted programmes and projects

#### MEDICRIME: risk management and prevention

Public health needs to be protected from falsified/counterfeit medicines and similar crimes involving threats to public health. Not only do these crimes pose a major threat to patients, who are particularly vulnerable, they also compromise the integrity of healthcare systems, public safety and the general welfare of the population.

The CD-P-PH Steering Committee and the Committee of Experts on Minimising the Public Health Risks Posed by Counterfeiting of Medical Products and Similar Crimes (CD-P-PH/CMED) continuously develop and promote best practices for 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 signatory states with a powerful legal framework to prevent and combat counterfeiting of medical products and similar crimes. It introduces

### Publications, databases and websites

The annual update by the CD-P-PC/PHO leading to the 2014 classification recommendations was concluded and is available on the EDQM website<sup>5</sup>. Furthermore, the review of the classification of chemotherapeutics for topical use was completed and published on the EDQM website. The classification of corticosteroids for topical use was reviewed and will be published on the EDQM website in 2015.

The internet database (Melclass, [www.edqm.eu/melclass](http://www.edqm.eu/melclass)), which presents the classification status of medicines in the member states, was continually updated in 2014.

### Communication with partners and stakeholders

A meeting with industry stakeholders took place in autumn 2014 to share views on the working procedures of the Council of Europe in the area of medicinal product classification (CD-P-PH/PHO Committee of Experts) and to discuss the possibility of stakeholders contributing to and commenting on the CD-P-PH/PHO’s work.

### Events

The quality indicators for the pharmaceutical care project was presented at the Pharmaceutical Care Network Europe (PCNE) Working Symposium, which was held in March 2014 in Sliema (Malta).

An expert workshop, focusing on over-the-counter (OTC) medicines and the importance of good classification practices in promoting medication safety and accessibility in Europe, was co-organised by the EDQM and the Croatian Agency for Medicinal Products and Medical Devices (HALMED) in Zagreb (Croatia) in November 2014. The workshop showed the stakeholders’ commitment to taking a constructive approach to harmonisation of good classification practices for OTC medicines that would ultimately promote medicinal product safety and accessibility in Europe. It also highlighted the need for CD-P-PH/PHO to strengthen its role in health literacy and address issues related to new medicine supply channels (for instance, internet), and the wider distribution of OTC products in some European countries when issuing recommendations for the classification of medicines and updating the Melclass database accordingly.

5. 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/>.



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 significantly in 2014 to promoting the signature and ratification of the MEDICRIME Convention. As of December 2014, 23 states have signed the MEDICRIME Convention, including three states outside Europe. Four (4) states in Europe have legally implemented ("ratified") the Convention in their domestic legislation.

■ In March 2014, the EDQM launched a secure and restricted database ("KnowX") in which comprehensive information on individual medicrime cases where a criminal investigation has been completed is stored. (See below for further details).

■ Inspired by the Convention's specific provisions, the networking approach of single points of contact (SPOCs) to the fight against medicrime relies on a Council of Europe model for cooperation and is maintained by the CD-P-PH/CMED and its secretariat.

■ The EDQM training platform contributed to the global promotion of the MEDICRIME Convention through a training programme carried out in November 2014 by CD-P-PH/CMED. The course was hosted by the Moroccan competent authorities in cooperation with CIVI.POL Conseil as part of an EU funded project against the trafficking of falsified medical products (REPT).

■ In the same vein, the EDQM has contributed to work done by the Asia-Pacific Economic Cooperation (APEC) Life Sciences Innovation Forum (LSIF) to develop a comprehensive strategic plan for promoting medical product integrity & supply chain security. The plan includes a gap assessment, the development of toolkits and the delivery of training courses. The EDQM has been appointed leader of the "Single Point of Contact (SPOC)" workstream and is mandated to help set up a harmonised approach for cooperation among SPOCs in APEC and other regions of the world. A third of the APEC member economies are either member states or hold observer status with the Council of Europe or the European Pharmacopoeia Commission.

■ In 2014, a pilot study designed to evaluate an approach for screening medicrime-induced health damage involved healthcare establishments from five member states and three hundred patients. The study has been finalised for further consultation with stakeholders in 2015 and confirmed the usefulness of a decision-making tool that would help physicians identify at-risk patients through an evaluation of pre-disposing factors (use of medicines that have been reported as falsified [counterfeit] and life style choices).

### **Anti-counterfeiting traceability service for medicines**

■ As part of its holistic anti-counterfeiting strategy, the EDQM supports anti-counterfeiting initiatives such as the development of mass serialisation systems by promoting a harmonised approach in Europe and by encouraging public governance of all traceability systems to prevent any misuse of data.

■ To this end, the Council of Europe/EDQM has expanded its expertise in the field and maintains close contact with health authorities, business stakeholders (i.e. operators in the medicines supply chain: manufacturers, distributors, pharmacies), healthcare professionals and patients' associations working on the development of such systems, throughout the 37 member states of the Ph. Eur. Pharmacopoeia Convention and beyond.

### **API Fingerprint Programme**

■ In 2014 a pilot Market Surveillance Study (MSS) was completed on selected groups of active substances (or APIs), i.e. macrolide antibiotics and statins. Chemometric analysis was added to the initial GC-MS analysis of residual solvents in order to cluster sources of APIs. The outcome of the study was used to fine-tune the API Fingerprint project concept, based on authenticity checks and Market Surveillance Studies

### **Publications, databases and websites**

■ In March 2014, the EDQM launched a secure and restricted database ("KnowX") for the storage of comprehensive information on individual medicrime cases after a criminal investigation has been completed. KnowX hosts information related to chemical-analytical identification of the substances in question as well as data on the modus operandi and risk management and prevention measures taken by the competent health or enforcement authorities. CD-P-PH/CMED has cooperated with the OMCL working group on counterfeit medicines (see Chapter on The European Network of OMCL page 27) throughout development and is also involved in the ongoing promotion of the database and user training. The database will enable health and law enforcement authorities to act on cases of suspect medicines more rapidly and provide support to the signatory states of the MEDICRIME Convention in terms of trend monitoring and follow-up. About 50 officials of law enforcement bodies including health authorities use the system.

## 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 a satellite event organised by the Council of Europe Vienna Office at the May 2014 session of the Commission for Crime Prevention and Criminal Justice (CCPCJ) of the United Nations Office for Drugs and Crime (UNODC). They also contributed to a Regional “MEDICRIME Conference” co-organised by the Council of Europe in June 2014 together with the competent authorities in Skopje, Former Yugoslav Republic of Macedonia.

## COSMETICS AND FOOD CONTACT MATERIALS



## Consumer Health Protection

■ Cosmetics and materials that come into contact with food are used by European citizens on a daily basis. These products must be safe and must not endanger consumer health. 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 with public health responsibilities. More than 200 experts from 34 member states and 4 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 can send representatives to the meetings of this Committee and its subordinate expert groups.

■ In the field of cosmetics, work focusses on the European network of Official Cosmetics Control Laboratories (OCCLs). Food contact material quality and safety requirements for materials are being harmonised and test methods are being developed and updated.

■ The work programme defined by the CD-P-SC is put into action by two subordinate Committees of Experts, the Committee of Experts on Cosmetic Products (P-SC-COS) and the Committee of Experts on Packaging Materials for Food Products (P-SC-EMB).

## Key facts and Figures

### Cosmetics control laboratories join the European Network

■ The European Network of national OCCLs was set up in 2010 on a voluntary membership basis. More than 30 OCCLs participate in regular network activities, including laboratories in 16 member states of the European Union. The main task of an OCCL is to check the quality of products on the market. Under the aegis of the EDQM, testing competences are registered and technical experience shared. The overall aim is to optimise the use of resources and to enhance quality management in each laboratory in accordance with international standards. The long-standing experience with the network of Official Medicines Control Laboratories (OMCLs) is an asset in the coordination of the network. The OCCL network has established close contacts with the European Commission the JRC and the European Committee for standardisation (CEN). In 2014, OCCLs, the JRC and CEN jointly elaborated a common approach for the validation of analytical test methods developed by single laboratories.

### Quality check for cosmetics: market surveillance studies (MSS)

■ Cosmetics may contain trace amounts of many metals, some of which are technically unavoidable. However, the presence of antimony, cadmium, chromium, lead, mercury or nickel may give rise to health concerns. To investigate the amounts of metal present in cosmetics, several countries collected samples of make-up (foundation, eye-shadow, eye-liner, lip gloss etc.). Results of this MSS are shared between authorities and may be used to establish common guidance values.

■ The quality of cosmetic products that are designed to appeal to children was tested in an MSS completed in 2014. Shampoos, skin creams, make-up, bath lotions and several other product types were checked for compliance with European regulations. More than one third of the samples were considered non-compliant and several contained relevant amounts of nitrosamines, forbidden colorants or lead.

## Proficiency testing programme

Proficiency Testing Scheme (PTS) studies are carried out to verify laboratory performance and to ensure that test results are comparable within Europe. In 2014, the study programme included a test for formaldehyde in cosmetics that contain formaldehyde-releasing preservatives. OCCLs in 12 European countries took part in the study. Another study focussed on the amounts of UV filters in sunscreens and again 12 countries participated.

## Tattoos and permanent make-up

To implement the recommendations of Council of Europe Resolution AP (2008) 1 “on tattoos and permanent make-up”, safety and documentation requirements for tattoos and permanent make-up are currently being prepared. This document should be finalised and published in 2015 in parallel with the new EU regulations on tattoos and permanent make-up which are currently being prepared by the European Consumer Safety Network, sub-group on tattoos (analytical methods for cosmetic testing); several delegations of the P-SC-COS take part in this process.

## Food contact materials and articles

The review of existing resolutions and technical documents elaborated under the former Council of Europe Partial Agreement in the Social and Public Health Field (dissolved on 31 December 2008) by P-SC-EMB Committee of Experts continues. The work has been assigned to rapporteurs who will prepare draft provisions for materials such as cork, ion exchange resins or paper and board. Work will continue in 2015.



## Publications, databases and websites

A practical guide “Metals and alloys used in food contact materials and articles” for manufacturers and regulators, based on Resolution CM/Res(2013)9 was published in 2013. This document defines quality requirements for materials such as aluminium foil, kitchen utensils and 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. The French language version of this guide (“*Métaux et alliages constitutifs des matériaux et objets pour contact alimentaire*”) was published in 2014.

## Events

In April, the EDQM organised the 3<sup>rd</sup> OCCL Seminar on “Sun Protection”. The meeting was hosted by Portuguese National Authority for Medicines and Health Products (Infarmed) and was attended by participants and experts from 8 countries. An equipment supplier was invited to provide insight into sun protection factor (SPF) testing and to answer technical questions. The participants were also given the opportunity to learn via “hands-on” practice of application techniques and to share their experience acquired with recently developed techniques.

In November, the EDQM and the Slovenian health authorities jointly organised a symposium on the “Safety of metals and alloys used in food contact materials”. Participants from 22 countries in Europe, Asia and South America representing national authorities, control laboratories, industry, consultancies, retailers and consumer associations as well as the Joint Research Centre (JRC) of the European Commission and the European Food Safety Authority (EFSA) attended.

The programme gave an overview of the European regulations and recommendations that apply to food packaging and utensils on the market and offered delegates an opportunity to share best practices related to product safety and testing for compliance. Currently, there are wide disparities in national regulations in Europe and European harmonisation is on-going to address this. Transitional measures have been recommended to national food authorities.

During the meeting, the EDQM’s “Practical Guide for manufacturers and regulators” and its work in this field was presented.





# List of committees coordinated by the EDQM

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## The European Pharmacopoeia Commission

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■ 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, the Commission now has 38 members, all signatory parties to the Convention (37 states and the European Union). The 27 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 and their components to be applied in 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 2014, 2,267 quality standards and 349 general texts including methods of analysis had 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 for the protection of public health. It is intended for use by healthcare professionals working with medicines, and has become the gold standard reference in the sector.

## The biological Standardisation programme (BSP) Steering Committee

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■ 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 with particular focus on reducing, refining and replacing the use of animals (3Rs initiative). These activities are supervised by the BSP Steering Committee.

## Network of Official Medicines Control Laboratories (OMCL) Advisory Groups

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■ About 35 countries have taken part in the activities of the OMCL Network since 1994; these activities are co-funded by the European Commission and are coordinated 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 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 and Israel (for human vaccines only). For the CAP and the OCABR activities, advisory groups ensure continuity of operations in the interval between the annual meetings of each specific network.

## **Certification of suitability to Ph. Eur. Monographs Steering Committee**

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■ 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)**

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■ The 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 Group on the "Guide to the Preparation, Use and Quality Assurance of Blood Components".

## **European Committee on Organ Transplantation (CD-P-TO)**

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■ The Steering Committee focuses on elaborating and promoting the principle of non-commercialisation of organ, tissue and cell donation, strengthening measures to avoid trafficking and elaborating high ethical, quality and safety standards in the field of transplantation. The members and observers of this Committee represent 41 countries from Europe and elsewhere. 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.

## **European Committee on Pharmaceuticals and Pharmaceutical Care (CD-P-PH)**

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■ 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)**

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■ The CD-P-SC is responsible for managing the work programme and the decision-making process in the areas of cosmetics and packaging for food. Health authorities in the 37 European countries that have signed the Convention on the Elaboration of a European Pharmacopoeia and the European Union are represented at the CD-P-SC and its subordinate bodies. In addition, observer states contribute to the work programme.

■ 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 addresses questions of product quality and safety. Guidance has been developed for safety assessors and manufacturers to avoid the use of cosmetic ingredients that may be harmful.

■ The P-SC-COS interacts with the European network of Official Cosmetics Control Laboratories (OCCLs). The EDQM coordinates the work of this network whose points of focus are quality management, analytical methodology and mutual recognition. OCCLs implement the national and European regulations on cosmetic products. Proficiency studies and market surveillance studies are organised with the aim of improving the quality of cosmetic products on the market. Common testing approaches are developed in close cooperation with the European Commission (EC) and the Joint Research Centre (JRC).

■ In addition to its work on cosmetics, the P-SC-COS also has a working group that addresses health issues related to tattoos and permanent make-up.

# Glossary

3Rs	Reduction, Refinement and Replacement of animal testing
ADD	Automated Dose Dispensing
AdG	Advisory Group
AFNOR	Association Française de normalisation
AGES	Austrian Agency for Health and Food Safety
ANVISA	Brazilian Regulatory authority
APEC	Asian-Pacific Economic Cooperation
API	Active Pharmaceutical Ingredients
B-MJA	Blood Mutual Joint Audits
B-MJV	Blood Mutual Joint Visits
B-PTS	Blood Proficiency Testing Scheme
B-QM	Blood Quality Management
B-TV	Blood Training Visits
BE	Blood Establishments
BET	Bacterial endotoxins
BRP	Biological Reference Preparation
BSP	Biological Standardisation Programme
BWP	Biologics Working Party (BWP)
CAP	Centrally Authorised Product
CEN	European Committee for Standardization
CEP	Certificate of Suitability to the Monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use (EMA)
CLP	Classification, Labelling and Packaging
CM	Committee of Ministers
COE	Council of Europe
CRS	Chemical Reference Substance
CVMP	Committee for Medicinal Products for Veterinary Use (EMA)
DCD	Donation after circulatory death
DCP	Decentralised Procedure
DG Sanco	EU Directorate General for Health, Consumer Protection and Animal Health
DH-BIO	Council of Europe's Committee on Bioethics
EATB	European Association of Tissue Banks
ECBS	WHO Expert Committee on Biological Standardization
EDQM	European Directorate for the Quality of Medicines & HealthCare
EDTCO	European Donation & Transplant Coordination Organisation
EEA	European Economic Area
EMA	European Medicines Agency
EODD	European Day for Organ Donation & Transplantation
EU	European Union



EUCTP	EU-China Trade Project
FRC	Functionality Related Characteristics
GC-MS	Gas Chromatography-Mass Spectrometry
GEON	General European Network of Official Medicines Control Laboratories
GMP	Good Manufacturing Practice
GTP	Gene Therapy Products
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HRS	Herbal Reference Standards
HTOR	Human trafficking for the purpose of organ removal
ICH	International Conference on Harmonisation (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
ICRS	International Chemical Reference Substance
IDMP	Identification of medicinal products
IPA	Indian Pharmaceutical Association
IPFA	International Plasma Fractionation Association
ISA	International Standard for Antibiotics
ISBT	International Society of Blood Transfusion
ISO/IEC	International Organization for Standardization/International Electrotechnical Commission
IVMP	Immunological Veterinary Medicinal Products
JP	Japanese Pharmacopoeia
JRC	Joint Research Center
LBP	Live Biotherapeutic Products
LNS	National Health Laboratory Luxembourg
MA	Marketing Authorisation
MJA	Mutual Joint Audit
MJV	Mutual Joint Visits
MRP	Mutual Recognition Procedure
MSSIP	Market Surveillance Studies on Suspicious Illegal Products
MSSs	market surveillance studies
NAB	National Accreditation Bodies
NIFDC	Chinese National Institute for Food and Drug Control
NMR	Nuclear Magnetic Resonance
NPA	National Pharmacopoeia Authorities
OCABR	Official Control Authority Batch Release
OCCL	European network of national official cosmetics control laboratories
OMCL	Official Medicines Control Laboratory
OTC	Over-the-counter
P4	Procedure 4
PaedF	Paediatric Formulary
PDG	Pharmacopoeial Discussion Group
PEI	Paul Ehrlich Institute
Ph. Eur.	European Pharmacopoeia
PIC/S	Pharmaceutical Inspection Co-operation Scheme

PTS	Proficiency Testing Scheme
Q3D	Code for ICH guideline on Elemental Impurities
QbD	Quality by design
QMS	Quality Management System
QWP	Quality Working Party (EMA)
RS	Reference Standard
SIT	Second Identification Test
SPOCs	Single points of contact
STWP	Standard Terms Working Party
SWISSMEDIC	Swiss Agency for Therapeutic Products
TFDA	Taiwan Food and Drug Administration
TGA	Therapeutic Goods Administration (Australia)
THO	Trafficking in human organs
TV	Training Visits
UNODC	United Nations Office on Drugs and Crime
UPLC-MS	Ultra Performance Liquid Chromatography-Mass Spectrometry
UPP	Unlicensed Pharmaceutical Preparations
USFDA	United States Food and Drug Administration
USP	United States Pharmacopoeia
VBRN	Veterinary Batch Release Network
WHO	World Health Organization

This publication presents the work carried out in 2014 by the European Directorate for the Quality of Medicines & HealthCare, Council of Europe, highlighting its particular achievements.

[www.coe.int](http://www.coe.int)

The Council of Europe is the continent's leading human rights organisation. 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. The European Court of Human Rights oversees the implementation of the Convention in the member states.