

EDQM & European Pharmacopoeia: State-of-the-art Science for Tomorrow's Medicines

International Conference organised by the European Directorate
for the Quality of Medicines & HealthCare (EDQM),

Council of Europe

19-20 June 2019, Strasbourg, France

EDQM & European Pharmacopoeia: State-of-the-art Science for Tomorrow's Medicines

Opening Plenary Session

The Certification of Suitability Procedure

25 Years of a Success Story

Dr Jean-Louis Robert,
Luxembourg
Chair of the Certification Steering Committee

Overview

Presentation on general aspects of the CEP
CEP Breakout session on technical aspects

- Background of the Procedure
- Current situation
- Some statistics
- Conclusions

Background of the Procedure

- Discussion at QWP (late 80ies):
 - Multiple sources of APIs with potential different synthesis leading to potential different impurity profiles
 - What do we actually control or which impurities can be controlled by a pharmacopoeial monograph?
 - For what does a pharmacopoeial monograph stand for?

Background of the Procedure (2)

- These questions have led to the establishment of the “Certification European Pharmacopoeia” procedure
- Objective:
 - Demonstration of compliance of a substance specific manufacturer (source) with the monograph of the Ph. Eur. mainly with regard to the impurities' content

Development over the Years (1)

- Beginning of the procedure:
 - Good “Will” but start in “Isolation”
 - Lack of procedures, of transparency, of communication,
 - Still valid CEP:
 - Promethazine HCl (Sanofi, FR) (1992 – 002)

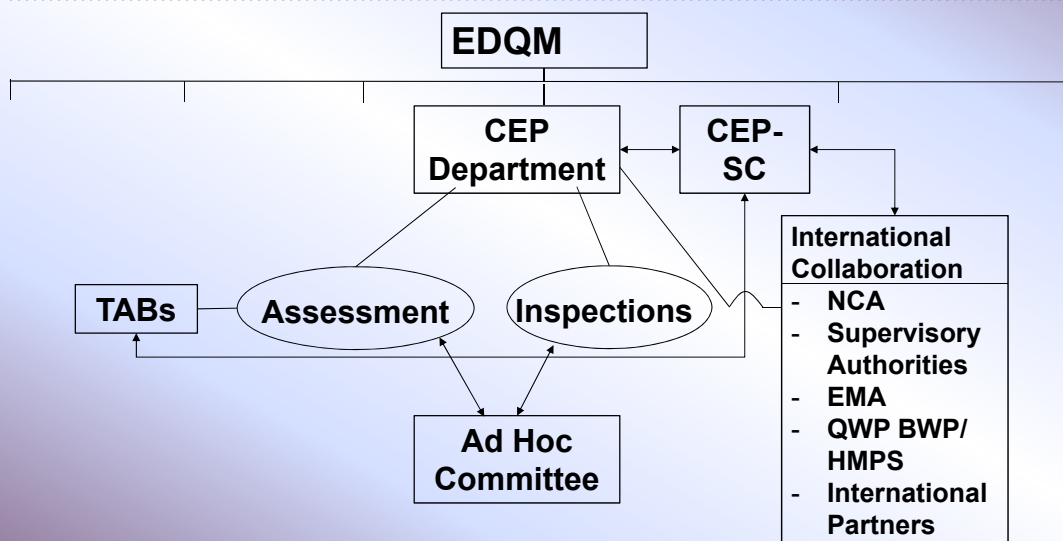
Development over the Years (2)

- Acceptance:
 - Different attitudes from MS towards the CEP procedure
 - Assessors (MSs) to get used to a certificate and not to require further information/data
- Assessors back home questioning the assessment procedure in their own agency: potential drift to divergences in assessment policy between MS and CEP!

Development over the Years (3) “Professionalization” of the procedure

- Steering Committee (SC)
- Technical Advisory Board (TAB)
- CEP own guidelines reviewed by QWP (in line with QWP guidelines)
- Inspection: information about suspension/withdrawal
- CEPs more transparent with annexes
- ARs available on request from NCAs’ assessors (secure on-line data base)
- Close collaboration CHMP/CVMP QWP

CEP Department: Structure



Composition of CEP SC

- The Chairs of the CHMP/CVMP Quality Working Party (QWP), of the CHMP Biologics Working Party (BWP) and of the GMP/GDP Inspectors Working Group (GMDP IWG);
- The Chair of the Herbal Medicinal Products Committee (HMPC);
- A representative of a licensing authority from a country that is a member of the Convention on the Elaboration of a Ph. Eur., but is not a member of the EU/EEA,
- A representative of an inspectorate from a country that is a member of the Convention on the Elaboration of a Ph. Eur., but is not a member of the EU/EEA,
- The Chair of the European Pharmacopoeia Commission;
- The Chairs of the Technical Advisory Boards (TAB);
- A representative of the European Commission;
- A representative of the European Medicines Agency (EMA);
- The Director of the European Directorate for the Quality of Medicines & HealthCare
- Expert(s) from relevant authorities who can be co-opted by the SC, as necessary.

CEP – Scope (adopted over time)

- For substances for which a monograph exists:
 - Organic/inorganic (active –excipients) manufactured or extracted
 - Herbals
 - Substances produced by fermentation as indirect gene products
 - Products with risk of transmitting agents of animal spongiform encephalopathies (TSE certificate)

CEP – Scope (adopted over time)

- Not applicable:
 - Direct gene products (proteins)
 - Animal tissues
 - Vaccines
 - Blood products

CEP - Network

- Chemical
 - 83 Assessors (25 countries) including CDN, ISL, NO, BA, CH, RS, AUS & CDN
 - 15 EDQM assessors
- TSE: 8 Assessors (5 countries) including CH
- Herbals: 6 Assessors (5 countries), 1 EDQM
- Inspectors
 - 32 inspectors (16 EU/EEA countries, incl. CH)

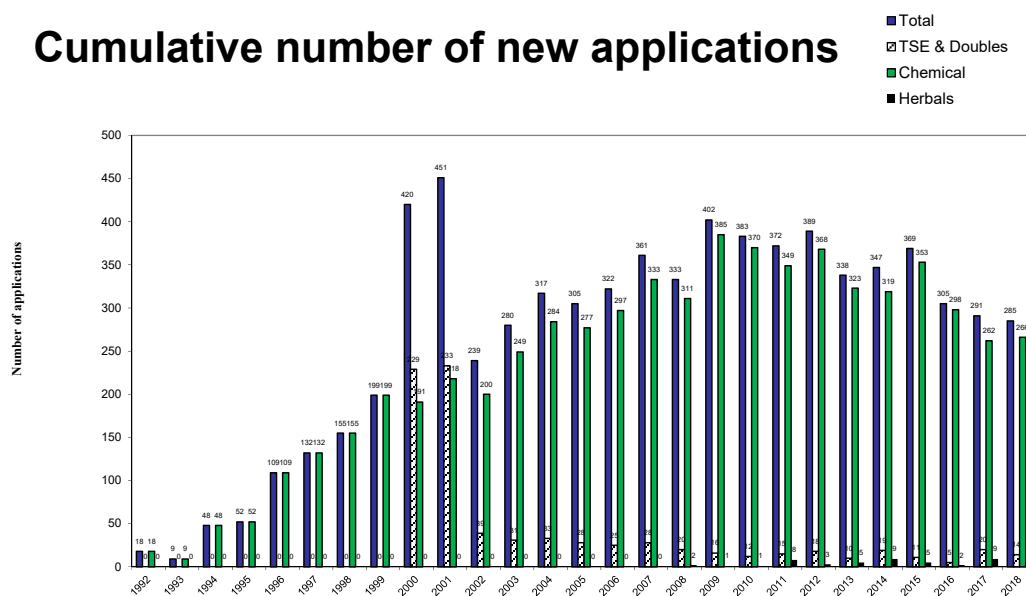
Assessment -Procedure

- Performed by assessors of NCAs and EDQM
- Efficient process: new applications treated in 3 rounds (initial assessment + 2 requests for information maximum)
- Applications treated within official deadlines
- Technical Advisory Board to take decisions in case of disagreements and to identify needs for harmonised policies → brought to QWP and/or BWP

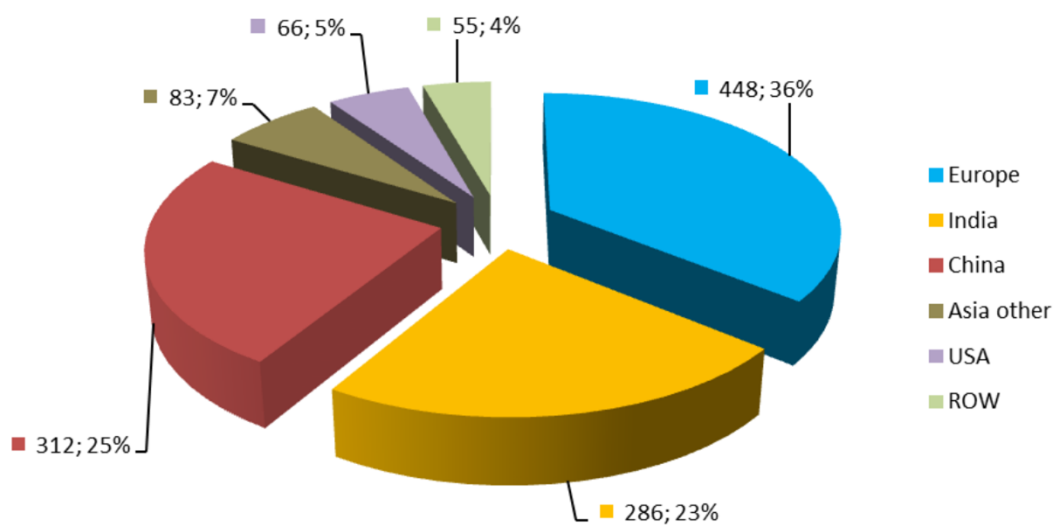
Some Statistics

- April 2019: ~ 5.000 valid CEPs
- Each year
 - ~ 300 new applications and
 - ~1.800 revisions

Cumulative number of new applications



Repartition of manufacturers having a valid CEP - April 2019



CEP – Inspection (1)

- To verify the compliance with EU GMP Part II (equivalent to ICH Q7) & any applicable annex (eg. Annex 1 for sterile substances, 11 for computerised systems etc).
- EDQM establishes an annual inspection programme
- Selection of sites eligible to be inspected by EDQM according to a **risk-based approach** (in line with EU guidance on GMP inspections)

CEP – Inspection (2)

- Inspection performed by team composed of one EDQM inspector and one inspector from an EU/EEA/MRA authority (joint inspections may also be performed, e.g. with WHO, TGA, USFDA, PMDA)
- Optimisation of use of inspection resources by exchange of information (planned inspections and inspection results/reports)

CEP – Inspection (3)

- In case of positive conclusion of the inspection combined with a satisfactory evaluation of the submitted CAPA (and the CEP dossier is up-to-date), an inspection attestation is delivered by EDQM, stating compliance with the CEP and with GMP.
- A GMP Certificate is issued by the EU/EEA/MRA participating Inspectorate via the EUDRAGMDP data base (public information)

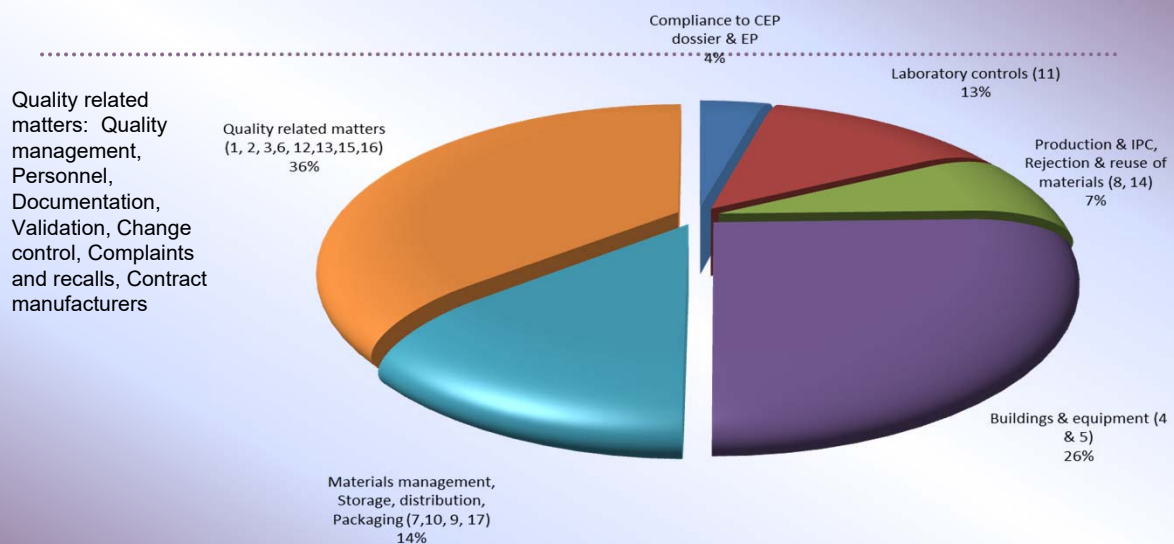
CEP – Inspection (4)

- In case of critical/major deficiencies to GMP and/or the CEP dossier. Actions taken:
 - ✓ CEP(s) of the site are suspended or withdrawn
 - ✓ site removed from the list if more than one involved in a CEP dossier
 - ✓ on-going CEP application(s) rejected
- A Statement of Non-Compliance is issued by the EU/EEA/ MRA participating Inspectorate via the EUDRAGMDP data base (public information)

Inspection - Some Statistics -2018

- 36 on-site inspections → 4 non-compliances (all with critical findings)
- 46 sites covered by exchange of information (mainly inspections by EEA inspectorates) + distant assessment → 1 Statement of GMP non-compliance

Distribution of deficiencies from 2006 to 2018



Conclusion (1)

- Good example of a successful harmonisation
- Collaboration of experts from different NCAs
- Well established procedure
- Centralized procedure: less administrative burden
- Benefit for the Ph. Eur.
 - Improvement of monographs
 - Transparent monographs with list of impurities (specified – other detectable)

Conclusion (2)

- Increased exchange of information between CEPs and Competent authorities
 - Inspection and assessment
 - Recent case: Nitrosamines
- Recognition outside of Europe
 - AUS, CDN, Ghana, Morocco, NZ, Saudi-Arabia, South Africa, Singapore, Taiwan, WHO, ...
 - Brazil in progress
- TSE certificates used worldwide

.....

Thank you for your attention

THE EUROPEAN DIRECTORATE FOR THE QUALITY OF MEDICINES & HEALTHCARE (EDQM)



**EDQM and European Pharmacopoeia:
State-of-the-art Science for Tomorrow's Medicines
19-20 June 2019, Strasbourg, France**

**Combatting falsified medical
products - The EDQM's holistic
approach in support of the
MEDICRIME Convention**

**Karl-Heinz Buchheit, Ph.D.
EDQM, Council of Europe**



Pictures: www.gstatic.com

Falsified Medicines: Some Data

- 50% of medicines bought over internet from sites that conceal their physical address are counterfeits
- Developed countries (e.g. EU, US, Canada, Japan): low proportion of falsified medicines (< 1% of market value)
- Africa: 10-30% considered falsified
- Anti-malaria drugs: up to 60% considered falsified

(Source: WHO IMPACT Study)

Content

1. MEDICRIME Convention

2. Conformity assessment of traceability systems
3. Committee of Experts on Minimising Public Health Risks Posed by Falsification of Medical Products and Similar Crimes (CMED)
4. OMCL Network
5. KnowX database

1. MEDICRIME Convention

CoE Convention on Counterfeiting of Medical Products and Similar Crimes involving Threats to Public Health

- “Counterfeit” used in MEDICRIME Convention consistent with meaning of “falsified”, now more commonly used term
- Falsified medical product according to convention: deliberately false representation of its source and/or identity
- Medical products: medicines (human and veterinary use) & medical devices
- Similar crimes: manufacturing, storing, trafficking, selling without necessary authorisation

1. MEDICRIME Convention

- 1st International criminal law instrument allowing criminalising falsification
 - Incl. falsification of documents
 - Effective, proportionate, dissuasive sanctions
 - Focus on public health rather than intellectual property rights
 - No need for actual damage

1. MEDICRIME Convention

- Aggravating circumstances
 - Death, physical or mental damage to victim
 - Abuse of confidence (professionals)
- Protection of rights of victims (e.g. in criminal investigations)
- Promoting national/international cooperation & information exchange
- Not in scope
 - Non-intentional breaches of quality/good practice in manufacture and distribution
 - Violation of Intellectual Property Rights (IPR)

1. MEDICRIME - Falsified Medicines Directive (FMD)

FMD 2011/62/EU amending 2001/83/EC on medicinal products for human use, as regards prevention of entry into legal supply chain of falsified medicinal products

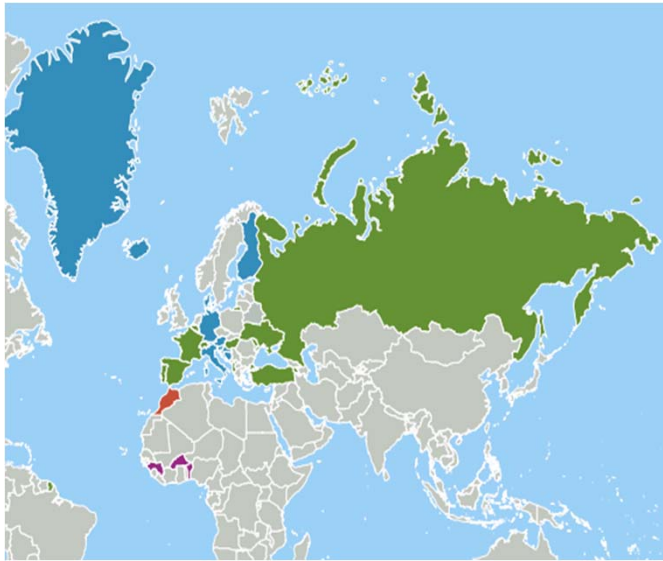
MEDICRIME (28/10/2011) Convention on counterfeiting of medical products & similar crimes involving threats to public health

	FMD	MEDICRIME
Goal	Protect public health, integrity of legal supply, get a good product to the consumer	
Means	Regulate supply	Criminal Law
Scope	Medicines	Medicines & Medical devices
Focus	Products	Consumers/victims have rights & compensation

1. MEDICRIME: Status (1)

- Opening of the treaty: Moscow, 28/10/11
- Open to CoE MS and non-MS
- Entry into force: 01/01/2016 - 5 Ratifications including at least 3 MS of CoE
- 10th ratification: August 2017
- 1st meeting of Committee of the Parties: December 2018
- On 15/4/19
 - Signatures: 14 (not yet followed by ratifications)
 - Ratifications: 15

1. MEDICRIME: Status (2)



- Signature CoE MS
- Ratification CoE MS
- Sign. Non-CoE S
- Ratific. Non-CoE S

1. MEDICRIME: Committee of the Parties (1)

- Elaboration of Rules of Procedure
- Establishing rules on the monitoring system
- Collaboration with other committees:
 - European Committee on Pharmaceuticals & Pharmaceutical Care (CD-P-PH), in particular CMED
 - Commission of the European Pharmacopoeia
 - Advisory Group of OMCL Network

1. MEDICRIME: Committee of the Parties (2)

- Facilitate collection, analysis & exchange of information, experience & good practice between states
- Facilitate use & implementation of Convention
- Make recommendations to Parties

1. MEDICRIME: Issues

- Low priority for medicines related crime in some countries
- Lack of reliable data on impact of falsified medicines on public health and economy (especially in Western countries)
- Need for interaction of justice and health sectors

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2. Conformity Assessment Traceability Systems

- EU-FMD: Delegated Regulation on Safety Features, (EU) 2016/161
- Detailed rules for safety features appearing on the packaging of medicinal products for human use
- Aim: tackling problem of falsified medicines and improved traceability
- In force as of 9 February 2019
- Consequences:
 - Barcode on packages (unique identifier)
 - Central database (European Hub)
 - National databases



2. Conformity Assessment Traceability Systems

- European Hub (EMVO):
 - EDQM coordinates audit scheme based on an agreement with EMVO
 - Assessment of conformity of IT processes, systems control/security strategies & governance with standards and specifications
- National systems
 - EDQM offers support to Member States in implementation of supervision of traceability systems
 - Trainings for inspectors of national systems
 - Limited number of inspections during pilot phase

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3. CMED

- Committee of Experts on Minimising Public Health Risks Posed by Falsification of Medical Products and Similar Crimes (CMED)
- Subordinate committee of European Committee for Pharmaceuticals and Pharmaceutical Care (CD-P-PH)
- Ph. Eur. Member- & Observer States participate in CMED activities
- Delegates from health authorities, law enforcement, customs

3. CMED: Key Tasks

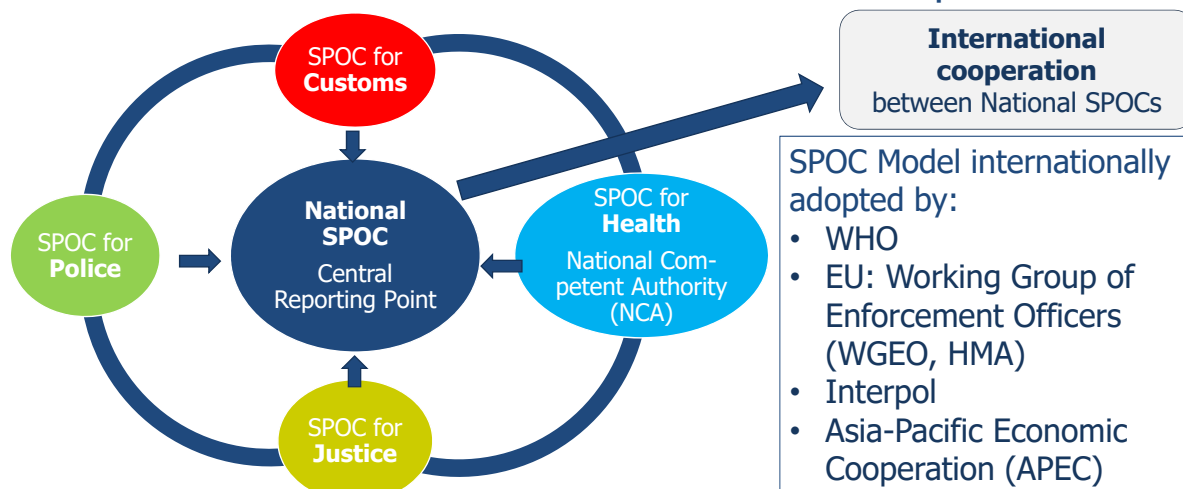
Promote the MEDICRIME convention and its future Committee of the Parties by

- Support implementation
- Links with national, European and international institutions and organisations
- Facilitating networking and co-operation among member states (**SPOC Network**)
- Multi-sectorial **training**
- **Awareness raising campaigns** for general public on perils of medical products from dubious sources



3. CMED: Single Points Of Contact (SPOC)

- MEDICRIME fosters national and international cooperation



3. CMED: Training

- **General**
 - MEDICRIME Convention
 - Setting up / maintaining SPOC network
- **Targeted**
 - GMP/GDP/Pharmacy Inspectors of a region; raising awareness to signals for possible falsified products

Workshops	18	Plus 6 conferences during same time frame
Participants	423	From 58 countries
Trainers	42	From 18 countries

3. CMED: Awareness Raising Campaigns

Promotion of awareness-raising campaigns addressed to public

- EDQM Psycho-pedagogical concept guide for teachers "Open Minds, Free Minds"
- Available online for free

<https://www.edqm.eu/en/Counterfeit-medicines-and-similar-crimes-1625.html>

Using interactive storytelling as a teaching concept



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4. OMCL Network

Presentations at this meeting

- **Contributions of the European OMCL Network to the Protection of Public Health**

Ms Patricia Courselle, Former Chair of the OMCL Advisory Group

- **The contributions of OMCLs in the fight against Falsified and Illegal Medicines**

Mr Stephen Young, Medicines and Healthcare products Regulatory Agency (MHRA), United Kingdom
(In workshop OMCL Network, 19 June 2019)

4. OMCL Network - Situation in Europe

- Legal supply chain relatively secure
- Cases of falsified medicines in legal supply chain mainly linked to stolen and diverted products often involving parallel trade
- Main issues encountered with illegally purchased medicines via internet and with "Medicines in Disguise"
- Such products (e.g. food supplements, cosmetics, teas...) could also be purchased from legal vendors - e.g. pharmacies, drug stores

4. OMCL Network

- OMCLs collaborate already for many years with **customs, police, justice, health authorities** on identification and quantification of mainly falsified/illegal medicines
- **2004** decision to
 - better **coordinate** work of OMCLs on falsified/illegal medicines testing
 - **share information** between all members
 - set up **common programmes**
 - Activities coordinated by EDQM


4. OMCL Network – Ways of Collaboration

- Testing
- Competence Pooling
- Training and Know-how Exchange
- Data Collection and Exchange (shared between OMCL Network & health authorities/police/customs)


4. OMCL Network - Testing

- Common testing programme since 2012
- 3 Market surveillance studies on suspected illegal products, e.g.
 - Slimming dietary supplements
 - Dietary Supplements advertised as Sexual Potency Enhancers
 - About 2740 samples covered
- 3 Market surveillance fingerprint study projects (chemometrics)

4. OMCL Network – Competence Pooling



OMCL INVENTORY DATABASE



European Directorate for the Quality of Medicines
EDQM - Direction européenne
de la qualité des médicaments
EDQM - European Directorate
for the Quality of Medicines

HOME SIGN IN

Search results for

- Lab activity: Counterfeit/Illegal medicines

27 records / 71

Search results for

- Counterfeit/Illegal Medicine Testing: True

161 records / 5200

HPLC
NMR

MS/MS
Ion trap MS

Raman
Spectroscopy

Time of flight (TOF) MS

X-Ray fluorescence
spectrometry (XRF)

NIR

X-Ray diffraction

Scanning electron
microscopy

4. OMCL Network: Training & Exchange

- OMCL Counterfeit/Illegal Medicines Working Group
- Suspicious Unknown Product (SUP) scheme
 - PTS-like study on unknown samples
 - Laboratories to identify and possibly quantify API in sample(s)
 - 8 SUPs performed; 23 labs/study on average
- Technical training sessions
 - 16 trainings done (e.g. Ultra Performance LC, NIR Spectroscopy, X-ray powder diffraction)
- Symposia
 - 3 done, next in 2020

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5. KnowX Database: Data Collection & Exchange

- Reports on falsified and illegal medical products detected in Council of Europe Member States
- Individual exemplary cases
 - Analytical identification
 - Follow-up actions taken by authorities
- Accessible to OMCLs/health-/police-/customs authorities
- Supports fast reaction of involved authorities
- Restricted access
- In place since March 2014
- Number of reports: about 4000 (status April 2019)

Take home message (1)

- The CoE **MEDICRIME Convention** offers legal framework for **world-wide co-operation** to combat the falsification of medical products and similar crimes, by
 - Obliging states to criminalise falsifications
 - Protection of victims
 - Promotion of collaboration
- The work of the Committee of the Parties has started
- Ratifications should be encouraged

Take home message (2)

- Activities organised by EDQM (conformity assessment, KnowX) or co-ordinated by EDQM (CMED, OMCL Network) complement/support MEDICRIME in fight against falsified medical products
- Activities help to prevent that falsified medical products get into the supply chain and if they are in, identify and remove them

CoE/EDQM's holistic approach helps to protect patients

Thanks to colleagues for their support

Ivan Koedjiov
Frédéric Broise
Thomas Hecker
Ines du Plessis
Richard Wanko

Thank you for your attention



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THE EUROPEAN DIRECTORATE FOR THE QUALITY OF MEDICINES & HEALTHCARE (EDQM)



Content

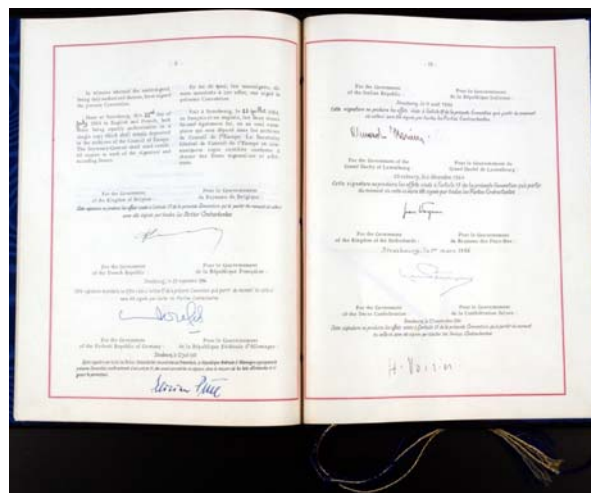
- Where it all started – and what has been achieved
- The EDQM
- The OMCL Network – celebrating its 25th anniversary
- The Certification of Suitability Procedure – celebrating its 25th anniversary
- The European Pharmacopoeia – the 10th edition

Where it all started – the Ph. Eur. Convention

Article 1:

The Contracting Parties undertake:

- to progressively to elaborate a Pharmacopoeia which shall be common to the countries concerned and which shall be entitled "European Pharmacopoeia";
- to take the necessary measures to ensure that the monographs which will be adopted... and which will constitute the European Pharmacopoeia shall become the official standards applicable within their respective countries.



Strasbourg, 22. July 1964

The 10th Edition....



.... Time to reflect about achievements

- **1964:** establishment of the Secretariat of the European Pharmacopoeia Commission based on a convention signed by 8 member States of the Council of Europe
- **2019:** EDQM has almost 400 staff; 38 member States and the European Union have ratified the convention; 28 countries from all continents, the Taiwan FDA and WHO have been granted observer status



.. And since the Tallinn Conference...

- A new signatory party: Republic of **Moldova**
- Three new observers:,   
- Decision to open up Groups of Experts/Working Parties to experts from around the globe
- EDQM is observer to the ICH Assembly and the International Pharmaceutical Regulators Program (IPRP)
- Important contributor to  & IPRP Working Groups

The European OMCL Network

- From the development of a common vision of the European Commission and the EDQM in 1994 to an established and important integral part of the European regulatory network
- A successful cooperation and work-sharing between 70+ OMCLs in more than 40 countries, used as a model in other parts of the world



OMCL High-lights since Tallinn Conference

- Important role in addressing the sartans' issue
- Extension of CAP testing to
 - Biosimilars
 - Parallel distributed CAPs (focus on authenticity testing)
 - API testing
- Market surveillance programmes incorporate refined risk based approaches for selection of samples and test parameters
- Use of chemometric methods to process analytical data sets

OMCL High-lights since Tallinn Conference

- Network-wide implementation of new ISO/IEC 17025:2017 standard
- OCABR network actively addressed and mitigated potential BREXIT impact
- OCABR network pursues approaches on reducing animal testing, e.g. replacement of rabbit pyrogen testing by MAT
-



The Certification of Suitability (CEP) Procedure

- 1992: initiated as pilot to demonstrate usefulness of Ph. Eur.
1994: established as routine procedure
1999: complemented by inspection programme
- True success story due to collaboration with national competent authorities and inspectorates, incl. Health Canada and Therapeutic Goods Administration Australia
 - Added value for the Ph. Eur. Commission
 - Centralised assessment reduces work-load for competent authorities and industry alike
- Accepted by Ph. Eur. Member States and competent authorities around the world, e.g. Australia, Canada, Singapore, South Africa...

High-Lights since the Tallinn Conference

- Implementation of ICH Q3D
- Road-map for e-submissions published – moving towards “eCTD only” in 2020
- Official acceptance of CEPs in Canada without additional DMF submission
- Important contributions to the IPRP Quality of Generics Working Group
- Pivotal role in handling the sartans’ issue
-

Ph. Eur. High-lights since the Tallinn Conference

- The 10th Edition:
 - **2 420 monographs,**
 - **374 general texts** (including general monographs and methods of analysis)
 - around **2 780 descriptions of reagents.**
- **Compared to the 9th Edition:**
 - **114 new** and **683 revised texts =>**
approximately **30% of the content is new or revised**

... and in 3Rs....

- Major progress in the field of biologicals and in 3Rs, including complete deletion of ATT (reflected in WHO recommendation)
- “New” general chapter 5.2.14 “Substitution of in vivo methods by in vitro methods for the quality control of vaccines” to facilitate transition
- Replacement of histamine sensitisation test in mice (HIST) by standardised CHO cell-clustering assay for residual toxin testing; deletion of test for irreversibility of pertussin toxoid
-

In the field of general chapters

What is the objective?

- ✓ To move from reactive to pro-active approach
- ✓ To include recent techniques and ensure that the European Pharmacopoeia is scientifically state-of-the-art
- ✓ To improve existing methods to take into account recent progress in analytical technology and regulatory practice
- ✓ To standardise the content and format of the texts
- ✓ To introduce and/or improve elements of equipment performance and qualification -> increase user-friendliness
- ✓ To introduce and/or improve system suitability tests
- ✓ To minimise or eliminate use of toxic materials

What have we done?

Recently newly elaborated / revised general methods

- ✓ Melting point 2.2.14 (Supplement 9.1)
- ✓ Standardisation of volumetric solutions 4.2.2 (Supplement 9.2)
- ✓ Clarity and degree of opalescence 2.2.1 (Supplement 9.2)
- ✓ Functionality Related Characteristics 5.15 (Supplement 9.2)
- ✓ X-Ray fluorescence spectrometry 2.2.37 (Supplement 9.3)
- ✓ Nickel in hydrogenated vegetable oils 2.4.31 (Supplement 9.4)
- ✓ Water: micro determination 2.5.32 (Supplement 9.4)
- ✓ Infrared Absorption Spectrophotometry 2.2.24 (Supplement 9.7)
- ✓ Loss on drying 2.2.32 (Supplement 9.8)
- ✓ Osmolality 2.2.35 (Supplement 9.8)
- ✓ UV-VIS spectrophotometry 2.2.25 (Edition 10.0)
- ✓ Scanning electron microscopy 2.9.52 (Edition 10.0)

What have we done?

Recently newly elaborated / revised general chapters

- 5.15 Functionality Related Characteristics (Supplement 9.2)
- 5.1.6 Alternative methods for control of microbiological quality standards (Supplement 9.2)
- 5.24 Chemical imaging (Supplement 9.3)
- 5.20 Elemental impurities (Supplement 9.3)
- 5.4 Residual solvents (*keeping up-to-date with ICH guideline*) (Supplement 9.5)
- 5.12 Reference standards (Supplement 9.5)
- 5.25 Process Analytical Technology (Edition 10.0)



What we have in the pipeline: some examples

- Balances 2.1.7
- Evaporative light scattering detection 2.2.62
- Direct amperometric and pulsed electrochemical detection 2.2.63
- Congealing point using rotating thermometer 2.2.68
- Implementation of pharmacopoeial methods 5.26
- Cross-validation 5.27
- Multivariate statistical process control 5.28



What are the challenges?

- To increase visibility before and during the revision process (≠ monographs for which users are notified)
- Finding information on new instruments
- Enrolling method specialists
- Versatility of instruments and methods
- Finding the right balance not to turn the GM into a textbook
- Whether to perform lab testing or not
- Impact on many existing monographs
 - Loss on drying: ~1100 monographs
 - IR: ~1200 monographs
- Revision of some of the historical methods (wet chemistry)
- It takes time to come up with a **good quality text** !



In the field of Finished Product Monographs

Finished Product Monographs

- **2012:** Ph. Eur. Commission reconsidered its strategy => **Pilot phase** initiated with examples of single-source and multi-source products
- **2014:** Strategy to widen the scope of Ph. Eur. agreed, starting with focus on single-source products=> **First monograph** *Sitagliptin tablets* published in Pharmeuropa
- **2015:** Monograph adopted and published in Ph. Eur. 8.7
- **2016:** First monograph came into force on April 1st

9 adopted & published:

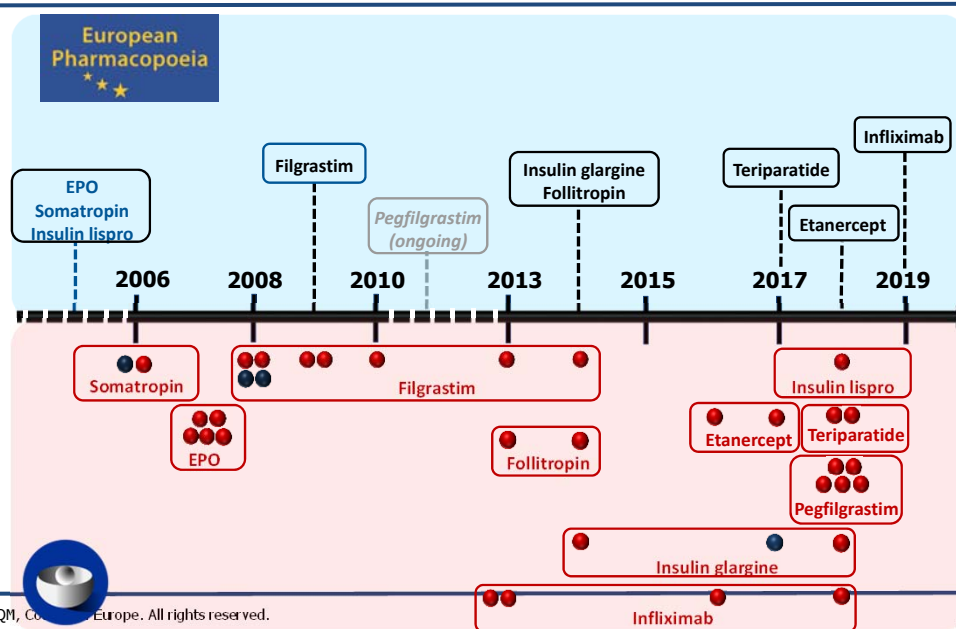
Sitagliptin tablets (8.7)
Raltegravir tablets (9.5)
Raltegravir chewable tablets (9.5)
Deferiprone oral solution (9.7)
Lacosamide oral solution (9.7)
Lacosamide infusion (9.7)
Deferiprone tablets (9.8)
Lacosamide tablets (9.8)
Rosuvastatin tablets (10.1)

Finished Product Monographs

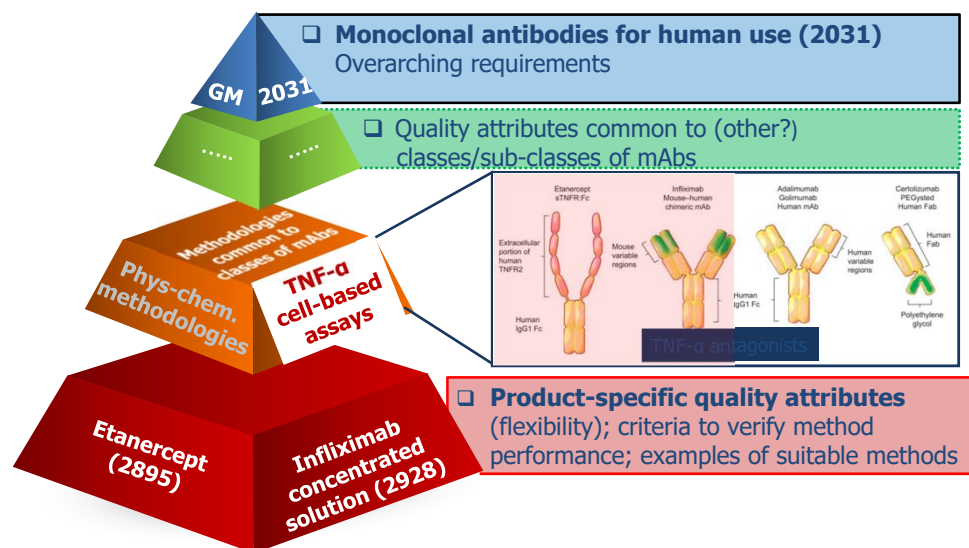
- Ph. Eur. Commission developed “General principles for Monographs on Finished Products (FPs) containing chemically defined active substances”
- Topics under discussion:
 - Dissolution test in individual monographs
 - P1 procedure => impact on already registered FPs

In the field of biologicals

European Pharmacopoeia and Biosimilars



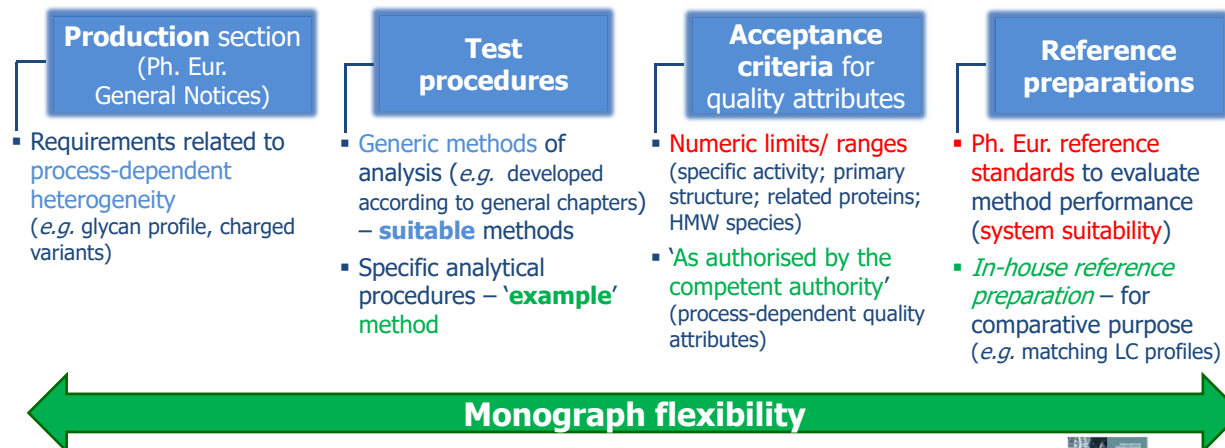
MAB Pilot Phase: Current Activities



Ph. Eur. Monograph Elaboration/Revision: the Process



Ph. Eur. Monographs for Biotherapeutics: **Flexibility**



EDQM website: *Technical guide for the elaboration of monographs on recombinant DNA proteins and synthetic peptides (2018)*



In the field of ... control of impurities

Control of impurities in Ph. Eur.

Organic impurities

Inorganic impurities

Volatile impurities,
Water and residual solvents

Special groups e.g. genotoxic imps,
inorganics subjected to Q3D

Organic impurities: A strength of the Ph. Eur.

- Represent an essential part of individual monographs
- Control strategy implements ICH Q3 A
- Principles are laid down in general monograph 2034
« Substances for pharmaceutical use »
- « Transparency list » at end of a monograph: provides
list of impurities controlled by the test(s) described in
the monograph
- Limits defined for « specified », « unspecified » and a
total of impurities

Other impurities controlled

- **Inorganics:** general tests (e.g. sulfated ash, heavy metals (only for substances for veterinary use), specific tests (AAS, ICP))

Ph. Eur. Commission further fine-tuned implementation strategy of ICH Q3D and adopted revised versions of general monographs on *Substances for pharmaceutical use* (2034) and *Pharmaceutical preparations* (2619), of general chapters on *Elemental Impurities* (5.20) and on *Determination of elemental impurities* (2.4.20).

- **Volatiles:** residual solvents controlled according to general text 5.4 and general chapter 2.4.24. Class 3 solvents may be controlled by LOD (up to 0.5 %). Water most often controlled by semi-micro determination, coulometry or loss on drying.
- **Genotoxic (DNA-reactive) impurities:** as from 1st January 2016 subjected to ICH M7. Control tests in monographs in the test or production section.

Get prepared for the workshops!

Some questions for consideration during the workshops

- ✓ Are the approaches still appropriate?
- ✓ What should we do differently?
- ✓ What more could we do?
- ✓ How to address or circumvent challenges?

Thank you for your attention



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