EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

The European Pharmacopeia & Quality of Medicines: Tackling Future Challenges Together

Tallinn, Estonia 27-28 September 2016

Presented by Prof Guido Rasi on 27 September 2016

An agency of the European Union

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EMA/EURN (global?) regulatory challenges

Sustainability

- Health systems (medicines prices)
- R & D (patient access to innovation, Europe competitiveness)

Quality

- Medicines (safety, efficacy, availability)
- Scientific opinions (complexity)

Regulatory Challenges

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New Medicines

- Innovative products and regulatory challenges (ITF trends)
- Biologicals and Biosimilars
- Vaccines (in view of regulatory challenges)
- ATMPs (gene therapy, stem cell and tissue therapy)

Methodological Challenges

- Globalisation
- New marketing authorisation and monitoring procedures
- New ways to generate evidence (RWE)
- New evaluation methods (Mapp, Prime, Joint HTA-SA)

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ITF recent trends analysis (2013-2015)

- **Borderline products and Novel and technologies**
  - Cosmetic / Food
  - Biomaterials
  - Demarcation towards cell, tissue and blood regulation
  - Combination products
  - Nanotechnology
- **Regulatory framework** for "really" **Personalised Medicines**
  - N=1 trials
  - treatment algorithms
  - Modelling and Simulation / Extrapolation
- **eHealth**
  - Health Apps,
  - electronic data collection / processing in CTs / e-consent
- **Bedside manufacturing**
  - bring the (individualised) product to the patient,
  - technical integration / cont. manufacturing / QbD

Biologicals: rapid innovation + growth in many areas, e.g.

- Monoclonal antibodies: realising their potential
  - *Antibody - Drug Conjugates, ADC: Kadcyla (trastuzumab emtansine) - breast cancer*
  - *Bispecific antibodies: Blincyto (blinatumomab) – B cell ALL*
  - *PD1 inhibitors: Keytruda (pembrolizumab), Opdivo (nivolumab) – metastatic melanoma*
  - *Immunotherapy (oncology)*
- Antimicrobial resistance / Health threats
  - *Bacteriophage therapy: cocktail targeted to bacteria*
  - *Ebola (e.g. VSV vectored vaccines, mAbs); Zika*
- Improved manufacturing processes, diagnostics and analytical methods
  - *Modular, continuous manufacture, Companion diagnostics*
  - *Characterisation tools, in-vitro bioassays: Quality foundation for biosimilars*

Regulatory challenges - vaccines

- Improve definition of immune markers of protection
- Communication aspects (HPV vaccines referral on POTS/CRPS)
- Need for expedited regulatory pathways for emergency (Ebola & Zika)
- Development stage related constraints and supply availability
- Flexible approach to efficacy/effectiveness study design during an outbreak
- International collaboration (WHO, art 58 or Joint reviews)

Regulatory challenges – ATMPs (gene, cell and tissue engineered products)

ATMP Scientific field is moving rapidly

- Challenge to keep scientific guidelines up to date
- Current regulatory framework needs to be adapted

ATMPs are expensive products

- Small batches (e.g. autologous products: 1 batch = 1 patient) → High production and testing cost
- Often orphan indication: limited return on investment
- Early engagement with HTA's essential

What is a condition (disease)?

"There is a compelling case for reforming the taxonomy of human disease by moving away from traditional diagnostic criteria alone to ones that incorporate the scientific advances in molecular and genetic medicine.."

"Failure to do so perpetuates ineffective treatment in medicine…"

Nature Reviews Drug Discovery **10**, 641-642 (September 2011) | doi:10.1038/nrd3534

A call to reform the taxonomy of human disease

Ismail Kola[1] & John Bell[2]

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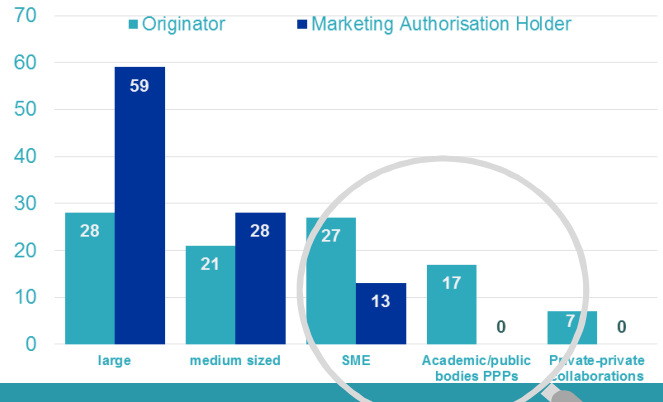
Responding to globalisation of industry and R&D

- Major theme of **EU Medicines Agencies Network Strategy to 2020**
- Regulators must respond to support global drug development <u>while also</u> ensuring public health imperatives are met ('we are **facilitators** and **gate-keepers**')
- Collaboration and work-sharing to promote **convergence, avoid duplication**
- **PRIME**
- **Adaptive Pathways**

Innovation

Origins of new medicines

EU 2010-2012



Of 94 novel *authorised* medicinal products:

- Large majority marketed by large or intermediate sized companies.
- SMEs and academia at the origin of innovation.

The typical long route of medicines to patients

Development phase:

Chance of reaching access for a product entering the development phase:

0.01-0.1% 5-10% 50-60% 75-90%

Regulatory provisions primarily targeting the time to access:

- Conditional MA,
- Accelerated Assessment,
- Compassionate Use …

Regulatory provisions primarily targeting the risk of development failure:

- Scientific advice
- Support to SMEs …

Why do drug development programs fail (or get delayed)?

A) "if further development proves initial hypotheses wrong." **Often inevitable**

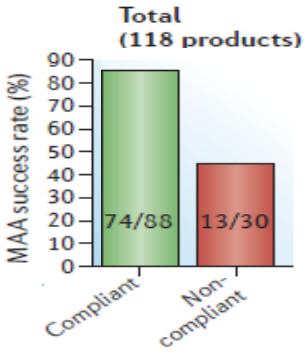
B) Inappropriate development program, wrong studies **Usually preventable**

Who takes the risk?

Companies, investors, **and trial patients**

Positive impact of SA adherence on MAA outcome

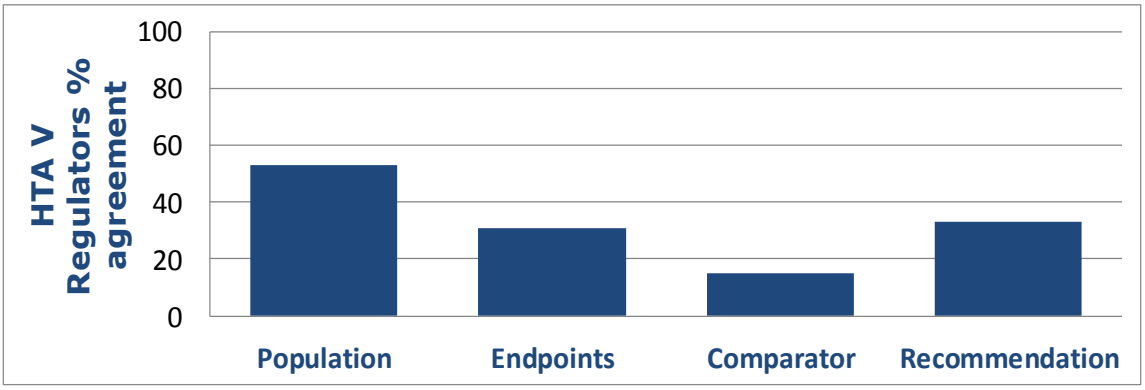
MAA success for MAAs with SA/PA submitted in 2008–2012



Hofer et al, Nat Rev Drug Discov, 2015

Making the case

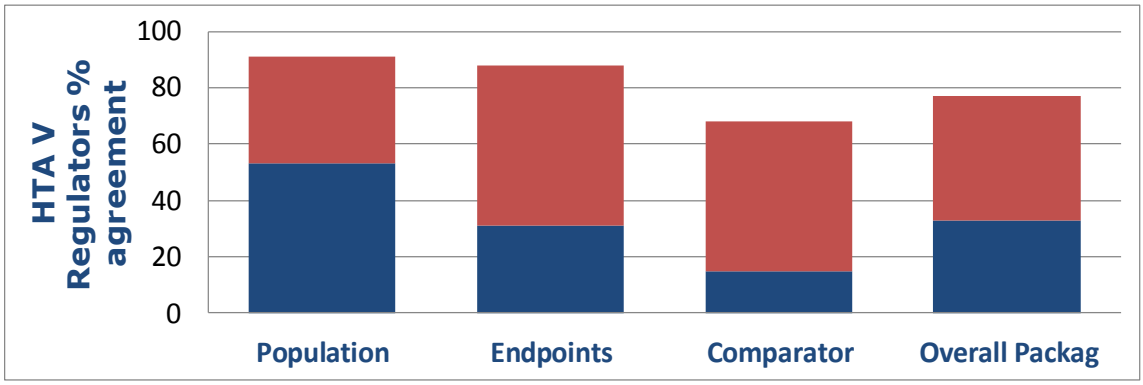
56 products



http://www.efpia.eu/documents/189/61/HTA-Accelerator-In-Depth-Analysis-Final-report

Can Parallel Advice Help?

Commonality?



What we do not have

- A robust environment of venture capital
- A clear strategy to attract investments
- A single approach to access for patients
- A lean regulatory process

What we do have

- A strong and productive academic environment
- A sufficient number of start-up and SME

and….

An effective and supportive regulatory network

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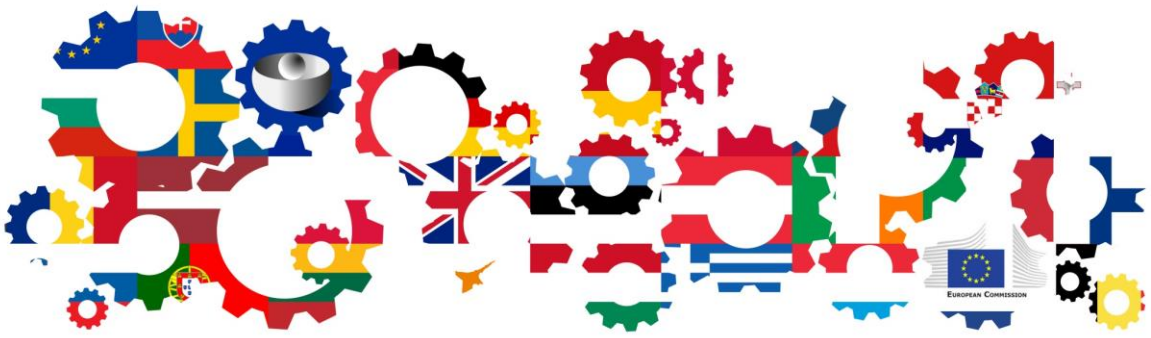
The European medicines regulatory network



~ 50 national regulatory authorities | European Commission | European Medicines Agency

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Strong national authorities are essential for EU sustainability and quality

- Hub of expertise for the centralised & national assessment
- Hub for local academia & industry
- Hub for pharmacovigilance
- Link to HC systems, Health Care Professionals and patients
- Hub for post marketing data generation (HTA/payers)

ITF/EUIN

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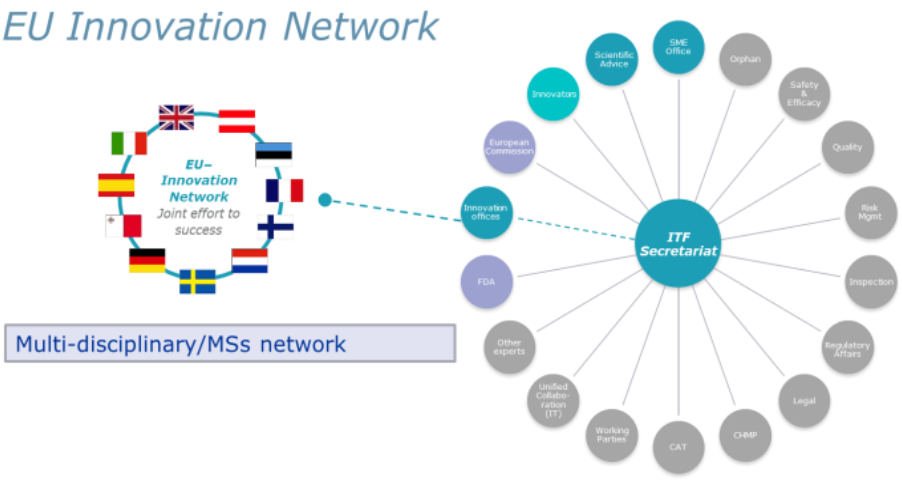
- **"Expertise" gap / bridge** for SA during drug development



……. And we have EDQM!

EMA-EDQM cooperation

Aims for

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

In Key Areas

- Sampling and Testing Programme
- Various fields in relation to Quality of medicines
- Cooperation in Good Manufacturing Practice Standards and Inspection

EMA-EDQM cooperation: Sampling and Testing

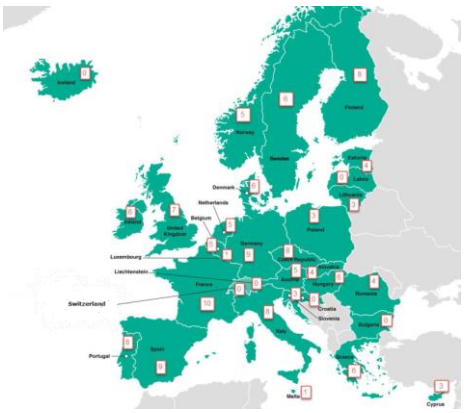
- EMA legal requirement: Art 57 r) of Reg 726/2004
- Scope: verify compliance of CAPs with authorised quality specifications
- Pilot phase in 1998; regular annual programmes from 1999
- 1998-2013: approximately 550 CAPs tested (Human and Veterinary)

EMA-EDQM cooperation: CAP Sampling and Testing

Risk Based Selection Model

Sample Human and Vet / CHEM / BIO / Orphan / other specialised products e.g radiopharmaceuticals.

- Samples taken across EU.
- Samples taken from 3 climatic zones.
- Testing involving OMCL's across EU.
- EDQM co-ordination with excellent interim and final reports to EMA



EMA-EDQM cooperation: Quality & GMP

Regular interactions between EMA and EDQM in different areas:

- EDQM - observer to
  - QWP, BWP, PAT Team
  - CAT, HMPC
  - Good Manufacturing and Distribution Practice Inspectors Working Group (GMDP IWG).

EMA observer to Ph. Eur. Groups and WPs

- e.g Group 6B, 7, 15, PAT, Finished Product Monographs
- Certification of suitability to the Monographs of the European Pharmacopoeia Steering Committee Meeting.

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EMA-EDQM cooperation: Quality & GMP

- 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 Comm meetings
- 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: Good Manufacturing Practice

Recent/current topics:

- Ensure efficient use of resources – EMA and EDQM collaboration through API International Inspection Programme
  - Exchanges of site of interest and inspection plans and schedules
  - Alignment of inspection triggers
  - Rational use of inspector resources
- Collaboration on cases of serious non-compliance with GMP – Impact on CEP's / MA's
- Co-processed excipients monograph.

Conclusions

- The future will see technical and regulatory challenges from new products, new production technologies, new evaluation methods.
- Globalisation of manufacturing supply chains will continue in future
- The need to assure quality of medicines and appropriate manufacturing standards are applied will remain unchanged;

EMA & EDQM collaboration and dialogue is essential
To ensure we achieve our mission of

protection of public and animal health.

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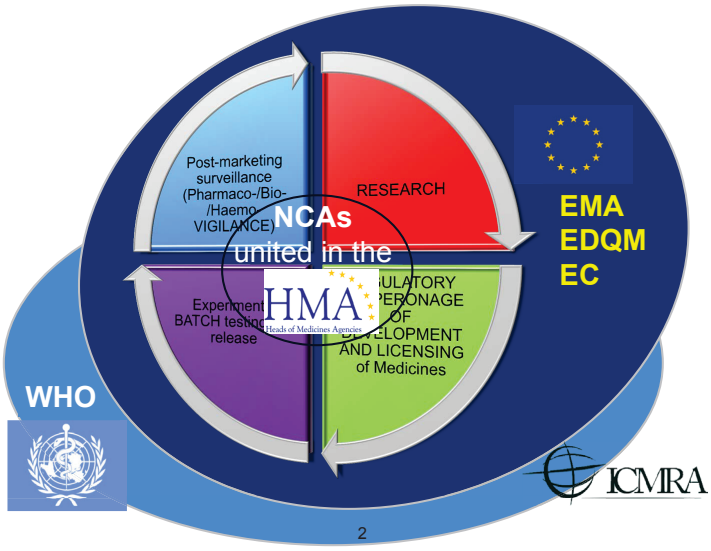
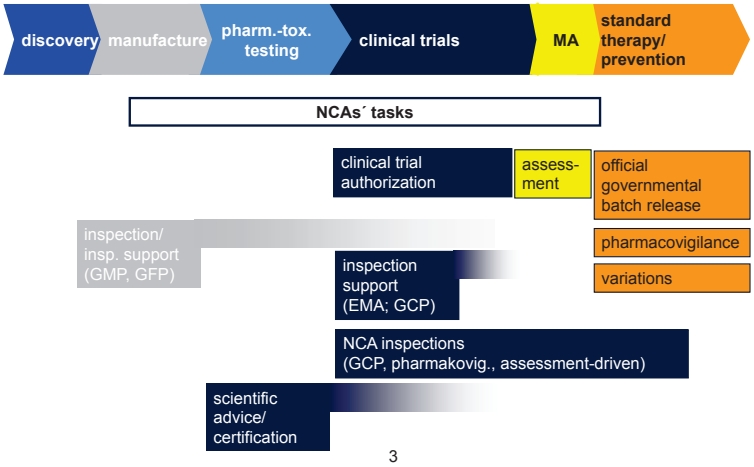
EDQM and HMA cooperation on the quality of medicines

- **HMAs mission, vision, strategy**
- EDQM´s and NCAs´ complementary roles
- Pharmacopoiea
- OMCL network
- Biological reference preparations
- Blood and tissue products
- OMCL Gene Therapy Working Group

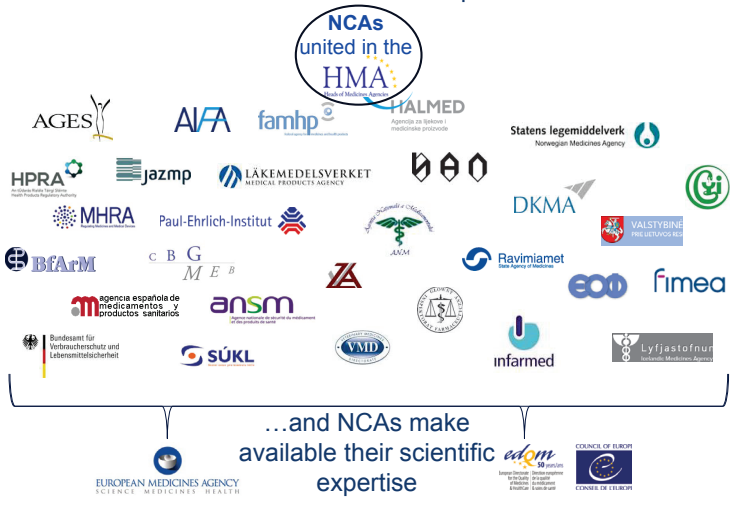
Klaus Cichutek
chair, HMA MG



NCAs support all phases of medicinal product development

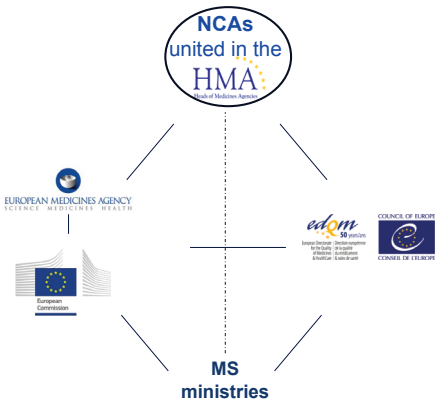


European medicines regulatory network includes all EU MS and EEA NCAs represented in the HMA…

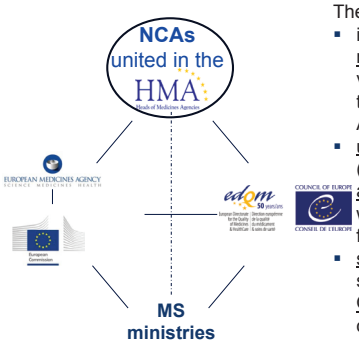


HMA meetings
with EDQM Director as invited observer

Regulating medicines in Europe



Regulating medicines in Europe



The **European medicines regulatory network**

- is based on network of all national medicines regulatory authorities for both human and veterinary medicines from Member States in the European Union and European Economic Area,
- united in the Heads of Medicines Agencies (HMA),
- and the European Medicines Agency (EMA), working closely together in an integrated fashion,
- supported by other European organisations such as the European Directorate for the Quality of Medicines & HealthCare (EDQM) of the Council of Europe.

Milestones: HMA strategic documents

1) EU Medicines Agencies Network Strategy til 2020

- First „high level" HMA / EMA Strategy covering the most important themes and challenges

2) HMA Multi-Annual Work Plan

- 11 key business priorities
- 41 goals
- covering all the themes laid down in the Strategy

HMA Priorities
Antimicrobial resistance
Availability of good quality appropriately authorised medicines
Competence development programme through the EU Network Training Centre
Developing an efficient, effective and collaborative approach on inspections to address sustainability
Innovation and access to new medicines
International collaboration
Optimisation of the regulatory operations
Responding to public and animal health emergencies.
Strengthen surveillance
Implementation of the Telematics strategy
Support for better use of medicine

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EDQM´s mission

- to **contribute** to the basic human right of **access to good quality medicines and healthcare** and
- to **promote and protect human and animal health**

- **EDQM actions to achieve its mission**
  - related to pharmaceuticals
  - establishing and providing official standards which apply to the manufacture and quality control of medicines (in all signatory States of the "Convention on the Elaboration of a European Pharmacopoeia" and beyond)
  - ensuring the application of these official standards to substances used in the production of medicines;
  - co-ordinating a network of Official Medicines Control Laboratories (OMCL) to collaborate and share expertise among Member States and to effectively use limited resources;
  - related to blood and tissues
  - proposing ethical, safety and quality standards:
  - for the collection, preparation, storage, distribution and appropriate use of blood components I n blood transfusion;
  - for the transplantation of organs, tissues and cells;
  - combat of counterfeits of medicines
  - collaborating with national, European and international organisations in efforts to combat counterfeiting of medical products and similar crimes;
  - safe use of medicines
  - providing policies and model approaches for the safe use of medicines in Europe, including guidelines on pharmaceutical care; and by
  - ~~cosmetics and food packaging~~
  - establishing standards and co-ordinating controls for cosmetics and food packaging.

Cosmetics and food packaging not HMA-related

EDQM´s mission

- establishing and providing official standards which apply to the manufacture and quality control of medicines (based on the ("Convention on the Elaboration of a European Pharmacopoeia")

EDQM´s output

- Pharmacopoiea monographs
- Certificates of suitability
- Guidelines
- Reference material for assay standardization

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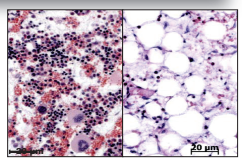
- European Union Directives 2001/82/EC, 2001/83/EC, and 2003/63/EC, as amended, on medicines for human and veterinary use. These maintain the mandatory character of European Pharmacopoeia monographs when requesting marketing authorisation.

NCAs´ role

- assure adherence to Pharmacopoiea standards of manufacturers
  - in the assessment of applications for
    - manufacturing authorization
    - clinical trial authorization
    - marketing authorization application
  - in GMP inspections
- Controlling provision of measures as shown by certificates of suitability in MAAs
- Promoting the use of reference material during product testing

Quality matters for vaccines: „calf hemorrhagic disease“ post vaccination of cows with a vaccine showing quality defect

- bovine neonatale pancytopenia – new syndrome since 2007
- hemorraghic disease (spontaneous bleeding, unstoppable bleedings, bldgs following injections, ear marks contreived)
- thrombocytopenia and leukopenia in calves < 1 month old (fed with colostrum), born from mother cows vaccinated against bovine diarrheal disease (BVD)
- caused by BVD- vaccine Pregsure with quality defect
- transfer of anti-cell antibodies to calves binding to bone marrow cells



Bone marrow: left side from a healthy 3-week old calf: all progenitor cells indlg. Megacaryyocytes; detectable; right side: from a 3-wwek old calf suffering from BNP (no progenitor cells detectable)

Fotos: Bianca Weber und, Mathias Büttner, LGL Bayern

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Cooperation between EDQM and NCAs: Development of Ph.Eur. Monographs (1)

Example: New product specific monograph 2928:
„Infliximab concentrated solution“

- Text developed between 2013 and 2016 in the MAB Working Group
- Monograph includes detailed test procedures to check the pharmaceutical quality of the drug substance.
- Verification of tests performed at PEI, Immunochemistry Section:
  - Peptide mapping
  - Isoelectric focusing (IEF)
  - Ion exchange chromatography (IEX)
  - *N*-linked oligosaccharides map
  - Capillary electrophoresis (CE-SDS)
  - Size exclusion HPLC (SEC)
  - Protein concentration

Cooperation between EDQM and NCAs: Development of Ph.Eur. Monographs (2)

- Infliximab monograph
  - sets quality product standard for Infliximab
  - which is legally binding and
  - facilitates the assessment of counterfeits or biosimilars
- Currently licensed Infliximab monoclonals:
- Originator:
  - Remicade (Roche)
- Biosimilars:
  - Remsima (Celltrion)
  - Inflectra (Hospira)
  - Flixabi (Samsung Bioepis)

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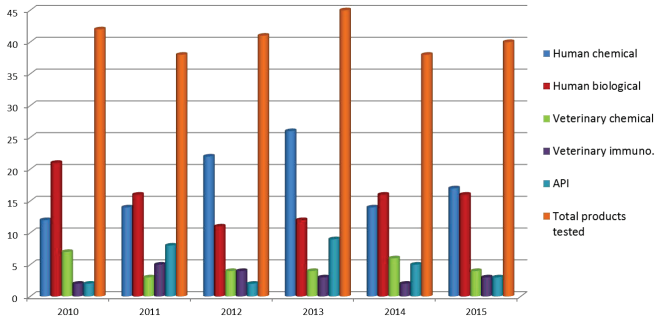
OMCL network (GEON) collaboration

- **1994** joint project of EU Commission und Council of Europe
- **1995 EDQM established as Secretariat/Coordinator of the General European OMCL Network (GEON)**
  - General:
    - Quality Assurance-Programs (ToRs, QM-Guidelines)
    - Proficiency Testing Scheme - Studies
    - Market Surveillance Scheme
    - Training programs
    - Development of methods and standards
  - Product-Specific:
    - CAP
    - MRP/DCP – Post Marketing Surveillance
    - OCABR-human
    - OCABR/OBPR-veterinär (VBRN)

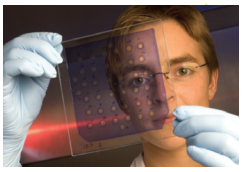
CAP Programme 2014 and 2015

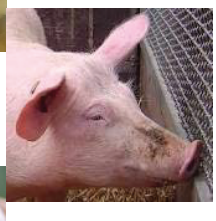
- 2014
  - 30 human products (16 biologicals, 14 chemicals) and 8 vet. products; Generic programme for Pramipexole and Telmisartan
  - Sampling in 26 member states
  - Participation of 36 OMCLs from 27 member states
- 2015
  - 33 human products (16 biologicals, 17 chemicals) and 7 vet. products; Generic Programme for Irbesartan and Temozolomide
  - Sampling in 28 member states
  - Participation of 35 OMCLs from 25 member states

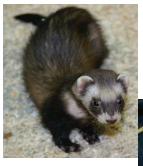
Number of products tested in the CAP programme 2010-2015



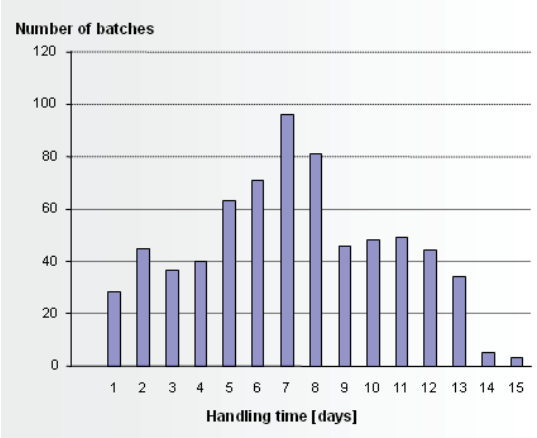
Tasks: Batch Release







OCABR of plasma derivatives: handling time much shorter than the legally set time of 2 months



Recalls, refusals and withdrawals of allergen product batches 2009-2014

Year	Product Group	Recalls Refusals	With-drawals	Total	Details
2009	Test allergens[1]		1	2	OOS[3] Protein content
	Therapy allergens[2]	1			No efficiacy documented
2010	Test allergens		9	11	OOS Aluminum concentration. Phenol concentration, Protein content
	Therapy allergens		2		Raw material changed
					Non-conformity with Ph. Eur.
2011	Test allergens		15	25	No identification test, missing protein determination
	Therapy allergens		10		OOS potency determination
					Deviation from authorized specification
					Mislabelling
2012	Test allergens	21		38	Stability problems
	Therapy allergens	9	8		No product acc. §3 (2) TAV
					Vigilance case
					OOS protein content, potency
2013	Test allergens	1	4	34	OOS stability
	Therapy allergens	16	13		OOS protein content, potency
2014	Test allergens	24	10	37	OOS stability
	Therapy allergens	3			OOS protein content, potency

[1] Prick- and Provocation tests
[2] Therapy allergens and allergens subjected for therapeutical use according Therapy Allergens Ordinance (TAO)

OCABR of veterinary vaccines

Table 2: Examples of findings during OCABR.

Category	Observation	Conclusion
Visual aspect	• Lyophilisate colour does not comply with description in the dossier	• Wrong vaccine – No release
Composition	• Amount of adjuvant not homogeneous (separation during filling) • Reduced stability of emulsion • Residual moisture content too high	• No release • No release • No release
Quality	• Prolonged dissolution time of the lyophilisate pellet (problems with lyophilisation) • Foreign object in the lyophilisate pellet • Bacterial and fungal contamination detected • Non approved primary container	• No release • No release, GMP-inspectors informed • No release • Release after approval
Safety	• Endotoxin content too high • Extraneous agent testing not performed according to accepted validated test	• No release • Release after validation and approval of new test
Potency	• Result of potency test OOS • Product inconsistencies: inconsistency of protein content due to blending faults.	• No release • No release

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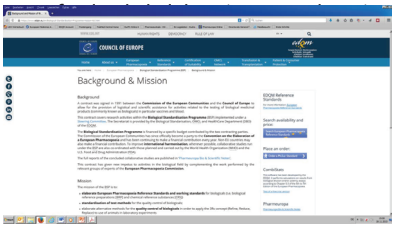
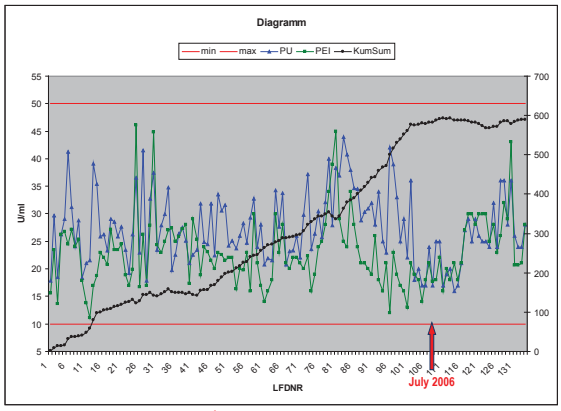
Mission of the EDQM BSP

- **Elaborate European Pharmacopoeia Reference Standards and working standards** for biologicals (i.e. biological reference preparations [BRP] and chemical reference substances [CRS])
- **Standardisation of test methods** for the quality control of biologicals;
- Elaborate **alternative methods** for the quality control of biologicals in order to apply the **3Rs concept (Refine, Reduce, Replace)** to



The value of standards: CuSum clotting factor XIII; component of a fibrin glue



Implementation 1st Int. Standard for Faktor XIII: 2005

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EDQM and HMA cooperation on the quality of medicines

- HMAs mission, vision, strategy
- EDQM´s and NCAs´ complementary roles
- Pharmacopoiea
- OMCL network
- Biological reference preparations
- **Blood and tissue products**
- OMCL Gene Therapy Working Group

European Committee on Blood Transfusion (Steering Committee; CD-P-TS)

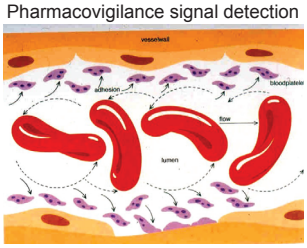
- Guide to the preparation, use and quality assurance of blood components
  - One of the most influential guidance documents in transfusion medicine
  - Bi-annual updates; 18th Ed.
- Interaction Group 6B and OMCL Network
  - The monographs and general chapters of the European Pharmacopoeia set out the official standards for medicinal products.
  - The elaboration and revision of methods and texts is carried out by the Ph. Eur. Groups of Experts and Working Parties.
  - Group 6B covers this work in the field of human blood and blood products.

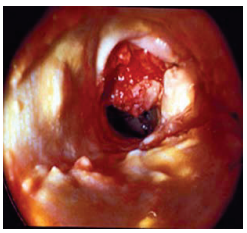
Interaction Group 6B and OMCL Network
Examples

- Assay for human coagulation factor II (2.7.18)
- Prekallikrein activator test (2.6.15) in human albumin (0255) and human normal immunoglobulins for intravenous administration(0918)
- Monograph „human normal immunoglobulins for intravenous administration“ (0918) and monograph „human normal immunoglobulins for subcutaneous administration“ (02788): Need for a harmonised test for procoagulant activities
- Monograph „Fibrin sealant kit“ (0903): Clarification regarding the test for coagulation factor XIII
- Monograph „human anti-D immunoglobulin for intravenous administration“ (1527): Anti-A/B haemagglutinin testing
- Monograph „Human albumin solution“ (0255): Molecular size distribution

Thrombembolic events post IVIG administration caused by contamination with activated clotting factor XIa

- Manufacturing process altered
- pH changes led to insufficient abrogation of clotting factor XIa contaminants
- Pharmacovigilance signal detection





Interaction Group 6B and OMCL Network
Procoagulant activities in IVIGs (1)

Initiating the development of a test method for monograph „Human normal immunoglobulins for intravenous administration“ (0918) with respect to procoagulant activities

- Based on discussions with regulators and OMCLs, Expert Group 6B decided to include a test for procoagulant activity in the monographs for IVIG and SCIG products
- Group 6B developed a strategy paper which was endorsed by BWP and Ph. Eur. Commission
- Group 6B filed the request for a collaborative study to the EDQM Biological Standardization Steering Committee (BSP-SC)
- BSP-SC endorsed the project during their June/July 2015 meeting (initiation of BSP143)

Interaction Group 6B and OMCL Network
Procoagulant activities in IVIGs (2)

Initiating the development of a test method for monograph „Human normal immunoglobulins for intravenous administration“ (0918) with respect to procoagulant activities

- Objective of study: Investigate and establish one or several Ph. Eur. method(s) for the control of procoagulant activities in immunoglobulin products
  - Identify suitable tests with the required sensitivity and robustness for a monograph test
    - Specific FXIa activity assay or a global assay for procoagulant activity, e.g. Thrombin Generation Assay or non-activated partial thromboplastin time
  - Propose standard testing procedures
  - Support establishment of assay system suitability samples
- Joint effort between EDQM, USP, FDA, NIBSC
- Current status: ongoing; a meeting between interested parties, e.g. industry, EDQM, USP, FDA, NIBS and OMCLs was held at 7./8. September 2016 in Rockville/Washington

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EDQM and HMA cooperation on the quality of medicines

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- Biological reference preparations
- Blood and tissue products
- **OMCL Gene Therapy Working Group**

OMCL Gene Therapy Working Group at the EDQM (since 2008)

- **Aim of the Gene Therapy Working Group:**
  - Development of test methods for Gene Therapy Medicinal Products (GTMPs)
  - Preparing the OMCLs for surveillance of the quality of authorised GTMPs
    → sharing of resources, knowledge and technologies
    → foster collaboration
    → save time
- **Annual meetings:**
  - Discussion of relevant topics
  - Review activities of the past year
  - Define work programme of the following year
- **Current participants:**
  - AGES, Austria
  - IPH, Belgium
  - HC, Canada
  - DHMA, Denmark
  - ANSM, France
  - PEI, Germany
  - ISS, Italy
  - INFARMED, Portugal
  - MPA, Sweden
  - Swissmedic, Switzerland
  - NIBSC, UK

OMCL Gene Therapy Working Group (since 2008)

- **Work program:** priorities based on GTMPs close to or on the market
  - Adenovirus → postponed
  - Adeno-associated virus (AAV)
  - Herpes simplex virus (HSV)
  - Plasmids
  - Poxvirus
  - Retro/Lentivirus (RV/LV)
- **GTMPs on the market:**
  - Glybera: AAV vector; since 25/10/2012
  - Imlygic: oncolytic HSV; since 16/12/2015
  - Strimvelis: genetically modified autologous cells (RV vector); since 26/05/2016
- **Completed collaborative studies:**
  - **Plasmids:**

  → plasmid topology by CE and HPLC: Swissmedic, ANSM
  → plasmid concentration by UV absorbance: ANSM, PEI, Swissmedic
  - **Manuscript for publication in *Pharmeuropa Bio & Scientific Notes* titled:**
    Assessment of UV-Photometry for Determination of plasmid DNA Concentration in Vector Preparations for Human Gene Therapy Products

OMCL Gene Therapy Working Group (since 2008)

- **Ongoing collaborative studies:**
  - → AAV2 viral genome titre by qPCR: ANSM, DHMA, HC, IPH, NIBSC, PEI, Swissmedic
  - → AAV2 infectious genome titre by qPCR: ANSM, DHMA, HC, IPH, NIBSC, PEI

  Further analyses on potential reasons for the observed high inter-laboratory variability of determined titres:
  → PEI: stability testing of linearized plasmid standard by droplet digital PCR

- **Planned collaborative studies:**
  - → AAV8 physical particles by ELISA: NIBSC, PEI, Swissmedic, …
  - → residual host-cell DNA by qPCR: ANSM, IPH, …

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EDQM and HMA cooperation on the quality of medicines

- HMAs mission, vision, strategy includes safe use of high quality medicines in the EU and the EEA
- EDQM´s and NCAs´ complementary roles
- NCAs contribute to establishing Pharmacopoiea monographs
- OMCL network is an example of well coordinated effort support industry in assuring each batch to be in specification
- Biological reference preparations make assays reliable and comparable
- Blood and tissue products need as much care as pharmaceuticals
- OMCL Gene Therapy Working Group and others prepare for future market surveillance

EDQM Conference, 27-28 September 2016, Tallinn, Estonia

The EDQM in the context of the European Regulatory Environment: International Developments

swissmedic

Dr. Petra Dörr, Head of Communication & Networking, Deputy Executive Director

swissmedic

Outline

- Overarching trends and concepts
- Multilateral initiatives: ICH, ICMRA, IGDRP, IPRF
- Role of the EDQM
- Summary

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Overarching trends and concepts

- Bilateral → Multilateral
  Multilateral initiatives are increasing; they are considered more efficient that bilateral activities. Bilateral agreements may still have there role – as a basis for an intensified cooperation in multilateral initiatives (exchange of confidential information, reliance/work-sharing)
- Operational → Strategic
  International cooperation needs a strategic direction: within an individual agency a strategic approach needs to be defined. Cooperation initiatives also need to define their strategy (positioning, vision/mission, business model, benefits for members).

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Overarching trends and concepts

- Information sharing → Work-sharing / reliance

  More and more regulatory authorities adopt work-sharing and reliance concepts, as it becomes obvious that they do not have the capacity to deal with the current and future challenges by themselves. The same applies to international/multilateral initiatives, who are moving from information sharing to work-sharing.

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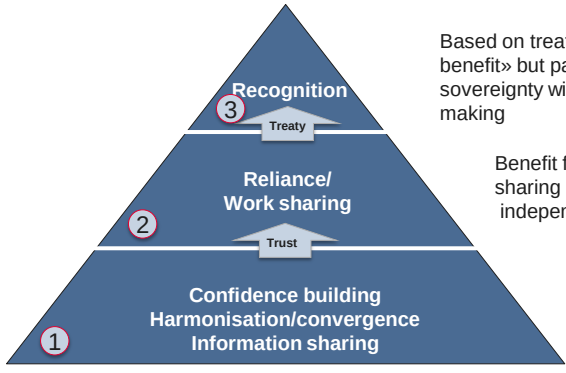
Overarching trends and concepts

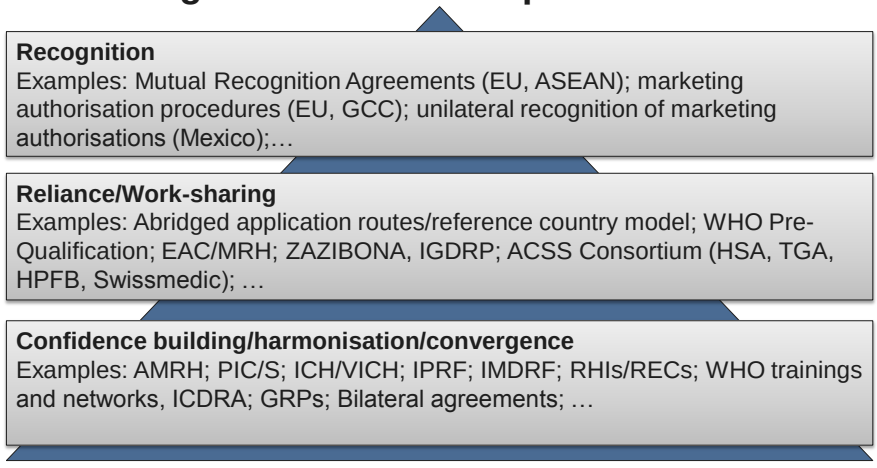


Based on treaties; «maximal benefit» but partial loss of sovereignty with regard to decision-making

Benefit for regulators; sharing of workload, but independent decisions

«Foundation», Equivalence of requirements; establishing trust

Overarching trends and concepts



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Multilateral initiatives: ICH, ICMRA, IGDRP, IPRF

ICH Members and Observers

Members

- Founding Regulatory: EC, MHLW/PMDA, FDA
- Founding Industry: EFPIA, JPMA, PhRMA
- Standing Regulatory: Swissmedic, Health Canada
- Industry: IGBA, WSMI

Standing Observers

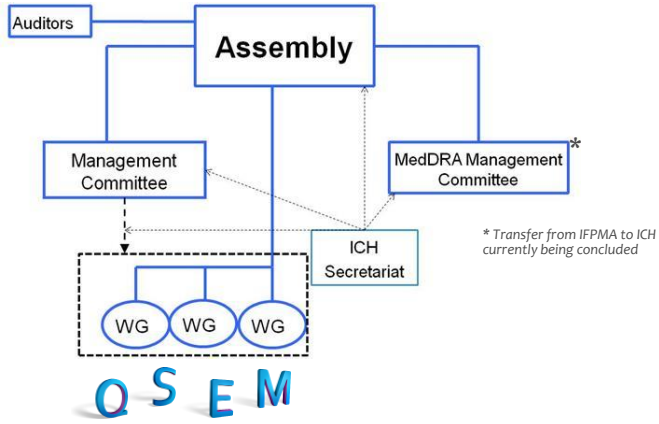
WHO, IFPMA

Observers

Regulatory authorities, RHIs, international industry pharmaceutical organisations, international organisations with an interest in pharmaceuticals

Multilateral initiatives: ICH, ICMRA, IGDRP, IPRF

Structure of the ICH Association



Multilateral initiatives: ICH, ICMRA, IGDRP, IPRF

Remit of Assembly and Management Committee

The **Assembly** is:

- The overarching body of the Association, composed of all Members that takes decisions, regarding Articles of Association, Rules of Procedures, admission of new Members, adoption of ICH Guidelines, etc.

The **Management Committee** is:

- The body that oversees operational aspects of the Association on behalf of all members, including administrative and financial matters and oversight of the WGs.

For further information: Articles of Association

Multilateral initiatives: ICH, ICMRA, IGDRP, IPRF

Decision-making for ICH Guidelines

The **Management Committee** provides recommendations on the selection of new topics for harmonisation as well as on the adoption, withdrawal or amendments of ICH Guidelines.

The **Assembly** takes decisions

- By consensus
- In the absence of consensus: vote in accordance with the Articles of Association, where only regulatory members have the right to vote

Multilateral initiatives: ICH, ICMRA, IGDRP, IPRF

Keys to ICH success

- Involves both regulators and industry with an enhanced role for regulators
- Science-based, consensus driven
- Clear and effectively managed process
- Close collaboration of parties with comparable regulatory and technical capability
- Commitment of regulators to implement products of harmonisation
- Common global platform and tools

Multilateral initiatives: ICH, ICMRA, IGDRP, IPRF

Summary

- ICH has achieved international harmonisation of technical guidelines, with engagement of regulators and industry
- ICH has clear governance and increasingly global membership following ICH reform
- Five transparent steps in the ICH process for Guideline development

Multilateral initiatives: ICH, ICMRA, IGDRP, IPRF

The International Coalition of Medicines Regulatory Authorities (ICMRA) is a voluntary, executive-level, strategic coordinating, advocacy and leadership entity of regulatory authorities that work together to

- address current and emerging human medicine regulatory and safety challenges globally, strategically and in an on-going, transparent, authoritative and institutional manner
- provide direction for areas and activities common to many regulatory authorities' missions
- identify areas for potential synergies
- wherever possible, leverage existing initiatives/enablers and resources

Multilateral initiatives: ICH, ICMRA, IGDRP, IPRF

The ICMRA will provide a global architecture to support enhanced communication, information sharing, crisis response and address regulatory science issues.

http://www.icmra.info/

Multilateral initiatives: ICH, ICMRA, IGDRP, IPRF

Strategic Initiatives

- GMP
- Generics
- Capacity Building
- Mapping Project
- Supply Chain Integrity
- Pharmacovigilance
- Crisis Management

Adopted in November 2015

Multilateral initiatives: ICH, ICMRA, IGDRP, IPRF

Output

- Overview training/capacity building for regulators (http://www.icmra.info/CapacityBuilding/index.html)
- Ebola statement (http://www.icmra.info/docs/Consolidated_Joint_ICMRA_statement_Ebola.pdf
- Zika virus disease press release (http://www.icmra.info/docs/ICMRA_Zika_press_release_FINAL_9_2_16.pdf)

Multilateral initiatives: ICH, ICMRA, IGDRP, IPRF

Meeting highlights (9-12 May 2016, hosted by EDQM)

Draft Roadmap prepared to guide future direction and ensure a common understanding of current and future strategic priorities and objectives. Final document will be available end of 2016.

Generic Products Regulatory Gap Analysis on requirements and approaches of IGDRP members / Gap Analysis on ASMF/DMF frameworks and procedures have been finalised and are expected to be published shortly.

Update on the IGDRP EU Decentralised/Centralised Procedure Information sharing pilots was given. Information on the generic drug product applications was shared and reviewed.

Multilateral initiatives: ICH, ICMRA, IGDRP, IPRF

Projects

- Active Substance Master Files/ Drug Master File (ASMF/DMF) Working Group
- Biowaivers Working Group
- Information and Work Sharing projects
  - EU Decentralised and Centralised Procedures
  - Pilot involving Health Canada, Swissmedic, Taiwan FDA and Therapeutic Goods Administration

Stakeholder Engagement

- A stakeholder meeting was held on 13 May 2016.

Multilateral initiatives: ICH, ICMRA, IGDRP, IPRF

IPRF Strategy for 2016 – 2020

The work of IPRF has evolved since its establishment. With the regulatory environment changing in a dynamic manner IPRF is expected to develop, if it wants to continue to provide value for members and external stakeholders.

- Management Committee initiated a strategy development process at the meeting in December 2015
- Final outcomes will be adopted at the Management Committee meeting in November 2016.
- At the Meeting in June, the Management Committee completed the strategy analysis and developed the future business model for the initiative.

Multilateral initiatives: ICH, ICMRA, IGDRP, IPRF

New chair and co-chair

- After three years, Dr. Petra Doerr (Swissmedic) as chair and Dr. Naoyuki Yasuda (MHLW/PMDA) as the co-chair stepped down from their responsibilities.
- The Management Committee unanimously appointed Joan Blair (US-FDA) as the new chair and Patrícia Pereira Tagliari (ANVISA) as the new co-chair, effective 15 September 2016.
- The US-FDA is also taking over from Swissmedic the secretariat for the initiative starting from 1 October 2016.

Multilateral initiatives: ICH, ICMRA, IGDRP, IPRF

Working Groups

- Biosimilars
- Cell therapy products
- Gene therapy products
- Nanomedicines
- **NEW**: Implementation of Identification of Medicinal Products (IDMP) standards (nomination of experts is ongoing)

Multilateral initiatives: ICH, ICMRA, IGDRP, IPRF

Biosimilars: current activities

- PASIB: Publication of 'public assessment of summary information for biosimilars' (Public Assessment Summary Information for Biosimilar (PASIB) – final documents after consultation)
- Publication of scientific reflection paper for extrapolation of indications (Draft Reflection Paper on Extrapolation of Indications in Authorization of Biosimilar Products)
- Development of manual for regulatory reviewers: Analytical tool for comparability of biosimilar Mab

https://www.i-p-r-f.org/index.php/en/working-groups/biosimilars-working-group/

Multilateral initiatives: ICH, ICMRA, IGDRP, IPRF

Regulatory member- and observership in ICH, ICMRA, IGDRP and IPRF

Authority	ICH	ICMRA	IGDRP	IPRF
TGA	O*	M*	M	M
ANVISA	O	M	M	M
HC	M	M	M	M
TFDA	O		M	M
CFDA		M	M	
EMA/DG Santé	M	M	M	M
CDSCO	O	M		
MHLW/PMDA	M	M	M	M
MFDS	O	M	M	M
Cofepris	O	M	M	M
Medsafe		M	M	

*O = Observer; M = Member

Authority	ICH	ICMRA	IGDRP	IPRF
NAFDAC		M		
Roszdravna-dzor	O		M	M
HSA	O	M	M	M
MCC		M	M	
Swissmedic	M	M	M	M
US-FDA	M	M	O	M
WHO	O	O	O	O
EDQM	O		M	
RHIs**	O			M
EU Comp.Auth.		M		

**Regional Harmonisation Initiatives: APEC, ASEAN, EAC, GCC, PANDRH, SADC

Outline

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Role of the EDQM / the European Pharmacopoeia

The European Pharmacopoeia today

- 37 member countries and the EU, 27 observers, of which 18 are outside Europe …
- Globalisation of manufacturing operations: Ph. Eur. used in more than 100 countries

→ Impact goes clearly beyond European continent

- High standards with regard to timeliness and scientific level of work.
- Global harmonisation (EP, USP, JP, WHO): slowly but steadily?

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Role of the EDQM / the European Pharmacopoeia

A few thoughts about the future…

- Innovation
  - Looking into new activities and tasks
  - Continue science-based approach; more rapid introduction of new technologies into monographs
- Relevance/value for members
  - Continue to increase work-sharing activities
  - More training and possibilities for knowledge transfer
- Efficiency
  - Use of IT/communication tools to facilitate work and decision-making
  - Choosing the most efficient approach: creating a new monograph may be more efficient than updating an existing one

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Summary

- Multilateral initiatives are increasing in numbers and are gaining momentum.
- Mandates and work programmes should not overlap with other initiatives (avoid duplication).
- Regulatory authorities move from information sharing to reliance and work-sharing.
- Regulatory authorities take a more strategic approach towards international cooperation characterised by increasing benefits and efficiency.

Summary

- As a multinational organisation, involved in a number of work-sharing activities, EDQM is well-positioned to continue to play an important role in tackling the future challenges of the quality of medicines!
- Focus on science and value for members needs to be maintained.
- Support from members and experts is a key element for the future role and impact of the EDQM.

Thank you for your attention…

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List of Abbreviations (in alphabetical order)

ACSS	Australia-Canada-Singapore-Switzerland (“ACSS Consortium”)
AMRH	African Medicines Regulatory Harmonisation
ANVISA	Brazilian Health Surveillance Agency
APEC	Asia-Pacific Economic Cooperation
ASEAN	Association of Southeast Asian Nations
CDSCO	Central Drugs Standard Control Organisation, India
CFDA	China Food and Drug Administration
DG Santé	Directorate General for Health and Food Safety, EU-Commission
EAC	East African Community
EAC MRH	EAC Medicines Regulatory Harmonisation
EDQM	European Directorate for the Quality of Medicines and Healthcare
EMA	European Medicines Agency
EU	European Union
GCC	Gulf Cooperation Council
GRP	Good Regulatory Practices
HPFB	Health Products and Food Branch, Canada
HSA	Health Sciences Authority, Singapore
ICDRA	International Conference of Drug Regulatory Authorities
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMRA	International Coalition of Medicines Regulatory Authorities
IGDRP	International Generic Drug Regulators Programme
IMDRF	International Medical Device Regulators Forum
IPRF	International Pharmaceutical Regulators Forum
MCC	Medicines Control Council, currently transitioning into the South African Health Products Regulatory Authority
MFDS	Ministry of Food and Drug Safety, Korea
MHLW	Ministry of Health, Labour and Welfare, Japan
MoU	Memorandum of Understanding
MRA	Mutual Recognition Agreement
NAFDAC	National Agency for Food and Drug Administration and Control, Nigeria
PANDRH	Pan-American Network for Regulatory Harmonisation
PIC/S	Pharmaceutical Inspections Cooperation Scheme
PMDA	Pharmaceuticals and Medical Devices Agency, Japan
REC	Regional Economic Community
RHI	Regional Harmonisation Initiative
Roszdrav-nadzor	Federal Service for Surveillance in Healthcare, Russia
TFDA	Taiwan Food and Drug Admistration, Chinese Taipei
TGA	Therapeutic Goods Administration, Australia
US-FDA	United States Food and Drug Administration
VICH	International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products
WHO	World Health Organisation
ZAZIBONA	Zambia-Zimbabwe-Botswana-Namibia (Collaborative medicines registration process)

The European Directorate for the Quality of Medicines & HealthCare

Ph. Eur. : Tackling future challenges of the Quality of Medicines together

Tallinn, Estonia
27-28 September 2016

Dr Susanne Keitel

EDQM Director

Agenda

- The EDQM in the European regulatory framework
- The 9th Edition of the European Pharmacopoeia
- Current hot topics - Introduction to the workshops

The Council of Europe

Founded in 1949

Development of European common and democratic principles

47 member countries

Headquarters in Strasbourg

Core values:

– protection of human rights
– pluralist democracy and the rule of law

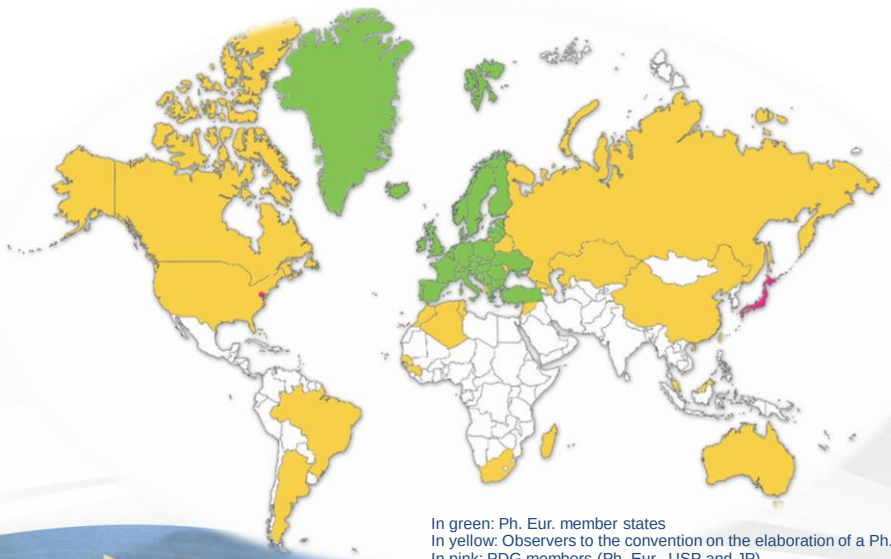
The Council of Europe is not the European Union!

- **European Union (EU):** a unique economic and political partnership between currently 28 European countries ⇒ more than 500 million citizens.
- **European Council:** The EU's main decision-making body. It defines the general political direction and priorities of the European Union.

European Directorate for the Quality of Medicines & HealthCare

- A Council of Europe Directorate, based on the Convention on the Elaboration of a European Pharmacopoeia (PA, 1964)
- **Mission:** to contribute to a basic human right: access to good quality medicines and healthcare

Members and Observers



In green: Ph. Eur. member states
In yellow: Observers to the convention on the elaboration of a Ph. Eur.
In pink: PDG members (Ph. Eur., USP and JP)

Ph. Eur. / National Pharmacopoeia / 3rd country Pharmacopoeia in the EU

Ph. Eur.

With respect to the quality part (chemical, pharmaceutical and biological) of the dossier, all monographs including general monographs and general chapters of the European Pharmacopoeia are applicable.

Nat. Ph.

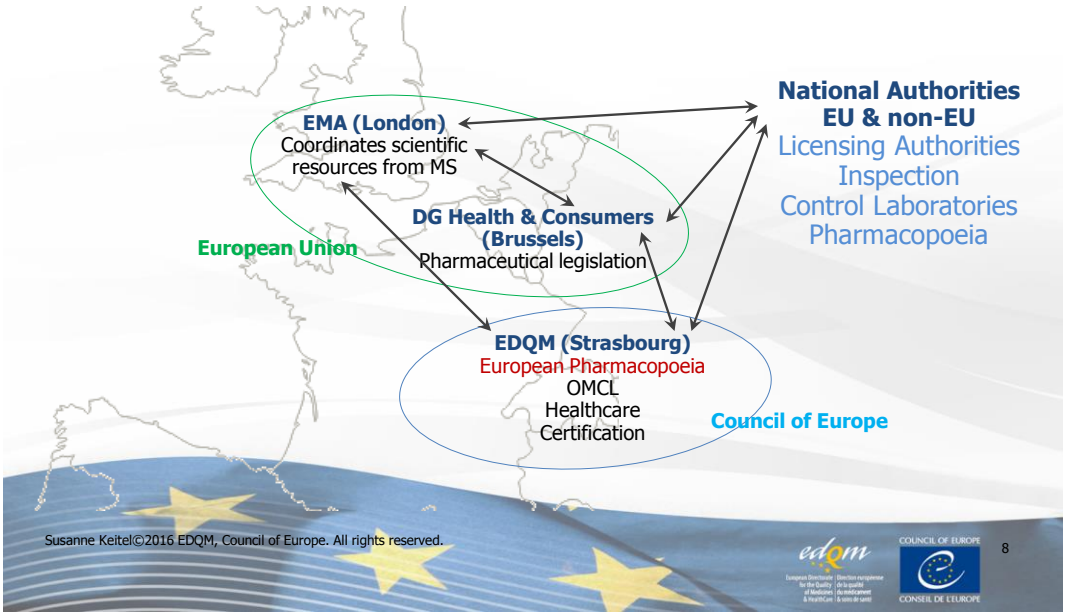
The monographs of the European Pharmacopoeia shall be applicable to all substances, preparations and pharmaceutical forms appearing in it. In respect of other substances, each Member State may require observance of its own national pharmacopoeia.

3rd country Ph.

In case where starting and raw materials, active substance(s) or excipient(s) are described neither in the European Pharmacopoeia nor in the pharmacopoeia of a Member State, compliance with the monograph of a third country pharmacopoeia can be accepted. In such cases, the applicant shall submit a copy of the monograph accompanied by the validation of the analytical procedures contained in the monograph and by a translation where appropriate.

Annexe to Directive 2001/83/EC as ammended, 3. MODULE 3: CHEMICAL, PHARMACEUTICAL AND BIOLOGICAL INFORMATION FOR MEDICINAL PRODUCTS CONTAINING CHEMICAL AND/OR BIOLOGICAL ACTIVE SUBSTANCES, 3.2 Content and Basic Principles

Key players for the quality of medicines in Europe



Agenda

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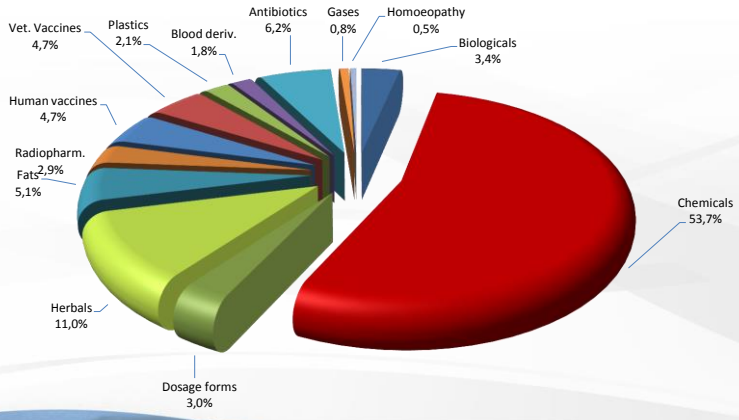
- Current hot topics - Introduction to the workshops

The Ph.Eur. - one decision body …

The Ph. Eur. Commission:

- 3 sessions per year
- 38 delegations (37 member states + EU) of up to three representatives
- All technical decisions by consensus
- The Ph. Eur. Commission welcomes participation of its currently 28 observers

… covering a large portfolio …



… and going in one direction: The Ph. Eur. - A success story!

- A unique example of an efficient collaborative process between member states:
  37 member states contributing resources to this collaborative process rather than developing national standards
  (as soon as 2 member states interested in one topic it is added to the Ph. Eur. work programme)
- Opportunities:
  - saving of resources
  - no subsequent need to harmonise national positions
- Concrete outcomes: 2329 monographs and 358 general texts adopted and published in Ph. Eur. 9.0

The Ph. Eur. texts are …

- Elaborated or revised by:
  - 58 active Groups of Experts/Working Parties, supported by additional 13 "dormant" groups
- Adopted by the Ph. Eur. Commission for publication
- Legally binding in all 37 Ph. Eur. member states and the EU - and applied in over 100 countries worldwide

The Ph. Eur. network: an asset!

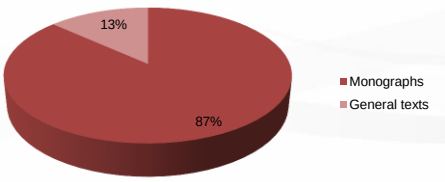
- More than 700 members in Ph. Eur. Groups
- With a well balanced expertise:
  - Approx. 1/3 from Health Authorities
  - Approx. 1/3 from Industry
  - Approx. 1/3 from University, Hospital
- Appointed by the Ph. Eur. Commission
- Currently supported by nearly 60 observers (e.g. from Algeria, Armenia, Australia, Belarus, Canada, Israel, Malaysia, Russian Federation, TFDA, USA)
- Until 2016 => nominated by Member States;
  as of 2016: open to experts from all around the world!

The result :

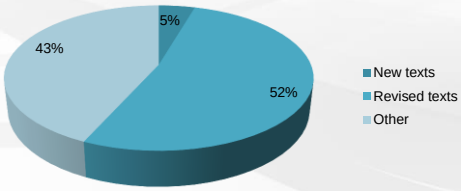
The 9th Edition (9.0):

- 2687 texts [2329 monographs + 358 general texts]

Monographs Vs general texts



New and revised texts



- around 2600 descriptions of reagents

Agenda

- The EDQM in the European regulatory framework
- The 9th Edition of the European Pharmacopoeia
- Current hot topics - Introduction to the workshops

We want your feed-back…

- A lot going on in various fields
- Important to exchange, share and consult with users on key topics:
  - Pharmacopoeial standards for biotherapeutic products
  - New technologies and their potential impact on monographs
  - Control of elemental impurities;
  - Excipients and international harmonisation.

Feedback from users regularly sought:

- During Pharmeuropa enquiries
- During dedicated hearings and workshops
- During international conferences such as this one:
  - In Prague in 2010
  - In Strasbourg in 2014

⇨ Outcome and feedback to be shared with the Ph. Eur. Commission to fine-tune their 3-years priorities (2016-2019)

Major events since *EDQM 50th anniversary* event

- March 2015: Webinar "Biologicals of the twenty-PhEur-st century"
- April 2015: Webinar "Reverse osmosis - Water for injection"
- July 2015: Ph. Eur. training session – Chemicals
- December 2015: Webinar "Glass containers for pharmaceutical use"
- December 2015: Ph. Eur. training session – Chemicals
- February 2016: Webinar on finished product monographs
- May 2016: Symposium on fish vaccines
- July 2016: Webinar on "Call for experts"
- July 2016: Ph. Eur. training session - Chemicals

Planned:

- *February 2017: Ph. Eur. training session – Biologicals*
- *July and December 2017: Ph. Eur. training session – Chemicals*

With many more to come....

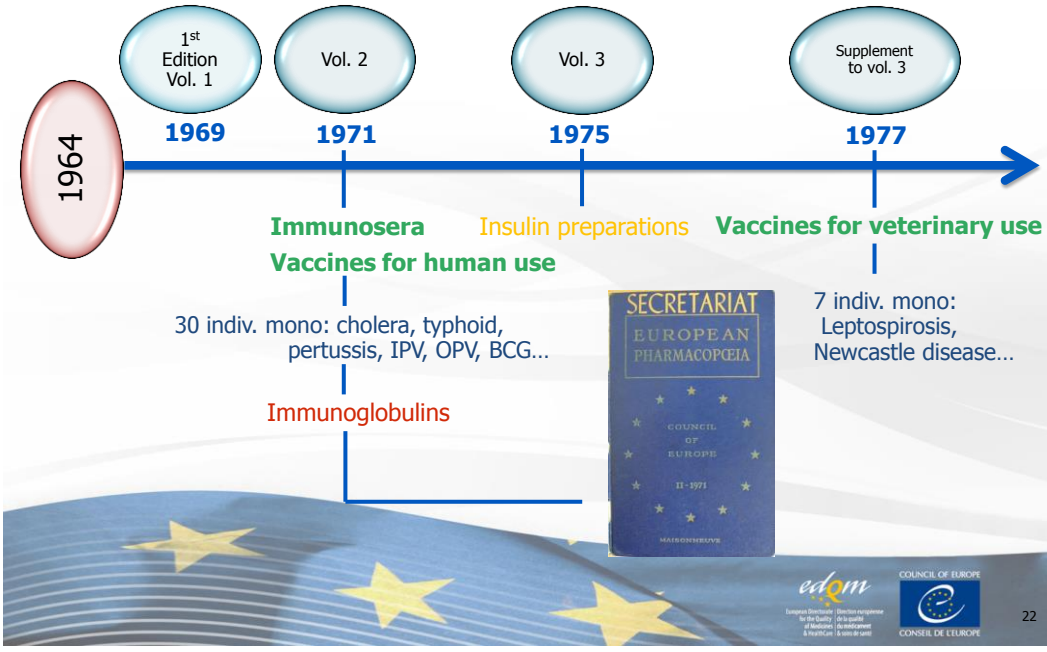
Four workshops

WORKSHOP SESSIONS

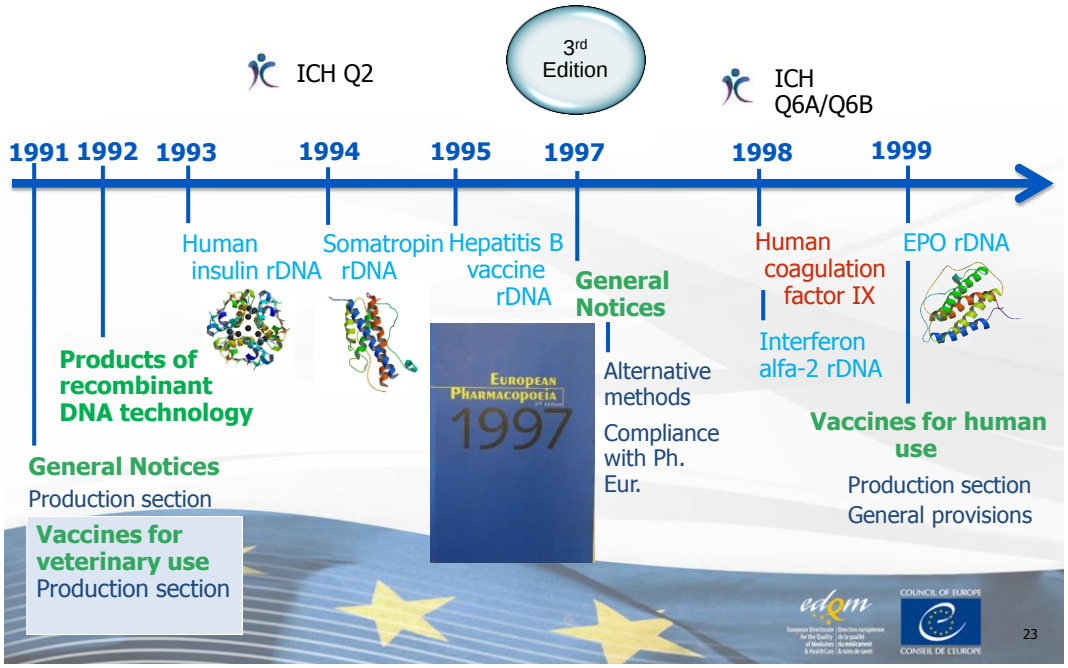
Four workshops will be run in parallel with each session being repeated once, except for the Biotherapeutic Products workshop which consists of two different sessions

WORKSHOPS	SETTING PHARMACOPOEIAL STANDARDS FOR BIOTHERAPEUTIC PRODUCTS	CONTROL OF ELEMENTAL IMPURITIES	NEW TECHNOLOGIES	EXCIPIENTS, OTHER COMPONENTS & INTERNATIONAL HARMONISATION
Tuesday, 27 September 2016 (afternoon)				
14:00-17:30	**Bolero**	**Grande 3**	**Grande 2**	**Grande 1**
Wednesday, 28 September 2016 (morning)				
9:00-12:30	**Bolero**	**Grande 3**	**Grande 2**	**Grande 1**

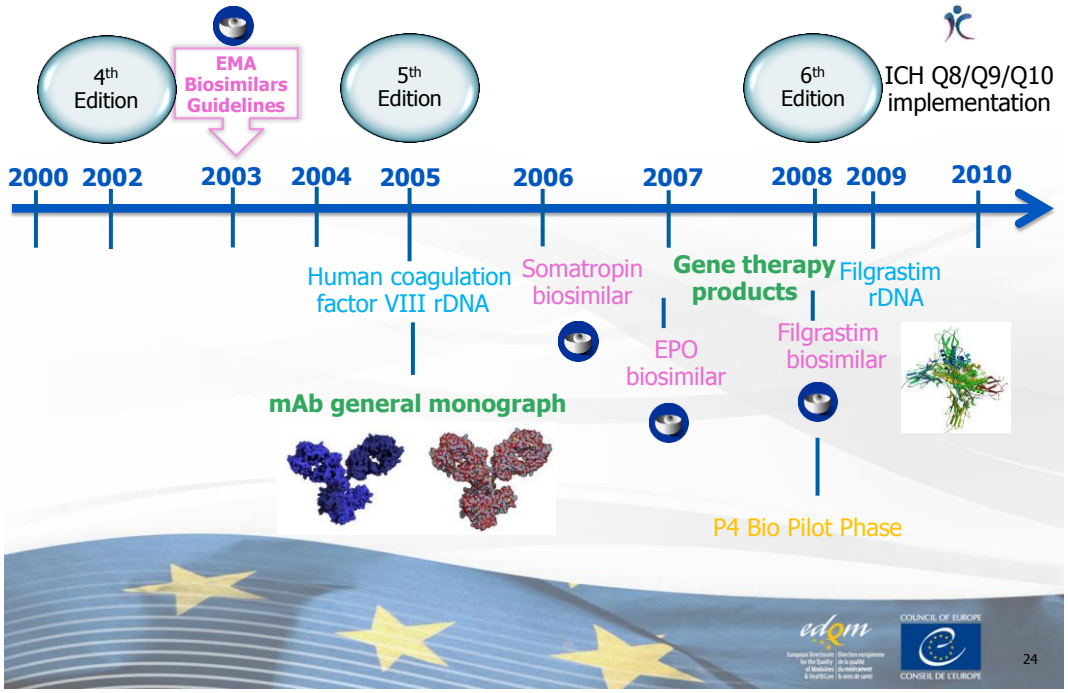
The seventies: Vaccines for human and veterinary use



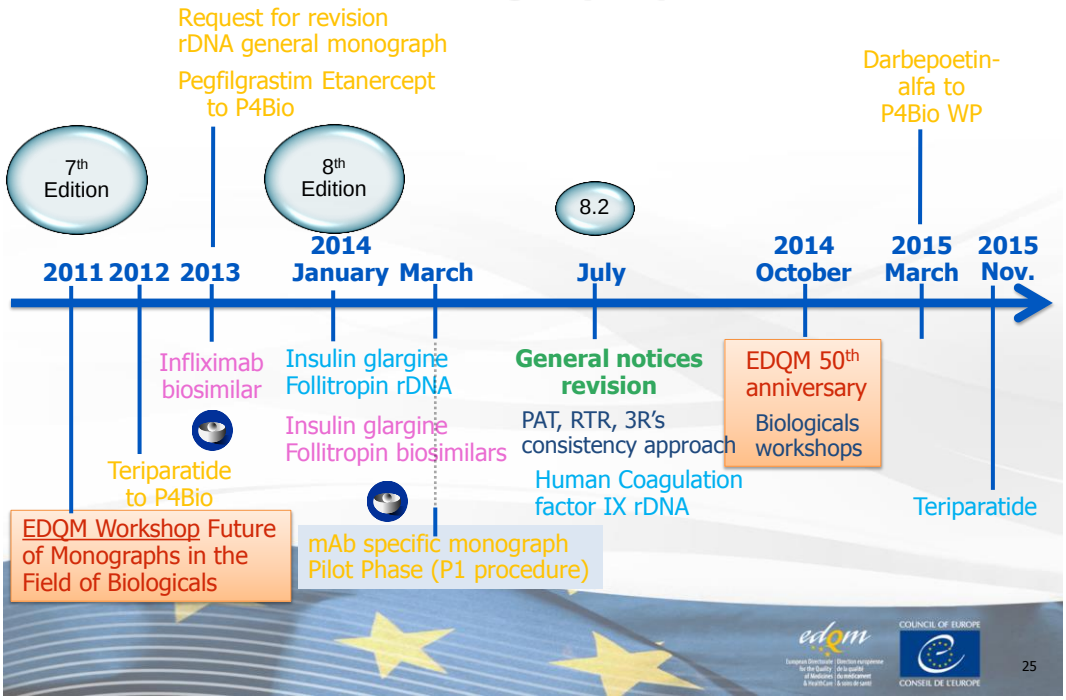
The nineties: rDNA products



The 21st century: 1st decade



The 21st century: present activities and future challenges (1/2)



In the field of … Biotherapeutic Products

- Since 2012 three P4Bio monographs have been adopted (the last one, Teriparatide, in 2015)
- Two other monographs on Pegfilgrastim and Etanercept were published in Pharmeuropa 28.2, the end of the consultation period for NPAs was 31/08/16.
- The first monograph on a monoclonal antibody, Infliximab, will be published in Pharmeuropa 28.4 for public enquiry. The methods provided in this monograph have undergone extensive verification.

Next:

- A whole-day workshop on setting pharmacopoeial standards for biotherapeutic products to gather feedback and recommendations from users.

=> Get involved!

In the field of … Impurities

- **Control of impurities:** a strength of the Ph. Eur., esp. the transparency list => need input from users to update it when and where needed.
- **Control of impurities in Antibiotics:** is and will remain a particular challenge and field of attention of the Ph. Eur. Commission in the coming months and years.
- **Ph. Eur. implementation strategy of ICH M7 Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk:** under "fine-tuning" in the relevant Ph. Eur. groups.

In the field of … Impurities

- **Ph. Eur. implementation strategy of the ICH Q3D guideline on elemental impurities:**
  - alignment with regulators ensured.
  - impact on all types of ingredients such as mined excipients under assessment.
  - Following public enquiry, revised general monographs on Substances for pharmaceutical use (2034) and on Pharmaceutical preparations (2619) as well as the revised chapters 2.4.20 and 5.20 to be proposed for adoption at the November 2016 session of the Ph. Eur. Commission.

  ↳ To allow the Ph. Eur. Commission to take an informed decision, organisation a ½-day workshop on control of elemental impurities.
  Feedback from users gathered during this workshop => recommendations will be used to finalise the Ph. Eur. implementation strategy
  => Help us to shape future requirements!

  - harmonisation of the general method 2.4.20 with USP and JP within PDG.

In the field of … New Technologies

- Important for the applicability of the requirements in the Ph. Eur. to use techniques that are commonly used in practice.
- Highly sophisticated and less commonly used techniques may still be the method of choice when relevant quality parameters cannot be determined otherwise.

⇨ Need for further reflection on allowing techniques to become the new standard method once they are commonly used and have replaced old standard methods (e.g. fast HPLC to replace HPLC).

⇨ Need to assist unexperienced users => need to establish guidance for new techniques (e.g. as done for chemometrics) to be discussed and assessed.

- Feedback from users will be gathered during the workshop and provided to the Commission at an upcoming session. It will help determining the need to revise existing and elaborate new chapters.

Have a say – express your needs!

In the field of …
Excipients & International harmonisation

- A project to elaborate a monograph on co-processed excipients

Does it match your needs?

- Use of non-distillation techniques for the production of WFI – a happy end?
- Developments in the field of packaging materials

In the field of …

Excipients & International harmonisation

- A key area of interest of many users and stakeholders of the Pharmacopoeias
- Several initiatives going on:
  - PDG
  - GPhP
  - And surely a lot more … acronyms!!
- Feedback from users will be gathered during this workshop and provided to the Ph Eur Commission at an upcoming session (and/or to PDG if relevant) .

=> Watch the space!

Thanks a lot for your attention!

We are looking forward to receiving your input!