*International Conference, 19-21 September 2022*

# Collaboration, Innovation and Scientific Excellence: the European Pharmacopoeia 11th Edition

## Closing Plenary Session

**European Pharmacopoeia: What to expect for the future?**

Moderator: Salvador Cañigueral

Chair of the European Pharmacopoeia Commission




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

edqm
European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé

COUNCIL OF EUROPE
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## Alternatives to animal testing (3Rs)

# Ph. Eur. recent achievements and roadmap

Dr. Emmanuelle Charton

Head of Division B
European Pharmacopoeia Department
EDQM, Council of Europe

*Collaboration, Innovation and Scientific Excellence: the European Pharmacopoeia 11th Edition*

 

## Achievements of the Ph. Eur. Commission for **3Rs**


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

**What was the trigger?**
**How?**
**What was the outcome/ impact?**



What has been achieved over the last decade?

 

# Medicines concerned by animal testing for QC purposes

**Vaccines for human use and for veterinary use**

Blood products

Biological and biotechnological products

Antibiotics

Radiopharmaceuticals




# **Deletion** of the Target Animal Batch Safety Test (TABST)

**VICH GL 41 and 44**

**Experts of the Ph. Eur.**

- Questionable scientific justification
- Retrospective analysis carried out

**Deletion** of TABST in 80 individual monographs

**Ph. Eur. 2013**

**VICH GL 50R and 55**

**Animals saved**: horses, cattle/calves, pigs/piglets, sheep/lamb, dogs, ferrets, cats (often 8-12 weeks old), rabbits, guinea-pigs (tetanus vaccine), chickens and turkeys (often 14 to 28 days old), domestic ducks, fish (salmonids).

# **Deletion** of the Abnormal Toxicity Test (ATT)

Paul-Ehrlich-Institut

The European Partnership for Alternative Approaches to Animal Testing

**Experts of the Ph. Eur.**

- Lack of scientific relevance
- Lack of scientific justification
- Retrospective analysis carried out

**Deletion** of ATT in 49 individual monographs; suppression of chapter 2.6.9

**Animals saved**: mice, guinea-pigs

**Ph. Eur. 2018**

World Health Organization **2018**

**VICH GL 59**




# Biological Standardisation Programme achievements

Co-funded by the European Union

EUROPEAN UNION

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Co-funded and implemented by the Council of Europe

**Submission of a validated alternative method by a manufacturer/OMCL/a partner**

**Collaborative study involving all interested parties**

***BSP 107 Assay of hepatitis A vaccine (2.7.14)***
validated ELISA method as alternative to the serology assay in mice

**Ph. Eur. 2015**

**BSP 114** ***Replacement of HIST (by CHO cell assay 2.6.33)***
Validated alternative method to the *test for residual pertussis toxin in mice*

**Ph. Eur. 2020**

# EDQM events

Ph. Eur. 2017


13 February 2012, Strasbourg, France
EDQM WORKSHOP ON ALTERNATIVES TO THE LEPTOSPIROSIS BATCH POTENCY TEST, 26-27 January 2012, Strasbourg, France

- In vitro method as the preferred method for the batch potency test
- Consistency of production

**BSP 130** *cell based assays for in-process toxicity and antigenicity testing of Clostridium septicum vaccine antigens*

epaa The European Partnership for Alternative Approaches to Animal Testing
European Commission
edqm European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé
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**Novel *in-vitro* model as alternative to *in-vivo* toxoid vaccines testing: *Clostridium septicum* vaccine as proof of concept**

**Virtual Workshop**
**Webinar Sessions on 9 & 10 March 2021**

Ph. Eur. 2022

- Humane end points
- replacement of mice by specific cell lines as an indicator of toxicity



# The "substitution" concept

**Experts of the Ph. Eur.**

**When a direct head-to-head comparison with an existing *in vivo* method is not possible**

**New chapter *Substitution of in vivo method(s) by in vitro method(s) for the quality control of vaccines (5.2.14)***

Ph. Eur. 2018

**Experts of the Ph. Eur.**

- due to the variability inherent in the *in vivo* methods
- Scientific relevance of the in vitro method

- encourages transition from *in vivo* to *in vitro* methods
- provides guidelines on validation of substitute methods

## Systematic re-evaluation of the relevance of animal tests mentioned in Ph. Eur. texts

**Experts of the Ph. Eur.**

- ❑ **Review of toxicity testing requirements for acellular pertussis vaccines (human)** As a consequence of BSP 114 — **Ph. Eur. 2020**
- ❑ **Review of toxicity testing requirements for tetanus vaccines (human and vet)** — **Ph. Eur. 2021**
- ❑ **Review of veterinary vaccine monographs to promote the 3R principles** *Canine parvovirosis vaccine (live), Equine herpesvirus vaccine (inactivated), Avian infectious bronchitis vaccine (live)* ***… +8 monographs in Pharmeuropa 34.2*** — **Ph. Eur. 2017**

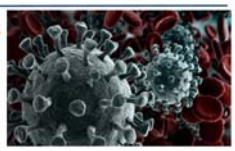
 

## Testing for extraneous agents (human and veterinary vaccines)

- ❑ **Revision of testing strategy for extraneous agents: risk-based approach**
- ❑ **Moving quality requirements upstream (healthy flocks) (vet)**
- ❑ **Revision of chapters to delete animal tests as far as possible, based on available literature (human)**
- ❑ **Reference to molecular methods**

***For more details, please refer to Featured session 5***

- EDQM/Ph. Eur. achievements in the control of extraneous agents for vaccines & perspectives on HTS



Featured Session on Microbiological and Viral Safety
20 September 2022
*Catherine Lang and Gwenael Cirefice, EDQM*

# New Pyrogenicity strategy

*For more details, please refer to Featured session 5*

| 1971 | 1987 | 2010 | 2020 |
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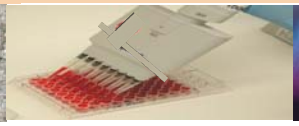
|  |  |  |  |
| Pyrogens (2.6.8) | BET (2.6.14) | MAT (2.6.30) | BET using rFC (2.6.32) |

**The RPT continues to be widely performed**

**Experts of the Ph. Eur.**

epaa The European Partnership for Alternative Approaches to Animal Testing

## Proposal:

**Pharmeuropa 35.1**

**New chapter *5.13* Pyrogenicity**
**Deletion of the rabbit pyrogen test from 60 Ph. Eur. texts by 2025 and suppression of chapter *2.6.8* from the Ph. Eur. by 2026**



# New Pyrogenicity strategy

- https://go.edqm.eu/NewPyrogenicityStrategy



**Strategy for removing or replacing the rabbit pyrogen test:**
**New pyrogenicity strategy of the European Pharmacopoeia Commission**
**September 2022**

# EPAA/EDQM International Public Conference

*To mark the first official milestone in the strategy, i.e. the publication of revised Ph. Eur. texts omitting the RPT in Pharmeuropa 35.1 (January 2023)*

Date: **14-16 February 2023**

Venue: European Commission premises, Brussels

# What's on the horizon for the future?

Vaccines for human use and for veterinary use

Blood products

Biological and biotechnological products

Antibiotics

Radiopharmaceuticals

# What's on the horizon for the future?

Vaccines for human use and for veterinary use

**BSP Projects underway**
**e.g.**
- BSP 148 rabies (human) in vitro assay
- BSP136 BINACLE for toxicity of tetanus toxoid

Blood products

**2026 Pyrogenicity strategy**

Biological and biotechnological products

**A few remaining challenges**

Antibiotics

Radiopharmaceuticals

**Status quo**

# EDQM collaborations

**Experts of the Ph. Eur.**

European Commission

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

**EURL ECVAM**

epaa
The European Partnership for Alternative Approaches to Animal Testing

The European Network of Official Medicines Control Laboratories (OMCLs)

World Health Organization

vac2vac

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- Prof. J.-M. Person Chair of Group 15V, Vaccines for veterinary use
- Dr. Ingo Spreitzer, Chair of BET WP, Bacterial endotoxins

…. and at the EDQM: Catherine Lang, Gwenaël Ciréfice and Mihaela Buda


 

# Thank you for your attention


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# BSP METHODS AND STANDARDS TO COME

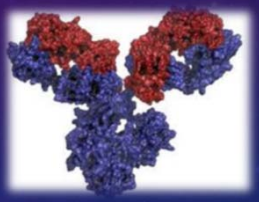
LUKAS BRUCKNER, SWISS DELEGATION TO THE PH. EUR. COMMISSION

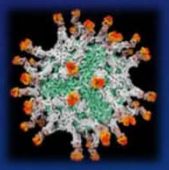
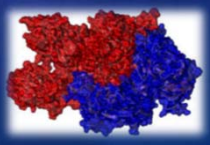
CHAIR OF THE BSP STEERING COMMITTEE

## MISSION OF THE BIOLOGICAL STANDARDISATION PROGRAMME (BSP)

- **establish and maintain Ph. Eur. Reference Standards and working standards** for biologicals (i.e. biological reference preparations [BRP], biological reference reagents [BRR] and certain chemical reference substances [CRS])
- **standardisation of test methods** for the quality control of biologicals in the Ph. Eur.
- promote, through collaborative studies, alternative methods for the **quality control of biologicals** in order to apply the 3Rs concept (refine, reduce, replace) to use of animals in laboratory experiments
- **contribute to the activities of international harmonisation** e.g. with WHO, WOAH, and the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) in the field of biologicals.

# SCOPE

- Biotech products (Group 6, [MAB, P4BIO])
  (hormones, cytokines, anticoagulants (heparins), mAbs…)
- Blood derived medicinal products, contaminants (Group 6B)
  (immunoglobulins, coagulation factors…)
- Vaccines, sera for human use (Group 15)
- Vaccines, sera for veterinary use (Group 15V)
- Miscellaneous (specific working groups)
  (allergens, endotoxins, mycoplasma…)

# PROJECTS – AN OVERVIEW

Current ‘BSP’ catalogue includes 60 References (BRP / CRS / BRR)

- 170 Projects initiated/concluded
- 44 Projects on method development
- 23 Projects on 3Rs methods

Projects are run as multi-phase collaborative studies

- projects can be ‘simple’ 1-2 years or highly complex 5 years +

Study outcomes published in Pharmeuropa Bio & Scientific Notes

available free online

https://www.edqm.eu/en/web/edqm/pharmeuropa-pharmeuropa-bio-scientific-notes

# STOCK REPLACEMENT OF EXISTING BRP / BRR / CRSs

Important part of ongoing work

Current 3R related examples

- Vaccines for Human Use / Vaccines for Veterinary Use
  - Diphtheria toxin BRP for Vero cell assay
  - Hepatitis A virus Coating Reagent for ELISA BRR
  - Clostridia multi-component rabbit anti-serum BRP
  - …

Work programme at: https://www.edqm.eu/en/bsp-work-programme#{%22337134%22:[]}

# EXAMPLES OF NEW / ONGOING 3R METHOD PROJECTS

- *in vitro* Potency test for Human Rabies Vaccine
- Tetanus Vaccine (safety)
- Erythropoietin *in vitro* assay
- Tetanus/diphtheria Vaccine (content / potency)

# *IN VITRO* POTENCY TEST FOR HUMAN RABIES VACCINE

BSP148, Project leaders: S. Morgeaux (ANSM), J.M. Chapsal (independent)

- Sandwich ELISA method for quantification of rabies glycoprotein developed – follow on from 2012-2015 EPAA study
- 2 suitable, highly characterised monoclonal antibodies selected
  - → Bind conformational epitopes on well-defined antigenic sites of the glycoprotein inducing protection
  - → recognise most rabies virus seed strains used for human vaccines
  - → Discriminate subpotent vaccine lots
  - → Owned by public institutes and available for commercial distribution worldwide
- > 30 laboratories worldwide (manufacturers and public laboratories) enrolled in an international collaborative study
- Data analysis and report are ongoing
- Reporting phase for real-life use under preparation

# TETANUS (SAFETY)

BSP136, Project leaders: H. Behrensdorf-Nicol, (B. Krämer) (PEI)

- Test for *in vitro* determination of tetanus toxicity by an endopeptidase assay linked to a ganglioside-binding step (BINACLE test) developed at PEI
- Initial Collaborative phase completed
  - outcome confirmed assay potential but results obtained by the participants varied widely, some but not all and not all of the laboratories were able to achieve a sensitive detection of active Tetanus Neurotoxin
  - BINACLE method requires further standardisation
- New collaborative phase in preparation
  - protocol refinement, qualification of samples and critical components underway in the PL's laboratory

# ERYTHROPOIETIN *IN VITRO* ASSAY

BSP162, Project Leader: K. Partridge (NIBSC)

- BRP calibrated against the International Standard with the *in vivo* bioassay
- Validation of an *in vitro* assay, in cell culture
  - establish a robust *in vitro* method that may be used to measure the potency of recombinant human erythropoietin preparations, relative to a standard of identical origin whose potency has already been assigned by *in vivo* assay
- Transferability study organised in a small number of laboratories
- Data analysis underway

# TETANUS / DIPHTHERIA (POTENCY)

Early stage project

Validation of *in vitro* antigen content assay for consistency evaluation of diphtheria and tetanus toxoids – follow up of VAC2VAC project

- Characterisation of relevant monoclonal antibodies and their use in *in vitro* assays was included as part of the VAC2VAC project
- Further preliminary research phase with the alternative method with additional validation data to be generated by the laboratories which developed the method.
- Monoclonal antibodies will be available from NIBSC through agreement with the VAC2VAC consortium members / antibody owners
- Further BSP steps awaiting publication of VAC2VAC study outcome

# COOPERATION

The BSP programme functions through synergy and co-operation with partners including:

- OMCLs
- Manufacturers
- WHO
- Other regional standard setting bodies e.g. FDA/USP, Health Canada
- Research consortia and associations
  - VAC2VAC
  - EPAA
  - …

# WIDER PERSPECTIVE AND CONCLUSIONS

- The BSP is anchored in the context of the Ph. Eur. however recognises the global scope of biological medicinal products
- Promoting 3Rs and implementation of harmonised alternatives to animal testing is a key goal achieved through exchange and transparency of results through publications like EDQM's Pharmeuropa Bio & Scientific Notes and symposia
- Successful outcomes are possible thanks to the contributions of many; from development and proposal of validated assays, donation of study materials and candidate reference materials, study leadership, study participation and expert consultation to name a few.

# ACKNOWLEDGMENTS


- EDQM Biological Standardisation, OMCL Network and HealthCare Department (DBO)


# THANK YOU FOR YOUR ATTENTION

# Review of animal testing requirements in WHO Guidelines for vaccines and biological therapeutics : Implementation of 3Rs principles

Richard Isbrucker, WHO, Norms & Standards for Biologic Products Unit (NSB)
Elliot Lilley, UK NC3Rs

Ph. Eur. conference, 19-21 Sept 2022



## WHO guidelines

**WHO Guidelines on quality, safety and efficacy of vaccines and biological therapeutics:**

- Provide key principles and specifications on which regulators may set national requirements and also for WHO prequalification
  - Facilitate scientific and risk-based evaluations and post-approval change management
- Increase international harmonization on product specifications
- Improve communications and expectations between industry and regulators
- Meant to complement existing national and international regulations/guidelines and provide guidance where none may exist
- Written by international experts/drafting group members and through public consultation processes
- Reviewed and adopted by the WHO Expert Committee on Biological Standardization (ECBS) and published as Annexes to the WHO Technical Report Series (TRS)

## 3Rs Project background :

The purpose of this project is to review WHO guidelines to determine:

- How much/which animal testing is recommended in WHO guidance documents for the quality control and batch release testing of vaccines and biological therapeutics?
- What 3Rs strategies are currently available that are not considered within the existing WHO guidance documents?
- What are the needs and barriers to better adoption of 3Rs by NRAs/NCLs and manufacturers in the quality control and batch release testing of these products?
- What strategy or response by WHO would be helpful in promoting the adoption of harmonized animal-free methods and/or implementation of 3Rs principles by NRAs/NCLs and manufacturers?



## 3Rs Project background :

| In Scope | Out of Scope |
|---|---|
| • Review of publicly available WHO guidance documents for vaccines and biological therapeutics (those adopted by ECBS)<br>• Methods used in their quality control and batch release testing<br>• All 3Rs (i.e. Refinement, Reduction and Replacement)<br>• Identification of barriers towards adopting 3Rs strategies in the quality control and lot release of vaccines and biological therapeutics | • Documents not publicly accessible, which are not considered by ECBS, or are non-WHO guidance documents<br>• Animal methods not related to the QC of vaccines and biological therapeutics (e.g. during product development)<br>• Development or validation of 3Rs methods<br>• Ethical review of the use of animals<br>• Non-constructive criticisms of WHO, member states, NRAs/NCLs, or manufacturers |

# 3Rs Project background (Stage 1):

World Health Organization

## Review and Recommendations (Audit):

3-year timeline (2020 - 2023)

Led by an external agency (UK NC3Rs)

- Avoid potential bias inherent in self-reviews
- Manage the project and deliver the final report
- Establish international working group, and focus groups (WHO is a participant)
- Organize workshops / meetings
- Conduct survey of NRA/NCLs and manufacturers




# 3Rs Project background (Stage 2):

World Health Organization

## Response and Implementation:

Led by WHO / NSB in consultation with ECBS

Dependent on outcomes and recommendations in final report from Stage 1

- Recommendations should be based on sound scientific principles
- Supported by findings from the surveys

ECBS requested the report include the database of all guidance documents reviewed, along with suggested revisions to text

- Adoption of the suggested text to be subject to WHO drafting processes for revisions to guidelines

## 3Rs Project background :

This project was presented to ECBS in Oct 2019 (TRS 1024, section 2.2.2)

Funding secured : BMGF & NC3Rs

International working group established :

- 14 NRA/NCLs
- 9 Manufacturers
- 7 Organizations
- 17 Countries

Timelines and milestones established including regular stakeholder engagement :

- Bi-annual meetings of working group
- Regional workshops (virtual)
- Surveys to NRA/NCLs and manufacturers



## Progress to date :


81 guidance documents reviewed (dating from 1972 – 2022)

350 animal tests for QC / lot release testing identified in 61 guidelines

5 thematic test categories emerged from the review and focus groups were formed to draft proposed revisions to the text:

- Potency/immunogenicity testing
- Endotoxin and pyrogenicity testing
- Neurovirulence testing
- Adventitious agent testing
- Specific toxicity testing

Alternative text emphasising 3Rs for most tests finalised

# Findings from guideline review :

**High variability in language between guidelines**

E.g. Pyrogenicity and endotoxin testing of final bulk or product:

Each filling lot shall be tested for pyrogenicity by the intravenous injection of rabbits. Three or more healthy rabbits…

Each final lot should be tested for pyrogenic substances. The test procedures should be approved by the national regulatory authority.

The vaccine in the final container should be tested for pyrogenic activity by intravenous injection into rabbits or by a Limulus amoebocyte lysate (LAL) test, which should be validated for this purpose.

The endotoxin content of the final product should be determined using a suitable in vitro assay such as a LAL test. When required, the monocyte activation test (MAT) or rabbit pyrogenicity test may be used for monitoring potential pyrogenic activity subject to the agreement of the NRA.

The need for pyrogenicity testing should be determined during the manufacturing development process. It should also be evaluated following any changes in the production process or relevant reported production inconsistencies that could influence the quality of the product with regard to its pyrogenicity...



# Stakeholder engagement :

## Understanding regional opportunities and challenges

Providing an opportunity for the vaccines and biologicals community to help inform the recommendations and their implementation by the WHO.

## Regional workshops

Workshops held virtually to allow participation during travel restrictions

- Europe (2 March 2022)
- Asia/Oceania (28 April 2022)
- Pan-American, coordinated with PAHO (26 September 2022)
- Africa (date tbd)

Additional stakeholder meetings are anticipated throughout the project

## Surveys of NRA/NCLs and manufacturers

# Highlights from Manufacturer Survey :

World Health Organization

## Demographics

- 28 complete responses
- 14 different countries

## GST/ATT

- 22/28 aware of WHO removal of GST requirement
- 16/28 still performing the test

## 3Rs

- 19/28 indicated that some in vivo batch/lot release tests were not fit for purpose
- 18/28 use non-animal methods when available
- Ethical concerns, cost savings, reduced QC test duration and high variability of in vivo assays are benefits of 3Rs
- Concerns over failing to meet regulatory requirements main barrier to adoption of 3Rs
- Updates to WHO guidance to implement 3Rs and a WHO 3Rs statements rated highly as factors to support 3Rs



# Expected outcomes (Stage 1) :

World Health Organization

## Publications and Presentations :

- Lilley *et al*. Integrating 3Rs approaches in WHO guidelines for the batch release testing of biologicals. Biologicals, 74 (2021) 24–27
- Report on manufacturer survey (submitted) and NRA/NCL survey (being drafted)
- Report on regional workshops (being drafted)
- Presentations to 2023 World Clinical Pharmacology Congress and WC12 World Congress on Alternatives and Animal Use in the Life Sciences

## Final Report to ECBS :

- October 2023
- Change the *emphasis* in WHO guidelines to *promote* adoption of non-animal alternatives
- All 3Rs will be considered based on robust science
- Animal tests will only be recommended for deletion with a sound scientific basis
- Propose 3Rs guidance to promote the scientific benefits of non-animal alternatives, optimised experimental design and high standards of animal welfare
- Proposal for better consistency of language across the guidelines
- Include the database of guidelines reviewed and proposed changes to the text

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Paul Stickings
Youchun Wang

Bill and Melinda Gates Foundation

UK National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs)




World Health Organization

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

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COUNCIL OF EUROPE
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# Towards the 12th Edition of the European Pharmacopoeia

## What's in the pipeline?

### An overview of current and future activities

Emmanuelle Charton and Bruno Spieldenner, EDQM

## General Monograph Radiopharmaceutical preparations (0125)

Substantial revision Ph. Eur. Supplement 11.1

Main points:

- Clarification on how to deal with control of radionuclide precursors in a continuous process
- Production section updated **to reflect current state-of-the-art** radionuclide production methods
- Sections added to cover tests for pH, Elemental impurities and Particulate contamination
- Restriction of physiological distribution testing, in-line with **3R** principles

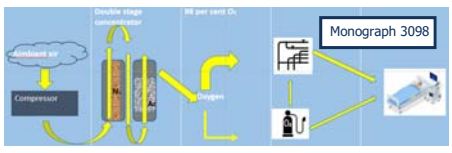
Ongoing revision:

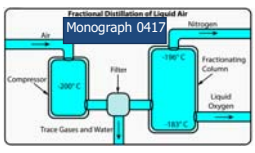
- Replacement of Rabbit Pyrogen Test

## New monograph on Oxygen (98 per cent) (3098)

- Oxygen obtained via cryodistillation (*Oxygen (0417)* and obtained via concentration of ambient air (*Oxygen (93 per cent )(2455), Oxygen (98 per cent) (3098)*)
- Different impurity profiles
- New monograph (3098) under elaboration by medicinal gases expert group – publication in **Pharmeuropa 33.4** – examination of extensive comments
- Revised text prepared by the experts
- Second round of publication: **Pharmeuropa 34.4**



# Water monographs: BET using rFc

## Purified Water (0008) and Water for Injections (0169)

- Test for bacterial endotoxins (BET)
  - Current version: LAL, a reagent derived from the horseshoecrab

  - Proposed revision: LAL or recombinant Factor C, a reagent produced by rDNA technology (chapter 2.6.32 of the Ph. Eur.)

OR

- **Pharmeuropa 34.3** (July 2022)

- EDQM News item https://www.edqm.eu/en/-/european-pharmacopoeia-seeking-user-feedback-on-use-of-recombinant-factor-c-for-control-of-bacterial-endotoxins-in-its-water-monographs




# Gene therapy medicinal products - new approach


**General chapter**
*Gene transfer medicinal products for human use (5.14)*


**General monograph**
*Gene therapy medicinal products for human use (3186)*

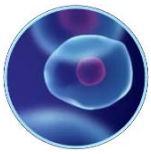

**General chapter**
*Additional information on gene therapy medicinal products for human use (5.34)*

**General chapter**
*Raw materials of biological origin for the production of cell-based and gene therapy medicinal products (5.2.12)*



**Pharmeuropa 34.3**
*Public deadline: 30 Sep 2022*
*NPA deadline: 30 Nov 2022*

# New general chapter 5.32 Cell based preparations



Approval of a number of cell-based therapy medicinal products in Europe
→ Rapid evolution in recent years

Need for a general text covering quality of cell-based preparations

Chapter ought to be general enough to encompass both:
- products that are already on the market
- new products to come

**Cell-based preparations (5.32)**

***General requirements***
- Production
  - → Source cells
  - → Preparation and processing of cells
  - → Substances used in production
  - → In-process controls
- Final lot
  - → Identification
  - → Tests
  - → Assays


***Specific sections***
- Mesenchymal stem cells
- Haematopoietic stem cells
- Limbal stem cells
- Chondrocytes

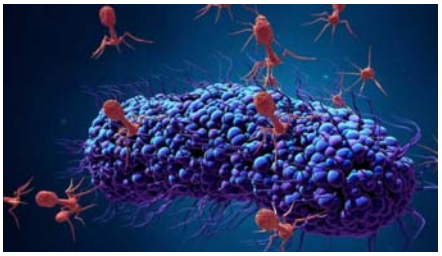


# New general chapter on Bacteriophages

## Phage therapy active substances and medicinal products for human and veterinary use (chapter 5.31)

- Phage therapy: alternative to antibiotic treatment
- Text under elaboration by BACT Working Party
- Publication in Pharmeuropa (tentative): 2023



# New general chapter on HTS

- *"High Throughput Sequencing for the detection of extraneous agents in biological products* (2.6.41)"
- Non-binding general chapter
- Proposed content: description of the technology, **guidelines for method validation**
- Publication in Pharmeuropa (tentative): 2023

10:40-11:35 **Towards the 12th edition of the European Pharmacopoeia: new approaches and technologies in the quality control of medicines: next challenges for the European Pharmacopoeia**
Adapting Ph. Eur. to new approaches and technologies for quality control, Michel Ulmschneider, Chair of the Spectroscopy and Data Analysis (SDA) and General Methods (MG) Working Parties
ICH Q5A (viral safety), High-throughput sequencing (HTS), Laurent Mallet, EDQM, Council of Europe
Activities in the field of nanomedicines, Gerrit Borchard, Chair of the Non-biological Complexes (NBC) Working Party

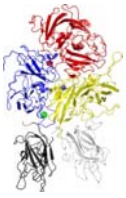
 

# Human coagulation factor VIII (rDNA) monographs

**Human coagulation factor VIII (rDNA) (1643)**

Covers both **active substance** and **medicinal product**

Applies to **full-length** and **B-domain-deleted** rFVIII



FUTURE

Human coagulation factor VIII (rDNA), **concentrated solution** (3105)

Human coagulation factor VIII (rDNA), *B-domain deleted*, **concentrated solution** (3107)

Human coagulation factor VIII (rDNA), **powder for injection (3106)**

Human coagulation factor VIII (rDNA), *B-domain deleted*, **powder for injection** (3108)

WORK IN PROGRESS

# Quality standards for monoclonal antibodies

**Adalimumab** (3147)[a]

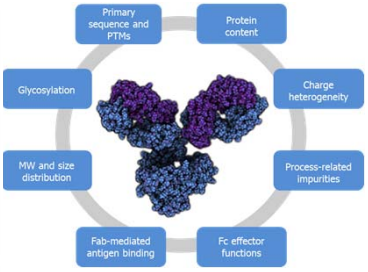
**Golimumab** concentrated solution (3103)[b]

**Ustekinumab** (3165)[b]

**Golimumab injection** (3187)[b]

**Ustekinumab injection** (3188)[b]

## Monographs





## Performance -based standards (general chapters)


Size-exclusion chromatography for recombinant therapeutic monoclonal antibodies (2.5.43)

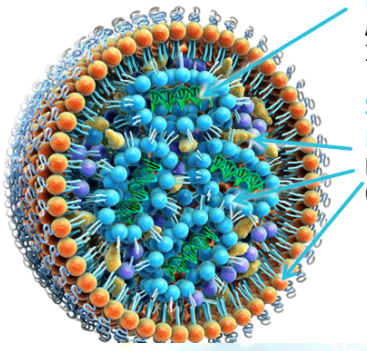
Capillary isoelectric focusing for recombinant therapeutic monoclonal antibodies (2.5.44)


[a] procedure P1 (multi-source); [b] procedure P4 (single-source)




# Quality of mRNA vaccines and their components

RNA & DNA are large molecules that require nanoparticle delivery technologies to get into tissues and cells.



**RNA or DNA**
Active Pharmaceutical Ingredient (API)

**Synthetic Lipids or Polymers**
Delivery technologies (excipients)

**New Working Party mRNAVAC:**

- To be appointed by the Ph. Eur. Commission at its November session
- News item https://www.edqm.eu/en/-/ph.-eur.-commission-establishes-a-new-working-party-on-mrna-vaccines?p_l_back_url=%2Fen%2Fsearch-edqm%3Fq%3DmRNAVAC

10:40-11:35 **Towards the 12th edition of the European Pharmacopoeia: new approaches and technologies in the quality control of medicines: next challenges for the European Pharmacopoeia**
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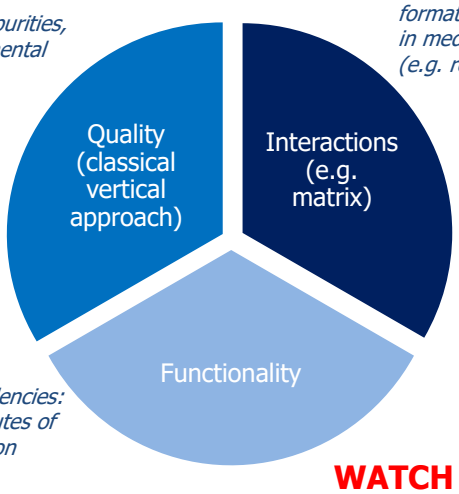
ICH Q5A (viral safety), High-throughput sequencing (HTS), Laurent Mallet, EDQM, Council of Europe
Activities in the field of nanomedicines, Gerrit Borchard, Chair of the Non-biological Complexes (NBC) Working Party

# Ph. Eur. Strategy for excipients

- Review the current approach of the Ph. Eur. when setting standards (fully fit for purpose)?
- Decision of the Ph. Eur. Commission to create a dedicated WP (EXS) – work will start in 2023

*Presence of mutagenic impurities, solvents, elemental impurities?*

*Role of excipients in formation of N-nitrosamines in medicinal products (e.g. residual nitrite)*

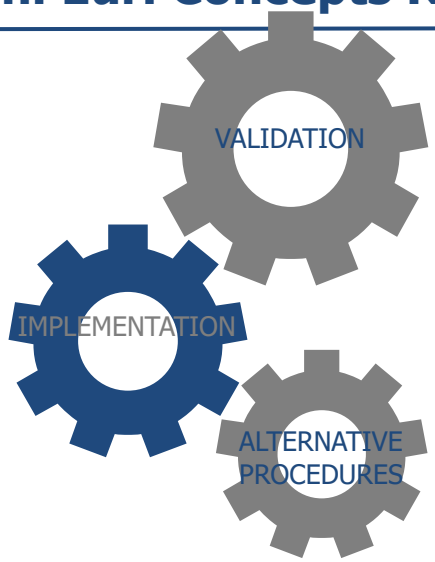



*Interdependencies: Different routes of administration*

**WATCH THE SPACE !**

# Ph. Eur. Concepts Related to Analytical Procedures




**Ph. Eur. General Notices**

The analytical procedures given in an individual monograph have been **validated** in accordance with accepted scientific practice and recommendations on analytical validation. Unless otherwise stated in the individual monograph or in the corresponding general chapter, validation of these procedures by the user is not required.

When **implementing** a Ph. Eur. analytical procedure, the user must assess whether and to what extent its suitability under the actual conditions of use needs to be demonstrated according to relevant monographs, general chapters and quality systems.

The tests and assays described are the official analytical procedures upon which the standards of the Ph. Eur. are based. With the agreement of the competent authority, **alternative analytical procedures** may be used for control purposes, provided that they enable an unequivocal decision to be made as to whether compliance with the standards of the monographs would be achieved if the official procedures were used. In the event of doubt or dispute, the analytical procedures of the Ph. Eur. are alone authoritative.

# Comparability of alternative analytical procedures, 5.27

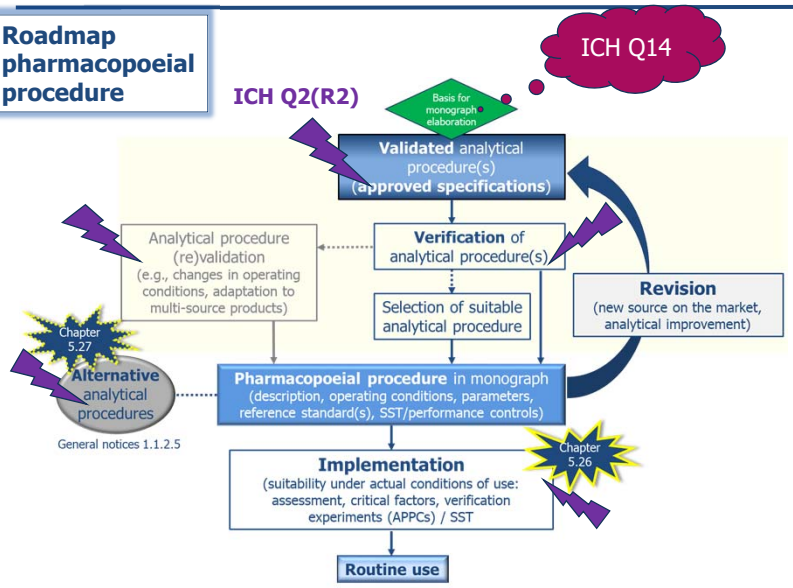
- ✓Provide additional information on a way to use alternative procedures
- ✓Component of flexibility in the Ph. Eur., extract of the General Notices (1.1.2.5)
- ✓Users' responsibility to demonstrate comparability to the satisfaction of the *competent authority*
- ✓Compliance required, but alternative procedures may be used: same pass/fail decision
- ✓The pharmacopoeial procedure is the reference procedure in case of doubt and dispute
- ✓Alternative analytical procedure = validated according to relevant scientific guidance
- ✓Need to implement the Ph. Eur. analytical procedure
- ✓Comparison study with head-to-head testing format with same experiments – where feasible, using the same samples
- ✓method for data evaluation proposed by comparison of the means and standard deviations (TOST)


CHAPTER 5.27 "COMPARABILITY OF ALTERNATIVE ANALYTICAL PROCEDURES"
(RECENT PUBLIC CONSULTATION: PHARMEUROPA 34.2)
MANY COMMENTS RECEIVED ➔ HIGH INTEREST

# Analytical Quality by Design ('enhanced approach')

**Roadmap pharmacopoeial procedure**



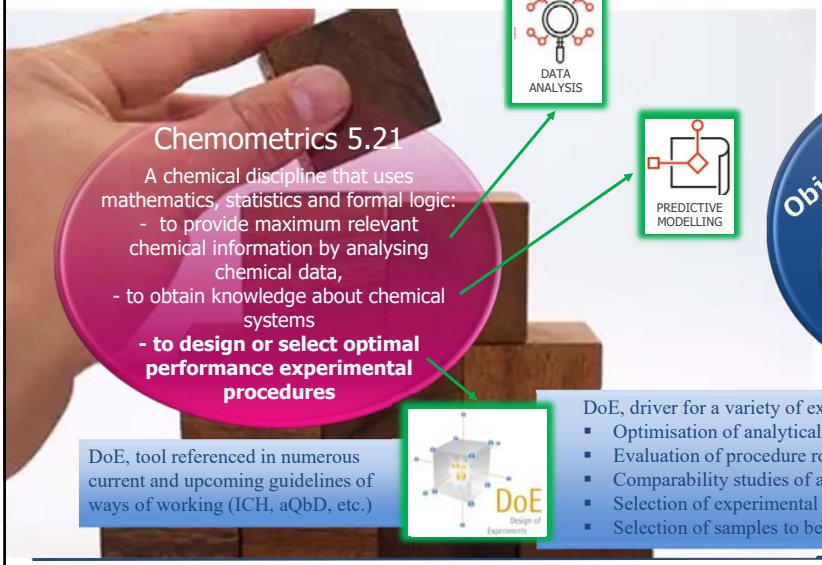

**Share your expertise and join the new AQbD Working Party**

- ➢ Assess the feasibility and impact of incorporating analytical procedures developed using the concepts of AQbD in Ph. Eur. monographs
- ➢ Advise the Commission and expert groups on appropriate elaboration/revision strategies for incorporating such analytical procedures in monographs
- ➢ Identify verification and revision approaches for analytical procedures developed using AQbD

# General Chapter on Design of experiments (5.33)

Pharmeuropa 34.4



DATA ANALYSIS

PREDICTIVE MODELLING

## Chemometrics 5.21

A chemical discipline that uses mathematics, statistics and formal logic:
- to provide maximum relevant chemical information by analysing chemical data,
- to obtain knowledge about chemical systems
- **to design or select optimal performance experimental procedures**

DoE, tool referenced in numerous current and upcoming guidelines of ways of working (ICH, aQbD, etc.)

DoE

DoE, driver for a variety of experimental situations:
- Optimisation of analytical procedures
- Evaluation of procedure robustness
- Comparability studies of analytical procedures
- Selection of experimental and instrument settings
- Selection of samples to be prepared for calibration of NIR, Raman, etc.

**Objectives 5.33**

- Introduction to the use of DoE
- Provide guidance on good practice
- Set out the regulatory framework and critical aspects that needs to be addressed

# Medicinal product monographs (chemically defined API)

**2012** — **Start of the pilot phase:**
* 1 single-source product (P4)
* 1 multi-source product (P1)

**2014** — **Scope of the Ph. Eur. widened:**
* P4 mono. in Pharmeuropa
* Focus on single-source

**2015**
* Adoption of the first P4 mono. ***'Sitagliptin tablets'***
* Addition to the WP of the first P1 mono.

**2019**
* Adoption of the first P1 mono. ***'Rosuvastatin tablets'***
* Creation of group 17 (multi-source products)

**2022**
* Addition to the WP of the first mono. on combination product

**18** monographs adopted (16 P4 & 2 P1)

**2** **Expert groups** highly involved in the elaboration of **30 monographs** (17 P4 & 13 P1)

**11th Edition**

**6** monographs in Pharmeuropa

**Elaboration frame established** (e.g. impurity control, dissolution test, API salts and solvates)
**Dedicated Technical Guide**

**12th Edition**

**Increase the number of medicinal product monographs in the Ph. Eur.**

# Cannabis flower monograph (3028)

***Some highlights of the ongoing elaboration of this herbal drug monograph***

- **DEFINITION & IDENTIFICATION by HPTLC: specifications for 3 different types of herbal drug (THC-rich, CBD-rich & THC/CBD-intermediate).**
- **TEST FOR TOTAL CBN (i.e. CBN + CBNA) by LC: selective for 17 cannabinoids.**
- **TEST FOR FOREIGN MATTER & LOSS ON DRYING: ad-hoc specifications for the herbal drug when prescribed to patients.**
- **ELEMENTAL IMPURITIES: specifications for Arsenic, Cadmium, Lead & Mercury.**
- **ASSAY FOR TOTAL CBD (CBD+CBDA) & TOTAL THC (THC+THCA) by LC.**


***Publication in Pharmeuropa (tentative 34.4)***

# Join us in paving the way for the future…


Contribute to the protection of public health by:

➢Making your comments count !!!

PHARMEUROPA ONLINE


➢Being part of a dynamic scientific community !!!



# Thank you for your attention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Facebook: **@EDQMCouncilofEurope**

# *Investing in the future*

**Adapting the Ph. Eur. to new approaches and technologies for quality control**

**Michel Ulmschneider, PhD, *habil*.**

**Chair of MG and SDA Working Parties**

**F. Hoffmann - La Roche AG**
Pharmaceutical Division Quality Control
Analytical Sciences and Technology



## Waves of innovations

New technologies and digitisation to control quality in medicines

**Two examples of innovative industrial projects:**

- Process control solution based on in-line spectroscopy and Machine Learning, to optimise antibody production and reduce manufacturing costs.
  - The goal is to make therapeutic products accessible to as many patients as possible.
- Optimisation of the culture of cell layers in bioreactors, thanks to innovative online optical sensors, Machine Learning and automated real-time feedback control coupled with a digital twin, and a Quality-by-Design (QbD) approach for process modelling.
  - The goal is to increase yield and efficiency in control.

**Required** are advanced process monitoring and control techniques, the application of Process Analytical Technologies (PAT) combined with Data Mining for process understanding, the continuous supervision of the entire process to detect drifts in real time for a dynamic control by coupling models to automatic control loops.

## New technologies, new approaches

**Measuring**

- New sources, sensors and devices (e.g. cascade quantum lasers for IR)
- Downsizing, miniaturisation, e.g. spectrometers on a chip
- Distribution, multiplication of measurement devices, IoT
- In-line and on-line

**Quality by Design, QbD**

- Real-time release testing (RTRT)
- Multi-attribute measurements (MAM)

**Computation**

- Cloud/edge computing
- Modelling and simulation of cQAs for predictions
- Digital twins



## Digitisation and data, toward a new paradigm
### Algorithms

**Data sciences in general**

- Usage of Artificial Intelligence accelerates
- Automation and robotics

**Machine Learning techniques**

- Transfer learning
- Ensemble methods
- Batch modelling and forecasting

**Self-calibration**

- Dynamic evolution of models, continuous updating and refreshing of models
- Adaptive models with different metaparameters
- Continuous and autonomous self-evaluation of models

## Digitisation and data, toward a new paradigm, *cont.*
Data

**All about Data**

- Big Data, Data lake, Data mining, Databases
- Data flow, rapidly replaced and updated data sets
- Re-sampling, Data fusion
- Data augmentation

**Control of data**

- Data set consistency over time
- Traceability
- Blockchain techniques, NFT



## Adapting Ph. Eur. to evolutions in analytical technologies
How do we proceed?

**Tracking evolutions of existing techniques**

- Update of existing chapters
  Examples: IR (*2.2.24*), Raman (*2.2.48*), NIR (*2.2.40*), XRF (*2.2.37*), UV (*2.2.25*), etc.

**Taking widespread innovations into account**

- New chapters, for emerged and widespread new technologies
  Examples: chemical imaging (*5.24*), electron microscopy (*2.9.52*), etc.

**Considering new ways of working**

- Chapter on PAT (*5.25*)
- Chapter on large sample size (*2.9.47*)

## Coverage of Data Sciences in Ph. Eur.

What is available?

**A series of data science chapters**

- Chemometrics (*5.21*)
- MSPC (*5.28*)
- DoE (*5.33*)

**Ph. Eur. was at the very forefront with above chapters**

- Chapters to be considered as a platform
- Providing information, essential clues for good practice
- More enabling than constraining
- Clarifying concepts and wording within the Ph. Eur.
- Could be considered as introductions to the field, starting material, but not a textbook
- Scope limited, but not limiting field of application



## Digitisation impact

Big Data, AI, and Interfaces

Machine learning and data sciences have become a key enabler across more and more activities and processes.
*Could data-driven control of medicine override mandatory quality standards?*

**Comfort**

- Ease of use, intuitive interfaces, automation
- Pre-established procedures, enhanced data visualisation
- Speed
- Continuous, automatic updates

**Impact on users**

- Excessive trust in systems, decisions delegated to machines and applications
- Less understanding, less shared experience, less knowledge
- Less critical, less awareness of limits, less control

## Maintain good practices in rapidly changing conditions

Embracing the full potential of the transformations we will face

**Decision delegation may result in less control and lower quality in medicines**

- Still fixing limits to instruments and physical parameters may not be the only solution
- Ongoing progress in technology, in data sciences, and computing cannot be planned
- Speed of changes make it difficult to fix standards and references

**Increasing deployment of models**

- Chemometric and ML model life cycle to be revisited for models that are constantly updated
- Move from a strict procedural formalism toward a more flexible controlling procedure
- Design specific processes for model self-evaluation
- More focusing on Data than on modelling



## To conclude

Maintain foundations while shaping the *future-friendly* Pharmacopoeia

**The deployment of data-driven applications will support next generation analytical techniques. Ph. Eur. should be ready to support this massive transformation.**

**Facing new, complex, unforeseen situations**

- Chapters like a platform providing scientific information with essential clues for good practice
- Enabling new technologies, not constraining, with series of “5.x” chapters
- Flexibility, transparency
- Speeding-up revisions and chapter adjustments or additions

**Strict position maintained**

- Guardian of good practices in analytical sciences
- Safe harbour for fundamentals

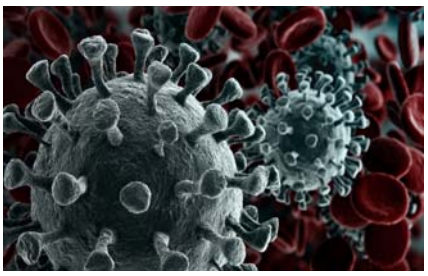
*Thank you for your attention*

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

edqm
European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé

COUNCIL OF EUROPE
CONSEIL DE L'EUROPE

- Next Generation Sequencing for detection of Extraneous Agents in Biological Products: overview of EDQM/Ph. Eur. achievements & perspectives and ICH Q5A revision



Collaboration, Innovation and Scientific Excellence: the European Pharmacopoeia 11th Edition

International Conference, 19-21 September 2022

*Laurent Mallet, EDQM*

# Outline

- Next Generation Sequencing: What is it?
- Extraneous agents testing for vaccines and viral vectors used as gene therapy products: evolution of the Ph. Eur.
  - Drivers for revising Ph. Eur. requirements
  - Evolution of Ph. Eur. 5.2.3 & 2.6.16
  - The concept of Substitution to replace *in vivo* methods as described in Ph. Eur. 5.2.14
- Perspectives on HTS and elaboration of a Ph. Eur. chapter
- Update on ICH Q5A guideline revision
- Conclusion

# Next Generation Sequencing: What is it?

- Also called High Throughput Sequencing (HTS) or Massive Parallel Sequencing
- Sequencing of acid nucleics with high throughput, scalability and speed
- Different technologies
  - Short reads, long reads
  - Read length from a hundreds of nucleotides to 50+ Kb
- Application to the detection and identification of viral Extraneous/Adventitious Agents:
  - Sensitivity
  - Breadth of detection: capability to detect both known and unkown viruses

# ▸ Extraneous agents testing for vaccines and viral vectors used as gene therapy products: evolution of the Ph. Eur.

# Extraneous agents testing for vaccines: drivers for change

- Contamination of a Rotavirus vaccine by Porcine Circovirus (2010)
  - Victoria *et al.* (Journal of virology): results showed the presence of PCV1 viral sequences using a new high throughput molecular biology method (MPS)
- Emergence of broad molecular methods for extraneous agent detection
- Revised WHO TRS 978 Annex 3 "*Recommendations for the evaluation of animal cell cultures as substrates for the manufacture of biological medicinal products and for the characterization of cell banks*" (adopted in 2010)
  - Risk assessment strategy and new methodologies (e.g. NGS)
- Convergence with FDA Guidance for Industry (2010) on testing methodologies
- 3Rs context in Europe:
  - European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes (Council of Europe), EU Directive 2010/63/EU

# Extraneous agents testing for vaccines: drivers for change

- EDQM survey (2012) with Vaccine Manufacturers and CROs regarding contamination cases over a period of 10 years
- Publications* highlighting gaps in compendial tests:
  - Evaluation and comparison of the sensitivity of current testing packages for detection of extraneous agents → poor sensitivity of *in vivo* methods, gaps in testing packages

*J Gombold *et al*. *Systemic evaluation of in vitro and in vivo adventitious virus assays for the detection of viral contamination of cell banks and biological products* (Vaccine) 2014

*R Sheets and P Duncan, in *Vaccine Analysis: Strategies, Principles, and Control*, Springer-Verlag Berlin Heidelberg 2015


of Ph. Eur. requirements!

# Evolution of Ph. Eur. chapters for vaccines


01/2018:50203

5.2.3. CELL SUBSTRATES FOR THE PRODUCTION OF VACCINES FOR HUMAN USE

This general chapter deals with diploid cell lines and

07/2020:20616

2.6.16. TESTS FOR EXTRANEOUS AGENTS IN VIRAL VACCINES FOR HUMAN USE

INTRODUCTION

A strategy for testing extraneous agents in viral vaccines must be developed based on a risk assessment following the principles of viral contamination risk detailed in general

01/2018:50214

5.2.14. SUBSTITUTION OF *IN VIVO* METHOD(S) BY *IN VITRO* METHOD(S) FOR THE QUALITY CONTROL OF VACCINES

PURPOSE

The purpose of this general

is to provide guidance
*in vitro* methods as
thods, in cases where a
on is not appropriate for
of one or more *in vitro*
not discuss the details of
e principles are described

ily to vaccines for human
ciples described may also
ra.

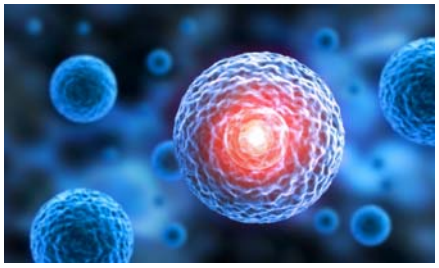
| | Ph. Eur. Chapter 5.2.3 *Cell substrates for the production of vaccines for human use* | Ph. Eur. Chapter 2.6.16 *Tests for extraneous agents in viral vaccines for human use* | Ph. Eur. Chapter 5.2.14 *Substitution of in vivo methods for the QC of vaccines* |
|---|---|---|---|
| Scope | **Testing of cell substrates** (including extraneous agent testing) | Extraneous agent **testing of viral seed lots/harvests** | Concept of **Substitution to replace *in vivo* methods** |
| Year introduced or year of last major update | July 2017 (Ph. Eur. Suppl. 9.3) | July 2017 (Ph. Eur. Suppl. 9.3) | July 2017 (Ph. Eur. Suppl. 9.3) |

- Revision of chapters 5.2.3 & 2.6.16
- Elaboration of chapter 5.2.14 (concept of Substitution)

## 5.2.3 *Cell substrates for the production of vaccines for human use*

- Scope: diploid cell lines and continuous cell lines used as cell substrates for the production of vaccines



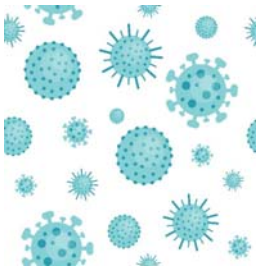
- *Chapter 5.2.3 revised in 2017 (Suppl. 9.3) to introduce the risk assessment, allow the use of broad molecular methods (e.g. HTS), and remove an in vivo test (test in adult mice)*
- Extraneous agents: testing strategy is to be based on a risk assessment considering e.g. choice of permissive cells, nature of cell lines (e.g. insect cells), cell lines shown to express endogenous retroviral particles, *in vivo* tests to be justified if maintained


- A strategy is given in chapter 5.2.3. Alternative strategies could focus on more extensive testing of the MCB or WCB

## 2.6.16 *Tests for extraneous agents in viral vaccines for human use*

- Applies to starting materials and substrates used for production and control of viral vaccines (virus seed lots, virus harvests, control cells/eggs)



- *Chapter 2.6.16 revised in 2017 (Suppl. 9.3) to introduce the risk assessment, allow the use of broad molecular methods (e.g. HTS), and remove two in vivo tests (tests in adult mice, guinea pigs)*
- Panel of *in vivo* and *in vitro* methods
  - Cell culture methods
  - *In vivo* tests (suckling mice, fertilised eggs): to be justified if maintained
  - Molecular methods (for specific extraneous agent or broad virus detection)


- Testing strategy (package of suitable tests) is to be built based on a risk assessment

## 5.2.14 *Substitution of in vivo methods for the QC of vaccines*

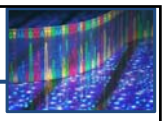
- Chapter elaborated to facilitate the transition to *in vitro* methods (e.g. HTS)
- Chapter 5.2.14 provides guidance on how to introduce alternative *in vitro* methods, where a head-to-head comparison is not possible
- Envisages the possibility that the relevance and performance of the *in vitro* method be demonstrated without such head-to-head comparison: concept of "substitution" as an alternative approach for replacement
- Focus on the scientific rationale behind the *in vitro* methods and the validation package

# Perspectives on HTS and elaboration of a new Ph. Eur. chapter

## Perspectives on HTS



- Ph. Eur. chapters 5.2.3 & 2.6.16 mention HTS and foresee its use as part of the testing strategy for extraneous agents
- However, HTS methods are currently not described in details in any regulatory document and no guidance for their validation is available
- The availability of regulatory standards including validation guidelines in the Ph. Eur. will serve as a reference for regulators and manufacturers, while:
  - HTS is planned to be introduced in the revised ICH Q5A guideline (*Viral safety evaluation of biotechnology products*)
  - FDA has recently developed panels of viruses as reference preparations for HTS (adopted by WHO ECBS)

## Elaboration of a new Ph. Eur. chapter on HTS

- *"High Throughput Sequencing for the detection of extraneous agents in biological products* (2.6.41)"
- Non-binding general chapter
- Proposed content: description of the technology, guidelines for method validation


- Under elaboration by the HTS Drafting Group of Ph. Eur. Group of Expert 15 (international group of regulators, OMCLs, industry)

# Update on ICH Q5A guideline revision

# ICH Q5A(R2): Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin

Presentation for External Audience

Created November 2019

Updated December 2021

Updated May 2022

## Disclaimer:

- **Expert Working Group (EWG)** members are appointed by their nominating ICH Member or Observer party and are responsible for representing the views of that party, which may not necessarily reflect their personal views.
- Working Group experts do not respond personally to external inquires but are directed to forward any inquiries they receive to their nominating party or the ICH Secretariat for a response on behalf of either their ICH party or the ICH Association as appropriate.
- *Optional Disclaimer:*

The views presented are those of the author do not necessarily reflect the views of the ICH EWG.

## Singapore Meeting Nov 2019

- Agreed final themes for revision:
  1. **New classes of biotechnology products** (e.g., virus-like particles (VLPs), subunit proteins, and viral-vectored products)
  2. Additional validation approaches for virus clearance (e.g., **modular validation)**
  3. New virus assays and alternative analytical methods (e.g. **PCR, NGS**).
  4. Virus clearance validation and risk mitigation strategies for advanced manufacturing (e.g. **continuous manufacturing**).
  5. Aspects of virus clearance validation that have emerged or evolved

# New virus assays and alternative analytical methods

- Specifically, nucleic acid-based assays such as Polymerase Chain Reaction (PCR) and Next Generation Sequencing (HTS/NGS) may provide rapid and sensitive detection of adventitious and endogenous viruses in the starting and harvest materials.
- However, these nucleic acid-based assays have limitations as they cannot distinguish between infectious and noninfectious particles and therefore detection of a signal may need a confirmatory test with an infectivity assay for risk-assessment.
- For this reason, additional justification describing their use should be provided. Moreover, general principles for the inclusion of new assays and potential replacement/supplement of existing assays should be presented in order to continue to support future development of new technology.
- For some key tests (e.g., the *in vivo* test), discussed the retention, elimination, or replacement by a broad screen molecular method (e.g., NGS)
- Discussion on the retention, elimination, or substitution by PCR or a broad screen molecular method (e.g., NGS) for some tests (HAP, MAP, and RAP)
- Discussed differentiated between testing at certain places relative to risk (MCB, WCB, LIVCA/EOPC, etc.)
- Confirmed intent regarding level of detail for NGS

# Work Plan: Expected Future Key Milestones

| Estimated Future Completion Date | Milestone |
|---|---|
| | |
| May 2022 | Consensus Final Draft |
| July 2022 | Step 1 sign off and Step 2 a/b endorsement |
| Nov 2023 | Step 3 Sign-off and Step 4 Adoption |

Public comments

Period for public comments varies between international Regions
Typically, a period of 4 months is foreseen in the European Union

# Conclusion

- NGS has been successfully introduced in the Ph. Eur. within the testing strategy of cell substrates/viral seeds/viral harvests of vaccines (and gene therapy viral vectors)

- The concept of substitution in Ph. Eur. 5.2.14 can be applied to the replacement of *in vivo* tests for the detection of extraneous agents by NGS without a head-to-head comparison
- NGS introduction is also foreseen in the revised ICHQ5A guideline
- The future chapter 2.6.41 on NGS will provide a detailed description of the technology together with validation guidelines

→ More to come at the 3rd IABS NGS Conference on September 27 & 28th, USA

# Thank you for your attention

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# Activities in the Field of Nanomedicines

Gerrit Borchard, PharmD, PhD

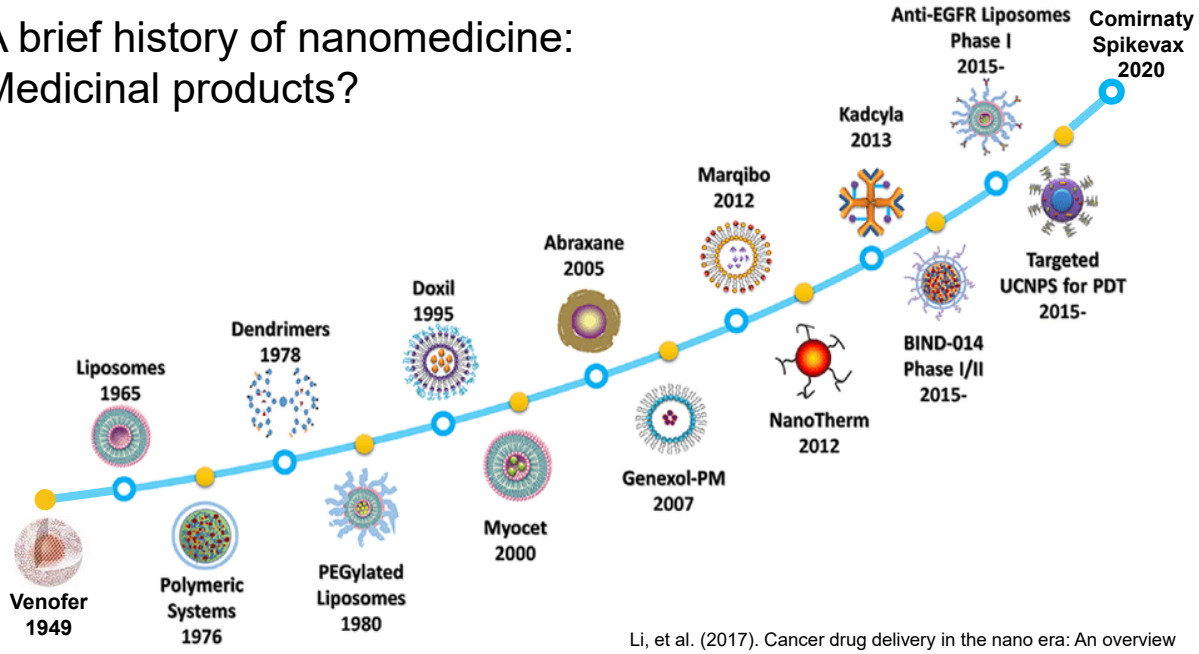
School of Pharmaceutical Sciences
University of Geneva
Switzerland

EDQM International Conference
19-21 September 2022, Strasbourg, France

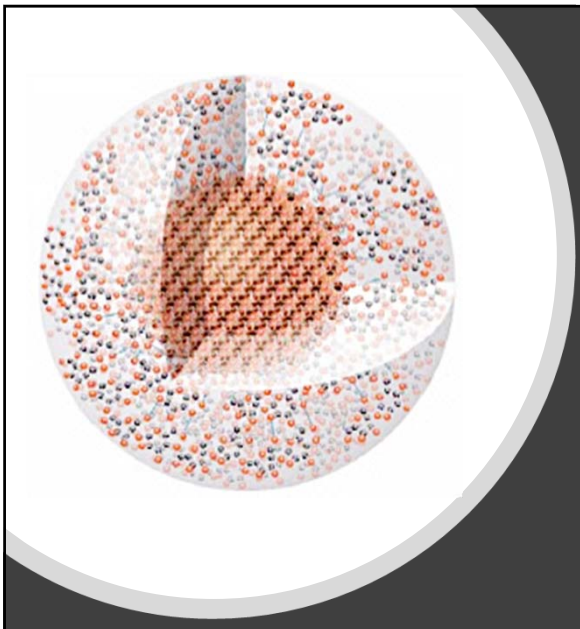
## Declaration of interests

- Member of the Non-Biological Complex Drug (NBCD) Working Group, a non-profit organisation managed by Lygature (Utrecht, NL)
- Member of the cientific Advisory Board of EU projects EU-NCL and REFINE
- Consultant for TEVA (former) and VIFOR Pharma (Glattbrugg, CH, current)

# A brief history of nanomedicine: Medicinal products?

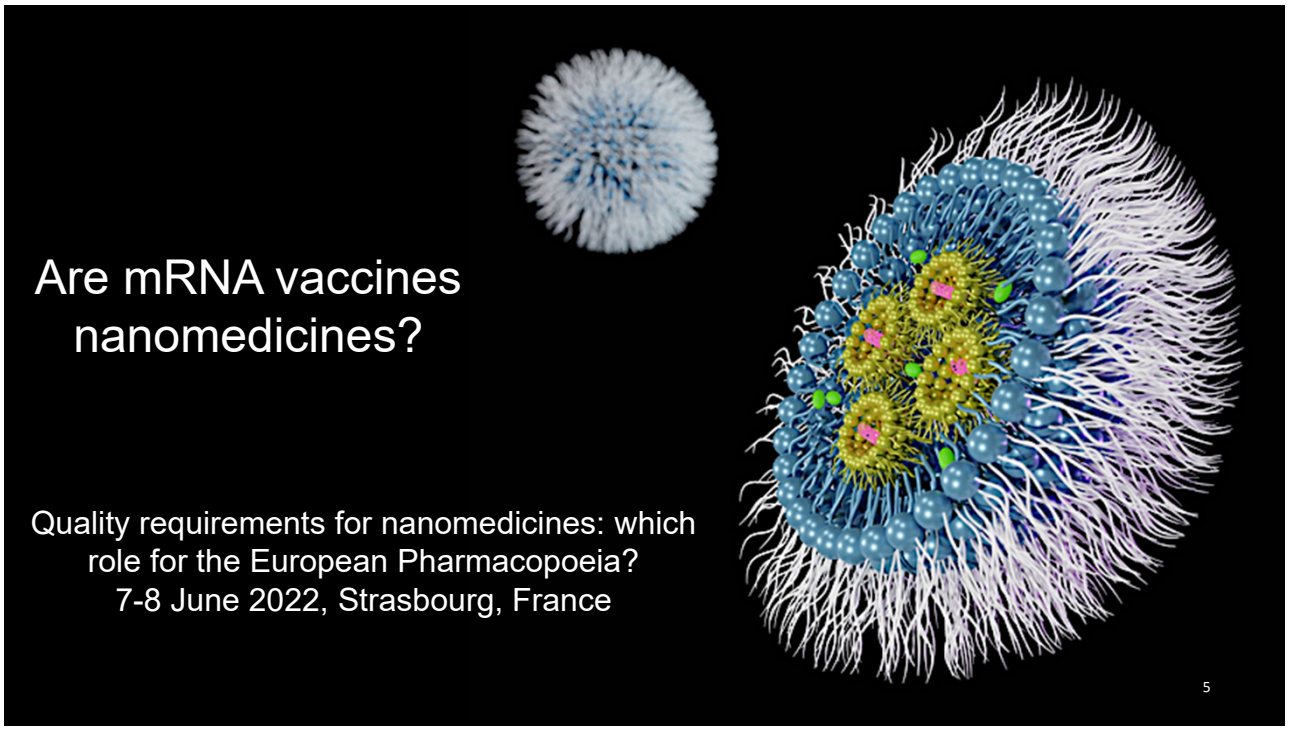



Li, et al. (2017). Cancer drug delivery in the nano era: An overview and perspectives. Oncology Reports. 38. doi: 10.3892/or.2017.5718.



# Non-Biological Complexes (NBC) Working Party

- Created following the decision of the Ph. Eur. Commission to add on its work programme the elaboration of a monograph on ***Iron sucrose concentrated solution***.
- Elaboration of monographs on **non-biological complexes** (e.g., nanoparticle solutions, like for example iron sucrose concentrated solution) allocated to the group by the Commission.
- Members from academia, industry (originator, follow-on), regulatory authorities and public research institutes




## Motivation

- The COVID-19 pandemic and the emergence of mRNA vaccines have highlighted the importance of nanoparticle formulations - especially lipid-based systems - used for nucleic acid-based APIs.
- These nanoparticle-based formulations can be used to produce safe and efficacious medicinal products.
- Modern formulations using nanoparticle systems (e.g., liposomes) have long been the focus of pharmaceutical research, and we are beginning to see advanced medicinal products based on these formulations.
- Consequently, attention is turning increasingly to issues surrounding the creation and implementation of standards for such formulations.
- The aim of this event was to identify any gaps and opportunities for standards concerning modern nanoparticle-based formulations which can be filled by the European Pharmacopoeia (Ph. Eur.), notably by setting common quality standards across Europe and beyond.

COMIRNATY®
(COVID-19 Vaccine, mRNA)

- **Pfizer has gone the usual way as per definitions. mRNA is the active substance in both submissions, to the FDA and the EMA.**
- **Consequently, the lipids are added in the drug product manufacturing and considered as inactive ingredients i.e. excipients.**

| FDA | EMA |
|---|---|
| **Drug Substance BNT162b2**<br>BNT162b2 DS= modRNA<br><br>**Drug Product**<br>modRNA DS + lipids + buffer + and cryoprotectant<br><br>manufactured by mixing the modRNA DS with lipids during lipid particle (LNP) formulation followed bv by fill/finish | **Drug Substance**<br>BNT162b2 active substance = modRNA<br><br>**Drug Product**<br>modRNA DS + lipids + buffer + and cryoprotectant<br><br>active substance thawing and dilution, LNP formation and stabilisation, buffer exchange, concentration and filtration, concentration adjustment and addition of cryoprotectant, sterile filtration, aseptic filling, visual inspection, labelling, freezing and storage |

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spikevax™
COVID-19 Vaccine, mRNA

- **Moderna considers the mRNA encapsulated with the 4 lipids as a drug substance meaning the mRNA-LNP complex is the active ingredient including the lipids!**
- **In line with this, the 4 lipids are NOT considered excipients.**
- **FDA accepted this approach, EMA did not.**

| FDA | EMA |
|---|---|
| **Drug Substance mRNA-1273 LNP**<br>CX-024414 mRNA Drug Substance (DS) intermediate + Lipids<br><br>**Drug Product**<br>Drug product is the m-RNA-1273 LNP + water +sucrose+ buffers<br>**In the Vial**<br>  | **Drug Substance**<br>Active substance (CX-024414) = mRNA<br><br>**Drug Product**<br>mRNA is encapsulated by 4 lipid excipients leading to a mRNA-loaded LNP intermediate which is further processed to produce the finished product (step consists of dilution of the mRNA-loaded LNP intermediate with a formulation buffer followed by 0.2 µm sterile filtration, filling, stoppering, capping inspection, labelling and packaging). |

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## Target audience:

- Vaccine manufacturers
- Pharmaceutical manufacturers from other fields using nanotechnologies
- Specialist suppliers (including raw material suppliers)
- Representatives from national and international regulatory bodies
- Scientists involved in the quality control of nanomedicines



## Consequences


- Creation of a Working Party on mRNA vaccines (mRNAVAC)
- Appointment at November session of the Ph. Eur. Commission
- Develop a consolidated strategy for future standards addressing these vaccines and their components.
- The ideas and proposals put forward on this topic during the recent EDQM Symposium on Nanomedicines will be taken into account.

https://www.edqm.eu/en/-/quality-requirements-for-nanomedicines-what-role-should-the-european-pharmacopoeia-play-

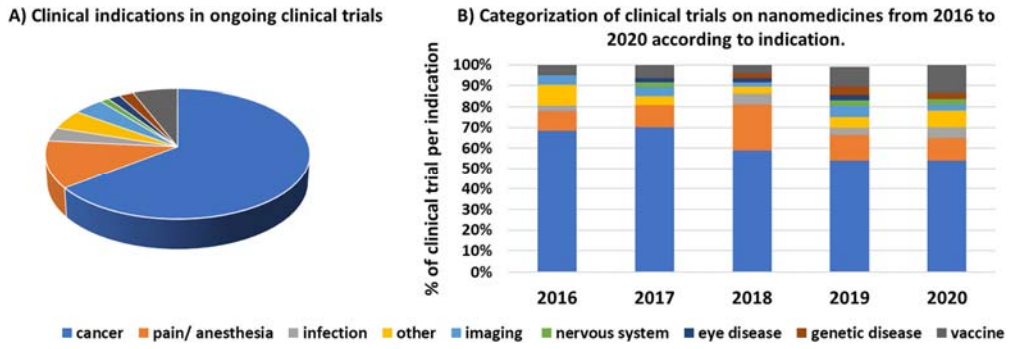
## Suggestions...


- For a pharmacopoeial text, what would be the choice of characterization assays for nanomedicines, and mRNA vaccines in particular?
- Can Critical Quality Attributes (CQAs) be defined for mRNA vaccines in a general monograph?
- Is a staggered approach reasonable:
  1. General guidance on which CQAs to control, specifications,..
  2. Description of test methods, possibly specific for each product
- General monograph on “lipids for liposomal formulations” covering common analytical methods applicable to all lipids.
- Suggestion to draft monographs for specific excipients currently in use in drug products, would facilitate the approval process.

## Suggestions...

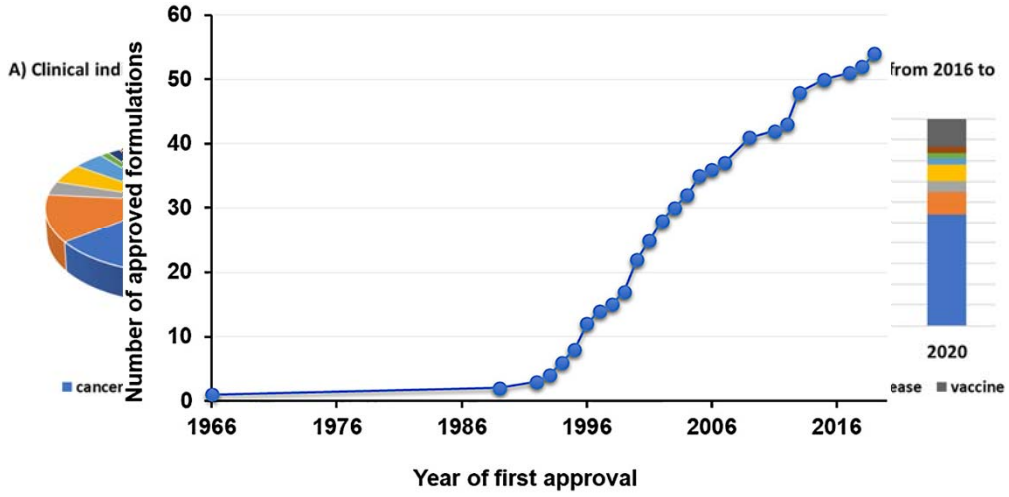

- Keep in mind that technology - nanotechnology as well as analytical methods to characterize them - are fast evolving.
- LNPs are the big trend currently, but other delivery vehicles will mostly likely be used in the future.
- Other types of nucleic acids beyond mRNA (siRNA, miRNA, etc.) will be used.
- Suggestion for a «class monograph» covering minimum requirements for nanomedicines. Further parameters would be product-specific.
- May draft a general text that covers mRNA as drug substance (!) and another general text covering carrier systems, i.e. specific classes of vehicles used to deliver mRNA (e.g., LNPs, liposomes, polymeric particles).

# Clinical trials and approvals of nanomedicines



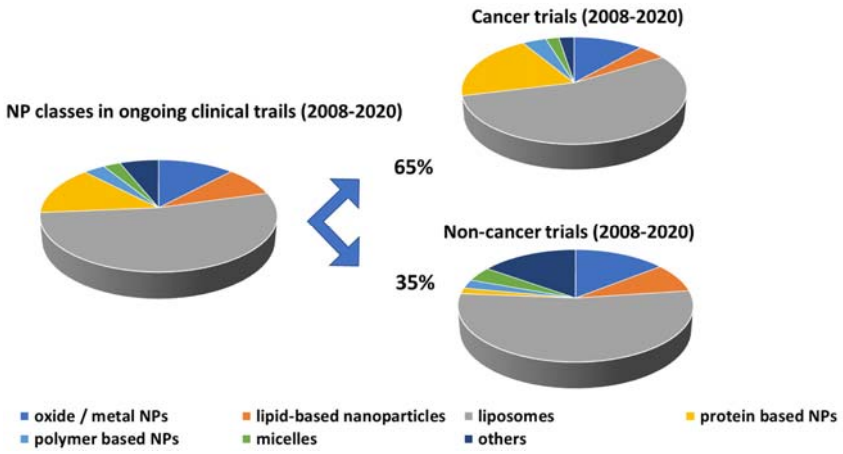

Germain, et al., Delivering the power of nanomedicine to patients today, J. Control. Rel., 326, 2020, 164-171. https://doi.org/10.1016/j.jconrel.2020.07.007.

# Clinical trials and approvals of nanomedicines




Germain, et al., Delivering the power of nanomedicine to patients today, J. Control. Rel., 326, 2020, 164-171. https://doi.org/10.1016/j.jconrel.2020.07.007.

## Clinical trials and types of nanomedicines




Germain, et al., Delivering the power of nanomedicine to patients today, J. Control. Rel., 326, 2020, 164-171. https://doi.org/10.1016/j.jconrel.2020.07.007.

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

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the European Pharmacopoeia 11th Edition
September 2022

# "CEP of the Future" and Future of CEPs

**Hélène BRUGUERA** | **EDQM**
**Certification of Substances**

**1992-2022**

**30th anniversary of the Pilot Phase for the Certification of Suitability (CEP) procedure**

## The CEP procedure in short

Certification of Suitability to the monographs of the Ph. Eur.

- Assessment of applications and granting certificates:
  - Chemical substances, fermentation products, herbal products (APIs, excipients) covered by Ph. Eur. individual monographs, for quality evaluation
  - Products with risk of TSE contamination (APIs, excipients, raw materials, culture media, material used in medical device), for evaluation of compliance to the respective general monograph
- Coordination and conduct of GMP inspections of API manufacturers involved in CEPs

# The CEP procedure in short

- The procedure is supported by a large network of quality assessors from authorities and GMP inspectors for running the activities
- Centralised assessment - saves time and resources and facilitates management of MAAs and variations
- CEPs are widely accepted in the Ph. Eur member states and beyond
  - Australia, Canada, Ghana, Morocco, Saudi Arabia, Singapore, South Africa, Taiwan, WHO etc…

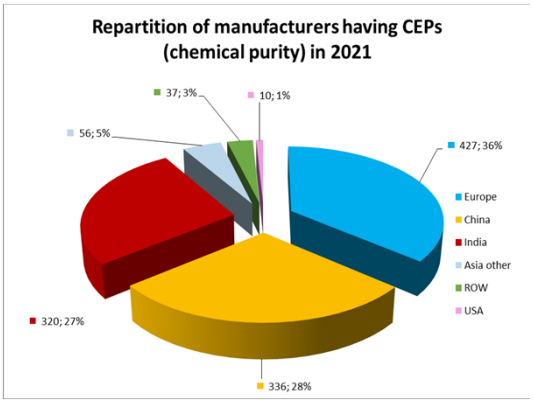
# Close connections with the Ph. Eur

- Ph. Eur. monographs are necessary to get a CEP
  - ✓ A new monograph for a blockbuster triggers a wave of CEP applications
- The CEP procedure provides information to revise Ph. Eur. monographs
  - ✓ About 25 requests for revision/year communicated to the Ph. Eur. secretariat (triggered by assessment of applications)
  - ✓ Addressing specific requests for information from the Ph. Eur. secretariat
- Revision of monographs have an impact on CEPs
  - ✓ Need to update specification accordingly and sometimes to demonstrate suitability of the revised monograph to control the impurities
  - ✓ Systematic process, which gives assurance that a CEP always refer to the current version of a monograph

# **Today** - Where do we stand

- About **5900** valid CEPs, mostly for chemical purity, 500 for TSE, 60 for Herbals
  - Top 5 substances: Clopidogrel hydrogen sulfate, Venlafaxine HCl, Quetiapine Fumarate, Sodium Hyaluronate, Pantoprazole Na sesquihydrate
- **5** CEP dossiers submitted in 1992 still open with a valid CEP
  - All for European API manufacturers
- **1200** manufacturers, in **51** countries
  - About 50% of sites located in India & China covered by the EDQM inspection programme







# **Getting ready** for the future…

**Evolving environment:** manufacturing of APIs, regulatory requirements, scientific and technical developments

**Increasing use** of CEPs

Need to maintain a performing,
state-of-the art, **reliable procedure**

# Performance

- Maintain high quality assessment of CEP applications
- Time matters (deadlines, good applications) !
- Enhance GMP inspection tools, including sites management
- Digital transformation & e-submissions

# Reliance

**A priority** for health authorities worldwide

Working towards **Mutual Reliance** for CEPs

- Transparency of processes
- Good use of CEPs
- Regular communication & information sharing
- Bilateral confidentiality agreements and cooperation programmes

## **Tomorrow**...and later

The "**CEP of the Future"**

The CEP document has not significantly changed since its creation (slight evolutions only)

Evolving environment, needs and feedback received regulary from stakeholders

➔On-going project: the "CEP of the Future"

## The "CEP of the Future"

Goals:

- Meet the current needs of stakeholders: CEP holders/manufacturers, drug product manufacturers, regulatory agencies (worldwide) including quality assessors
- Ease the registration activities linked to the use of CEPs
- Increase the acceptance of CEPs

➔ Wide public consultation in 2020

- Outcome available on the EDQM website here

## Work areas

- Review information to be stated on the CEP
- Reduce revisions of CEPs and facilitate handling of changes
- Enhance digital tools and public databases
- Foster information sharing between CEP holders and medicines manufacturers
- Train users on content and use of CEP

## Status of the project and next steps

| September 2022 | Q4 2022 | Q1 2023 | May 2023 |
|---|---|---|---|
| Targeted consultations with Industry and Authorities (open issues) | Final decisions by the CEP Steering Committee | ○ Communication about new expectations regarding CEP dossiers<br>○ Communication about future changes to the CEP document<br>○ Start implementation process<br>○ Start development of IT tools (databases) | Implementation of the "new look" CEP |

**Major impact for users of CEPs !**

# Future of CEPs

- **Excipients**
  - ✓ They are in scope – however currently CEPs are perceived to give limited benefit
  - ✓ Needs regarding quality of excipients are increasing
  - ✓ In the CEP procedure, as soon as an excipient may be used as an API , it is an "Atypical API". To get a CEP the requirements for APIs apply (some flexibility with regard to GMP)

  ➔Explore how to « adapt » CEP requirements in the future

- **Scope of the CEP procedure**
  - ✓ Identify areas where centralisation of assessment may provide benefits, for the future

# Future of CEPs **in the EU**

- EU Pharma strategy adopted in November 2020, roadmap published in March 2021
  - ✓Ensuring access to affordable medicines
  - ✓Fostering innovation and sustainability
  - ✓Enhancing crisis preparedness and improving security of supply
  - ✓Etc.

  https://ec.europa.eu/health/medicinal-products/pharmaceutical-strategy-europe_en

## Future of CEPs **in the EU**

- As part of the EU Roadmap: Elements to be covered by policy options:
  - *"b) **Simplify legislation and create regulatory attractiveness** with the aim to reduce, where possible, regulatory approval times and regulatory costs while keeping the high standards of robust assessment of quality safety and efficacy...*
  - *h) **Provide for a single assessment process across Member States for active substances** used for different generic medicines (active substance master files) to facilitate their authorisation and life-cycle management…"*
- Several options being discussed – adoption of policy options foreseen end 2022
- EDQM position:
  - Support to concept of separate and centralised place for API assessment
  - Use EDQM significant experience in this area - the CEP procedure could play a key role (in particular for pharmacopoeial APIs)

## Conclusion

- The links between the Ph. Eur. and CEPs are key
- The CEP procedure is going through a key period of changes and needs to maintain performance and reliance
- The CEP of the Future will be implemented in 2023 and will have an impact on stakeholders
- And there is more to do in the future...

**Watch the space**

# Thank you for your attention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