

**EUROPEAN PHARMACOPOEIA:
TACKLING FUTURE CHALLENGES OF THE
QUALITY OF MEDICINES TOGETHER
27-28 September 2016, Tallinn, Estonia**

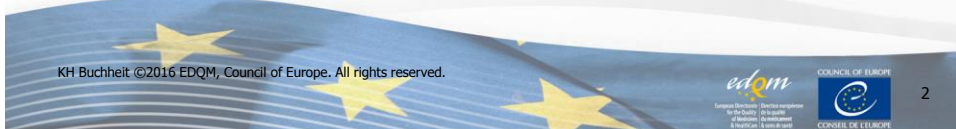
**Replacement of animal tests in the
European Pharmacopoeia**

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Contents

- Why do we want to replace animal tests for QC of medicines?
- Legal situation
- Principles and approaches
- What has been achieved?
- What needs to be done?
- What are the obstacles?
- Conclusions



Why do we want to replace animal tests for QC of medicines?

- Ethical concern for animal welfare
- Public pressure (*2013 European Civil Initiative «Stop Vivisection»; 1.2 Mio signatures*)
- Variability of results
- Costs
- Advances in analytics & production of medicines
- **Replacement of animals of high importance for Ph. Eur./EDQM**

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Legal situation (1)

“European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes”

Council of Europe, 1986

Starting point for

- Change of national/European legislation
- Ph. Eur. for replacement of animal tests

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Legal situation (2)

- Directive 86/609/EEC, **Protection of animals used for experimental and other scientific purposes**, European Union, 1986, based on CoE convention
- Directive 2010/63/EU, **Protection of animals used for scientific purposes**, European Union, effective since 1/1/13.
 - Current legislation implemented in all EU Member States
 - Requires use of alternative methods where available

Principles and approaches (1)

Refine, Reduce, Replace (3Rs)

Russell & Burch (1959)

Approaches for Ph. Eur. (3Ds)

Direct towards use of alternatives

Delete tests/requirements

Develop new methods

Principles and approaches (2)

Involved Parties	Contributions
<ul style="list-style-type: none">• Expert Groups• Ph. Eur. Commission• Biological Standardisation Programme<ul style="list-style-type: none">• OMCLs• Manufacturers• Competent Authorities (non-European Countries)	<ul style="list-style-type: none">• Direct, Delete• Direct, Delete• Develop

Broad basis for 3Rs methods

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What has been achieved? (1)

- **Direct** towards application of 3Rs (i.e. in most cases no alternative described in Ph. Eur.)
- **Delete** tests/requirements
- **Develop** new methods

Review P. Castle (2007): 488 monographs with 3Rs changes (Pharmeuropa)

Only selection of examples can be presented

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What has been achieved? (2)

Soon after publication of Directive 2010/63 Ph. Eur. Commission decided that Expert Groups review all texts where use of animals was prescribed (141st session November 2011).

Ongoing commitment to apply 3Rs principles in Ph. Eur.

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Direct towards 3Rs (1)

General statement on animal usage

(in II. Introduction)

- Ph. Eur. refers to European Convention (Council of Europe, 1986)
- "Commission is committed to the reduction of animal usage wherever possible .., and encourages those associated with its work to seek alternative procedures."

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Direct towards 3Rs (2)

Use of alternative Methods (In General Notices)

“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 ...as to whether compliance with the standards of the monographs would be achieved if the official methods were used”.

Manufacturers can use their own 3Rs methods

Direct towards 3Rs (3)

Use of consistency approach (In General Notices)

- Not all tests in monograph need to be performed to assess compliance with Ph. Eur.
- Assurance that product is of Ph. Eur. quality ...on basis of its design, control strategy & data derived, e.g. validation studies of manufacturing process or in-process controls.

Ph. Eur. permits use of consistency approach

Direct towards 3Rs (4)

Use of humane endpoints

Rabies vaccine (human & veterinary use, potency assay)

- Past: lethal endpoint
- Now: Observation of clinical signs; allows earlier termination of experiment; to be used once test established for routine use; examples for clinical signs are given

Ph. Eur. requests use of humane endpoints

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Direct towards 3Rs (5)

Guidance

Guideline Group 15

Substitution of in vivo methods by in vitro methods for the quality control of vaccines.

(Future chapter 5.2.14 in 9th edition)

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Delete tests (1)

- Abnormal toxicity test for:
 - Blood products (complete deletion),
 - Vaccines (deletion for routine use)
- Test for depressor substances: for heparin, INF-alfa, urofollitropin, some antibiotics (e.g. bleomycin, daunorubicin, gentamicin)
- Safety test for veterinary vaccines: waiver after testing of initial batches

Delete tests (2)

Veterinary vaccine monographs

- Deletion of Target Animal Batch Safety Test (TABST), 4/2013
- Reduction of number of animals in development tests, 4/2013
- Revision of requirements for inactivation testing of all inactivated veterinary vaccines (41 monographs), 11/2015

Develop new methods (1)

- Detailed description of method in Ph. Eur.
- Most tedious/time-consuming approach
- Origin
 - Biological Standardisation Programme (BSP)
 - External source



Biological Standardisation Programme (BSP)

- Joint Programme Council of Europe & EU Commission
- Application of 3Rs to QC methods for biologicals
- Started in 1993
- 145 Projects initiated/concluded
- 38 Projects on method development
- **21 Projects on 3Rs methods**
- 86 Projects on reference standards



Develop new methods (2)

- Replacement of lethal challenge test by serological assay (& significant reduction of number of animals) for
 - Tetanus vaccine
 - Diphtheria vaccine
 - Acellular pertussis vaccine
 - Rabies vaccine (vet. use)
 - Swine erysipelas vaccine

Reduce/Refine

Develop new methods (3)

Replacement in vivo test by in vitro tests

- Hepatitis A vaccine
- Inactivated Poliomyelitis Vaccine (IPV)
- Histamine sensitisation test (HIST) for acellular pertussis vaccine
- Newcastle disease vaccine
- Tetanus immunoglobulin
- Somatropin

Replace

Develop new methods (4)

Current/future BSP projects

- BINACLE assay: in vitro test to replace in vivo test for "Absence of toxin and irreversibility of toxoid"
- Tetanus- & diphtheria vaccine: ELISA to replace in vivo potency assay
- Rabies vaccine (human use): dito
- Clostridium septicum vaccine: in vitro test to replace tests in mice to determine antigenicity & toxicity of toxin and toxoid

Methods from external sources

Examples

- MAPREC test: replacement of neurovirulence test in monkeys for OPV type 3 by genetic marker in vitro test
- Monocyte Activation Test (MAT): replacement of rabbit pyrogen test by in vitro test
- cell culture assay for avian vaccines to replace tests for extraneous agents

What has been achieved? (3)

Ph. Eur.

- Provides flexibility for use of
 - Alternative methods (even if not described)
 - Consistency approach
- Gives guidance for use of 3R methods
- Requests use of human endpoints
- Has deleted many animal tests
- Invests heavily in establishing 3R methods

What needs to be done? (1)

Examples

- Erythropoietin, potency assay in mice: in vitro assays for individual products available but no common assay suitable for Ph. Eur.
- Old human vaccines: potency assays, specific toxicity test: dito, BSP projects underway
- Extraneous agents (human, vet. vaccines): some test deleted/replaced; still many animals used

What needs to be done? (2)

- Veterinary vaccines, potency assays: still many in vivo tests use; in most cases no efforts to replace tests
- Abnormal toxicity test: efforts to delete from Ph. Eur. underway; need for international harmonisation; involvement of WHO

Despite strong efforts still some animal tests in Ph. Eur.



What are the obstacles? (1)

- Acceptance of alternative approaches
 - Do we reach the same result/conclusion as with in vivo test
 - In most cases no direct correlation; thus same result not reached; however same conclusion should be reached (release/rejection of batch); need to complement direct release data with other data (consistency approach)
- Acceptance outside Europe
 - Collaboration with WHO, non-European authorities, OIE, ECVAM, EPAA, regulators (JEG 3Rs), political initiatives



What are the obstacles? (2)

- Setting release specifications
- Availability of highly specific reagents
- General applicability of methods
- Availability of common reference standards



Conclusions

- High & continuous importance for Ph. Eur.
- Enormous progress for replacement of animal experiments
- Some areas need more attention in the future
- Many achievements through active search for alternatives in collaboration with partners from OMCLs & industry in BSP
- **Ph. Eur. has acquired leading role in replacing animals tests for QC of medicines**



More information

EDQM website

<https://www.edqm.eu/en/Alternatives-to-animal-testing-1483.html>

Thank you for your interest

The 9th edition & current hot topics

Cathie Vielle

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1

During these 2 days several fields were already covered:

- Pharmacopoeial standards for biotherapeutic products
- Control of elemental impurities
- New technologies
- Harmonisation Initiatives, Co-processed excipients, packaging materials and Water for Injections (Use of RO)

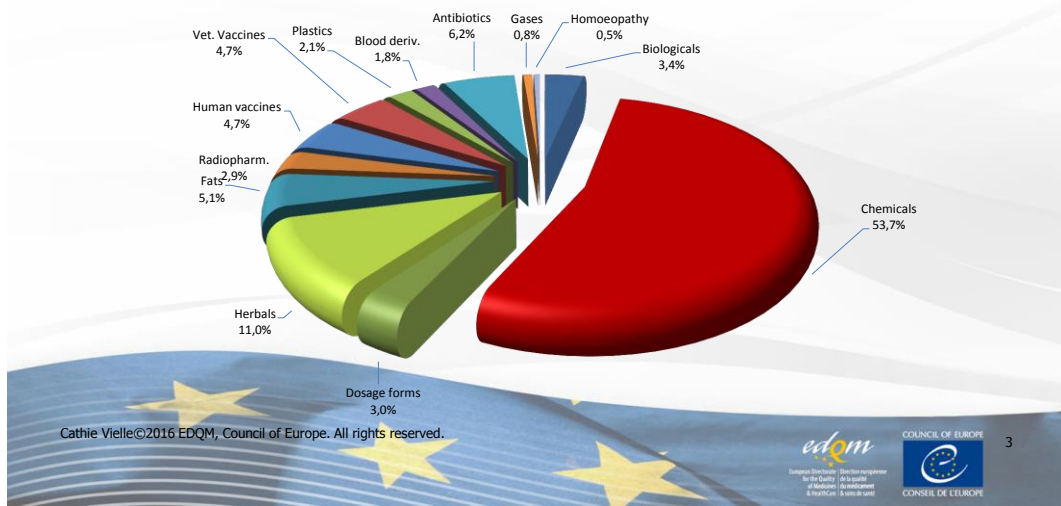
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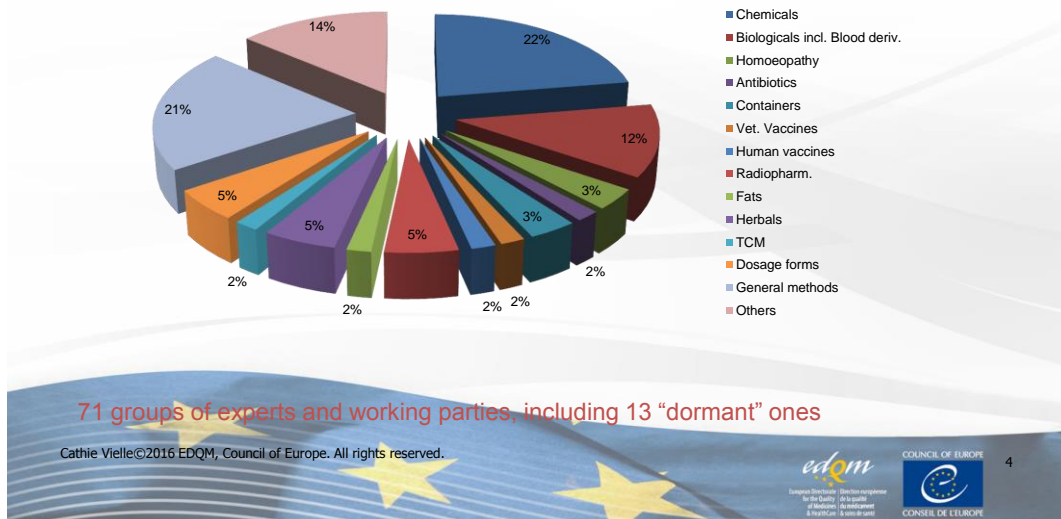
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Agenda

.... But of course the Ph. Eur. is also active in a lot of others!

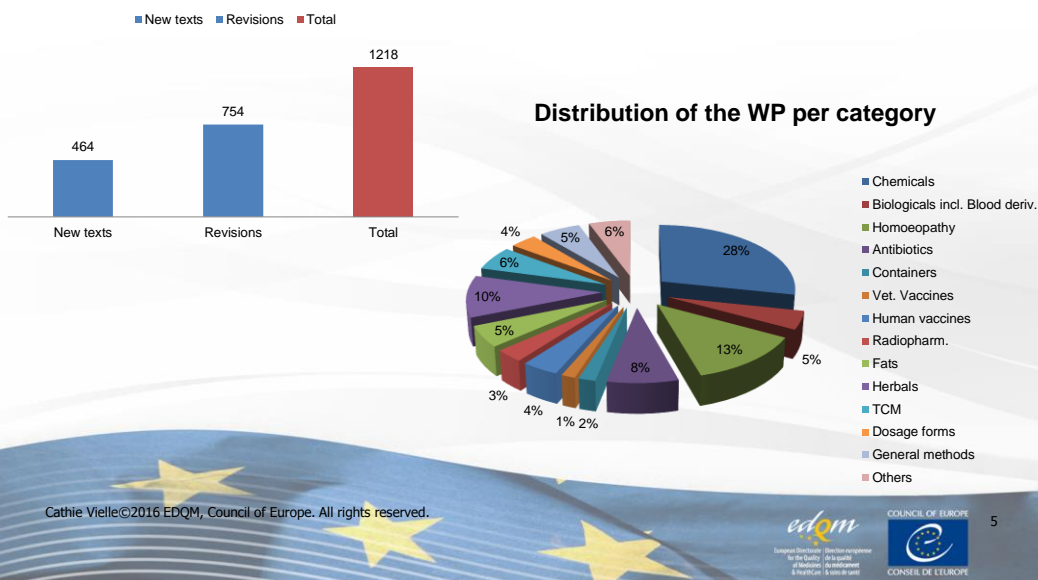


58 active Groups of experts and working parties



1218 items on the work programme (June 2016)

Ph. Eur. work programme



In the field of ... finished product monographs (FPM)

- Elaboration of a guidance document available on EDQM website
- Adoption of the monograph on Sitagliptin tablets (P4) by the Ph. Eur. Commission at its 151st session (March 2015) _ Publication in Suppl. 8.7
- Webinar organised on 4 February 2016
- 16 FPM on the work programme
- 2 new monographs published in Pharmeuropa 28.4 (Raltegravir tablets + chewable tablets) Oct. 2016

A revolution?

- Provide public standard to harmonise specifications throughout Europe
- Following existing rules for elaboration and revision
- Public consultation in Pharmedropa online
- Based on approved specifications in Europe
- Backed up by batch data
- Active substance monograph exists or is elaborated in parallel

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An evolution

- Basis for independent judgement on quality of the medicine
- Cover different formulations and strengths
- full flexibility in framework offered by Ph. Eur.
- Provide shelf-life specifications
- Demonstration of suitability of monograph needed

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Demonstration of suitability

Monograph tests mandatory **unless otherwise justified and authorised**

Each MAA still to provide to the competent authority

- A **complete dossier** including P2 pharmaceutical development
- Demonstrate that **tests in the monograph are appropriate** for the quality control of their product (e.g. dissolution, related substances)

In the field of ... finished product monographs (FPM)

Current focus

Follows critical assessment and discussions: Takes into account usefulness of Ph. Eur. monograph and impact on registered products

- Priority on **Single-source monographs** on products that are potential future generics
- **Immediate release** dosage forms
- **Solid and liquid** formulations
- Will be expanded subsequently

In the field of ... Biologicals

- General chapter 5.2.12 *Raw materials for the production of cell-based and gene therapy medicinal products* (9th Edition):
 - ✓ harmonises current practices
 - ✓ helps users to identify the critical quality attributes of raw materials
 - ✓ helps users to manage batch-to-batch variability and change control for raw materials
 - ✓ encourages raw material manufacturers to record and share information on the origin and quality of the raw material
- General chapter 2.6.34 *Host Cell Protein assays* (Suppl. 9.1):
 - ✓ Provide guidance for the development and validation of HCP assay used to test products obtained by recombinant DNA technology.
 - ✓ Use of alternative approaches acceptable to CA not excluded

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General chapters on microbiology

Chapter	Topic or modification	Improvements
5.1.1 Methods of preparation of sterile products (Suppl. 9.2)	<p>Extensive revision</p> <p>New layout for each sterilisation process section :</p> <ul style="list-style-type: none"> -Principle -Equipment -Sterilisation cycle -Cycle effectiveness -Routine control 	<ul style="list-style-type: none"> -Addition of modern concepts for validation of steam -Expansion of the sections on gas sterilisation, dry heat sterilisation and aseptic assembly (<i>e.g</i> alkylating and oxidising agents, wider description of equipments, freeze-drying under aseptic conditions...)
5.1.2 Biological indicators of sterilisation (Suppl. 9.2)	<p>Extensive revision and New title:</p> <p>"5.1.2 <i>Biological indicators and related microbial preparations used in the manufacture of sterile products</i>"</p>	<ul style="list-style-type: none"> -Description of different types of BI and quality requirements -Guidance on how BIs are selected and how they are used to characterise sterilisation processes -Addition of microbial preparations for sterilisation grade filtration

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General chapters on microbiology

Chapter	Topic or modification	Improvements
5.1.6 Alternative microbiological methods (Suppl. 9.2)	Extensive revision to take account of technological developments in alternative methods.	-Update and addition of new methods -Guidance on how to validate an alternative microbiological methods -Requirements on databases used for identification tests & their validation -Example validation of alternative methods added in knowledge database
5.1.11 Determination of bactericidal, fungicidal or yeasticidal activity of antiseptic medicinal products (New) (Suppl. 9.2)	New chapter dealing with the determination of antimicrobial activity of medicinal products intended for administration by direct contact with skin or mucous membranes	Basic tests for the determination of -Bactericidal activities -Fungicidal activities -Yeasticidal activities

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In the field of Cell Therapeutic Products

- A revised version of 2.6.27, entitled now:
Microbiological examination of cell-based preparations

(Suppl. 9.2)

Topic or modification	Improvements
New title and Extensive revision to take account of technological developments in rapid microbiological methods and their benefits for the cell therapeutic products	-Guidance on how to select the microbiological examination method depending on the characteristics and constraints inherent to the cell-based preparation characteristics: – automated growth-based methods; – a combination of preculturing and detection by alternative methods (5.1.6); – direct detection by alternative methods (5.1.6); – methods based on the sterility test prescribed in general chapter 2.6.1.

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In the field of Live Biotherapeutic Products

Context: no regulatory texts for Live Biotherapeutic medicinal products in Europe

-Elaboration of a general monograph dealing with their quality requirements and specifications

-Elaboration of 2 chapters on microbiological examination for the Live Biotherapeutic Products as chapters 2.6.12 and 2.6.13 on microbiological examination are not adapted for medicinal products containing live micro-organisms

New Ph. Eur. policy on bacterial endotoxins in substances for pharmaceutical use

European Pharmacopoeia policy on bacterial endotoxins in substances for pharmaceutical use

Approved by the European Pharmacopoeia Commission at its 149th Session, June 2014

1. Reasons for requirement of compliance with the test for bacterial endotoxins

Bacterial endotoxins are contaminants from gram-negative bacteria and are the most common cause of pyrogenicity in pharmaceutical products. Any preparation administered parenterally should be sterile and comply with the test for bacterial endotoxins (BET) as described in the European Pharmacopoeia.

Problem statements

- There is a lack of harmonisation in the way the BET is prescribed in substances monographs
- The final use of the substance is not always known
- There can be contradictions between limits in individual monographs and calculated limits (e.g. tightened by regulators)
- The limits cannot take account of all different dosages
- The limits in individual monographs are not always appropriate for paediatric use

New Ph. Eur. policy: elaboration of new monographs

BET is not included in individual monographs, unless

- specific method description is needed (e.g. sample preparation)
- Specific method is needed (e.g. method E of chapter 2.6.14)

If BET is included, **no limit** is prescribed

Ph. Eur. policy: revision of existing monographs

- No retrospective revision to delete BET requirements
- Keep well established testing practice
- The test remains, unless a specific need to revise/delete the test or the limit have been raised: can be discussed on a case-by-case basis

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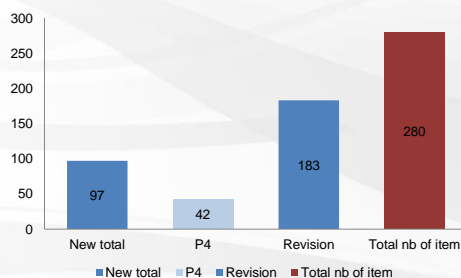


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In the field of ... chemicals

Dealt with by mainly 7 groups (Groups P4, 10A-B [*organic chemistry*], 9 [*inorganic*], 11 [*organic chemistry; natural origin*]),

Current work programme:



Revision => mainly *Related substances* section

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Basis for monographs

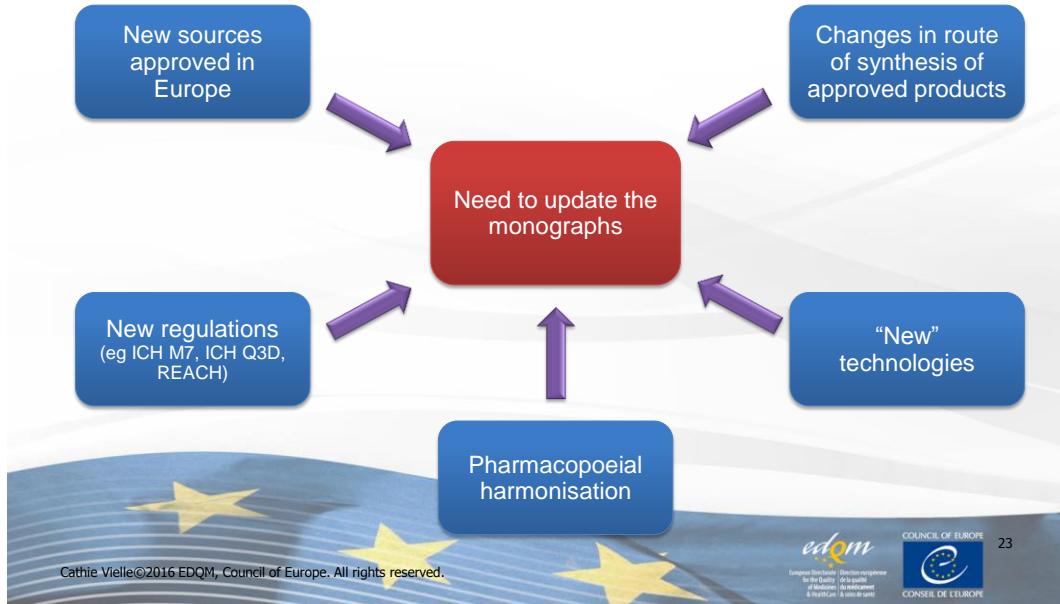
- Monographs must take account of all currently **approved products** on the European market
- **Approved specification(s)** are the main basis backed up by **batch data**
- Draft monographs are **checked by regulatory authorities** at Pharmeuropa stage
- Policy for monograph development is given in:
Technical Guide for the Elaboration of Monographs
recently revised (7th **Edition** – 2015) (available on the EDQM website)

In the field of ... Control of Impurities

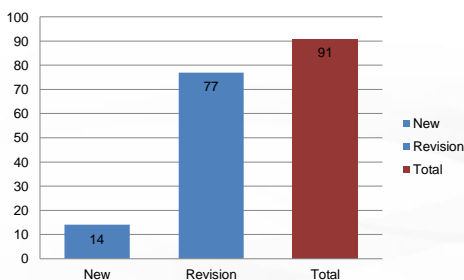
Organic impurities: *A strength of the Ph. Eur.*

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

Revision of monographs: ∞



In the field of ... Antibiotics (Group of expert 7)

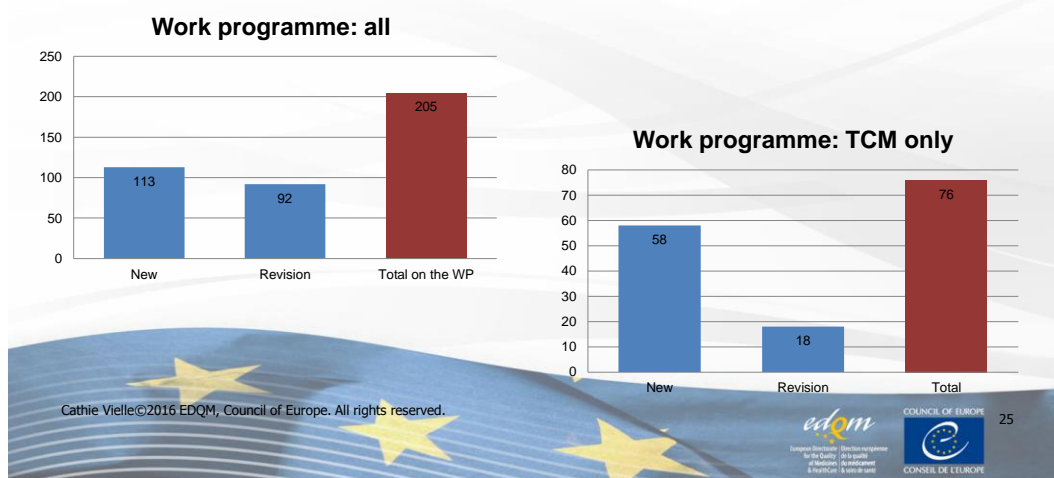


- Dealt with by group 7
- implementation of the EMA Guideline on setting specifications for related impurities in antibiotics : work still ongoing

Application of the requirements whenever possible – otherwise: case-by-case decision of the Ph Eur Commission to go for a stepwise approach

In the field of ... Herbals

- Represent 11% of the monographs published in the Ph Eur



Recent development

Adoption in November 2015 of the chapter Qualitative HPTLC of herbal drugs and herbal drug preparations (2.8.25) (publication 9.0):

- established to improve the reproducibility of identification methods and tests on adulteration by better standardising the high performance thin-layer chromatography.
- Practical applicability shown in e.g. monographs on Birch leaf (1174), Roman Chamomile flower (0380), St. John's wort (1438), St. John's wort dry extract, quantified (1874).
- To support the user, pictures of sample chromatograms published in the knowledge database showing the natural variability of the herbal drugs and herbal drug extracts.

Provision of “Qualified samples”

- Scope: monographs on herbals
- Provision to interested users with a qualified samples (sample shown to be suitable for the intended purpose) for testing in the Pharmeuropa stage
- Objective: to allow future users of the monograph to verify the methods during public consultation (Pharmeuropa stage)
- important mainly for not commercially available substances, e. g. mixtures of impurities, spiked samples
- 3 years pilot phase started in 2015

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In the field of ... radiopharmaceuticals

Adoption of the new monograph Chemical precursors for radiopharmaceutical preparations (2902) in June 2015 (Suppl. 8.8)

- Provides a self-contained set of quality criteria for chemical precursors and gives guidance on further aspects to be considered.
- Takes into account how they are produced and intended to be used and adopts a realistic and practical approach.
- Complementary monograph to the existing general monograph for Radiopharmaceutical Preparations (0125) which has been updated accordingly.

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Agenda

- The European Pharmacopoeia or how to turn challenges into opportunities and successes
- Structure of the European Pharmacopoeia
- Some example of recent developments
- **2016: call for experts!**

2016: CALL FOR EXPERTS

- All groups to be re-appointed in November 2016
- **New** : nomination process opened up to experts from non Ph. Eur. member states and from non-Observers
- The **final decision** to nominate a member to a Group of experts or working party is taken by the **Ph. Eur. Commission**

Thank you for your attention

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How to become an expert?

- What is needed to apply?
 - A completed nomination form
 - A completed declaration of interest form
 - An up-to-date *Curriculum vitae* [highlighting the expertise in the technical field covered by the Group]
- What we will make available to support candidates:
 - The nomination form *to be completed*
 - The *declaration of interest* form *to be completed*
 - The terms of reference and profile for experts
 - Our time and support in case of questions ...

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Why joining the Ph. Eur. network?



- Help shaping Ph. Eur. texts at an early stage
- Be part of and help build a network with assessors, OMCLs, academics and Industry representatives. This will provide you with unique opportunities:
 - To share information and experience
 - to better understand difficulties linked to the elaboration and revision of pharmacopoeial texts,
 - To find a common way forward based on a mutual understanding,
- To network and exchange experiences in an European and International environment!
- Make your CV stand out from the crowd!
Becoming an expert will give you a great opportunity to expand your knowledge of the Ph. Eur. and the European regulatory system.

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Work programme: 16 finished products

Raltegravir tablets	Fosaprepitant powder for solution for infusion
Raltegravir chewable tablets	Lacosamide tablets
Daptomycin powder for solution for infusion	Lacosamide oral solution
Deferasirox dispersible tablets	Lacosamide solution for infusion
Deferiprone tablets	Sorafenib tablets
Deferiprone oral solution	Rivaroxaban tablets
Dronedarone tablets	Regorafenib tablets
	Rosuvastatin tablets (P1)
	Teriflunomide tablets

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