EDQM: 50 YEARS OF LEADERSHIP IN THE QUALITY OF MEDICINES

PAVING THE WAY FOR THE FUTURE

6-8 October 2014
Strasbourg, France

OPENING PLENARY SESSION

The European Regulatory Landscape

Setting the Scene
The European Regulatory Landscape: Setting the Scene

EDQM Conference: 50 Years of Leadership in the Quality of Medicines
08 October 2014, Strasbourg

Presented by: Anabela Marcal
Head of Compliance and Inspections Department

The European Regulatory System
A brief history

Almost 50 years of European harmonisation

- 1965: First Directive (65/65/EEC) on key principles of approval triggered by the thalidomide catastrophe with aim to protect public health
- 1975: First pharmaceutical testing Directive, listing all required test and trials needed to support a new medicinal product
- 1980’s: EU evaluation by scientific committee for high-tech products needed (CPMP, today’s CHMP)
The European Regulatory System
A brief history

50 years of European harmonisation

- 1993: Regulation (EC) No 2309/93 adopted; centralised evaluation procedure mandatory for certain products, establishment of EU Agency
- 1995: Agency officially opens for business
- 2001: Directive 2001/83/EC (replacing old Directives) - the core legislation governing the regulation of medicines in EU, provides the framework for regulation of medicines at national level

EMA Mission statement

“To foster scientific excellence in the evaluation and supervision of medicines, for the benefit of public and animal health”
Aim of the EMA

- Rapid Access by users to safe and effective innovative medicines through single EU Marketing Authorisation
- Monitoring safety and quality of medicines
- Facilitate innovation and stimulate research and contribute to competitiveness of EU based Pharmaceutical Industry
- Mobilise and co-ordinate EU Scientific resources to provide high quality evaluation of medicinal products
- To advise on research and development programmes
- To coordinate inspections (GXP)
- To provide useful and clear information to users and healthcare professionals

The European Regulatory Environment since 1995 ...

- 1995
  - EMEA Centralised Procedure
  - Mutual Recognition Procedure
  - Orphan Drugs Reg
  - Annex I (to Directive 2001/83/EC) (CTD)

- 2000
  - New Legislation Title IV of Reg.
  - 726/04 immediate
  - Legislation on Paediatrics

- 2003
  - New Legislation fully into force
  - Legislation on Advanced Therapy

- 2004
  - Enlargement (to 25 MS (CY, CZ, EE, HU, LT, LV, MT, PL, SI, SK))

- 2005
  - Enlargement to 27 MS (BG & RO)

- 2006
  - PRAC July
  - New PhV Legislation
  - Falsified Medicines Directive

- 2007
  - Legislation on Advanced Therapy

- 2008
  - Enlargement Scope of CP

- 2010
  - New Variation Regulation

- 2012
  - PRAC July
  - Accession of Croatia June 2013
EMA – EU Network

28 + 3 EEA MS
4,500 European experts

Committee for Orphan Medicinal Products (COMP)
Committee for Medicinal Products for Human Use (CHMP)
Committee on Advanced Therapies (CAT)
Committee for Veterinary Medicinal Products (CVMP)
Committee for Herbal Medicinal Products (HMPC)
Paediatric Committee (PDCO)

EU institutions:
Commission, Parliament

HCP
SA
BWP*
QWP*
ChMP
Pharmacogenomics
Radiopharmaceuticals
Pharmacokinetics
Vaccines
Cardiovascular
HCP
Biosimilars
Biostatistics
Blood Prod
CNS
Infectious Diseases
Rheumatology
Immunology
Oncology

6 The European Regulatory System of Medicines
EMA-EU Network: the role of Working Parties

Quality Working Party:

- Preparation, review and update of quality guidelines
- Provision of scientific advice on general and product-specific matters relating to quality
- Resolution of national divergences regarding the assessment of quality issues
- Liaison with interested parties
- International cooperation on quality related matters, including with EDQM

A Networking Agency

- Member States have pooled their sovereignty for authorisation of medicines
- EMA is designed to coordinate the existing scientific resources of MS
- European experts’ network underpins the work of EMA’s Committees and working parties
- A ‘virtual’ agency, interfacing between all partners
- All parties linked by an IT network (EudraNet)
The European System Post Nov 2005

- Centralised Procedure (via EMA)
- Mutual Recognition procedure
- Decentralised Procedure

- Different authorisation routes: one set of common rules
  - Better Resource Utilisation
  - Harmonised Scientific Opinions
  - Harmonised Information to Doctors / Patients

All Systems allow
EMA-EDQM cooperation

- Sampling and Testing Programme
- Various fields in relation to Quality of medicines
- GMP issues
EMA-EDQM cooperation: Sampling and Testing

- EMA legal requirement: Art 57 r) of Reg 726/2004
- Scope: verify compliance of CAPs with authorised quality specifications
- Pilot phase in 1998; regular annual programmes from 1999
- 1998-2013: approximately 550 CAPs tested (Human and Veterinary)

Number of Centrally Authorised Products tested 1998 – 2013
EMA-EDQM cooperation: Sampling and Testing

Framework contract defining roles and responsibilities:

- EMA proposes annual list of products/pharmaceutical forms
- EDQM coordinates OMCLs Network resources and samplers, and reports on testing results
- EDQM provides advice for the development of the Programmes through Advisory Group Meetings and Network General Meeting
- Significant contributions to the improvement of the Programmes e.g. risk-based approach selection of products for testing; checks of products’ labels
EMA-EDQM cooperation: Sampling and Testing (the future)

- New Agreement to reflect new needs and experiences and consolidate cooperation
- Increase visibility with the stakeholders
- Focus on competences/resources of OMCLs Network (biologicals, IVMP, gases, radio-labelled products)
- Improve supervision through specific actions (biosimilar and generics programmes)
- Harmonisation of risk-based selection of products

EMA-EDQM cooperation: Quality

Regular interactions between EMA and EDQM on different fields:

- EDQM - observer to
  - QWP, BWP, PAT Team
  - Also CAT, HMPC

- EMA observer to Ph. Eur. Groups and WPs
  - e.g Group 6B, 7, 15, PAT, Finished Product Monographs

- Advice from different working parties: BWP, QWP, SWP

- EMA Requests to Ph.Eur for revision of monographs & general chapters (e.g teicoplanin, heparin, blood products)
EMA-EDQM cooperation: Quality

- CEP & QWP
  - Input from QWP on policy documents
  - API starting materials
  - Advice to specific requests

- EMA following Biological Standardisation Programme

- Regular update on EMA and QWP activities at Ph. Eur Commission meetings

  Assessors – Ph.Eur/ EDQM - collaboration and dialogue is essential!

EMA-EDQM cooperation: GMP

- EDQM has observer status at GMP/GDP IWG
- EDQM organises GMP inspections of API manufacturers
  (GMP/GDP IWG consulted on the inspection plans)
- Since last year EMA request to expand scope of inspections to APIs connected to CAPs
- EDQM part of API inspection collaboration project
- EudraGMDP: full read access and write access to planning module
EMA-EDQM cooperation: GMP

Recent/current topics:
- Alignment of inspection triggers
- Ensure efficient use of resources
- Acceptance/Follow-up of negative inspection outcomes
- Inspection report format

EMA-EDQM cooperation

- Continuous and strengthened collaboration
- Harmonisation as relevant
- Efficient use of resources
- Coordination and communication (information exchange)

To ensure that together we achieve our mission of protection to public and animal health.
Congratulations

Good job!
EDQM, 50th Anniversary

The Regulatory Landscape: A National Regulatory Authority’s Perspective

Outline

- Introduction: The Council of Europe, EDQM and Switzerland
- The European Pharmacopoeia: A collaborative network
- Work-Sharing: Certification and OMCL
- Counterfeiting and the Medicrime Convention
- Summary
Introduction: CoE, EDQM and Switzerland

Switzerland: Member of the Council of Europe and EFTA

Switzerland: Swissmedic, Swiss Agency for Therapeutic Products as the competent authority for medicinal products and medical devices

Some key figures about Swissmedic
- Headcount: 360 FTE (= 440 employees)
- Budget: 90 Mio CHF

International network
- 13 agreements with partner agencies
- ACSS Consortium with Australia, Canada, Singapore
Introduction: CoE, EDQM and Switzerland

Quality in the Center…

Mission Statement EDQM
Our mission is to contribute to the basic human right of access to good quality medicines and healthcare and to promote and protect human and animal health…

Mission Statement Swissmedic
…. ensure that authorised therapeutic products are of high quality, effective and safe.
…. contribution towards protecting the health of humans and animals.

What EDQM does…

HealthCare  The European Pharmacopoeia  Control of Medicines  Certification of Suitability
Introduction: CoE, EDQM and Switzerland

... and how it interacts with a National Regulatory Authority like Swissmedic

**Marketing authorisation:** Standards for and documentation of quality for active ingredients and excipients; CEP

**Market surveillance:** Tools/mechanisms and international platforms for dealing with illegal medicines, CMED

**Licensing:** Blood products/transfusions, standards and cooperation GEON, European Pharmacopoeia

**Legal Service:** Penal enforcement of cases of illegal import/trade; Medicrime Convention

**Communication and Networking:** International cooperation, coordination/prioritisation

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**The European Pharmacopoeia**

**Regional and Global Status of the European Pharmacopoeia**

- Member States of the European Pharmacopoeia Convention: Legally binding
- Widely used internationally – impact beyond membership to the Convention
- Cooperation with other pharmacopoeias (international harmonisation)
- Switzerland is a founding member of the Convention, together with seven other countries (B, D, F, I, LUX, NL, UK)
The European Pharmacopoeia

**Governance** of the European Pharmacopoeia
- **European Pharmacopoeia Commission (COM)**
  - Approves the monographs of the European Pharmacopoeia
  - Consists of the delegations of the members states of the European Pharmacopoeia Convention
  - National delegation: three members, three alternate members
- **Groups of Experts**
  - Approx. 20 standing groups; cover a broad range of topics
- **Working Parties**
  - approx. 50 „ad hoc“ working parties; new scientific and technical developments

Swissmedic is the National Pharmacopoeia Authority in Switzerland which has the following responsibilities
- Ensuring cooperation with and contribution to the work of the European Pharmacopoeia
- Providing the national point of contact for the European Pharmacopoeia
- Submitting national comments
- Elaborating the Swiss Pharmacopoeia, complementing the European Pharmacopoeia
- Coordinating work of Swiss experts
- Providing the scientific secretariat for the Swiss network
The national components: **Swiss Pharmacopoeia Bodies**

**Swiss Pharmacopoeia Commission**
- Advisory role for Swissmedic
- Approves monographs of the Swiss Pharmacopoeia
- Consists of heads of technical committees and working groups

**Technical committees**
- Chemistry, Biological products, herbals, complementary medicinal products, galenics
- Develop texts of the Swiss Pharmacopoeia
- Provide feedback on draft monographs of the European Pharmacopoeia (collated feedback is submitted to EDQM by Swissmedic)

**Working groups**
- Ad hoc groups for specific topics

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**The Swiss Network: A joint effort…**

Technical experts involved in the work to elaborate monographs come from:

- Swissmedic (pharmacopoeia, OMCL, marketing authorisation, market surveillance)
- Other Federal Offices (e.g. Institute for Virology and Immunology)
- Cantons (cantonal pharmacists)
- Universities
- Pharmaceutical industry
- Hospital pharmacies
- Laboratory pharmacies ("Offizinapotheke")
- Pharmacy of the Swiss Army
- Drugstores ("Drogerien")
In summary: how does it work…?

The European Pharmacopoeia

Challenges for the European Pharmacopoeia
- Increasing number of members (and observers) → unanimous decision-making?
- Sustainability of the process (Experts, translations)?
- Increasing importance of harmonisation
- Increasing influence of globalisation (USP, JP, Int. Ph.) with an increasing need for cooperation

→ Harmonised, transparent and up-to-date quality standards are increasingly important with complex, globalised supply chains
Work-Sharing: Certification and OMCL

Reliance and Work-Sharing: a true benefit of international cooperation

**Recognition**

Unilateral or mutual recognition (GMP inspections, marketing authorisations)

**Reliance**

Work-sharing, relying on assessment or inspection reports from other regulators

**Confidence building/harmonisation/convergence**

Confidentiality agreements, international cooperation initiatives aiming at harmonisation/convergence, staff exchanges, international peer review, networking events

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Work-Sharing: Certification and OMCL

Prioritisation and Reliance: The Swissmedic Approach

**National context**

**Prioritisation**

- Focussing on risk
- Conduct own assessment of innovative medicinal product applications
- Focus on maintaining high GXP standards in own territory

**Reliance**

- Equivalence & trust
- Consideration of other regulators assessments for generic applications
- Rely on outcome of other regulators’ inspections for foreign manufacturing sites
Benefits of the Certification Procedure

• Work-sharing approach in the assessment of applications as well as in the inspection of manufacturers
• Gain experience in the harmonised implementation of current requirements and guidelines
• Capacity to review applications containing CEP is low (compared to a DMF-procedure or review of CTD content)
• Changes and variations can be submitted as notifications, again saving review capacity

The Official Medicines Control Laboratories Network

• 57 full members, 9 associated members and three limited members
• Coordinated by EDQM

All Members
• QA Programme
• Proficiency Testing Studies (PTS)
• General Market Surveillance Scheme (MSS)
• Educational activities
• Applied analytical research and standards development

EU/EEA*
• Centrally authorised Products Sampling and Testing Programme (CAP)
• MRP/DCP Post-Marketing Surveillance Scheme
• OCABR (Official Control Authority Batch Release) and OBPR (Official Batch Protocol Review)**

* Switzerland “where appropriate”/**based on MRA
Benefits of the General OMCL Network (GEON)

- Facilitate the exchange of information, know-how/expertise and results
- Collaborative projects:
  - Joint databases (OCABR)
  - Trainings (technical/quality, IT, staff visits)
  - Annual OMCL Meeting (2014: Interlaken CH)
- Harmonisation of analytical activities based on the utilisation of common standards
- Promotion of trust amongst members
- Work-sharing (batch release vaccines/blood products)

Counterfeiting and the Medicrime Convention

The Council of Europe Medicrime Convention is the first international agreement that aims to combat the illegal trade of medical products.

The ratification of the Medicrime Convention

Council of Europe convention on the counterfeiting of medicinal products and similar crimes involving threats to public health.

Consultation procedure

The Council of Europe Medicrime Convention is the first international agreement that aims to combat the illegal trade in medicinal products. Switzerland signed the Convention on 28 October 2011.

With the Therapeutic Products Act and associated ordinances, Switzerland has a very good basis for prosecuting counterfeits of medicines. However, before the Convention can be ratified, some adjustments to the Therapeutic Products Act (TPA) and the Criminal Procedure Code (CPG) are required. These revisions in particular focus on improving the exchange of information, expanding methods of criminal investigation and clarifying the legal situation regarding the provision of medicinal products.

Counterfeiting and the Medicrime Convention

The Medicrime Convention
The ratification of the Medicrime Convention is the perfect occasion to:

- Make political actors and the public aware of the risks of counterfeit medical products
- Assess the system in place and improve it
- Improve and strengthen domestic and international cooperation
- In Switzerland, the ratification process is ongoing and planned to be completed in 2017.

Committee of Experts on Minimising Public Health Risks posed by Counterfeiting of Medical Products and Similar Crimes (CMED)

- Creation of the „SPOC model“: network of SPOCs (Single Points of Contact) for fighting illegal medical products, promoting and supporting the establishment of national and international SPOCs networks
- Trainings of national authorities on how to combat counterfeiting medical products and to protect public health
- Establishing a database of counterfeit and illegal medicinal products („KnowX“ database)
- Promoting the Medicrime Convention and its implementation
- Communication and Publications, e.g. Counterfeit Medicines Facts and – practical advice/risk communication
Summary

How working with EDQM supports Swissmedic to achieve its goals

- Harmonised quality standards contribute to **transparency** of requirements
- **Ratification of Medicrime Convention** provides necessary tools for enforcement
- **Exchange of information** between the members of the networks in the different areas and **work-sharing** across members contributes to increased efficiency
- Harmonised quality standards contribute to **quality/consistency** of review/ regulatory actions

→ In summary, contribution to initiatives of EDQM helps to effectively use resources

Systematically/consistently increase transparency
Strengthen enforcement and increase awareness
Focus international cooperation on benefits
Define and implement quality requirements
Effectively use resources

Happy 50th Anniversary!
EDQM: 50 Years of Leadership in the Quality of Medicines
Paving the Way for the Future

50 years European Pharmacopoeia
Achievements & future challenges

Dr. Jean-Louis ROBERT
Chair European Pharmacopoeia Commission

Overview

- Role of a pharmacopoeia
- European Pharmacopoeia
  - Organization
  - Strengths
  - Achievements
  - Future challenges
- Conclusion
Role of a Pharmacopoeia

- Pharmacopoeia (derived from the ancient greek):
  - pharmaco: drug
  - poiesis: making

- Collection of criteria for the quality of substances for pharmaceutical use

- Harmonization of these quality criteria and establishment of common standards

- Essential basis for the free movement of medicines within a legal/political entity

European Pharmacopoeia

- **Post 1945:** Brussels Pact, Western European Union, Partial Agreement of the Council of Europe ........
- **1961:** Initial discussions on medicines within the Common Market
  1st agreement:
  > Need for common standards, need for a common pharmacopoeia
- **1964:** Creation of the European Pharmacopoeia
  (within the Partial Agreement of the Council of Europe)
  Founder states:
  BeNeLux, DE, FR, IT + CH and UK
- **2014:** 38 signatory parties + 27 observers
- **First centralized body in the pharmaceutical field!**
Lab

Meinau
Today

Status: Legally Binding Reference

• The Ph. Eur. is legally binding in all the signatory states of the Convention.
  • The monographs of the European Pharmacopoeia shall be applicable to all substances, preparations and pharmaceutical forms appearing in it.
  • For other substances, each member state can require compliance with its own pharmacopoeia.
Ph. Eur. Organisational chart

Ph. Eur. Commission
38 signatory parties:
- 28 EU member states
- European Commission
- 9 non-EU member states
- 27 observers:
  8 European countries, 17 non-European countries,
  Taiwan Food and Drug Administration (TFDA)
  World Health Organization (WHO)

Presidium:
- chair
- 2 vice-chairs
- Ph. Eur. secretariat

Meetings of the
Presidium +
Chairs of groups of
experts

Groups of experts

Contributors:
- National Pharmacopoeia Authorities
- National Competent Authorities
- Industries
- OMCL Network

Publication

- Table of contents
- Volume 1
  - Introduction
  - General chapters
  - General texts
- Volume 2
  - Individual monographs

Volume 1 (1969): ± 120 texts
Volume 8 (2014): > 2600 texts
Process: Creation or revision of a text

Ph. Eur. Commission

Adoption
Creation/revision

Final adoption

Group of experts

Public consultation

Contents of the European Pharmacopoeia:
More than 2300 Monographs and 330 General chapters

Biologicals 3,4%
Chemicals 53,7%
Dosage forms 3,0%
Herbals 11,0%
Blood deriv. 1,8%
Plastics 2,1%
Antibiotics 6,2%
Fats 5,1%
Human vaccines 4,7%
Radiopharm. 2,9%
Vet. Vaccines 4,7%
Homoeopathy 0,5%
Biologics 3,4%
Gases 0,8%

Strengths of the Ph. Eur.

- Composition of the COM: member states
- Guarantees acceptability of monographs
- Composition of the groups of experts:
  - Contribution of national expertise
  - Mixture of experts from competent authorities, universities, industry
    - Guarantees a high scientific standard
- Close collaboration with the national and European licensing authorities
  - Up to date with regulatory developments
  - Allows regular re-adjustment of quality criteria

Strengths of the Ph. Eur. (2)

- Collaboration at the international level
- Certification Procedure (CEP)
  - Permanent re-evaluation of monographs
- Flexibility of texts whilst guaranteeing quality: ultimately the Ph. Eur. prevails
Contributions of the Ph. Eur. to the Quality of Medicines

- Thanks to all its strengths, the Ph. Eur. guarantees:
  - A high standard of quality
  - Predictability for pharmaceutical manufacturers
  - Effective test methods to be used by official medicines control laboratories
- Ultimately: medicines that are safe for use by patients

Major Achievements

- Bringing people together, forum for dialogue, harmonisation, better understanding .....  
- Essential role in the pharmaceutical area  
  Adaptation to regulatory and scientific-technological development  
  – Taking into account the need of licensing authorities and of industry  
  – Change from tlc to hplc  
  – Alternative methods  
  – “QbD” principles  
  – ....................
**Major Achievements**

- “Transparent” monographs
- Certification of Suitability (CEP)
  - Chemicals
  - TSE
- Knowledge database

**Recent Developments**

- Preparation of:
  - Individual monographs on finished products (pharmaceutical preparations)
    - *Specific request from third countries*
  - General monographs on high-technology methods of analysis to keep up with scientific progress and new techniques for pharmaceutical development and manufacturing of medicines
Challenges for the future

- Strengthen the position of the Ph. Eur. in a globalised world
  - Ph. Eur. to act as reference for the quality of medicines
- Effect of globalisation:
  - Increase in the number of pharmaceutical players
  - Need to guarantee a global quality that takes into account different manufacturing processes
- Guarantee quality in the face of a growing demand for generic medicines
- Adapt to technical and scientific progress
- Adapt to changes in legislation

Challenges for the future (2):
Continuous improvement
Conclusion

• European Pharmacopoeia: A big success

• First centralized body in Europe in the pharmaceutical area.

• An example of collaboration among countries

• Absolute need to be further supported with national expertise
The Certification of suitability procedure
20 years after its official implementation
in Europe - the benefits of work-sharing
between Member States

Dr Marianne Ek, Chair, Steering Committee Certification
Senior expert/Pharmacopoeia strategist
Medical Products Agency, Uppsala, Sweden

HISTORY

• In the late 80's
  – Request from QWP to Ph. Eur to better understand what is
    controlled by monographs with regards to impurities
    • Due to arrival of new sources of active substances in Europe,
      with various routes of synthesis
  – Followed by discussions between licensing authorities,
    pharmacopoeia and industry about how to ensure
    adequate impurity limits
    • They saw a need
      – for more transparency of the pharmacopoeia monographs
      – for a harmonisation among licensing authorities
      – to strengthen the relations between the pharmacopoeia, the
        licensing authorities and the pharmaceutical industry
HISTORY

• **1992**
  – The Certification Procedure was started as a pilot project
    • the manufacturer was requested to demonstrate that a
      substance could be adequately controlled by the monograph
      in the European Pharmacopoeia.
      – thus ensuring the link between manufacturer, licensing dossier
        and the European Pharmacopoeia.
      – the European Pharmacopoeia Commission agreed at its 82nd
        meeting that this was to be considered as an investment for the
        future since there would be considerable saving of resources at
        all levels in the long term.

HISTORY

• **June 1993**
  – The Procedure for the certification of suitability of
    monographs of the European Pharmacopoeia was
    adopted by the Public Health Committee (Partial
    Agreement) (CD-P-SP) in its resolutions AP-CSP (93) 5
    ➢ The Administrative phase started at the secretariat level

• **April 1994**
  – a special account for receiving the dossier fees for the
    Certification of suitability exercise was opened by a
    decision of the Representatives on the Committee of
    Ministers of the States Parties to the Convention on the
    Elaboration of a European Pharmacopoeia
    ➢ The procedure could start
**HISTORY**

- **June 1994**
  - Formal decision by the European Pharmacopoeia Commission to implement the procedure
    - Decision to create a Technical Advisory board (TAB)
- **1999**
  - The procedure was extended to include products with a risk of transmissible spongiform encephalopathy (TSE),
    - thus enabling their certification on the basis of the European Pharmacopoeia general chapter 5.2.8
  - The EDQM initiated an inspection programme for manufacturing sites, covered by an application for certificate(s) of suitability to the monographs of the European Pharmacopoeia (CEPs).
    - Pilot phase with volunteer companies

- **March 2000**
  - The European Pharmacopoeia Commission took the decision to create a Steering Committee with representatives from both the Pharmacopoeia and the licensing authorities
    - The mandate for the new Steering Committee was administrative matters and to resolve interface problems between the licensing authorities and Pharmacopoeia.
    - The mandate for TAB was general supervision of scientific evaluations
- **2003**
  - The procedure was extended to include Herbals
    - 1st dossier was received 2008
20 years after the official start

GOVERNING DOCUMENT FOR THE CERTIFICATION PROCEDURE

• Resolution AP-CSP (07) 1
  adopted by the Public Health Committee of the Council of Europe
  – Describes the process for the procedure
  – Available on the EDQM website www.edqm.eu
SCOPE OF THE CEP PROCEDURE

• Substances described in monographs in the Ph. Eur. (Active substances, excipients, herbal drugs / herbal preparations)
  → “Chemical” or “Herbal” CEP

• Products with risk of TSE (starting materials, intermediates, reagents,..)
  → “TSE” CEP

• Open to any manufacturer regardless of geographical origin

OUT OF SCOPE OF THE CEP PROCEDURE

• Substances not included in Ph. Eur.
• Biologicals
• Human tissues derivatives, blood derivatives, vaccines
• Mixtures of API with excipients (unless justified)
• Substances which do not comply with the Definition section of the monograph, if applicable
STRUCTURE OF THE PROCEDURE

• A Steering Committee:
  – implements the 3Cs (consultation, co-ordination and co-operation) that characterise the certification procedure. Its members are representatives of public health authorities (representatives of the main regulatory bodies are involved). Its primary responsibilities are to:
    • take decisions on general policy
    • review and comment on issues raised by the Technical Advisory Boards
    • adopt guidelines and the inspection programme
    • co-ordinate issues between the parties represented
    • appoint the assessors and the Technical Advisory Boards (TABs) and their respective Chairs.

STEERING COMMITTEE MEMBERS

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

• Technical Advisory Boards (Chemical substances, TSE, Herbals):
  – Experienced assessors in the procedure
    • Assist other assessors
    • Prepare technical guidance for adoption by the Steering Committee
    • Divergences in assessment are brought to the TAB for clarification and harmonisation
• Assessors from the Ph. Eur Licensing Authorities
• Inspectors from EU/EEA supervisory Authorities

STRUCTURE OF THE PROCEDURE

• EDQM Certification of Substances Division:
  – a team of scientific Officers, Inspectors, Secretaries and Technicians responsible for managing, in a confidential manner, the applications and the inspections.
  – coordinate the procedure
WHO PERFORMS THE EVALUATION?

- **Assessors**
  - with suitable experience and competence in the relevant domain (chemical evaluation, TSE risk, herbal products, toxicologists)
  - proposed by National Competent Authorities from Ph.Eur. Licensing Authorities
  - and approved by Steering Committee.

- **Come regularly to EDQM premises for the evaluation of dossiers**
  - 80 assessors from 21 countries for chemical evaluation (In total 466 days in 2013)
  - 7 assessors for Herbals
  - 7 assessors for TSE
HOW LONG DOES IT TAKE?

• Applicant notified by EDQM on the assessment conclusion within 5 months of receipt of the new dossier
• If additional information is requested, responses from applicant expected within 6 months
• Responses assessed within 4 months
• Strict procedure applied - only one request for additional information

CEP: WHAT DOES IT MEAN

• A chemical CEP certifies that the quality of the substance is suitably controlled by the Ph. Eur. monograph with addition of tests if necessary (mentioned on the CEP)
• A TSE CEP certifies that the substance complies with the EMA NfG on minimising the TSE risk. It DOES NOT certify that the quality of the substance is suitably controlled by a specific Ph. Eur. monograph
• It DOES NOT replace a certificate of analysis
• It IS NOT a GMP certificate
WHERE CAN I SUBMIT A CEP?

- In all Ph. Eur Member States (n=37)
- In Australia, Canada, Saudi Arabia, Singapore, South Africa, Taiwan
- And other countries…

NB. Authorities outside the EU/EEA may have special requirements (copy of DMF, certified copies of CEPs, etc)

EDQM Inspection programme

- Integral part of the Certification Procedure
- 24 active inspectors
- Inspections involve sites holding or applying for CEP(s) and are performed before or after the CEP is granted
- Inspections performed mainly outside Europe (mainly India, China)
- Selection of sites to be inspected with a risk based approach
- Aim: to verify the compliance with:
  - submitted dossier
  - EU GMP Part II
  - EU GMP Annexes (e.g. Annex 1 / sterile substances)
INSPECTIONS

• Inspections are performed by team composed of an EDQM inspector and an inspector coming from an EU/EEA Competent Authority

• Immediate actions are taken in case of major/critical deficiencies (suspension/withdrawal of CEP)

INSPECTION OUTCOMES

• Positive outcome:
  – GMP certificate granted by EU/EEA inspector (EudraGMP)
  – Attestation granted by EDQM

• Negative outcome:
  – Non-compliance statement issued by EU/EEA inspector (EudraGMP)
  – Suspension/withdrawal of CEPs by EDQM
INSPECTION FIGURES IN 2013

• 34 sites covered by EDQM inspections
• 29 sites covered by exchange of information (inspections by EEA inspectorates)
• 2 sites refused to be inspected (suspension of CEPs)

NB: high non compliance rate is observed with re-inspections of sites inspected in the past!

- No sustainable GMP!
- Up to 50% of the inspections are re-inspections

INTERNATIONAL COLLABORATION

• Confidentiality agreements with authorities from Australia, Brazil, Canada, Russia, Singapore, Chinese Taipei, Ukraine, USA, and WHO
  – Covers inspection results and/or evaluation of dossiers
• Visit of officials from different authorities (Brazil, Malaysia, Singapore, Saudi Arabia ……)
  ➢ Increases acceptance of CEPs worldwide
INTERNATIONAL COLLABORATION

• Collaborations for inspections
  – Joint inspections (US FDA, WHO)
  – Regular exchange of inspection results with authorities
    “worldwide”
  – International API inspection programme
  – PIC/S

EDQM is also involved in

• EU ASMF Work-sharing:
  – Pilot ASMF – group
  – Opportunities for work-sharing between ASMF and CEPs
  – CEP evaluation reports available on-line (securely) for the authorities from Ph. Eur. Member States

• IGDRP (International Generic Drugs Regulatory Pilot):
  – Benefit of CEPs experience
SUMMARY

• Key figures
  – Since 1994, more than 5600 CEP applications received for 850 different substances
  – Currently more than 3800 valid CEPs
  – 1000 manufacturers from 50 different countries

• These numbers change frequently as new applications are received and existing CEPs are revised daily.

Repartition of manufacturers (2013)
SUMMARY

• Benefits - Saving resources
  – the assessment of the Active Substances Master file (ASMF) is centralised
  – contribute to the harmonisation of the assessment of ASMF:s
  – a help to keep the European Pharmacopoeia up-dated
  – contribute to the Inspection of the active substance manufacturers
  – link between the assessors, industry and pharmacopoeia

SUMMARY

• Saving resources for the assessors
  Example:
  – On average, it takes 3 day´s to assess an ASMF
  – You do it once
  – If the CEP is used in 10 countries
    ➢ save 27 day´s
• We have 3800 CEP:s ---
  and you can submit them to all Ph. Eur Member States (n=37), to Australia, Canada, Saudi Arabia, Singapore, South Africa, Taiwan and to other countries...
I want to thank Hélène Bruguera, Head of the Division Certification of substances for her help with the material to this presentation.

I also want to thank all of you for listening.
20 years of the European OMCL – Network Contribution to Safeguarding Public Health

Carmen Jungbäck
Chair of GEON Advisory Group

Strasbourg, October 2014

Background

- 1994: EU – Commission and Council of Europe:
  Decision on collaboration on quality control of marketed medicinal products for human and veterinary use

- 1995: EDQM mandated with the responsibility to run this activity
OMCL

- **Official Medical Control Laboratories (OMCL´s)**
  - Support regulatory authorities in controlling the quality of the medicinal products

- **Terms of Reference (ToRs) define the OMCL´s**
  - Public institution
  - Independent from manufactures
  - Clear mandate in the field of quality control of medicinal products

EDQM

- **Network´s secretariat responsible for:**
  - Coordinating the structural network activities
  - Organisation of different joint programmes
Network’s Mission

- Mutual recognition of test results
- Improve communication among OMCL’s
- Facilitate knowledge and worksharing
- Exchange information on work programmes
- Coordinated activities among OMCLs
- Harmonize working methods
- Organize collaborative studies on validation of methods
- Promote development of harmonised standards
- Contribute to the establishment of reference substances and preparations
- Collaborate with the relevant partners

Level of collaboration

- General activities open to all members
  - Quality Assurance programme
  - Proficiency Testing Scheme (PTS) studies
  - General Market Surveillance Scheme (MSS)
  - Educational activities
  - Applied analytical research and standardization development

- Special activities for OMCL’s from EU and EEA
  - Centrally Authorised Product (CAP) – sampling and testing
  - Mutual Recognition Procedure (MRP) and Decentralized Procedure (DCP) Post Marketing Surveillance Scheme
  - Official Control Authority Batch Release (OCABR) for human biological products
  - OCABR and Official Batch Protocol Review (OBPR) for immunological veterinary medicinal products (IVMP)
GEON Advisory Group (1)

- **Role:**
  - Represents the GEON between the annual meetings
  - Helps to run the GEON
  - Discussion body
  - Gives advice on the work programme

- **Composition:**
  - 8 Representatives elected by GEON
  - Director of EDQM or authorised representative
  - Representative of EU Commission
  - Representative of EMA (observer)

- **Meetings:**
  - 2 times a year and upon convocation
  - draft agenda open for proposals from the GEON
GEON Advisory Group (2)

- Responsibilities:
  - Procedures for testing
  - Databases of communication and exchange of results
  - Draft agenda of the Annual Meeting (General Session)
  - Draft annual work programme for the GEON
  - Topics of particular interest for discussion and promoting mutual recognition
  - Future developments for independent testing
  - Quality Management System
  - Status of applicants and members of the GEON
  - New documents

20 years of the European OMCL – Network Contribution to Safeguarding Public Health

Milestones (1)

- 1994: EU Commission mandates
  OMCL Network activity to Council of Europe - EDQM
  1st PTS
- 1995: 1st network procedures and guidelines
  1st plenary meeting H-OCABR [1995 (V)-1996(B)]
- 1996: 1st GEON OMCL Meeting with Annual Reports
  1st QA guidance docs
- 1997: 1st MSS
  MJV/MJA begins
- 1998: CAP testing pilot programme
- 1999: Regular CAP programme launched
  VBRN discussions commence
- 2000: 1st VBRN Annual Meeting
  MRP/DCP Trial phase Post Marketing Surveillance (PMS)
- 2001: H-OCABR Annual Meeting joins GEON Annual Meeting
Milestones (2)

- 2003: Common Reference for QMS of OMCLs is ISO/IEC 17025
- 2004: VBRN Annual Meeting joins GEON Annual Meeting
  PTS opened to manufacturers
- 2006: Start of data collection on illegal medicines testing
  MRP/DCP Regular PMS
- 2007: OMCL inventory database launched
  MRP/DCP product testing database launched
  1st Joint MJA with National Accreditation Bodies (NAB)
- 2008: 1st Suspicious Unknown Product Study (SUP)
- 2009: H-OCABR database launched
- 2011: API WG
  Counterfeit/Illegal Medicines WG
- 2012/2013: First MSS on Illegal Products (MSSIP)
- 2013: First MSS on Medical Devices
- 2014: KnowX database launched

Membership Status 2014

- 57 Full members
- 9 Associated members
- 3 Limited members

coming from 40 countries (members and observers of Ph Eur)

Annual Meeting 2014

220 Participants
55 OMCL’s
35 Countries
OMCL Annual Meetings

Meeting takes place once a year in a Member State of the GEON

1996 Strasbourg, FR 2006 Limassol, CY
1997 Bled, SL 2007 Prague, CZ
1998 Vendargues / Montpellier, FR 2008 Strasbourg, FR
1999 Hillerod, DK 2009 Vienna, AT
2000 Lisbon, PT 2010 Split, HR
2001 Uppsala, SE 2011 Düsseldorf, DE
2002 Bilthoven, NL 2012 Copenhagen, DK
2003 Warsaw, PL 2013 Helsinki, FI
2004 Langen, DE 2014 Interlaken, CH
## Quality Management (QM) Programmes

**Goal:**
Harmonise the quality management policies of the OMCLs

**Tools:**
- Quality management guidelines to implement ISO/IEC 17025
- Recommendation documents providing additional guidance
- Mutual Joint Visits (MJVs) 1997-2013: 50 MJVs
- Mutual Joint Audits (MJAs) 1997-2013: 107 MJAs
- Education activities 1997-2013: 20 Training visits
  - Training of OMCL staff in QM
  - Training of auditors

## PTS studies

- **Performed since 1995**

  - **Physico-chemical products:** 4-6 studies/year
    - 28-49 OMCLs/study
    - 27-40 non-OMCLs/study
    (since 2007)

  - **Biological products:** 2-7 studies/year – first study 1998
    - 11-24 OMCLs/study
    - 10-13 non-OMCLs/study
    (since 2007)
**MSS studies**

- Performed since 1995
- Outcome induces revision of a large number of Ph. Eur. monographs
- 2-6 studies/year
- 12-20 (-all) OMCLs/study

**OCABR for Human Biologicals**

- Started in 1994 based on earlier networking activities begun by EU MS in 1989 to support Directive 89/342 EEC
- OCABR-specific network within the GEON (EU/EEA + MR partners)
- Advisory Group: 6 representatives
- Legal basis: Art. 114 of Dir. 2001/83/EC as amended
- Mandatory mutual recognition necessitates high confidence and application of codified working methods
- Administrative procedures in force
- Product-specific guidelines with protocol templates in place
- Pre-marketing testing
OCABR/OBPR for IVMPs

- Started 1999
- VBRN-specific network within the GEON (EU/EEA + MR partners)
- Advisory Group: 4 representatives
- Legal basis: OCABR: Art. 82 of Dir. 2001/82/EC as amended
  OBPR: Art. 81 of Dir. 2001/82/EC as amended
- Mandatory mutual recognition (OCABR) necessitates high confidence and application of codified working methods
- Administrative procedures in force
- Product-specific Guidelines Model Protocol Templates
- Pre-marketing testing

CAP sampling & testing programmes

- Started 1999 (regular programme after trial phase in 1998)
- Centrally authorized products (hum + vet)
- Sponsored by EMA
- Coordinated by EDQM (distribution, final report)
- Advisory Group: 6 OMCL representatives (plus 1 EMA representative)
- National inspection services gather sample products from the market (3 different countries)
- OMCLs perform testing
- Products to be tested identified by EMA
- 40 products per year to be tested
MRP/DCP – Post Marketing Surveillance Scheme

- Started 2000 (trial phase); since 2006 regular programme
- Products (including generics) licensed via MRP/DCP
- Voluntary basis
- No Advisory Group but Group of all participating OMCLs
- Avoids duplicate testing
- 700 medical products tested per year

Focus Groups

- 2008 Reflection Group on Quality Monitoring of Stockpiled Medicines
- 2008 Working Group on Gene Therapy
- 2011 OMCL Testing Group on Unlicensed Pharmaceutical Preparations
- 2011 API Working Group
- 2011 Counterfeit / illegal Medicines Working Group
Conclusion

OMCL Network:

- Leads to adjustment of quality of OMCLs’ work
- Fosters exchange of know-how between OMCLs
- Increases lab-to-lab comparability of results (OMCLs + manufacturers)
- Enables saving of resources
- Supports standardisation
- Increases transparency of test results
- Promotes mutual recognition

The Network's contribution to Safeguarding Public Health

- Rapid information of the outcome of testing to all OMCLs and NCAs leads to immediate identification of deficient products/batches
- Quick identification of OMCLs being able to perform tests in emergency situations via database
- Standardisation increases comparability of test results
- Increase of knowledge on product by access of all data on PTS, MSS, BRP and other collaborative studies
- Contributions to revisions of monographs of Ph. Eur. ensure that testing of medicinal products is performed to current scientific knowledge
The OMCL Network

coordinated by EDQM

is a very successful activity of

European Union
and Council of Europe

Happy Birthday and ad Multos Annos

General European OMCL Network
Progress and Achievements since the Prague Conference 2010

Dr Susanne Keitel
EDQM, Director

Agenda

• Outcomes of the Prague Conference
• Progress and Achievements
  o Biologicals
  o Control of Impurities
  o Application of 3R Principles
  o Adaption to regulatory, scientific and technical developments
• International Harmonisation
• Combatting Counterfeit/Falsified Medicines
Outcomes of the Prague Conference

1. Characterisation of biological molecules
   Ph. Eur. monographs fit for purpose giving further consideration to, e.g. specificity of monographs, standardisation of methods, speed of revision process.

2. New technologies
   e.g. RTRt, Design Space: currently limited experience on both sides (industries and regulators), but expected to rapidly increase.

3. Control of Impurities
   Upcoming technical developments such as fast-LC and new stationary phases, LC-MS techniques, NMR will find its use in the European Pharmacopoeia

4. Application of 3R principles
   Global harmonisation of requirements for animal tests is still a dream. Initiatives have been started.
   Need for:
   - Prioritisation of work programme
   - Global collaboration/communication
Outcomes of the Prague Conference

5. The European Pharmacopoeia – is it prepared for the future?
   Yes, with continuous adaptation to regulatory, technical and scientific challenges

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Biologicals

• New molecules need to be adequately covered in the Ph.Eur. and an overall strategy discussed
  ➢ A pegylated protein and a monoclonal antibody added to the Ph. Eur. work programme
  ➢ Closed workshop with representatives of competent authorities in Feb. 2011 to discuss how best to proceed, followed by a number of smaller meetings with regulators and members of Biologicals groups of the Ph. Eur. Commission

Biologicals

• Acknowledged that an appropriate equilibrium is crucial to ensure a monograph is
  ✓ flexible enough so that it can cover a large variety of products
  ✓ detailed enough so that analytical methods can be performed successfully in a control laboratory

• Discussions on future format of “biological monographs” ongoing
April 2013 EDQM/EMA Workshop: Raw materials considered to be the most critical from a quality perspective

Two New Working Parties

- **Raw Materials for the production of cell-based and gene therapy products (RCG):** To elaborate a text concerning the quality aspects of raw materials for the production of cell based and gene therapy products.

- **Host-Cell protein (HCP):** General chapter to provide recommendations with regard to the development, validation and use of in-house or commercial kits or test methods for the detection and quantification of host-cell proteins.
### Biologicals

- More to be shared during the workshop on Biologicals, e.g. update on the latest developments in the biological field
- Opportunity to discuss further how the Ph. Eur. can best serve its stakeholders in biopharmaceuticals of the future!

### Control of Impurities

- Use of **Fast-LC** identified as an issue - and taken up by the CST working party
- Use of **NMR** in the control of impurities and **more flexibility** in the use of LC-MS techniques are further topics to be followed-up
Control of Impurities

Potentially genotoxic impurities in monographs:

- **general monograph 2034 Substances for pharmaceutical use** revised in line with the CHMP Guideline on the limits of genotoxic impurities (in force since 1.1. 2007)
- “new” general chapters already introduced in the Ph.Eur. or *underway*:
  - 2.5.37 Methyl, ethyl and isopropyl methanesulfonate in ethanesulfonic acid
  - 2.5.38 Methyl, ethyl and isopropyl methanesulfonate
  - 2.5.39 Methanesulfonyl chloride in methanesulfonic acid
  - 2.5.40 Methyl, ethyl and isopropyl toluenesulfonate
  - 2.5.41 Methyl and ethyl benzenesulfonate

Control of Impurities

- ICH Q3D - Control of Elemental Impurities - step 4 sign-off scheduled for Sept. 2014
- Once adopted by CHMP
  - will replace the EMA guideline on the specification limits for residues of metal catalysts or metal reagents
  - as a consequence chapter 5.20 will be revised and chapter 2.4.20 reviewed
  - Reference to chapter 2.4.8 will be deleted from individual monographs (except for vet use only)
  - Impact on other chapters referenced in individual monographs and that cover elemental impurities in scope of the ICHQ3D guideline under evaluation
Control of Impurities

- Ph.Eur. known for its scientifically-sound policy on control of impurities
- Remains key feature of Ph. Eur. monographs
- cf workshop on Impurities

Application of 3Rs

- International Communication & Harmonisation
  - Project of European Commission to promote harmonisation on an international level
  - Collaboration of regulators for CAPs (JEG 3RS)
  - Work on application of «Consistency Approach» (EPAA)
  - Replacement of proof of correlation by proof of concordance for validation of alternative methods
- New EU Directive 2010/63 EU in force
Application of 3 Rs

- Progress in the Biological Standardisation Programme (BSP)
  - 3Rs Conference in 2011 on successful application of 3Rs concept to tetanus immunoglobulin, acellular pertussis vaccine and rabies vaccine for vet. use
  - 2012: in vitro assay for hepatitis A vaccine
  - 2013: Five 3Rs projects underway
- Establishment of EDQM website summarizing all 3Rs projects and achievements (BSP and Ph. Eur.)

"New Quality Paradigm"

the application of e.g. Quality by Design and RTRt

- Adoption of a number of new or revised texts to facilitate and encourage application of innovative approaches, e.g.:
  - update of General Notices to take account of EMA Guideline on the use of Near Infrared Spectroscopy (NIRS)
  - Revision of chapter 2.2.40 Near Infrared Spectroscopy, elaborated in parallel with the EMA Guideline
  - New optional chapter 2.9.47 Demonstration of Uniformity of Dosage Units Using Large Sample Sizes
“New Quality Paradigm”
the application of e.g. Quality by Design and RTRt

• On-going: new chapter 5.21 on chemometric methods applied to analytical data (*published in Pharmeuropa 26.2*); chapter on chemical imaging

• important to further follow developments, e.g. in the field of application of QbD principles to analytical methods

• cf. workshop on Quality by Design

General Methods

• Need to keep pace with technical and scientific developments

• Decision of the Ph. Eur. Commission to create a new working party (*General methods*) to reflect on:
  • best approaches to tackle revision needs of general methods
  • content and degree of details to be provided in general methods.
Finished Product Monographs

• In principle new for the Ph. Eur.
• Introduction of general monograph Pharmaceutical preparations (2619):
  • reference source of standards in the European Pharmacopoeia on active substances, excipients and dosage forms
  • not a guide on how to manufacture.

Finished Product Monographs

• crucial to ensure the required quality level of finished products in Europe and to maintain the essential role of the Ph. Eur. in the global protection of public health
• to be balanced with the need of not stifling innovation
Finished Product Monographs

• Pilot-project on finished product monographs initiated in 2012; outcome presented to Ph.Eur. Commission in March 2014 session
  ➔ 1st draft (Sitagliptin phosphate monohydrate tablets) published in Pharmeuropa 26.3 for public enquiry

• cf workshop on Finished Product Monographs

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**International Harmonisation**

- Pharmacopoeial Discussion Group (PDG)
- PDG-derived activities
- International Meeting of World Pharmacopoeias and Good Pharmacopoeial Practices

**Pharmacopoeial Harmonisation**

- More information will be provided during the workshop on Pharmacopoeial Harmonisation
- Opportunities and challenges: discussion to take place with sister Pharmacopoeias during the workshop session
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Combatting Counterfeiting

• Holistic Council of Europe strategy (legislation, detection, prevention)
• Council of Europe MEDICRIME Convention open for signature and ratification
• Support of Convention by
  • Training of health authorities
  • Setting up and maintaining network of Single Points of Contact (SPOCs)
  • Knowledge Database for OMCLs and enforcement authorities
Combatting Counterfeiting

- Support of work of OMCLs (Counterfeit Working Group)
  - Symposium on counterfeited APIs (2011)
  - Symposium on «Medicines in Disguise» (2014)
  - Technical training on detection of falsified products
  - PTS studies on Suspicious Unknown Products
  - Market Surveillance Studies on suspected illegal products
  - Market Surveillance Studies on APIs (API fingerprinting)

To Summarise....

- The Prague Conference has helped us to identify important issues to be followed up
- A lot has been achieved, but....
- .... protecting public health will continue posing challenges and will remain the focus of our work!
Thank you for your attention!