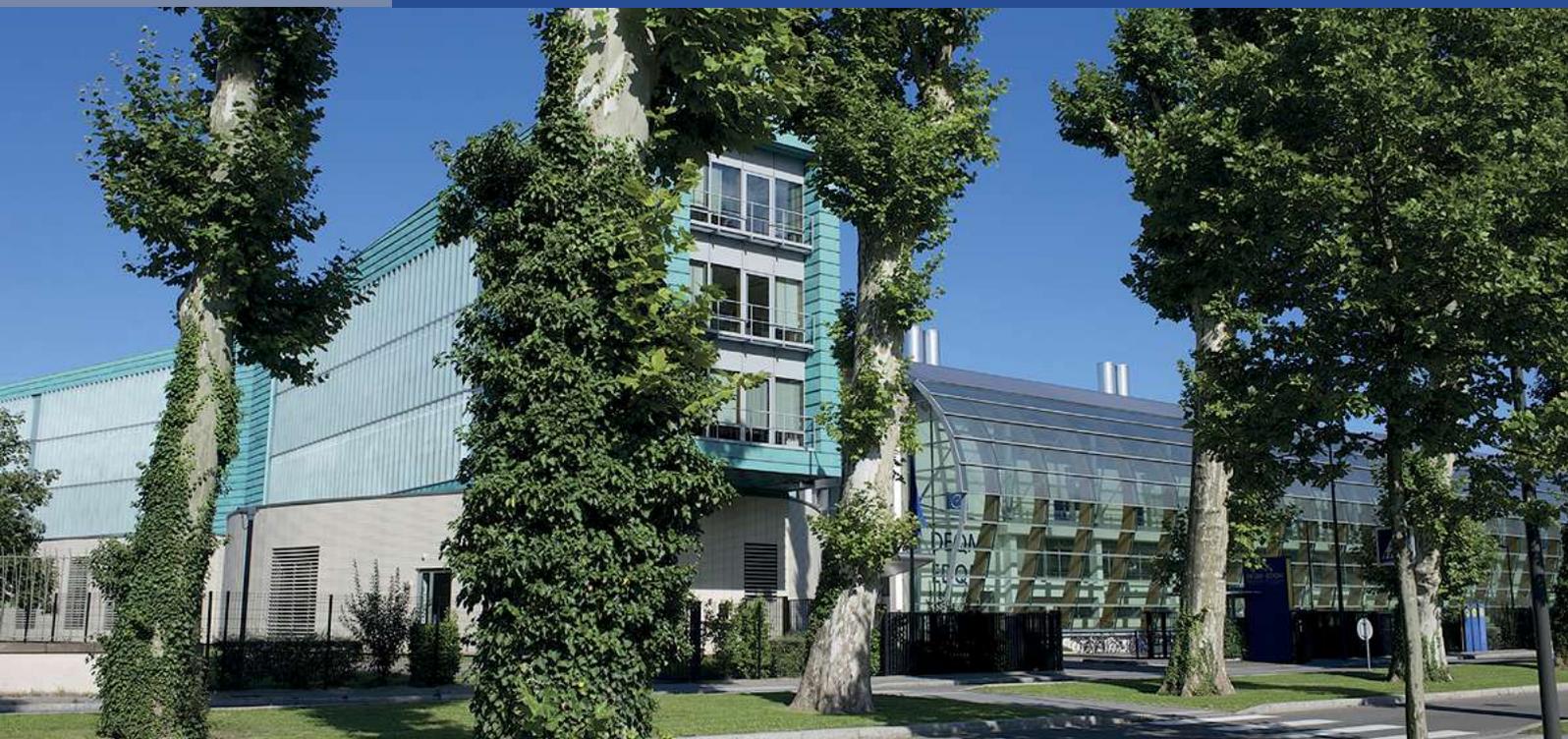


ANNUAL REPORT 2017



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

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& HealthCare (EDQM)

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Foreword

by *Susanne Keitel, Director*



2 017 was another remarkable year for the EDQM with various milestones reached on a number of our activities. Starting with the European Pharmacopoeia (Ph. Eur.), we are most pleased with the progress achieved in the fields of biotherapeutic products and animal protection, in addition to the 35 new and more than 220 revised texts adopted to incorporate scientific and technological progress and regulatory changes.

■ In particular, in 2017 the European Pharmacopoeia Commission adopted the first monograph on a monoclonal antibody (mAb): *Infliximab concentrated solution* (2928), an important milestone in relation to biotherapeutic products. The adoption of this monograph not only showed that setting public standards for a complex biological molecule is feasible, it also paved the way for the Ph. Eur. Commission's horizontal approach for therapeutic mAbs: looking into general requirements and methodologies applicable to this class of products.

■ Once more last year, much was achieved by the Ph. Eur. Commission in terms of implementing and promoting animal welfare in pharmacopoeial testing in Europe. In line with the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes, the Ph. Eur. Commission decided to completely remove the test for abnormal toxicity from the European Pharmacopoeia.

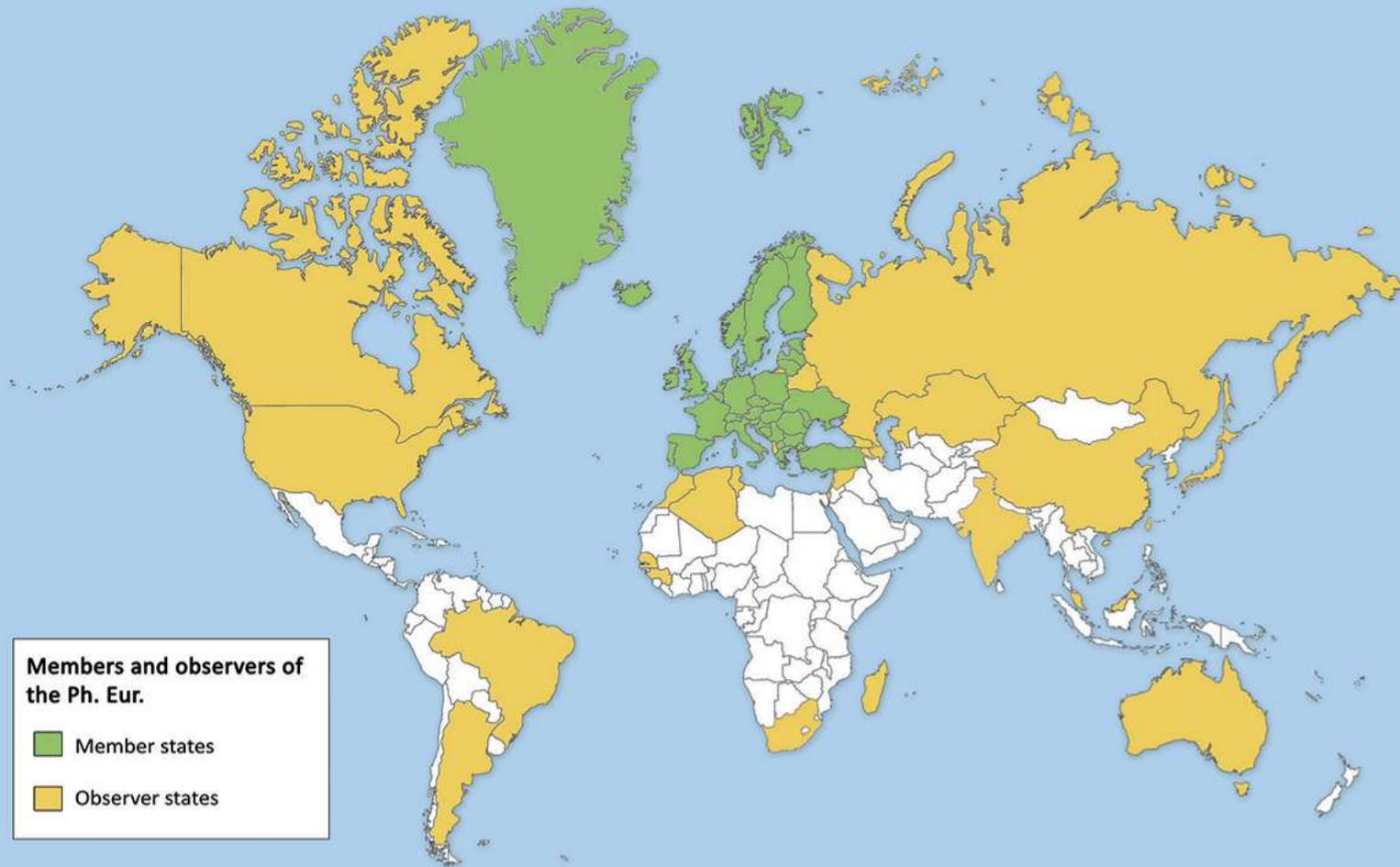
■ International cooperation and promoting science-based quality standards at global level also saw major achievements, with the EDQM signing two Memorandums of Understanding on co-operation in the field of medicines' quality and on pharmacopoeial standards with ANVISA, the Health Surveillance Agency of Brazil. A Memorandum of Understanding was also signed with the Chinese Pharmacopoeia Commission to promote co-operation on the safety and quality of medicines in both Europe and China.

■ Throughout 2017, the EDQM's cooperation with the European Union and its European Medicines Agency (EMA) continued to be strengthened for the benefit of European citizens and patients. The Official Medicines Control Laboratories (OMCLs) carried on with their joint work programmes under the GEON Network coordinated by the EDQM: mutual recognition of test results, harmonisation of working methods, sharing of expertise, laboratory resources and analytical data all featured high on the GEON agenda in 2017.

■ The work carried out by the EDQM on the healthcare side led to some important achievements too. In the area of blood transfusion, the EDQM kept supporting European Blood Establishments (BEs) in implementing Quality Management (QM) elements and addressing risk management, change control and validation/qualification, which are key aspects for ensuring the optimal use of blood, as well as the sound protection of both blood donors and recipients. In 2017, the EDQM also published the 3rd Edition of its guidelines to ensure the quality and safety of tissues and cells for human application. This guidance aims at helping healthcare and transplant professionals on a practical level and supporting successful and safe clinical use of tissues and cells. In the field of cosmetics, a new guide on safer tattooing provided an overview of current knowledge and challenges in the toxicological assessment of inks for tattoos and permanent make-up.

■ The support offered to the EDQM by Member States and their national competent authorities throughout the year has been of particular importance. I wish to express my gratitude to all; in particular, to the Hungarian authorities for their support in organising with us the annual meeting of the General European OMCL Network in Budapest; to the Cypriot authorities for hosting the Network of Official Cosmetics Control Laboratories in Nicosia to discuss analytical challenges related to cosmetics control, during the Cyprus Chairmanship of the Committee of Ministers of the Council of Europe; and to the Czech authorities for their support in hosting the International conference on the Certification Procedure in the global regulatory environment, which took place under the Czech Republic Chairmanship of the Committee of Ministers.

■ And of course – as always – I have to acknowledge the fact that the EDQM's achievements in 2017 would not have been possible without the remarkable efforts of our experts: joining us from national, European and international authorities, universities, scientific institutes and industry from across the world, they have made an invaluable contribution to our work with their excellent scientific competence. To all of them, as well as to the dedicated staff at the EDQM, I offer my heartfelt thanks.



Quality and use of medicines

THE EUROPEAN PHARMACOPOEIA

What it is and how it works

The European Pharmacopoeia (Ph. Eur.) lays down quality standards for the manufacture and control of medicines in Europe and beyond. The texts of the Ph. Eur. are elaborated and revised by a panel of 61 groups of experts and working parties which may be convened or disbanded by the European Pharmacopoeia Commission, the decision-making body of the Ph. Eur., depending on current regulatory, industrial and technical needs. Since the participation of external stakeholders and users in the Ph. Eur.'s public standards-setting process is vital for the development of authoritative and relevant monographs, these groups comprise representatives of national competent authorities, academia and industry.

The importance of the Ph. Eur. in Europe and beyond

The Ph. Eur., Europe's legal and scientific benchmark for pharmacopoeial standards, is legally binding in 38 European countries and used in over 100 countries worldwide. It delivers crucial information earlier than any other pharmacopoeia in Europe.

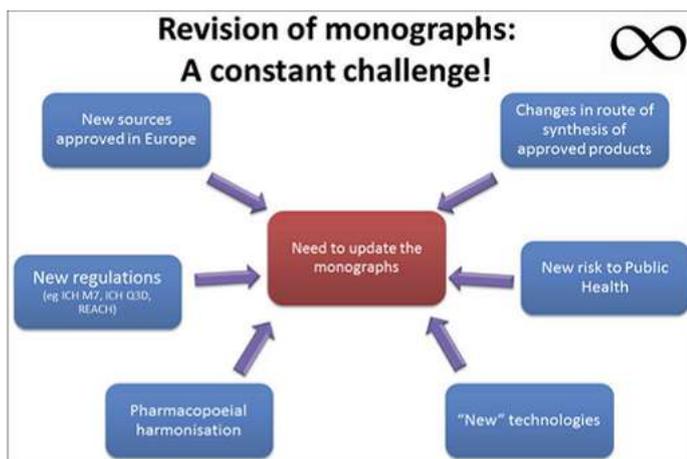
To reflect this global status of the Ph. Eur. and keep pace with the far-reaching changes the pharmaceutical world has undergone over the past 50 years which have created a globalised operating environment for medicinal products and their components, in 2015 the Ph. Eur. Commission reviewed its working procedures to allow for the nomination of experts from non-Ph. Eur. member states. This decision was part of a specific policy to further involve observer states, as well as manufacturers from outside Europe, in the work of the Ph. Eur. This new policy is applied for the nomination of Ph. Eur. experts since November 2016. The wide variety of scientific and cultural backgrounds of these experts, all volunteers, testifies to the international scope and reach of the Ph. Eur.

Key facts and figures

Wide participation

38 Member States and the EU are signatories of the Convention on the Elaboration of a European Pharmacopoeia (the Republic of Moldova being the latest Member State having accessed the Convention). In addition, by the end of 2017, there were 29 observers to the Ph. Eur. Commission: 27 countries from all over the world, the Taiwan Food and Drug Administration and the World Health Organization.

The Work Programme 2017



Year-on-year, the Ph. Eur. Commission works to provide the users of the Ph. Eur. with the most up-to-date and relevant information possible, revising existing monographs to incorporate newly developed methods and techniques, and approving new texts for products of high market relevance. The work programme for 2017 continued to reflect these efforts: 35 new monographs were adopted and 222 texts were revised to incorporate regulatory changes and scientific progress.

Scope of the 35 newly adopted Ph. Eur. monographs (2017)

Scope Newly adopted Ph. Eur. monographs	Number of monographs
Single source products still under patent amongst them:	7
– Finished products	2
– Active substances	5
Multisource Monoclonal Antibody (mAb)	1
Traditional Chinese Medicines (TCM)	7
Herbal drugs and herbal drugs preparations	3
Concentrated solutions for haemofiltration and haemodiafiltration	1
Radiopharmaceutical preparation	1
Other monographs	10

The Ph. Eur. Commission adopted two monographs on finished products, *Raltegravir tablets (2938)* and *Raltegravir chewable tablets (2939)*, elaborated under the P4 procedure (single-source products still under patent). These two monographs follow on from the decision of the Ph. Eur. Commission in 2014, after the positive results of a pilot phase, to make finished product monographs part of its regular work programme. The decision was based on various considerations including the fact that finished

product monographs help Official Medicines Control Laboratories (OMCLs) in their market surveillance tasks and can support the development of generic drugs, an essential point for the sustainability of healthcare systems. Finished product monographs also facilitate the assessment of marketing authorisation applications by regulatory authorities.

The European Pharmacopoeia works to provide its end-users with the most up-to-date and relevant information possible, elaborating new texts for products of high market relevance. The Ph. Eur. Commission adopted five new monographs on active substances elaborated under the P4 procedure.

Active substances	Pharmacotherapeutic group (source: EMA website)
Raltegravir potassium (2887)	Antivirals for treatment of HIV infections, combinations
Tigecycline (2825)	Antibacterials for systemic use
Lacosamide (2292)	Anti-epileptics
Deferiprone (2236)	All other therapeutic products (iron chelator)
Rotigotine (3014)	Anti-Parkinson drugs

The Ph. Eur. Commission achieved an important milestone in the field of biotherapeutic products with the adoption of the monograph for *Infliximab concentrated solution (2928)* in November 2017. This Infliximab monograph is the outcome of a collaborative effort by Ph. Eur. experts, and a successful example of the close cooperation between the Ph. Eur. and its key partners. The elaboration of the monograph included extensive and rigorous analytical testing by Ph. Eur. experts from Official Medicines Control Laboratories (OMCLs). This, together with the feedback received from stakeholders during the Pharmedica public consultation, demonstrated that it is feasible to set meaningful quality requirements for a complex mAb (150 kDa). The approach used to set the monograph specifications is oriented towards promoting flexibility, notably in addressing process-dependent product heterogeneity (e.g. glycosylation and charge profile). Significantly, criteria for verifying the performance of analytical methods are included as a way of supporting robust methodologies, while the provision of examples of suitable procedures for complex assays enables the use of alternative methods.

Going forward, the Ph. Eur. Commission will carry on setting public standards for therapeutic mAbs through the development of horizontal approaches: these aim to establish a suitable set of general requirements and methodologies applicable to various quality attributes common to (classes/sub-classes of) mAbs (e.g. TNF-alpha product-based standards).

In 2017, the Ph. Eur. Commission also continued its efforts in replacing animal testing whenever possible and endorsed the complete suppression of the test for abnormal toxicity from the Ph. Eur. As

part of this exercise, the Commission adopted 49 monographs revised to remove the test for abnormal toxicity; of these, 36 monographs were on vaccines for human use. In addition, the general chapter *Abnormal Toxicity* (2.6.9), which will no longer be referenced in any monograph, is likely to become obsolete and deleted completely from the Ph. Eur. In line with the Council of Europe Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes¹, the decision to suppress the test for abnormal toxicity demonstrates the Ph. Eur. Commission's commitment to reducing animal use wherever possible in pharmacopoeial testing.

■ The Ph. Eur. Commission also adopted a revised version of the general monograph on *Vaccines for human use* (0153) and the one on *Vaccines for veterinary use* (0062), this followed on from the new general chapter 5.2.14 on *Substitution of in vivo method(s) by in vitro methods for the quality control of vaccines*, which was originally adopted in 2016. This chapter is a guidance document (non-mandatory text) intended to facilitate the transition from *in vivo* to *in vitro* methods; it is an addition made available by the Ph. Eur. Commission to reduce animal testing and encourage the use of alternatives. Both general monographs 0153 and 0062 contain a section titled "Animal tests" providing recommendations on how to meet the animal welfare requirements of the Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes, in the context of vaccine control. The sentence, "Guidance on how to substitute *in vivo* methods by *in vitro* methods where a direct head-to-head comparison is not possible may be found in general chapter 5.2.14" was added in the section "Animal tests" of these two general monographs: it removes any ambiguity as regards the non-mandatory character of the chapter, but still directs the user to the new chapter 5.2.14.

■ The Ph. Eur. Commission also continued its efforts in replacing the use of hazardous chemicals whenever possible. For example 4 monographs on sutures for human or veterinary use (*Sutures, sterile non-absorbable* (0324), *Polyamide 6/6 suture, sterile, in distributor for veterinary use* (0610), *Polyamide 6 suture, sterile, in distributor for veterinary use* (0609), *Poly(ethylene terephthalate) suture, sterile, in distributor for veterinary use* (0607)) have been revised in order to replace the use of hazardous chemicals by infrared spectroscopy using attenuated total reflection for their identification and to include sutures composed of blends of materials cited in the monographs.

■ In 2017, the Ph. Eur. Commission decided to create a new Working Party on Pyrrolizidine Alkaloids (PA WP), tasked with the definition of a general method

for testing *Pyrrolizidine Alkaloids* (2.8.26). This decision was taken upon demand by European regulators and following reports in some Ph. Eur. Member States that herbal medicinal products, as well as food, were found to be contaminated with traces of plants containing pyrrolizidine alkaloids.

General matters and policies

Biological Standardisation Programme



■ The Biological Standardisation Programme (BSP) is a joint European Union (EU)/Council of Europe initiative, partly funded by the EU. Its mission is to establish reference materials for biologicals and to develop and validate new analytical methods for the quality control of biologicals, including alternative methods for the replacement of animals in laboratory experiments based on the 3Rs principle (Refine, Reduce, Replace).

■ In 2017, the programme ran 29 projects in different fields, from vaccines for human and veterinary use to plasma-derived and biotechnology products. Six were concluded in the year, leading to the establishment of 3 new and 5 replacement reference standards (see chapter on "Pharmaceutical Reference Standards", page 12).

■ The EDQM carried forward another 14 projects aimed at establishing replacement batches for existing reference standards for biologicals. Three projects for the elaboration of these reference standards for new monographs, or new requirements in existing monographs, were also pursued. Important achievements in this context were the establishment of assay standards, Biological Reference Preparations (BRPs), for monographs on biotherapeutics, such as Etanercept and Infliximab.

■ Nine projects focused on the development of new compendial methods, and 6 of these were dedicated to applying the 3Rs principle to the field of quality control of biologicals. The continued efforts of the BSP to elaborate, validate and implement analytical methods in line with the 3Rs principle were widely acknowledged in 2017.

Standard Terms database



■ Initially drawn up at the request of the Commission of the European Union for use in marketing authorisation applications, the lists of the "Standard

1. More information on the European Convention for the Protection of Vertebrate Animals can be found here: <https://go.edqm.eu/convprotectionanimals>

Terms" database provide users and prescribers with harmonised vocabularies to describe dosage forms, routes of administration, units of presentation, containers closures and delivery devices of medicinal products. It also includes a mapped terms function, which allows external databases across the world to introduce and map their own terms against Standard Terms, and web services (also known as application programming interfaces), which allow registered users to extract data directly from the database. By the end of 2017, the free, online Standard Terms database had almost 20 000 registered users and held 977 individual Standard Terms concepts translated into 34 languages, for a total of more than 27 000 entries.

■ In 2017, a new tagging function was also developed to allow the introduction of "non-traditional" Standard Terms intended for purposes other than marketing authorisation applications and labelling. In particular, this meant that certain terms necessary for pharmacovigilance could be introduced and led to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) voting to use Standard Terms lists for adverse event reports, hence further broadening the global use of the database.

The Pharmacopoeial Discussion Group and other international harmonisation initiatives

■ Through its active participation in the work of the Pharmacopoeial Discussion Group (PDG), the Ph. Eur. continued its efforts to reduce unnecessary duplication of testing and reporting during drug development and routine manufacturing testing. The Group, which comprises the Ph. Eur., the Japanese Pharmacopoeia (JP) and the United States Pharmacopoeia (USP) as members, as well as the World Health Organization (WHO) as an observer, was set up in 1989 to harmonise pharmacopoeial standards across the world. One face-to-face meeting was held in 2017, hosted by the USP in Rockville (USA, Maryland).

■ In 2017, the PDG agreed to the implementation of significant changes to the work structure, including:

- ▶ eliminating two stages of PDG harmonisation process to streamline and reduce the level of complexity;
- ▶ restructuring meeting format to engage more effectively at the technical level with regards to resolving issues on specific topics;
- ▶ and maintaining a twice-yearly meeting frequency with a focus on strategic direction setting.

■ Under the new structure, the harmonisation of other several PDG topics will be carried out in other collaborative venues, such as bilateral discussions or the adopt/adapt mechanisms mentioned in the Good

Pharmacopoeial Practices (GPhP). The Ph. Eur., JP, and USP will continue to share information and progress on these topics, which will however not be part of the trilateral work programme until further notice.

■ Approvals at the 2017 PDG meeting included a new General Chapter on "Conductivity" and the revision of 4 monographs, including Microcrystalline Cellulose, Hypromellose, Methylcellulose and Calcium Phosphate Dibasic Anhydrous. In-depth discussions on a number of additional items on the work programme also took place with a view to resolving outstanding issues and advancing items towards sign-off.

■ As a result, 28 of the 31 General Chapters and 45 of the 62 excipient monographs on the work programme were now harmonised between the PDG Pharmacopoeias in 2017.

Further harmonisation initiatives

■ The Ph. Eur. is actively involved in a number of other harmonisation initiatives at international level. It takes part in the International Meeting of World Pharmacopoeias, which is organised under the auspices of WHO and brings together pharmacopoeias from around the world to discuss possible ways of strengthening harmonisation and convergence. Amid the various projects carried out, the WHO initiative to draft Good Pharmacopoeial Practices (GPhP) stands out as a basis for improving cooperation and work-sharing among the pharmacopoeias of the world.

■ The 8th International Meeting of World Pharmacopoeias took place in August 2017 in Brasilia (Brazil) and was hosted by ANVISA, the Brazilian national health agency. This was an occasion for the pharmacopoeias to discuss and finalise the outstanding annexes of the GPhP core document (glossary and future chapters on compounding and on monographs on herbal medicines) and to discuss possible next steps. In the context of this meeting, the EDQM and ANVISA signed a Memorandum of Understanding on strengthening co-operation in the field of medicines' quality and pharmacopoeial standards.

Cooperation with national and European regulatory authorities

■ Throughout 2017, the Ph. Eur. Commission continued to work closely with national competent authorities and the European Medicines Agency (EMA). This on-going cooperation is crucial to ensuring continued consistency between the approaches of licensing authorities and the Ph. Eur.; the EMA scientific guidelines and the Ph. Eur. monographs and chapters are complementary instruments for ensuring the quality of medicinal products. More specifically,

- ▶ the Ph. Eur. sets legally binding harmonised specifications for pharmaceutical preparations, their constituents and containers; and

- ▶ the 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 groups of experts and working parties. National authorities and the EMA also take part in the work of the Ph. Eur. by submitting requests for revisions and reviewing draft texts issued for public consultation in *Pharmeuropa online*. Members of EMA working groups (i.e. for which the EMA provides the Secretariat) or members of the EMA Secretariat itself are observers to some of the Ph. Eur. Commission's groups of experts and working parties.

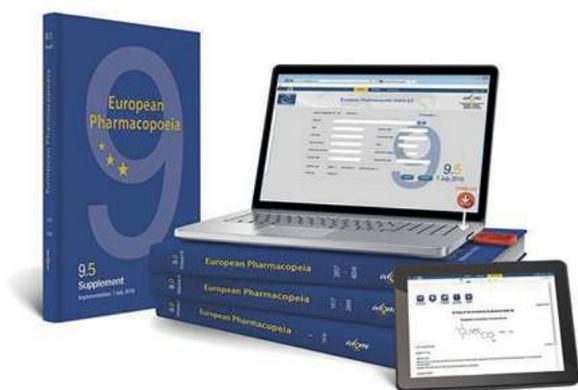
Likewise, the EDQM has observer status in a number of EMA bodies, such as the Committee for Advanced Therapies (CAT), the Herbal Medicinal Products Committee (HMPC), the joint CHMP/CVMP Quality Working Party (QWP), the Biologics Working Party (BWP), the Immunologicals Working Party (IWP) and the GMP/GDP Inspectors Working Group.

Cooperation with National Pharmacopoeia Authorities

The EDQM organises an annual meeting of National Pharmacopoeia Authorities (NPAs) of Ph. Eur. Member States to facilitate and coordinate activities of common interest, and to provide an informal forum for exchanging information. The 2017 meeting was hosted by the EDQM in Strasbourg in June. Among other topics, discussions focused on the Ph. Eur. work programme and on process improvements.

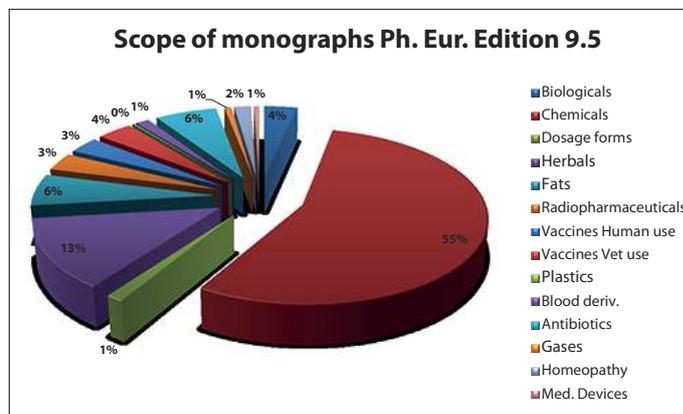
Cooperation with other stakeholders

Stakeholders' involvement in the elaboration and revision of Ph. Eur. texts is of crucial importance, and the EDQM strives to ensure regular exchanges with all those concerned by its work. In 2017, various bilateral meetings were held with a variety of stakeholders to promote exchanges on all aspects related to the work of the EDQM, and also to ensure that the feedback from users could be taken into account.



Publications, databases and website

The 9th Edition of the European Pharmacopoeia (with its latest Supplement 9.5) contains 2 376 monographs (including dosage forms), 361 general texts (including general monographs and methods of analysis) and around 2 676 descriptions of reagents.



Pharmeuropa online is the free online publication, in which draft Ph. Eur. texts are launched for public consultation. Easily and widely accessible, *Pharmeuropa online* aims to optimise interactions between the Ph. Eur. Commission and its stakeholders: it provides interested parties with enough time to comment on draft texts and ensures access to all stakeholders across the globe. Texts are published on an on-going basis and comments can be submitted on the basis of 4 deadlines per year. In 2017, 157 draft texts were published on *Pharmeuropa online*, which was accessed from 155 countries worldwide in the course of the year.

REFERENCE STANDARDS

What are reference standards and why are they needed?

Ph. Eur. reference standards

Official reference standards (RSs) are an essential part of the quality standards of the Ph. Eur.: they are used in conjunction with the documentary texts and are produced specifically for the intended use described. Reference standards include Chemical Reference Substances (CRSs), Herbal Reference Standards (HRSs), Biological Reference Preparations (BRPs), Biological Reference Reagents (BRRs) and reference spectra. The official Ph. Eur. reference standards are established and distributed by the EDQM and officially adopted by the Ph. Eur. Commission; only the official Ph. Eur. reference standards are authoritative in case of arbitration.



■ The EDQM's RSs portfolio constantly evolves, as new standards are introduced to complement new or revised Ph. Eur. texts, or to replace existing RS when corresponding stocks run out. The overall lifecycle management of the RS portfolio covers a wide range of tasks: from the procurement, characterisation, storage, establishment distribution, labelling and packing of candidate materials, to quality control, quality assurance, release and monitoring.

EDQM activities for WHO on Reference Standards

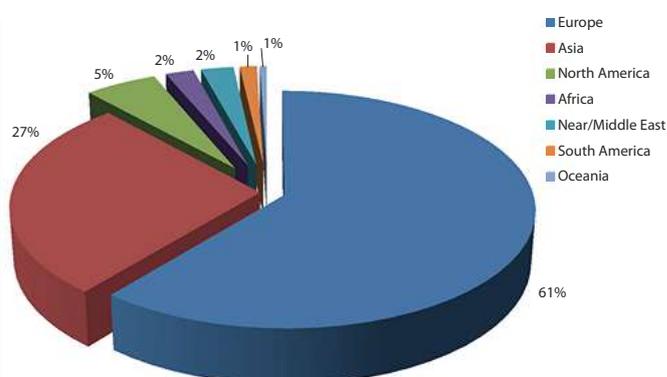
■ The EDQM is an observer to the World Health Organization (WHO) Expert Committee on Specifications for Pharmaceutical Preparations and the Expert Committee on Biological Standardisation. The tasks entrusted to these Committees include the development of standards and guidelines to promote the quality assurance and quality control of medicinal products around the world. In 2017, the EDQM Laboratory participated in two collaborative studies organised by the WHO for the establishment of two International Standards: Activated Factor IX and anti-D Immunoglobulin.

■ The EDQM is responsible for the establishment, storage and distribution of WHO International Standards for Antibiotics (ISAs), which are essential for the standardisation and quality control of antibiotic drug substances and medicinal products. These standards are supplied across the entire world for microbiological assays performed in the context of the quality control of antibiotics.

■ The establishment, monitoring and distribution of WHO International Chemical Reference Substances (ICRSs) are also under the responsibility of the EDQM. These reference substances are used in conjunction with the monographs and texts of the International Pharmacopoeia, which is published and maintained by the WHO and used worldwide.

Key facts and figures

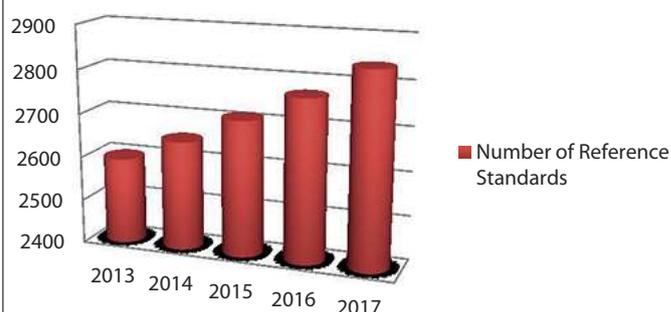
Distribution of RS across the world in 2017



■ At the end of 2017, there were 2 838 reference standards available in the Ph. Eur. catalogue.

■ Globalisation of the pharmaceutical industry means that Ph. Eur. RSs are widely used around the world: in 2017, the EDQM distributed its Ph. Eur. RSs directly to 115 countries.

Growth of the RS portfolio



Ph. Eur. RSs adopted in 2017

■ In 2017, the Ph. Eur. Commission adopted 70 new and 247 replacement RSs.

■ The RSs used for assays must be thoroughly characterised before they can be assigned a quantitative content value. In 2017, the EDQM Laboratory established 95 assay RSs, 46 of which required inter-laboratory studies involving official national control laboratories and other centres of excellence.

■ The international collaborative studies performed by the Biological Standardisation Programme (BSP) in 2017 led to the conclusion of 6 projects and to the adoption of 3 new reference standards by the Ph. Eur. Commission: *Erythropoietin for SEC system suitability CRS*, *Etanercept BRP* and *Equine Influenza Subtype 2 American-Like Strain A/eq/Richmond/1/2007 Horse Antiserum BRP*. Furthermore, 5 replacement standards were established: *Hepatitis A vaccine ELISA detection*

antibodies set BRR, Heparin low-molecular-mass for calibration CRS, Human immunoglobulin for Fc function BRP, Human immunoglobulin for anticomplementary activity BRP and Human immunoglobulin (molecular size) BRP. (See chapter "The European Pharmacopoeia", page 7).

The WHO ICRS board adopted 5 establishment reports submitted by the EDQM Laboratory: *Artesunate ICRS2*, *Lumefantrine ICRS2*, *Atazanavir sulfate ICRS1*, *Lopinavir ICRS1*, *Trimethoprim ICRS2*, whereas no further needs to establish replacement batches for any of the existing ISA emerged in the course of 2017.

General matters and policies

Extended competence in RS establishment

In line with its continuous effort to improve characterisation and establishment of reference standards and remain abreast of rapidly evolving technologies, the EDQM Laboratory has participated in a pilot study on quantitative NMR in 2017 which was organised by the *Bureau International des Poids et des Mesures* (BIPM), the international organisation dealing with matters related to measurement science and measurement standards.

Collaboration with the ISO

The EDQM also continued its participation as an observer in the activities of the International Organization for Standardization (ISO) Committee on Reference Materials (REMCO).

Collaboration with national laboratories

Some RSs, usually those for assay/potency tests, are established through collaborative studies involving several laboratories. Continuous collaboration with national laboratories and centres of excellence is fundamental for these studies. In 2017, the establishment of RSs also benefited from contributions from a panel of 38 Official Medicines Control Laboratories from 27 different countries contributed.

Publications, databases and website

Throughout 2017, the EDQM continued to run and maintain its "Reference Standards Online Database" providing access to all standards officially valid for the uses prescribed in the European Pharmacopoeia monographs. The database has been further fine-tuned to help users find the standards as rapidly as possible: RSs can be searched by code, name, monograph number or CAS number; also, RS Batch Validity Statements (BVSs) are available to users for documenting the validity of the particular RS batch supplied at the time of use. Downloadable Safety Data

Sheets and Safety Data Statements, as well as leaflets are also available in the EDQM's Online Database².

In 2017, the EDQM issued 352 leaflets giving RS users additional information such as a chromatogram, assigned value, etc. for a given substance.

  Celecoxib Safety Data Sheet <small>Safety Data Sheet in accordance with regulation (EC) No 1907/2006, as amended. Date of issue: 31/05/2017 Version: 1.0</small>	
SECTION 1: Identification of the substance/mixture and of the company/undertaking	
1.1. Product identifier	
Product form	: Substance
Substance name	: Celecoxib
Product code	: 2016001175
Synonyms	: Celecoxib, salts, hydrates, isomers and impurities where applicable
Other means of identification	: Ph.Eur. 2591
1.2. Relevant identified uses of the substance or mixture and uses advised against	
1.2.1. Relevant identified uses	
Main use category	: The product is intended for research, analysis and scientific education.
Use of the substance/mixture	: For professional use only
Function or use category	: Laboratory chemicals
1.2.2. Uses advised against	
Restrictions on use	: Do not use : Ingestion, inhalation, Dermal
1.3. Details of the supplier of the safety data sheet	
European Directorate for the Quality of Medicines & Healthcare EDQM, Council of Europe 07081 Strasbourg - France T +33(0)388412035 - F +33(0)388412771 sdsh@edqm.eu - www.edqm.eu	
1.4. Emergency telephone number	
Emergency number	: +33(0)390215608
SECTION 2: Hazards identification	
2.1. Classification of the substance or mixture	
Classification according to Regulation (EC) No. 1272/2008 [CLP] Acute toxicity (oral), Category 4 H302 Full text of H statements : see section 16	
Adverse physicochemical, human health and environmental effects Expert judgement and weight of evidence determination.	
2.2. Label elements	
Labelling according to Regulation (EC) No. 1272/2008 [CLP] Hazard pictograms (CLP)	
	
Signal word (CLP)	: Warning
Hazard statements (CLP)	: H302 - Harmful if swallowed
Precautionary statements (CLP)	: P301+P312 - IF SWALLOWED: Call a doctor if you feel unwell
Labelling according to: exemption for inner packaging where the contents do not exceed 10ml	
No labelling required	
2.3. Other hazards	
No additional information available	
SECTION 3: Composition/information on ingredients	
3.1. Substances	

In addition, Safety Data Sheets and outer labels have been either created or updated for hazardous chemicals in accordance with EU regulations on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) and on Classification, Labelling and Packaging (CLP). Safety Data Statements have been either created or updated for biohazardous materials within the scope of Directive 2000/54/EC. This brings to a total of 788 Safety Data Sheets and 11 Safety Data Statements directly downloadable from the EDQM website. Safety Data Sheets and labels are provided in 27 languages.



2. The EDQM Online database can be accessed here: <https://crs.edqm.eu/>

CERTIFICATION OF SUITABILITY TO THE PH. EUR. MONOGRAPHS

The Certification procedure is becoming increasingly recognised worldwide

The Certificate of Suitability (CEP) procedure has been set up to evaluate and validate the capacity of Ph. Eur. standards to control the quality of substances used in the manufacture of medicinal products. As the world's economy continues to evolve, extra-European production of pharmaceutical ingredients has become increasingly common, creating challenges as regards the monitoring and quality control of substances used in the manufacture of medicines.

To apply for a Certificate, manufacturers submit a dossier describing how their product is manufactured and how its quality is controlled, and demonstrating that Ph. Eur. monographs are suitable for its quality control. The EDQM evaluates the data in this dossier and may then grant a CEP. The procedure centralises the evaluation of data for the benefit of regulatory authorities and industry alike, 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 drug substances covered by CEPs. Inspections 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 quality section of the registration file submitted for substances used in medicinal products.

Key facts and figures

The EDQM received 291 new applications in 2017, including 19 for the risk of transmissible spongiform encephalopathy (TSE) and 9 for herbal preparations; these figures are stable compared to 2016. Additionally, an increasing number of requests for revision of CEPs were received: 1868 (10% more compared to the previous year).

In the course of 2017, a total of 306 new certificates and 1505 revised certificates were issued. Overall, about 90% of applications, including new applications and requests for revision, were dealt with within official timelines.

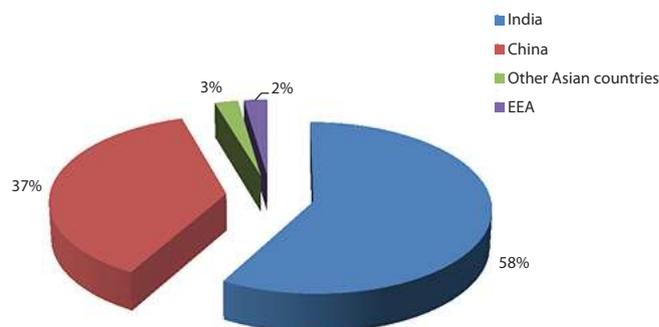
In order to assess the applications, the EDQM's Certification Department relied on a Network of about 100 assessors from competent authorities of 25 different countries.

In December 2017, there were more than 4800 valid CEPs covering chemical purity, TSE and herbal drug preparations.

As part of the EDQM inspection programme, 44 manufacturing sites from all continents were inspected in 2017 (including 25 inspections in India and 16 in China). These inspections were conducted by the EDQM jointly with inspectors from national supervisory authorities. In addition, by exchanging data with inspectorates from Member States and international partners, the EDQM obtained information on GMP compliance for 37 other sites. In total 81 manufacturing sites were assessed for GMP compliance.

As part of its collaboration with international partners worldwide, the EDQM also performed 1 joint inspection with the Pharmaceuticals and Medical Devices Agency (PMDA) of Japan in 2017, and contributed to inspections coordinated by the European Medicines Agency (EMA).

Location of EDQM inspections in 2017

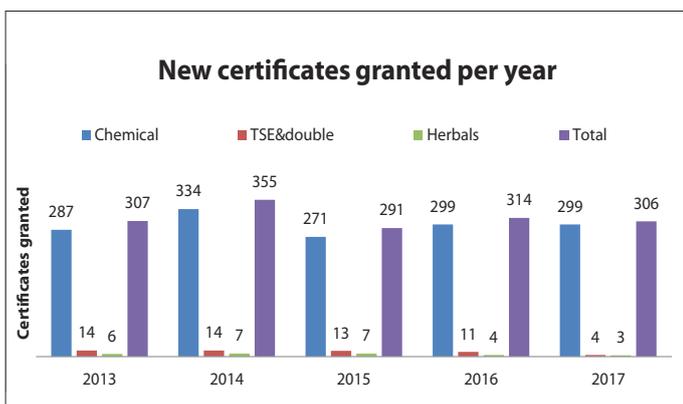


Following non-compliance cases within concerned companies, the EDQM has suspended 20 CEPs and withdrawn 5 CEPs in 2017. In two cases in 2017, actions were taken on CEPs after EU/EEA supervisory authorities issued statements of non-compliance for sites involved in CEP applications.

General matters and policies

In 2017, the Certification Department also published a number of guidelines and policies³ to

3. Available on the EDQM website <https://go.edqm.eu/CEPgI>



support applicants in their communication with the EDQM and in the preparation of their CEP dossiers. This includes in particular the revised guideline “Management of applications for new CEPs and applications for revision /renewal of CEPs” (which describes the way CEP applications are treated), and the document “Top 10 deficiencies in CEP applications”.

■ The EDQM continued to implement its roadmap for the submission of CEP applications in electronic format. The EDQM expects to move towards the exclusive use of the Electronic Common Technical Document (eCTD) format by 2020 (with the exception of TSE dossiers and of substances for veterinary use only).

Communication with partners and stakeholders

■ In 2017, the Certification Department took part in a number of international platforms for collaboration, such as the International Generic Drugs Regulatory Programme (IGDRP), the international Active Pharmaceutical Ingredients (API) inspection programme, and the Pharmaceutical Inspection Co-operation Scheme (PIC/S).

■ In the context of the Certification procedure a Memorandum of Understanding was signed with ANVISA of Brazil in order to strengthen co-operation and exchange of information on the quality of pharmaceutical substances and ANVISA will consider the use of CEPs as support documentation for the quality evaluation of substances.

■ Finally, a 2-day conference on the Certification procedure took place in Prague in September 2017. The event was aimed at exchanging information on recent developments and on the future of the procedure with the pharmaceutical sector worldwide, authorities and manufacturers alike. The event was attended by 175 participants from all continents. Feedback received during the conference shows that the EDQM’s CEP procedure is becoming increasingly recognised and used beyond Europe.

(OMCL), the GEON, which supports national authorities responsible for controlling the quality of medicinal products for human and veterinary use marketed in Europe. The coordination of the OMCL Network is partly funded by the EU Commission.

■ Created to prevent substandard medicinal products from reaching patients and compromising the efficacy of their treatment and potentially their health, the OMCL Network brings together official laboratories based in more than 40 European member states. Operating independently of manufacturers and thus without any conflicts of interest, this Network allows pooling resources and latest technologies with a view to saving public money and sharing expertise and best practices across Europe.

■ The Network operates on the basis of common standards, procedures and guidelines, as well as on the basis of mutual recognition of test results. Its work gives Member States the support they need to monitor the quality of medicines.

Quality Management programme

■ In 2017, the Network continued to implement, maintain, assess and improve the Quality Management (QM) programme for its members. The main goals are:

- ▶ to ensure harmonisation of quality management systems (QMS) among OMCLs, and
- ▶ to achieve appropriate quality levels for exchanging results among members (e.g. batch release of biologicals, market surveillance of CAPs).

Mutual Joint Audits/Visits and Training Visits

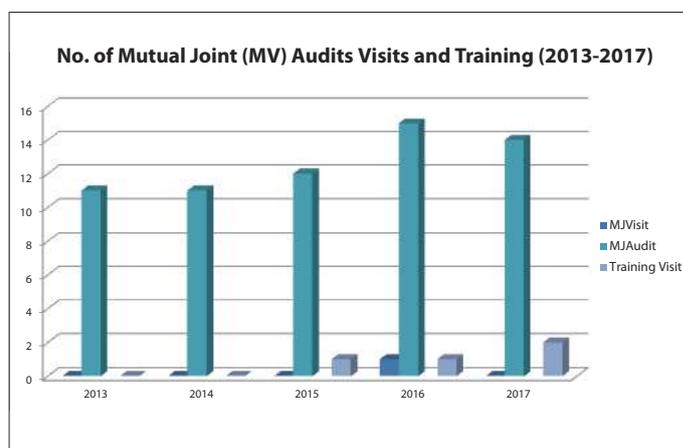
■ Mutual Joint Audits/Visits (MJAs/MJVs) are designed to assess the compliance of OMCL QMS with the requirements laid down in ISO/IEC 17025, the Network QM guidelines and the European Pharmacopoeia. In 2017, 14 MJAs and 2 Training Visits (TVs) were carried out, bringing the total number to 169 MJAs, 51 MJVs and 24 TVs/Tutorials since the programme was launched in 1997.

THE EUROPEAN NETWORK OF OFFICIAL MEDICINES CONTROL LABORATORIES



The importance of a network for pan-European cooperation

■ Throughout 2017, the EDQM continued to coordinate activities and programmes of its General Network of Official Medicines Control Laboratories





Participants in the 22nd Annual Meeting of GEON in Budapest (Hungary)

OMCL Network Quality Management Guidelines

Quality Management Guidelines (QM) are elaborated by experts of the Network and updated on a regular basis, under the coordination of the EDQM Secretariat. They were established to support laboratories in the implementation of the ISO/IEC 17025 requirements. The following table lists the QM Guidelines and Recommendation documents discussed in 2017.⁴

Status	Guideline/Recommendation documents
Adopted ¹	Change control
	Qualification of Equipment – Core document
Under adoption	Qualification of Mass Spectrometers
	Qualification of Liquid Chromatography Equipment
	Qualification of Piston Pipettes
	Validation of Computerised System
Under revision	Qualification of balances
	Uncertainty of Measurements

Training Courses/Workshops

In order to share experiences among OMCLs and harmonise best practices, in 2017 EDQM organised a training session on the revised Guideline on “Use and handling of non-compendial reference standards” and a workshop on “Uncertainty of Measurements”.

4. Available on the EDQM website <https://go.edqm.eu/QAQMgl>

Proficiency Testing Scheme studies

The EDQM Proficiency Testing Scheme (PTS) provides laboratories with an objective means to assess and demonstrate the reliability of their data. In 2017, five studies were organised in the physico-chemical field: “PTS176 Osmolality”, “PTS177 Liquid Chromatography”, “PTS178 Dissolution”, “PTS179 Thin Layer Chromatography” and “PTS175 Gas Chromatography”. On average 98 laboratories (OMCLs and other pharmaceutical control laboratories from industry, hospital pharmacies, universities and pharmacy associations) took part in each study.

Five biological studies were organised in 2017, with on average 18 participating laboratories for each study. They covered “PTS180 Hepatitis E virus detection by Nucleic-acid Amplification Techniques (NAT)”, “PTS181 Hepatitis A virus NAT”, “PTS185 Hepatitis C virus NAT” and “PTS182 Human coagulation factor VIII potency assay”.

Collaboration with the European Co-operation for Accreditation (EA)

The EDQM reached out to the European Co-operation for Accreditation (EA), with the aim of evaluating the cooperation opportunities between the two institutions, focusing on exchanges of know-how, participation in mutual meetings as observers and running joint audits with National Accreditation Bodies (NAB) and EDQM/MJA auditors. For this purpose a joint EA-EDQM communication document has been elaborated and adopted in 2017. Two joint audits were also carried out in 2017.

General OMCL Network (GEON) activities

GEON Annual General Meeting

■ The 22nd GEON Annual Meeting was held in Budapest (Hungary) from 15 to 19 May 2017 and was organised with the support of the Hungarian National Institute of Pharmacy and Nutrition (NIP). More than 230 experts from 61 OMCLs and national medicine agencies from 38 countries, including non-European countries, such as Canada, Israel, Kazakhstan and Singapore, attended the meeting, which was divided into 9 individual sessions.

General market surveillance studies

■ Market Surveillance Studies (MSSs) provide an overview of the quality of medicinal products available on the European market in a given therapeutic class.

■ In 2017, 3 MSSs, 1 MSS on Subdivision of Tablets (MSS048), 1 MSS on Repaglinide Tablets (MSS052) and 1 MSS on Leflunomide Tablets (MSS053), were carried out.

■ The testing phases of two MSSs launched in 2016 on Foreign Matter in Herbal Drugs (MSS051) and Hyaluronic acid-based Dermal Fillers (MSS050) were also completed.

■ Two new MSSs on Zoledronic Acid Preparations for Parenteral Application (MSS055) and on Meloxicam APIs and Solutions for Injection (MSS056) were initiated.

■ On average 12 OMCLs from the General European OMCL Network participated in each of these studies.

Active Pharmaceutical Ingredients (API) Working Group

■ The 10th meeting of the API Working Group took place in October 2017. Discussions focused on Fingerprint MSSs, on omeprazole and morphine and on other classical API MSSs. Other core topics were also addressed, such as the API testing database – a common working tool for OMCLs, the application of chemometric analysis for OMCLs and ways of improving the collaboration with Good Manufacturing Practices (GMP) inspectors for the collection of API samples.

■ Lessons learned from the first fingerprint MSSs were discussed to further improve the testing scheme in preparation for future studies. In order to facilitate the access to API samples, the group reconsidered the possibility of combining classical API MSSs with the fingerprint programme.

Counterfeit/Illegal Medicines Working Group

■ The Counterfeit/Illegal Medicines Working Group met twice in the course of 2017. A new MSS on Suspected Illegal Products (MSSIPs) was initiated;

it covers “medicines in disguise” that contain non-declared active pharmaceutical ingredients in quantities similar to authorised medicines.

■ The Group also discussed the outcome of the 3rd Counterfeit Symposium for OMCLs (Nicosia, Cyprus, 28-29 March 2017) which brought together more than 90 experts. Closer collaboration with stakeholders is one of the top priorities of the Working Group and for the two group meetings in 2017, police and customs experts were invited to exchange their expertise in the field of falsified medicines with the OMCLs.

■ Three technical training sessions for OMCL members were organised by the EDQM jointly with the Swedish and Belgian OMCLs. They covered NMR, LC-MS and chemometric methods applied for the analysis of falsified medicines.

■ The EDQM's Know-X database is secure and restricted and stores comprehensive information on individual cases of falsified medical products. The Know-X database, which was launched in March 2014, underwent a major re-structuring in 2017 to make it more user-friendly and attractive in particular for specific user groups, such as police, customs and health authorities, but also to introduce new features. By the end of 2017 more than 3 600 individual cases had been uploaded by OMCLs on the Know-X database (see “Know-X database”, page 20).

Gene Therapy Products Working Group

■ The OMCL Working Group for Gene Therapy Products (GTP) was created in 2008 to foster collaboration between OMCLs working in the GTP field, and to save time and resources through sharing of knowledge and latest technological advancements. Currently, 11 OMCLs are active members of this Working Group.

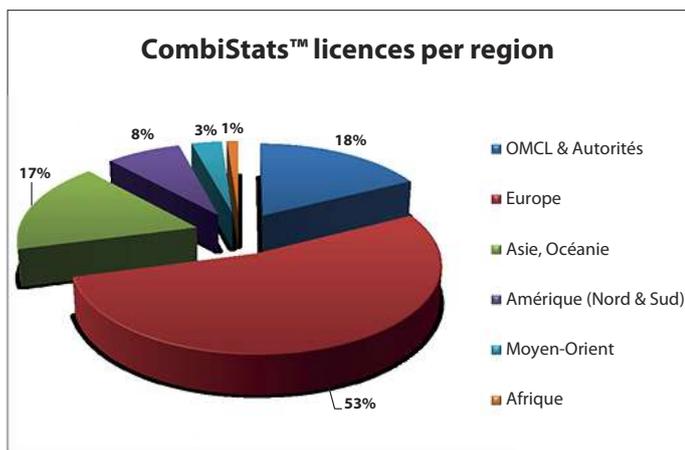
■ The validation of standard methods for the determination of viral and infectious genomes in Adeno-Associated Virus (AAV) vector products was pursued throughout 2017. Furthermore, preliminary work for the validation of the ELISA method for AAV8 Physical Particles Titre (PPT) was satisfactorily completed in 2017, while the collaborative study for its full validation will be organised in the course of 2018. The validation of the AAV2 PPT ELISA is also expected to be completed in early 2018. The preliminary work on the standard method for determination of residual mammalian host cell DNA in GTPs was initiated in 2017 with 3 OMCLs. Various methods are being investigated, with the aim of identifying a method which would be applicable also to different types of products, such as vaccines or recombinant DNA technology products.

■ A manuscript on the validation of UV-spectrophotometry methods for the determination of plasmid DNA concentration and purity was published in *Pharmeuropa Bio and Scientific Notes*.

CombiStats™

CombiStats™ is a computer software, developed by the EDQM, for the statistical evaluation of biological dilution assays in accordance with Chapter 5.3 of the Ph. Eur. Initially designed for OMCLs, CombiStats™ is now available also to other laboratories. The current version 5.0 introduced new features such as equivalence testing, robust regression, 5-parameter asymmetric sigmoid curves and password protection of datasheets. The on-line manual, a tutorial and other background information for CombiStats are available on the EDQM website⁵, while training courses for users are organised at the EDQM once a year.

In 2017, a total of 615 licences were issued, and CombiStats™ was used in 31 countries in Europe and 26 countries in the rest of the world. CombiStats™ has thus evolved into a common internationally agreed reference in its domain and contributes to the mutual recognition of data and results by all interested parties.



EU/EEA-specific activities

Market Surveillance for Products with a Centralised Marketing Authorisation

Every year since 1999, the EMA and the EDQM have joined forces on an annual programme for Centrally Authorised Products (CAPs) Sampling & Testing. The EMA sponsors the programme and has overall responsibility for it, while the EDQM coordinates the sampling and testing operations. The list of products to be included in the annual programme is prepared by the EMA Secretariat together with the EMA Scientific Committees on a risk-based approach. In 2017, the work programme featured 33 products for human use (12 biologicals and 21 chemical products, including 1 radiopharmaceutical product) and 6 products for veterinary use (3 immunobiological products and 3 chemical products). API testing was performed in

5. These publications are available on the EDQM website <https://go.edqm.eu/combistats>

1 case. In addition to the regular CAP programme, 2 generics programmes were run in 2017, during which 7 branded Zoledronic acid products and 12 branded Meloxicam products (generic medicinal products and their respective reference medicinal products) were tested. In addition, 10 samples of meloxicam API were also tested.

As part of the 2017 CAP Programme, 152 sampling operations were performed from 28 countries, and 33 OMCLs were involved in the testing operations. The results showed that the vast majority of the products tested were of the expected quality and complied with authorised specifications. Two “confirmed out-of-specification” results and several regulatory or technical findings were reported and followed up by the EMA.

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

The OMCLs involved in the programme met twice in 2017 (29th and 30th meeting) to evaluate the programme and discuss ways of optimising collaboration. Progress was made with discussions on common risk-assessment procedures. In the future programmes, the strong points of the CAP generics and MRP/DCP testing schemes will be combined in order to further optimise the testing coverage of generics available on the European market.

The 13th regular programme for the market surveillance of medicinal products authorised in the EU/EEA via the MRP or DCP was carried out in 2017. About 1 400 product testing records were added to the 2017 programme, representing an increase of more than 20% compared to 2016. The testing reports for 2017 were submitted by 28 different OMCLs and 9% of the tested products were for veterinary use. The generic products tested included most frequently the APIs hydrochlorothiazide, amlodipine, valsartan, telmisartan and perindopril (treatment of high blood pressure), quetiapine and aripiprazole (antipsychotic), pregabalin (antiepileptic), pantoprazole (gastric acid blocker) and voriconazole (antifungal).

Regulatory issues were identified in around 3% of the materials tested. These mostly consisted of insufficient details on testing methods and labelling issues; in addition, one or more out-of-specification results were reported in a further 2% of the cases.

As of January 2018, the MRP/DCP Product Testing Database, set-up in 2007 for planning, sampling and reporting activities carried out within the Post Marketing Surveillance Scheme for Mutual Recognition Procedure (MRP)/Decentralised Procedure (DCP), held some 9900 MRP- and DCP-product testing records, with contributions from 34 different OMCLs.

Official Control Authority Batch Release of Biologicals for Human Use

■ The harmonised application of Article 114 of EU Directive 2001/83/EC across Europe is carried out through the activities of the Network for Official Control Authority Batch Release (OCABR) of Biologicals for Human Use. This Network fosters the mandatory mutual recognition of batch release for human vaccines and medicinal products derived from human blood and plasma, which involves a quality review through testing and protocol review. OMCLs remained vigilant and over the course of the year evaluated tens of thousands of final lots and plasma pools, so that products' quality could be independently confirmed before they reach patients.

■ The OCABR sessions of the Annual Meeting in Budapest were attended by more than 70 participants, who used this opportunity to exchange expertise with the goal of optimising resources for solving common problems. The OMCLs discussed technical issues and strategies that would lead to better and more efficient control of products such as vaccines for children and combination vaccines containing Diphtheria, Tetanus and acellular Pertussis. To further extend co-operation on a global level, the OCABR Network, jointly with the OMCL from Israel, signed a Memorandum of Understanding to exchange data and expertise in the field of human blood derived medicinal products. The Network also looked closely at the potential impact of Brexit in order to put in place strategies for handling any necessary changes.

■ In the course of 2017, 3 revised guidelines for vaccines came into force, as did 2 revisions of the EU Administrative Procedure for OCABR and a number of internal Network Guidelines. The OCABR Advisory Group and drafting group for vaccines each met twice during the year to further the work of the OCABR Network in between annual meetings. A workshop to foster harmonised testing in the safety of oral polio bulks was also held for OMCLs and involved manufacturers.

Official Control Authority Batch Release of Immunological Veterinary Medicinal Products

■ Together with competent authorities at national level, this subset of specialised OMCLs is responsible for the independent control of immunological veterinary medicinal products (IVMPs) according to Articles 81 and 82 of EU Directive 2001/82/EC as amended.

■ Twenty-four participants from 17 Member States took part in the Veterinary Batch Release Network (VBRN) session of the OMCL annual meeting. The focus was on communication and cooperation. Network members reacted to the Lumpy Skin Disease crisis and have signalled to competent authorities their

competencies and readiness to intervene with testing as needed. The VBRN's testing priorities were re-evaluated using a risk based approach and it was agreed to remove erysipelas vaccine (inactivated) from the list of products eligible for OCABR. At the same time, the VBRN put in place a pilot phase to better coordinate activities for post-marketing surveillance of this and other products. The VBRN Advisory group met twice during the year to advance important issues and met on 1 occasion with representatives from the manufacturers' association to foster exchange on issues of common concern.

ANTI-COUNTERFEITING ACTIVITIES

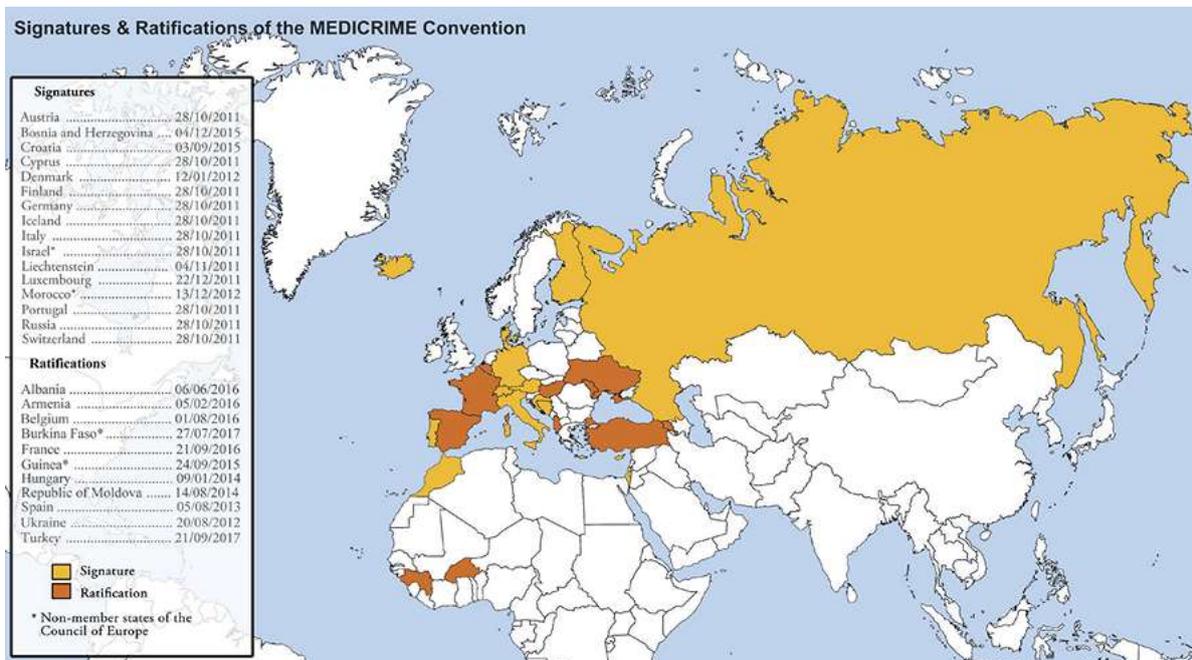
Combating crime to protect public health

■ The EDQM continued to promote cooperation among authorities at national and international level in the fight against falsified/counterfeit medical products (medicinal products and medical devices). One of the most powerful tools at its disposal is the Council of Europe's MEDICRIME Convention, the first and only binding international instrument in the field of criminal law that addresses the falsification/counterfeiting of medical products. The experts in the European Committee on Pharmaceuticals and Pharmaceutical Care (CD-P-PH), the steering body, together with its subordinate Committee of Experts on Minimising the Public Health Risks Posed by Falsification of Medical Products and Similar Crimes (CD-P-PH/CMED) continued to develop and promote programmes and projects aimed at disseminating best practices in the fight against falsified/counterfeit medical products.

Key facts

■ Efforts focused on encouraging authorities and governments to sign and ratify the Convention. Together with the Council of Europe's Criminal Law Division of the Directorate General Human Rights and Rule of Law, the EDQM contributed to various regional conferences and workshops promoting the MEDICRIME Convention, which entered into force on 1 January 2016, following its 5th ratification, by Guinea. As of the end of 2017, the Convention had been ratified in total by 11 countries. The 10th ratification, by Burkina Faso, will trigger the set-up of the convention's monitoring body – the Committee of the Parties, expected to take place in the course of 2018. The future MEDICRIME Committee of the Parties will play an active role in supervising implementation of the Convention by the signatory states.

■ The promotion of the MEDICRIME Convention goes hand-in-hand with the actions taken by the EDQM and its experts to implement the Convention and its tools. One example is the creation of a Network



of Single Points of Contact (SPOCs) involving health authorities, customs and law enforcement agencies and other competent authorities at local, national and international level, through which information and data on counterfeit products is collected and shared. In 2017, the EDQM organised an event with the Belgian Health Authority (FAMHP) for the SPOC Network with the aim of establishing best practices, improving cooperation within and between countries, optimising data sharing and enhancing cooperation with other international organisations. SPOC contacts from 22 countries participated in this event, together with representatives from WHO, the International Criminal Police Organization (Interpol) and the World Customs Organization (WCO).

■ In October 2017, the second MEDICRIME workshop for Good Distribution Practices (GDP), Good Manufacturing Practices (GMP) and Pharmacy Inspectors took place in Warsaw (Poland). Jointly organised with the Chief Pharmaceutical Inspectorate, this technical workshop was attended by 23 inspectors, plus two participants with legal background, coming from Poland, the Czech Republic, the Slovak Republic, Hungary and Ukraine.

Mass serialisation systems for medicines

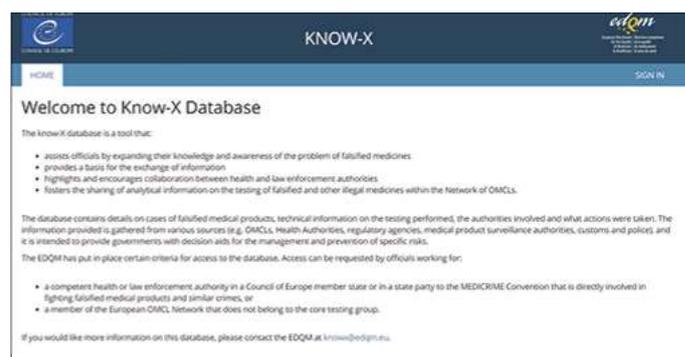
■ The EDQM continued to support the development of mass serialisation systems as tools to prevent the contamination of the legal supply chain with counterfeit, falsified medicines. To this end, the EDQM strived to promote a harmonised approach in the management of mass serialisation systems in Europe by working closely with supervisory authorities and supply chain operators in charge of developing and managing systems for secure data handling.

■ As a result of the agreement signed in 2015 between the EDQM and the European Medicines

Verification Organisation (EMVO), which is comprised of various European supply-chain operators, the EDQM performed two conformity assessments of the EMVO's traceability system. In 2017, the EDQM started verifying that the system is designed, managed and operated in accordance with the standards in the delegated regulation on the Unique Identifier (EU) 2016/161 which implements the EU Falsified Medicine Directive (Directive 2011/62/EU). This initiative will help establish Member States in their role as supervisors of traceability systems.

Publications, databases and website

■ The EDQM's Know-X database is secure and restricted and stores comprehensive information on individual cases of falsified medical products. The database is a tool for sharing information and enables health and law enforcement authorities across Europe to act more rapidly on cases of suspect medical products. The information provided in the Know-X database covers the analytical identification of medicinal products and the related follow-up actions undertaken by the competent health or enforcement authorities. The CD-P-PH/CMED assists the OMCL Counterfeit/Illegal Medicines Working Group with the



maintenance of the database and is also involved in promoting it and training users. The database has gone through a major update in the course of 2017. This was done in cooperation with the OMCL Network and with the involvement of experts coming from the OMCLs and the CMED committee. The new database will be launched in early 2018 (see also the chapter “The Official Medicines Control Laboratories Network”, page 17).

■ Between 2007 and 2017, the EDQM has organised or contributed to 18 trainings and 6 conferences. A total of 423 participants from 58 countries mostly in Europe, but also in other parts of the world⁶, have participated in training sessions related to counterfeit and falsified medical products.

Communication with partners and stakeholders

■ Throughout 2017, representatives of the EDQM have participated regularly in the meetings of the EU Heads of Medicines Agencies’ Working Group of Enforcement Officers (HMA-WGEO), and have attended a number of conferences in Europe and Africa with the purpose of raising awareness for the MEDICRIME Convention.



PHARMACEUTICALS AND PHARMACEUTICAL CARE

Optimal use of medicines for improving patients’ quality of life

■ Activities in this area are led by the European Committee on Pharmaceuticals and Pharmaceutical Care (CD-P-PH) and its subordinate bodies, the Committee of Experts on Quality and Safety Standards in Pharmaceutical Practices and Pharmaceutical Care (CD-P-PH/PC), the Committee of Experts on the Classification of Medicines as Regards their Supply (CD-P-PH/PHO) and the Committee of Experts on Minimising Public Health Risks Posed by Falsification

6. Overview of activities related to MEDICRIME: <https://go.edqm.eu/MDCRacts16>

of Medical Products and Similar Crimes (CD-P-PH/CMED) (see also the “List of Committees coordinated by the EDQM”, page 35).

Key Facts

■ The final report of the EDQM Pharmaceutical Care Indicators Project was published in 2017; it presents the results of the multinational validation study aimed at validating 4 basic sets of indicators to assess the quality of pharmaceutical care in Europe. It also contains the data collection forms developed for and used in the validation study. The Pharmaceutical Care Indicators Project is aimed at supporting stakeholders involved in the medication process and competent authorities alike, in their tasks of assessing the impact of pharmaceutical care and promoting the efficient and safe use of medicines⁷.

■ In the course of 2017, significant progress was also made on the drafting of a Council of Europe resolution for the promotion and implementation of pharmaceutical care in Europe. The resolution will promote patient-centred care and advance appropriate and safe use of medications through the implementation of the pharmaceutical care philosophy and its working methods in daily practices. The resolution will also encourage the evaluation of the quality of pharmaceutical care practices, as a way of monitoring, assessing and improving the medication use process and quality of care between member states.

■ Following a public consultation among a wide range of concerned parties, the draft guidelines on best practices for Automated Dose Dispensing (ADD) were adopted in 2017. These guidelines recommend standards and approaches for regulating and providing ADD services across Europe; in particular, they will assist ADD providers and national authorities in ensuring that ADD services are provided at a consistently high standard that can maintain the safe supply of medicines to patients. The guidelines are expected to be made available to the public in 2018.

■ The CD-P-PH/PHO issued its annual recommendations on the classification of medicines and their supply conditions (prescription and non-prescription). This work is of relevance to health authorities and all stakeholders across the medication supply chain, it helps ensure patient safety and accessibility of medicines in Europe. The annual recommendations of the CD-P-PC/PHO are included in the Melclass database⁸, which provides information on the classification and conditions for supply of medicines.

■ With a view to avoiding duplication of work and promoting synergies in the area of classification

7. The EDQM publications are accessible here: <https://register.edqm.eu/freepub>

8. The Melclass database is accessible here: <https://melclass.edqm.eu/>

of medicines, cooperation was established between the CD-P-PH/PHO and the Co-ordination Group for Mutual Recognition and Decentralised procedures – Human (CMDh) Non-prescription Medicinal Products Task Force.

Publications, databases and website

The review of the classification of medicines containing anti-inflammatory and anti-rheumatic active substances was completed and will be available on the EDQM website in the course of 2018.

RNN	ATC Code	Classification	Last update
ABACAVIR	J55AF06	PGM	
ABARELIX	L02BK01	Currently not available	23-10-2013
ABATACEPT	LD4AA24	PGM	
ADONIMAB	B01AC13	I	
ADKATERONE	L02BK03	I (I)	23-10-2013
ACAMPROSATE	N02BA03	Currently not available	
ACARBOSZ	A10BF01	II	
ACECLOFENAC	M01AB16	II	
ACEMETACIN	M01AB11	I	30-11-2016
ACENICUMABROL	B01AA07	I	

The Melclass database was continually updated throughout 2017 with relevant recommendations from the Committee of Experts CD-P-PH/PHO to national health authorities on the classification of medicines and their supply conditions. The Melclass database also contains national information about the classification status and supply conditions of medicines across signatory Member States to the Convention on the Elaboration of a European Pharmacopoeia.

Communication with partners and stakeholders

Various interactions took place in 2017 with international organisations and professional bodies active in the field of public health and pharmacy practice, such as the South-Eastern Europe Health Network (SEEHN), the European Association of Hospital Pharmacists (EAHP) and the European Federation of Nurses Associations (EFN), in order to align efforts aimed at ensuring safe and appropriate use of medicines in Europe.

Resolution CM/Res(2016)2 on “Good Reconstitution Practices in Health Care Establishments for Medicinal Products for Parenteral Use” was presented at the 22nd Congress of the EAHP in Cannes (France) in March and at the 20th European Conference of the professional international association Group of Evaluation and Research for Protection in Areas under Control (GERPAC) in Hyères (France) in October to promote its use.

EUROPEAN PAEDIATRIC FORMULARY

A future pan-European free online platform to improve the health of children patients

The European Committee on Pharmaceuticals and Pharmaceutical Care (CD-P-PH) and the Ph. Eur. Commission carried on their programme for developing a European paediatric formulary. With authorised medicines not always suitable for the treatment of children, national or regional formularies on pharmacy preparations still play an important role in this field and the European paediatric formulary project aims at improving the availability of extemporaneous formulations of quality paediatric medicines across Europe.

The European Paediatric Formulary is a collection of formulations currently in national formularies or in general well-established in European countries, which aims at supporting clinicians and pharmacists in accessing appropriate formulations and delivering preparations when no licensed products are available. Most importantly, the European Paediatric Formulary also aims to address requirements in EU and international legislation to increase the number of authorised paediatric medicines.

Following the definition of criteria for inclusion and evaluation of formulations in 2015, a dedicated working party - composed of experts from hospital pharmacies, academia and national authorities from 14 countries - was set-up under the auspices of the European Pharmacopoeia Commission to prepare the content of the formulary. The first phase of the work was partially completed in 2017 and was based on the recommendations on paediatric needs by the European Medicines Agency’s (EMA) Paediatric Committee and on other sets of criteria, such as recently filed Paediatric Investigation Plans. For the next phase, some selected high priority formulations are being prepared to be launched for public consultation, so as to obtain feedback from all concerned parties before finalisation.

At the end of 2017, 8 monographs were on the work programme, of which two pilot monographs – Hydrochlorothiazide 0.5 mg/mL oral solution and Sotalol 20 mg/mL oral solution – were already in the drafting phase and will be published soon for public enquiry.

HealthCare

Throughout 2017, the EDQM has continued to work diligently to protect public health in Europe by proposing trusted and ethical safety and quality standards for the collection, preparation, storage, distribution and appropriate use of blood components for blood transfusions, as well as for the transplantation of organs, tissues and cells. The work related to enhancing and developing standards in the field of food contact materials was also continued, along with the coordination of market studies and proficiency schemes in the area of quality control for cosmetics.

BLOOD TRANSFUSION

Promoting blood safety and quality in Europe and beyond

The EDQM is responsible for the Council of Europe's activities in the area of blood transfusion. These are built around three major principles: promoting voluntary and non-remunerated donation, optimal use of blood and protecting both donors and recipients of labile blood components. The EDQM addresses ethical, legal and organisational aspects of blood transfusion to ensure the safety, quality and optimal use of blood supplies, increasing their availability and avoiding wastage.

The European Committee on Blood Transfusion (CD-P-TS) is the Steering Committee for blood transfusion activities at the EDQM; it elaborates guidelines and recommendations and oversees the tasks of its subordinate working groups. It is composed of internationally recognised experts from Council of Europe member states, observer countries, the EU Commission, WHO, the US Food and Drug Administration (US FDA) and the Council of Europe's Committee on Bioethics (DH-BIO).

Key facts and figures



The EDQM continued to run the Blood Proficiency Testing Scheme (B-PTS) and the Blood Quality Management (B-QM) Programme. Both support BEs in the implementation of current EU blood legislation, the Blood Guide and the GPGs. Both programmes benefit from financial support by the EU Commission.

Nucleic Amplification Techniques (NAT)

- B-PTS030 HBV, HCV, HIV NAT
- B-PTS031 HEV NAT

Serology

- B-PTS032 Anti-HCV
- B-PTS033 Anti-HIV/p24
- B-PTS034 Anti-Treponema
- B-PTS035 HBsAg/Anti-HBc

Immuno-Haematology

- B-PTS036 ABO, Rhesus, Kell, extended phenotyping and Irregular antibodies

B-PTS studies conducted in 2017

Blood Proficiency Testing Scheme (B-PTS)

■ The external assessment of the testing capability of European BEs continued in 2017 through PTS studies⁹. A total of 7 studies were organised and an average of 72 laboratories participated in each study.

Blood Quality Management (B-QM) Programme

■ This programme¹⁰ provides tools enabling European BEs to develop, implement and improve their Quality Management Systems (QMS). The programme offers 3 types of schemes which are all run by experts from European BEs:

- ▶ Blood Training Visit (B-TV): on-site visit and tailor-made training on technical and QMS topics;
- ▶ Blood Mutual Joint Visit (B-MJV): audit to assess the QMS against minimum European standards¹¹, report on it and issue recommendations;
- ▶ Blood Mutual Joint Audit (B-MJA): audit to check compliance of the QMS against minimum European standards¹¹ report on it and follow-up of corrective and preventative actions.
- ▶ In 2017 3 B-MJVs were carried out.

■ The conference “Sharing Best practices: Quality Risk Management, Change Control, Validation and Qualification”, which was organised in October in Strasbourg and attended by 134 participants including BEs, national authorities and suppliers from 33 countries, was not only an opportunity for exchanging on these topics and on their practical implementation, but also a way of supporting BEs in implementing the Good Practice Guidelines (GPG). The proceedings, including recommendations and conclusions, will be issued in 2018.

General matters and policies

Good Practice Guidelines (GPGs)

■ The EU Commission included in its Directive 2016/1214 published in July 2016, the Good Practice Guidelines issued in the 19th edition of the Blood Guide. As a result, the EDQM's Good Practice Guidelines will function as a new legal instrument; EU and EEA Member States will have to bring it into force by 15 February 2018.

9. <https://go.edqm.eu/BPTS>

10. <https://go.edqm.eu/BQM>

11. *Minimum Standards: the EU blood legislation, the GPG and the Blood Guide. Other standards followed by visited BEs (e.g. ISO Standards, GMP) may also be used.*



Participants in the Conference Sharing Best Practices: Quality Risk Management, Change Control, Validation and Qualification, Strasbourg (France)

Risk behaviours with an impact on blood donor management and transfusion safety

■ As required by Resolution CM/Res(2013)3¹², a dedicated Working Group is responsible for the continuous collection of data on the incidence and prevalence of sexually transmitted infections jeopardising the safety of transfusions. Member States took different decisions on the deferral policies for men having sex with men: the Working Group will map these policies to illustrate the lack of harmonisation and will also provide advice on the need for future revisions of the Resolution.

Optimal use of clotting factors

■ Resolution CM/Res(2017)43¹² on principles concerning haemophilia therapies (replacing CM/Res (2015)3) was adopted by the Committee of Ministers in December 2017, a major outcome of the recommendations made at the European Symposium: “Wildbad Kreuth Initiative - Optimal use of clotting factors and platelets” which took place in Freising, Germany in May 2016, organised by the EDQM, the Paul Ehrlich Institut (PEI) and the University of Munich.

Publications, databases and website

■ The 19th edition of the “Guide for the Preparation, Use and Quality Assurance of Blood Components” (commonly referred to as the “Blood Guide”)¹³ was published in March 2017, elaborated by the dedicated Working Group entrusted with updating the Blood Guide and keeping it abreast of the scientific developments and regulatory changes that have occurred in the two-year period between editions of the guide.

■ The first edition of *Guidance on Root Cause Analysis of non-satisfactory external quality assessment results*¹³ was issued in June 2017.

12. Available on the EDQM website <https://go.edqm.eu/BTrec>

13. The EDQM publications are available here: <https://register.edqm.eu/freepub>



ORGAN TRANSPLANTATION AND TISSUES AND CELLS FOR HUMAN APPLICATION

Promoting strict quality and safety standards

The European Committee on Organ Transplantation (CD-P-TO) is the Steering Committee in charge of transplantation activities at the EDQM. Its mandate includes elaborating guidelines and recommendations aimed at improving access to transplantation and strict safety, quality and ethical standards. The CD-P-TO is composed of internationally recognised experts from Council of Europe member states, observer countries, the EU Commission, WHO, relevant professional associations and the Council of Europe Committee on Bioethics (DH-BIO).

General Matters and Policies

Transplantation is now a well-established, life-saving therapy; however, the supply is unable to keep pace with the demand for organs.

Many countries are developing and optimising living donor programmes either to complement the limited availability of organs from deceased donors or as the only source of organs, while they develop deceased donor programmes.

While in present globalised times, many countries are accepting non-resident living donors, relevant differences remain in how countries accept these donors, such as in the screening and consent process, the reimbursement of justifiable expenses and the access to post-operative and follow-up care. In view of this situation, the Committee of Ministers of the Council of Europe has adopted Resolution CM/Res(2017)1¹⁴ on principles for the selection, evaluation, donation and follow-up of the non-resident living organ donors.

This new resolution is aimed at protecting non-resident living donors who, for a number of reasons – economic, emotional, cultural or physical – may be particularly vulnerable, and whose post-donation care and follow-up may be difficult to guarantee.

There are exceptional circumstances in which some of the patients may be properly referred for transplantation abroad by their treating physicians. In addition, organ shortages, or lack of access to a deceased-donor programme, may lead patients awaiting an organ to seek their transplant through illegal and dangerous practices, such as organ trafficking or human trafficking for the purpose of organ removal. Patients who have received an

The European database of Frozen Blood Units of Rare Blood Groups, the tool that supports blood establishments in their searches for frozen blood units of rare blood groups, has been fully operational since January 2016. Six Blood Establishments (BEs) have already provided on a voluntary basis their lists of frozen units of rare blood groups available to patients in need.

Communication with partners and stakeholders

Cooperation with the European Commission

2017 was a year of intense and fruitful collaboration with the EU Commission. In particular, this included the analysis of the EU Serious Adverse Reactions and Events (SARE) related to blood components and the contribution of the EDQM to the public consultation on the evaluation of the EU blood legislation. This collaboration is expected to continue steadily for the near future, as the EDQM pursues its goal of supporting the implementation of the EU blood legislation and maintaining an ongoing dialogue with the EU Commission in relation to regulatory changes and new scientific advancements in the field.

The EDQM will continue to participate as an observer in the meetings of the EU competent authorities for blood, which are organised by the EU Commission.

Pharmaceutical Inspection Co-operation Scheme (PIC/S)

In the context of the revision of the PIC/S GMP Guide for Blood Establishments, the EDQM was invited to join the drafting group in charge of revising the text. Its participation aims at harmonising the PIC/S document with the GPG in the Blood Guide.

International Society of Blood Transfusion (ISBT)

The EDQM has observer status on the ISBT Board of Directors and is a member of various dedicated ISBT working groups: the Standing Committee of Ethics and the Quality Management Working Party. The EDQM also participated in the annual ISBT congress held in Copenhagen (Denmark) in June 2017.

14. Available on the EDQM website <https://go.edqm.eu/OTrec>

organ transplant abroad, either upon referral of their treating physician or illicitly, typically return to their country of origin shortly after the transplantation procedure to receive post-transplantation care. The new Resolution CM/Res(2017)2 establishes procedures for the management of patients having received an organ transplant abroad upon return to their home country to receive follow-up care, regardless of the circumstances in which the transplant was obtained. The proposed measures protect patients, reinforce transparency of practices and facilitate traceability.

■ In the context of Resolution CM/Res(2013)55 and Resolution CM/Res(2017)2, Member States designated National Focal Points (NFP) on transplant related-crimes, based at national transplantation bodies or Ministries of Health.

■ In June 2017 the “International database on Travel for Transplantation” was launched. Through this data collection exercise, NFPs were requested to provide information about all patients who received a kidney transplant abroad in 2015. The exchange of information on these patients at international level will help better understand and analyse the phenomenon of “transplant tourism”, appreciate the long-term outcomes and potentials risks to both individuals and public health and identify hotspots of transplant tourism.

■ During the “2nd Workshop for NFP on Transplant Related Crimes” (Strasbourg, November 2017), NFP jointly examined the data collection exercise, shared the lessons learned after their first year in their role as NFPs and participated in breakout sessions where case studies were analysed in order to develop tools and reach conclusions on the best practices to prevent and address illicit transplantation practices.

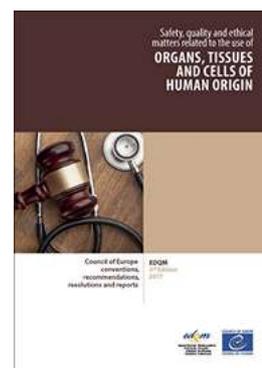
Publications and website

■ The “Guide to the Quality and Safety of Organs for Transplantation” (usually referred to as the “Organ Guide”) and the “Guide to the Quality and Safety of Tissues and Cells for Human Application” (referred to as the “Tissues and Cells Guide”) have become gold standard references in Europe and beyond. In order to ensure maximum dissemination, the electronic versions of both Guides are available free of charge¹⁵.



■ In 2017, the 3rd edition of the Tissues and Cells Guide was published. The EU Commission has partially funded its elaboration and was involved in the drafting

¹⁵ The EDQM publications are available here: <https://register.edqm.eu/freepub>



process, thus ensuring that the standards set out under EU Directives are compatible with and complemented by the Council of Europe’s guidance. Several professional associations actively participated in the elaboration of this Guide, in particular, the American Association of Tissue Banks (AATB), the European Eye Bank Association (EEBA), the European Society for Human Reproduction and Embryology (ESHRE), the European Society for Blood and Marrow Transplantation (EBMT), the Joint Accreditation Committee-ISCT & EBMT (JACIE) and the International Council for Commonality in Blood Banking Automation (ICCBBA).

■ A compilation of Council of Europe resolutions, recommendations and reports – 3rd Edition (2017) was also published.

■ The EDQM/Council of Europe publishes “Newsletter Transplant”, the only official source of international figures on organ, tissue and haematopoietic stem cell donation and transplantation in Europe. The information provided in it allows analysing trends and amending policies accordingly. This work is coordinated by the Spanish National Transplant Organisation (ONT) which, every year, analyses international figures collected through a Network of health authorities and officially designated focal points worldwide. The latest issue provides figures from 67 countries for the year 2016.

Communication with partners and stakeholders

Cooperation with the European Commission

Under the framework of its standing cooperation with the European Commission, the EDQM took over the international annual vigilance exercise on Serious Adverse Reactions and Events (SARE) in the EU in the fields of blood and tissues and cells (see also the “Blood transfusion” chapter, page 23).

Cooperation with professional associations

Key professional associations in the field of organ, tissues and cells transplantation are participating in the work of the EDQM.

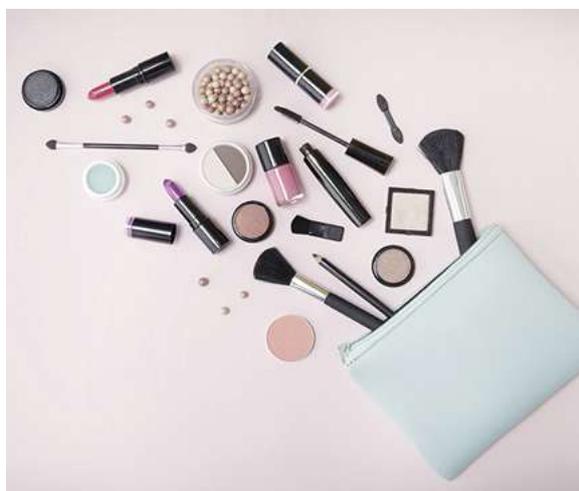
COSMETICS AND FOOD CONTACT MATERIALS

Protecting consumer health

The Consumer Health Protection Committee (CD-P-SC, Steering Committee), composed of representatives from national ministries with public health responsibilities, establishes the work programme for cosmetics and for materials that come into contact with food. In 2017, approximately 280 experts in 34 Member States and 3 observers to the Ph. Eur. Convention contributed actively to the work of this Committee.

The work programme in the field of food contact materials aims at harmonising quality and safety requirements across Europe, together with efforts in the development and update of testing methods.

In the field of cosmetics, the work of the EDQM focuses on product safety and surveillance; the cooperation among Member States on this topic



is facilitated by the European Network of Official Cosmetics Control Laboratories (OCCLs).

Key facts

OCCL Network

The European OCCL Network was set up in 2010; to date, more than 40 OCCLs participate regularly in the Network activities, among these are laboratories from 19 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 made accessible to all network members, hence bringing considerable added value in terms of better use of resources and enhanced management of quality in accordance with international standards.

When Cyprus chaired the Committee of Ministers of the Council of Europe from November 2016 to May 2017, health authorities were invited to Nicosia in order to discuss analytical challenges related to cosmetics control. This event organised in March 2017 was attended by 30 experts from 15 countries and the programme also covered national perspectives on how to step up cooperation in the field of cosmetics.

Most sunscreens on the market indicate the level of protection against harmful effects of UV radiation. The so-called Sun Protection Factor (SPF) is typically set based on data from human studies. In 2017, collaborative trials were initiated to develop an *in vitro* test protocol that could be used instead of protocols involving humans.

Quality check for cosmetics: Market Surveillance Studies

Following some alarming findings in cosmetic products, the EDQM has been collecting national data on the quality of shampoos for children, creams and make-up, lotions and several other types of products for the past years. Initial findings confirmed the earlier observation that most of the cosmetic products for skin care comply with the regulations. However, decorative cosmetics (face-paint for children, shower gels with cartoon characters and other “children cosmetics”) continue to raise concerns. In conclusion, national authorities will need to intensify their controls of certain product categories.

National data were also collected on tooth whitening products and a report on their compliance with EU Regulation No 1223/2009 can be expected in early 2018.

Proficiency Testing Scheme (PTS) studies

Proficiency testing is an essential part of quality control management in testing laboratories.

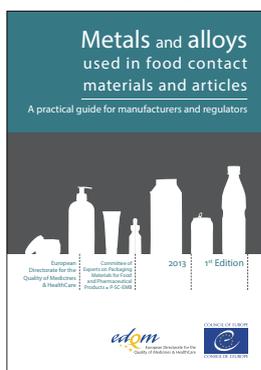
Analytical studies are carried out on identical samples in different laboratories to verify each laboratory's ability to quantify, for example, the amount of prohibited substance, and to ensure that test results are comparable across Europe. The EDQM PTS programme is designed as a benchmarking tool for study participants, it allows them to share their expertise and improve their technical skills in the field of analytics.

■ The amounts of parabens found in lipsticks were the focus of this activity in 2017. Testing lipsticks can be challenging since colourants, waxes, oils and other ingredients can interfere with the quantification of parabens when using High Performance Liquid Chromatography (HPLC).

Food contact materials and articles

■ Throughout 2017, the Committee of Experts on Food Contact Materials (P-SC-EMB) continued to review resolutions and technical documents elaborated in the past; the Federal Institute for Risk Assessment (BfR) of Germany and the Agency for Health and Food Safety (AGES) of Austria both hosted expert meetings aimed at updating the provisions for materials such as printed paper and paperboard.

■ Food contact materials made from metals and alloys have been addressed in a practical guide for manufacturers and regulators, which was first published in 2013. Amendments have been foreseen on the work programme in 2017 and will be included



in the second edition of the guide. To this end, an ad-hoc working group, composed of experts from competent authorities, official and private control laboratories and industry, held two meetings in 2017; both were hosted by the Scientific Institute of Public Health (known as WIV-ISP) of Belgium.

■ The EDQM, national authorities and the Food Ingredients and Packaging (FIP) Network coordinated by the Food Safety Authority of the European Union (EFSA) joined forces and defined a work programme to ensure the safety of coatings that are used in food packaging such as beverage cans. This work is expected to be finalised in 2019.

Tattoos and permanent make-up

■ In order to implement the recommendations of Council of Europe Resolution ResAP(2008)1, the EDQM compiled safety and documentation requirements for tattoos and permanent make-up in a report which was finalised and published in 2017. The EDQM work

on the safety of tattoos and permanent make-up provided input for the preparation of related restriction proposals by the Chemicals Agency of the European Union (ECHA).

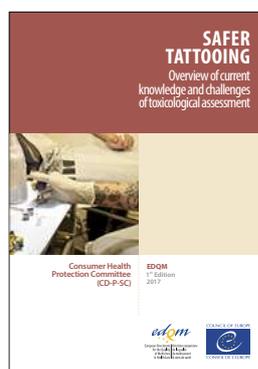
Communication with partners and stakeholders

■ Representatives of the EU Commission, its Joint Research Centre (JRC) and EFSA attend the meetings of Steering Committees and subordinate Working Groups. The EDQM exchanges views on market surveillance with the Working Groups of the EU PEMSAC (Platform of European Market Surveillance Authorities for Cosmetics of the European Union) and notably, in response to a great number of products that do not comply with the European regulations on cosmetics. The long-standing experience with the OMCL Network is an asset for the coordination of the OCCL Network.

Publications and website

■ To facilitate the work of control laboratories, reliable and reproducible analytical procedures for cosmetics can be downloaded free of charge from the EDQM website (e.g. method for the determination of free formaldehyde and of hydrogen peroxide in cosmetics¹⁶).

■ The guide "Safer tattooing" provides an overview of current knowledge and challenges of toxicological assessment¹⁶. A dedicated webpage on this topic can be found on the EDQM website¹⁷.



16. The EDQM publications are available here: <https://register.edqm.eu/freepub>
17. <https://go.edqm.eu/tattoospmu>

Quality management system

Investment in EDQM's quality management system continued to be a priority in 2017, with the ISO 9001 first surveillance audit according to the 2015 version of the standard, and the surveillance audit of the laboratory ISO 17025:2005 accreditation. The ISO 17025 technical scope has been extended with eight "limit tests" such as acid value (Ph. Eur. 2.5.1.) and iodine value (Ph. Eur. 2.5.4.), in addition to analytical techniques already covered. The EDQM is committed not only to maintaining, but also to continuously improving its standards for quality throughout all its activities; its customers and stakeholders can rest assured that the goods and services provided are of consistent quality.



493-TEST

2017: A year rich in events and meetings

SYMPOSIA AND WORKSHOPS - FOCUSED TOPIC MEETINGS

International conference on the place of the Certification Procedure in the global regulatory environment (19-20 September, Prague)

■ With the EDQM's Certification Procedure becoming increasingly used worldwide, this two-day conference was aimed at keeping authorities and manufacturers alike informed of recent developments and of its future in the global regulatory environment. The conference was attended by 175 participants from all continents.

■ The programme covered the experience of European regulators and trade associations from Europe, China and India, as well as international initiatives and the use of CEPs by authorities beyond Europe. The conference also included dedicated workshops that focused on specific aspects of the Certification procedure, such as the content of a CEP application, the change to electronic submissions, and information on GMP (Good Manufacturing Practices) inspections.

■ The conference was held under the Czech Republic's Chairmanship of the Committee of Ministers of the Council of Europe. The EDQM is grateful to the Czech authorities, in particular the Ministry of Health and the State Institute for Drug Control (SUKL), for their support and assistance in preparing this event.

International Microbiology Symposium (10-11 October, Strasbourg)

■ In October, the EDQM organised a symposium on microbiology in the pharmaceutical sector. The aim of this event was to gather feedback from users of the Ph. Eur. on alternative testing methods for microbiological control and sterilisation processes.

■ Among topics covered was the use of modern methods for microbiological control, with specific sessions focusing on sterilisation and biological indicators, rapid microbiological methods and control methods for cell therapy products and pharmaceutical water. Reports on successful new methods gave an overview of the potential benefits in terms of costs and time efficiency and, most importantly, in terms of quality. Authorities, manufacturers and suppliers of new technologies also discussed the current acceptance of these new methods at regulatory level across the world.



Participants in the international conference on the certification procedure, Prague (Czech Republic)



Participants in the International Symposium on Microbiological control, Strasbourg (France)

■ During the symposium, a consensus emerged among participants that alternative methods for the detection, enumeration and identification of microorganisms are at present sufficiently well covered in Pharmacopoeias world-wide. General agreement was also reached that developments in Pharmacopoeias now allow manufacturers of medicines to start using modern technologies for effective microbiological control.

■ The symposium was attended by a wide range of experts in the pharmaceutical and microbiological fields who reviewed the latest trends and innovations in the field of microbiology, in addition to pharmacopoeial approaches and related regulatory requirements.

Workshop for National Focal Points on Transplant Related Crimes (9-10 November, Strasbourg)

■ The EDQM organised the 2nd workshop for National Focal Points (NFP) on transplant related crimes. The aim was to examine the data collected through the "International Travel for Transplantation" database on patients who received organ transplants abroad and later returned to their country of origin to receive follow-up care. The initiative is essential to cast a light on the phenomenon of travel for transplantation and will allow looking into ensuring comprehensive support against transplant-related crimes and to victims and patients. (See the "Organ transplantation and tissues and cells for human application" chapter, page 25).

Conference "Sharing Best practices: Quality Risk Management, Change Control, Validation and Qualification" (17-19 October, Strasbourg)

■ The conference was an opportunity for exchanging on these topics and on their practical implementation, and also a way of supporting BEs in implementing the Good Practice Guidelines (GPG). Proceedings, including recommendations and conclusions, will be issued in 2018. (See the "Blood Transfusion" chapter, page 23).

TRAINING SESSIONS

■ The EDQM organised two European Pharmacopoeia specific training sessions last year. The first focused on biologicals and enabled participants to expand their knowledge on the work and procedures of the Ph. Eur. on the topic. Specific workshops were organised in the programme on various classes of biologicals (e.g. biotherapeutic products including monoclonal antibodies, vaccines for human use, plasma-derived products and synthetic peptides) based on real case studies.

■ In addition participants were given the opportunity to attend a Joint EDQM/EMA Satellite Meeting on Biosimilars. The Ph. Eur. has driven the setting of quality standards for biotherapeutic products in Europe for more than two decades. The aim of this meeting was to clarify the role that the Ph. Eur. monographs play in the assessment and marketing authorisation of a biosimilar medicine at European Union level. The event and the Q&A session that followed were broadcast live on the internet, thus allowing greater visibility, reach and engagement with concerned stakeholders.

■ The second training focused on European regulations for medicines, references standards and the certification procedure and its inspection programme. Participants had the opportunity to ask questions directly to EDQM experts.

■ The sessions were recorded and the videos made available on the EDQM website¹⁸.

WEBINARS

■ Webinars are an important tool for reaching out to the EDQM's stakeholders who benefit from detailed information on the EDQM's expertise and activities, while being able to express their needs and challenges directly to the EDQM and without having to travel.

■ Two webinars were organised on "Elemental Impurities: Implementation of ICH Q3D", in January and May. The ICH Q3D guideline, which establishes acceptable safety limits for elemental impurities and applies to new finished medicines, as well as new medicines containing existing active substances, has been applicable since June 2016. The webinars illustrated the impact of the guideline on the texts of the Ph. Eur. and on the assessment of CEP applications and introduced a number of practical case studies providing users with greater understanding of the requirements in the guideline. A total of 1 700 participants connected to these webinars.

■ A webinar was also organised on raw materials for cell-based and gene therapy products; it provided

¹⁸. Training resources available here: www.go.edqm.eu/pheurtraining

participants with an insight into the context of the elaboration of the new Ph. Eur. general chapter on “Raw materials of biological origin for the production of cell-based and gene therapy medicinal products” and its scope. Topics covered included an introduction to the general Ph. Eur. chapter 5.2.12 and its place within the EU regulatory Network, the context of its elaboration, and an overview of the raw materials of biological origin covered by the chapter.

■ Another webinar focused on the Certification Procedure and more specifically on “How to get acceptance of CEP revisions quickly”. The way to use the “Guideline on requirements for revisions and renewals” was explained, the different categories of changes and the supporting documentation required, best practices and the do’s and don’ts when preparing a revision application. This webinar attracted a lot of interest with over 750 participants joining in.

■ The EDQM and EMA organised a joint webinar on “Water for Injections (WFI)”, focusing on the recently updated Ph. Eur. monograph for WFI and progress made towards the elaboration of additional guidance on GMP requirements for WFI production by non-distillation methods and biofilm control strategies. This webinar was specifically targeted towards regulators from all EEA National Competent Authorities (NCAs) and to Pharmaceutical Inspection Co-operation Scheme (PIC/S) participating authorities.

■ Live Q&A sessions followed each of the webinars, allowing delegates to raise specific issues covered in the presentations. All webinar recordings were posted on the EDQM website and made available for later access.¹⁹

PARTICIPATION IN KEY INTERNATIONAL MEETINGS

■ In 2017, the EDQM took part in several major international meetings and events worldwide, including:

- ▶ Indian Pharmaceutical Association (IPA) Conference: “Towards excellence in Quality”, (India),
- ▶ Annual Conference of International Pharmaceutical Excipients Council (IPEC), (Monaco),
- ▶ 22nd Congress of the European Association of Hospital Pharmacies (EAHP), (France),
- ▶ Meetings of the ICH Assembly and Expert Working Groups, (Canada and Switzerland),
- ▶ China Chamber of Commerce for Import and Export of Medicines and Health Products (CCCPMHPIE) symposium, (China),

- ▶ AESGP Meeting (AEGSP Association of the European Self-Medication Industry), (Belgium),
- ▶ 20th Annual Meeting of the Israel Analytical Society, (Israel),
- ▶ 9th European Paediatric Formulation Initiative Conference, (Poland),
- ▶ 9th NIFDC National Drug Reference Standards Committee (China),
- ▶ 6th International Conference on Reference Materials (China),
- ▶ 8th International Meeting of World Pharmacopoeias in Brasilia (Brazil), hosted by the Brazilian national health agency ANVISA,
- ▶ 19th Annual Conference PharmMed Obrushenie (Russian Federation).



INTERNATIONAL FAIRS & CONGRESS – EXPANDING GLOBAL PRESENCE

■ The EDQM participated in three pharmaceutical fairs in 2017, namely CPhI China (Shanghai), CPhI Worldwide (Frankfurt) and CPhI India (Mumbai). These specialised tradeshows bring together a whole spectrum of chemical and pharmaceutical industries - every sector of the pharmaceutical market is represented under one roof. Hence they provided the EDQM with a one-stop-shop for engaging with existing clients and partners, along with meeting and growing a new audience.

■ In addition, the EDQM participated in the 27th Regional Congress of the International Society of Blood Transfusion (ISBT) which was held in Copenhagen (Denmark). The Congress was organised in conjunction with the 35th Annual Conference of the British Blood Transfusion Society. The event attracted healthcare professionals involved in blood transfusion and transfusion medicine to discuss state of the art topics in the field of transfusion medicine. The latest edition of the Blood Guide was presented at the fair and visitors were able to collect information on the EDQM’s activities in this area and learn more on the EDQM’s Blood-PTS Scheme and Blood Quality Management Programme (B-QM).

¹⁹ Training resources available here: www.go.edqm.eu/pheurtraining and here: www.go.edqm.eu/CEPtraining



The Eurasian Economic Commission visit, Strasbourg

VISITS

The Eurasian Economic Commission visit, Strasbourg

■ A high-level delegation of the Eurasian Economic Commission (EEC), headed by the Minister for Technical Regulation of the EEC, Valery Nikolaevich Koreshkov, visited the EDQM in November 2017. Discussions included the collaboration between the Eurasian Economic Union Pharmacopoeia and the Ph. Eur. and other topics of common interest.

■ The EDQM Certification Department received the visit of officials from ANVISA (Brazil), and from the Saudi Arabia Food & Drug Administration respectively, in 2017. Visitors were given an overview of the assessment and inspection activities related to the Certification (CEP) procedure; the visits were also an opportunity to strengthen the collaboration between EDQM and these authorities.

■ In April, the EDQM received a delegation from the Swiss competent authority Swissmedic interested in learning more about the EDQM and the general working policies of the Ph. Eur. Commission.

■ The European Union Commissioner for Health & Food Safety, Vytenis Andriukaitis, came for an official visit to the EDQM on 13 June to participate in a roundtable on the on-going cooperation in protecting public health between the EDQM and the Commission of the European Union, a signatory party to the Ph. Eur. Convention since 1994. Topics covered the role of the OMCLs, blood transfusion and organ transplantation.



The EU Health & Food Safety Commissioner Vytenis Andriukaitis visiting the EDQM

■ A delegation from the Brazilian Pharmacopoeia interested in the working policies of the Ph. Eur. Commission visited the EDQM in Strasbourg to strengthen the collaboration between the two Pharmacopoeias. On the occasion, the Brazilian Pharmacopoeia representatives were given a tour of the EDQM's laboratory facilities.

■ The Shandong Food and Drug Administration and the China Institute of Veterinary Drug Control (IVDC) were at the EDQM to establish preliminary grounds for international exchanges and cooperation in the field of medicines quality. The visits were an opportunity for the EDQM and the Chinese Authorities to become familiar with their respective missions.

PUBLIC AWARENESS CAMPAIGNS

Organ, Cells and Tissue Transplantation

■ The 18th European Day for Organ Donation and Transplantation (EODD) took place on 9 September in Bern (Switzerland). The EDQM run a campaign in the months leading up to the EODD; it was based on the theme "Bring back hope to the thousands of patients on waiting lists in Europe!". Activities included the production of posters, videos and infographics, as well as social media presence with a new Facebook account showcasing the EDQM's own activities, as well as those of national competent authorities, in the field of organ, cells and tissue donation and transplantation.

Blood Transfusion

■ On the occasion of World Haemophilia Day 2017, the EDQM hosted an event, organised by the European Haemophilia Consortium (EHC). The focus was on an important set of new recommendations directed at improving haemophilia care and treatment throughout Europe.

■ Two blood donor sessions were also organised by the EDQM for Council of Europe staff and their families, in order to raise awareness on blood donation among staff based in Strasbourg.

List of committees coordinated by the EDQM

THE EUROPEAN PHARMACOPOEIA COMMISSION

■ The Ph. Eur. Commission was set up in 1964 in accordance with the Convention on the Elaboration of a European Pharmacopoeia. The Commission has 39 members, all signatory parties to the Convention (38 Member States and the European Union). Also, 29 observers from all over the world confirm the importance of the work of the Ph. Eur. 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 its member states. A total of 61 expert groups and working parties established by the Commission carry out the Ph. Eur. work programme. The texts are regularly revised in order to keep pace with the latest technical and scientific advances in the development, production and quality control of medicines. The Ph. Eur. 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

■ 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 which is composed of the chairs of Ph. Eur. Groups of Experts 6 (Biological and biotechnological substances), 6B (Human plasma and plasma products), 15 (Human vaccines and sera), 15V (Veterinary vaccines and sera) as well as co-opted experts and delegates from the EU Commission, EMA, BWP, IWP and WHO and the EDQM Director.

NETWORK OF OFFICIAL MEDICINES CONTROL LABORATORIES ADVISORY GROUPS

■ The role of this Network is to ensure that the quality of medicines marketed in the Member States is consistent; this also happens through the mutual recognition of results of the processes for the control of medicines quality. Major decisions are taken during 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 Ph. Eur. Convention and the observer states. These activities cover work in the area of quality management systems (QMS), such as audits and proficiency testing studies, as well as market surveillance studies and contribute towards combating counterfeit and illegal medicines. General activities are prepared and followed by the General OMCL Advisory Group; and,
- ▶ activities restricted to the EU and the European Economic Area (EEA), and concerning products approved via the centralised procedure and 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

■ A Network of about 100 assessors and 30 national inspectors participates in the work required for the evaluation of API quality dossiers and the inspection of manufacturing sites. The activities associated with the procedure for certification of suitability to Ph. Eur. monographs are guided by a Steering Committee and 3 Technical Advisory Boards (TAB). This 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.

EUROPEAN COMMITTEE ON BLOOD TRANSFUSION

■ This Steering Committee (CD-P-TS) addresses ethical, legal and organisational issues related to blood transfusion, in order to ensure the safety and quality of transfusions and the protection of donors and recipients, and to promote the optimal use of blood and minimal wastage. It supervises the work of a number of individual projects and working groups, e.g. the European database of Frozen Blood of Rare Groups, Plasma Supply 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

■ This Steering Committee (CD-P-TO) 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. It supervises the activities of a number of individual projects and the ad hoc Working Groups on the "Guide to the Quality and Safety of Organs for Transplantation" and the "Guide to the Quality and Safety of Tissues and Cells for Human Application".

EUROPEAN COMMITTEE ON PHARMACEUTICALS AND PHARMACEUTICAL CARE

■ This Steering Committee (CD-P-PH) is in charge of activities in the field of the classification of medicines as regards their supply, pharmaceutical practices and pharmaceutical care, and combatting falsified medical products and similar crimes. It is supported by its subordinate committees: the Committee of Experts on the Classification of Medicines as Regards their Supply (CD-P-PH/PHO); the Committee of Experts on Quality and Safety Standards for Pharmaceutical Practices and Pharmaceutical Care (CD-P-PH/PC); and the Committee of Experts on Minimising Public Health Risks Posed by Falsification of Medical Products and Similar Crimes (CD-P-PH/CMED).

EUROPEAN COMMITTEE ON CONSUMER HEALTH PROTECTION

■ In 2017, the Steering Committee (CD-P-SC) was responsible for managing work programmes and decision-making processes in the areas of cosmetics and food contact materials. The Committee examined health-related issues, evaluated their risks and drafted reports and recommendations for regulatory approaches. Two sub-committees supported the work: the Committee of Experts on Food Contact Materials (P-SC-EMB) and the Committee of Experts on Cosmetic Products (P-SC-COS). At the end of term, the CD-P-SC was dissolved and separate committees established for the two activity areas, based on the corresponding decision of the Committee of Ministers. The work programme of the subordinate Committees of Experts will be pursued under the new structure.

■ In addition, the European Network of Official Cosmetics Control Laboratories (OCCLs) contributes to consumer health protection and supports market surveillance activities of the competent authorities. The Network was set up on a voluntary basis; more than 40 OCCLs participate in regular Network activities, including laboratories in Member States of the European Union. Besides the EU, participation is open to other Council of Europe states having signed the Convention on the Elaboration of a European Pharmacopoeia.

Glossary

3Rs	Refine, Reduce, Replace (animal testing)
AAV	Adeno-Associated Virus
ANVISA	Brazilian National Health Agency
B-MJA	Blood Mutual Joint Audit
B-MJV	Blood Mutual Joint Visit
B-PTS	Blood Proficiency Testing Scheme
B-QM	Blood Quality Management
B-TV	Blood Training Visits
BE	Blood Establishment
BRP	Biological Reference Preparation
BRR	Biological Reference Reagents
BSP	Biological Standardisation Programme
BWP	Biologics Working Party
CAP	Centrally Authorised Product
CD-P-PH	European Committee on Pharmaceuticals and Pharmaceutical Care
CD-P-PH/CMED	Committee of Experts on Minimising the Public Health Risks Posed by Falsification of Medical Products and Similar Crimes
CD-P-PH/PC	Committee of Experts on Quality and Safety Standards in Pharmaceutical Practices and Pharmaceutical Care
CD-P-PH/PHO	Committee of Experts on the Classification of Medicines as Regards their Supply
CD-P-SC	European Committee on Consumer Health Protection
CD-P-TS	European Committee on Blood Transfusion
CD-P-TO	European Committee on Organ Transplantation
CEP	Certificate of Suitability to the Monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use (EMA)
CM	Committee of Ministers
CRS	Chemical Reference Substance
CVMP	Committee for Medicinal Products for Veterinary Use (EMA)
DCP	Decentralised Procedure
DH-BIO	Council of Europe's Committee on Bioethics
EAHP	European Association of Hospital Pharmacists
EBMT	European Society for Blood and Marrow Transplantation
EDQM	European Directorate for the Quality of Medicines & HealthCare
EEA	European Economic Area
EFSA	European Food Safety Authority

EMA	European Medicines Agency
EODD	European Day for Organ Donation and Transplantation
ESHRE	European Society for Human Reproduction and Embryology
EU	European Union
GEON	General European Network of Official Medicines Control Laboratories (OMCLs)
GMP	Good Manufacturing Practice
GPhP	Good Pharmacopoeial Practices
GTP	Gene Therapy Products
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICRS	International Chemical Reference Substance
ISA	International Standard for Antibiotics
ISBT	International Society of Blood Transfusion
ISO/IEC	International Organization for Standardization/International Electrotechnical Commission
IWP	Immunologicals Working Party
JP	Japanese Pharmacopoeia
MAA	Marketing Authorisation Applications
MAB	Monoclonal Antibody
MJA	Mutual Joint Audit
MJV	Mutual Joint Visit
MRP	Mutual Recognition Procedure
MSS	Market Surveillance Studies
NMR	Nuclear Magnetic Resonance
NPA	National Pharmacopoeia Authorities
OCABR	Official Control Authority Batch Release
OCCL	Official Cosmetics Control Laboratory
OMCL	Official Medicines Control Laboratory
P4	Procedure 4
P-SC-COS	EDQM Committee of Experts on Cosmetic Products
P-SC-EMB	EDQM Committee of Experts on Food Contact Materials
PDG	Pharmacopoeial Discussion Group
Ph. Eur.	European Pharmacopoeia
PIC/S	Pharmaceutical Inspection Co-operation Scheme
PTS	Proficiency Testing Scheme
Q3D	Code for ICH Guideline on Elemental Impurities
QM	Quality Management
QMS	Quality Management System
QWP	Quality Working Party (EMA)
REACH	Regulation (EC) No 1907/2006
SPOC	Single Point of Contact (MEDICRIME Convention)

TAB	Technical Advisory Boards
TV	Training Visits
US FDA	United States Food and Drug Administration
USP	United States Pharmacopeia
VBRN	Veterinary Batch Release Network
WFI	Water For Injections
WGEO HMA	Working Group of Enforcement Officers of the Health and Medicines Agencies of the European Union
WHO	World Health Organization

This publication presents the work carried out in 2017 by the European Directorate for the Quality of Medicines & HealthCare, Council of Europe, highlighting its particular achievements.

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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.