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

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Particulate contamination in parenteral preparations: what's new in the Ph. Eur.?

Are monoclonal antibodies a special case?

14 December 2021

Dr Mihaela Buda, Dr Dirk Leutner, Dr Erika Stippler

EDQM, Council of Europe

Outline

- **General Information about the Ph. Eur. Content and structure**
  – Dr Dirk Leutner
- **Particulate Contamination – a walk through the relevant texts and what has changed**
  – Dr Erika Stippler
- **Are Monoclonal Antibodies a Special Case?**
  – Dr Mihaela Buda

General Information about the Ph. Eur. Content and structure

The Council of Europe: the EDQM's parent organisation

- Founded in 1949
- Headquarters in Strasbourg, France
- 47 MEMBER STATES
  >820 millions citizens
- The oldest pan-European organisation dedicated to fostering co-operation in Europe
  - Promotes DEMOCRACY
  - Protects HUMAN RIGHTS
  - Protects THE RULE OF LAW
- NOT the European Union

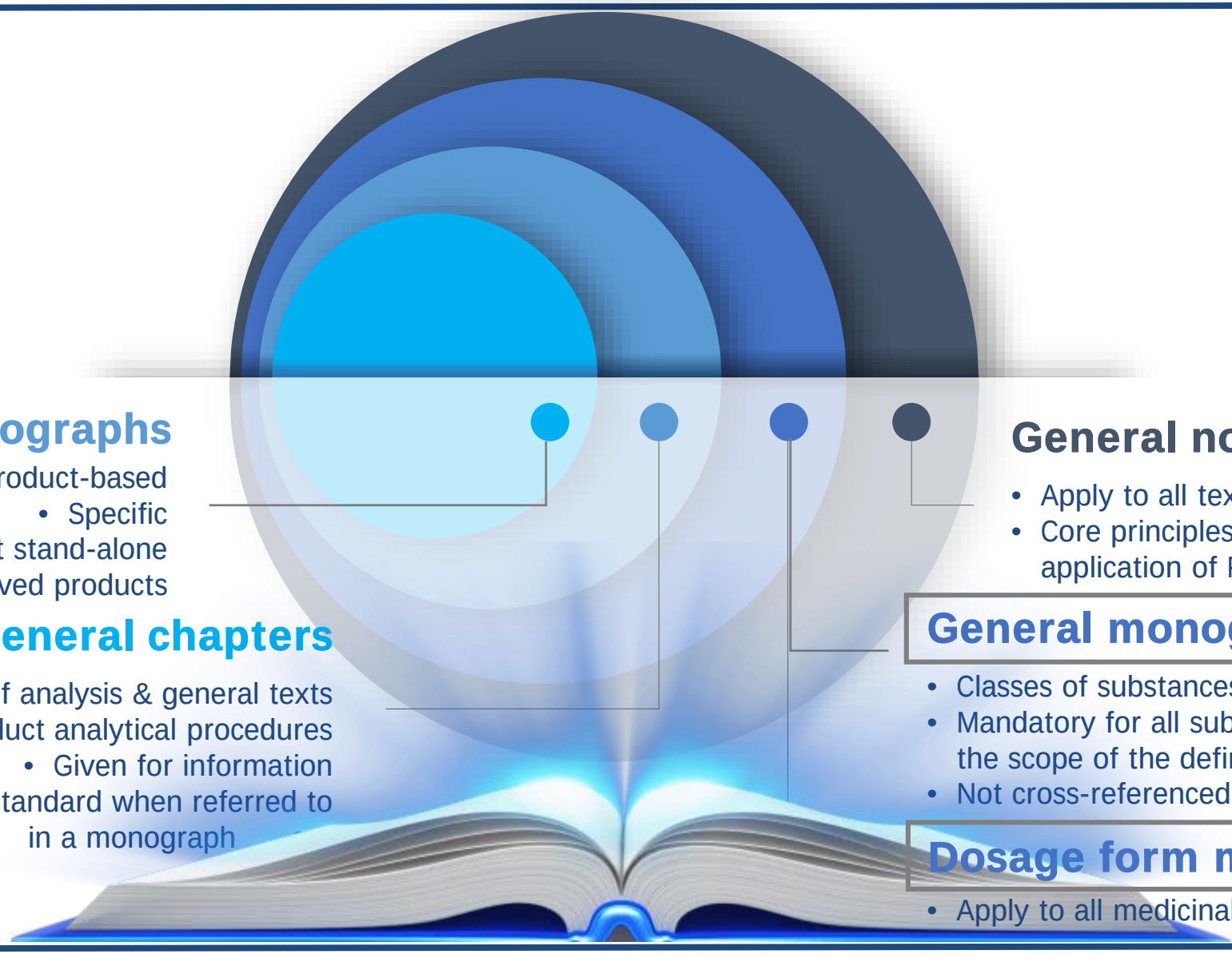
European Pharmacopoeia in 2021

- Based on the Convention on the elaboration of a European Pharmacopoeia (Partial Agreement, 1964)
- Protecting public health – one common compulsory quality standard
- Applied by all licencing authorities
- Legally binding for all medicinal products

- Mandatory on the same date for all Members

- 39 Member States & European Union
- 30 Observers (5 European, 23 non-European countries, TFDA, WHO)
- 10th Edition (including Supplement 10.8): 2447 monographs, 378 general texts

Ph. Eur.: Content and Structure



Individual monographs

- Substance/product-based
  - Specific
  - Not stand-alone
- Take account of approved products

General chapters

- Methods of analysis & general texts
- Multi-product analytical procedures
  - Given for information
- Part of the standard when referred to in a monograph

General notices

- Apply to all texts of the Ph. Eur.
- Core principles for interpretation and application of Ph. Eur. texts

General monographs

- Classes of substances/medicinal products
- Mandatory for all substances/preparations within the scope of the definition
- Not cross-referenced in individual monographs

Dosage form monographs

- Apply to all medicinal products of the type defined

Examples

General monographs

(e.g. Pharmaceutical Preparations, Monoclonal Antibodies for Human Use)

Dosage form monographs

(e.g. Parenteral preparations)

General Notices

Alternative methods

Validation of methods

Implementation of methods

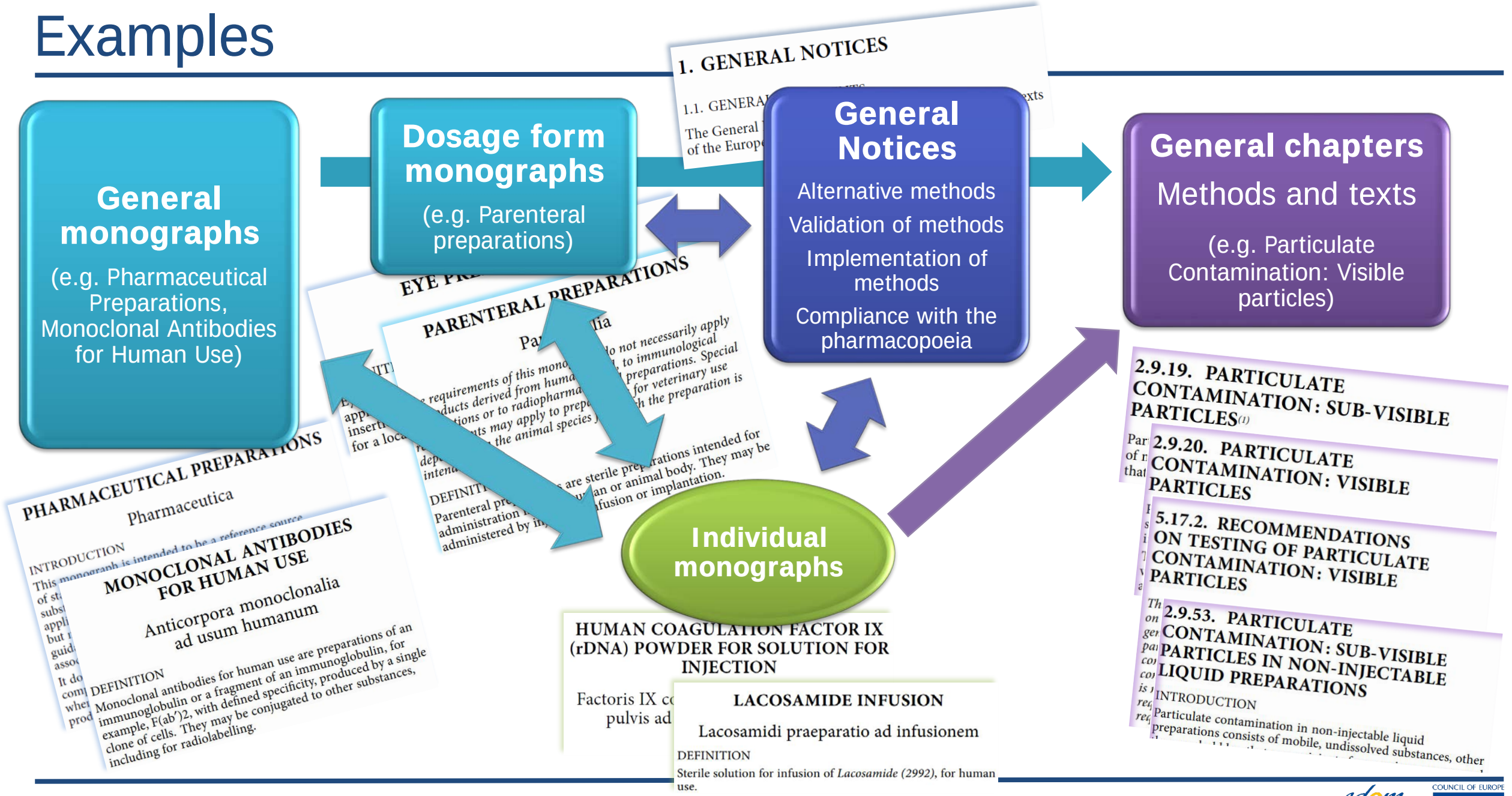
Compliance with the pharmacopoeia

General chapters

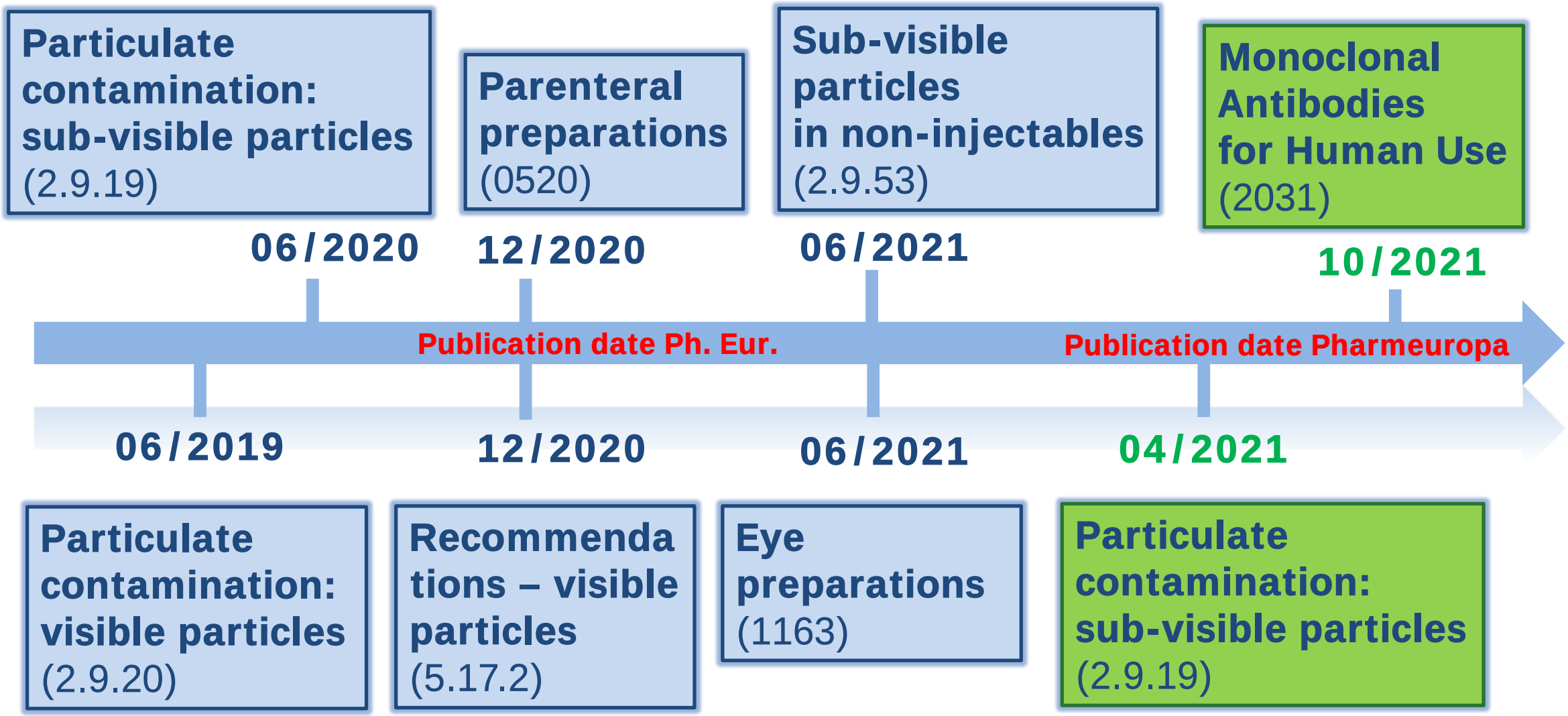
Methods and texts

(e.g. Particulate Contamination: Visible particles)

Individual monographs



Particulate Contamination – What's new?



Particulate Contamination – a walk through the relevant texts and what has changed

Particulate contamination – Practically free from particles

- General chapters – Pharmaceutical technical procedures/General texts
  - Sub-visible particles - for injections and infusions: 2.9.19
  - Visible particles: 2.9.20
  - *Sub-visible particles – for non-injectable liquid preparations: 2.9.53*
  - *Recommendations on testing of visible particles: 5.17.2*
- Dosage forms
  - Parenteral preparations (0520)
  - Eye Preparations (1163)
  - Preparations for irrigation (1116)
  - *Intravesical preparations (2811)*
- General monographs
  - Monoclonal antibodies for human use (2031)

Particulate contamination – Practically free from particles

- Monographs
  - Solutions for organ preservation (1264)
  - Anticoagulant and preservative solutions for human blood (0209)

- Material for containers and containers
  - Sets for the transfusion of blood and blood components (3.3.7)
  - Sterile single-use plastic syringes (3.3.8)

2.9.19 Particulate contamination: sub-visible particles

- PDG harmonised
- Revised text published in Ph. Eur. 10.3 – introduced local requirements
  - Implementation date: January 2021
  - Alternative procedures to allow testing of small volume preparations

- New revision of the general chapter is in progress – PDG harmonisation
  - Proposed revision published in Pharmeuropa 33.2 (deadline for comments June 2021)

2.9.19 – Light obscuration test

- Procedure
  - For large-volume parenterals - single units are tested
  - For small-volume parenterals:
    - If the nominal volume is 25 mL or more - single units are tested
    - Otherwise 10 or more units are combined to obtain a volume of at least 25 mL

  4 portions of not less than 5 mL each are tested.

- Alternative procedure – considers instrument capability
  - For parenteral preparations that have sufficient volume to permit testing - single units are tested
  - If the volume is not sufficient – suitable number of units are combined to obtain a volume suitable for a single test

  Testing of 1 mL to 5 mL may be acceptable if permitted by the instrument

The number of specimens tested is based on a statistically sound sampling plan

2.9.19 – Microscopic particle count test

- Procedure
  - For large-volume parenterals - single units are tested
  - For small-volume parenterals
    - If the nominal volume is 25 mL or more - single units are tested
    - Otherwise 10 or more units are combined to obtain a volume of at least 25 mL

- Alternative procedure – considers instrument capability
  - For parenteral preparations that have sufficient volume to permit testing - single units are tested
  - If the volume is not sufficient – suitable number of units are combined to obtain a volume suitable for a single test

  Testing of 1 mL to 5 mL may be acceptable if permitted by the instrument

The number of specimens tested is based on a statistically sound sampling plan

2.9.19 Evaluation

- Acceptance criteria
  - PDG harmonised
    - *Test 1.A/2.A* - preparations supplied in containers with a nominal volume of more than 100 mL
    - *Test 1.B/2.B* - preparations supplied in containers with a nominal volume of less than 100 mL
  - Local requirement
    - *Test 1.B/2.B* - preparations supplied in containers with a nominal volume of 100 mL

Pharmeuropa 33.2 - proposed revision of 2.9.19

Text as agreed upon by PDG – Revision 2, Stage 2, Version 2

- Light obscuration count test
- Microscopic particle count test
  - Procedure - the alternative test procedure is proposed to be the only test procedure
    - The text stipulates that a volume sufficient for a single test based on instrument capabilities and sample properties is to be used.
    - A preference for testing single units has been added.
  - Evaluation – wording clarified
    - "*Preparations supplied in units that contain a nominal content of…"* vs. "*Solutions for infusion or injection supplied in containers with a nominal content of…*"
    - Each unit tested has to comply
    - If combination of units is needed – the number of particles corresponding to one container to be calculated

2.9.20 Particulate contamination: visible particles

- Revised text published in Ph. Eur. 10.0
- Implementation date: January 2020
- Procedure for liquid preparations and for those after reconstitution
- Equipment
  - A horizontal non-glare white panel included in the description
  - Light-emitting diode (LED) added as light source
  - Higher illumination intensity is allowed in case of
    - Coloured glass
    - Plastic containers
    - Coloured or turbid preparations
- Procedure
  - Visual observation without magnification
  - Longer times for observation is allowed in certain cases
  - Transfer of contents is allowed when visual observation in original container is not possible

5.17.2 Recommendations on testing of particulate contamination: visible particles

- General text – non-mandatory – published in Ph. Eur. 10.3
- Implementation date: January 2021
- Provides information on visible particle testing of liquid preparations
- Defines the requirement “practically free from visible particles”
  - Introduction
    - Definition – particles that are unintentionally present
    - Classification of particles
      - Extrinsic – derived from environment, equipment, primary package, etc.
      - Intrinsic – formulation and process related contamination
  - Visual inspection: General considerations when inspection of particles is difficult
    - Use of defect sets together with negative and positive controls
    - Training of operators
    - Use of light intensity higher than 3750 lux
    - Longer inspection times

5.17.2 Recommendations on testing of particulate contamination: visible particles

- Visual inspection during production – non destructive test
  - 100% inspection and removing those in which particulates are observed
    - Manual
    - Semi-automated
    - Automated
  - Spot-check
  - Acceptable Quality Level (AQL) testing
- Visual inspection for quality control
  - Liquid products
  - Reconstituted solutions
  - Freeze-dried products
- Visual inspection within stability studies with emphasis on stability indicating attributes
  - Precipitation
  - Agglomeration
  - Discoloration of glass

5.17.2 Recommendations on testing of particulate contamination: visible particles

- Evaluation
  - in case of 100% visual inspection followed by AQL testing, the QC test may be omitted
  - A successful AQL indicates batch compliance with the requirement “practically free from visible particles”
  - In case of freeze-dried products quality control testing on reconstituted product is required
  - In case of products administered using a filter – the filtrate complies with the requirement

0520 Parenteral preparations

- Revised text published in Ph. Eur. 10.5
- Implementation date: July 2021
  - Production
    - Statement added that liquid preparations for injection or infusion are practically free from particles
    - Reference to new general chapter *5.17.2*
  - Tests
    - **Liquid preparations** (include suspensions, emulsions and gels) for injection or infusion comply with general chapter 2.9.19
    - **Liquid preparations** (include suspensions, emulsions and gels) for injection or infusion are practically free from particles – reference to 2.9.20 and 5.17.2
  - Intravitreal preparations

2811 Intravesical preparations

- New text published in Ph. Eur. 10.5
- Implementation date: July 2021
  - Production
    - Intravesical solutions are *practically free from particles*
    - Reference to the general chapter *5.17.2*
  - Tests
    - Intravesical solutions including those after reconstitution *are practically free from particles* – reference to 2.9.20 and 5.17.2

2.9.53 Particulate contamination: sub-visible particles in non-injectable liquid preparations

- New general chapter published in Ph. Eur. 10.6
- Implementation date: January 2022
  - Applies for those preparations for which the test is invoked in the general monograph, e.g. Eye preparations
  - Describes the test procedures for testing of sub-visible particles
    - Light obscuration particle count test
    - Microscopic particle count
  - Acceptance criteria for the different preparations are given in the individual dosage form monographs

1163 Eye preparations

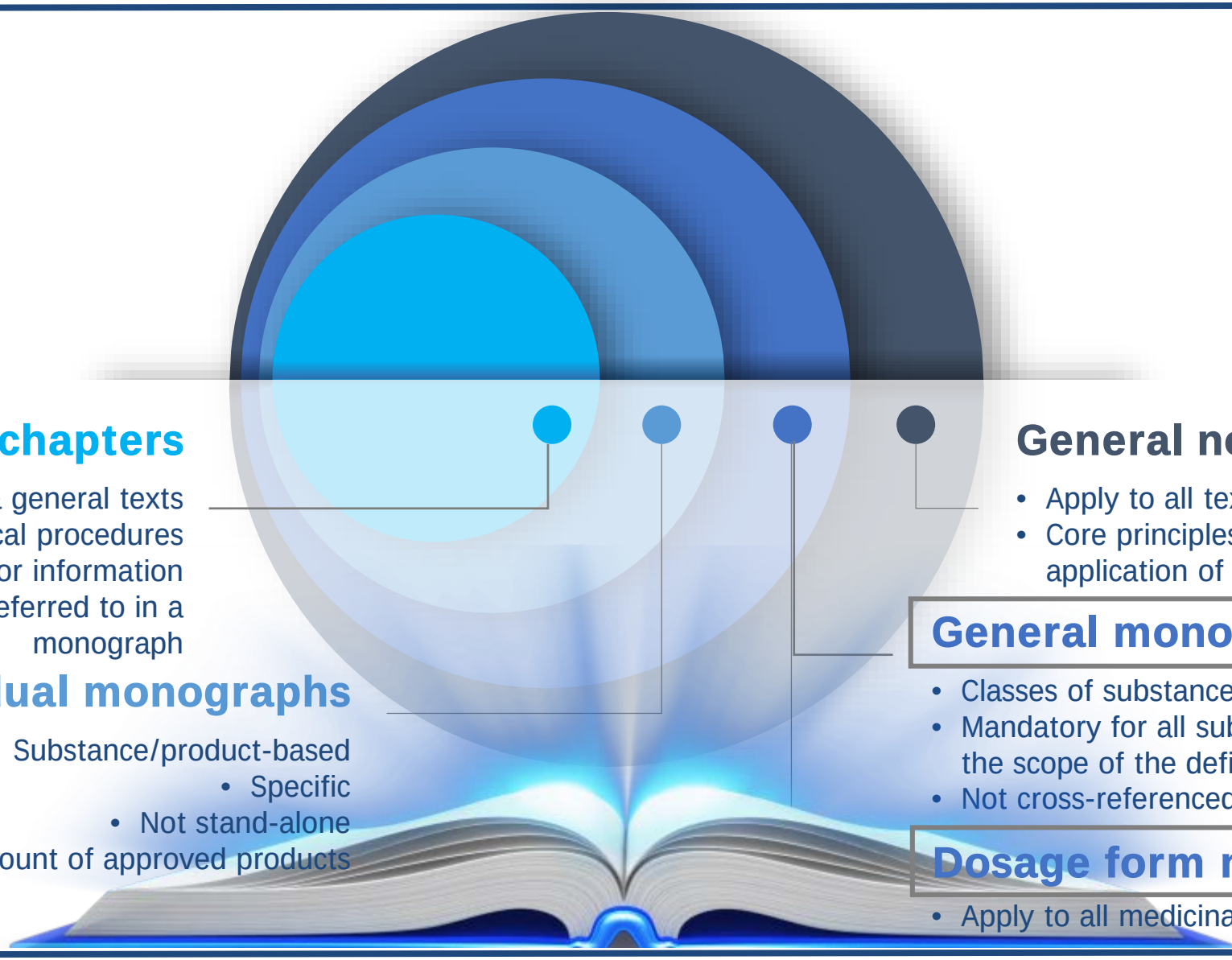
- Revised text published in Ph. Eur. 10.6
- Implementation date: January 2022
- Eye drops and eye lotions - added
  - Test for particulate contamination: sub-visible particles according to 2.9.53
  - Acceptance criteria for sub-visible particles

Are Monoclonal Antibodies a Special Case?

Presentation Outline

- **Background history** -- requirements for particles in the general monograph on *Monoclonal antibodies for human use (2031)*
- **Overview of rationale and proposed amendments** in the mAbs general monograph
- **Update on the current status of the monograph revision**

Ph. Eur.: Content and Structure



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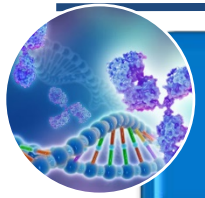
Monoclonal Antibodies for Human Use (2031)

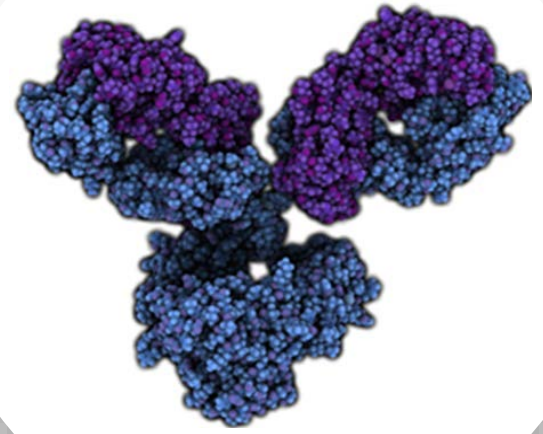


General monographs

- Pharmaceutical preparations (2619)
- Products of recombinant DNA technology (0784)

General chapters

- Clarity and degree of opalescence of liquids (2.2.1)
- Degree of coloration of liquids (2.2.2)
- pH (2.2.3), Osmolality (2.2.35), Water (2.5.12)
- Extractable volume (2.9.17)
- Sterility (2.6.1), BET (2.6.14)
- Total protein (2.5.33) .....



Dosage form monographs

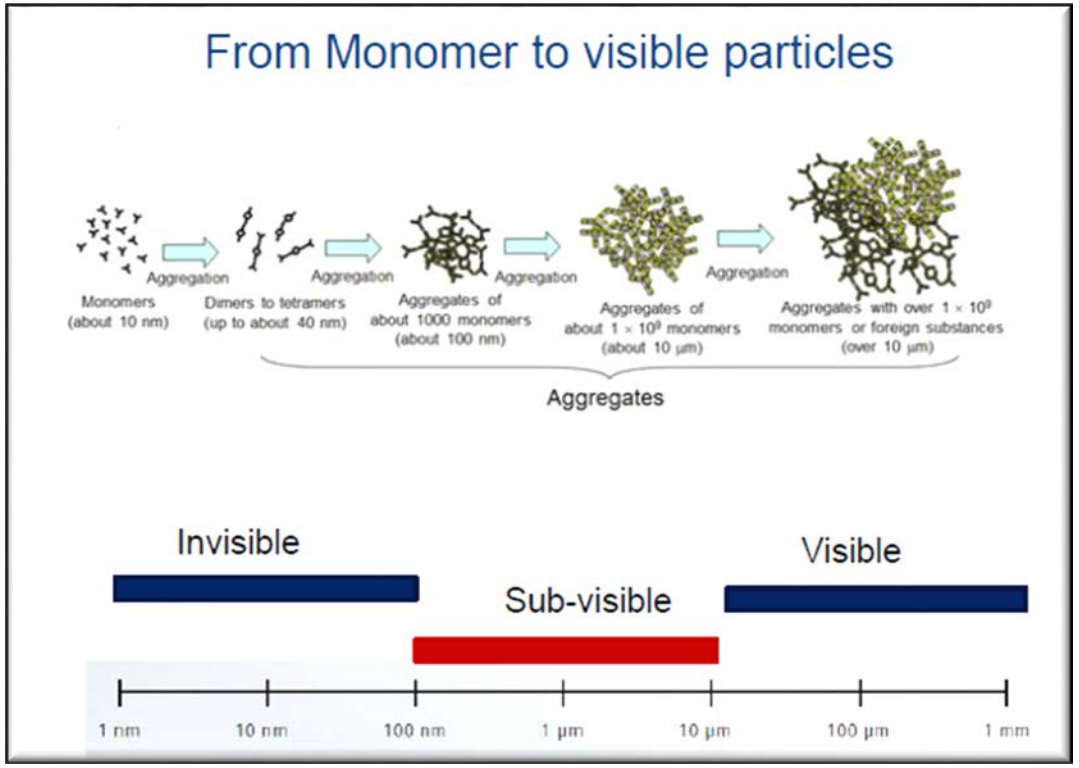
- **Parenteral preparations (0520)**
- Eye preparations (1163)

General requirements for:

- Active substance, final bulk, final lot
- Medicinal product:
  - **Visible particles**
  - Molecular identity and structural integrity
  - Molecular-size distribution
  - Purity .....

Monoclonal Antibodies: Particulate Matter

- **Key quality attribute**; monitored and controlled throughout therapeutic antibody development
- **Visible and sub-visible particulates** may pose safety and **immunogenicity risks** to patients
- Tightly **controlled and regulated**
- Three categories of particulate matter:
  - **extrinsic particles** from the materials outside the process of drug production;
  - **intrinsic particles** from the materials within the processes of drug production;
  - **inherent particles** (e.g., proteinaceous aggregates) from drug formulation.



PDA Europe Conference Particles in Injectables, 2017

MAbs Monograph 2031: Background History

2005

Published in Ph. Eur. Supplement 5.2

CHARACTERS: "without visible particles"

TESTS.

Appearance. "without visible particles"

Solubility: resulting solution "[...] without visible particles"

2006

Request for revision

To align with *Parenteral preparations (0520)*

[DEFINITION: "practically free from particles"]

2008

Ph. Eur. MAB WP proposes changes

TESTS.

Appearance. "without visible particles, unless otherwise justified and authorised"

Solubility: resulting solution "[...] without visible particles, as approved for the particular product"

2009/ 2010

Revised draft monograph published for comment

PHARMEUROPA 21.1
PHARMEUROPA 22.1

2011

Published in Ph. Eur. Supplement 7.3

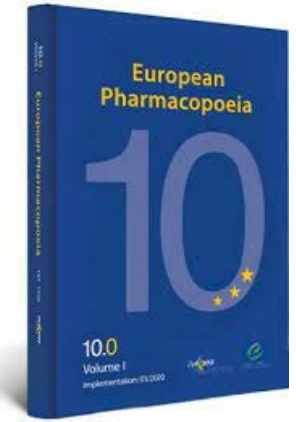
(additional changes)

DEFINITION: "practically free from particles"

PRODUCTION. *FINAL LOT:* **new paragraph** added with considerations on visible particles (in-process control) and proteinaceous particles (development and manufacturing process)

TESTS. Appearance. "without visible particles, unless otherwise justified and authorised"

Monoclonal Antibodies for Human Use (2031)



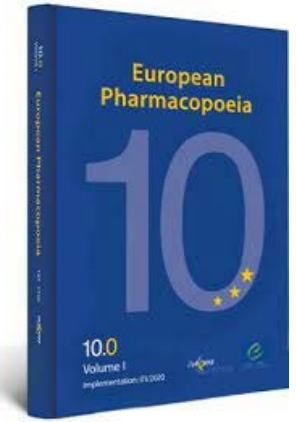
Particles: current requirements

- **DEFINTION**
  - examined under suitable conditions of visibility, practically free from particles

→ **In line with *Parenteral preparations (0520)***

- **PRODUCTION.** *FINAL LOT*
  - **in-process control**:
    - each container (vial, syringe or ampoule) is inspected after filling to eliminate containers that contain visible particles;
  - **during development**:
    - it must be demonstrated that either the process will not generate visible proteinaceous particles in the final lot or such particles are reduced to a low level as justified and authorised;
- **TESTS. Appearance**
  - without visible particles, unless otherwise justified and authorised.

Monoclonal Antibodies for Human Use (2031)



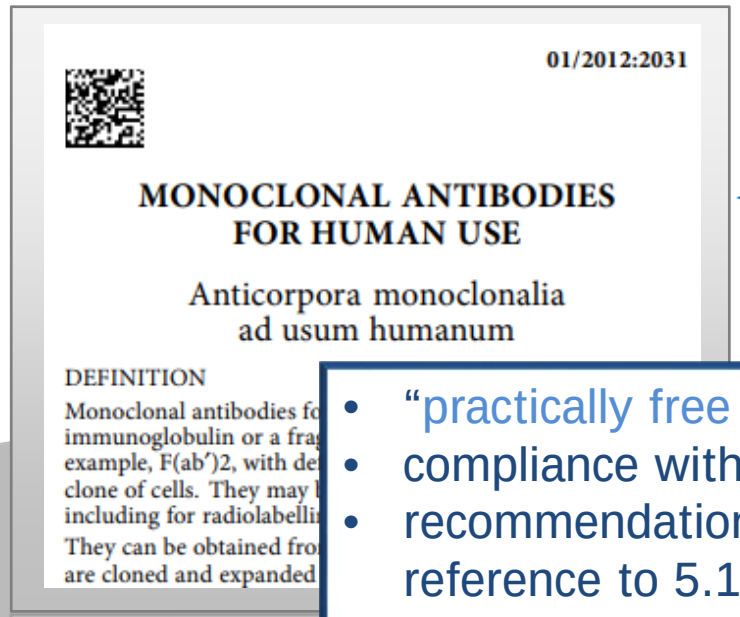
Particles: current requirements

- **DEFINTION**
  - practically free from particl
- **PRODUCTION**
  - **in-process control**:
    - each container (vial, sy
      eliminate containers th
  - **during development**:
    - it must be demonstrate
      proteinaceous particles
      low level as justified and authorised;
- **TESTS. Appearance**
  - without visible particles, unless otherwise justified and authorised.

- **'without visible particles'**: had been intentionally kept to give clear guidance to producers of mAbs that the presence of visible particles is unwanted and that appropriate formulation studies should be performed during development to find an optimal formulation;
- **'unless otherwise justified and authorised'**: escape clause for products in cases where producers can demonstrate that it is not possible to remove all visible particles.

Particulate Contamination: Monograph Alignment

2031 **Monoclonal antibodies for human use**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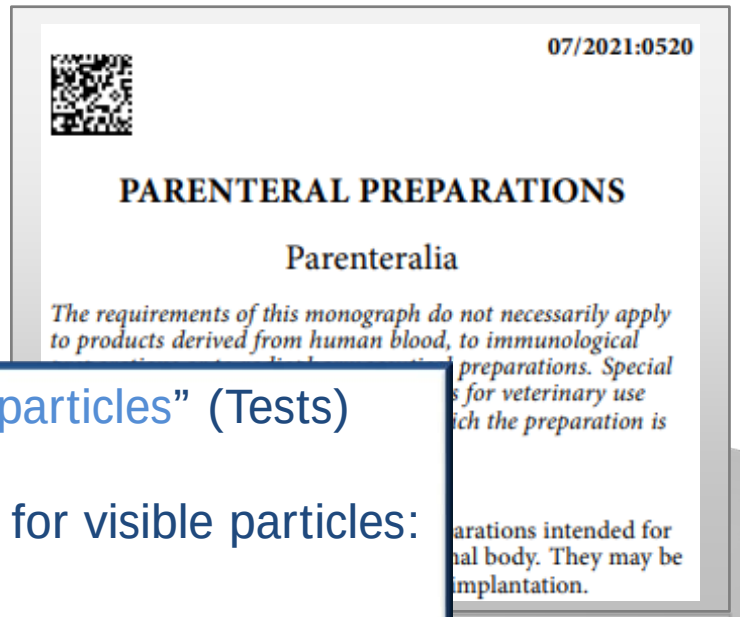
MONOCLONAL ANTIBODIES FOR HUMAN USE

Anticorpora monoclonalia ad usum humanum

DEFINITION

Monoclonal antibodies fo
immunoglobulin or a frag
example, F(ab′)2, with de
clone of cells. They may
including for radiolabelli
They can be obtained fro
are cloned and expanded

0520 **Parenteral preparations**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PARENTERAL PREPARATIONS

Parenteralia

The requirements of this monograph do not necessarily apply to products derived from human blood, to immunological preparations. Special for veterinary use ich the preparation is

arations intended for
al body. They may be
implantation.

- "practically free from visible particles" (Tests)
- compliance with 2.9.20
- recommendations on testing for visible particles: reference to 5.17.2
- products administered using a final filter

Under revision

✓ **Revised text published in Ph. Eur. 10.5**
✓ **Implementation date: July 2021**

Monoclonal Antibodies for Human Use (2031) (1/2)

Particles: proposed amendments

- **PRODUCTION section** [*FINAL LOT*]
  - Statement added that liquid preparations for injection or infusion, examined under suitable conditions of visibility, are **practically free from particles**
  - Recommendations added on testing for visible particles and **reference to new general chapter 5.17.2**

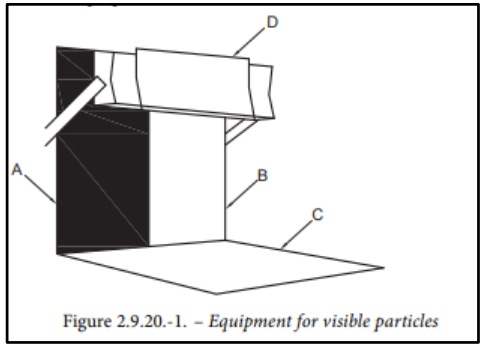


Figure 2.9.20.-1. – *Equipment for visible particles*

Parenteral preparations (0520)

Monoclonal Antibodies for Human Use (2031) (2/2)

Particles: proposed amendments

- **TESTS. Appearance**
  - **Compliance with general chapter 2.9.20**
  - "Without visible particles" replaced with "**practically free from visible particles**":
    - "**unless otherwise justified and authorised**" intentionally kept for cases in which manufacturers can demonstrate that it is not possible to remove all visible particles, due to the inherent nature of monoclonal antibodies;
  - Recommendations added on testing for visible particles and **reference to new general chapter 5.17.2**
  - Specific provisions added for **products administered using a final filter**, as stated on the label.

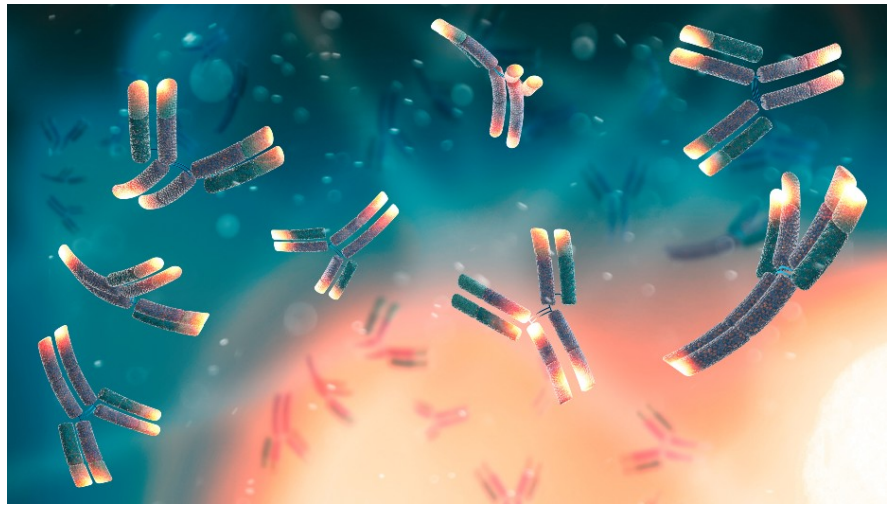
"'**Practically free from visible particles**' reflects the capability of the manufacturing and testing process. The term is applicable at the batch level of a medicinal product, not for single units examined individually. However unrealistic, a 'zero particles' product is nonetheless a worthy goal. " **(5.17.2)**

"'**Unless otherwise justified and authorised**'. This expression means that the requirements must be met, unless the competent authority authorises a modification (e.g. of an analytical procedure or limit) or an exemption, if justified by the manufacturer in a particular case.
(Ph. Eur. General Notices)

Products administered using a filter
With some parenteral products, for example products for which there is insufficient product knowledge, filters may be used to reduce the risks related to particles that may form during **storage**. However, the use of such filters does not constitute acceptance of particles after manufacture or allow particulate contamination per se. If justified and authorised, products administered using a filter can be exempt from the 'practically free from particles' requirement, providing it has been demonstrated that the filter delivers a filtrate that complies. **(5.17.2)**

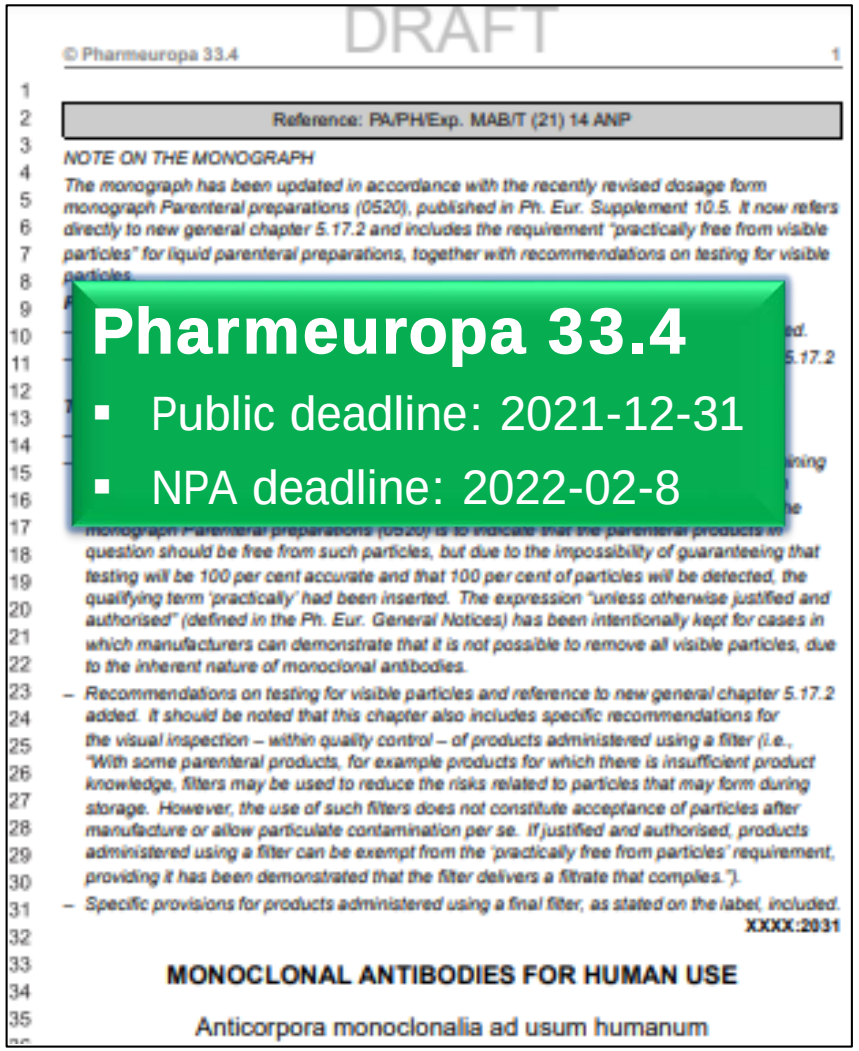
Proposed Revision MAbs GM 2031: Summary

- Particles: key quality attribute
- Inspection and detection is probabilistic and the requirement "*practically free*" reflects that; "*without visible particles*" is the aspiration, but not a workable requirement or specification
- An adequate overall monitoring setup is required (100%, AQL, QC release and stability)



PUBLIC CONSULTATION

Proposed Revision MAbs GM 2031: Next Steps



DRAFT

© Pharmeuropa 33.4 1

Reference: PA/PH/Exp. MAB/T (21) 14 ANP

NOTE ON THE MONOGRAPH

The monograph has been updated in accordance with the recently revised dosage form monograph Parenteral preparations (0520), published in Ph. Eur. Supplement 10.5. It now refers directly to new general chapter 5.17.2 and includes the requirement "practically free from visible particles" for liquid parenteral preparations, together with recommendations on testing for visible particles.

question should be free from such particles, but due to the impossibility of guaranteeing that testing will be 100 per cent accurate and that 100 per cent of particles will be detected, the qualifying term 'practically' had been inserted. The expression "unless otherwise justified and authorised" (defined in the Ph. Eur. General Notices) has been intentionally kept for cases in which manufacturers can demonstrate that it is not possible to remove all visible particles, due to the inherent nature of monoclonal antibodies.

– *Recommendations on testing for visible particles and reference to new general chapter 5.17.2 added. It should be noted that this chapter also includes specific recommendations for the visual inspection – within quality control – of products administered using a filter (i.e., "With some parenteral products, for example products for which there is insufficient product knowledge, filters may be used to reduce the risks related to particles that may form during storage. However, the use of such filters does not constitute acceptance of particles after manufacture or allow particulate contamination per se. If justified and authorised, products administered using a filter can be exempt from the 'practically free from particles' requirement, providing it has been demonstrated that the filter delivers a filtrate that complies.").*

– *Specific provisions for products administered using a final filter, as stated on the label, included.*

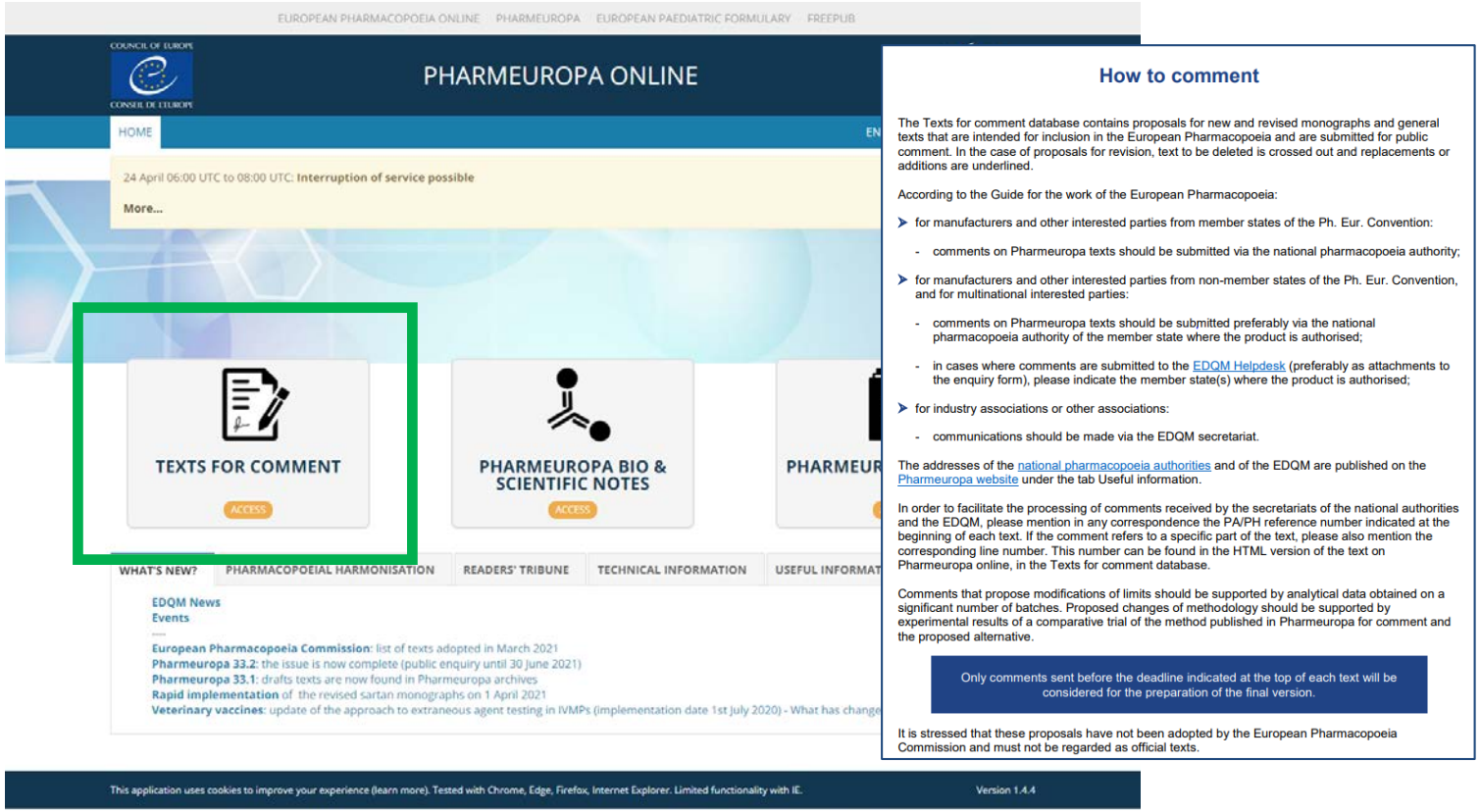
XXXX:2031

MONOCLONAL ANTIBODIES FOR HUMAN USE

Anticorpora monoclonalia ad usum humanum

Pharmeuropa 33.4

- Public deadline: 2021-12-31
- NPA deadline: 2022-02-8

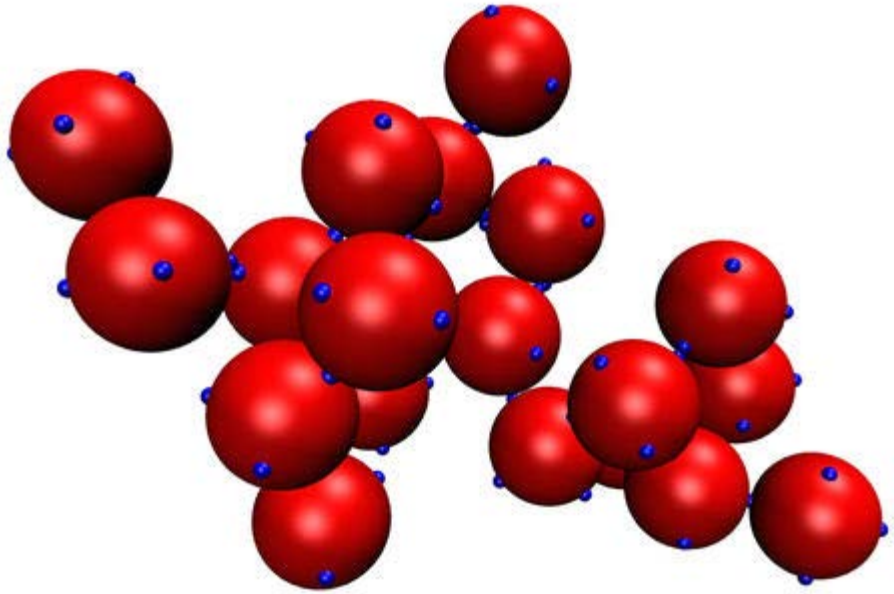


https://pharmeuropa.edqm.eu/media/homepage/documents/2020/11/26/How_to_comment.pdf

All interested parties are invited to review the revised monograph draft and submit comments

Acknowledgements

- **Experts of the Ph. Eur. Group 12**
- **Experts of the Ph. Eur. MAB Working Party**
- **EDQM Colleagues**



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