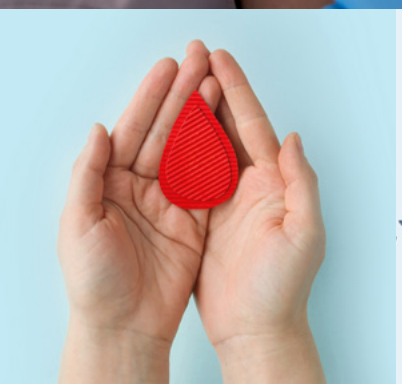
2021 HIGHLIGHTS



EDQM annual report

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

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2021 HIGHLIGHTS
EDQM ANNUAL REPORT

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

Council of Europe, EDQM

French edition

Les points forts de 2021 – Rapport annuel de l'EDQM

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Message from the Director

In 2021, in the face of the global pandemic and its impact on the quality of medicines and healthcare, the European Directorate for the Quality of Medicines & HealthCare (EDQM) continued to fulfil its mission to protect public health with great determination. Despite adverse conditions, the EDQM experts, stakeholders and staff pulled together to keep the vast majority of activities moving forward as planned, with necessary adaptations to keep the organisation in "business-as-usual" mode, yet ensuring the EDQM stays ahead of the curve in the post-COVID-19 environment.

The EDQM Director, Susanne Keitel, retired in September 2021 after 14 years of inspired leadership. Her tenure opened with the move to a new, state-of-the-art facility and was marked by the broadening of the EDQM's mandate, the deepening of international co-operation and harmonisation, and the raising of the bar in terms of health protection standards across the board.

In 2021, the second year of the pandemic, the European Pharmacopoeia Commission adopted more than 200 texts, reference standard availability was ensured at a level of over 99% and the production of reference standards was fully maintained. Two major projects were completed: the real-time remote inspection pilot project, which has been successfully integrated as a routine inspection system, and the EDQM reference standards contingency stock project, involving the recently completed secondary site. The EDQM also organised numerous virtual events and training sessions, attracting a broad range of participants from around the globe and enhancing engagement with the organisation's stakeholders. The Council of Europe 2022-2025 programme and budget, adopted by the Committee of Ministers at the end of the year, foresees a major investment programme for the EDQM. Under this programme, the EDQM will construct a third building to accommodate future growth alongside the establishment of state-of-the-art technologies in the laboratories and production areas.

Looking forward, the main event in 2022 will be the publication of the 11th Edition of the European Pharmacopoeia, with an international conference planned from 19 to 21 September to mark this milestone. Work will of course continue on the implementation of the Certificate of suitability (CEP) of the future, and we also envisage increased collaboration with the European Union (EU) in the field of substances of human origin. Amendments to EU legislation on blood, tissues and cells, and the revision of legislation on pharmaceuticals will have an impact on the EDQM. We will continue to work closely with our EU partners to ensure that responsibilities and activities are co-ordinated and complimentary, and that everyone in Europe benefits from the most efficient and effective approach to public health.

In response to the challenges and developments in our environment, the EDQM has defined a number of strategic focus areas that will help guide our work in the coming years. These include the development of a future business model for the EDQM to ensure sustainability, enhancement of our relationships with external stakeholders, process improvements and strategic organisational development.

The EDQM proudly continues to deliver on its mandate to contribute to access to quality medicines and healthcare and to promote and protect human and animal health. Now more than ever, this would not be possible without the support of our networks of experts, the collaboration with our partners and the commitment and expertise of the EDQM staff members. As the new Director of the EDQM, I would like to take this opportunity to thank each and every one for their excellent contributions and support.

Petra Doerr, PhD
Director, EDQM, Council of Europe

2021 at a glance

Outreach

31
events organised

10 000+
attendees from over
60
countries

4 500+
views of recorded sessions

6
new publications

Ph. Eur. Commission members and observers (2021)

* TFDA: Taiwan Food and Drug Administration; WHO: World Health Organization

European Pharmacopoeia activities

Selected European Pharmacopoeia texts adopted in 2021

Two monographs elaborated under the P4 procedure in close collaboration with the innovator: *Deferasirox dispersible tablets (2934)* and *Teriflunomide tablets (3037)*.

Four new general chapters: *Monographs on essential oils (5.30), Implementation of pharmacopoeial procedures (5.26), Assay of Bet v1 allergen (2.7.36)* and *Microbiological examination of human tissues (2.6.39).*

Rapid implementation of the revised monographs on sartans with a tetrazole ring, namely *Valsartan (2423)*, *Losartan potassium (2232)*, *Irbesartan (2465), Candesartan cilexetil (2573)* and *Olmesartan medoxomil (2600),* to align them with the latest regulatory recommendations issued by the CHMP on the EMA website (13 November 2020).

Other revised texts: *Raman Spectroscopy (2.2.48)*, *Vaccines for veterinary use (0062)*, *Chromatographic separation techniques (2.2.46)* and *Liquid preparations for cutaneous application (0927).*

Suspension of monograph *Gonadotrophin, equine serum, for veterinary use (0719).*

Biological Standardisation Programme achievements

Total number of projects **16**

Concluded projects **2**

Projects still running **14**

Standard Terms Database Key figures

Registered users **36 000**

Individual standard terms concepts **1 035**

Entries **29 500**

Reference standards

99% RS portfolio availability ensured

1.4 million+ vials produced

550+ batches produced

Batches of Ph. Eur. RSs adopted in 2021

New RSs	Replacement RS batches adopted	Countries to which EDQM distributed RSs directly	Number of RSs available
60	**329**	**132**	**3114**

Certification of Suitability to the European Pharmacopoeia monographs (CEP)

Total valid and issued CEPs in 2021

New certificates **269**

Revised certificates **1471**

Valid certificates **> 5600**

Official Medicines Control Laboratories (OMCLs)

The OMCL Network general activities

Mutual Joint Audits (MJAs) conducted	14
Proficiency Testing Scheme (PTS) studies carried out	10
Market Surveillance Studies (MSSs) launched	2

European Paediatric Formulary

PaedForm Online Platform

New users 187

Registered users 1155

Substances of human origin

Organs, tissues and cells

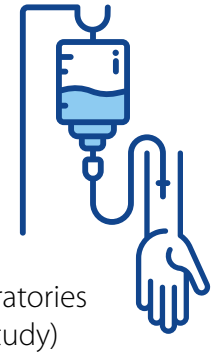
Registry of International Travel for Transplantation Activity (RITTA)

34
designated national focal points (NFPs)

Information from almost

600
patients included

Blood transfusion



6
B-PTS studies conducted

53
participating laboratories (on average, per study)

Nucleic Amplification Technique (NAT)

B-PTS056 HBV/HCV/HIV NAT

Serology

B-PTS057 anti-HCV
B-PTS058 anti-HIV/p24
B-PTS059 anti-Treponema
B-PTS060 HBsAg/Anti-HBc

Immuno-haematology

B-PTS061 ABO, Rhesus, Kell, extended phenotyping and irregular antibodies

Quality management system (QMS)

The EDQM continued to invest in its QMS as a priority matter in 2021, with a specific focus on European Pharmacopoeia reference standards. While the organisation also worked to improve its ISO 9001 compliance, the audit by the certification body for the renewal of its ISO 9001 certificate was postponed to early 2022. Its ISO 17025:2017 accreditation was confirmed subsequent to audits by the responsible body, and the EDQM is now accredited for 21 tests, including nuclear magnetic resonance spectroscopy (NMR) and quantitative nuclear magnetic resonance spectroscopy (qNMR). The EDQM's customers and stakeholders can therefore rest assured of the consistent quality of the goods and services it provides, as well as its commitment not only to maintain, but also to continuously improve quality standards for all its activities.

Co-operation with international partners

The EDQM places high value on its co-operation with a range of international partners. None of its activities would be possible without the support of national pharmacopoeia authorities (NPAs), national competent authorities (NCAs), Official Medicines Control Laboratories (OMCLs), inspectorates and more than 2 000 experts in pharmaceutical sciences and practices, as well as specialists in healthcare issues such as blood transfusion, organ transplantation and quality of cosmetics and food contact materials, from around the globe. Similarly, as an integral part of the European regulatory network, the EDQM meets and collaborates regularly with national regulatory authorities and the European Commission, as well as its technical agencies, such as the European Medicines Agency (EMA).

Co-operation with national authorities

Representatives of NCAs are members of the Ph. Eur. Commission and its 59 expert groups and working parties. NCAs also take part in the work of the Ph. Eur. by submitting requests for revision and reviewing draft texts published in *Pharmeuropa* online.

Communication with NPAs of Ph. Eur. member states was strengthened in 2020 to support authorities in the context of the COVID-19 pandemic, initially via weekly meetings but moving to monthly meetings after the summer break and into 2021.

The 2021 annual meeting of NPAs, initially foreseen to take place in Helsinki, was replaced by a virtual meeting (see "European Pharmacopoeia", below).

The General European OMCL Network (GEON) Annual General Meeting, originally planned as a face-to-face meeting in Oslo, Norway, was held as a web conference from 6 to 10 September 2021. The online format enabled a larger audience to attend with, in all, about 500 participants joining the different sessions over the conference week (see also "The European Network of Medicines Control Laboratories", below).

NCAs represent their member states in the eight intergovernmental committees for which the EDQM ensures the secretariat, and in this capacity contributed in 2021 to the elaboration of the deliverables of these committees in the form of recommendations or resolutions adopted by the Committee of Ministers of the Council of Europe or guidance documents.

The EDQM has observer status to the Heads of Medicines Agencies (HMA), the network of the heads of the NCAs whose organisations are responsible for the regulation of medicinal products for human and veterinary use in the European Economic Area. In particular, in 2021 the EDQM continued to work with the HMA Working Group of Enforcement Officers (HMA-WGEO) on the issue of falsified medicines and contributed to in-depth discussions with the Task Force on Non-Prescription Medicinal Products to explore convergence on classification of medicines as regards their supply. The EDQM is also a member of its Working Group of Quality Managers (WGQM).

Involvement in international harmonisation

Globalisation and expansion in international trade have created a growing need to develop global quality standards for medicines. The EDQM has a long-established collaboration with sister pharmacopoeias to harmonise pharmacopoeial monographs. The most prominent example in this area is the Pharmacopoeial Discussion Group (PDG), jointly run with the United States Pharmacopeia (USP) and the Japanese Pharmacopoeia (JP), with the World Health Organization (WHO) and its International Pharmacopoeia as observers.

In addition, the EDQM has played a crucial role in the drafting of a Good Pharmacopoeial Practices guide and its annexes, under the auspices of the WHO International Meeting of World Pharmacopoeias (IMWP) platform, since its inception in 2012.

The EDQM represents the Ph. Eur. within these initiatives. All the relevant groups of experts and working parties of the Ph. Eur. are involved (see also "The European Pharmacopoeia", below).

The EDQM also participates in the Innovative Medicines Initiative's (IMI) VAC2VAC ("vaccine batch to vaccine batch comparison by consistency testing") project by contributing to its Scientific and Ethics Advisory board. The overall objective of the project is to provide proof of concept of the consistency approach for batch release testing of established vaccines with the target of replacing some of the *in vivo* methods still used to test human and veterinary vaccines. The *in vitro* methods developed and qualified/validated within the initiative may be further evaluated through their inclusion in the Biological Standardisation Programme (BSP) and ultimately included in the Ph. Eur. depending on the outcome of the BSP studies.

The EDQM also participates in another global international harmonisation effort aimed at finding alternatives to the use of animals to test biological products. This effort is led by the National Centre for the Replacement, Refinement & Reduction of Animals in Research (NC3Rs, UK) on behalf of WHO with a view to integrating the 3R principles into WHO guidelines. The EDQM contributes to the NC3Rs working group and focus groups in order to promote the use of EDQM 3R achievements and ongoing 3R activities as a basis for further revisions of the WHO guidelines.

In addition, the EDQM continues to play an active role in international harmonisation and collaboration activities and has observer status to the ICH Assembly. EDQM scientists actively participate in the development and revision of ICH guidelines that are important for the quality of medicines, including guidelines Q3C, Q3D, Q3E, Q2/Q14, Q5A, Q9 and Q13, and play an important role in ICH discussion forums such as the Quality Discussion Group (QDG) and the Generics Discussion Group (GDG). Participating in the QDG is of particular strategic relevance for the EDQM as this group is a think-tank for matters related to the quality of medicines and associated harmonised guidance for the ICH Management Committee and Assembly.

The same holds true for the EDQM's engagement in the International Pharmaceutical Regulators Program (IPRP), where the organisation is an observer to the Management Committee and co-chairs the Quality Working Group.

The EDQM is also involved in the veterinary counterpart to the ICH, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Veterinary Use (VICH), and the Pharmaceutical Inspection Co-operation Scheme (PIC/S) (see also "Certification of suitability to the Ph. Eur. monographs" and "Blood transfusion", below).

All the activities in the eight intergovernmental committees are geared towards encouraging member states to implement harmonised guidance. Efforts in 2021 included harmonisation work in the field of pharmaceutical care through discussions with the South-East European Health Network (SEEHN) and with the Organisation for Economic Co-operation and Development (OECD) on the application of Resolution CM/Res(2020)3 on the implementation of pharmaceutical care for the benefit of patients and health.

With their positive impact on the availability and use of good quality medicines and healthcare worldwide, these are obviously an important and valuable part of the EDQM's activities.

The EDQM works with internationally renowned experts to regularly review and update common technical standards in the field of substances of human origin (SoHO), such as the *Guide for the preparation, use and quality assurance of blood components* (commonly referred to as the "Blood Guide") and Good Practice Guidelines for blood establishments (GPGs for BEs), the *Guide to the quality and safety of tissues and cells for human application* and the *Guide to the quality and safety of organs for transplantation*. The GPGs are now referenced in Commission Directive 2016/1214, ensuring that BEs in all EU/EEA member states take into account the standards and specifications set out in the GPGs when implementing their quality systems.

These reference works are internationally recognised as gold standards in the field.

In addition, to ensure consistency in approaches, the EDQM plays an active role in the work of the United Nations Office on Drugs and Crime (UNODC) with regard to the fight against organ trafficking.

Co-operation with the EU

The EDQM works closely with the European Commission, communicating regularly to share information on current developments in work programmes and potential developments in EU legislation.

It is also a member of the European Union Network Data Board (EUNDB), created at the end of 2014 and co-chaired by the EMA and an NCA, and of the

International Standards on Identification of Medicinal Products in the EU Task Force (EU ISO IDMP, created in 2015), including the corresponding subordinate groups.

The EDQM works closely with the EMA and national authorities to ensure continued consistency with the approaches of licensing authorities, for example regarding the Ph. Eur. and Certification activities. It has observer status with a number of EMA bodies, including the Committee for Advanced Therapies (CAT), the Herbal Medicinal Products Committee (HMPC), the joint CHMP/CVMP Quality Working Party (QWP), the Good Manufacturing and Distribution Practice Inspectors Working Group (GMDP IWG), the Biologics Working Party (BWP) and the Immunologicals Working Party (IWP). Members of EMA working groups (for which the EMA provides the secretariat) or of the EMA Secretariat itself are observers to some of the Ph. Eur. Commission's groups of experts and working parties, for example 6B (human blood and blood products), 15 and 15V (vaccines and sera for human use and veterinary use), and the BSP Steering Committee.

The EDQM and the EMA communicate regularly on the Certification procedure: the EMA is a member of the Certification Steering Committee, and channels for regular communication are in place for the inspection programme and its outcomes.

The EDQM and the EMA continue to collaborate on operating a long-established Centrally Authorised Product (CAP) Sampling and Testing Programme for products for human and veterinary use (see also "The European Network of Medicines Control Laboratories", below).

The EDQM also continues its close technical collaboration with the European Commission, through its co-ordination of a number of SoHO activities: the Blood Quality Management (B-QM) and Blood Proficiency Testing Scheme (B-PTS) Programmes, the Blood Supply Contingency and Emergency Plan (B-SCEP) Project, the Quality Management and Serious Adverse Reactions and Events (SARE) training sessions in the field of tissues and cells, the project on Harmonising Activity Data Collection Exercises in the Field of Tissues and Cells in Europe, and through its analysis of and reporting on the EU SARE related to blood components and tissues and cells.

In 2021, the EDQM actively participated and contributed to the impact assessment and stakeholder consultation and workshops, organised by the European Commission, on the revision of the EU blood legislation. It is expected that the EDQM will become an expert body in the revision process.

The EDQM continues to participate as an observer at meetings of the EU NCAs for blood, tissues and cells, and organs. National authorities also take part in the work of the European Steering Committee on Blood Transfusion (CD-P-TS) and the European Steering Committee on Organ Transplantation (CD-P-TO) through their participation where nominated as steering committee members and through their submissions in the consultation for the guides on blood, tissues and cells, and organs. In addition, to ensure consistency in approaches, the EDQM actively participates in the EMA work cluster on blood products.

Co-operation on inspections

In 2021, the EDQM's Certification Department continued to be involved in the International API Inspection Programme (co-ordinated by the EMA) and the Pharmaceutical Inspection Co-operation Scheme (PIC/S).

The EDQM also participated in the PIC/S Expert Circle on Human Blood, Tissues and Cells in the context of the revision of the "PIC/S GMP Guide for Blood Establishments" and ensured that the revised document published by PIC/S is harmonised with the text of the GPGs for BEs.

As was the case for many supervisory authorities worldwide, the COVID-19 pandemic continued to affect the EDQM Good Manufacturing Practice (GMP) inspection programme for manufacturers of active substances, because on-site inspections could not be performed. In response to this situation, the EDQM extended its programme of real-time remote inspections (RTEMIS) in collaboration with national inspectorates.

Co-operation with WHO

The EDQM co-operates extensively with WHO in a number of joint meetings and consultations. WHO is an observer to the Ph. Eur. Commission, while the EDQM:

- is an observer to the WHO Programme on International Nonproprietary Names (INNs, used in Ph. Eur. monographs);
- takes part in the WHO Expert Committee on Biological Standardization, with WHO participating as an observer in the meetings of the EDQM BSP Steering Committee, thus guaranteeing a smooth exchange of information;
- participates in the WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) (see also "Reference standards", below);
- plays a role in the WHO drafting group (oral polio vaccine) and the WHO working groups (messenger ribonucleic acid vaccines, etc.) to provide expertise on related topics;
- shares data and joint inspections relating to the API Certification process.

The IMWP elaborated and published two IMWP monographs: one on *Favipiravir* and one on *Favipiravir tablets*. These monographs are an outcome of the pharmacopoeial alert system, which was established in 2019 at the 9th IMWP in Da Nang (Vietnam) to ensure pharmacopoeias work together in any relevant public health crisis. The main purpose of the IMWP monographs is to ensure that test specifications are available free of charge for those who need them in an emergency, such as the current pandemic. The IMWP monographs can be used to control the quality of the substances and medicinal products they cover and can be one of the tools used to help prevent the circulation of substandard and falsified products. They are not intended to become official standards (although they could be used as a basis for future standards) or legally binding. The IMWP monographs on *Favipiravir* and on *Favipiravir tablets* were made publicly available and can be used on a voluntary basis.

The EDQM is responsible for establishing, monitoring and distributing WHO International Standards for Antibiotics (ISAs) and International Chemical Reference Substances (ICRSs) (for more details, see "Reference standards", below).

The EDQM also contributes to the activities of the COVID-19 Vaccines Global Access (COVAX) Regulatory Advisory Group (RAG),[1] in particular by providing expertise on the testing of COVID-19 vaccines, linked to its activities in the field of Official Control Authority Batch Release (OCABR) and quality assurance in vaccine manufacturing and testing. The Coalition for Epidemic Preparedness Innovations (CEPI), Gavi and WHO co-lead COVAX, with the United Nations Children's Fund (Unicef) as a key delivery partner, to ensure equitable access to COVID-19 vaccines.

The EDQM also collaborates with WHO in the fields of pharmaceuticals, pharmaceutical care, blood transfusion and organ transplantation. In particular, discussions took place with WHO on the model for Single Points of Contact as described in the MEDICRIME Convention on falsified medical products and the WHO network of national focal points dealing with incidents linked with falsified medicines.

Co-operation with other stakeholders

Stakeholders are consulted during the elaboration of standards by the intergovernmental committees under the responsibility of the EDQM. The consultation process takes place either within drafting groups, involving experts representing the stakeholders comprehensively in a given field, or through survey-based consultations with targeted stakeholders, including with patient and donor associations.

The EDQM continues to hold annual bilateral meetings with industry associations to promote exchanges on all aspects related to the work of the EDQM and to collect feedback on its activities. Since the beginning of the health crisis, the EDQM has also organised regular meetings with all European industry organisations to keep them informed about the EDQM's business continuity plan and operating framework, and to discuss how the EDQM could help the pharmaceutical industry ensure a continued supply of quality medicines and support developers of COVID-19-related vaccines and medicines.

The EDQM held two webinars on *N*-nitrosamine impurities to share the latest updates with stakeholders and to present approaches for CEPs and the Ph. Eur. strategy with regard to nitrosamine control.

1. See https://epi.tghn.org/covax-overview/regulatory-advisory-group.

Initiatives in the context of COVID-19

Availability of and access to safe, quality medicines for patients is more important than ever in the context of the current COVID-19 pandemic. This is why the EDQM has prioritised the continuous supply of its products and services to support public health protection.

In addition, the EDQM has openly shared knowledge, thus demonstrating its commitment to supporting competent authorities, health professionals, and manufacturers and developers of medicines and vaccines, as well as to universities and research centres contributing to the wider global effort to combat the virus.

Vaccine and therapy guidance, quality standards, European quality control programme for COVID-19 vaccines and training

The EDQM has provided support in the form of guidance documents, quality standards and training materials, among others, since efforts to develop COVID-19 vaccines began.

Official Control Authority Batch Release

To prepare for independent batch controls by Official Medicines Control Laboratories (OMCLs) before release for authorised COVID-19 vaccines, the EDQM mobilised the EU OCABR Network members and facilitated early exchanges with manufacturers. A recommendation document for manufacturers on early method transfer and an OMCL competency list, based on control techniques for the different categories of COVID-19 vaccine candidates, were released initially in July 2020 and were supplied to manufacturers on request throughout 2021. The competency list was updated twice in 2021 to help manufacturers identify OMCLs with the relevant skill sets.

Three new OCABR guidelines outlining the tests to be performed by OMCLs in the EU OCABR Network and providing model protocols for manufacturers were also released. These guidelines were published at an early stage for transparency and to help anticipate the launch of each vaccine, thus allowing OMCLs and manufacturers to take the necessary steps to prepare for OCABR and preventing delays while still ensuring their quality and safety. Thanks to efficient interaction with the manufacturers and the use of parallel testing, OCABR certification did not delay the vaccines reaching patients. Over the course of 2021, OMCLs released more than 1 600 lots – representing billions of doses – of the four COVID-19 vaccines conditionally approved in the EU combined. EU OCABR certificates issued for compliant lots provided an assurance of quality for patients in the EU/EEA and beyond.

The European Pharmacopoeia

In 2021, the European Pharmacopoeia (Ph. Eur.) continued to deliver on its mission of ensuring that regulators, manufacturers and other stakeholders from Europe and beyond have timely access to relevant, up-to-date, legally binding and harmonised European standards. The foundations laid in early 2020 – before the pandemic swept the globe – supported the deployment of more agile, flexible and digital working methods in 2021, allowing a "business-as-usual" outlook to be maintained when e-working was, by necessity, massively adopted. These changes were further supported by an internal reorganisation allowing a seamless transition to the new processes, with enhanced traceability and efficiency.

The Ph. Eur. and its groups of experts and working parties revised existing monographs to incorporate newly developed analytical procedures and techniques and reflect approved products on the European market. New texts were elaborated for products of high market relevance and emerging domains. The three Ph. Eur. Commission sessions in March, June and November were held online: 18 new monographs, four new general chapters and 204 revised texts were adopted over the year. Group meetings were also held as scheduled, albeit online, and the contribution of the 59 active expert groups and working parties – whose approx. 830 experts volunteer their skills, experience and knowledge during the elaboration of Ph. Eur. science-based and data-driven quality standards – was, as always, remarkable. While no new groups were set up by the Commission in 2021, the recently created BACT Working Party (Bacteriophages) met for the first time to assess the feasibility, applicability and consequences of elaborating a general chapter that sets quality standards in the emerging field of bacteriophage active substances.

The Ph. Eur. also continued to nurture its close relationship with NPAs through monthly meetings, acknowledging the importance of co-operation and dialogue in an increasingly complex and global regulatory landscape, particularly during a worldwide health crisis.

The year 2021 marked the end of the publication cycle for the 10th Edition of the Ph. Eur. The challenges of the last two years notwithstanding, with the addition of the texts adopted at the 171st session of the Ph. Eur. Commission that will be published in the 11th Edition, the Ph. Eur. comprises 2 469 monographs, 386 general chapters and more than 2 800 reagent descriptions.

Wide participation

Despite the many constraints of the pandemic – not least the embargo on international travel – and its widespread impact on global activities, the EDQM and Ph. Eur. continued to reach out to users by organising a series of webinars that attracted unprecedentedly high numbers of attendees. With participants from far beyond the boundaries of Europe (many of whom were attending a Ph. Eur. event for the first time), these truly global events allowed the Ph. Eur. to maintain, reaffirm and refresh the role played by its quality standards in public health protection. In addition to these topic-specific events, three general Ph. Eur. training sessions were also held as simulive webinars, which combine a pre-recorded presentation with live interaction on the broadcast date. The format, accessibility and high educational value of all 2021's webinars were universally praised.

An extremely successful webinar was held in April, entitled "Using recombinant factor C (rFC) for bacterial endotoxin testing in the Ph. Eur.: how far have we come, how far have we to go?". It was intended to support users with the implementation of the new rFC chapter: *Test for bacterial endotoxins using recombinant factor C (2.6.32)*. This test may be chosen instead of the current test for bacterial endotoxins

that describes the use of a lysate for which there is currently only one source, 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. Other widely acclaimed events included, in May, a webinar on impurity control in the Ph. Eur., again attracting an audience of over 1 000; by popular demand, this session was repeated in June, reaching an additional 1 100 users and other interested parties. The year closed with, in December, "Particulate contamination in parenteral preparations: what's new in the Ph. Eur.?", also to support users with the implementation of new requirements and, in response to comments received, clarify the meaning of "practically-free from particles".

During the extremely challenging conditions of 2021, these webinars enabled the Ph. Eur. to build on its reputation as a pragmatic and trusted partner of all stakeholders involved in the medicinal product supply chain and to maintain and even increase its visibility and impact worldwide.

Work programme

3R principles

The Ph. Eur. Commission continued its efforts to promote the 3R principles of replacing, reducing and refining the use of animals in scientific procedures when it agreed, at its 170th session in June 2021, to engage on a path that should gradually lead to the complete phasing-out of the rabbit pyrogen test (RPT) in the Ph. Eur. within approximately five years.

The Ph. Eur. test for pyrogens (general chapter *2.6.8*) consists of measuring the rise in body temperature evoked in rabbits by the intravenous injection of a sterile solution of the substance to be examined. It was first published in the Ph. Eur. in 1986.

The majority of pyrogens are bacterial endotoxins and these can be detected using the bacterial endotoxins test (BET) described in Ph. Eur. general chapters *2.6.14. Bacterial endotoxins* and *2.6.32. Test for bacterial endotoxins using recombinant factor C*. However, in some cases, non-endotoxin pyrogens may also be present and these are not detected by the BET. A test covering all types of pyrogens is therefore required to confirm the absence of non-endotoxin pyrogens.

General chapter *2.6.30. Monocyte-activation test* (MAT) was added to the Ph. Eur. in 2009, providing an *in vitro* alternative to the RPT that is capable of detecting both endotoxin and non-endotoxin pyrogens. The publication of this chapter was a significant step forward in terms of animal welfare, in accordance with the Council of Europe's European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes.

However, despite multiple efforts since then to encourage developers to apply the MAT instead of the RPT, rabbits continue to be used extensively to detect pyrogenic substances.

Fifty-nine Ph. Eur. texts refer to the RPT; all will be affected by this large-scale project since the Ph. Eur. is committed to replacing the current test for pyrogens with a suitable *in vitro* alternative. The ultimate goal is the complete elimination of the RPT from the Ph. Eur. In the meantime, users are actively encouraged to seek alternatives to chapter *2.6.8*, the preferred option being the MAT.

Oxygen

After much discussion and debate in the course of 2020 prompted by the COVID-19 pandemic and the sudden rise in global oxygen requirements, a new draft monograph, *Oxygen (98 per cent) (3098)*, was published for comment in *Pharmeuropa* (33.4, September 2021), the Ph. Eur. online forum.

The Ph. Eur. already has two monographs on oxygen, *Oxygen (0417)* and *Oxygen (93 per cent) (2455)*, published over 50 and 11 years ago, respectively. The new monograph describes an additional quality produced by two-stage concentrators that could provide a pragmatic solution to potential oxygen shortages. The draft monograph is the outcome of a thorough examination of the substantial response to the request for feedback issued in April 2020 that prompted lively and constructive discussions with regulatory experts in the field, as well as a series of dedicated Ph. Eur. expert meetings. The input representing different standpoints from a diverse range of stakeholders, including regulators, hospital pharmacists, industry representatives (gas producers and producers of oxygen-generating equipment) and academics, allowed participants to approach the topic with the highest level of expertise. Depending on the feedback received during the public consultation phase that closed at the end of 2021, the new monograph – modified if necessary – will be submitted for adoption in 2022.

General Notices

The Ph. Eur. *General Notices* (chapter *1*), the vade mecum chapter that provides detailed insight into how to interpret and use the Ph. Eur. as a whole, underwent a major overhaul in 2020, and the revised text was finally adopted at the 169th session of the Ph. Eur. Commission (March 2021).

The aim was to provide greater clarity for users, with both the structure and content of the chapter coming under scrutiny and the terminology adjusted in accordance with internationally recognised

guidelines. The new-look chapter features additions such as a section on monographs for medicinal products containing chemically defined active substances, reproducing the paragraphs on dissolution and disintegration as adopted by the Ph. Eur. Commission in November 2020. This new section also provides information on related substances and impurities taken from the relevant technical guide (*Technical Guide for the elaboration of monographs on medicinal products containing chemically defined active substances,* 2020).

The wording and terminology have been harmonised and clarified, with potentially confusing synonyms weeded out (for example, "medicinal product" selected over the formerly interchangeable "finished product" and "pharmaceutical preparation").

Further terminological changes include "shelf life" and "re-test period" instead of "period of validity" and "period of use", in accordance with the ICH guidelines. Definitions have also been added for "freshly prepared solution" and "immediately before use".

The scope of the first and second identification series and of alternative identifications described in monographs has been clarified and several changes, including an explanation of the rounding rule and information on chiral substances, have been introduced in the tests and assays section of the *General Notices*.

Lastly, all the paragraphs concerning monographs on herbal drugs that were previously dispersed throughout the text are now gathered together in a single section for enhanced readability.

Other successes

General methods and chapters continue to form the backbone of the Ph. Eur. and a landmark achievement was the adoption, at the 171st session of the Commission in November 2021, of a new version of *2.2.46. Chromatographic separation techniques*. This chapter has relevance for the vast majority of Ph. Eur. monographs as chromatographic separation techniques are fundamental in the quality control of pharmaceutical substances and preparations and are therefore among the most widely used methods. The text was revised to take account of the pharmacopoeial harmonisation text, signed-off on 28 September 2021 by the Pharmacopoeial Discussion Group, comprising the European, Japanese and US Pharmacopoeias with WHO as observer (see "Cooperation with international partners", above), and its adoption is a significant success since it has been on the work programme since 2009. The final consensus on the new technical content and wording had been long awaited.

The harmonised requirements included in the chapter promote the development of individual monographs with a consistent approach and enhance understanding of basic requirements by users in all three PDG regions.

Three new general chapters were also adopted at the 171st session. *Implementation of pharmacopoeial procedures (5.26)* elaborates on the requirement expressed succinctly in the *General Notices*, instructing users to assess whether and to what extent the suitability of the pharmacopoeial procedure under the actual conditions of use needs to be demonstrated in compliance with relevant monographs, general chapters and quality systems. The second, *Assay of Bet v 1 allergen (2.7.36)*, provides standardised test methods for the determination of birch pollen allergen content (useful in the diagnosis and treatment of the extremely common birch pollen allergy). Lastly, *Microbiological examination of human tissues (2.6.39)*, provides recommendations on the selection of analytical methods for the assessment of the microbiological quality of human tissues These chapters will be published in the 11th Edition of the Ph. Eur. (July 2022), and have an implementation date of 1 January 2023.

Essential oils

The Ph. Eur. also continues to recognise the role and popularity of natural remedies in the traditional medicines arsenal with numerous new individual monographs adopted in 2021. As is the case with any medicines, there is a need to ensure that users can safely place their trust in the quality of these products and the starting materials used in their manufacture. To this end, the general monograph on *Essential oils (2098)* was revised, with many of the sections, notably the definition, production, test and labelling sections, expanded to include more detail and clarity. The text now also offers more information concerning the herbal drugs and quality of water to be used for the preparation of essential oils and gives requirements for heavy metals *(2.4.27)*, pesticide residues *(2.8.13)*, aflatoxin B1 *(2.8.18)* and microbiological quality *(5.1.4* or *5.1.8)*. In a similar vein, a new chapter, *Monographs on essential oils (information chapter) (5.30)*, was elaborated, providing underlying principles for the elaboration of monographs on essential oils, with details of production methods, chromatographic profiles and potential contaminants. Both were adopted at the 169th session of the Commission (March 2021).

Pyrrolizidine alkaloids

After its adoption by the Commission in November 2020, the new general chapter *Contaminant pyrrolizidine alkaloids (2.8.26)* was published in Ph. Eur. Supplement 10.6 on 1 July 2021, with an implementation date of 1 January 2022. The chapter was elaborated to address the demands of European regulators following reports in some Ph. Eur. member states of contamination of herbal medicinal products (HMPs) and foods with pyrrolizidine alkaloids (PAs). The text

describes 28 target PAs and allows for the use of any procedure consisting of chromatography coupled with tandem mass spectrometry (MS/MS) or high-resolution mass spectrometry that meets the validation requirements given in the chapter.

Joint programmes

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

In 2021, the programme ran 16 projects in different fields, from vaccines for human and veterinary use to plasma-derived and biotechnology products. Two were concluded during the year, leading to the establishment of replacement reference standards (see "Reference standards", below).

The EDQM carried forward another seven projects aimed at establishing replacement batches for existing reference standards and two for a new reference standard for biologicals.

Five ongoing projects focused on the development of new compendial methods. Four of these projects are dedicated to applying the 3R principles to the field of quality control of biologicals.

The virtual workshop "Novel *in vitro* model as alternative to *in vivo* toxoid vaccines testing: Clostridium septicum vaccine as proof of concept" presented the successful outcome of a BSP project in this context to a broad audience from industry and regulators.

Standard Terms database

Initially drawn up at the request of the European Commission for use in marketing authorisation applications, the Standard Terms database 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.

International co-operation and harmonisation initiatives

The Pharmacopoeial Discussion Group

Since it was founded in 1989, the PDG has successfully harmonised and maintained 29 general chapters, including important analytical procedures such as *Dissolution Testing, Sterility, Microbiological Examination* and, recently, *Chromatography*. The Group has also harmonised 48 excipient monographs and has 12 additional texts in the pipeline.

The major development for the PDG in 2021 was the decision to launch a pilot project aimed at integrating other world pharmacopoeias. This is a critical step in the PDG's commitment to expanding recognition of harmonised pharmacopoeial standards with a view to achieving global convergence.

The project structure was defined and endorsed by the Group in a series of preparatory meetings in 2021, and a detailed plan for extension with entry criteria for applicant members drawn up. This plan will help ensure that the successes of the past 32 years are not compromised by expansion beyond the three founders and that the current pharmacopoeial harmonisation model can continue to work effectively with new members. The PDG will further adjust its working methods based on the lessons learnt after the expansion procedure is rolled out.

This project marks a new departure for the Group and is a major milestone in its history. The aim is to extend the PDG's significant success story to further jurisdictions/regions and to create an inclusive global platform from which to elaborate robust, harmonised and science-based pharmacopoeial standards.

The final sign-off of the harmonised general chapter *Chromatography* took place on 28 September 2021. This is another significant and long-awaited accomplishment since the chapter had been on the PDG work programme since 2009, after the need for harmonisation was identified during a joint PDG–industry meeting. Although the chapters in question differed in content and format, it was considered feasible to develop a chapter describing *core requirements* applicable for TLC, HPLC and GC while leaving aside more general (textbook-style) descriptions as each of the PDG pharmacopoeias has its own approach, decided at regional level.

The harmonised chapter will be published as *2.2.46. Chromatographic separation techniques* in the 11th Edition of the Ph. Eur. which will be available in July 2022 (implementation date: 1 January 2023).

Reference standards

The EDQM ensures the supply of its reference standards (RSs) to help safeguard the availability of quality medicines in Europe and beyond. Official reference standards are an integral part of the Ph. Eur. since they are used in conjunction with Ph. Eur. documentary standards to perform the analytical procedures described in monographs. The EDQM distributes its RSs worldwide 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.

Activities

Following an in-depth risk analysis, the EDQM launched the construction of a secondary site in Ars-Laquenexy (near Metz, France). The facility was inaugurated at the end of 2019 and commissioned in 2020. Its primary purpose is to secure the storage and shipment of reference standards should a problem arise in the main building in Strasbourg.

The secondary site is now up and running and it currently houses almost one million vials of reference standards that have been transferred from the main building. Transfer will continue in 2022 with temperature-regulated standards and those regulated for road transport.

The Ph. Eur. reference standard portfolio consists of 3 114 RSs. In 2021, the European Pharmacopoeia Commission adopted 384 reference standards based on establishment reports submitted by the EDQM Laboratory.

The EDQM distributed Ph. Eur. RSs directly to 132 countries in 2021 (123 in 2020).

Joint programmes

The international collaborative studies (co-funded by the European Union) performed as part of the BSP led, in 2021, to the adoption of two replacement batches (BSP155 and BSP160).

International co-operation

Collaboration with WHO

The EDQM is responsible for establishing, manufacturing, monitoring and distributing WHO ICRSs. Currently, the ICRS catalogue consists of 217 reference standards. ICRSs are used worldwide in conjunction with the texts of the International Pharmacopoeia, which is published and maintained by the WHO ECSPP.

In 2021, the WHO ECSPP adopted two new ICRSs and two replacement ICRSs, based on establishment reports submitted by the EDQM Laboratory.

The EDQM is also responsible for establishing, manufacturing, storing and distributing WHO ISAs, which are essential for the standardisation and quality control of antibiotic drug substances and medicinal products. There are currently 23 reference standards in the ISA catalogue.

Collaboration with ISO

The EDQM participated as liaison organisation in the activities of ISO TC 334, the ISO Technical Committee on Reference Materials.

Collaboration with national laboratories

The EDQM Laboratory can count on a number of official laboratories for support when collaborative studies are required for the establishment of Ph. Eur. reference standards. In 2021, 32 OMCLs, representing 25 countries, enrolled in such RS establishment studies.

Publications, databases and website

Throughout 2021, the EDQM continued to run and maintain its Reference Standards Online Database (https://crs.edqm.eu), 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 (SDSs) and Biological Safety Data Statements, as well as leaflets, are also available in the EDQM's online database.

In 2021, the EDQM issued 570 leaflets providing RS users with additional information, such as a chromatogram or assigned value, for a given substance.

Certification of suitability to the Ph. Eur. monographs

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. Extra-European production of pharmaceutical ingredients has become increasingly common as the world's economies continue to evolve, creating challenges for the monitoring and quality control of substances used in the manufacture of medicines.

Activities

New and revised Certificates of suitability granted

In 2021, the EDQM received 412 new CEP applications (+14% over 2020) and more than 1 880 CEP revision requests (+19%). Some 269 new certificates (+20%) and 1 471 revised certificates (+3%) were issued. As of 31 December 2021, there were more than 5 600 valid CEPs covering chemical purity, transmissible spongiform encephalopathy (TSE) and herbal drug preparations.

Processing times were impacted both by the increase in requests (new dossiers and revisions) and by the inability of quality experts from competent authorities to support the EDQM's Certification Department in the assessment of dossiers due to the COVID-19 pandemic. For these reasons, the EDQM was still treating CEP applications with delays at the end of 2021.

In October 2021, the EDQM's Certification Department implemented a new IT tool for the management of its activities. This entailed changes to both the handling of CEP applications and how the EDQM communicates with applicants and CEP holders.

CEPs suspended and/or withdrawn

In 2021, 24 CEPs were suspended and/or withdrawn, mainly due to the inability of the respective CEP holders to meet the requirements of the procedure [manu-facturing] for the maintenance of their dossiers, or their inability to address the presence of impurities. On the other hand, nine CEPs were restored following the success of action taken by companies in response to the suspension of their CEP.

Communication with Ph. Eur. groups of experts: requests for revision

In 2021, 17 requests for revision of Ph. Eur. monographs were submitted to the relevant Ph. Eur. groups of experts for consideration, mainly proposing the addition of specified impurities to the monograph's transparency list, together with a suitable test method.

Inspections carried out and Real-Time Remote Inspections (RTEMIS)

The EDQM GMP inspection programme for active substance manufacturers was, like many supervisory programmes worldwide, again impacted by the COVID-19 pandemic in 2021 because no on-site inspections could be performed. The EDQM extended its pilot programme for real-time remote inspections (RTEMIS) and 11 such inspections were carried out (in India and China). The results obtained were satisfactory, both from a technical point of view and in terms of expected outcomes. The pilot phase was a success and the RTEMIS procedure will be included in the tools used routinely for the supervision of the GMP compliance of manufacturing sites for which CEP applications are submitted. In addition, the EDQM performed desktop assessments for 39 manufacturing sites by exchanging data with inspectorates from international partners. More information is available on the EDQM website (*Medicines > Certification of Suitability > The Inspection Programme*)

Potentially mutagenic azido impurities in sartan active substances

In 2021, the EDQM and health authorities were informed about the possible presence of potentially mutagenic azido impurities in certain sartan active substances. CEP holders concerned were contacted to investigate the issue further.

Measures were taken to ensure that any contaminated active substance with impurities above the acceptable level would not be released onto the market and any impacted holders of a CEP were asked to take corrective action to ensure that such impurities do not exceed their acceptable limits in the future. The EDQM review of these corrective actions has been completed for most manufacturers.

The EDQM has been working closely with the EU regulatory network and international partners to address the issue.

International co-operation

Throughout 2021, the Certification Department continued to work closely with the EMA and NCAs in Europe and beyond. This continued co-operation is crucial to ensuring consistency in the approaches applied for the assessment of quality information pertaining to active substances, as well as for GMP implementation.

Communication with applicants, partners and stakeholders

The "CEP of the future" project

The EDQM continues to work on the "CEP of the future" project, to better fit the emerging needs of stakeholders. An online survey was launched at the end of 2020, the results were analysed and a roadmap was established in 2021. Five areas of work to design the CEP of the future emerged from the survey and the report has been published on the EDQM website ("Outcome of the public consultation on the 'CEP of the future'" (PA/PH/CEP (21) 60).

The European Network of Official Medicines Control Laboratories

The OMCL Network brings together official laboratories based in 36 European member states and in seven non-European partners. Their collective objectives are to ensure the quality of medicines on the market and to prevent substandard and falsified medicinal products from reaching patients and animals and compromising the efficacy of their treatment and potentially their health.

Despite the challenges related to the COVID-19 pandemic, which again made it necessary to reorganise and redeploy resources in 2021, the EDQM successfully continued to co-ordinate activities and carry out the work programme of the General European OMCL Network (GEON), which is partially funded by the EU.

Quality management

Work programme

- *Mutual Joint Audits/Visits (MJA/Vs) and Training Visits (TVs)*

Harmonising QMSs among OMCLs and achieving appropriate quality levels that enable mutual recognition of test results between members (for example, official batch release testing of biologicals, market surveillance of authorised medicines and falsified medicines testing) remain the principal goals of this programme.

In response to the pandemic, the audit programme continued remotely via videoconferences; the initial focus on QMS assessment was expanded to the technical part of the revised ISO/IEC 17025:2017 standard.

Fourteen remote MJAs were carried out in 2021. Since the launch of the QM programme for OMCLs in 1997, a total of 207 MJAs, 53 MJVs and 28 TVs/tutorials have been conducted.

- *Training courses/workshops*

The EDQM organised a workshop for trained auditors to share experience regarding remote audits and the application of the revised ISO standard. A training course for new QMS auditors to enrich the existing pool of MJA auditors was also conducted.

- *Proficiency Testing Scheme studies*

The EDQM PTS provides laboratories with an objective means of assessing and demonstrating the reliability of their data. In 2021, five studies each were organised in the physico-chemical and biological fields.

A specific PTS programme was also co-ordinated by the EDQM in collaboration with WHO, with three studies of the External Quality Assurance Assessment Scheme (EQAAS) finalised in 2021.

International co-operation

The EDQM is a recognised stakeholder of the European Co-operation for Accreditation association (EA) and regularly attends the EA/Laboratory Committee (EA/LC) meetings in order to strengthen collaboration with EA/LC members, clarify technical questions of interest to the OMCL Network related to the interpretation of ISO 17025 requirements, and share experience in the field of auditing.

Publications, databases and website

Common QM guidelines are drafted by experts belonging to the network and updated on a regular basis. Under the co-ordination of the EDQM Secretariat, seven QM guidelines supporting laboratories in the implementation of ISO 17025 requirements were drafted or revised and subsequently adopted by the OMCL Network.

Quality management documents elaborated in 2021

Topic	Status	Guideline/Recommendation document
Annex V to Qualification of Equipment – Qualification of Automatic Titrators	Adopted	Guideline
Management of Volumetric Glassware	Under revision	Guideline
Evaluation and Reporting of Results	Under revision	Guideline
Expiry dates for reagents	Adopted	Recommendation document
General requirements for infrequently performed techniques	Under revision	Guideline
Management of Documents and Records	Adopted	Guideline
Qualification and re-qualification of personnel involved in laboratory activities	Adopted	Guideline

GEON activities

Work programme

- *GEON Annual General Meeting*

The GEON Annual General Meeting was held by webinar in September 2021, gathering a wider audience than usual with about 500 participants overall joining the different sessions organised.

The growing need of the network for specialised testing activities due to the rising complexity of chemical and biological analytical techniques was a common theme throughout the meeting week, where different examples were presented and discussed.

The impact of the pandemic on the work carried out by OMCLs and the network's programmes in 2021 was reflected in several presentations given at the meeting that focussed on different areas including remote MJAs and OCABR of COVID-19 vaccines. The four strategic goals of the network were addressed at the meeting through specific examples.

- *General market surveillance studies*

Two market surveillance studies (MSSs), "Tadalafil drug substance and tablets" (MSS059) and "Breaking of glass ampoules" (MSS061), were launched in 2021.

- *Active Pharmaceutical Ingredients (API) Working Group*

One videoconference was held in 2021 to discuss strategic objectives and the status of ongoing studies and to schedule a new study (MSSFP005 Tadalafil). The results of two fingerprint studies on Omeprazol and Sildenafil were published in scientific journals.[2] The group also worked on a shared API testing plan.

- *OMCL Falsified Medicines Working Group*

The working group met once in 2021. During the meeting, it was decided to launch a new MSS on Selective Androgen Receptor Modulators (SARMs) and related substances.

A CD-P-PH/CMED-OMCL teamwork plan was established and discussed at the CMED meeting in May 2021 and in the OMCL working group meeting in September 2021. Several topics of common interest were identified, such as information exchange on new trends in the field of falsified medicines (see "Anti-Falsification Activities", below, for more information on CMED).

- *Gene Therapy Products Working Group*

The OMCL Gene Therapy Products Working Group (GTWG) is currently composed of 10 OMCLs. Due to the COVID-19 pandemic, resources were re-allocated to more urgent activities, leading to a reduction in the OMCL GTWG activities. Nevertheless, the results of a network survey carried out in 2020 on future needs with regard to resources and financing in the field of gene therapy were presented to the GEON Advisory Group and gave rise to a dedicated session on Gene Therapy Techniques at the OMCL annual meeting. A drafting group has also begun work on a white paper that will include recommendations. The annual meeting was held virtually in December.

International co-operation

The OMCL Falsified Medicines Working Group continued its collaboration with the Customs Laboratories European Network (CLEN).

2. "European fingerprint study on omeprazole drug substances using a multi analytical approach and chemometrics as a tool for the discrimination of manufacturing sources", DOI: 10.1016/j.jpba.2021.114444. "GEONs API fingerprint project: Selection of analytical techniques for clustering of sildenafil citrate API samples", DOI: 10.1016/j.talanta.2021.123123.

Publications, databases and website

After performing several fingerprint studies, the API Working Group decided to publish the results of two studies (Omeprazol and Sildenafil, see footnote 2, above) in scientific journals. The publications focus on the interpretation of analytical results, the benefits of chemometric methodology and the collaboration between laboratories.

The results of an MSS on suspected illegal products (MSSIP) containing non-ATC-INN molecules were published in a scientific journal.[3] A summary of the study was also made available on the EDQM website in June 2021.

CombiStats™ is a recognised reference tool for the statistical analysis of bioassay results, which contributes to the mutual recognition of data and results by all interested parties. In 2021, 921 licences were issued and CombiStats™ was used in 28 countries in Europe and 30 countries in the rest of the world. Training sessions for beginners and advanced users were held as webinars in October, with over 150 participants from 50 countries joining.

EU/EEA-specific activities

Work programme

- *Market surveillance for products with a centralised marketing authorisation*

The Centrally Authorised Product (CAP) Regular programme covers an annual list of products prepared by the EMA Secretariat together with the EMA Scientific Committees and with final input from the OMCL CAP Advisory Group. In 2021, 33 medicinal products for human and six for veterinary use, as well as one API, were scheduled for testing.

The 2021 CAP Generics programme included aripiprazole, olanzapine and rivastigmine products.

The CAP Biosimilar programme comprises three projects to be conducted over a five-year period (2019-2023), covering filgrastim, etanercept and rituximab products.

An additional CAP market surveillance programme focuses on authenticity checks on parallel-distributed products. The list of products of interest is provided on a yearly basis by the EMA. Five products were tested in 2021. The presence of nitrosamines was also checked in a few CAPs.

The results showed that the vast majority of the products tested were of the expected quality and complied with authorised specifications. By 31 December 2021, two out-of-specification results had been found and, together with a few regulatory or technical findings, reported to and followed up by the EMA.

- *Mutual Recognition Procedure/Decentralised Procedure post-marketing surveillance scheme*

The 17th regular programme was carried out in 2021. Some 1 400 product testing projects were covered in this programme. Testing reports for 2021 were issued by 25 different OMCLs and 17% of the tested products were for veterinary use. Regulatory issues were identified in around 4% of projects. In 1.8% of cases, one or more out-of-specification results were reported.

The OMCLs involved in this activity met once in 2021 to evaluate the programme and discuss ways of optimising collaboration.

A new HMA/OMCL network group comprising GMP inspectors, quality assessors and representatives from quality defect units, OMCLs and the EDQM has been created to work on the extension of an existing risk-assessment tool for Mutual Recognition Procedure/Decentralised Procedure (MRP/DCP) products to post-marketing risk factors.

- *OCABR of biologicals for human use*

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.

The human OCABR annual meeting focused on blood products, vaccines and common issues, and provided an opportunity to exchange expertise and optimise resources to solve common problems.

Priority activities in 2021 included maintaining regular batch release to ensure a steady supply of essential medicines – such as childhood vaccines and human clotting factors – to the public, together with the high demand for batch release of approved COVID-19 vaccines and the preparations for new COVID-19 vaccines in development. Thanks to co-ordination within the network and to careful contingency planning by OMCLs, levels of "regular" batch release carried out in 2021 were unaffected. OMCLs evaluated more than 12 600 final batches and screened around 10 000 plasma pools for safety. This included the release of more than 1 600 lots of COVID-19 vaccines, thus independently confirming the products' quality before they reached patients. Further activities linked to COVID-19 vaccines are highlighted in "Initiatives in the context of COVID-19", above.

In 2021, the OCABR Advisory Group broke with its usual schedule, meeting three times instead of the usual two in order to accommodate the change in the OMCL Annual Meeting date from June to Sep-

3. "The occurrence of non-anatomical therapeutic chemical-international nonproprietary name molecules in suspected illegal or illegally traded health products in Europe: A retrospective and prospective study", DOI: 10.1002/dta.3001.

tember. Numerous ad hoc teleconferences were also held over the year. The OCABR Vaccine Drafting Group held numerous ad hoc meetings in addition to the two regular meetings on the schedule. Additional meetings were held with stakeholders from industry and other organisations, such as the Coalition for Epidemic Preparedness Innovations (CEPI) and Vaccines Europe (VE), to foster information sharing and define strategies in preparation for OCABR of COVID-19 candidate vaccines and for OCABR in general.

A workshop to foster harmonised safety testing of oral polio bulks was organised for OMCLs and manufacturers.

The EDQM supported the human OCABR Network and stakeholders for the post-Brexit transition through communication on dedicated pages of the EDQM website.

- *Batch release of immunological veterinary medicinal products*

The Veterinary Batch Release Network (VBRN) Advisory Group also met exceptionally three times in 2021 to move forward on important issues and prepare for the later-than-usual annual meeting in September. The regular Official Batch Protocol Review (OBPR) and OCABR activities for immunological veterinary medicinal products (IVMPs) were largely unaffected by the COVID-19 pandemic conditions thanks to careful planning by the OMCLs. The 2021 annual meeting included elections for three new members of the Advisory Group.

The pilot phase to better co-ordinate activities for post-marketing surveillance was continued with four OMCLs contributing data in 2021.

The Advisory Group actively prepared for the implementation of the new EU veterinary legislation in January 2022 by updating relevant documents and submitting documents with priority status, such as the EU Administrative Procedures for OCABR and OBPR and OCABR product-specific guidelines and protocol templates, to the network for adoption.

International co-operation

In an extension of global co-operation, representatives from the Therapeutic Goods Administration (TGA), Australia, participated as observers for the first time in the closed human OCABR Network, vaccine and common sessions, under the conditions of the memorandum of understanding (MOU) signed with the human OCABR Network in 2020.

In January 2021, following the Brexit transition period, the human OCABR Network signed an MOU on the exchange of confidential information on batch release activities for vaccines and blood derived medicines with the National Institute for Biological Standards and Control (NIBSC, UK). This MOU meant that NIBSC representatives were able to take part in the 2021 annual meeting as observers.

The VBRN accepted a similar MOU application from the Veterinary Medicines Directorate, UK, at the 2021 annual meeting. The MOU agreement was signed in December.

Publications, databases and website

By the cut-off date of 31 December 2021, the MRP/DCP Product Testing Database – set up in 2007 to improve co-operation on planning, sampling and reporting of testing activities carried out on MRP and DCP products within the OMCL Network – held more than 14 500 records, with contributions from 36 different OMCLs. Database access is restricted to OMCLs and health authorities. A special training webinar for OMCL users of the database was held in 2021.

Risk-assessment templates for MRP and DCP products have been regularly transferred to this database since March 2020. The templates, which also include test recommendations, will support planning of market surveillance testing activities in the member states. In 2021, 142 templates were transferred into the database.

Five new and 16 revised guidelines for vaccines for human use came into force.

One new and one revised VBRN guideline also came into force. Updates to the legal references in the Administrative Procedures for OCABR and OBPR, 15 product-specific guidelines and four protocol templates were adopted and circulated, and came into force in line with the legislation implementation date in January 2022.

Response to nitrosamine contamination

Certain types of nitrosamines (*N*-nitrosodiethylamine [NDEA] and *N*-nitrosodimethylamine [NDMA]) were detected in a number of active substances used in the treatment of hypertension and in related medicines in 2018. Nitrosamines are known as possible carcinogens for humans and only very low amounts are acceptable according to current regulatory requirements.

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 at various levels to address this problem, co-operating continually with regulatory authorities at international and EU level. Details of EDQM initiatives concerning nitrosamine contamination can be found below. More information is available on the EDQM's dedicated web page.

Ph. Eur. strategy

Rapid implementation of revised sartan monographs

In February 2021, the Ph. Eur. Commission published five revised monographs on sartans containing a tetrazole ring – namely *Valsartan (2423), Losartan potassium (2232), Irbesartan (2465), Candesartan cilexetil (2573)* and *Olmesartan medoxomil (2600)* – using its rapid-revision procedure, for implementation on 1 April 2021. Revision focussed on keeping Ph. Eur. requirements in line with the latest EMA regulatory decisions, with the "Production" section of the monographs reworded and now including a reference to general chapter *2.5.42.* N-*Nitrosamines in active substances* to assist manufacturers and the *N*-nitrosamines test section deleted. The PDF versions of the texts were published on the EDQM website together with general chapter *2.5.42*, providing analytical procedures to test for the relevant *N*-nitrosamine impurities.

General monographs under revision

The Ph. Eur. Commission undertook the revision of the "Production" section of the general monographs *Substances for pharmaceutical use (2034)* and *Pharmaceutical preparations (2619)*, in line with the EMA CHMP opinion regarding the detection, management and prevention of the presence of *N*-nitrosamines in medicinal products for human use[4] and the CHMP decision to apply these recommendations to "sartans medicinal products".[5] The objective was to add a recommendation to conduct a risk assessment of the manufacturing process and implement a strategy for the detection and control of *N*-nitrosamine impurities. The draft monographs were published in *Pharmeuropa* 33.2 (April 2021) for public enquiry. The Ph. Eur. Commission has carefully reviewed all comments received and dialogue with the competent authorities is ongoing, to ensure that the requirements provided in these monographs remain fully in line with regulators' decisions.

In parallel, the Ph. Eur. Commission also initiated a reflection on the impact the addition of requirements in the two general monographs might have on individual monographs.

Actions on CEPs

The EDQM Certification Department has continued to review risk assessments and updated applications received from CEP holders. The assessment work for high- and medium-priority dossiers (based on the level of risk for the presence of these impurities) is nearly finished and a small number CEPs have been revised when specific tests on the active substances were deemed necessary or were implemented by the respective manufacturers. The evaluation of the potential presence of nitrosamines is performed routinely

4. See EMA CHMP opinion EMA/369136/2020 pursuant to Article 5(3) of Regulation EC (No) 726/2004 regarding the detection, management and prevention of the presence of *N*-nitrosamines in medicinal products for human use, 25 June 2020: www.ema.europa.eu/en/documents/referral/nitrosamines-emea-h-a53-1490-assessment-report_en.pdf.
5. See EMA news item, 13 November 2020: www.ema.europa.eu/en/news/nitrosamines-ema-aligns-recommendations-sartans-those-other-medicines.

in all new CEP applications and at the time of renewal, as well as in revisions likely to impact the level of risk, based on data to be submitted by applicants.

Collaboration and communication

Collaboration with European and international partners

The EDQM has continued working closely with the EU regulatory network and international partners on the presence of nitrosamines in order to share information and to ensure co-ordinated and harmonised approaches on the issue. The Certification Department participates in regular meetings of the Nitrosamines International Strategic Group (NISG), of the EU Nitrosamine Implementation Oversight Group (NIOG) and the QWP Nitrosamines Expert Group.

Communication with stakeholders

The year 2021 began with two hugely successful online events organised jointly by EDQM departments whose activities had been impacted by *N*-nitrosamine impurity contamination issues. In total, more than 3 000 participants registered for these webinars that provided practical information and guidance for users on the Ph. Eur. approach to the control of *N*-nitrosamine impurities in sartan medicines and the impact on CEPs granted for the substances affected.

- *N*-nitrosamine impurities: Latest update on the Ph. Eur. approach (January 2021)
- Approaches for CEPs and the Ph. Eur. strategy with regard to nitrosamine control: Current guidance and practical implementation (April 2021)

The relevant presentations and recording are available on the EDQM website (*Events & training > Catalogue of events and training resources*)

Sampling strategies and testing methods with OMCLs

Members of the GEON have been involved in various activities concerning the detection of nitrosamines in APIs and medicinal products since mid-2018. A dedicated OMCL working group has met 14 times since then and has extended its scope beyond the nitrosamine group to the determination of mutagenic impurities at trace levels (e.g. azido impurities reported in tetrazole sartans).

The OMCL Mutagenic Contaminants Testing Group met twice in 2021 to discuss future testing strategies and exchange information about ongoing international initiatives in this area. Group members are currently involved in a rifampicin testing campaign launched jointly with the EMA/CMDh in February 2021. The network also updated the list of in-house methods published on the EDQM website. Based on recent cases, the group has widened its scope and is developing methods for determination of other mutagenic substances in sartans such as AZBT (azidomethyl biphenyl tetrazole) or AZBC (azidomethyl biphenyl carbonitrile). Finally, as an outcome of the EMA lessons learnt exercise in response to the sartan incident, the EDQM, with the help of the OMCL Network, began to implement recommendations for sampling and testing.

Anti-falsification activities

EDQM activities in the fight against falsified medical products medicines and medical devices) are conducted mainly through the three channels. The European Committee on Pharmaceuticals and Pharmaceutical Care (CD-P-PH) and its subordinate Committee of Experts on Minimising the Public Health Risks Posed by Falsification of Medical Products and Similar Crimes (CD-P-PH/CMED) develop and promote programmes and projects aimed at disseminating best practices in the fight against falsified medical products. The OMCL Falsified Medicines Working Group (see "OMCL Network", above) strengthens collaboration between OMCLs in the field of testing of falsified medicines and similar products. Finally, the EDQM provides support to the Convention on the Counterfeiting of Medical Products and Similar Crimes involving Threats to Public Health (MEDICRIME Convention, CETS No. 211) and its Committee of the Parties (CoP).

Work programme

In the area of traceability in the medicines supply chain, EDQM support to EU member states for the Conformity Assessment of the repositories system fulfilled its objectives and was phased out at the end of 2021.

A network of experts on borderline products was established within the framework of the CD-P-PH and its terms of reference were drafted. The network is primarily aimed at working on borderline issues related to enforcement or supervision of the legislation concerning medicinal products and currently comprises experts from 30 countries. An online meeting of the Borderline Products Network brought together 45 participants from 23 countries.

The EDQM attended the plenary meetings of the MEDICRIME CoP and actively worked with its secretariat on aligning activities, for example in providing support to the establishment of a 24/7 network, and in other fields where the CD-P-PH/CMED had projects underway.

Regarding the impact of COVID-19 in this area, dedicated information exchanges among experts were held throughout 2021.

Communication with partners and stakeholders

Throughout 2021, representatives of the EDQM took part in the meetings of the EU Heads of Medicines Agencies' Working Group of Enforcement Officers (HMA-WGEO) to strengthen co-operation.

Dedicated discussions with partner organisations, like WHO (and WHO EURO), made it possible to better address co-operation between relevant authorities, such as for the Network of Single Points of Contact (SPOCs). In this area, the EDQM contributed to a WHO EURO focal point-of-contact workshop and shared its experience on the matter.

An online meeting with private stakeholders active in the field of falsified medical products and pharmaceutical care was organised jointly with the Committee of Experts on Quality and Safety Standards in Pharmaceutical Practices and Pharmaceutical Care (CD-P-PH/PC).

Publications, databases and website

In 2021, the CD-P-PH/CMED published a guide entitled "Social media best practices for health authorities", based on experience gathered from health regulatory authorities on how best to promote their messages and advance their objectives using social media.

The EDQM's Know-X database stores comprehensive information on individual cases of falsified medical products. The database enables health and law-enforcement authorities across Europe to share information and to act more rapidly in cases of suspect medical products (for instance via its "Rapid Alert" function that allows users to alert others to new cases in real time). The CD-P-PH/CMED and the OMCL Falsified Medicines Working Group work together to maintain the database, and continue to work on improvements. They also co-operate in promoting the database and offer training to users. For example, a webinar on the use of the database targeting enforcement officers from health regulatory authorities was organised in 2021.

More information is available on the EDQM web site (*Medicines > Anti-falsification activities > Publications on falsified medical products and related crimes*).

Pharmaceuticals and pharmaceutical care

The European Committee on Pharmaceuticals and Pharmaceutical Care (CD-P-PH) contributes to the optimal use of medicines and to improving patient quality of life, public health and access to good quality medicines and healthcare, with the support of three 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).

Activities

Despite the obvious challenges related to the COVID-19 pandemic, 2021 saw a number of new projects launched and others completed.

A new project was launched to promote the safe and correct use of herbal food supplements by patients through the provision of appropriate advice and access to trustworthy and reliable information on use and the risks associated with these products.

A working group was established and given the task of developing a best practice document for the traceability of medicines in hospital settings to minimise the occurrence of medication administration errors and ensure patient safety.

A webinar was organised on Resolution Res/CM(2016)2 on good reconstitution practices in health care establishments for medicinal products for parenteral use. The webinar aimed to discuss the implementation of this resolution in national legislation and in hospital settings.

The CD-P-PH/PHO held three virtual meetings, at which it issued 31 recommendations on the classification of medicines and their supply conditions (prescription and non-prescription status).

A survey was carried out among the members of the CD-P-PH/PHO, Co-ordination Group for Mutual Recognition and Decentralised procedures – Human (CMDh) and CMDh Non-Prescription Medicinal Products Task Force. The goal of the survey was to gain an insight into how the Melclass database (containing national data on the legal status of medicines in Europe collected by the CD-P-PH/PHO) was used by NCAs and to evaluate any need for improvement.

Communication with partners and stakeholders

Exchanges took place with international organisations and professional bodies active in the public health and pharmacy sectors, such as the OECD and the European Association of Hospital Pharmacists (EAHP), to harmonise the promotion of patient-centred care and safe and effective use of medications in Europe.

A pilot project was launched to monitor how the seven South-Eastern Europe Health Network (SEEHN) member states apply Resolution CM/Res(2020)3 on the implementation of pharmaceutical care for the benefit of patients and health services. The survey created for this purpose will be run in 2022.

Publications, databases and website

Reviews of the classification of medicines

Reviews of the classification of medicines were completed for opium alkaloids and derivatives (Anatomical Therapeutic Chemical (ATC) group: R05DA), other cough suppressants (ATC group: R05DB) and doxylamine (ATC code: R06AA09). These will be published on the EDQM website in 2022.

Melclass

The Melclass database (melclass.edqm.eu) 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. Melclass was also updated with national related information.

European Paediatric Formulary

The European Paediatric Formulary (PaedForm) is a freely available, pan-European collection of formulations for extemporaneous preparations currently described in national formularies and formulations that are already well established in European countries. Its aim is to give clinicians, pharmacists and healthcare providers access to formulations of appropriate quality, allowing the preparation of medicinal products for children when no licensed alternative is available on the market.

Increased participation

The working party welcomed a new member in 2021, with a representative joining from Ireland. In addition, the EAHP provided the names of specialists from Turkey, Luxembourg, Iceland, Montenegro and the Czech Republic that are willing to provide information about formulations used and available locally from countries currently not represented in the working party. Additional one-to-one contacts were also made with individual hospital manufacturing units, an excellent means of communicating the purpose of the European Paediatric Formulary to hospital pharmacists and obtaining data for formulations that could be shared widely.

Work programme

The European Paediatric Formulary itself continued to grow in 2021 thanks to the dedication of its working party members, with the inclusion of the monograph on *Phosphate 60 mg/mL Oral Solution (F0011),* used in the treatment of hypophosphataemia.

Two new formulations, *Clonidine hydrochloride oral liquid* and *Midazolam nasal spray*, were added to the work programme, bringing the total number of monographs in development to 13. In keeping with the founding principle of the Formulary, these products are medicines intended to satisfy unmet paediatric needs as identified by the experts following a review of scientific data published by the EMA, for example. Further candidate formulations are currently in the assessment pipeline.

The end of 2021 saw two monographs published for public consultation: a revision of the recently published *Phosphate 60 mg/mL Oral Solution (F0011)* and *Simple syrup (preservative-free) (F0008),* which provides a standardised formulation and target strength for a widely used vehicle. This simple syrup can be used not only to suspend crushed tablets or other licensed products but, importantly, to prepare the formulations already published in the Formulary. The *General Principles text (F9002)* also underwent a minor revision to clarify that the specifications given in a monograph apply throughout the shelf life of the product and has been republished in the Formulary.

Communication with partners and stakeholders

The EDQM maintained its link with the Paediatric Committee (PDCO) of the EMA. This link is vital in shaping the work programme because it enables the prioritisation of monographs for products for which there is a current and/or foreseen unmet need. This ensures that the European Paediatric Formulary complements licensed medicines for use in the paediatric population.

The EDQM looks forward to continued partnerships with national formularies, hospital pharmacies and universities, and to developing connections with other stakeholders.

European Paediatric Formulary activities

Addition of an annex to monographs comprising a list of known licensed options that prescribers or pharmacists may consider when treating individual patients.

Two monographs experimentally evaluated and published for public consultation.

Two monographs added to the work programme.

European Paediatric Formulary work programme (2021)

- Baclofen oral liquid
- Chloral hydrate oral solution
- Chloral hydrate rectal solution
- Clonidine oral liquid
- Ethambutol oral suspension
- Flecainide oral liquid
- Furosemide oral solution
- Isoniazid oral solution
- Lorazepam oral solution
- Midazolam nasal spray
- Omeprazole oral suspension
- Pyrazinamide oral liquid
- Vehicle for oral solution or suspension (Simple syrup, preservative-free)

Candidates for addition to the work programme

- Bosentan
- Etoposide
- Phenytoin

Quality and safety of substances of human origin

Blood transfusion

The EDQM is responsible for the Council of Europe's activities in the area of blood transfusion, built around the major guiding principles of promoting voluntary and non-remunerated donation,[6] mutual assistance, optimal use of blood and blood components and the protection of donors and recipients. It 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 blood transfusion activities at the EDQM; it elaborates guidelines and recommendations, supports their implementation and oversees the tasks of its subordinate working groups.

Key activities

Blood Guide

The EDQM regularly reviews and updates common technical standards for blood and blood components in its *Guide for the preparation, use and quality assurance of blood components* (the "Blood Guide") and Good Practice Guidelines for blood establishments (GPGs for BEs).

In 2021, the dedicated working group entrusted with updating the Blood Guide and ensuring it keeps abreast of scientific developments and regulatory changes, worked actively on the drafting of the 21st edition, scheduled for publication in 2023.

B-PTS and B-QM Programmes

The EDQM continued to run the Blood Proficiency Testing Scheme (B-PTS) and the Blood Quality Management (B-QM) Programme to support BEs in implementing EU blood legislation, as well as the standards laid out in the Blood Guide and the GPGs. Both programmes have been co-funded by the European Commission and the EDQM since 2010.

The external assessment of the testing capability of European BEs also continued in 2021. Six B-PTS studies were organised, with an average of 53 laboratories participating in each.

In order to ensure continuity of the B-QM Programme despite the travel restrictions in place in 2021, the EDQM initiated remote educational training sessions and auditing schemes.

In October 2021, a pilot Blood Virtual Audit (B-VA) was conducted for the first time, during which one European BE benefited from peers' experience to further strengthen their QMS. This pilot scheme will be used as the basis to develop a fully fledged remote audit programme for European BEs as of 2022.

A webinar entitled "Data Protection in the Blood Sector – Impact & Challenges for Blood Establishments" was held on 17 February 2021. It covered data protection and how it applies to blood transfusion, as well as BEs' responsibilities, the challenges they face and the strategies they use in managing the various types of data they process.

6. See Recommendation No. R (95) 14 on the protection of health of donors and recipients in the area of blood transfusion, available at https://rm.coe.int/native/09000016804da051.

In November 2021, a virtual training programme on Quality Risk Management was organised, taking place over a period of five weeks and attracting 80 BE participants on average. Weekly supporting materials and exercises were distributed to participants. The programme concluded with a two-day live session during which practical examples and case studies were discussed in an interactive format.

Blood Supply Contingency and Emergency Plan

With a view to strengthening national and European plans ensuring the continuity of blood supply in emergency situations, the EDQM initiated the Blood Supply Contingency and Emergency Plan (B-SCEP) project in 2019. In 2021, a survey gathered information on the existing national-level frameworks and contingency/emergency measures in place for the blood supply among European countries. Recommendations and a "Model Preparedness Plan" were drafted to provide support for European countries in establishing, implementing and maintaining a B-SCEP, to ensure preparedness in the event of an emergency. They will be published in 2022.

Romanian Blood System reorganisation project

In 2020, the European Commission's DG REFORM entrusted the EDQM with co-ordinating the reorganisation of the Romanian Blood System (RBS), including both the blood transfusion service and its regulatory oversight.

In 2021, the EDQM project team conducted an in-depth study of the RBS, to better understand how it functions and its specificities. This included desk-based research, questionnaires sent to all RBS stakeholders and a number of workshops with Romanian experts to consolidate the results and get their views on the challenges they face. In 2022, the outcomes of these activities will be used to build a well-designed, fit-for-purpose and implementable model for a restructured national blood system meeting the EU blood legislation requirements and EDQM/Council of Europe standards.

General matters and policies

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, 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. This working group compiled a compendium of deferral policies applied by member states to donors displaying behaviour that creates risks for the safety of transfusion.

Publications, databases and website

Report on the collection, testing and use of blood and blood components in Europe

The EDQM collects activity data on the donors, collection, testing, use and quality aspects of blood and blood components. Council of Europe member and observer states supply this data in response to an annual questionnaire. The 2016 report was published in 2021. Data were collected for the years 2017-2019, and a report for this period will be published in 2022.

B-SCEP survey report

A report on the outcomes of the above-mentioned B-SCEP survey was published and is available on the EDQM website (*Substances of human origin > Blood Transfusion > B-SCEP programme*).

European database of frozen blood units of rare blood groups

This database continued to support BEs in their efforts to source blood with rare phenotypes for patients in need of a transfusion. To date, six BEs have voluntarily contributed their lists of frozen units of rare blood groups.

Organs, tissues and cells

The European Committee on Organ Transplantation (CD-P-TO) is the steering committee responsible for transplantation activities. Its main objective is to promote quality and safety standards, and its mandate includes drafting guidelines aimed at improving access to transplantation, establishing strict safety, quality and ethical standards, collecting international data, monitoring practices in Europe and contributing to the fight against organ trafficking.

Work programme

Travel for transplantation

In exceptional circumstances, patients may be referred for transplantation abroad via the official channels for medical, organisational or social reasons; other patients with no or limited access to transplantation in their home countries may, in desperation, also resort to transplantation abroad outside of official channels. Travel for transplantation becomes "transplant tourism", and thus unethical, when it involves trafficking or when resources (including organs) are devoted to providing transplants to non-resident patients, undermining a country's ability to provide transplant services for its own population. Travel for transplantation is currently a largely unexplored topic.

To date, 34 member states have designated national focal points (NFPs) to the International Network of National Focal Points on Travel for Transplantation. This network is in charge of regularly collecting data on patients travelling abroad for transplantation, in the framework of Resolutions CM/Res(2013)55 and CM/Res(2017)2,[7] for inclusion in the Registry of International Travel for Transplantation Activity (RITTA), the first database of its kind. This registry was overhauled in 2021 and the information it contains will shed light on this phenomenon, help identify possible transplant tourism hotspots and improve knowledge of the profile of the donors and recipients involved, as well as the quality of the transfer of recipient care and its impact on post-transplant outcomes. By the end of 2021, the RITTA database contained information on almost 600 patients. The network of NFPs met in November 2021 and discussed the aggregated data submitted to RITTA. It emerged that some member states seemed to be destinations for potentially unethical transplant procedures, requiring careful investigation.

In November 2021, Costa Rica ratified the Council of Europe Convention against Trafficking in Human Organs.[8]

Donation after circulatory determination of death

The CD-P-TO adopted a seminal legal instrument recommending that member states develop and optimise programmes for the donation of organs after the circulatory determination of death due to their potential to increase significantly the donor pool and thus the number of available organs. This text was submitted to the Committee of Ministers, for adoption in 2022.

European Day for Organ Donation and Transplantation

The European Day for Organ Donation and Transplantation (EODD) was celebrated virtually on 9 October 2021. This event recalled the crucial importance of organ, tissue and cell donation, particularly in view of the severe consequences of the COVID-19 pandemic on transplant programmes worldwide and on the number of patients waiting to receive an organ.

7. Resolution CM/Res(2013)55 on establishing procedures for the collection and dissemination of data on transplantation activities outside a domestic transplantation system, available at https://search.coe.int/cm/Pages/result_details.aspx?ObjectId=09000016805c6cda; Resolution CM/Res(2017)2 on establishing procedures for the management of patients having received an organ transplant abroad upon return to their home country to receive follow-up care, available at https://search.coe.int/cm/Pages/result_details.aspx?ObjectId=0900001680726fb8.
8. See www.coe.int/en/web/conventions/full-list/-/conventions/treaty/216.

Data collection

The EDQM co-ordinated a project entitled "Harmonising activity data collection exercises in the field of tissues and cells in Europe"[9] launched as part of a co-operation Grant Agreement with the European Commission. A realistic assessment of supply and demand for human cells and tissues is fundamental to rational, fair and effective distribution and, most importantly, to achieving self-sufficiency and avoiding overreliance on a limited number of countries. Furthermore, understanding the figures on SAREs related to their use requires accurate activity data. This project entailed the identification of a minimum dataset to collect activity data in the field, as well as issuing recommendations on who should be accountable for the collection and validation of this data and ensure dissemination among all relevant stakeholders. This exercise is of particular importance in the context of the upcoming revision of the EU legislation in the field of tissues and cells.

Biovigilance training

As part of this same Grant Agreement, the EDQM organised the "1st European training course in Biovigilance for tissues and cells",[10] targeting biovigilance officers and health authorities, and the "1st European training course on Quality Management for Tissue Establishments"[11] over a period of five to six weeks, aimed at providing tissue establishments in Europe with the tools required for the successful implementation of a QMS, from identification of a potential donor through processing and storage of the tissues or cells, to the final preparation for application to the patient.

The EDQM was also in charge of the annual analysis of SAREs associated with the use of tissues and cells for the treatment of patients in the EU.

Publications

The CD-P-TO published a new booklet entitled "Fertility preservation: a guide for people facing an illness or life events that may affect their fertility",[12] drafted in collaboration with the European Society of Human Reproduction and Embryology (ESHRE). This booklet aims to provide clear, accurate and balanced information on fertility preservation, situations in which fertility preservation may be considered, cryopreservation techniques and the possible uses of stored cells, tissues and embryos.

Several other outcomes of the CD-P-TO's work were also published, including:

- "Newsletter Transplant",[13] co-ordinated by the Spanish National Transplant Organisation (Organización Nacional de Trasplantes). 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 71 countries worldwide on donation and transplantation activities, management of waiting lists, organ donation refusals and authorised centres for transplantation activities;
- "Critical pathway for deceased tissue donation: a novel adaptative European systematic approach", published in *Transplant International*;[14]
- "Access of non-residents to transplantation of deceased donor organs: practices and strategies in the European setting", published in *Transplant International*;[15]
- "International Travel for Transplantation: Time for Transparency", published in *Transplantation*.[16]

9. See www.edqm.eu: *Substances of human origin > Organs, tissues and cells > Areas of work - Transplantation.*
10. See www.edqm.eu: *Events & training > Catalogue of events and training resources > Training Course on Biovigilance for Tissues and Cells*.
11. See www.edqm.eu: *Events & training > Catalogue of events and training resources > Training: Quality Management for Tissue Establishments*.
12. See www.edqm.eu/: *Substances of human origin > Organs, tissues and cells > Organs, tissues and cells - Publications > Booklets.*
13. See https://freepub.edqm.eu/publications/PUBSD-87/detail.
14. See https://doi.org/10.1111/tri.13841.
15. See https://doi.org/10.1111/tri.14113.
16. See https://doi.org/10.1097/TP.0000000000003971.

Consumer health

Cosmetics

The cosmetics work programme is aimed at protecting human health across Europe through common quality and safety requirements, as well as through the co-ordination of official controls, the development of common analytical procedures and the verification of testing proficiency.

Activities

The European Committee for Cosmetics and Consumer Health (CD-P-COS) held one videoconference with all its members and observers and took part in a joint meeting with the Network of Official Cosmetics Control Laboratories (OCCL Network) to co-ordinate efforts in market surveillance of cosmetic products.

Safe cosmetics for young children

The first edition of this guidance document that provides safety recommendations for the risk assessment of cosmetic products for young children was released in 2012.[17] A complete update was undertaken in 2021 to address the issues of endocrine disruptors and nanomaterials. The new edition will be released in 2022.

OCCL Network

Quality control of cosmetics: market surveillance studies

The third phase of the MSS on cosmetics for children, started in 2011, was completed in 2021. Results confirmed that the overall compliance of "kids' cosmetics" (cosmetics designed to appeal to children and often perceived as toys) with European regulations was low compared to common care products. Authorities objected to 25% of the kids' cosmetics considered and recalled or banned 5% of products. The presence of nitrosamines and sensitising preservatives was among the reasons for sales bans.

The OCCL Network launched a new MSS to determine the content of formaldehyde, a presumed carcinogenic, mutagenic or reprotoxic (CMR) substance, in cosmetic products.

Sunscreens

OCCLs shared their strategies for the market surveillance of sunscreens within the network. Several laboratories worked on the development of alternative methods for sun-protection factor determination.

Proficiency Testing Scheme studies

In 2021, three PTS studies were finalised, giving the participants the opportunity to assess their ability to determine phthalates in nail varnish and perfume, 1,4-dioxane in bath products, and methylisothiazolinone/methylchloroisothiazolinone and colorants in cosmetic products. In addition, a PTS study was launched on skin-whitening products with 21 laboratories registered.

Communication with partners and stakeholders

The EDQM shared information on market surveillance activities with the Platform of European Market Surveillance Authorities for Cosmetics of the European Union (EU PEMSAC) and with the European Commission.

17. See www.edqm.eu: *Consumer health > Cosmetics & tattoos > Publications on cosmetic products and tattoo inks*.

Food contact materials and articles

The work programme for food contact materials and articles aims to protect human health across Europe through common quality and safety requirements for food contact materials and articles, as well as through the definition of test protocols and common analytical procedures.

Council of Europe Resolution CM/Res(2020)9 on the safety and quality of materials and articles for contact with food[18] includes guiding principles for the implementation of suitable policies and serves as a framework for all technical guidance published by the EDQM on specific food contact materials.

Communication with partners and stakeholders

National health authorities contribute to the elaboration of guidelines, provide expertise and carry out experimental testing. The EDQM collaborates with the European Commission and the European Food Safety Authority to ensure consistency and complementarity of Council of Europe resolutions and technical guidelines with relevant regulations and guidelines in the EU.

Publications

A new technical guide "Paper and board used in food contact materials and articles" was released for download on FreePub.[19] To protect consumers from contaminants in food that originate from packaging materials or containers, specific instructions for business operators have been included on how to ensure the safety and quality of materials intended for food contact.

A guide entitled "Food contact materials and articles – Substances migrating from printing inks to food or food simulants" was also released for download on FreePub.[20] The detailed procedures for the extraction of food and analytical testing using gas or liquid chromatography, both coupled to tandem mass spectrometry, had been successfully validated in an inter-laboratory study, with the participation of 11 control laboratories.

A survey report "Metal release from enamelware", based on data collection from official control authorities in Europe between 2015 and 2018, was released for download on FreePub.[21] For cadmium and lead, 10 out of the 15 participating laboratories in different countries referred to the Specific Release Limits set out in the Council of Europe's Technical Guide, with stricter limits than the European Ceramics Directive (2005, under revision). NCAs have planned further MSSs and two expert meetings were organised in 2021 to review the different testing conditions and release limits they apply.

Best practices for the documentation of compliance of food contact materials and articles were discussed among regulators, control laboratories and stakeholders. The CD-P-MCA instructed a group of experts to elaborate guidelines on the extent of information to be reflected in the documentation and to prepare a related checklist for use by authorities and manufacturers.

The CD-P-MCA agreed on amendments proposed by experts from competent authorities, official control laboratories and industry for a second edition of the practical guide for manufacturers and regulators "Metals and alloys used in food contact materials and articles" (2013), to be drafted in 2022.[22]

18. See https://search.coe.int/cm/pages/result_details.aspx?ObjectId=09000016809fe04a.
19. See https://freepub.edqm.eu/publications/PUBSD-115/detail.
20. See https://freepub.edqm.eu/publications/PUBSD-161/detail.
21. See https://freepub.edqm.eu/publications/PUBSD-159/detail.
22. See www.edqm.eu: *Consumer health > Food contact materials and articles > Publications on Food contact materials and articles*.

Appendix

Table of abbreviations

3Rs	replacement, reduction and refinement
API	active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical
AZBC	azidomethyl biphenyl carbonitrile
AZBT	azidomethyl biphenyl tetrazole
BE	blood establishment
BET	bacterial endotoxins test
B-PTS	Blood Proficiency Testing Scheme
B-QM	Blood Quality Management
B-SCEP	Blood Supply Contingency and Emergency Plan
BSP	Biological Standardisation Programme
B-VA	Blood Virtual Audit
BVS	batch validity statement
CAP	Centrally Authorised Product
CAS Registry Number	Chemical Abstracts Service Registry Number
CD-P-COS	European Committee for Cosmetics and Consumer Health
CD-P-MCA	European Committee for Food Contact Materials and Articles
CD-P-PH	European Committee on Pharmaceuticals and Pharmaceutical Care
CD-P-PH/CMED	Committee of Experts on Minimising the Public Health Risks Posed by Falsification of Medical Products and Similar Crimes
CD-P-PH/PC	Committee of Experts on Quality and Safety Standards in Pharmaceutical Practices and Pharmaceutical Care
CD-P-PH/PHO	Committee of Experts on the Classification of Medicines as Regards their Supply
CD-P-TO	European Committee on Organ Transplantation
CD-P-TS	European Committee on Blood Transfusion
CEP	Certificate of Suitability to the Ph. Eur. monographs
CEPI	Coalition for Epidemic Preparedness Innovations
CHMP	Committee for Human Medicinal Products
CLEN	Customs Laboratories European Network
CMDh	Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human
CMDv	Co-ordination Group for Mutual Recognition and Decentralised Procedures – Veterinary
CMR	carcinogenic, mutagenic or reprotoxic

CoP	Committee of the Parties
COVAX	COVID-19 Vaccines Global Access
DCP	decentralised procedure
DH-BIO	Council of Europe Committee on Bioethics
EA	European Co-operation for Accreditation
EA/LC	European Co-operation for Accreditation/Laboratory Committee
EAHP	European Association of Hospital Pharmacists
EATCB	European Association of Tissue and Cell Banks
ECSPP	Expert Committee on Specifications for Pharmaceutical Preparations
EDQM	European Directorate for the Quality of Medicines & HealthCare
EEA	European Economic Area
EMA	European Medicines Agency
EMA PDCO	EMA Paediatric Committee
EODD	European Day for Organ Donation and Transplantation
EQAAS	External Quality Assurance Assessment Scheme
ESHRE	European Society of Human Reproduction and Embryology
EU	European Union
EUNDB	European Union Network Data Board
GC	gas chromatography
GEON	General European OMCL Network
GMP	Good Manufacturing Practice
GPG	Good Practice Guidelines
GTWG	Gene Therapy Products Working Group
HMP	herbal medicinal product
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICRS	International Chemical Reference Substance
IPRP	International Pharmaceutical Regulators Programme
ISA	International Standards for Antibiotics
ISO/IEC	International Organization for Standardization/International Electrotechnical Commission
IVMP	immunological veterinary medicinal product
JP	Japanese Pharmacopoeia
LC	liquid chromatography
MAT	monocyte-activation test
MJA	Mutual Joint Audit
MJV	Mutual Joint Visit
MOU	memorandum of understanding
MRP	mutual recognition procedure
MSS	market surveillance study
MSSIP	market surveillance study on suspected illegal products
NC3Rs	National Centre for the Replacement, Refinement & Reduction of Animals in Research (United Kingdom)
NCA	national competent authority
NDEA	*N*-nitrosodiethylamine
NFP	national focal point

NISG	Nitrosamines International Strategic Group
NMR	nuclear magnetic resonance
NPA	national pharmacopoeia authority
OBPR	Official Batch Protocol Review
OCABR	Official Control Authority Batch Release
OCCL	Official Cosmetics Control Laboratory
OECD	Organisation for Economic Co-operation and Development
OMCL	Official Medicines Control Laboratory
PA	pyrrolizidine alkaloid
PDG	Pharmacopoeial Discussion Group
PTS	Proficiency Testing Scheme
QM	quality management
QMS	quality management system
QWP	Quality Working Party
RBS	Romanian Blood System
RITTA	Registry of International Travel for Transplantation Activity
RPT	rabbit pyrogen test
RS	reference standard
RTEMIS	Real-Time Remote Inspections
SAREs	serious adverse reactions and events
SARM	Selective Androgen Receptor Modulator
SDS	safety data sheet
SEEHN	South-eastern Europe Health Network
SoHO	substances of human origin
SPOC	Single Point of Contact
TFDA	Taiwan Food and Drug Administration
TGA	Therapeutic Goods Administration, Australia
TSE	transmissible spongiform encephalopathy
Unicef	United Nations Children's Fund
UNODC	United Nations Office on Drugs and Crime
USFDA	United States Food and Drug Administration
USP	United States Pharmacopeia
VBRN	Veterinary Batch Release Network
WHO	World Health Organization

This publication presents the work carried out in 2021 by the European Directorate for the Quality of Medicines & HealthCare, Council of Europe, highlighting its particular achievements.

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