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

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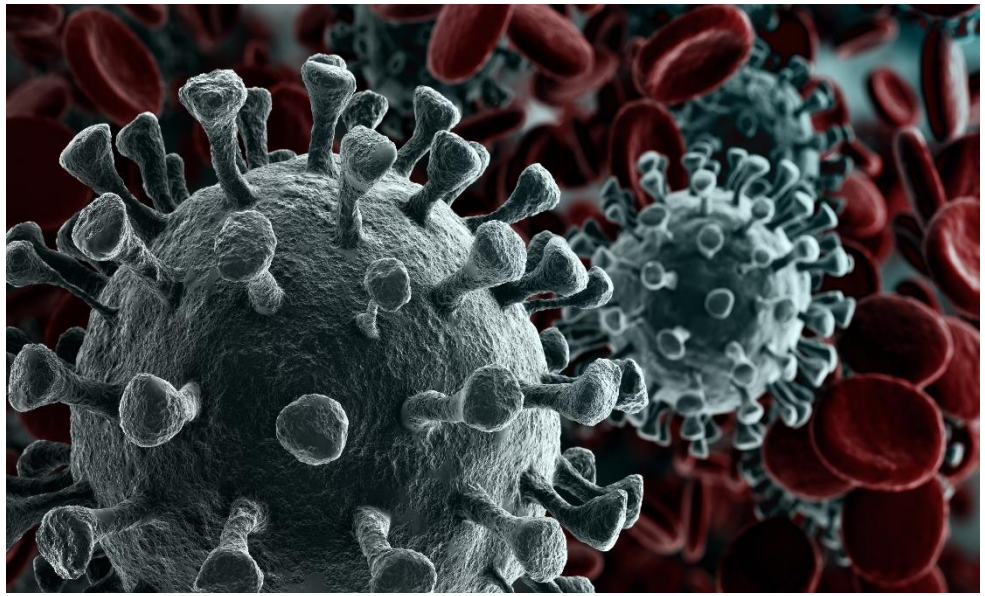
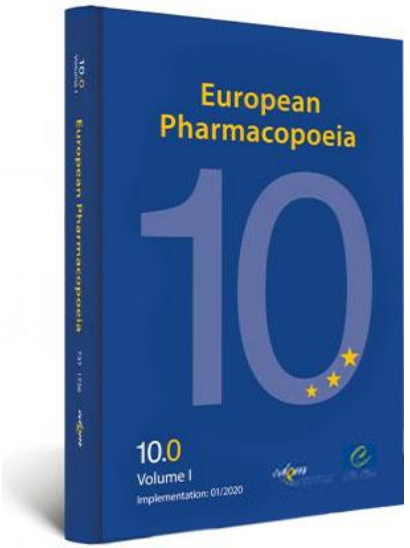
EDQM/Ph. Eur. achievements and perspectives on Next Generation Sequencing





IABS/DCVMN Webinar on Next Generation Sequencing

20 July 2022

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Outline

- Council of Europe, EDQM & the European Pharmacopoeia (Ph. Eur.)
- Extraneous agents testing for vaccines: evolution of the Ph. Eur.
  - Drivers for revising Ph. Eur. requirements
  - Evolution of Ph. Eur. 5.2.3 & 2.6.16
    - Risk assessment to define the testing strategy
    - Use of molecular methods
  - 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
- Conclusion

Council of Europe and EDQM

Council of Europe

- EDQM's parent organisation
- Founded in 1949, headquarters in Strasbourg (France)
- 46 Member states
- The oldest pan-European organisation dedicated to fostering co-operation in Europe
- Promotes democracy, protects the rule of law and human rights

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

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

Place of the Ph. Eur. within the EU regulatory network

- Lays down common, compulsory quality standards for all medicinal products in Europe
- Mandatory on the same date in 39 states (CoE) and the European Union
- The Ph. Eur. is legally binding. The legislation also includes a mechanism to provide the pharmacopoeia authority with information on the quality of products on the market;
- The European Pharmacopoeia needs to keep pace
  - with the regulatory needs of licensing, control and inspection authorities in the public health area,
  - with industrial constraints,
  - with technological and scientific advances

Structure of the Ph. Eur.

General Notices (essential reading; applicable to all texts)

General monographs

- classes of substances or products, dosage forms;
- mandatory for all the products within their scope.

Individual monographs

- based on approved specification(s) backed up by batch data;
- validated analytical procedures*; acceptance criteria (*unless otherwise stated).

General chapters

- general recommendations for analytical procedures;
- guidance for design of analytical methods and for analysis of their results;
- mandatory <u>when referred to</u> in a monograph.

Reference Standards

Established specifically and exclusively for use in monographs, as prescribed in the procedures given

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*" (2010-2013)
  - 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

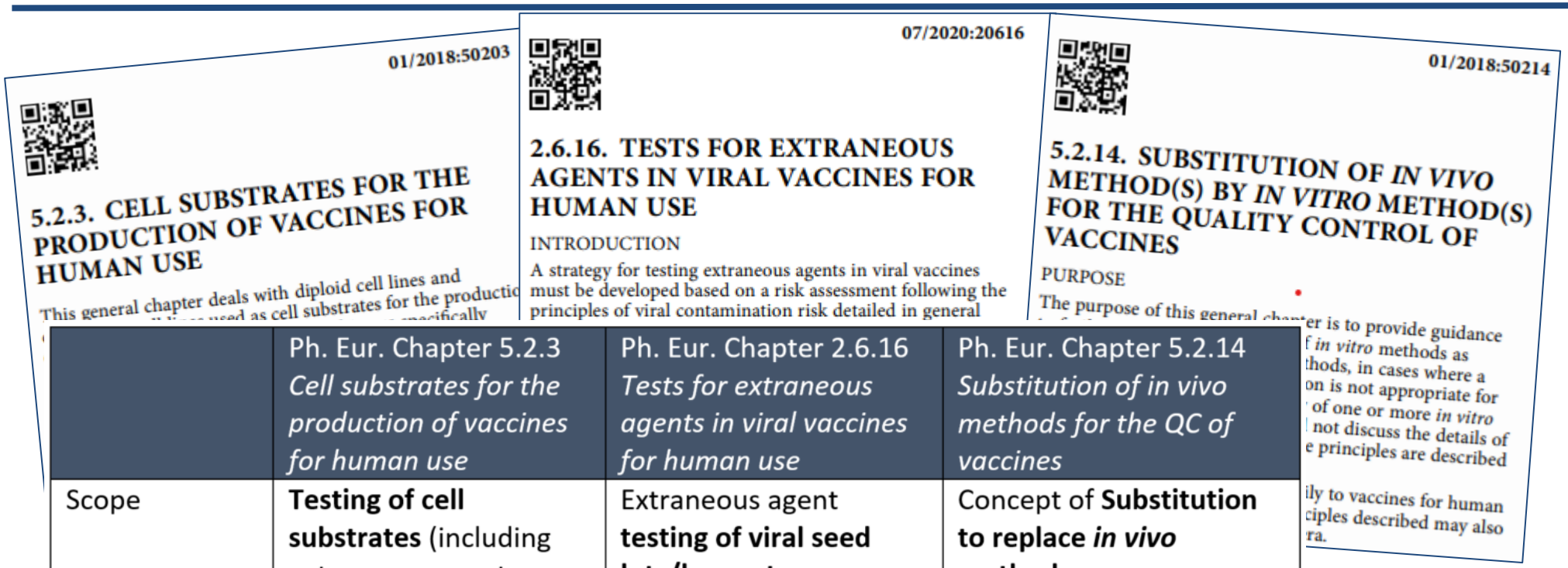
- Several publications* highlighting gaps in compendial tests:
  - Evaluation and comparison of the sensitivity of current testing packages for detection of extraneous agents → poor sensitivity of *in vivo* methods, gaps in testing packages

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

This general chapter deals with diploid cell lines and

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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

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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

er 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

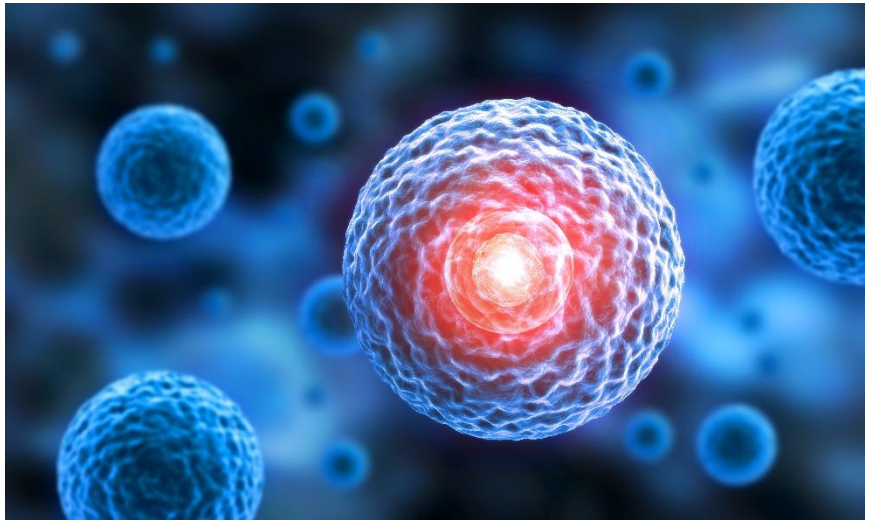
ily to vaccines for human
ciples described may also
ra.

	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

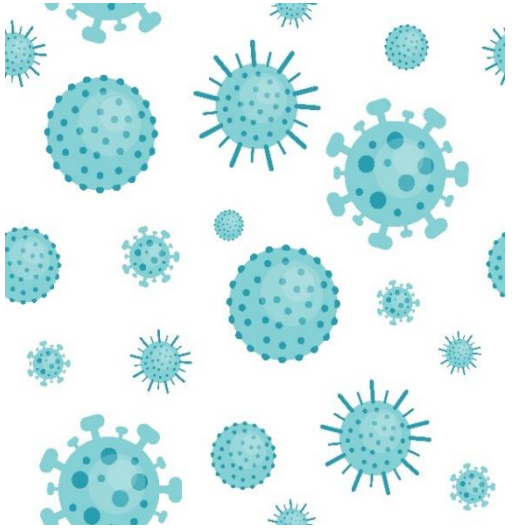


- *Chapter 5.2.3 revised in 2017 (Suppl. 9.3) to introduce the risk assessment, allow the use of broad molecular methods (e.g. HTS), and remove an in vivo test (test in adult mice)*

- 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 validity 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, relative to what is provided with current *in vivo* methods

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

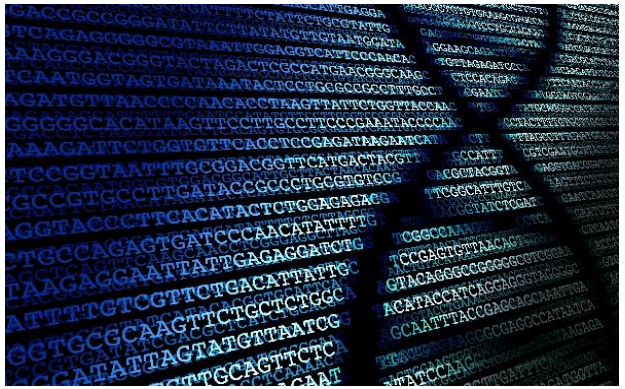
- The availability of regulatory standards including validation guidelines in the Ph. Eur. will accelerate the worldwide adoption of the technology, while:
  - HTS is foreseen to be introduced in the revised ICH Q5A guideline (*Viral safety evaluation of biotechnology products*)
  - FDA has recently developed panels of viruses as reference preparations for HTS (adopted by WHO ECBS)

Elaboration of a 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 HTS method, guidelines for method validation

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

Conclusion



- In the Ph. Eur., HTS has been successfully introduced 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 HTS without a head-to-head comparison

- The future chapter 2.6.41 on HTS will provide a detailed description of the technology together with validation guidelines

→ More to come at the 3rd IABS NGS Conference in September!

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