



EDQM HIGHLIGHTS

2019 ANNUAL REPORT

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2019 **ANNUAL REPORT**

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

French edition

*Les points forts de l'EDQM –
Rapport annuel 2019*

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MESSAGE FROM SUSANNE KEITEL, DIRECTOR

The year 2019 was another very productive and successful one for the EDQM and saw important progress in all our activities. The European Pharmacopoeia Commission appointed more than 850 members to its groups of experts and working parties for a new term of office of three years. These experts come from national pharmacopoeial authorities, official medicines control laboratories, licensing authorities or inspectorates, and others work in the private sector, academia or research organisations, a well-balanced background which ensures expertise from all relevant domains. Equally important, they come from Europe and numerous countries around the world, which gives the European Pharmacopoeia (Ph. Eur.) its truly international dimension, reflecting the globalisation of the pharmaceutical supply chain.

A new group of experts was established to deal with the elaboration and revision of finished-product monographs. This initiative responds to the demand for these types of monographs, which facilitate the development of generic medicines, crucial for the sustainability of healthcare systems around the world, as well as the assessment of quality dossiers and market surveillance studies by regulatory authorities and official medicines control laboratories.

Altogether, the Ph. Eur. was complemented with 19 new monographs and 5 new chapters in 2019, and 233 texts were revised to incorporate scientific progress and regulatory changes, a key aspect of ensuring constant alignment with state-of-the-art technologies and regulatory developments.

The year 2019 also saw the ratification of the Convention on the Elaboration of a European Pharmacopoeia by a new member state, Albania, in November, showing the continued appeal of the Ph. Eur., which as of February 2020 now counts 39 European countries and the European Union as signatory parties, in addition to 30 observers from all over the world.



The EDQM's portfolio of reference standards again grew in 2019, as the European Pharmacopoeia Commission adopted the establishment reports submitted by the EDQM Laboratory for 98 new reference standards, in addition to the 278 replacement batches of existing reference standards.

In 2019, the EDQM inaugurated its secondary site near Metz in eastern France, as part of its business continuity strategy which includes the creation of a full backup stock of reference standards in order to mitigate risks of disruptions to supplies should the EDQM building in Strasbourg be affected by an incident of any kind. This project is part of our commitment to ensure the continuous availability of our reference standards to users, enabling the release of batches of medicines to the market.

The certification of suitability to the monographs of the European Pharmacopoeia (CEP) procedure saw yet another increase in both requests for new and revised CEPs, bringing the total number of valid CEPs to more than 5200 by the end of 2019. The continued interest in CEPs demonstrates the added value of the procedure due to its centralised assessment which lessens the workload for both applicants and regulatory authorities.

For the European Network of Official Medicines Control Laboratories (OMCLs), an activity co-funded by the European Union and the Council of Europe/EDQM, 2019 was also a very active year. New testing programmes for biosimilars and parallel-distributed products were added to the work programme for the network restricted to EU/EEA OMCLs in the context of market surveillance testing of centrally authorised products. An upgraded Official Control Authority Batch Release (OCABR) database was implemented, as was a plan ensuring Brexit preparedness for OCABR testing, crucial for the continued release of vaccines and blood-derived products to the market.

The Ph. Eur. Commission, the OMCL Network and the Certification Department played a crucial role in further measures taken to investigate and prevent the contamination of active pharmaceutical ingredients and medicinal products with nitrosamines. European and national authorities worldwide were supported through the revision of monographs, the development of analytical testing methods, the evaluation of data requested from CEP holders and the inspections of impacted manufacturing sites.

In addition to the testing of suspected falsified or illicit medicines by the OMCL network, the EDQM continued to promote the signature and ratification of the Council of Europe Convention on the Counterfeiting of Medical Products and Similar Crimes Involving Threats to Public Health (MEDICRIME Convention) and to support its implementation, for example by organising a workshop focused on the enforcement of borderline products.

Last year also saw the completion of a Council of Europe resolution for the promotion and implementation of pharmaceutical care in Europe, which will advance patient-centred care, support medicines optimisation and encourage responsible use of resources through the implementation of pharmaceutical care in daily practice.

In the field of blood, a plasma supply management symposium, organised in collaboration with the European Commission, produced a set of recommendations outlining future steps in the field of plasma. The 20th edition of the *Guide to the preparation, use and quality assurance of blood components* was adopted and will be published in June 2020.

In the field of organ, tissue and cell transplantation, the 4th edition of the *Guide to the quality and safety of tissues and cells for human application* was published, as were the results of a survey entitled “Critical factors for success in deceased donation”. Co-operation with the European Commission in the field of tissue and cells

also moved forward with the signing of a new three-year grant agreement with the EU.

In the field of consumer health, a survey on the protection of healthy volunteers in studies related to the use, quality and effects of cosmetics was completed and nine recommendations were prepared for the attention of health authorities in order to help them establish better protection for healthy volunteers. The European Network of Official Cosmetics Control Laboratories (OCCLs) continued to develop its testing programmes.

All these activities, and many more, continue to underline the relevance of the work of the European Directorate for the Quality of Medicines & HealthCare for the health of citizens in our member states and around the world. However, as always, we must acknowledge the fact that the EDQM's achievements in 2019 would not have been possible without the remarkable efforts of the experts from national, European and international authorities, universities, scientific institutes and industry who, through their expertise in a wide variety of scientific fields, have made such valuable contributions to our work. To all of them, as well as to the dedicated staff at the EDQM, I offer my heartfelt thanks.

Susanne Keitel, PhD
Director, EDQM, Council of Europe

The background image shows a person in a white lab coat holding a smartphone. Overlaid on this are several white icons: a hand with bandages, a molecular structure, a line graph, a DNA helix, a globe with a network of dots, and a series of vertical lines at the bottom. The overall theme is medical and technological.

QUALITY AND USE OF MEDICINES

In 2019, much was accomplished in the field of setting quality standards for the manufacture and control of medicines in Europe and beyond.

Year-on-year, the Ph. Eur. Commission works to provide Ph. Eur. users with the most up-to-date and relevant information possible.

The procedure for the certification of suitability to the Ph. Eur. monographs again demonstrated its added value for regulatory authorities and the industry, and the work-sharing within the network of European

Official Medicines Control Laboratories (OMCLs) allowed members to cover a broad range of products on the market and to address emerging risks to public health. The MEDICRIME Convention continued to offer the relevant legal framework to better tackle the falsification of medicines at international level. Achievements in Pharmaceutical Care

and the European Paediatric Formulary provided professionals in healthcare with useful guidance, resolutions and tools.

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 60 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 standard-setting process is vital for the development of authoritative and relevant monographs, these groups comprise representatives of national competent authorities, academia and industry.

The members of the currently 60 groups of experts and working parties were appointed for a three-year term at the Ph. Eur. Commission's November 2019 session. Of the more than 900 applications received and reviewed, the Commission appointed more than 850 members to these groups based on the member profiles listed in each group's terms of reference.

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

As Europe's scientific benchmark for pharmacopoeial standards, the Ph. Eur. is legally binding in 38 European countries¹

1. As of 31 December 2019.

and used in over 120 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, the Ph. Eur. Commission reviewed its working procedures in 2016 to allow for experts from non-Ph. Eur. member states to be appointed to its groups and working parties. This decision was part of a deliberate move to further involve both observer states and manufacturers from outside Europe in the

work of the Ph. Eur., giving them a unique opportunity to expand their knowledge of the pharmacopoeia and the European regulatory system. 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

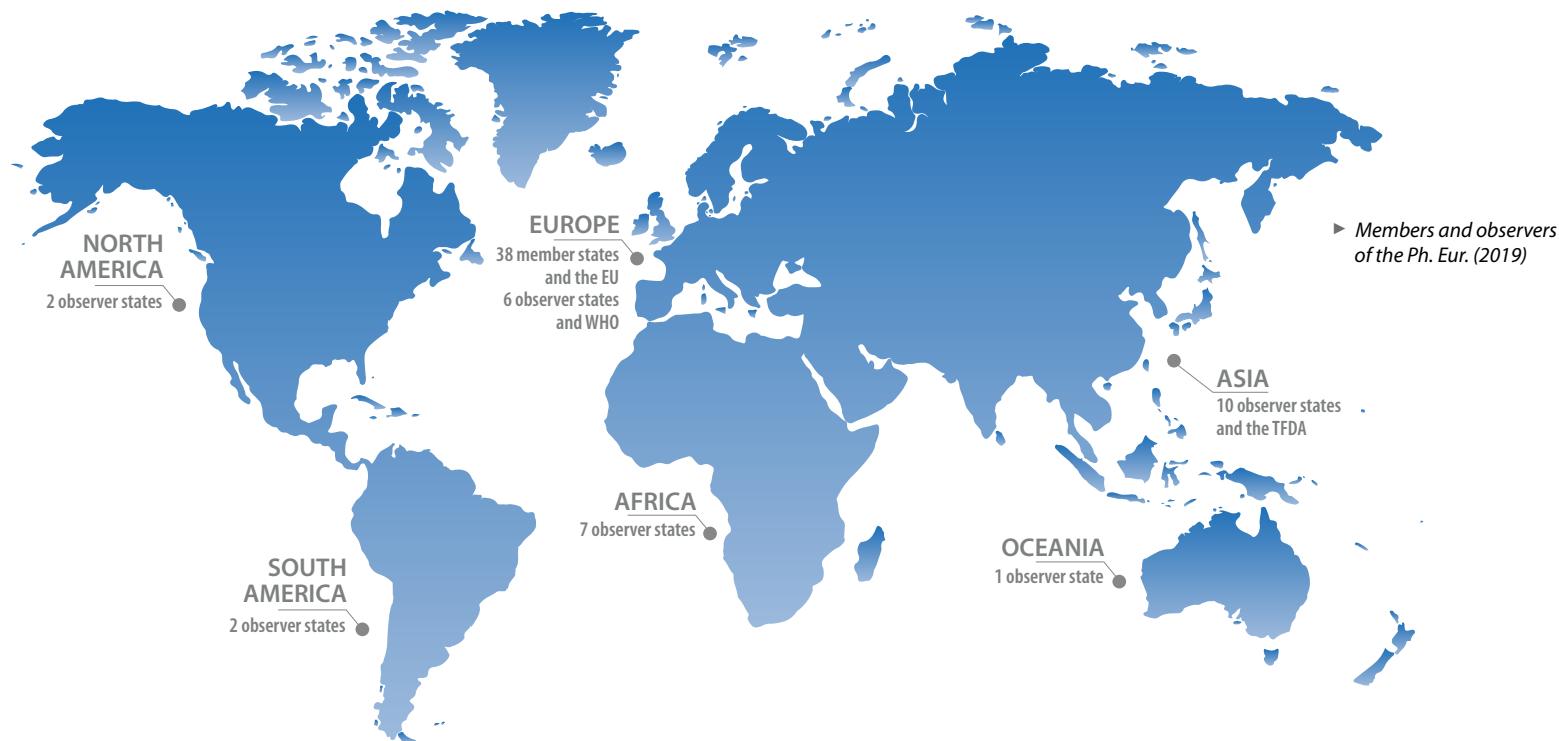
Wide participation

Thirty-eight member states and the EU were Contracting Parties to the Convention on the Elaboration of a European Pharmacopoeia as of 31 December 2019 (with Albania scheduled

The European Pharmacopoeia activities 2019

- ▶ 19 new monographs
- ▶ 5 new chapters
- ▶ 233 revised texts
- ▶ and more than 850 experts appointed for a 3-year term





to accede to the convention in February 2020, becoming the 39th member state). The Ph. Eur. Commission also had a total of 30 observers in 2019, including countries from all over the world, the Taiwan Food and Drug Administration and the World Health Organization (WHO). All these observers are entitled to take part in the scientific work of the Ph. Eur. Commission and other EDQM activities, to benefit from European experience in the field of medicinal products for human and veterinary use, to exchange knowledge with experts from European licensing authorities and inspectorates and to take part in the work on the development of international quality controls for medicines and the methods of analysis used.

The work programme 2019

Year-on-year, the Ph. Eur. Commission works to provide Ph. Eur. users 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 2019 continued to reflect these efforts: 19 new monographs and five new chapters were adopted by the Commission and 233 texts were revised to incorporate regulatory changes and scientific progress.

These included two new monographs on finished products containing chemically defined active substances:

- *Dronedarone tablets (3038)* elaborated under the P4 procedure (single-source products still under patent). These tablets contain the chemically defined active substance dronedarone hydrochloride and are used in the treatment of patients with heart disorders;
- *Rosuvastatin tablets (3008)*. This is the first monograph on a multi-source medicinal product to have been adopted and the product itself is one of the most widely used and prescribed cholesterol-lowering medicines worldwide.

Selected Ph. Eur. texts adopted in 2019

- ▶ 2 new monographs on finished products containing chemically defined active substances *Dronedarone tablets* (3038) and *Rosuvastatin tablets* (3008) adopted
- ▶ 5 revised monographs on sartans
- ▶ 1 new chapter adopted (2.6.32) *Test for bacterial endotoxins using recombinant factor C (rFC)*
- ▶ 43 revised texts adopted to reflect new approach to extraneous agent testing of immunological veterinary medicinal products (IVMPs)

Both monographs are the result of close co-operation between manufacturer(s), experts and the EDQM.

The adoption of these monographs follows on from the Ph. Eur. Commission's decision in 2014 to add finished-product monographs containing chemically defined active substances (or FPMs for short) to its regular work programme, after a successful proof-of-concept pilot phase. The decision was based on various considerations, including the fact that finished-product monographs facilitate quality testing by national control laboratories, as well as the development of generic drugs and the assessment of marketing authorisation applications by regulatory authorities.

The Ph. Eur. Commission discussed the outcome of a user survey on the current

approach to dissolution testing in individual FPMs on solid oral dosage forms. Launched mid-January 2019, the survey sought the opinion of users on whether or not to include a mandatory dissolution test in these monographs. All the feedback received was examined closely by the Ph. Eur. Commission, which is continuing its reflection on the best possible approach.

The Commission also decided to create a new group of experts, Group 17, to deal with the elaboration and revision of FPMs. The members were appointed during the Ph. Eur.'s session in November 2019.

Three new active substance monographs elaborated under the P4 procedure, on *Deferasirox* (2933), *Rivaroxaban* (2932) and *Olanzapine embonate monohydrate* (3047), were also adopted in 2019 by the

Commission. Appropriate quality standards are therefore in place for these substances ahead of patent expiry and in preparation for the development of generics.

Following the identification of *N*-nitrosamine contamination in active pharmaceutical ingredients of the sartan class, the Commission revised the following monographs: *Valsartan* (2423), *Candesartan cilexetil* (2573), *Irbesartan* (2465), *Losartan potassium* (2232) and *Olmесartan medoxomil* (2600).

In November 2018, at its 162nd session, the Ph. Eur. Commission had decided to elaborate a new general chapter on the control of *N*-nitrosamine impurities in APIs (2.5.42), which is expected to be published in *Pharmeuropa* for public enquiry in 2020.

The Ph. Eur. Commission also proposed to revise the general monograph on *Substances for pharmaceutical use* (2034). This proposal was made further to the European Commission referral C(2019)2698 and the review initiated by the European Medicines Agency (EMA) in September 2019 under Article 5(3) of Regulation (EC) No. 726/2004² to provide guidance to marketing authorisation holders on how to avoid the presence of *N*-nitrosamine impurities in human medicines. The revised general monograph has since been published in *Pharmeuropa* 32.1 for public consultation from January to March 2020 (see "N-nitrosamine contamination in brief", page 30).

2. Available at <https://go.edqm.eu/ECReg7262004>.

For the current test for bacterial endotoxins (BET), the world currently depends on a single source of lysate, the horseshoe crab family, and more specifically, two species of the crab, *Limulus polyphemus* and *Tachypleus tridentatus*, both of which are known to be endangered. In 2019, the Ph. Eur. therefore launched a public consultation on a new general chapter, 2.6.32. *Test for bacterial endotoxins using recombinant factor C (rFC)*. The Ph. Eur. was one of the first pharmacopoeias to enter this new field, when chapter 5.1.10 *Guidelines for using the test for bacterial endotoxins* was revised to allow the use of the recombinant protein as an alternative to limulus amoebocyte lysate (Supplement 8.8; 2016).

The new chapter describes a BET that uses an rFC based on the gene sequence of the horseshoe crab for the quantification of endotoxins from gram-negative bacteria, combined with a fluorimetric end-point detection method. For now, only the fluorimetric method is described as the rFC kits currently available on the European market and most of the available scientific data are based on this method.

Chapter 2.6.32. *Test for bacterial endotoxins using recombinant factor C (rFC)* was adopted at the 165th session in November 2019 and will be published in Supplement 10.3. It is a standalone chapter which will therefore not be referenced in individual monographs.

Traditional Chinese Medicines (TCMs) have been on the Ph. Eur. Commission's agenda since 2005 and monographs setting standards for the safety and efficacy of a number of these herbal drugs have been published in the Ph. Eur., with more in the pipeline. In 2019,

the Commission decided to accept semi-quantitative high-performance thin-layer chromatography (HPTLC) as an alternative to liquid chromatography (LC) assays in TCM monographs after a year-long pilot study launched at the instigation of users and carried out by the Ph. Eur.'s TCM working party was successfully completed for two of the candidate materials, Thunberg fritillary bulb (*Fritillaria thunbergii* Miq.: Beimu) and Corydalis rhizome (*Corydalis yanhusuo* W. T. Wang: Yanhusuo). The laboratories taking part obtained reproducible results for marker levels, identity and system suitability using HPTLC, which was also found to give the same pass/fail results as the HPLC assay. Marker levels were evaluated by visual inspection or using appropriate software which converted the HPTLC chromatogram into peak profiles. Less costly and more readily accessible than LC, the use of HPTLC will also save on resources since the pilot study showed that if one or two reference solutions are added to the HPTLC carried out for identification of the herbal drug, the test can be evaluated semi-quantitatively, thereby obviating the need for the LC assay without compromising the level of quality control offered by the monograph. For the time being, this new approach will be limited to monographs on herbal drugs used in TCM that are not subject to marketing authorisations.

The Ph. Eur. Commission's new approach to extraneous agent testing of immunological veterinary medicinal products (IVMPs) prompted the revision and subsequent adoption of 43 texts. From starting material to final product, users will now have to follow an overall risk-management approach to ensure they apply the best testing strategies

in the context of a consistent manufacturing process.

This is a move from a prescriptive to a more flexible but nonetheless scientifically sound and targeted approach, and allows for the use of fit-for-purpose methods. The new approach is expected to encourage the use of state-of-the-art methods, with a preference for *in vitro* over less robust *in vivo* methods. Another positive outcome of this revision work is the future deletion of other animal tests, including serological tests for identification of vaccine antigen or detection of extraneous agents in certain specific inactivated vaccines.

In advance of the implementation of these 43 texts on 1 July 2020 and in order to help users prepare for the forthcoming changes, the EDQM organised a symposium on IVMPs in April 2020.

A new general chapter, 2.8.26. *Contaminant pyrrolizidine alkaloids*, was published in [Pharmeuropa 32.1](#) for public consultation and comments until 31 March 2020.

A growing public health concern, pyrrolizidine alkaloids (PAs) are nitrogen-containing compounds occurring naturally in plants and whose acute toxicity, genotoxicity and carcinogenic potential have been known for decades. Hundreds of structurally distinct PAs have been found in thousands of different plant species. Many of these plants are common weeds which can contaminate, usually at very low levels, the raw plant material used for the production of herbal medicinal products (HMPs). Patient exposure to PAs from HMPs must be kept to a minimum and must not exceed the maximum daily intakes agreed by the competent authorities.

The new general chapter 2.8.26 focuses on trace analysis of target PAs in herbal drugs, herbal drug preparations and HMPs contaminated with other plants, rather than the determination of PAs occurring naturally in plants. It describes 28 target PAs and allows for the use of any procedure comprising chromatography coupled with MS/MS or high-resolution MS that meets the validation requirements specified in the chapter itself. This pragmatic approach was adopted to address the considerable variation in the composition and matrices of the herbal drugs, herbal drug preparations and HMPs concerned, as well as in the applicable limits, which makes it difficult to describe all the methods suitable for quantitative analysis of the target PAs. The chapter gives an example of an analytical procedure that has been shown to be suitable for the determination of the 28 target PAs in a number of matrices. It also provides verification requirements analysts may need to meet to demonstrate that the analytical procedure selected is also valid for routine analysis.

General matters and policies

Biological Standardisation Programme



The Biological Standardisation Programme (BSP) is a joint Council of Europe/EU initiative, partly funded by the EU. Its mission is to establish reference materials for biologicals and to develop and validate

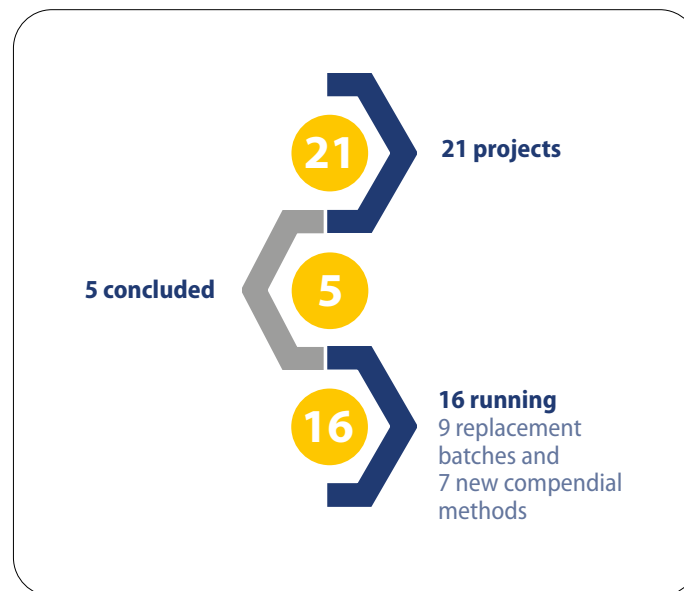
new analytical methods for the quality control of biologicals, including alternative methods for the replacement of animals in laboratory experiments based on the 3Rs principles (replacement, reduction and refinement).

In 2019, the programme ran 21 projects in different fields, from vaccines for human and veterinary use to plasma-derived and biotechnology products. Five were concluded during the year, leading to the establishment of three replacement reference standards (see “Reference Standards”, page 20) and the validation of two analytical methods as proposals for inclusion in the Ph. Eur.

The EDQM carried forward another nine projects aimed at establishing replacement batches for existing reference standards for biologicals.

Seven projects focused on the development of new compendial methods, two of which were brought to a successful conclusion. Four of these projects were dedicated to applying the 3Rs 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 principles were widely acknowledged in 2019.



► *Biological Standardisation Programme achievements (2019)*

Standard Terms database



Initially drawn up at the request of the European Commission for use in marketing authorisation applications, the database containing the list of Standard Terms provides users and prescribers with harmonised vocabularies to describe dosage forms, routes of administration, units of presentation, containers, closures and delivery devices for medicinal products. It also includes a mapped terms section, which allows users of 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 for use in their own systems.

By the end of 2019, the free, online Standard Terms database had over 29 000 registered users and held 1 003 individual Standard Terms concepts with translations in 34 languages, totalling more than 28 500 entries.

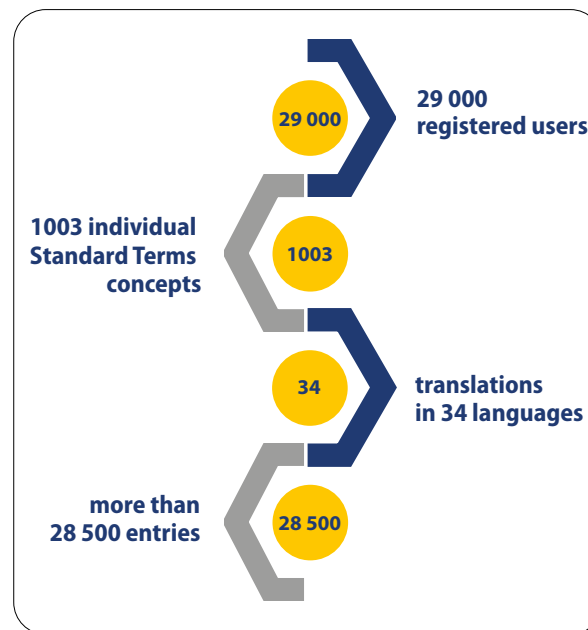
Collaboration between the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and the Standard Terms Working Party continued in 2019, with two new Standard Terms and three new mapped terms being added as a result of ICH requests, with mapped terms provided in both English and Japanese. In addition to its established use throughout Europe, interest in the Standard Terms database continued to spread among non-member states, reflecting the growing recognition of the importance of harmonising vocabularies used for the identification of medicinal products worldwide. The Standard Terms database remains at the forefront of the drive for global harmonisation in order to improve the health and safety of patients throughout the world.

The Pharmacopoeial Discussion Group and other international harmonisation initiatives

In a challenging context of ever more globalised supply chains, the Ph. Eur. continued its efforts to reduce unnecessary duplication of testing and reporting during drug development and routine manufacturing testing through its active

participation in the work of the Pharmacopoeial Discussion Group (PDG). The PDG, which has the Ph. Eur., the Japanese Pharmacopoeia (JP) and the United States Pharmacopoeia (USP) as members, together with WHO as an observer, was set up in 1989 to harmonise pharmacopoeial standards across the world. Two PDG meetings took place in 2019, one virtual (by videoconference) and one face-to-face which was hosted by the JP. Both meetings focused on strategic direction setting and were combined with technical teleconferences allowing geographically distant experts to discuss and resolve targeted technical topics, notably issues related to the revision of Q-09 *Particulate Contamination*.

A way forward for the future maintenance of the ICH Q4B (Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions) annexes was discussed and agreed upon. The timeline was presented to the ICH Assembly during the November 2019 ICH meeting and work has already started on updating the ICH Q4B annexes in accordance with the new maintenance process (Standard Operating Procedure of the ICH Working Groups Annex 5), which was approved by the ICH Assembly at its meeting in 2018. The PDG performed an initial review of all the ICH Q4B annexes, as well as the related sign-off texts and each pharmacopoeia's local texts. A mechanism for sharing the outcome of PDG evaluations of Q4B annexes and the drafts and final texts of pharmacopoeial activities



► The free online Standard Terms Database, key figures (2019)

with non-PDG pharmacopoeias was also discussed at the meeting. The PDG will share the scheme with the other pharmacopoeias at the next International Meeting of World Pharmacopoeias (IMWP).

Sign-offs at the 2019 PDG meeting included revisions to monographs on *E-55 Gelatin* and *E-60 Sodium Lauryl Sulfate*. The revision to *Q-07 Colour* was signed off by correspondence in June 2019.

As of 2019, 28 of the 31 general chapters and 46 of the 60 excipient monographs on the PDG work programme have now been harmonised.

Further harmonisation initiatives

The Ph. Eur. is actively involved in a number of other harmonisation initiatives at international level. It actively supports the IMWP, 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. Amongst the various projects carried out, the WHO initiative to draft Good Pharmacopoeial Practices (GPhP) stands out as a basis for improving co-operation and work-sharing among the pharmacopoeias of the world.

The 10th anniversary meeting of the World Pharmacopoeias was hosted by WHO in Geneva (Switzerland) in March 2019. Over 50 national and regional pharmacopoeial authorities, including the 38 countries represented by the Ph. Eur., renewed their commitment to strengthening their co-operation. This should ensure that quality standards for medical products are available and respected across borders, thereby improving public health outcomes for patients. A concrete step towards strengthened co-operation has been the development of a rapid alert system to exchange information and take urgent action during health emergencies. Procedures and pathways for collaboration are currently being established and a white paper will explain the role and added value of pharmacopoeias in the health system. The 11th IMWP took place in February 2020 at the EDQM's premises in Strasbourg (France).

Co-operation with national and European regulatory authorities

Throughout 2019, the Ph. Eur. Commission continued to work closely with national competent authorities and the EMA. This ongoing co-operation 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*³. Members of EMA working groups (i.e. for which the EMA provides the secretariat) and 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.

Co-operation with National Pharmacopoeia Authorities

The EDQM organises an annual meeting of National Pharmacopoeia Authorities (NPAs) of Ph. Eur. member states to facilitate and co-ordinate activities of common interest, and to provide an informal forum to exchange information. The 2019 meeting was hosted by the Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM) in Bonn (Germany) in May. Among other topics, discussions focused on the Ph. Eur. work programme and on process improvements.

Co-operation with other stakeholders

Stakeholder involvement in the elaboration and revision of Ph. Eur. texts is of crucial importance, and the EDQM endeavours to maintain regular exchanges with all interested parties. In 2019, a number of 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.

3. <https://pharmeuropa.edqm.eu/home>.



► Ph. Eur. 10th Edition (2019)

PUBLICATIONS, DATABASES AND WEBSITE

The 10th Edition of the Ph. Eur. (with its latest Supplement 10.2) contains 2 426 monographs (including dosage forms), 372 general texts (including general monographs and methods of analysis) and around 2 780 descriptions of reagents.

In July, a new electronic version was released, with a series of new features available to improve the user experience:

- access to the European Pharmacopoeia Online website from all recent common operating systems (tablet- and smartphone-friendly);
- an application fully compatible with recent Windows and Linux operating systems (Mac coming soon);
- individual use: install the application to one computer and to one USB stick, for online or offline use and easy access while on the move or in environments where using the book or the website is not possible or practical;

- shared use: install the application to several computers or USB sticks, for online or offline use, for example for non-nominative access in university libraries or laboratories.

Access to archives is included in the subscription. The Ph. Eur. online archives are available to all users with an up-to-date subscription (print or electronic).

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 around the globe. Texts are published on an ongoing basis and comments can be submitted on the basis of four deadlines per year.

REFERENCE STANDARDS

What are reference standards and why are they needed?

Ph. Eur. reference standards

Official reference standards (RSs) are an integral part of the Ph. Eur.: they complement the documentary texts 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. Ph. Eur. reference standards are established and distributed by the EDQM and adopted by the Ph. Eur. Commission; only the Ph. Eur. reference standards are official and authoritative in case of arbitration.

Distribution and portfolio

The EDQM distributes its reference standards to countries around the world and its portfolio is constantly evolving: new standards are regularly introduced to complement new or revised Ph. Eur. texts, or to replace existing RSs when corresponding stocks run out. The overall lifecycle management of the RS portfolio covers a wide range of tasks: from the procurement of candidate materials, characterisation and establishment, to manufacturing, quality control, quality assurance, release, distribution and monitoring.

EDQM activities for WHO reference substances

The EDQM is an observer to the WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) and the Expert Committee on Biological Standardisation (ECBS). 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.

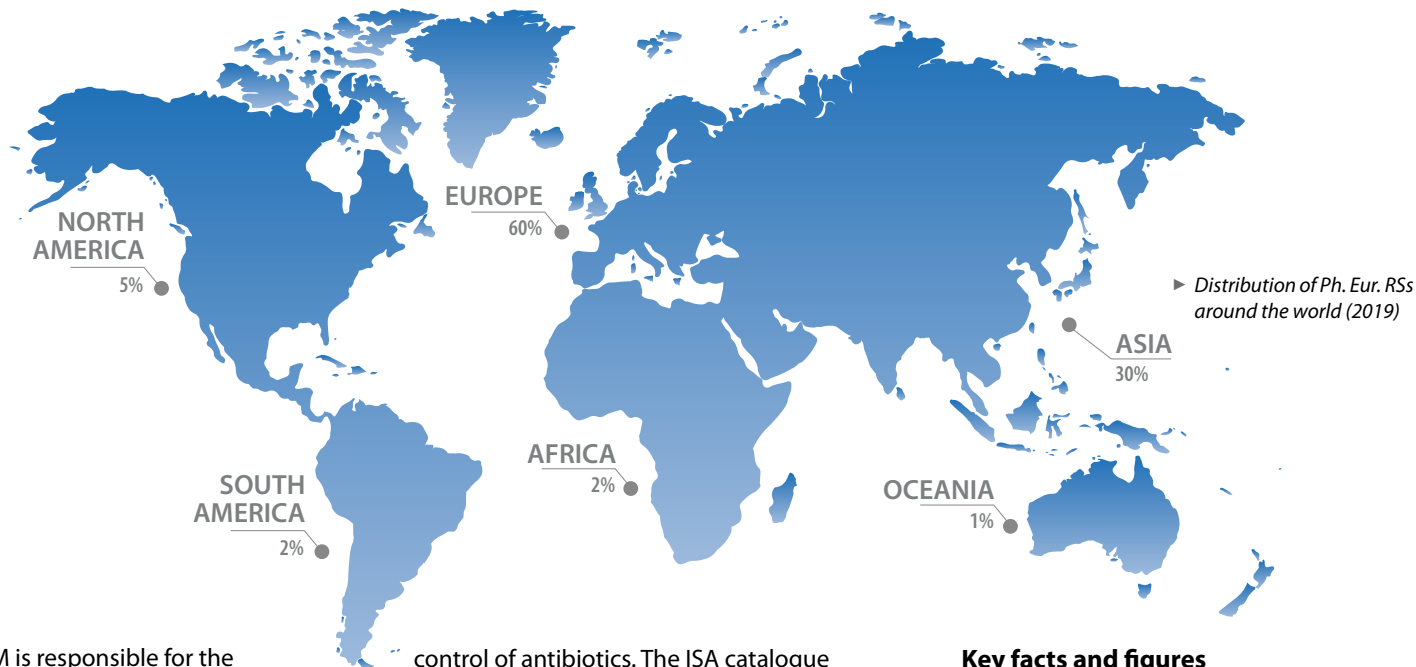
The EDQM is responsible for the establishment, manufacturing, monitoring and distribution of WHO International Chemical Reference Substances (ICRSs). These reference substances are used in conjunction with the monographs and texts of the International Pharmacopoeia, which is published and maintained by WHO, and used worldwide. The ICRS catalogue consists of 245 reference substances.

The ECSPP adopted the establishment reports submitted by the EDQM Laboratory for two new ICRSs and two replacement ICRSs.

Batches of Ph. Eur. reference standards adopted in 2019

- ▶ 98 new RSs
- ▶ 278 replacement RS batches were adopted
- ▶ Distributed directly by the EDQM to 122 countries





The EDQM is responsible for the establishment, manufacturing, 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 ISA catalogue consists of 23 reference standards.

The ECBS adopted the Third International Standard for Amphotericin B, established by the EDQM, at their meeting in October 2019.

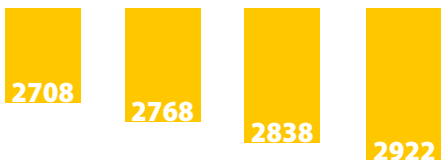
The EDQM Laboratory was one of the participants in the establishment study for the 1st International Standard for Adalimumab that was adopted by the ECBS in October 2019.

Key facts and figures

The Ph. Eur. RS portfolio consists of 2 996 Ph. Eur. RSs. It constantly evolves to complement new or revised Ph. Eur. texts, or to replace existing RSs when corresponding stocks run out.

In 2019, the EDQM distributed Ph. Eur. RSs directly to 122 countries.

2015 2016 2017 2018



► Growth of the Ph. Eur. RS Portfolio (2015-2019)

2019



Ph. Eur. RSs adopted in 2019

The Ph. Eur. Commission adopted the establishment reports submitted by the EDQM Laboratory for 98 new CRSs and 278 replacement CRSs.

The international collaborative studies performed as part of the BSP in 2019 led to the adoption of three replacement RSs by the Ph. Eur. Commission: *Human tetanus immunoglobulin BRP*, *Heparin Low*

Molecular-Mass for assay BRP and Prekallikrein activator in albumin BRP (see also “The European Pharmacopoeia”, page 14).

General matters and policies

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

In 2019, 29 of the 39 official control laboratories (representing 27 countries) available to support the EDQM Laboratory actually participated in collaborative studies for CRS establishment.

Scientific events related to RS

The 13th edition of the International Symposium on Pharmaceutical Reference Standards (IRSS) was held in Strasbourg on 13-14 March 2019. (See also “2019: A year rich in events and meetings”, page 54).

PUBLICATIONS, DATABASES AND WEBSITE

Search Database online | Reference substances 

Detailed view of Sitagliptin phosphate monohydrate CRS CRS

Catalogue Code	Y0001812	
Name	Sitagliptin phosphate monohydrate CRS	Batches
Current batch number	1	batch 1 is valid at this date ▾
Unit quantity per vial	160 mg	Print BVS
Number of vials per sales unit	1	
Used in monograph(s)	2778.2927	
Assigned content	See leaflet	
Additional information		
Leaflet	click to download the leaflet	
Chemical hazard	none identified	
Biological hazard	none identified	
SDS Product Code		
CAS Registry Number	654671-77-9	
Presentation		
Origin	click to download Origin Of Goods.pdf	
Proposed Import HS code	293359	
EDQM long term storage conditions	+5°C à 25°C	
Dispatching conditions	Ambient temp.	
UN Code	Not classified	
Shipping group	A1+	
Proph	29 GUS	
Availability	Available	
Sales restriction	No	

[New Search](#)

Throughout 2019, the EDQM continued to run and maintain its Reference Standards Online Database providing access to all standards officially valid for the use prescribed in the Ph. Eur. monographs. RSs can be searched by code, name, monograph number or CAS number. In addition, RS Batch Validity Statements (BVSs) are available to users to document 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 Database.⁴

In 2019, the EDQM issued 535 leaflets providing RS users with additional information, such as a chromatogram or assigned value, for a given substance.

In addition, Safety Data Sheets and outer labels have been 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 created or updated for biohazardous materials within the scope of Directive 2000/54/EC. Safety Data Sheets and labels are provided in 27 languages.

4. The EDQM Reference Standards Online Database can be accessed here: <https://crs.edqm.eu>.

CERTIFICATION OF SUITABILITY TO THE PH. EUR. MONOGRAPHS

The certification procedure is widely recognised around the world

The certification of suitability (CEP) procedure was 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 for the monitoring and quality control of substances used in the manufacture of medicines.

To apply for a CEP, manufacturers submit a dossier describing how their substance is manufactured and how its quality is controlled, and demonstrating that Ph. Eur. monographs are suitable to adequately control their quality. 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



Certification of suitability (CEP) procedure activities in 2019 – Applications received

- ▶ 306 new applications
- ▶ 1 824 requests for revision

ensure that Good Manufacturing Practice (GMP) is enforced and that the information supplied under the certification procedure is accurate.

In running the certification procedure, the EDQM's Certification Department relies on a network of about 100 assessors from competent authorities in 25 different countries (including Australia and Canada), and about 30 inspectors from 10 EU/EEA countries.

An increasing number of licensing authorities worldwide accept CEPs to replace (fully or partially) the section on the quality of active pharmaceutical ingredients (APIs) in marketing authorisation applications for medicinal products.

Key facts and figures

In 2019, the EDQM received 306 new CEP applications (+7% compared to 2018),

254

new
certificates
issued

1461

revised
certificates
were issued

5200

valid
certificates

▶ Total valid and issued CEPs in 2019

including nine for the risk of transmissible spongiform encephalopathy (TSE) and nine for herbal preparations; additionally, more than 1 800 requests for revision of CEPs were received (+3% compared with 2018).

In 2019, the *N*-nitrosamine issue continued to significantly impact the work of the Certification Department at the EDQM, with regard to CEP assessments and GMP inspections (see "*N*-nitrosamine contamination in brief", page 30).

In 2019, 254 new certificates and 1 461 revised certificates were issued. More than 95% of new applications were dealt with within official timelines. Concerning requests for revision, overall 52% were treated within official timelines. Processing times were significantly impacted by the need to dedicate resources to an extensive programme of review of dossiers in the context of the *N*-nitrosamine issue. However, the EDQM has taken a number of measures to correct the situation with deadlines for revisions, which should show a positive impact in 2020.

In December 2019, there were more than 5 200 valid CEPs covering chemical purity, TSE and herbal drug preparations.

As part of the EDQM inspection programme, 33 manufacturing sites (mainly located in Asia) were inspected in 2019. As part of its collaboration with international partners worldwide, the EDQM performed one joint inspection with the United States Food and Drug Administration (USFDA), and contributed to five inspections co-ordinated by the EMA. A number of inspections carried out in 2019 were triggered by the *N*-nitrosamine issue, (see “*N*-nitrosamine contamination in brief”, page 30).

In addition, by exchanging data with inspectorates from member states and international partners, the EDQM obtained information on GMP compliance for 21 other sites. In total 54 manufacturing sites were assessed for GMP compliance.

In 2019, the EDQM suspended and/or withdrew six CEPs from companies due

to non-compliance with GMP, which was observed either during on-site inspections performed by the EDQM or during inspections performed by EU supervisory authorities.

General matters and policies

The year 2019 was the first for the implementation of the revised EDQM “Guideline on requirements for revision/ renewal of Certificates of Suitability to the European Pharmacopoeia Monographs” (PA/PH/CEP (04) 2 7R); despite the fact that major changes were made for the treatment of some changes, no implementation issues were encountered.

In 2019, the Certification Department published a number of guidelines and policies⁵ to support its activities. In particular the Terms of Reference and the Code of Practice were revised to add clarifications on the operational aspects of the certification procedure.

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 in 2020 (with the exception of TSE dossiers and those of substances for veterinary use only).

COMMUNICATION WITH APPLICANTS, PARTNERS AND STAKEHOLDERS

In 2019, the Certification Department took part in a number of events, conferences and international fairs. This created opportunities to meet with applicants and provide them with advice on the CEP procedure. Additionally, five technical advice meetings were organised, either at the EDQM premises or by teleconference.

The Certification Department also took part in a number of international platforms for collaboration, such as ICH working groups, the International Pharmaceutical Regulators Programme (IPRP) Quality Working Group for Generics, the international Active Pharmaceutical Ingredients (API) inspection programme and the Pharmaceutical Inspection Co-operation Scheme (PIC/S).

The Certification Department continued to work on strengthening co-operation and exchange of information on the quality of pharmaceutical substances with authorities worldwide and on promoting the informed use of CEPs as support documentation for the quality evaluation of these substances.

5. Available on the EDQM website <https://go.edqm.eu/CEPgl>.

THE EUROPEAN NETWORK OF OFFICIAL MEDICINES CONTROL LABORATORIES

Funded
by the European Union
and the Council of Europe



Implemented
by the Council of Europe

The importance of a network for pan-European co-operation

Throughout 2019, the EDQM continued to co-ordinate the activities and programmes of its General Network of OMCLs, the GEON. The co-ordination of the OMCL Network is partly funded by the European Commission.

Created to prevent substandard medicinal products from reaching patients and compromising the efficacy of their treatment and potentially their health, the OMCL Network currently brings together official laboratories based in 36 European member states and seven non-European countries. Operating impartially and independently of manufacturers, and thus without any conflicts of interest, this network facilitates the pooling of resources and information on the latest technologies with a view to saving public money and sharing expertise and best practices across Europe.

The network operates on the basis of commonly agreed standards, procedures and guidelines, and follows the principle of mutual recognition of test results. Its work gives member states the support they need to monitor the quality of medicines.

In order to support regulatory action in response to *N*-nitrosamine contamination in APIs and finished products of the sartan class, ranitidine and metformin, the EDQM continued to co-ordinate the development of general test methods with the OMCL Network. For more information, see “*N*-nitrosamine contamination in brief”, (page 30).

In 2019, the Advisory Group of the GEON elaborated strategic goals for the network: four key topics were identified together with a number of follow-up actions aimed at strengthening the role of OMCLs as key contributors to public and animal health in Europe.

The OMCL Network General Activities in 2019

- ▶ 11 Mutual Joint Audits (MJAs)
- ▶ 1 Mutual Joint Visit (MJV)
- ▶ 14 Proficiency Testing Studies (PTS) carried out
- ▶ and 2 Market Surveillance Studies (MSSs) finalised

Quality Management programme

In 2019, the network continued to implement, maintain and assess the Quality Management (QM) programme for its members. The main goals of the programme are:

- ▶ to ensure harmonisation of Quality Management Systems (QMS) among OMCLs; and
- ▶ to achieve appropriate quality levels for the mutual recognition of test results among members (e.g. official batch release testing of biologicals, market surveillance and falsified medicines testing).

The activities co-ordinated by the EDQM in 2019 also focused on the implementation of the new ISO/IEC 17025:2017 standard that requires OMCLs to adapt to the new requirements within a transition period of three years.

Mutual Joint Audits/Visits and Training Visits

Mutual Joint Audits/Visits (MJAs/MJVs) are used to assess the compliance of OMCL QMSs with the requirements laid down in ISO/IEC 17025, the network's QM guidelines and the Ph. Eur. In 2019, 11 MJAs and one MJV were carried out and no training visits (TVs) took place, bringing the total to 180 MJAs, 53 MJVs and 28 TVs/tutorials since the programme was launched in 1997.

OMCL Network Quality Management Guidelines

QM guidelines are elaborated by network experts and updated on a regular basis,

Status	Guideline/Recommendation documents
Adopted	▶ Management of Reagents ▶ Evaluation of Measurement Uncertainty and its annexes and sub-annexes ▶ Qualification of Analytical Columns ▶ Qualification of Infrared Spectrophotometers
Under revision	▶ Validation of Analytical Procedures ▶ Qualification of Balances ▶ Handling and use of Non-Compendial Reference Standards in the OMCL Network ▶ Qualification of UV/Visible Spectrophotometers ▶ Qualification of GC Equipment ▶ Qualification of Automatic Titrators ▶ Qualification of Atomic Absorption/Atomic Emission Spectrometers ▶ Management of Environmental Conditions ▶ Management of Volumetric Glassware ▶ Change Control ▶ Management of Documents and Records ▶ Management of Samples ▶ Qualification and Re-qualification of Analysts ▶ Sub-Contracting of Tests

▶ *Quality Management Guidelines elaborated (2019)*

co-ordinated by the EDQM Secretariat. They are established to support laboratories in the implementation of the ISO/IEC 17025 requirements. The QMS Guidelines and Recommendation documents on the 2019⁶ working programme are listed above.

Training Courses/Workshops

A training course for new MJA/MJV scheme auditors was held to enlarge the pool of

competent auditors. A workshop was also organised for new and experienced auditors to prepare them for the transition to the new version of standard ISO 17025:2017. In addition, a webinar on the same subject for all OMCLs was held to help laboratories align with the new standard.

In connection with the new version of the standard, two one-and-a-half-day workshops on the theme of "Actions to address Risks and Opportunities" and a three-day hands-on workshop entitled "Measurement Uncertainty" were organised to help the

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

OMCLs to implement and understand the requirements of the new version of ISO 17025:2017.

Proficiency Testing Scheme studies

The EDQM Proficiency Testing Scheme (PTS) provides laboratories with objective means to assess and demonstrate the reliability of their data. In 2019, five studies were organised in the physico-chemical field: "PTS193 Water: Micro determination", "PTS194 Optical Rotation", "PTS195 Infrared Absorption Spectrophotometry", "PTS196 Dissolution" and "PTS197 Liquid Chromatography". An average of 98 laboratories (OMCLs and other pharmaceutical control laboratories from industry, hospital pharmacies, universities and pharmacy associations) took part in each study.

A specific PTS programme is also organised by the EDQM in collaboration with WHO. In 2019, three External Quality Assurance Assessment Scheme (EQAAS) studies were completed: "EQAAS 9.1 Assay by liquid chromatography", "EQAAS 9.2 Identification by Infrared Absorption Spectrophotometry" and "EQAAS 9.3 Dissolution". On average, 43 laboratories took part in each study.

Six studies in the field of biologicals were organised in 2019, with an average of 21 participating laboratories for each study. They covered "PTS198 Hepatitis E virus NAT", "PTS199 Hepatitis A virus NAT", "PTS200 Hepatitis C virus NAT", "PTS201 Immunoglobulin protein composition", "PTS202 Immunoglobulin molecular-size distribution" and "PTS203 Bacterial endotoxins (vaccine samples)".



► Participants at the 24th Annual Meeting of the GEON, London (United Kingdom)

Collaboration with the European Co-operation for Accreditation

The EDQM continued to work with the European Co-operation for Accreditation (EA), with the aim of evaluating co-operation opportunities, focusing on exchanges of know-how, mutual participation in meetings as observers and running joint audits with National Accreditation Bodies (NAB) and EDQM/MJA auditors. In 2019, a major subject of common interest was a harmonised interpretation of the requirements of the new ISO 17025:2017 standard.

General OMCL Network activities

GEON Annual General Meeting

The 24th GEON Annual Meeting was held in London (United Kingdom) from 13 to 17 May 2019 and was organised with the support of the Medicines and Healthcare products Regulatory Agency (MHRA) of the

United Kingdom. The meeting was attended by around 260 experts from 40 countries – representing 61 official laboratories and national competent authorities – including representatives from non-European partners Canada, Israel, Singapore and the Taiwan Food and Drug Administration.

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. Where possible, such studies are organised in conjunction with the CAP Generics and MRP/DCP testing schemes.

In 2019, two MSSs, were finalised: "MSS054 Liothyronine APIs and tablets", and "MSS057 Pioglitazone tablets".

On average, 14 OMCLs from the GEON participated in each of these studies.

Active Pharmaceutical Ingredients (API) Working Group

One face-to-face meeting and a teleconference were held to discuss strategic objectives, as well as the ongoing study planning. Other main topics were the Fingerprint Market Surveillance Studies on sildenafil, the collaboration with GMP inspectors and ways of enhancing co-operation with other related initiatives.

The first combined CAP, MSS and API Fingerprint study on sildenafil was initiated with the purpose of creating synergies for API sample collection and testing. This study takes advantage of collective sampling of APIs and medicinal products for concerted testing. The sampling phase was finalised in 2019 and the results indicated that a significant number of APIs from different sources could be sampled for the Fingerprint programme, one of the key objectives of this collective study. The actual testing phase will start in 2020.

After having performed several Fingerprint studies, the group discussed how to implement the experience gained from chemometric studies for quality testing of medicines. One of the practical applications is to identify API samples suspected of coming from non-authorised sources.

The API Working Group drafted a chemometrics guidance document⁷ which will function as a working tool for beginners to become acquainted with chemometrics and the possibilities this methodology offers.

7. "Benefits of Chemometrics for OMCLs", PA/PH/OMCL (19) 60 DEF, available at <https://go.edqm.eu/PAPHOMCL1960DEF>.

The document also provides guidance for more advanced users looking to build on their knowledge of chemometric methods.

OMCL Falsified Medicines Working Group

The group met twice in the course of 2019. A Market Surveillance Study on Suspected Illegal Products (MSSIPs) was finalised and a summary report published on the EDQM website. The study covers "medicines in disguise" which contain undeclared APIs from the ATC-INN list in amounts comparable to authorised medicines.

A new OMCL working group tasked with the elaboration of strategies for the detection of falsified monoclonal antibodies and antibody-containing fusion proteins became operative in December 2018 and held its first meeting in September 2019.

Two technical training sessions for OMCL members (the 16th and 17th in this series) were organised by the EDQM jointly with the official control laboratory at the Paul-Ehrlich-Institut (PEI) in Langen, Germany. The training focused on physicochemical test methods including Capillary Electrophoresis – Isoelectric Focusing (CE-IEF) and Peptide Mapping/Ultra Performance Liquid Chromatography (UPLC) for the identification of falsified therapeutic monoclonal antibodies. The sessions were attended by 20 trainees from 17 member states.

As regards the Suspicious Unknown Products (SUPs) programme, following the meeting of the working group in November 2018 in Copenhagen, the SUP procedure was revised

and a new study (SUP009) was launched in 2019.

A webinar on the Know-X database tailored to advanced OMCL users was held on 6 November 2019. In total, 24 participants attended the training, which focused on a new feature allowing the entry of analytical data into the application and on other practical aspects relevant for users with a laboratory background.

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 by sharing knowledge and information on the latest technological advancements. Currently, the working group is comprised of 11 OMCLs.

The validation of standard methods for quality control of GTPs was advanced with the determination of physical particles and viral and infectious genomes in Adeno-Associated Virus (AAV)-based vector products and the determination of residual mammalian host cell DNA.

The 10th meeting of the working group was held in Montpellier, France, and provided an opportunity to exchange views with the French Inspectorate and regulatory authorities. Discussions covered general matters related to the quality control of advanced therapy medicinal products (ATMPs), inspections of ATMP manufacturing sites, the increase in activities in the GT field at EU and global level and how the OMCLs can contribute to ensuring that products of good quality reach European patients.



CombiStats™

CombiStats™ is a software programme 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 also available to other laboratories. The current version 6.0 introduced features such as equivalence testing, robust regression, 5-parameter asymmetric sigmoid curves and password protection of datasheets. The online

manual, a tutorial and other background information for CombiStats™ are available on the EDQM website,⁸ while training courses for users are organised at the EDQM once a year.

In 2019, 808 licences were issued and CombiStats™ was used in 31 countries in Europe and 29 countries in the rest of the world. CombiStats™ has thus evolved into

an internationally recognised reference tool in its domain, which facilitates the mutual recognition of data and results by all interested parties.

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

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 Product (CAP) Sampling and Testing. The EMA sponsors the programme and has overall responsibility for it, while the EDQM co-ordinates the sampling and testing operations.

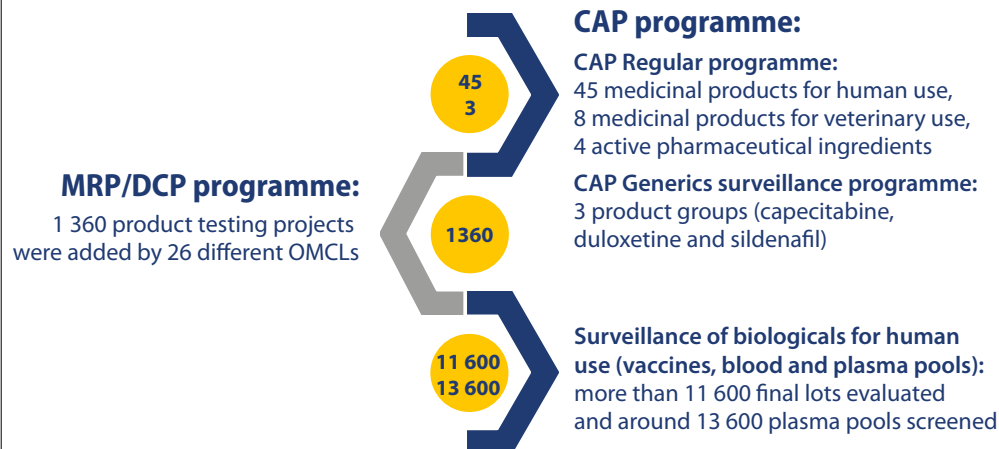
As of 2019, three additional programmes have been added to the well-established CAP Regular programme and Generics programme. Whereas the CAP Regular programme still covers an annual list of products prepared by the EMA Secretariat together with the EMA Scientific Committees and using a risk-based approach, the CAP Generics programme was updated in order to enlarge the number of tested products and include three programmes on generics every year.

A new Biosimilar programme was also introduced, due to the increasing number of biosimilars available. Three projects will be conducted over a period of five years (2019-2024), covering filgrastim, etanercept and rituximab products.

In addition, a dedicated programme for testing of products distributed in parallel was introduced; it currently focuses on authenticity checks.

In order to address the large percentage of APIs produced outside of the EU/EEA and used in the manufacture of medicines for the European market, an ad hoc CAP

► The OMCL Network EU/EEA specific activities in 2019



API programme has become part of the co-operation agreement with the EMA.

The results showed that the vast majority of the products tested were of the expected quality and complied with authorised specifications.

By 31 December 2019, one confirmed out-of-specification result and several regulatory or technical findings had been reported to and followed up by the EMA.

Mutual Recognition Procedure/ Decentralised Procedure post-marketing surveillance scheme

The OMCLs involved in this activity met twice in 2019 (34th and 35th meetings) to evaluate the programme and discuss ways of optimising collaboration. Progress was

made on the development of a common risk-assessment model.

The 15th regular programme for the market surveillance of medicinal products authorised in the EU/EEA via the Mutual Recognition Procedure (MRP) or Decentralised Procedure (DCP) was carried out in 2019. About 1 360 product testing projects were added to the 2019 programme, a similar figure to 2018. Testing reports for 2019 were issued by 26 different OMCLs and 17% of the tested products were for veterinary use.

Regulatory issues were identified in around 7% of the projects. They were mostly related to insufficient details on test methods and labelling. In addition, one or more out-of-specification results were reported in 4% of cases.

By the cut-off date of January 2020, the MRP/DCP Product Testing Database, which was created in 2007 to improve co-operation on planning, sampling and reporting of testing activities carried out within the OMCL Network on MRP and DCP products, held some 11 270 records, with contributions from 36 different OMCLs. Database access is restricted to OMCLs and health authorities.

Official Control Authority Batch Release of biologicals for human use

The Network for Official Control Authority Batch Release (OCABR) of biologicals for human use implements the harmonised application of Article 114 of EU Directive 2001/83/EC across Europe. Network activity fosters the mandatory mutual recognition of batch release for human vaccines and medicinal products derived from human blood and plasma. OMCLs perform a quality review of every batch through testing and protocol review. In 2019, OMCLs evaluated more than 11 600 final lots and screened around 13 600 plasma pools for safety, thus independently confirming the products' quality before they reach patients.

The OCABR sessions of the annual meeting in London were attended by over 90 participants. This meeting was an opportunity to exchange expertise and optimise resources to solve common problems. The OMCL representatives discussed technical issues and strategies that could lead to better and more efficient control of products such as human clotting factors and childhood vaccines. They also followed up on preparations for the withdrawal of

the United Kingdom from the EU to ensure a smooth transition. An upgraded OCABR database, housed and developed at the EDQM, was launched in 2019. This database allows the authorities involved to share confidential information on released batches.

Two new and 23 revised guidelines for vaccines came into force in 2019. Importantly, these revisions included the complete removal of the abnormal toxicity test from the guidelines. A revision to the EU Administrative Procedure for OCABR and a number of internal network guidelines also came into force in 2019. The OCABR Advisory Group and the drafting group for vaccines both met twice during the year to further the work of the OCABR Network between annual meetings. A workshop to foster harmonised testing for the safety of oral polio bulks was also held for OMCLs and manufacturers.

Official Control Authority Batch Release of immunological veterinary medicinal products

A subset of specialised OMCLs, together with national competent authorities, are 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.

Thirty-two participants from 18 member states took part in the Veterinary Batch Release Network (VBRN) session of the OMCL annual meeting. The VBRN agreed to re-evaluate their testing priorities by employing an established network procedure based on risk analysis. The advisory group analysed the first stage of a pilot phase

to better co-ordinate activities for post-marketing surveillance, in particular for IVMPs that are not selected for OCABR, and proposed to move ahead with the project. In anticipation of 3Rs developments for testing inactivated rabies vaccine, the OMCLs reviewed possibilities for transferring licensed *in vitro* approaches for use in OCABR. The VBRN also followed up on preparations for the United Kingdom's withdrawal from the EU so that appropriate measures could be taken to ensure batch release.

The VBRN Advisory Group met twice during the year to advance important issues. A successful training session for newcomers to OCABR/OBPR, open to both authorities and manufacturers, was held in October. Updates to four internal procedures came into force in 2019.



N-NITROSAMINE CONTAMINATION IN BRIEF

In 2018, *N*-nitrosamines (*N*-nitrosodiethylamine (NDEA) and *N*-nitrosodimethylamine (NDMA)) were first detected in a number of active substances used in the treatment of hypertension and in related medicines (sartans). *N*-nitrosamines are known as possible carcinogens for humans and only very low amounts are acceptable according to current regulatory requirements (ICH M7 “cohort of concern”⁹). Their detection requires highly sensitive analytical methods. In line with its mandate to promote and protect public health in Europe

by ensuring access to good quality medicines and healthcare, the EDQM has been working actively since 2018 at various levels to address the presence of *N*-nitrosamines in active substances and medicines by:

- ▶ undertaking a major reassessment of relevant CEP dossiers, and taking the necessary actions;
- ▶ conducting GMP inspections of manufacturing sites for the APIs concerned;
- ▶ revising relevant Ph. Eur. monographs to add limits for *N*-nitrosamine impurities, an important part of

ensuring the continuity of the supply of medicines for the benefit of patients in Europe;

- ▶ elaborating a general chapter providing analytical procedures to control the relevant *N*-nitrosamine impurities;
- ▶ working with its network of OMCLs to co-ordinate sampling and testing and to ensure that analytical test procedures for determination of *N*-nitrosamines are developed and made available to stakeholders;
- ▶ regularly updating all stakeholders concerned, from national authorities to manufacturers, on the state of the works and on initiatives taken.

In 2019, the EDQM continued to co-operate with regulatory authorities at national, international and EU level and published regular updates on its website.

Ph. Eur. activities

Following the identification of *N*-nitrosamine contamination in active pharmaceutical ingredients of the sartan class, the Ph. Eur. Commission revised the monographs for sartans containing a tetrazole structure:

- ▶ *Valsartan* (2423)
- ▶ *Candesartan cilexetil* (2573)
- ▶ *Irbesartan* (2465)
- ▶ *Losartan potassium* (2232)
- ▶ *Olmesartan medoxomil* (2600)

The “Production” and “Tests” sections of these monographs were revised to align, as far as possible, requirements on the control of

9. Available at <https://go.edqm.eu/ICHM7R1>.

N-nitrosamines with the recommendations issued by the Committee for Human Medicinal Products (CHMP) of the EMA, as published on 1 February 2019. The revised monographs were published in the 10th Edition of the Ph. Eur. with an implementation date of 1 January 2020.

The Ph. Eur. Commission discussed the need to further revise these monographs to remain compliant with the European Commission Decision C(2019) 2698 of 2 April 2019¹⁰ after the two-year transitional period ends in April 2021. In November 2018, at its 162nd session, the Ph. Eur. Commission had decided to elaborate a new general chapter on the control of *N*-nitrosamine impurities in APIs (2.5.42). This chapter was assigned to the Ph. Eur. General Methods Working Party. Methods developed by the OMCL Network for the specific testing of *N*-nitrosamines in sartans will be used as a basis. The draft chapter was published in *Pharmeuropa* for public enquiry at the beginning of 2020.

The Ph. Eur. Commission also proposed to revise the general monograph on *Substances for pharmaceutical use (2034)*. This proposal was made further to the European Commission referral C(2019) 2698 and the review initiated by the EMA in September 2019 under Article 5(3) of Regulation (EC) No. 726/2004¹¹ and by the EDQM for all holders of CEPs on chemically-synthesised API to provide guidance to marketing authorisation holders and API manufacturers on how to avoid the

presence of *N*-nitrosamine impurities in human medicines. The inclusion of a requirement to perform a risk assessment of the manufacturing process and to implement a control strategy for the detection and control of *N*-nitrosamine impurities in the “Production” section was proposed. In view of the impact of such a change, the Commission sought the opinion of users on the proposed application of those requirements to all substances for pharmaceutical use, whether they are:

- ▶ active substances (or intermediates, if justified) or excipients;
- ▶ substances for human use or for veterinary use;
- ▶ produced by chemical synthesis or obtained from natural sources, or produced by extraction from raw materials or fermentation.

The revised general monograph was published in *Pharmeuropa* 32.1 for public consultation from January to March 2020.

Action on CEPs

In 2018 and 2019, the EDQM conducted a complete review of the manufacturing information submitted in all CEP applications for sartans (about 125 applications), to confirm that there was no risk of presence of any kind of *N*-nitrosamine, and also to bring the CEPs in line with the revised Ph. Eur. monographs, which require a mandatory test for *N*-nitrosamines, before their implementation in January 2020.



The review was further extended to other active substances in 2019, following information received from manufacturers and regulatory authorities. In addition, all new CEP applications, renewals and any revisions where the synthetic route or sourcing has been modified – regardless of active substance – are systematically assessed for the risk of *N*-nitrosamines.

For sources of active substances in which *N*-nitrosamines were detected above the limits temporarily defined in the EU, the respective CEPs were suspended. A number of these CEPs were restored as soon as the companies implemented corrective actions which were assessed as satisfactory by the EDQM.

10. Available at <https://go.edqm.eu/ECDecC20192698>.

11. Available at <https://go.edqm.eu/ECReg7262004>.

The assessment work was supported by GMP inspections of manufacturing sites, confirming that GMP was in place and that appropriate actions had been put in place when necessary. These GMP inspections allowed the restoration of previously suspended CEPs after appropriate corrective measures had been taken.

In October 2019, the EDQM contacted all CEP holders and requested that they extend investigations to all chemically synthesised APIs. The work on *N*-nitrosamines is therefore expected to continue in 2020.

Work on sampling and testing methods with OMCLs

The EDQM continued to co-ordinate the development of testing procedures to ensure adequate control of impurities of the *N*-nitrosamine group. These procedures allowed all members of the European network of OMCLs with the necessary equipment on hand to ensure efficient and targeted controls on medicinal products containing APIs at risk of being contaminated with *N*-nitrosamines. As contaminations of ranitidine and metformin products were reported in 2019, this was a crucial step in providing strong and efficient technical support to regulatory authorities.

In spite of the challenges related to testing for *N*-nitrosamines, notably the need to develop highly sensitive detection methods, the broad coverage of *N*-nitrosamines and the need to test different types of APIs, since 2018 the OMCL Network has developed analytical methods for the determination of NDMA, following three general principles, as well as

specific methods for determining NDEA. In 2019, the published methods were further refined to make them suitable for a broader spectrum of molecules and/or to cover additional *N*-nitrosamines. As a consequence, test methods for additional *N*-nitrosamines, such as NDIPA (*N*-nitroso-diisopropylamine), NEIPA (*N*-nitroso-ethyl-isopropylamine), NDBA (*N*-nitrosodibutylamine), NMBA (*N*-nitroso-*N*-methyl-4-aminobutyric acid derived from the use of *N*-methylpyrrolidone) were developed by OMCLs.

Under the co-ordination of the EDQM, the OMCL Network also developed a common format for communicating sampling plans and testing results among participating laboratories, and a risk-oriented sampling plan in discussion with the EMA, the NCAs, inspectorates and CMDh representatives, which was continually amended. The purpose of the testing activities is to confirm levels of contamination in the products concerned, to perform market surveillance of similar products and of products theoretically of low concern, and to analyse samples derived from GMP inspections.

The analytical methods of the OMCL Network/EDQM are also used as a starting point for developing techniques for future Ph. Eur. work on general methods.

ANTI-FALSIFICATION ACTIVITIES

Combating pharmaceutical crime to protect public health

The EDQM continued to promote co-operation among authorities at national and international level in the fight against falsified medical products (medicinal products and medical devices) and similar crimes, as covered by the Council of Europe's MEDICRIME Convention, the first and only binding criminal law instrument to address the falsification of medical products at international level.

The experts in the European Committee on Pharmaceuticals and Pharmaceutical Care (CD-P-PH), 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 medical products.

Together with the Council of Europe 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 the Republic of Guinea.

Key facts

By the end of 2019, the convention had been ratified by 16 countries and signed by

another 16. A major milestone was achieved in December 2019 with the adoption of the Rules of Procedures of the convention's Committee of the Parties. This committee will play an important role in monitoring 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 falsified products is collected and shared. The EDQM actively promoted the SPOC model in co-operation

with other international organisations such as the Asia-Pacific Economic Cooperation (APEC) and the United Nations Office on Drugs and Crime (UNODC).

In October 2019, a joint working group of experts from CD-P-PH/CMED and the Committee of Experts on Quality and Safety Standards in Pharmaceutical Practices and Pharmaceutical Care (CD-P-PH/PC) held a workshop with focus on enforcement of borderline products, an issue discussed in several fora. The workshop succeeded in creating an informal expert network including non-EU countries. Discussions took place on how products were classified, and knowledge was shared about specific issues that agencies are facing in this particular field. The workshop was attended by 42 participants from 25 countries. A follow-up workshop is planned for 2020.



Anti-falsification activities in 2019

- ▶ In total, 16 countries have ratified the MEDICRIME Convention
- ▶ Adoption of Rules of Procedures of the convention's Committee of the Parties
- ▶ 4th MEDICRIME Inspector workshop for Good Distribution Practices (GDP), Good Manufacturing Practices (GMP) and Pharmacy Inspectors took place in Malta
- ▶ a Regional MEDICRIME workshop for Baltic countries was held
- ▶ a Workshop on Borderline Products was organised

In November 2019 a regional workshop on the MEDICRIME Convention and the framework it provides for international co-operation, mutual assistance in criminal law and measures for co-ordination at national level was held in co-operation with the Latvian Health Authorities. It was attended by participants from Latvia, Estonia, Lithuania, Poland and Sweden representing different disciplines (prosecutors, legal department of health inspectorate, ministry of health, justice, police, customs).

In December 2019, the fourth MEDICRIME workshop for Good Distribution Practices (GDP), Good Manufacturing Practice (GMP) and Pharmacy Inspectors took place in Malta. Jointly organised with the national Medicines Authority, this technical workshop was attended by 22 inspectors from Spain, Italy, Greece, Cyprus and Malta.

Mass serialisation systems for medicines

The EDQM continued to support the development of mass serialisation systems as tools to prevent falsified medicines from entering the legal supply chain. 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.

In 2019, by means of conformity assessments, the EDQM continued to support national health authorities in the supervision of the European Medicines Verification Organisation (EMVO) system, as well as systems at national level.

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 (medicines and medical devices). The database is a tool for sharing information which enables health and law-enforcement authorities across Europe to act more rapidly in cases of suspect medical products. To further enhance information exchanges, a new feature was introduced in 2019 allowing users to issue and share rapid alerts. The information provided in the Know-X database also covers the analytical identification of medicinal products and the related follow-up actions taken by the competent health or law-enforcement authorities. The CD-P-PH/CMED and the OMCL Falsified Medicines Working Group work together on the maintenance of the database, and in 2019 introduced other improvements; they also co-operate in promoting the database and offer training to its users.

Since 2007, the EDQM has organised or contributed to 25 training sessions, several workshops, and six conferences. In total, approximately 590 participants from 62 countries, mostly in Europe but also in other parts of the world,¹² participated in these programmes on falsified medical products.

COMMUNICATION WITH PARTNERS AND STAKEHOLDERS

Throughout 2019, representatives of the EDQM participated regularly in the meetings of the EU Heads of Medicines Agencies' Working Group of Enforcement Officers (HMA-WGEO), and attended a number of conferences with the purpose of raising awareness of the MEDICRIME Convention.

12. Overview of activities related to MEDICRIME 2007 2016: <https://go.edqm.eu/MDCRacts16>.

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 executed by 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 of Medical Products and Similar Crimes (CD-P-PH/CMED).

Key facts

In 2019, the drafting of a Council of Europe resolution for the promotion and implementation of pharmaceutical care in Europe was completed. The resolution¹³ will advance patient-centred care, support medicine optimisation and encourage responsible use of resources through the implementation of pharmaceutical care in daily practice in community and hospital settings.

Following up on the work on the above resolution, the CD-P-PH/PC established a subordinate working party entrusted with developing a guidance document to

harmonise the medication review process in different care settings for various target patient groups across Europe. The guidance will optimise the impact of medicines, improve patient safety and reduce waste.

An exploratory survey was carried out with the aim of mapping out how European countries ensure that foreign patients receive sufficient information on medications when they do not understand the language of the country where they are receiving medical care. The survey aimed at exploring the potential role that patient information leaflets in electronic format may have in improving access to medicine information. The outcomes of this survey were presented at an event organised by the Ministry of Health of

Pharmaceuticals and pharmaceutical care in 2019

- ▶ completion of the draft resolution for the **promotion and implementation of pharmaceutical care**
- ▶ launch of a new project aimed at harmonising the medication review process in Europe
- ▶ annual recommendations on the classification of medicines and their supply conditions (prescription and non-prescription)
- ▶ updates of the **Melclass database**
- ▶ reviews of the **classification of medicines containing nasal preparations and corticosteroids for topical use**



13. Resolution CM/Res(2020)3 on the implementation of pharmaceutical care for the benefit of patients and health services, adopted on 11 March 2020, available at <https://go.edqm.eu/ResPhCare20203>.

Iceland in Reykjavik in October 2019 within the framework of the Icelandic presidency of the Nordic Council of Ministers and focused on the role of electronic patient information leaflets in medicine and patient safety.

A joint working group comprising delegates from the CD-P-PH/PC, CD-P-PH/PHO and CD-P-PH/CMED was established in 2019 with a view to revising Resolution ResAP(2007)2 on good practices for distributing medicines via mail order. The aim of this new joint working group is to provide member states with state-of-the-art recommendations related to the remote provision of medicines.

The CD-P-PH/PHO issued its annual set of 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 in Europe, as it aims to ensure patient safety and accessibility of medicines. The annual recommendations of the CD-P-PH/PHO are included in the Melclass database.¹⁴

PUBLICATIONS, DATABASES AND WEBSITE

A scientific article entitled “Council of Europe Resolution CM/Res(2016)2: a major contribution to patient safety from reconstituted injectable medicines?” was published in the *European Journal of Hospital Pharmacy*.¹⁵ It summarises the rationale behind Resolution CM/Res(2016)2 on good reconstitution practices in healthcare establishments, its drafting process and main chapters. It also encourages the implementation of this resolution at national level to enable risk reduction in healthcare establishments and improve patient safety as regards reconstituted medicines.

Medicines containing nasal preparations in Melclass (2019)

The review of the classification of medicines containing nasal preparations and corticosteroids for topical use was completed and will be available on the EDQM website in the course of 2020.

Throughout 2019, the Melclass database was regularly updated with relevant recommendations from the 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 in member states parties to the Ph. Eur. Convention.

COMMUNICATION WITH PARTNERS AND STAKEHOLDERS

Interactions took place in 2019 with international organisations and professional bodies active in the field of public health and pharmacy practice, such as the European Association of Hospital Pharmacists (EAHP) and the Non-prescription Medicinal Products Task Force of the Co-ordination Group for Mutual Recognition and Decentralised procedures – Human (CMDh) in order to align efforts aimed at ensuring safe and appropriate use of medicines in Europe.

A presentation was given at the 24th EAHP Congress in Barcelona highlighting, among other things, the crucial role of Resolution CM/Res(2016)1 on quality and safety assurance requirements for medicinal products prepared in pharmacies for the special needs of patients and Resolution CM/Res(2016)2 on good reconstitution practices in healthcare establishments for medicinal products for parenteral use, in protecting patient safety and preventing quality and safety gaps between medicinal products prepared in pharmacies and those prepared on an industrial scale.

The role of the EDQM in harmonising the classification status of medicines and their related supply conditions in Europe and the work of the CD-P-PH/PHO were also presented at the 6th Croatian Congress on Pharmacy held in Dubrovnik in April 2019.

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

15. Beaney A. M. et al., available at <https://ejhp.bmj.com/content/early/2019/02/15/ejhp-pharm-2018-001723>.



European Paediatric Formulary in 2019

- ▶ first 2 monographs and general texts adopted
- ▶ officially launched in December 2019
- ▶ 8 monographs on the work programme

EUROPEAN PAEDIATRIC FORMULARY

In 2019, the European Committee on Pharmaceuticals and Pharmaceutical Care (CD-P-PH) and the Ph. Eur. Commission published the first texts in the European Paediatric Formulary (PaedForm). This is a major achievement for the PaedForm Working Party and all the stakeholders involved, since it reflects how their commitment has delivered a tool that will support clinicians, pharmacists and healthcare providers in preparing unlicensed paediatric medicines of acceptable quality.

The European Paediatric Formulary¹⁶ is a freely available, pan-European collection of formulations for extemporaneous preparations currently described in national formularies and formulations which are already well-established in European countries. The aim is to give pharmacists access to formulations of appropriate quality, allowing preparation of a medicinal product when no licensed alternative is available on the market.

16. <https://paedform.edqm.eu/home>.

In 2019, efforts focused on the review of the comments received from several countries on the first two monographs, *Hydrochlorothiazide 0.5 mg/mL oral solution* and *Sotalol hydrochloride 20 mg/mL oral solution*, which had been made available for public consultation. Along with the results from the full testing and verification of the monographs performed by the experts, the Pharmeuropa PaedForm comments helped to finalise the content of the monographs and to improve the instructions given in the

“Production Steps” section of the monograph. The comments received also allowed for a better understanding of the needs of healthcare professionals in Europe and led to improved texts.

These first two monographs, along with the two general texts introducing the formulary and its general principles, were – following the working procedure agreed on – first approved by the Ph. Eur. Commission at its June session and subsequently adopted for publication by the CD-P-PH in September.

The newly developed online platform for the [European Paediatric Formulary](#) was launched in December, providing free access to the finalised texts. This platform sits alongside *Pharmeuropa PaedForm*, which will remain active for public consultations with new draft monographs regularly made available for comments over a period of three months.

The completion of the pilot phase has not only seen the launch of the platforms and the establishment of efficient interactions with key stakeholders, it also allowed prioritisation of the work programme according to specific needs in terms of products and medicinal substances.

The EDQM also had regularly exchanges with the Paediatric Committee (PDCO) of the EMA, keeping the committee updated on the progress on the European Paediatric Formulary and on how the project can complement licensed medicines by improving access to safe paediatric preparations where there are unmet needs.

The EDQM also maintained its relationship with the European Association of Hospital

European Paediatric Formulary work programme (2019)

- ▶ Azathioprine oral suspension
- ▶ Chloral hydrate oral solution
- ▶ Furosemide 2 mg/mL oral solution
- ▶ Isoniazid 10 mg/mL oral solution
- ▶ Omeprazole 2 mg/mL oral suspension
- ▶ Oxybutynin 0.25 mg/mL intravesical solution
- ▶ Phosphate oral solution
- ▶ Vehicle for oral solution or suspension

Pharmacists (EAHP), a valuable link to hospital pharmacy units, with a focus on obtaining additional information from pharmacists preparing unlicensed formulations on a daily basis, a key aspect for better understanding their needs.

Special thanks are given to the Dutch Pharmacist's Formulary (FNA) and the German Neues Rezeptur-Formularium (NRF), who agreed to base the first monographs on data from their formularies for *Hydrochlorothiazide 0.5 mg/mL oral solution* and *Sotalol hydrochloride 20 mg/mL oral solution*. The EDQM looks forward to receiving continued support from national formularies, hospital pharmacies and universities. The working party will continue to expand the portfolio of the European Paediatric Formulary by finalising items on the work programme and adding new items.



QUALITY AND SAFETY OF SUBSTANCES OF HUMAN ORIGIN

Throughout 2019, the EDQM continued 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 transfusion and for the transplantation of organs, tissues and cells.

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, mutual assistance, 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 responsible for co-ordinating all blood transfusion activities at the EDQM. Supported by its subordinate bodies, it elaborates recommendations and guidelines, and supports their implementation through operational programmes.

Key facts and figures



Given the increased need for plasma-derived medicinal products (PDMPs) for European patients and dependence on plasma collected in the USA, the EDQM in collaboration with the European Commission organised a symposium on plasma supply management, held on 28 and 29 January 2019, to discuss ways to increasing plasma collection in Europe while ensuring the protection of donors. The symposium was a global success, with 150 participants from 33 countries. The main outcome is a set of recommendations suggesting courses of action to stakeholders to augment the collection of plasma for fractionation.

Pursuing the objective of ensuring optimal use of blood components and PDMPs, the EDQM in collaboration with the Paul-Ehrlich-Institut (PEI) and the University of Munich, organised the 5th Kreuth Symposium held on 7 and 8 June 2019, to discuss optimal treatments for haemophilia. In line with the previous Kreuth symposia, consensus recommendations were developed with a view to updating Committee of Ministers Resolution CM/Res(2017)43 on principles concerning haemophilia therapies, which provides governments with a course of action to ensure optimal therapies for haemophilia patients.

Blood transfusion activities in 2019

- ▶ **B-PTS programme continued:** 6 studies were performed
- ▶ **B-QM programme:** 3 Blood Mutual Joint Visits (B-MJVs) and 1 Blood Training Visit (B-TV) were carried out

The EDQM continued to run the Blood Proficiency Testing Scheme (B-PTS) and the Blood Quality Management (B-QM) programmes to support blood establishments (BEs) in the implementation of current EU blood legislation, the *Guide to the preparation, use and quality assurance of blood components* and the Good Practice Guidelines (GPGs). Both programmes have been co-funded by the European Commission and the EDQM since 2010.

Blood Proficiency Testing Scheme (B-PTS)

The external assessment of the testing capability of European BEs continued in 2019 through PTS studies:¹⁷ six studies were organised and an average of 56 laboratories participated in each study.

Nucleic Amplification Technique (NAT)

B-PTS043 HBV, HCV, HIV, NAT

Serology

B-PTS045 anti-HCV
B-PTS046 anti-HIV/p24
B-PTS047 anti-Treponema
B-PTS048 HBsAg/Anti-HBc

Immuno-Haematology

B-PTS049 ABO, Rhesus, Kell, extended phenotyping and irregular

► B-PTS studies conducted in 2019

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

Blood Quality Management (B-QM) Programme

This programme¹⁸ provides tools enabling European BEs to develop, implement and improve their QMS. The programme offers three 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 European standards,¹⁹ report findings and issue recommendations;
- Blood Mutual Joint Audit (B-MJA): audit to check compliance of the QMS against European standards, report findings and follow-up corrective and preventative actions.

In 2019, three B-MJVs and one B-TV were carried out.

General matters and policies

Guide to the preparation, use and quality assurance of blood components, and Good Practice Guidelines

The GTS group entrusted with the periodic revision of the *Guide to the preparation, use and quality assurance of blood components*²⁰ drafted its 20th edition, and revised

18. <https://go.edqm.eu/BQM>.
19. Minimum Standards: the EU blood legislation, the GPGs (www.edqm.eu/en/good-practice-guidelines-blood-establishments) and the Blood Guide (www.edqm.eu/en/blood-guide).
20. The EDQM publications are available here: <https://register.edqm.eu/freepub>.

the Good Practice Guidelines (GPGs), made mandatory since February 2018 in EU and EEA countries by the EU blood legislation. As well as ensuring the guide is up to date with scientific and regulatory developments, the GTS revised the guide to provide users with standards to facilitate the implementation of future EU legal requirements. The 20th edition of the guide was adopted by the CD-P-TS in November 2019 and will be published in 2020.

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

As required by Resolution CM/Res(2013)3 on sexual behaviours of blood donors that have an impact on transfusion safety,²¹ a dedicated working group is responsible for the continuous collection of data on the incidence and prevalence of sexually transmitted infections that might impact the safety of transfusions. The group is pursuing its tasks to map deferral policies for men having sex with men and identify the aspects requiring harmonisation.

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



PUBLICATIONS, DATABASES AND WEBSITE

The European database of frozen blood units of rare blood groups has been fully operational since 2016 and supports BEs in their searches for blood with rare phenotypes. To date, six BEs have voluntarily made their lists of frozen units of rare blood groups available to patients in need.

The proceedings of the 1st European Training Course on Statistical Process Control (SPC) were published in 2019. These provide BEs and inspectors with comprehensive guidance to support them to implement and inspect SPC.²²

COMMUNICATION WITH PARTNERS AND STAKEHOLDERS

Co-operation with the European Commission

The year 2019 was marked by a new grant agreement signed between the European Commission and the EDQM, which expands the current portfolio of co-funded activities and seeks to avoid duplication of efforts. In addition to the B-PTS and B-QM programmes, and the analysis of the EU Serious Adverse Reactions and Events (SARE), new projects encompass plasma supply management, contingency and emergency planning to ensure continuous blood supplies, training professionals on biovigilance and assessments of EU candidate, partner and neighbouring countries to ensure they have adequately implemented the EU legislation in the fields of blood and tissues and cells.

The EDQM continued to participate as an observer at meetings of the EU competent authorities for blood.

Pharmaceutical Inspection Co-operation Scheme (PIC/S)

The EDQM was invited to join the group responsible for revising the “PIC/S GMP Guide for Blood Establishments”. Most of the text of the GPGs has been included in the revised PIC/S document for the sake of international harmonisation.

International Society of Blood Transfusion (ISBT)

The EDQM has observer status on the ISBT Board of Directors and is a member of two 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 Basel (Switzerland) in June 2019.

22. Implementation of SPC is required by the EU blood legislation and the GPGs. For more information, see <https://go.edqm.eu/SPCproceedings>.



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 responsible for 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 collection of international data and monitoring of practices in Europe, and the fight against trafficking.

Key facts and figures

By the end of 2019, the Council of Europe Convention against Trafficking in Human Organs had been ratified by nine countries and signed by another 16. The experts of the CD-P-TO, together with its relevant subordinate bodies, continued to develop and promote programmes and projects aimed at disseminating best practices in the fight against transplant-related crimes.

In the context of Council of Europe Resolutions CM/Res(2013)55²³ and CM/Res(2017)2,²⁴ member states have

23. <https://go.edqm.eu/CMRes201355>.

24. <https://go.edqm.eu/CMRes20172>.

designated National Focal Points (NFPs) in charge of regularly collecting data on patients who travelled for transplantation abroad. This information is essential to gain better knowledge of this phenomenon and to ensure the same principles of transparency, traceability and continuity of care provided to patients having received an organ transplant in their country, also apply to those transplanted abroad. Data exchange at international level is helping to understand unethical transplantation practices (such as the so-called transplant tourism), their long-term outcomes and their potential risks for both individuals and public health; it also helps identify possible hotspots of transplant tourism. Ultimately, this exercise lays the factual basis needed for providing comprehensive and integrated information on these matters, and recommendations at national and international level; it also fosters interagency co-operation to address transplant-related crimes. The **Network of NFPs on Travel for Transplantation** met in Strasbourg in June 2019. During this meeting, the data submitted to the **EDQM International Database on Travel for Transplantation** was discussed. It emerged that some member states seem to be destinations for potentially unethical transplant procedures, requiring careful investigation by the countries involved (both the countries of origin and of destination of patients).

Organ transplantation and tissues and cells for human applications, 2019

- ▶ Publication of the 4th Edition of the *Guide to the quality and safety of tissues and cells for human application*
- ▶ "Newsletter Transplant 2019"
- ▶ development on the restricted and secure **International Database on Travel for Transplantation** continued



► *Critical factors for success in deceased donation: an international study (2019)*

The results of the survey were published on the EDQM website in the report “Critical factors for success in deceased donation: an international study”.²⁵

Every year the EDQM supports the organisation of the European Organ Donation Day (EODD). The main objectives are to raise public awareness and encourage public debate, to establish trust among the public towards organ, tissue and cell donation, and to engage policy-makers and the medical community. EODD is also an opportunity to honour all donors and their families and to thank transplantation professionals. The 2019 EODD was held in London (United Kingdom)

and focused on donation after circulatory death, novel technologies for organ preservation and perfusion and donation from under-represented ethnic groups (see “Public Awareness Campaigns”, page 57).

Publications and databases



The 4th edition of the *Guide to the quality and safety of tissues and cells for human application* was published in 2019. This new edition includes a number of important updates, in particular, Good Practice Guidelines for tissue establishments and tissue/cell monographs.

A new working group tasked with elaborating the *Guide to the quality and safety of organs for transplantation* was formed and started work on the 8th edition.

The “Newsletter Transplant 2019” was published in co-operation with the Spanish National Transplant Organisation (ONT). This publication continues to function as a unique source of official information, allowing the monitoring and benchmarking of practices in member states. It summarises comprehensive information and data from almost 70 countries worldwide on donation and transplantation activities, management of waiting lists, organ donation refusals and authorised centres for transplantation activities.

► *Guide to the quality and safety of tissues and cells for human application*



²⁵ Available at <https://go.edqm.eu/DeDo2019>.

A scientific article, assessing the efficiency of deceased donation programmes in several countries over a 15-year period using a new metric that measures donation activity relative to the potential for deceased donation, was published in the journal *Transplantation*.²⁶

A scientific article describing practices of donation after circulatory death (DCD) in Europe was published in the journal *Transplant International*,²⁷ which also issued a position paper on vascularised composite allotransplantation,²⁸ providing a comprehensive overview of the state of play and important elements to be considered in the development of such programmes.

The restricted **International Database on Travel for Transplantation** has continued to grow as more and more countries submit information about patients who travel abroad to receive an organ transplant. This data is analysed on a regular basis by the Network of NFPs on Travel for Transplantation (see page 43).

26. "Evolution of Deceased Organ Donation Activity Versus Efficiency Over a 15-year Period: An International Comparison", *Transplantation*. 2018 Oct;102(10):1768-1778.

27. "Donation After Circulatory Death Today: An Updated Overview of the European Landscape", *Transpl Int*. 2019 Sep 3. doi: 10.1111/tri.13506. [Epub ahead of print].

28. "Vascularized Composite Allotransplantation - A Council of Europe Position Paper", *Transpl Int*. 2019 Mar;32(3):233-240.

COMMUNICATION WITH PARTNERS AND STAKEHOLDERS

Co-operation with the European Commission

In 2019, a new three-year grant agreement between the European Commission and the EDQM was signed, expanding the areas of co-operation between both organisations in the field of tissues and cells for human application. This work will address various aspects, including the elaboration of quality and safety standards for tissue establishments, the harmonisation of data collection in the fields of tissues and cells, benchmarking post-mortem blood testing practices, reporting of serious adverse events and reactions (SARE) at EU level in the fields of tissues and cells and blood, training for professionals on biovigilance and quality management and country assessments in EU candidate, partner and neighbouring countries to ensure EU legislation in the fields of tissues and cells and blood has been adequately implemented.

As a way of enhancing co-operation between the two institutions and avoiding duplication of efforts, EDQM representatives attended meetings of EU competent authorities in the fields of organs and of tissues and cells, relevant meetings of expert sub-groups, as well as key meetings of relevant EU-funded projects, such as EuroGTP-II, VISTART and GAPP.

Co-operation with professional associations

Key professional associations in the field of organs, tissues and cells continued to participate in the work of the EDQM, in particular through the elaboration of technical guidance and the dissemination of the elaborated texts throughout the professional community.

CONSUMER HEALTH

Work related to the co-ordination of market studies and proficiency testing schemes in the area of quality control for cosmetics continued in 2019, along with efforts to enhance and develop standards in the field of food contact materials.



COSMETICS

The European Committee on Cosmetics and Consumer Health (CD-P-COS) is tasked with responding to emerging risks for health arising from the use of cosmetics. It also deals with the safety of tattoo inks and permanent make-up and promotes the principles laid down in Council of Europe Resolution ResAP(2008)1 on requirements and criteria for the safety of tattoos and permanent make-up. Activities on the work programme focus on fostering collaboration between member states and observers.

The European Network of Official Cosmetics Control Laboratories (OCCLs) contributes to consumer health protection by strengthening market surveillance and the enforcement of European regulations by the competent authorities. Participation in the activities of the network is open to members and observers of the Ph. Eur. Convention. The European OCCL Network was set up on a voluntary basis in 2010. Currently, more than 50 OCCLs follow the network activities, including laboratories from 21 EU member states, facilitating better use of resources and enhanced quality management in accordance with international standards. The long-standing experience of the EDQM with the OMCL Network is an asset for the co-ordination of the OCCL Network.



Cosmetics in 2019

- ▶ **32 member states** appointed **national representatives** in the two plenary sessions of the CD-P-COS
- ▶ More than **50 laboratories** participated in the two sessions of the **OCCL Network**
- ▶ **1 Proficiency Testing Study (PTS)** on **metals in face cream** and **1 analytical study** for the **determination of N-nitrosamines** were carried out
- ▶ **1 Market Surveillance Study (MSS)** on **cosmetic products claimed “perfume-free”** was launched and **1 survey on testing cosmetics on human volunteers** amongst CD-P-COS members was completed

Key facts

OCCL Network

EU regulations prohibit the use of heavy metals such as arsenic, nickel, barium or even asbestos in the production of cosmetic products. Traces of prohibited substances may in some cases be (technically) unavoidable. The OCCL Network members have collected information on the different threshold levels to be applied in quality control of cosmetic products. Manufacturers and other business operators should address the presence of substance traces in safety reports and closely monitor their concentration.

Protection of healthy volunteers in cosmetics testing

The CD-P-COS completed a survey of its members and reviewed information on the protection of healthy volunteers in studies related to the use, quality and effects of cosmetics. Nine recommendations were prepared for the attention of health authorities in order to help them establish better protection for healthy volunteers, while also taking into account guidelines and regulations already existing at national or European level.

Quality control of cosmetics: Market Surveillance Studies

Information on perfume content in cosmetics (such as a “perfume-free” label) is important information for consumers, as many fragrances can cause allergic reactions and affect sensitised persons. The OCCL Network launched a Europe-wide market surveillance study to check if perfume-free cosmetic products are as safe as they claim to be.

N-nitrosamines in cosmetics

As a way of enabling cosmetics control laboratories to test cosmetic products for the presence of toxic *N*-nitrosamines, a group of four laboratories jointly ran a common test protocol to assess the feasibility and reproducibility of their methods. The outcome of this analytical study was successful, as the analytical methods assessed were shown to be reliable for the determination of polar *N*-nitrosamines in nail polish.

Proficiency Testing Scheme (PTS) studies

Proficiency testing is an essential part of quality management in cosmetics control laboratories and helps to ensure that they produce reliable data and that test results are comparable across Europe.

In 2019, 20 control laboratories participated in a study aimed at assessing their ability to determine the concentration of arsenic, cadmium, lead, mercury, nickel and selenium in spiked samples of cosmetic creams. Participants had the opportunity to use different analytical techniques, such as atomic absorption or inductively coupled plasma mass spectrometry.

FOOD CONTACT MATERIALS AND ARTICLES

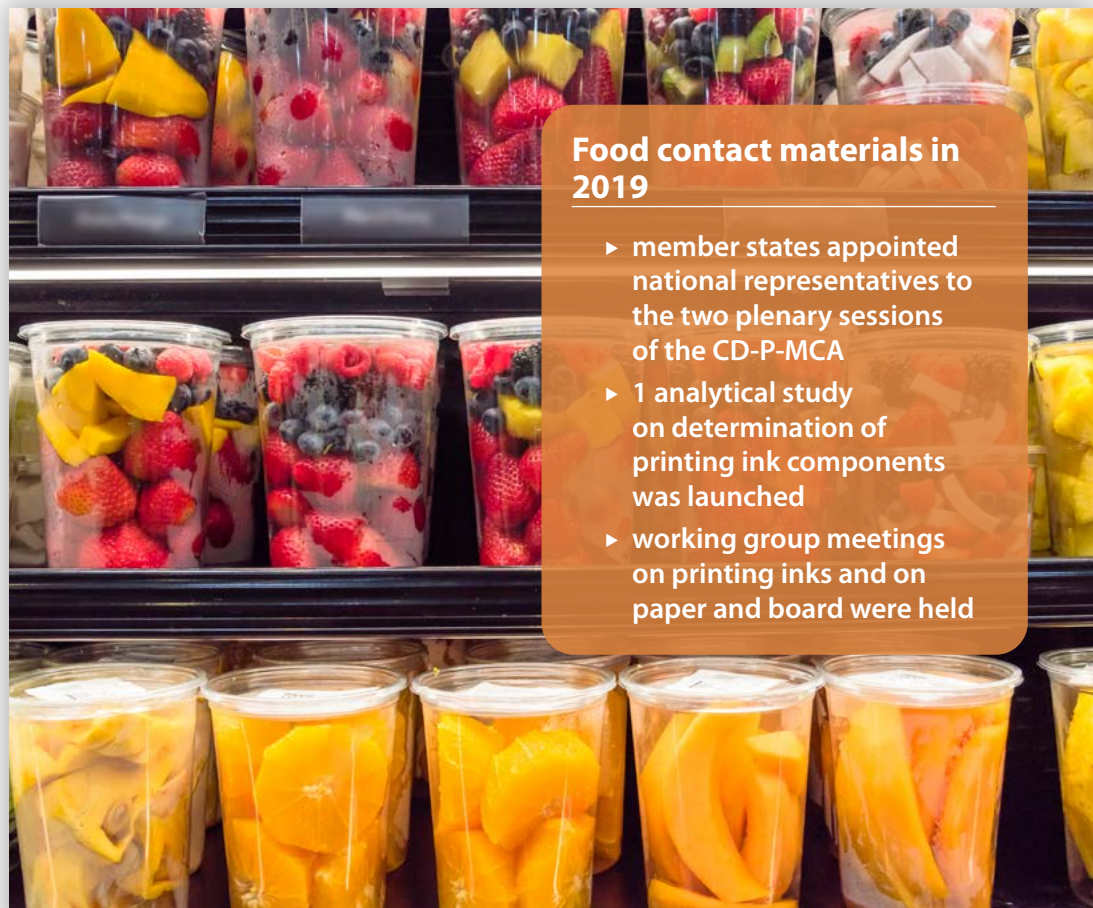
The European Committee for Food Contact Materials and Articles (CD-P-MCA) is tasked with the elaboration of harmonised measures that supplement EU and national legislation to ensure the safety of packaging, containers, utensils and other materials and articles for food contact.

The work programme is aimed at protecting human health across Europe through

common quality and safety requirements, as well as through the development and updating of testing methods.

The published technical guides are used as reference documents by manufacturers, safety evaluators and control laboratories.²⁹

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



Food contact materials in 2019

- ▶ member states appointed national representatives to the two plenary sessions of the CD-P-MCA
- ▶ 1 analytical study on determination of printing ink components was launched
- ▶ working group meetings on printing inks and on paper and board were held

Key facts

Two subordinate working groups support the work: one focuses on food contact materials made from paper and board and the other on printed food contact materials.

Throughout 2019, the national experts continued to review resolutions and technical documents elaborated in the past; the Federal Institute for Risk Assessment (BfR, Germany) and the General Chemical State Laboratory (GCSL, Greece) hosted expert meetings aimed at updating the provisions for paper and board and developing a multi-analysis test method for printing inks.

Food contact materials made from metals and alloys have been addressed in a practical guide³⁰ for manufacturers and regulators, which was first published in 2013. In view of new scientific evidence and the experience gathered following the first edition of the guide, the CD-P-MCA agreed on amendments proposed by experts from competent authorities, official and private control laboratories and industry for the second edition of the guide, which is presently under preparation.

The EDQM and national experts joined forces to prepare common rules for selecting the test conditions to be applied in the control of metals and alloys for food contact. This work is co-ordinated by the Joint Research Centre (JRC) of the European Commission.

Fourteen control laboratories agreed on a protocol for the determination of printing ink components in food samples and launched an analytical study to check the reproducibility of test results in view of publishing a harmonised test protocol in the absence of official methods.

The CD-P-MCA prepared guiding principles for the quality and safety of food contact materials to facilitate the updating of the existing Council of Europe technical documents and resolutions. Additional work has been initiated to help business operators ensure compliance with applicable regulations.

COMMUNICATION WITH PARTNERS AND STAKEHOLDERS

The EDQM exchanged information on market surveillance activities with the working groups of the Platform of European Market Surveillance Authorities for Cosmetics of the European Union (EU PEMSAC), notably in response to large numbers of products that were found not to comply with European regulations on cosmetics.

Representatives of the European Commission, the JRC and the European Food Safety Authority (EFSA) attended the meetings of the steering committees and of the subordinate working groups.

30. More information available at:
<https://go.edqm.eu/FCM>.

QUALITY MANAGEMENT SYSTEM

The EDQM continued to invest in its QMS as a priority matter in 2019, with a specific focus on Ph. Eur. reference standards.

Following the audits of official certification and accreditation bodies, the EDQM saw the confirmation of its ISO 9001:2015 certificate and was granted accreditation according to ISO 17025:2017. The EDQM is therefore certified for six processes and accredited for 21 tests, including nuclear magnetic resonance spectroscopy (NMR) and quantitative nuclear magnetic resonance spectroscopy (qNMR).

The EDQM's customers and interested parties can therefore rest assured of the consistent quality of the goods and services provided by the EDQM, as well as its commitment not only to maintain, but also continuously improve quality standards for all its activities.





APPENDICES

2019: A YEAR RICH IN EVENTS AND MEETINGS

SECONDARY SITE

On 15 November, Snežana Samardžić-Marković, Director General of Democracy of the Council of Europe, and Nicole Trisse, Deputy Chairperson of the Parliamentary Assembly of the Council of Europe, in the presence of a number of key local dignitaries, inaugurated the new secondary site of the EDQM. Located in Ars-Laquenexy, close to Metz in eastern France, the new site is intended to house contingency stocks of the EDQM's portfolio, including WHO International Reference Standards, of over 3 000 pharmaceutical reference standards.

This new site will not only increase the EDQM's storage capacity, it will also play a key role in ensuring the sustainability and continuity of the supply of pharmaceutical reference standards should an emergency situation affect the EDQM's main building in Strasbourg. The new site will have three main areas: one dedicated to logistics – including storage, preparation and delivery of reference standards, another for informatics and pharmaceutical support, and a technical area on the upper level. The site will be fully operational in the first half of 2020.

INTERNATIONAL CONFERENCE

In June, the EDQM held an international conference to mark the publication of the 10th Edition of the Ph. Eur. and the 25th Anniversary of the European OMCL Network and of the certification of suitability procedure. The conference, which was held under the patronage of the French Presidency of the Council of Europe, was opened by Snežana Samardžić-Marković, Director General of Democracy of the Council of Europe, Ambassador Jean-Baptiste Mattéi, Permanent Representative of France to the Council of Europe, and Susanne Keitel, Director of the EDQM.

The two-day conference included two plenary sessions and interactive workshops on seven specific themes: impurities, bioterapeutics, general methods, finished-product monographs, certification, 3Rs and ATMPs, and the OMCL Network. Over 300 participants from 47 countries attended the conference and the presentations and workshop conclusions were subsequently made available for download on the EDQM's website.³¹ The feedback and recommendations gathered were also presented to the Ph. Eur. Commission and will help define its work priorities for the next three years.

31. <https://go.edqm.eu/proceedings>.

► *Inauguration of the EDQM's Secondary Site (15 November 2019, Ars-Laquenexy, France)*





► *EDQM & European Pharmacopoeia: State-of-the-Art Science for Tomorrow's Medicines" (19-20 June 2019, Strasbourg)*

SYMPOSIA & WORKSHOPS – FOCUSED TOPIC MEETINGS

Joint EDQM – EC Plasma Supply Management Symposium (29-30 January 2019, Strasbourg)

The EDQM and the European Commission brought together stakeholders involved in the field of plasma to discuss ways forward for improving plasma supply management and donor protection. This symposium was the first opportunity for all stakeholders in the sector to exchange views on how to increase the supply of plasma for fractionation in Europe, while ensuring adequate protection of both donors and patients. The event was attended by 150 participants from 33 countries and the presentations and workshop conclusions were made available for download on the EDQM's website.³²

32. <https://go.edqm.eu/proceedings>.

Joint EDQM – USP Symposium on "Pharmaceutical Reference Standards" (13-14 March 2019, Strasbourg)

In March, the EDQM joined forces with the U.S. Pharmacopeia (USP) to organise the 13th meeting of the international symposium on Pharmaceutical Reference Standards (IRSS). The main focus of the two-day event was the use and establishment of pharmacopoeial reference standards for small molecules and biologicals. Pharmaceutical reference standards play a vital role in the development and production of medicines, as they are essential for their quality control. Reference standards help ensure consistent quality of medicines and packaging material, and provide a benchmark for testing their components. The event was attended by 130 participants from 28 countries and the

presentations and workshop conclusions were made available for download on the EDQM's website.³³

EDQM – Chinese Pharmacopoeia Commission (ChP) Joint Workshop on "International Standards" (5 July 2019, Jinan, China)

Around 400 participants attended this joint workshop, which focused on many important aspects of the work and procedures of the Chinese and European Pharmacopoeias (e.g. impurity control, new and revised chapters, the establishment of monographs on herbals). The programme also covered the establishment and use of Ph. Eur. reference standards, as well as an overview of the certification of suitability procedure (CEP).

Workshop on the European Pharmacopoeia (10-11 September 2019, New Jersey)

The two-day programme covered in depth important recent developments concerning the Ph. Eur. The workshop was attended by senior regulatory professionals with a good knowledge of the Ph. Eur.; it provided an excellent forum for the EDQM to exchange ideas and gather feedback from users. The EDQM would like to thank the New Jersey Pharmaceutical Quality Control Association (NJPQCA) for their support in the organisation of this workshop. All the presentations were made available for download on the EDQM website.³⁴

33. <https://go.edqm.eu/RStraining>.

34. <https://go.edqm.eu/pheurtraining>.

PARTICIPATION IN KEY INTERNATIONAL MEETINGS

In 2019, the EDQM participated in several major international meetings and events across the world:

- ▶ Indian Pharmaceutical Association (IPA) Conference: 4th Indian Pharmaceutical Forum (27-28 February 2019, Mumbai, India)
- ▶ Workshop on International Drug Standards Development and Standards Certification (20-21 June 2019, Xuzhou, China)
- ▶ Workshop on the Development and History of Pharmacopoeias (21-22 June 2019, Zaozhuang, China)

TRAINING SESSIONS

EDQM – Chinese Pharmacopoeia Commission (ChP) Executive Training Programme (10-14 December 2019, Strasbourg, France)

The EDQM, in close collaboration with the Chinese Pharmacopoeia Commission, organised an extensive four-day executive training programme for Chinese officials which was held in December. The aim was to provide, with the help of representatives from national authorities, an overview of the European regulatory landscape and of the working policies and procedures of the EDQM/Ph. Eur. The training session, which was opened by Sheng Yang, Deputy Director General of the China National Drug Administration, was specifically tailored to



▶ EDQM - Chinese Pharmacopoeia Commission (ChP) Executive Training Programme (10-14 December 2019, Strasbourg, France)

address the needs of the Chinese authority and provided an excellent forum for exchanges and discussions. The EDQM would like to thank the German Federal Institute for Drugs and Medical Devices (BfArM) and the Hungarian National Institute of Pharmacy and Nutrition (OGYÉI) for their support in delivering the training.

CombiStats™

A training session on CombiStats™, the EDQM software that can perform calculations according to chapter 5.3 of the Ph. Eur., was also organised in Strasbourg.

INTERNATIONAL FAIRS & CONGRESSES – EXPANDING GLOBAL PRESENCE

The EDQM participated in three pharmaceutical fairs in 2019: CPhI China (Shanghai), CPhI Worldwide (Frankfurt) and CPhI India (New Delhi). These trade shows are important platforms because they allow the EDQM to reach out to pharmaceutical professionals hailing from all four corners of the globe. Promotional materials distributed on the stand were centred around the

10th Edition of the Ph. Eur. and reference standards. Once again, the EDQM organised personalised one-to-one sessions with CEP staff during each of the fairs, allowing CEP applicants or users of CEPs to get advice and clarification on any aspect of the CEP procedure. CEP representatives also participated in parallel conferences and workshops organised during CPhI China.

The EDQM also participated in the 29th Regional Congress of the International Society of Blood Transfusion (ISBT) in Basel, Switzerland from 22 to 26 June. The congress, which was organised in collaboration with the Swiss Transfusion SRC (Swiss Red Cross) and the Swiss Association for Transfusion Medicine, was attended by approximately 1 850 delegates from 105 countries. ISBT represents an international community of professionals within the field of transfusion medicine, including blood services, hospitals, research institutes, universities and industry. The EDQM focused on the promotion of the EDQM/Council of Europe *Guide to the preparation, use and quality assurance of blood components* and the Blood Quality Programmes.

► *The Minister of Food and Drug Safety (MFDS) of South Korea, Prof. Eui-Kyung Lee, and Susanne Keitel, 19 December 2019*



VISITS

Many visitors with different profiles were welcomed at the EDQM premises in Strasbourg throughout 2019, including government officials, representatives from diplomatic missions, the Permanent Representatives to the Council of Europe, delegations to the Parliamentary Assembly (PACE), representatives of the national authorities of China and the Republic of Korea, German healthcare professionals, and students from France, Italy, Turkey and the United States of America.

In December, the EDQM met with representatives from the Shanghai Institute for Food and Pharma Packaging (SHMPCC). The meeting focused on the EU legislative framework for packaging and on the Ph. Eur. general requirements and texts dedicated to pharmaceutical packaging, containers and medical devices.

On 19 December, on the occasion of the signature of a Memorandum of Confidentiality, the EDQM met with the Minister of Food and Drug Safety (MFDS) of South Korea, Prof. Eui-Kyung Lee, and representatives from the Pharmaceutical Safety Bureau of the MFDS. The new Memorandum will provide a framework for closer co-operation and the exchange of information between the two institutions.

PUBLIC AWARENESS CAMPAIGNS

Organ, tissue and cell transplantation

The 20th European Day for Organ Donation and Transplantation (EODD³⁵) was organised in co-operation with the National Health Service Blood and Transplant (NHSBT) and held on 12 October in London (United Kingdom). The event, which has been organised by the EDQM/Council of Europe in a different country every year since 1996, is aimed at raising public awareness of the need for organs and to promote the principle of voluntary and non-remunerated donation.

The 2019 campaign "Give years of good life" was aimed at highlighting how organ donation improves the health and quality of life of the recipient. Campaign materials, such as social media graphics, posters and e-mail signature banners, were made available for download on the EDQM's website and helped national authorities to spread the message about the importance of organ donation.

A scientific conference for professionals in the sector was also held on the occasion of EODD 2019. Topics covered included new

technologies in preservation and perfusion, best practices around donation after circulatory death and increasing donation from under-represented donors, with an emphasis specifically on black and Asian donors. Some of the sessions were also broadcast live in the form of webinars, still available on the EDQM website, allowing transplantation professionals from around Europe and beyond to join remotely and follow the discussions.

Blood transfusion

World Blood Donor Day (WBDD) takes place on 14 June every year. The EDQM showed its public support for this worldwide campaign on its website and social media channels; a series of posts were shared on Twitter and Facebook highlighting the campaign and the actions taken by organisations around the globe.

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

35. <https://go.edqm.eu/EODD>.

LIST OF COMMITTEES CO-ORDINATED BY THE EDQM

EUROPEAN PHARMACOPOEIA COMMISSION

The Ph. Eur. Commission was set up in 1964 in accordance with the Convention on the Elaboration of a European Pharmacopoeia. As of 31 December 2019, the Commission had 39 members, all contracting parties to the convention (38 member states and the EU). In addition, 30 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 60 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.

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 replacing, reducing and refining 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) and 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 the quality of medicines. 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 falsified and illegal medicines. General activities are prepared and followed by the General OMCL Advisory Group;
- ▶ activities restricted to the EU and the 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 OCABR activities, advisory groups ensure continuity of operations in the interval between the annual meetings of each specific network.

CERTIFICATION OF SUITABILITY TO THE PH. EUR. MONOGRAPHS STEERING COMMITTEE

A network of about 100 assessors and 30 national inspectors participates in the work required for the evaluation of quality dossiers for pharmaceutical substances and the inspection of API manufacturing sites. The activities associated with the procedure for certification of suitability to the Ph. Eur. monographs are guided by a steering committee and three technical advisory boards (TABs). The steering committee is composed of representatives of European working groups, and of licensing authorities and inspectorates. It takes decisions on general policy, examines and comments on matters brought to its attention by the TABs, adopts guidelines and the inspection programme and co-ordinates questions among the represented parties. It is also responsible for appointing assessors, as well as the members of the TABs 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 is currently composed of representatives from authorities working in the field of blood transfusion or at national BEs from 33 member states of the Council of Europe and observers such as the European Commission, WHO, the USFDA and the Council of Europe's Committee on Bioethics (DH-BIO). It supervises the work of a number of individual projects and working groups, e.g. the working group in charge of the *Guide to the preparation, use and quality assurance of blood components*, the Plasma Supply Management Working Group and working groups responsible for quality management activities.

EUROPEAN COMMITTEE ON ORGAN TRANSPLANTATION

This steering committee (CD-P-TO) focuses on expounding and promoting the principle of non-commercialisation of organ, tissue and cell donation, strengthening measures to avoid trafficking and elaborating ethical, quality and safety standards in the field of

transplantation. It is currently composed of representatives from 36 member states of the Council of Europe, and observers including the European Commission, WHO, the Council of Europe's Committee on Bioethics (DH-BIO), Eurotransplant, Scandiatransplant, the European Society for Organ Transplantation (ESOT), The Transplantation Society (TTS), the European Association of Tissue and Cells Banks (EATCB), the European Eye Bank Association (EEBA), the European Society of Human Reproduction and Embryology (ESHRE) and the World Marrow Donor Association (WMDA). It supervises the activities of a number of individual projects and working groups, e.g. the ad hoc working groups that work on the elaboration of 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*. In addition, it oversees the work of the International Network of National Focal Points (NFPs) on Travel for Transplantation and that of multiple working groups and advisory groups that implement the activities in the field of tissues and cells included in the standing Grant Agreement with the European Commission.

EUROPEAN COMMITTEE ON PHARMACEUTICALS AND PHARMACEUTICAL CARE

This steering committee (CD-P-PH) supports authorities in times of increasing social gaps and resource constraints to make the medication process more safe, responsible and accessible to all who need it. It is currently composed of representatives from 32 member states of the Council of Europe, and observers.

Its work programme has three focus areas: classification of medicines as regards their supply, pharmaceutical care and practices, and combating 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 FOR COSMETICS AND CONSUMER HEALTH

The CD-P-COS was formed in early 2018 to respond to emerging risks for human health arising from the use of cosmetics. It replaces part of the former Committee on Consumer Health Protection (CD-P-SC), which was dissolved by decision of the Committee of Ministers at the end of 2017, and is currently composed of representatives from national ministries with public health responsibilities from 32 member states of the Council of Europe, and observers. Activities on the work programme focus on collaboration and knowledge sharing between participating countries. The CD-P-COS oversees 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 50 OCCLs participate in regular network activities, including laboratories from member states of the EU. Besides the EU, participation is open to other Council of Europe states having signed the Convention on the Elaboration of a European Pharmacopoeia.

EUROPEAN COMMITTEE FOR FOOD CONTACT MATERIALS AND ARTICLES

The CD-P-MCA was formed in early 2018. It replaces part of the former Committee on Consumer Health Protection (CD-P-SC), which was dissolved by decision of the Committee of Ministers at the end of 2017, and is currently composed of representatives from national ministries with public health responsibilities from 27 member states of the Council of Europe, and observers. Activities on the work programme focus on the safety of food contact materials and articles and define harmonised measures that supplement EU and national legislation. It is supported by two subordinate bodies: the working group on food contact materials made from paper and board and the working group on printed food contact materials. The technical guides published by the CD-P-MCA are used as reference documents by manufacturers and other business operators, safety evaluators and control laboratories.

GLOSSARY

3Rs	replacement, reduction and refinement (animal testing)
AAV	adeno-associated virus
APEC	Asia-Pacific Economic Cooperation
API	active pharmaceutical ingredient
ATMP	advance therapy medicinal product
BE	blood establishment
BET	bacterial endotoxin test
BfR	Federal Institute for Risk Assessment (Bundesinstitut für Risikobewertung), Germany
B-MJA	Blood Mutual Joint Audit
B-MJV	Blood Mutual Joint Visit
B-PTS	Blood Proficiency Testing Scheme
B-QM	Blood Quality Management
BRP	biological reference preparations
BRR	biological reference reagents
BSP	Biological Standardisation Programme
BVS	batch validity statements
BWP	Biologics Working Party
CAP	centrally authorised product
CAS number	Chemical Abstracts Service Registry number
CAT	Committee for Advanced Therapies
CD-P-COS	European Committee on Cosmetics and Consumer Health (see "List of committees co-ordinated by the EDQM", p. 60)

CD-P-PH	European Committee on Pharmaceuticals and Pharmaceutical Care (see "List of committees co-ordinated by the EDQM", p. 59)
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-TO	European Committee on Organ Transplantation (see "List of committees co-ordinated by the EDQM", p. 59)
CD-P-TS	European Committee on Blood Transfusion (see "List of committees co-ordinated by the EDQM", p. 59)
CEP	Certificate of suitability to the monographs of the European Pharmacopoeia
CHMP	EMA Committee for Medicinal Products for Human Use
ChP	Pharmacopoeia of the People's Republic of China
CLP	classification, labelling and packaging
CMDh	Coordination Group for Mutual Recognition and Decentralised procedures – Human
CPhI	Convention on Pharmaceutical Ingredients
CRS	chemical reference substance
DCD	donation after circulatory death
DCP	decentralised procedure
DH-BIO	Council of Europe Committee on Bioethics
DNA	deoxyribonucleic acid
EA	European Co-operation for Accreditation
EAHP	European Association of Hospital Pharmacists

EATCB	European Association of Tissue and Cells Banks	GPhP	Good Pharmacopoeial Practices
ECBS	WHO Expert Committee on Biological Standardization	GT	gene therapy
ECSPP	WHO Expert Committee on Specifications for Pharmaceutical Preparations	GTP	gene therapy products
eCTD	electronic common technical document	GTS	Ad hoc Working Group on the “Guide to the preparation, use and quality assurance of blood components”
EDQM	European Directorate for the Quality of Medicines & HealthCare	HMA-WGEO	EU Heads of Medicines Agencies’ Working Group of Enforcement Officers
EEA	European Economic Area	HMP	herbal medicinal product
EEBA	European Eye Bank Association	HPLC	high-performance liquid chromatography
EFSA	European Food Safety Authority	HMPC	Herbal Medicinal Products Committee
EMA	European Medicines Agency	HPTLC	high-performance thin-layer chromatography
EMVO	European Medicines Verification Organisation	HRS	herbal reference standards
EODD	European Day for Organ Donation and Transplantation	ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
EQAAS	External Quality Assurance Assessment Scheme	ICRS	International Chemical Reference Substance
ESHRE	European Society of Human Reproduction and Embryology	IMWP	International Meeting of World Pharmacopoeias
ESOT	European Society for Organ Transplantation	INN	International Non-proprietary Names
EU	European Union	IPA	Indian Pharmaceutical Association
FNA	Dutch Pharmacist’s Formulary	IPRP	International Pharmaceutical Regulators Programme
FPM	finished product monograph	IRSS	International Symposium on Pharmaceutical Reference Standards
GC	gas chromatography	ISA	International Standard for Antibiotics
GCSL	General Chemical State Laboratory, Greece	ISBT	International Society of Blood Transfusion
GDP	good distribution practice	ISO/IEC	International Organization for Standardization/ International Electrotechnical Commission
GEON	General European Network of Official Medicines Control Laboratories (OMCLs)	IVMP	immunological veterinary medicinal products
GMP	good manufacturing practice	IWP	Immunologicals Working Party
GPG	Good Practice Guidelines		

JP	Japanese Pharmacopoeia	PACE	Parliamentary Assembly of the Council of Europe
JRC	European Commission Joint Research Centre	PDG	Pharmacopoeial Discussion Group
LC	liquid chromatography	PDMP	plasma-derived medicinal products
MFDS	Minister of Food and Drug Safety, South Korea	PEI	Paul-Ehrlich-Institut
MHRA	Medicines and Healthcare products Regulatory Agency	PEMSAC	Platform of European Market Surveillance Authorities for Cosmetics
MJA	mutual joint audit	Ph. Eur.	European Pharmacopoeia
MJV	mutual joint visit	PIC/S	Pharmaceutical Inspection Co-operation Scheme
MRP	mutual recognition procedure	PTS	Proficiency Testing Scheme
MSS	market surveillance study	QM	quality management
MSSIP	market surveillance study on suspected illegal products	QMS	quality management system
NAB	national accreditation body	QWP	EMA Quality Working Party
NCA	national competent authority	REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals (Regulation (EC) No. 1907/2006)
NDEA	<i>N</i> -nitrosodiethylamine	REMCO	International Organization for Standardization Committee on Reference Materials
NDMA	<i>N</i> -nitrosodimethylamine	RS	reference standard
NFP	national focal point	SARE	serious adverse reactions and events
NHSBT	National Health Service Blood and Transplant, United Kingdom	SHMPCC	Shanghai Institute for Food and Pharma Packaging
NJPQCA	New Jersey Pharmaceutical Quality Control Association	SPC	statistical process control
NMR	nuclear magnetic resonance	SPOC	single point of contact
NPA	national pharmacopoeia authority	SRC	Swiss Red Cross
NRF	Neues Rezeptur-Formularium, Germany	SUP	suspicious unknown products
OCABR	Official Control Authority Batch Release	TAB	technical advisory boards
OCCL	Official Cosmetics Control Laboratories	TCM	traditional Chinese medicines
ONT	National Transplant Organisation, Spain	TSE	transmissible spongiform encephalopathy
P4	Procedure 4	TTS	The Transplantation Society
PA	pyrrolizidine alkaloids		

TV	training visits
UNODC	United Nations Office on Drugs and Crime
UPLC	ultra performance liquid chromatography
USFDA	United States Food and Drug Administration
USP	United States Pharmacopeia
VBRN	Veterinary Batch Release Network
WBDD	World Blood Donor Day
WGEO HMA	European Union Working Group of Enforcement Officers of the Health and Medicines Agencies
WHO	World Health Organization
WMDA	World Marrow Donor Association

This publication presents the work carried out in 2019 by the European Directorate for the Quality of Medicines & HealthCare, Council of Europe, highlighting its particular achievements.

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