The European Pharmacopoeia and the 3Rs

EU Expert Working Group on the information on the Three Rs
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Structure

- The Council of Europe, the EDQM, the European Pharmacopoeia (Ph. Eur.) and the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes
- How are 3rs methods integrated into the Ph. Eur.?
- Impact of Directive 2010/63 EC on the Ph. Eur.
- How can we improve from today's practice?
- How is the information disseminated?

The Council of Europe, the EDQM, the European Pharmacopoeia (Ph. Eur.) and the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes

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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 & the rule of law

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

- 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

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National Authorities

Licensing Authorities

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Inspection

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Control Laboratories

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Pharmacopoeia

European Union

EMA
(London)
Coordination of scientific resources from Member States

DG Health & Consumers
(Brussels)
Pharmaceutical Legislation

Council of Europe

EDQM

- European Pharmacopoeia
- Certification of Suitability
- OMCL
- Healthcare

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Convention on the elaboration of a European Pharmacopoeia

Summary

- The Convention aims to harmonise specifications for medicinal substances in their original state or in the form of pharmaceutical preparations.
- The Parties undertake progressively to elaborate a European pharmacopoeia.
- The European Pharmacopoeia becomes the official standard applicable within the respective Parties.

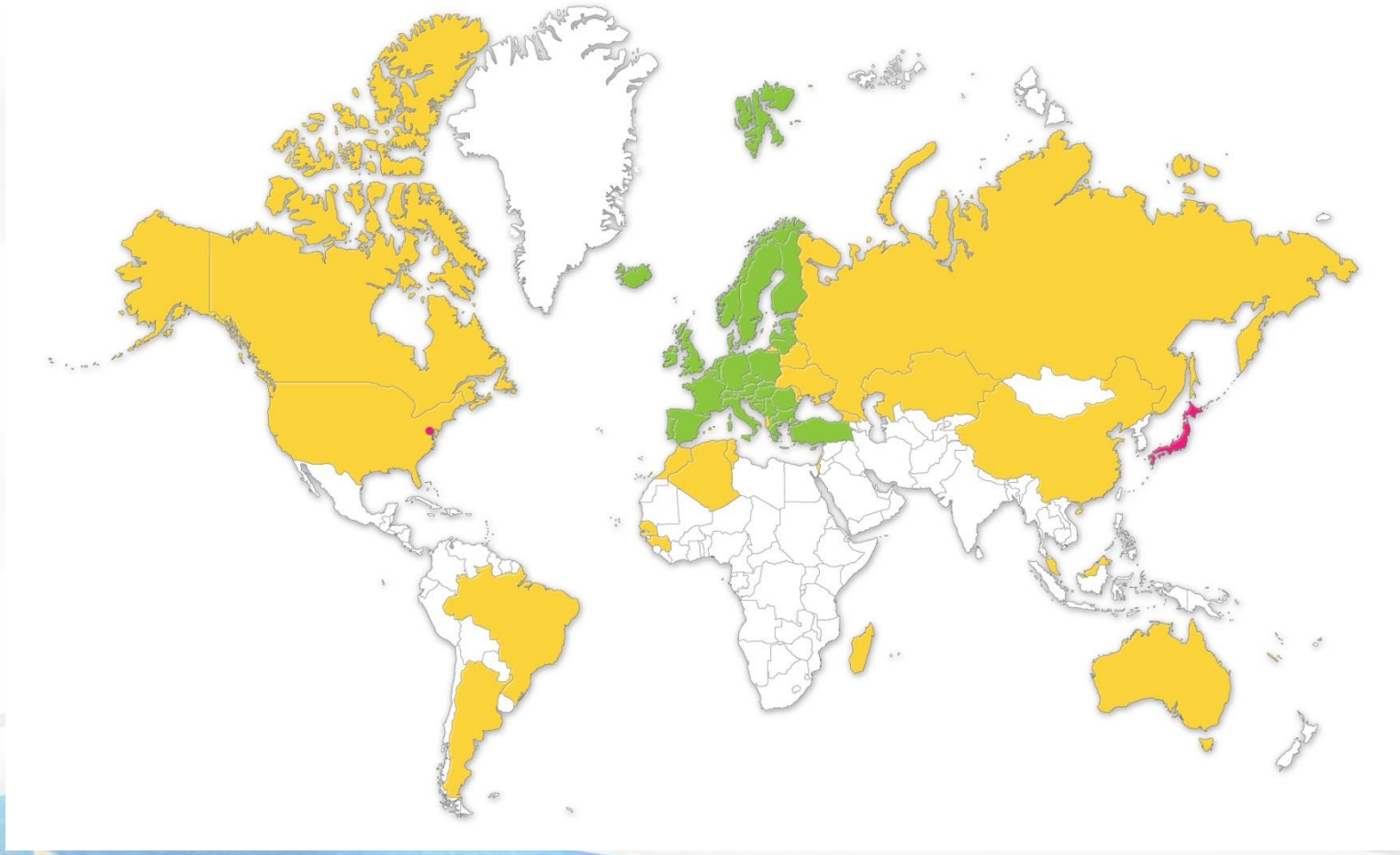
http://conventions.coe.int/Treaty/Commun/QueVoulezVous.asp?NT=050&CM=8&DF=29/07/2011&CL=ENG

Convention on the elaboration of a European Pharmacopoeia

Milestones

- 1964: open for signature
- 1975: Mandatory status reinforced in the EU pharmaceutical legislation
- 1994: EU signs the European Pharmacopoeia Convention
- Today: 36 member states + EU

Ph. Eur. Members and Observers



European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes

Summary (1/2)

- The Convention is designed primarily to reduce both the number of experiments and the number of animals used for such purposes.
- It encourages Parties not to experiment on animals except where there is no alternative.
- All research into alternative methods should be encouraged.

European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes

Summary (2/2)

- Animals to be experimented on should be selected on the basis of clearly established quantitative criteria and must be well cared for and spared avoidable suffering whenever possible.

http://conventions.coe.int/Treaty/Commun/QueVoulezVous.asp?NT=123&CM=8&DF=29/07/2011&CL=ENG

European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes

Milestones

- 1986: open for signature
- 1998: Ratification by EU
- 2006: revised Appendix A (Article 5 of the convention): guidelines for the accomodation and care of experimental animals
- Today: 21 member states + EU (6 countries have signed the convention but not ratified)

European Pharmacopoeia (Ph. Eur.)

- Protecting public health - one common compulsory standard
- The Ph. Eur. is the official pharmacopoeia in Europe – complemented by national pharmacopoeias for texts of interest to only one Member State
- Mandatory at the same date in 36 Member States (CoE) and the EU (decision of Ph. Eur. Commission).
- Legally binding quality standards for ALL medicinal products in its member states, i.e. raw material, preparations, dosage forms, containers must comply with the Ph. Eur. requirements when they exist.

The Pharmacopoeia in the EU Legislation

"The monographs of the European Pharmacopoeia shall be applicable to all substances, preparations and pharmaceutical forms appearing in it…"

Directive 2003/63/EC, 3. MODULE 3: CHEMICAL, PHARMACEUTICAL AND BIOLOGICAL INFORMATION FOR MEDICINAL PRODUCTS CONTAINING CHEMICAL AND/OR BIOLOGICAL ACTIVE SUBSTANCES, 3.2 Content and Basic Principles

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How are 3rs methods integrated into the Ph. Eur.?

The texts of the Ph. Eur.

- Introduction to the Ph. Eur.
- General notices
- General monographs
- Specific monographs
- General chapters

Introduction to the Ph. Eur.

- **Use of animals**. In accordance with the *European Convention on the protection of animals used for experimental and other scientific purposes (1986)*, the Commission is committed to the reduction of animal usage wherever possible in pharmacopoeial testing, and encourages those associated with its work to seek alternative procedures. An animal test is included in a monograph only if it has clearly been demonstrated that it is necessary to achieve satisfactory control for pharmacopoeial purposes.
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General Notices: Alternative Methods

"... The tests and assays described are the official methods upon which the standards of the Pharmacopoeia are based. With the agreement of the competent authority, alternative methods of analysis may be used for control purposes, provided that the methods used enable an unequivocal decision to be made as to whether compliance with the standards of the monographs would be achieved if the official methods were used.

In the event of doubt or dispute, the methods of analysis of the Pharmacopoeia are alone authoritative."

General monographs:
Reference to 3R Convention

- Example: **Vaccines for human use (0153)**
- Applies to all vaccines, including those for which there is no specific monograph.
- "In accordance with *European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (1986)* and the European Directive on the same principles, tests must be carried out in such a way as to use the minimum number of animals and to cause the least pain, suffering, distress or lasting harm"

Specific monographs

- Specific monographs encourage alternative "3R" methods, humane endpoints
- Example: Botulinum toxin type A for injection 2113

  ASSAY In accordance with the provisions of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes, tests must be carried out in such a way as to use the minimum number of animals and to cause the least pain, suffering, distress or lasting harm. The LD_{50} assay is associated with severe suffering of animals and manufacturers are strongly encouraged to develop and validate assays that will reduce the number of animals used, or refine or replace the test procedure with the goal of promoting animal welfare.

Specific monographs

- When a validated alternative method is available (e.g. via EDQM Biological Standardisation Programme collaborative study), a detailed protocol is given as an example
- Example Rabies vaccine (inactivated) for veterinary use (0451)

  Detail of serological assay, following BSP 105 (Supplement 7.7, implementation 1 April 2013)

Impact evaluation of EU Directive 2010/63/EU on the texts of the European Pharmacopoeia

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EU Directive 2010/63/EU

- *Article 13*
- **Choice of methods**
- 1. Without prejudice to national legislation prohibiting certain types of methods, Member States shall ensure that a procedure is not carried out if another method or testing strategy for obtaining the result sought, not entailing the use of a live animal, is recognised under the legislation of the Union.

Ph. Eur. wording

- **Either/or**: for EU, the *in vitro* alternative becomes obligatory. No problem with wording in Ph. Eur. texts.
- **The potentials for alternative testing (the so called "door openers") need to be identified as such,** especially when such strategies have not yet been validated by a collaborative study.
- **Conditions for carrying out/not carrying out alternatives**: to be detailed as much as possible so that lawyers (members of ethical committees) have no difficulty in interpreting them.
- **There is a possibility that not all animal tests can be replaced**, for good reasons, and this is acceptable.

How can we improve from today's practice?

General items for consideration

- **Validation criteria/guidelines** for validating *in vivo* methods: in close collaboration between the Ph. Eur. Commission/EDQM and the CHMP/CVMP
- **Harmonisation inside and outsise Europe**

- Harmonisation of regulatory enforcement in EU.
- Harmonisation of ethical committee considerations.
- Global harmonisation of the 3Rs.

How is the information on the possibility to use the 3Rs is disseminated?

How is the information on the 3Rs disseminated?

- Ph. Eur. is legally binding
- EDQM organises 3R conferences
  - Dubrovnik 2008
  - Strasbourg 2011
- EDQM publishes press releases after each Commision Session (3 times a year). 3R achievements are identified: example TABST deletion April 2012

How is the information disseminated?

- EDQM organises training sessions on the Ph. Eur.
- EDQM representatives are observers in European3R Groups (e.g. EPAA, JEG3R)
- EDQM website: dedicated page on the 3Rs
- To be released soon: list of 3Rs possibilities in the Ph. Eur.

Just released!

Thank you for your attention !

Website: www.edqm.eu

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