GMP for Advanced Therapy Medicinal Products (ATMP)

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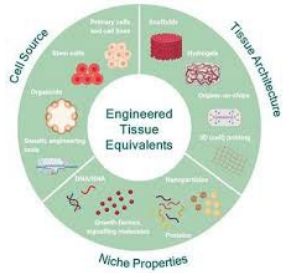
Overview

- Types of therapeutic goods
- How do we fulfill this mission
- Biologicals vs Biological Medicines
- What are ATMPs
- PIC/S Annex 2A Revision
- Key elements of contamination control strategy (CCS)
- The Don’ts of Cleanrooms
- Vulnerabilities - Influencing factors on implementing CCS inspection reviews
- Environmental monitoring
- Contamination control
- Questions

Types of therapeutic goods

Medicines and blood products
- prescription medicines
- over-the-counter medicines
- complementary medicines
- blood, blood components and plasma derivatives and HPCs

Medical devices
- Implants (artificial hip, breast implants)
- In-vitro diagnostics (pregnancy tests, blood glucose monitors, infectious disease testing and NAT testing)
- Low risk medical devices (bandages, tongue depressors, condoms)



Biologicals
- Human stem cells
- Tissue-based products (skin, bone, ocular, cardiovascular and amnion)
- Cell and gene based products

How do we fulfil this mission?

1. Good Manufacturing Practice or Manufacturing Principles: licensing Australian manufacturers and verifying compliance of overseas manufacturers using either a clearance pathway or a site inspection.

2. Premarket assessments: assessing therapeutic goods for quality and safety (the extent of the assessment depends on the type of product and level of associated risk), and for higher risk products also for efficacy or performance.

3. Post market assessments: monitoring of therapeutic goods and enforcement of standards.

What are biological / biotechnological medicines?

Therapeutic Goods Regulations definition

Are therapeutic goods derived from biological sources and are regulated as registered medicines. Include

- a medicine (other than an antibiotic) that is:
  i. a vaccine, a peptide, a protein or polysaccharide-based; and
  ii. derived from a human, animal or other organism, or produced through recombinant technology or biotechnology; and
  iii. of a kind specified in item 1 of Part 1 of Schedule 10 (includes biotechnology medicines); or a medicine that is a human blood product of a kind mentioned in Appendix A in Part 5 of the Poisons Standard.

Biotech medicines are a subset of Biological medicines.

Definition of Biologicals

For the product to meet the definition of a biological, it must be:

- a thing made from, or that contains, human cells or human tissues, and that is used to:
  - treat or prevent disease, ailment, defect or injury
  - diagnose a condition of a person
  - alter the physiological processes of a person
  - test the susceptibility of a person to disease
  - replace or modify a person's body parts

•faecal microbiota transplant products
•a thing that comprises or contains live animal cells, tissues or organs.

Note that the term biologics, biologicals and biological medicines can have different interpretations in different countries/jurisdictions.

Biologicals and Biological Medicines

Biological medicines are not biologicals – specified in the ***Therapeutic Goods (Things that are not Biologicals) (Determination No.1 of 2011)***

Biological

- tissue-based products
- cell-based products
- immunotherapy products containing human cells
- autologous human cells and tissue products (including stem cells)
- gene-modified cell therapies
  - regulated under the Biological regulatory framework

Australian Regulatory Guidelines for Biologicals (ARGB)

Biological Medicines

- recombinant products
- plasma derived products (or that contain plasma derived products)
- vaccines (that do not contain viable human cells)
- gene-therapy vectors alone
  - regulated as **prescription medicines**

Australian Regulatory Guidelines for Prescription Medicines (ARGPM)

What are ATMPs

Advanced Therapy Medicinal Product (ATMP) is the umbrella term for three drug product classes:

- somatic cell therapies - cell-based therapy medicinal products (CTMPs)
- gene therapeutics – genetic therapy medicinal products (GTMPs)
- engineered tissue preparations - tissue engineering products (TEPs)
- a combination products.

These ATMPs usually contain or consist of living cells or tissues and are therefore characterised by a high degree of complexity.

What is an ATMP?

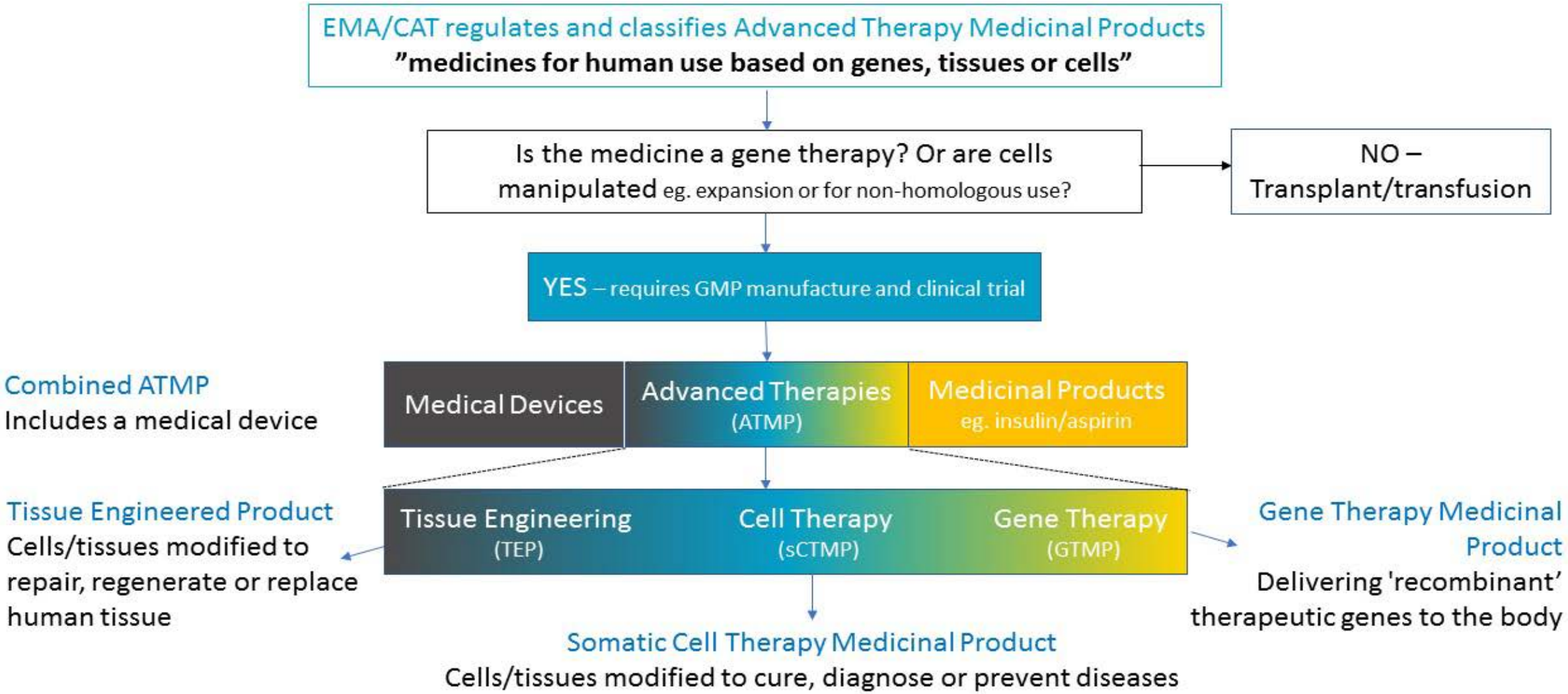


Image is a courtesy of EMA / CAT

PIC/S GMP Guideline - Revised Annex 2A for biological Substances and Products

- Revisions to the Pharmaceutical Inspection Co-operation Scheme (PIC/S) GMP Guide addressing the manufacturing of ATMPs as well as biological medicinal substances and products effective 1 May 2021.

- Annex 2A covers PIC/S GMP requirements for ATMPs, which cover cell and gene therapy products. The annex is divided into two parts:

  Part A - control over seed lots and cell banks through to finishing activities and testing

  Part B - more specific guidance on selected product types, such as animal sourced products and gene therapy products.

- Annex 2A " … is not a standalone document but it enables reasonable harmonization with the standalone ATMP guidelines published by the European Commission …" according to a PIC/S statement.

PIC/S Annex 2A Revision

- The revision of the requirements for ATMPs remained an integral part to the existing GMP guidelines and is not a standalone code. The Annex 2A that is specific to ATMP aimed at maintaining as close harmonisation as possible, and used the language of the “Guidelines on Good Manufacturing Practice (GMP) specific to Advanced Therapy Medicinal Products (ATMP)” where possible (the standard).

- Efforts were made to accommodate language that address challenges such as “diffuse manufacturing”.

- Efforts were made to accommodate language that permitted the standard to facilitate cross border movement of ATMP.

- The standard aimed to bridge across all the expectations for these products through all jurisdictions, even the countries that may not formally adopt it

PIC/S Annex 2A (1)

Compliance with Annex 2A is expected, however, it is acknowledged that there may be alternative processes but documented sound scientific rationale is required using Quality Risk Management (QRM) principles

National laws may be applicable to starting materials for ATMPs for example:

- Tissues and cells used as starting materials of ATMPs may be subject to other national legislation that cover donation, procurement, testing, processing, preservation, storage and distribution (e.g., TGO 108 and TGO 109 in Australia)

- For blood or blood components used as starting materials for ATMPs, national legislation - technical requirements for the selection of donors and the collection and testing of blood and blood components (TGO 102)

PIC/S Annex 2A (2)

Manufacture of ATMPs – product specific

- Different design approaches are possible

- Consider the manufacturing steps for the following:
  - Starting materials
  - ATMP active substance
  - Finished ATMP

- The manufacturing process between ATMP active substance and the final product can be continuous

PIC/S Annex 2A (3)

Genetically modified:

- The manufacture and control of genetically modified organisms also needs to comply with other local, national or regional requirements
- Appropriate containment should be established and maintained in facilities where any genetically modified organism is handled
- Advice should be obtained according to national law in order to establish and maintain the appropriate Biological Safety Level (BSL)
- GMP should be adhered alongside these requirements

Australia – Office of the Gene Technology Regulator (OGTR) – TGA has not yet adopted a definition of gene therapy.

PIC/S Annex 2A

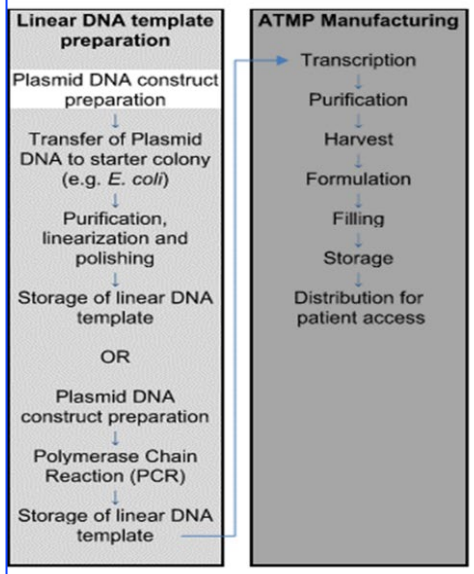
Table 1. Illustrative guide to manufacturing activities within the scope of Annex 2A

Example Products	Application of this Annex (see note (1))			
Gene therapy: mRNA	Linear DNA template preparation	In vitro cell free transcription	mRNA purification	Formulation, filling
Gene therapy: in vivo viral vectors	Plasmid manufacturing	Establishment of MCB, WCB (2)	Vector manufacturing and purification	Formulation, filling
Gene therapy: in vivo non viral vectors (naked DNA, lipoplexes, polyplexes, etc.,)	Plasmid manufacturing	Establishment of bacterial bank (2)	Fermentation and purification	Formulation, filling
Gene Therapy: ex-vivo genetically modified cells	Donation, procurement and testing of starting tissue / cells	Plasmid manufacturing	Ex-vivo genetic modification of cells	Formulation, filling
		Vector manufacturing (3)		
Somatic cell therapy	Donation, procurement and testing of starting tissue / cells	Establishment of MCB, WCB or primary cell lot or cell pool (2)	Cell Isolation, culture purification, combination with non-cellular components	Formulation, combination filling
Tissue engineered products	Donation, procurement and testing of starting tissue / cells	Initial processing, isolation and purification, establish MCB, WCB, primary cell lot or cell pool (2)	Cell Isolation, culture purification, combination with non-cellular components	Formulation, combination filling

1. Application of this annex applies to manufacturing steps illustrated in dark grey. Application of this annex or principles of this annex apply to steps illustrated in light grey apply depending on the requirements of national legislation.
2. Refer to points 5.32 for establishment of cell banks and seed lots.
3. In the case of gene therapy ex-vivo genetically modified cells, this guide applies to vector manufacturing except where otherwise authorised by national law where principles of GMP should apply.

PIC/S Annex 2A

Figure 1: Example of gene therapy mRNA ATMP manufacturing



- GMP requirements can vary from early steps in making the plasmid DNA construct to later steps but should align with Annex 2A and PIC/S GMP Guide Part II or principles of these requirements as applicable under national legislation.
- Refer to Section 5.23 for additional information in determining the appropriate application of GMP.

- A Marketing Authorisation Holder (MAH) may justify these steps to be a continuous process producing both the ATMP active substance and medicinal product.
- PIC/S GMP Part I and Part II along with applicable annexes apply as appropriate to the step of manufacture.

Figure 2: Example of in vivo viral vector gene therapy ATMP manufacturing

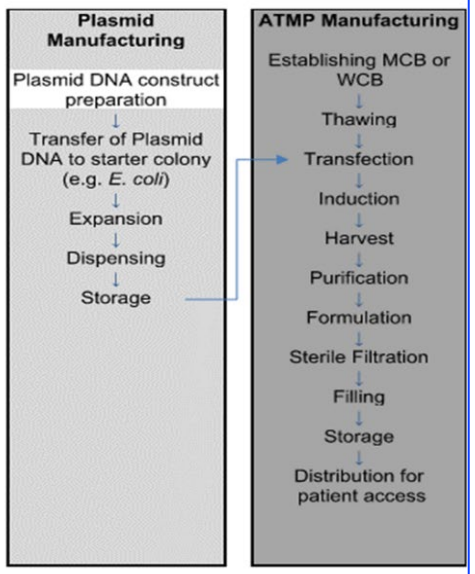


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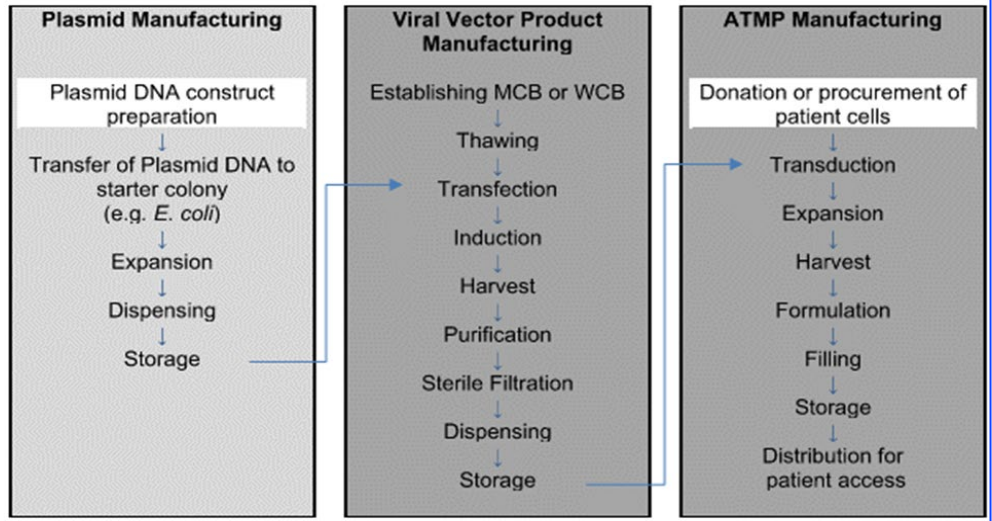
Figure 3: Example of autologous CAR-T therapy ATMP manufacturing

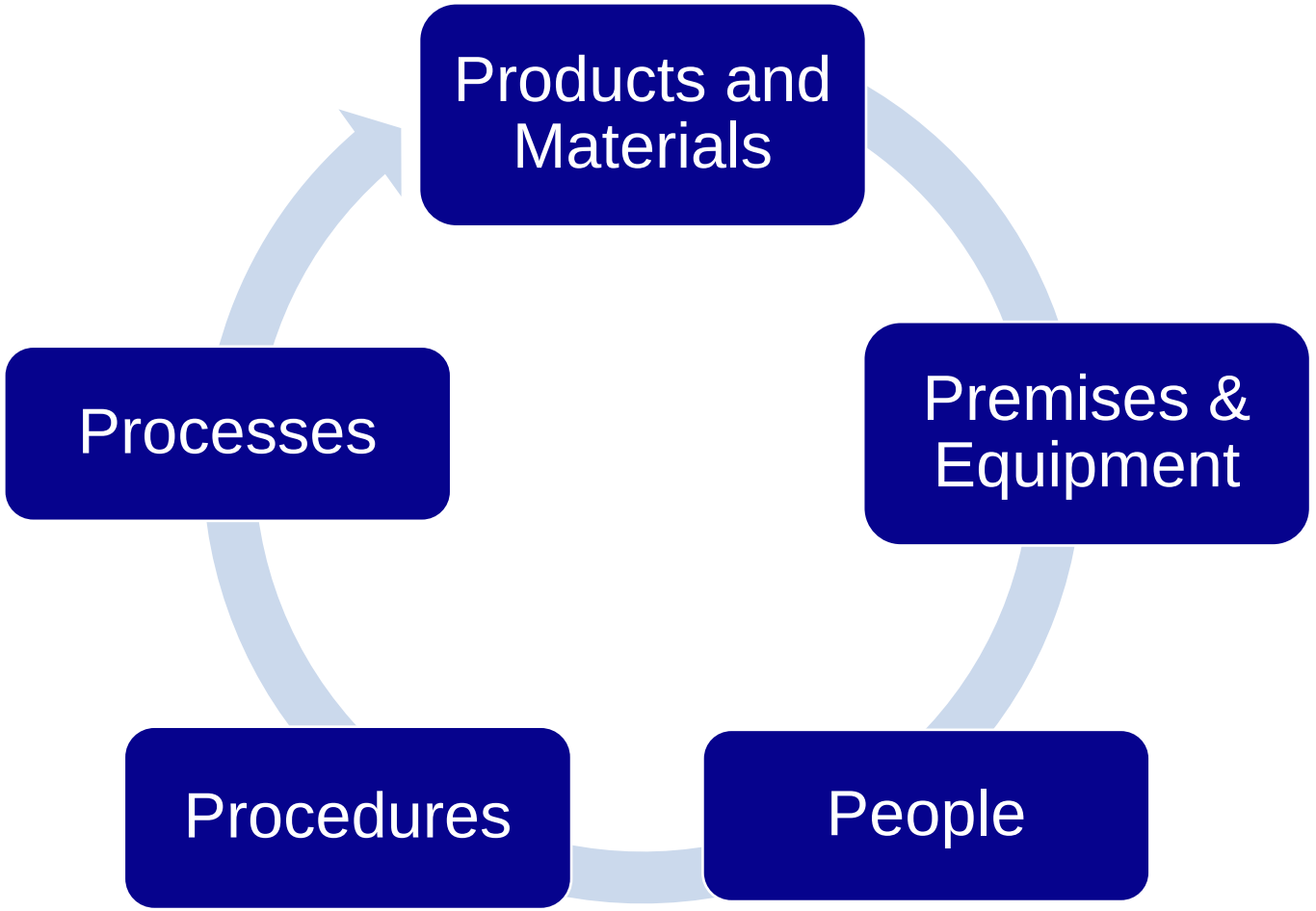


- GMP requirements can vary from early steps in making the plasmid DNA construct to later steps but should align with principles of Annex 2A and PIC/S GMP Guide Part II or principles of these requirements as applicable under national legislation.
- Refer to Section 5.23 for additional information in determining the appropriate application of GMP.

- GMP requirements applied to the manufacture of a viral vector should align with Annex 2A and PIC/S GMP Part II or principles of these requirements as applicable under national legislation.
- Refer to Section 5.23 for additional information in determining the appropriate application of GMP.

- The application of this guide does not include the donation or procurement of patient cells.
- A MAH may justify these steps to be a continuous process producing both the ATMP active substance and medicinal product.
- PIC/S GMP Part I and Part II along with applicable annexes apply as appropriate to the step of manufacture.

Key elements of Contamination Control Strategy (CCS) Design consideration



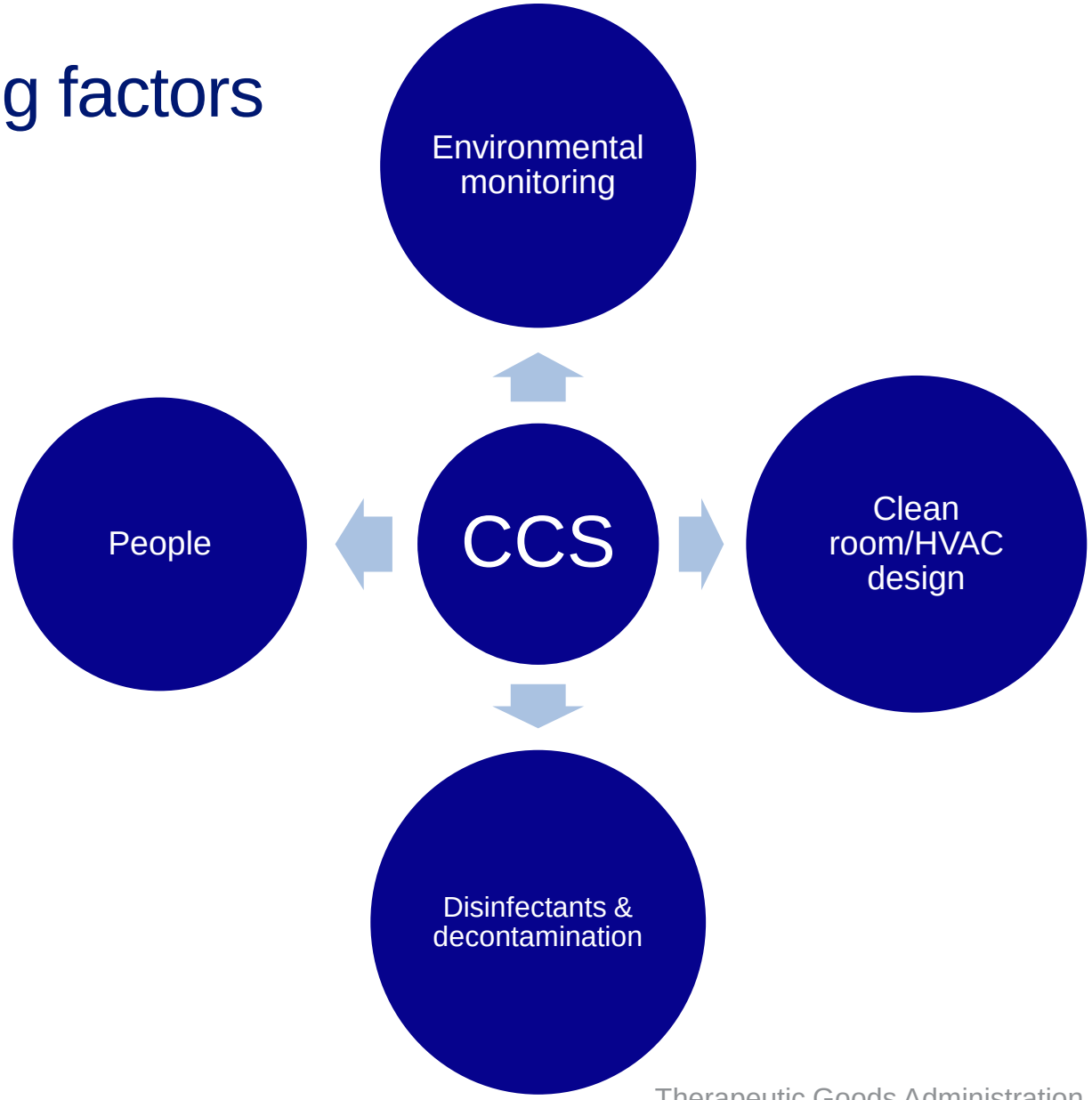
Importance of holistic end to end contamination control strategy (CCS) design

- Gap analysis (GA)- review all potential sources of contamination
- Identify vulnerabilities
- Complete risk assessments (RA)
- Identify critical control points (CCP)

- Review GA, vulnerabilities and completed RA
- Implement risk reduction strategies & ensure visibility is maintained for all vulnerabilities
- Undertake validations
- Implement robust risk based CCS strategy monitoring program

- Review data and implement continuous verification (OOT/OOE)
- Re-open RA when new input data available (i.e. deviations, OOS, CC)
- Maintain ongoing visibility on vulnerabilities

Vulnerabilities - Influencing factors on implementing CCS inspection reviews



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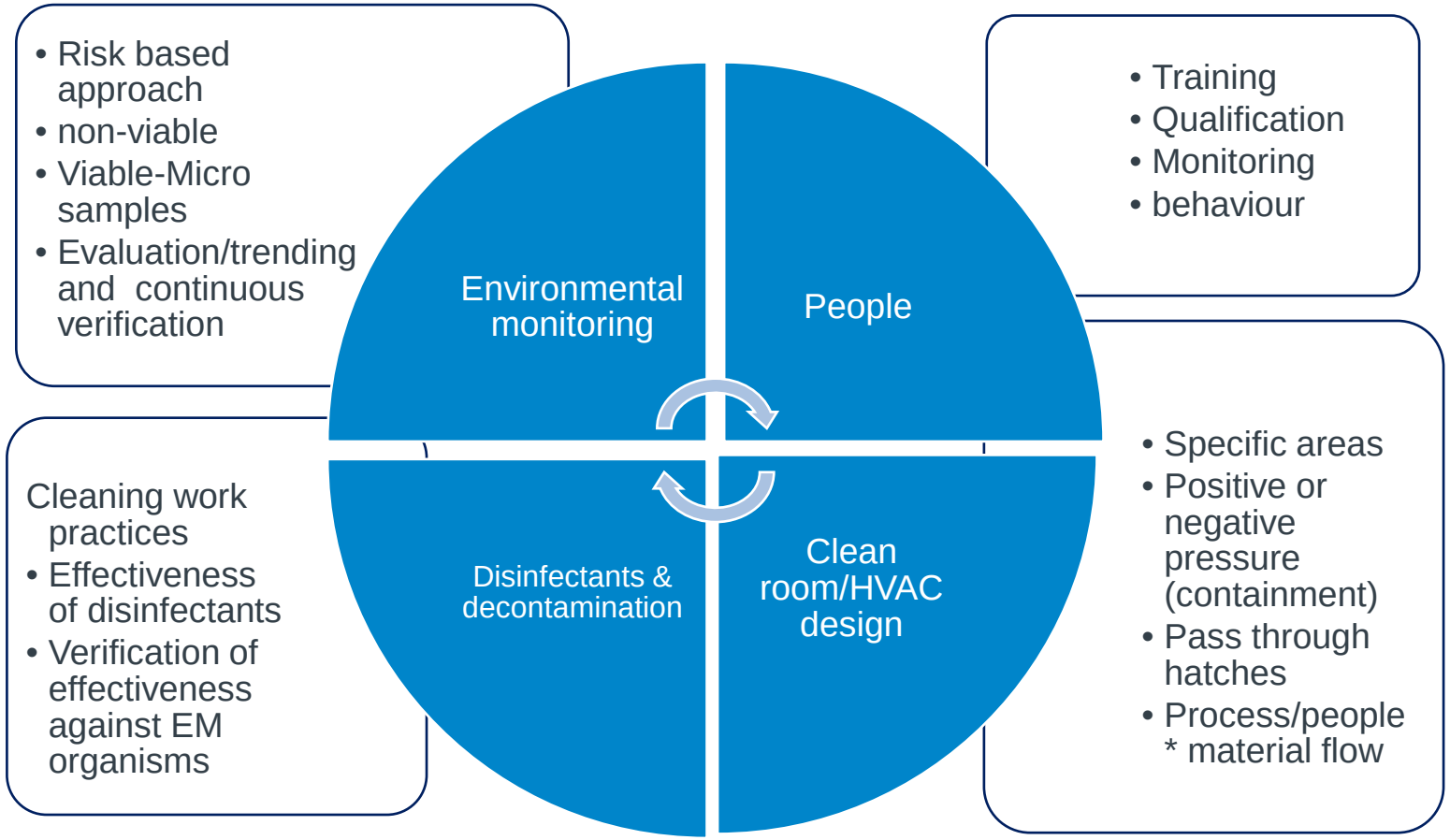


Vulnerabilities - Influencing factors on implementing CCS inspection reviews: Inspection hot spots

Environmental monitoring

- Monitoring worst case- monitoring critical control points
- Monitoring periods cover manufacturing duration and activities
- Media qualified
- Incubation periods/temperatures qualified
- Organisms identified for significance and action taken
- Review of disinfectant effectiveness against isolates
- Appropriate OOS investigations undertaken

People

- Training both initial and on-going relevant and complete
- Monitoring of personnel results match training/qualification
- Differences in ENV results against peers (i.e. OOT/OOE)
- Personnel attire, gowning / degowning observed and consistent with procedures and GMP
- Personnel clean room behaviour consistent with procedures and GMP

Vulnerabilities - Influencing factors on implementing CCS inspection reviews: Inspection hot spots

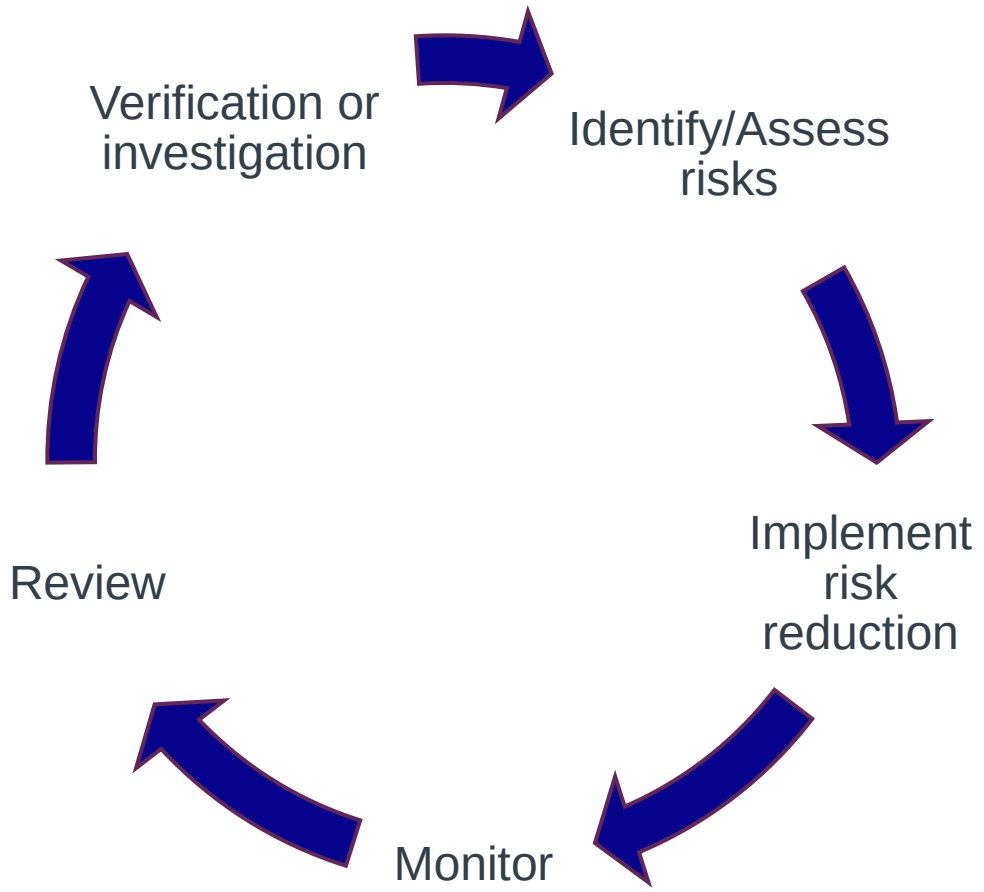
Disinfectants & decontamination

- Disinfectants within Expiry & clearly labelled
- Sterile disinfectants used or prepared in-house
- Validation of disinfectant efficacy worst case- includes at expiry disinfectants
- Sporicide used
- All materials entering clean room assessed as part of CCS
- Work practices and records match validation

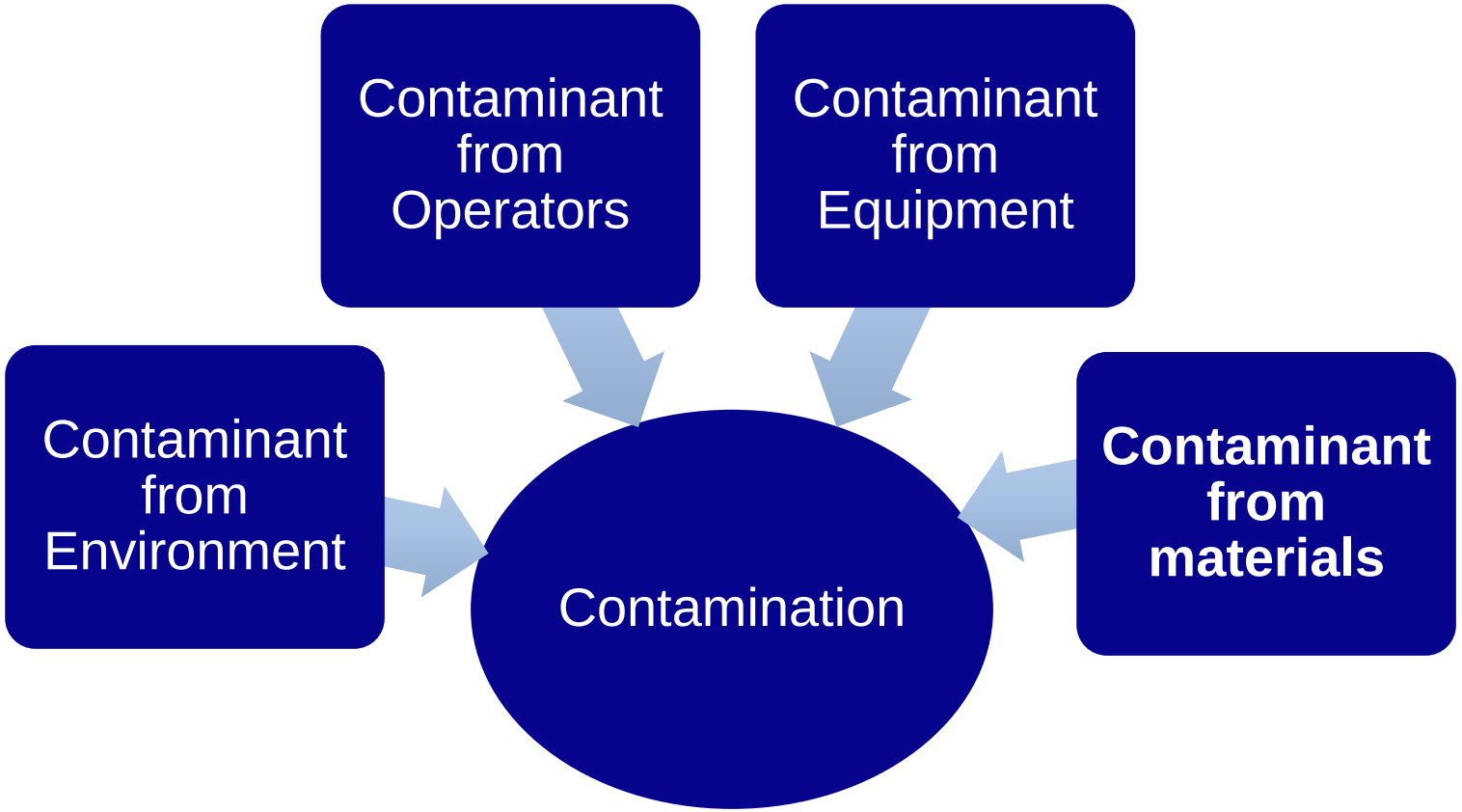
Clean room/HVAC design

- Adequate physical separation –airlocks
- Air pressures match design (negative or positive pressure)- Pressure trend records match qualification-no missing data
- Maintenance records demonstrate suitability & recommendations actioned
- Transfer Hatches suitable and qualified.
- Material transfer through Pass Through hatches validated, routine records match

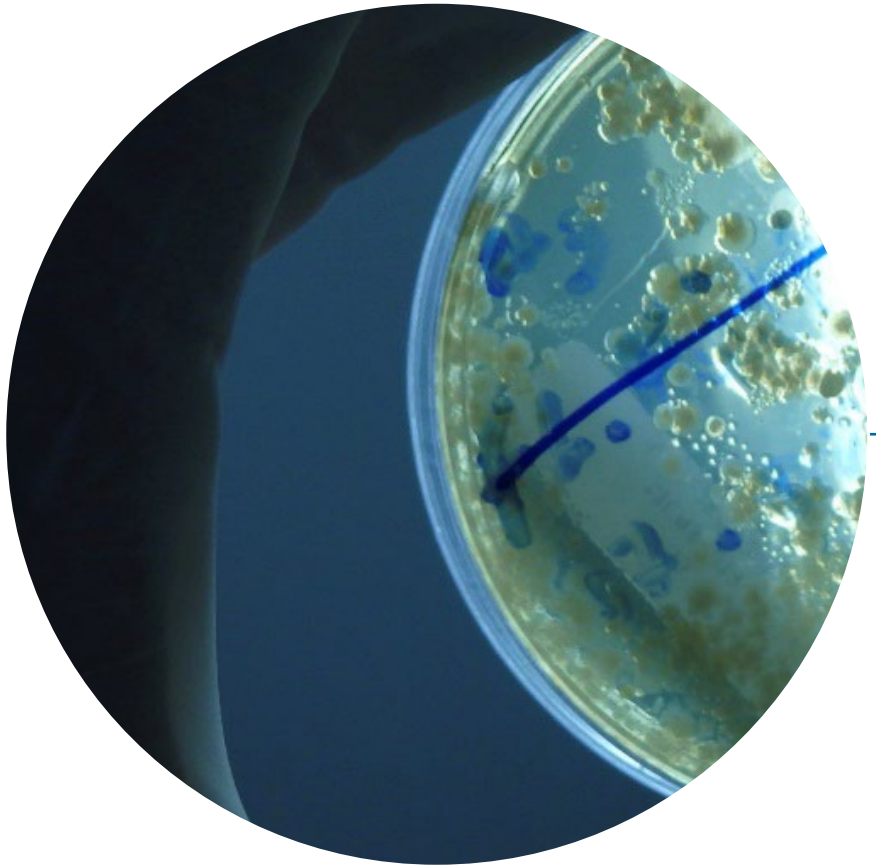
Lifecycle approach to contamination control



Lifecycle approach to contamination control



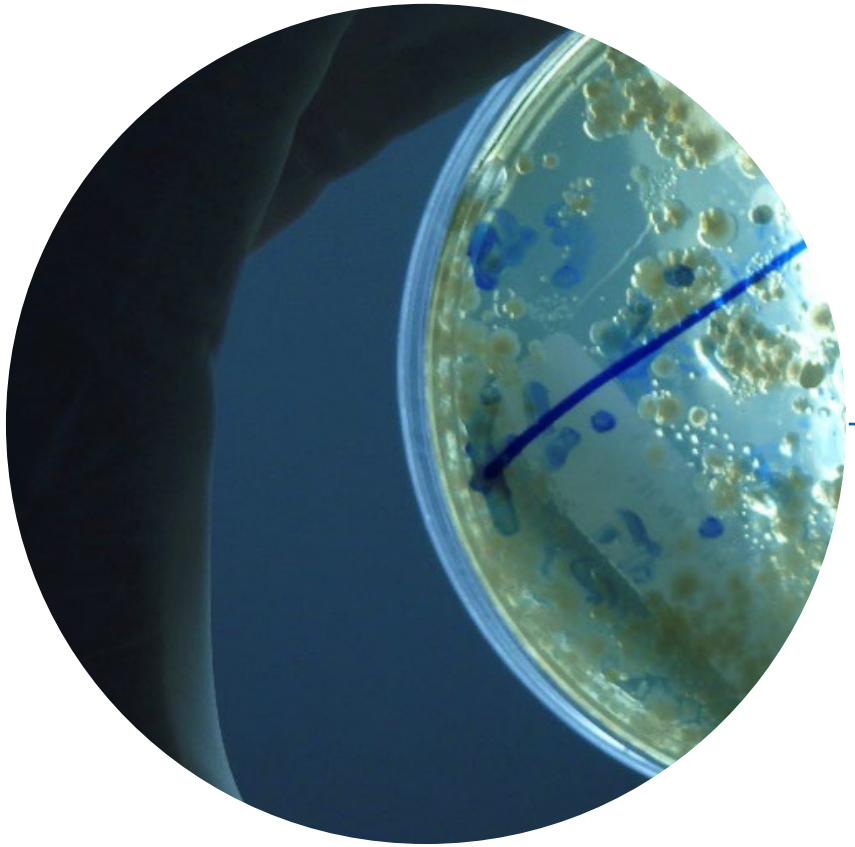
Vulnerabilities-Influencing factors on implementing CCS inspection reviews: Materials and Products - one



Patient Starting material

- High contamination risk-Autologous (lower)/allogeneic (higher)
- Contamination - Apheresis/leukapheresis collection-i.e. skin disinfection/venepuncture)
- Staff collecting material
- Patient collected material-micro contamination
- Storage/transport
- Outsourced collection activities

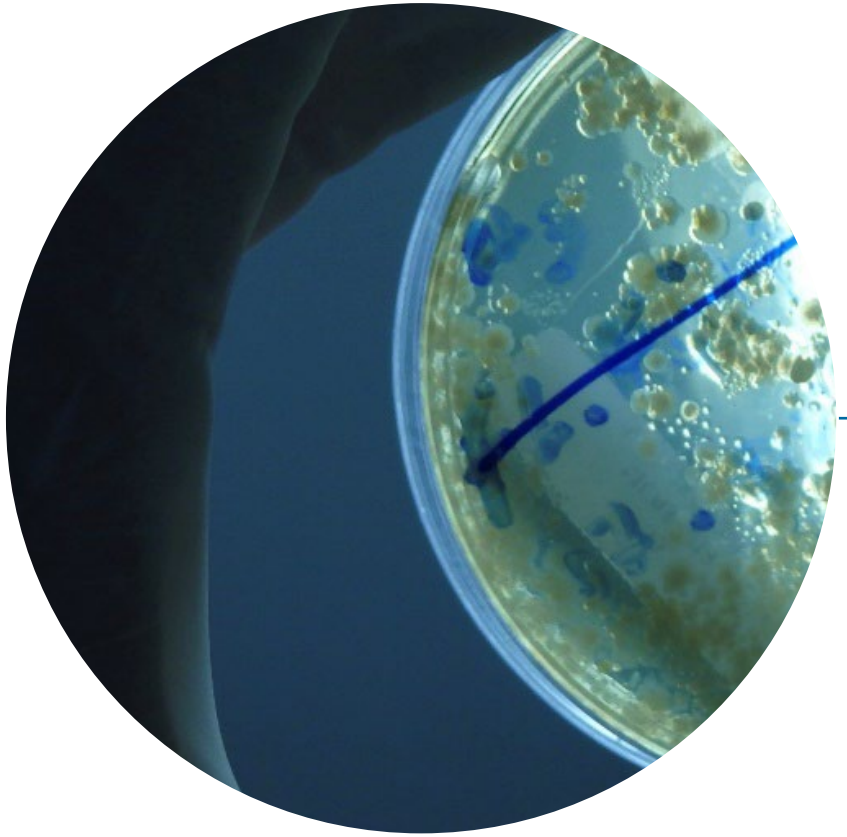
Vulnerabilities-Influencing factors on implementing CCS inspection reviews: Materials and Products - two



Materials

- Container closure integrity/sterility
- Media/buffer/process aid preparation
- Material specification
- Testing regimes-inhibition of microorganisms
- Stability
- Adequate records of receipt, quarantine, inspection, release, preparation, disposal, expiry
- Labels robust during storage-legibility

Vulnerabilities-Influencing factors on implementing CCS inspection reviews: Materials and Products - three

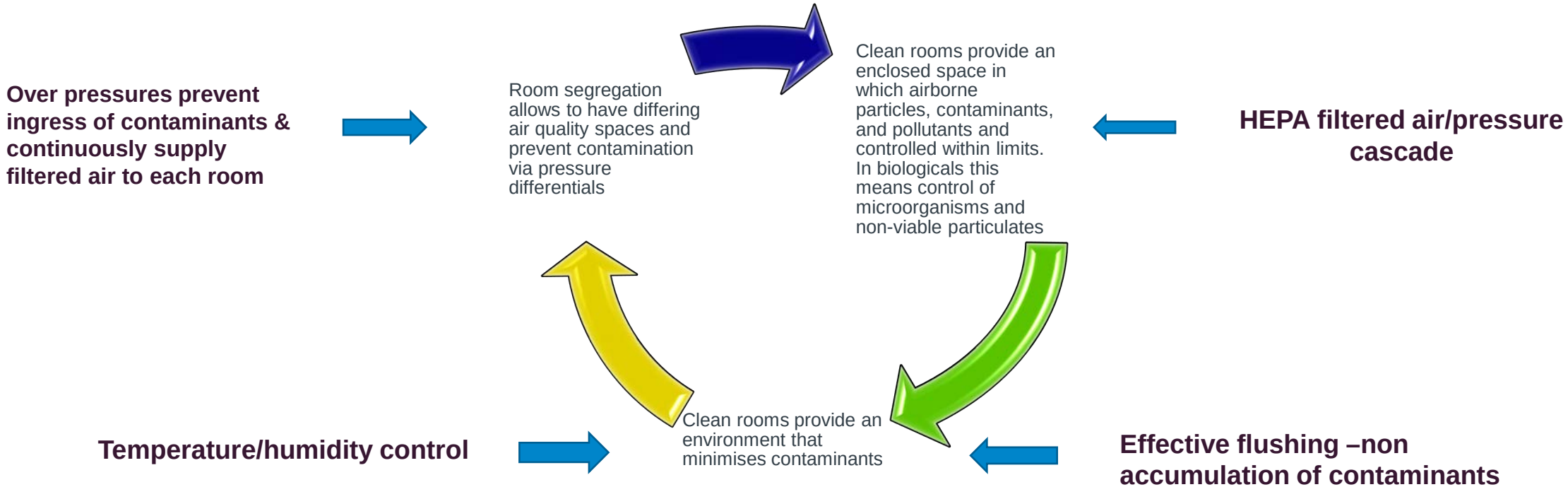


Process/ Product

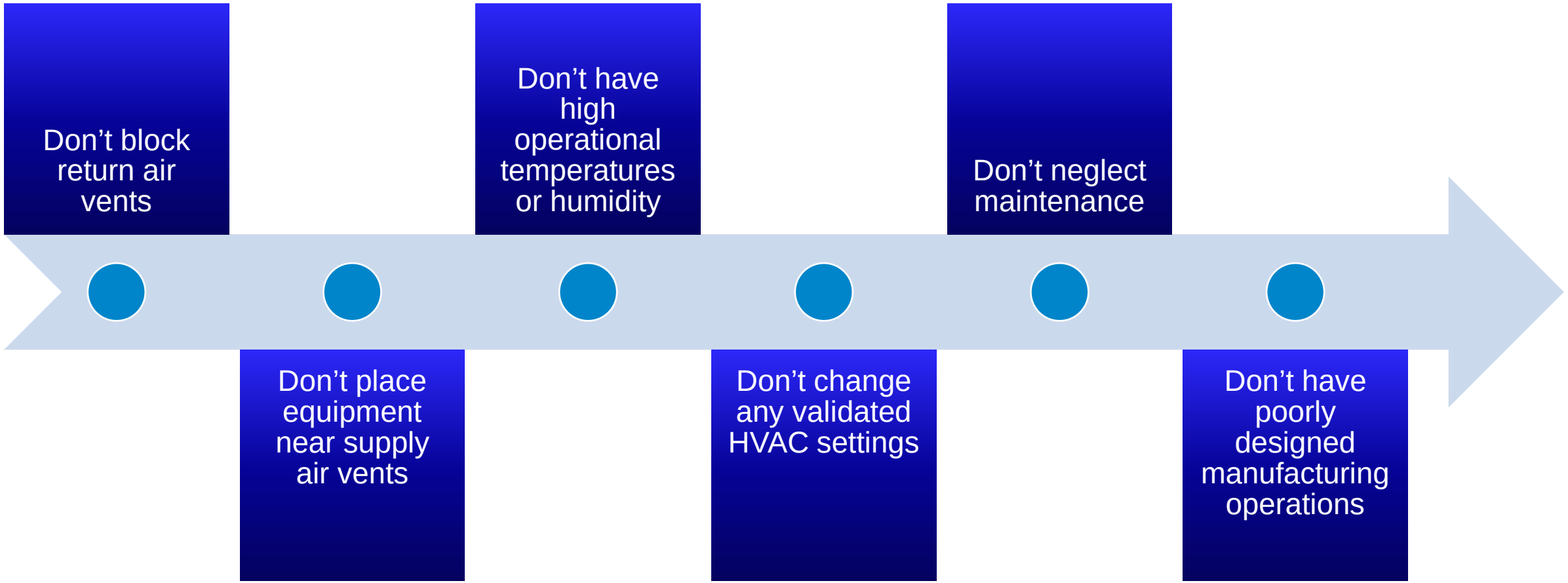
- Viral vector/plasmid- source, traceability, characterisation, qualification, storage, stability
- Manufacture of MCB/WCB
- Dedicated Facility for MCB/WCB/viral seed lots
- Testing, stability, storage, inventory, labels-legibility
- Back-up storage/Disaster recovery plan
- Impurities – intrinsic/extrinsic

Vulnerabilities-Influencing factors on implementing CCS inspection reviews: Premises and Equipment

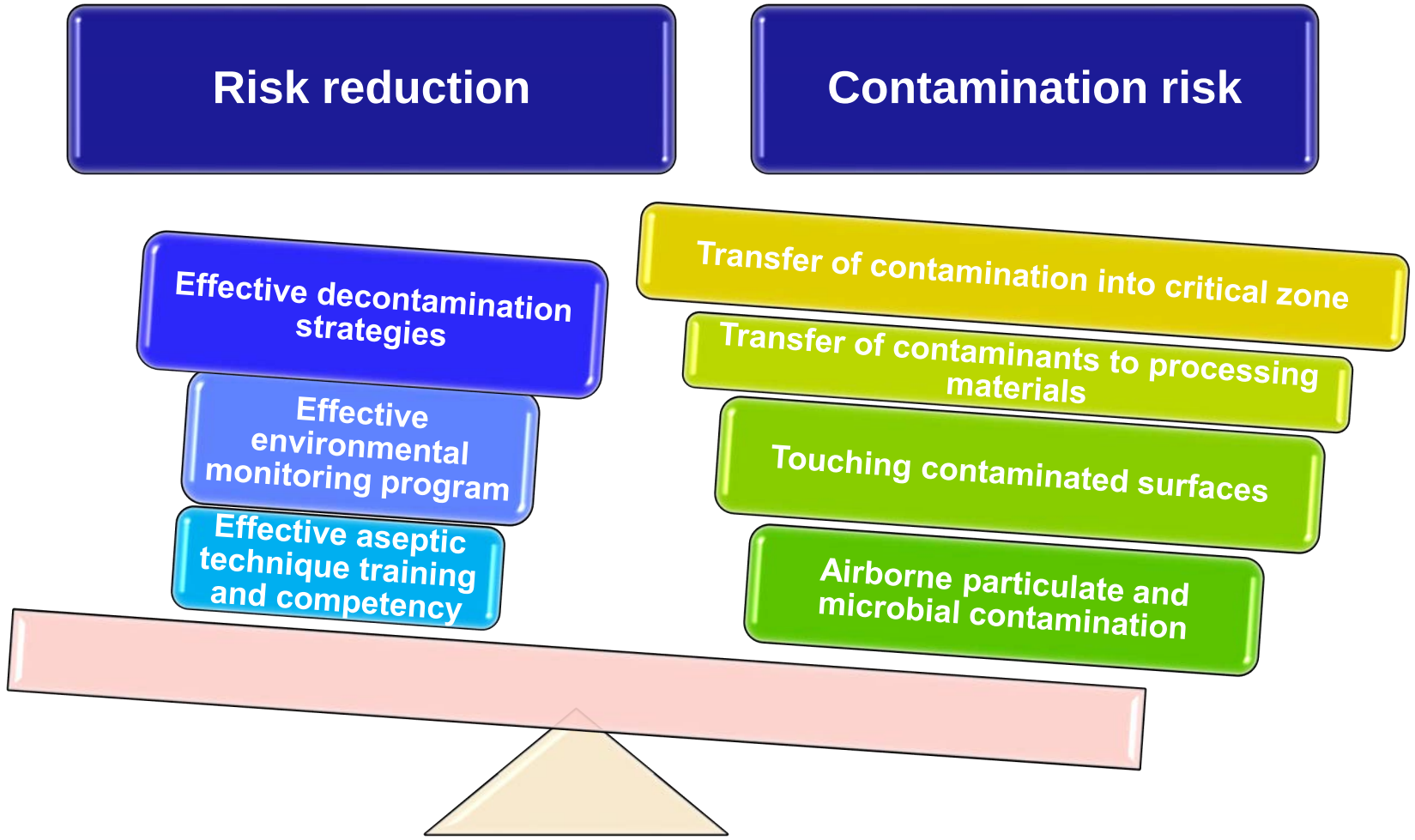
What clean rooms do



The Don’ts of Clean rooms

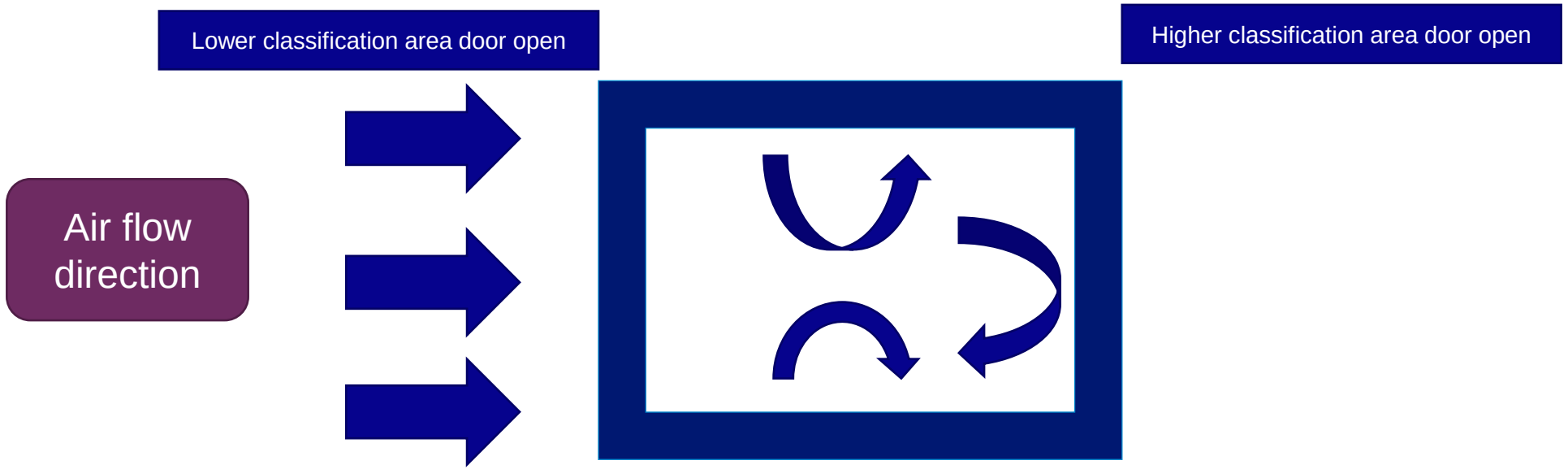


Critical Role of Decontamination



Vulnerabilities-Influencing factors on implementing CCS inspection reviews: Premises and equipment

Pass Through (PT) design contamination risk – Passive PT



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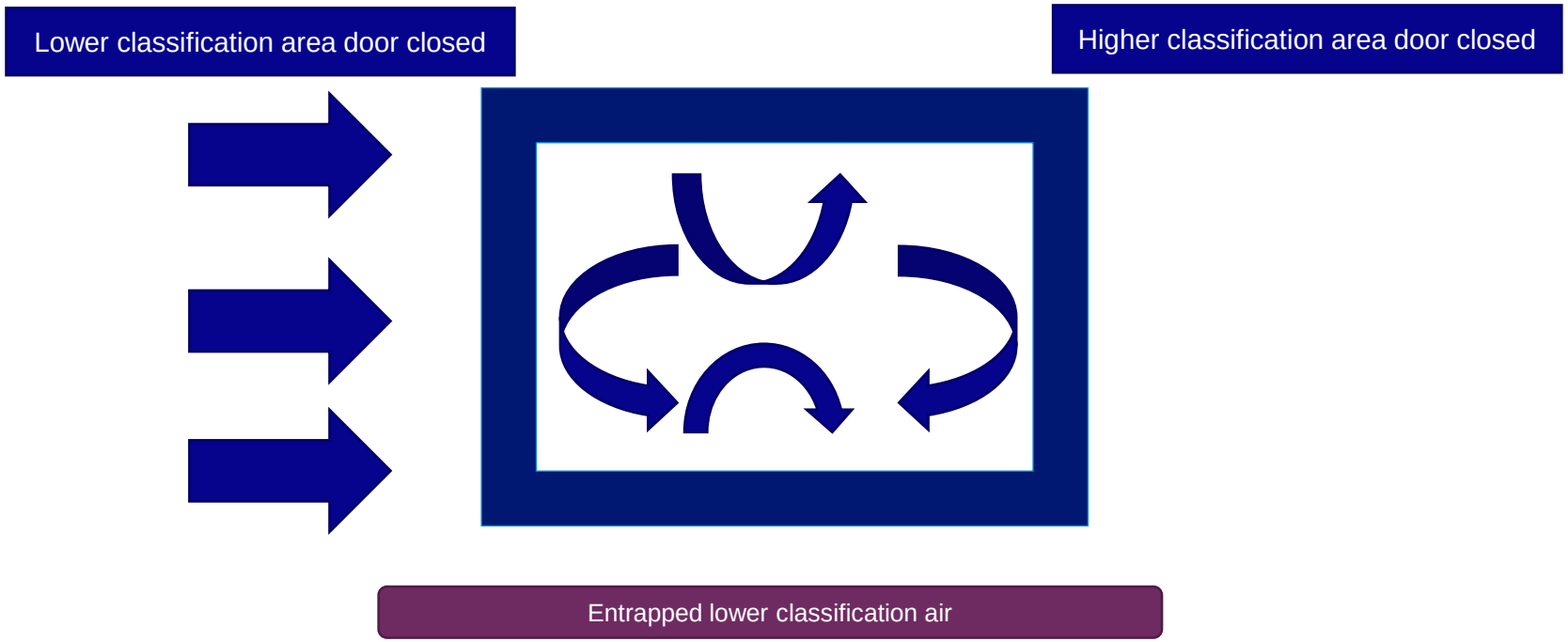

Vulnerabilities-Influencing factors on implementing CCS inspection reviews: Premises and equipment

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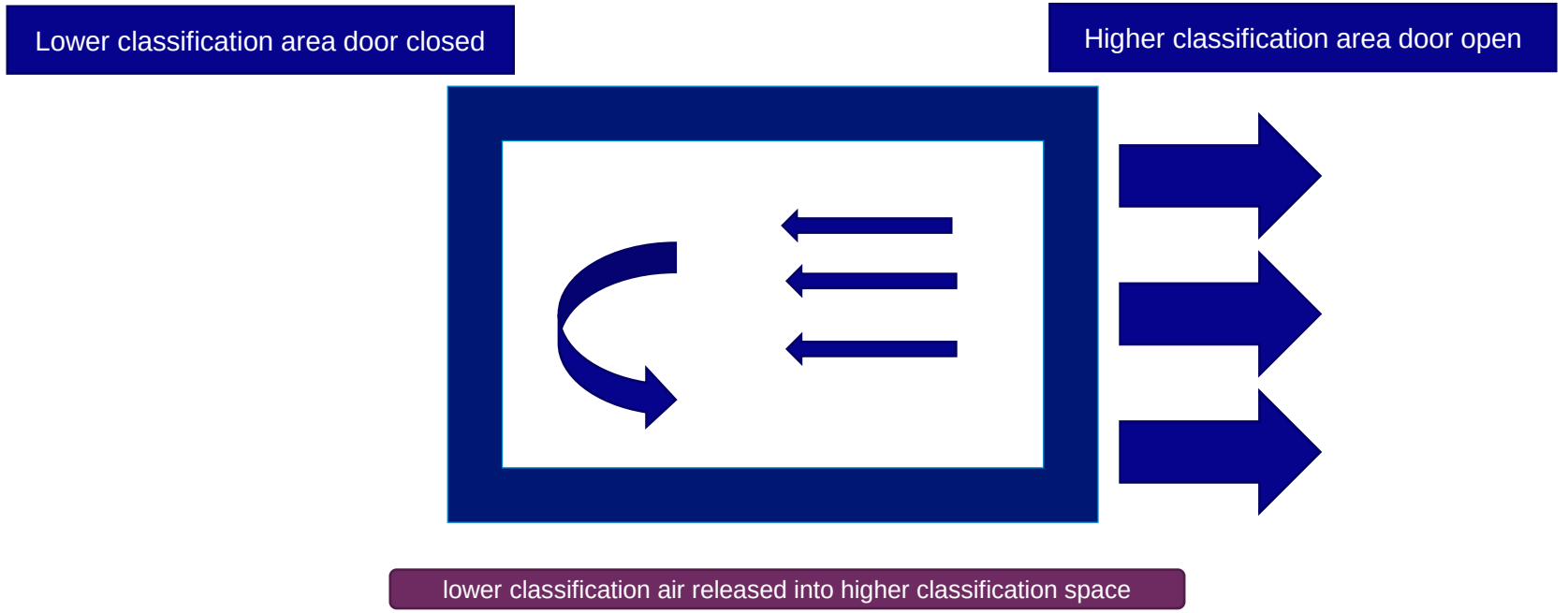
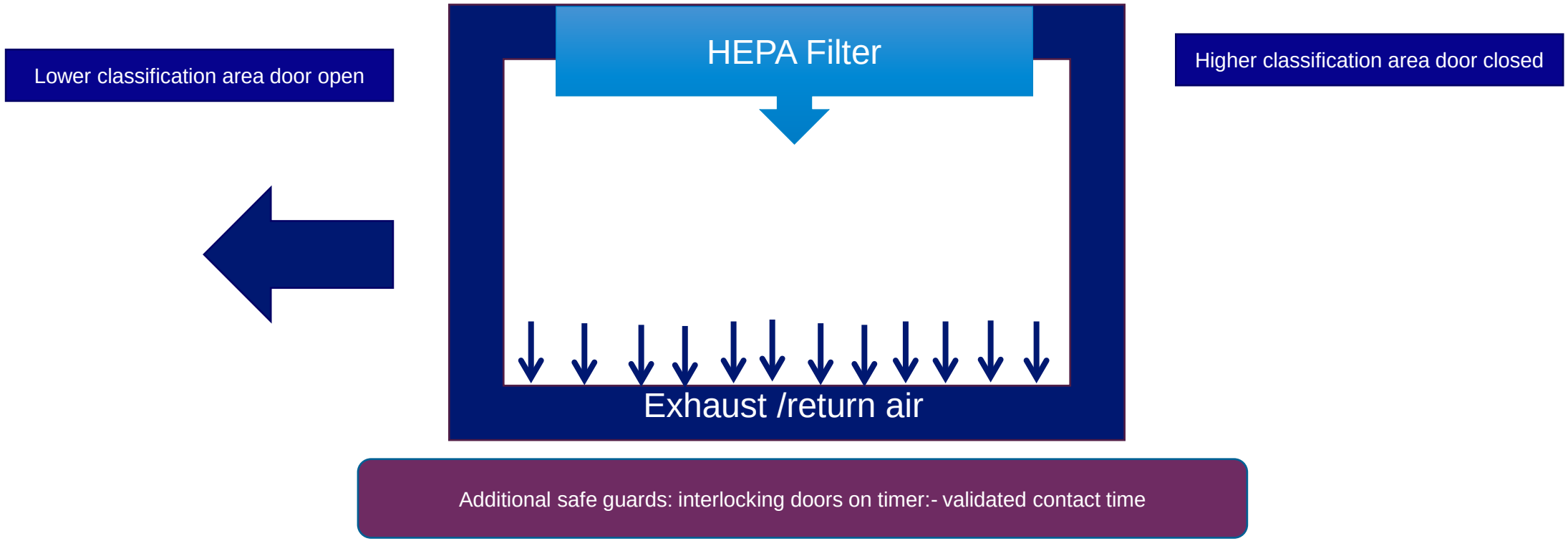
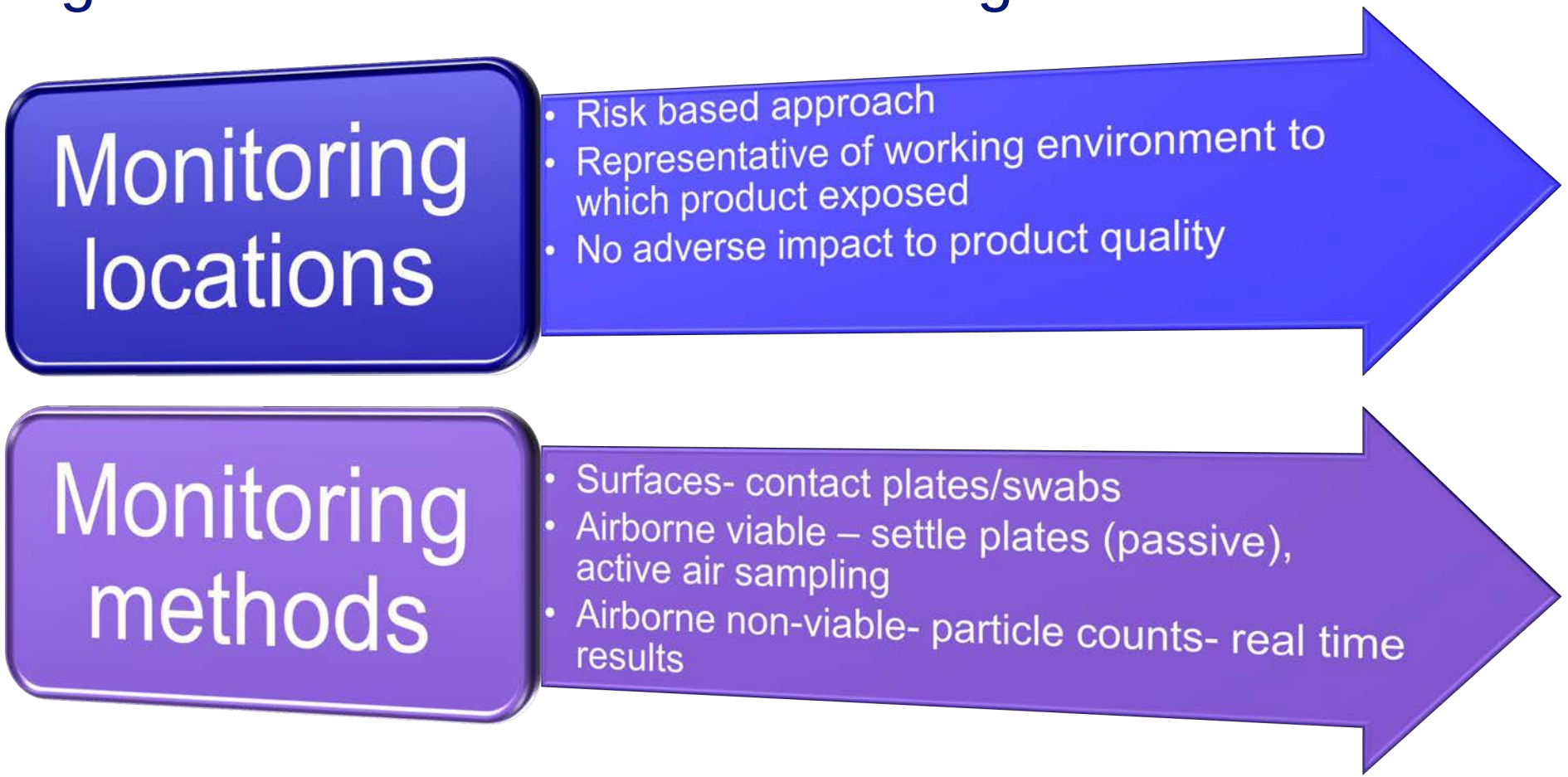


Vulnerabilities-Influencing factors on implementing CCS inspection reviews: Premises and equipment

Pass Through (PT) design contamination control risk reduction



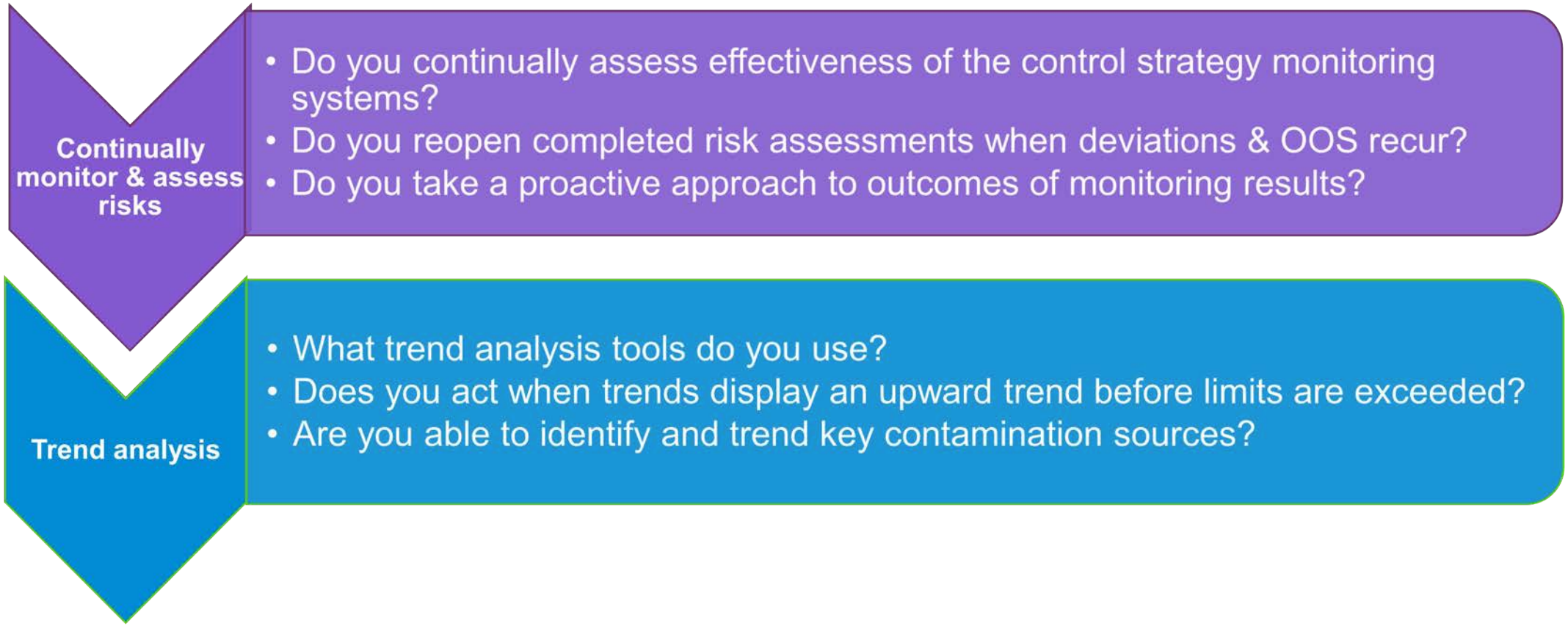
Environmental Monitoring – verifies contamination control strategies remain effective – Monitoring Plan - one



Environmental Monitoring – verifies contamination control strategies remain effective – Monitoring Plan - two

Contamination Control – Inspection Focus (one)

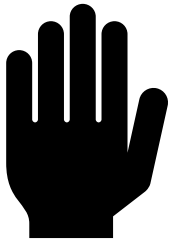
Contamination Control – Inspection Focus (two)



How to ask questions

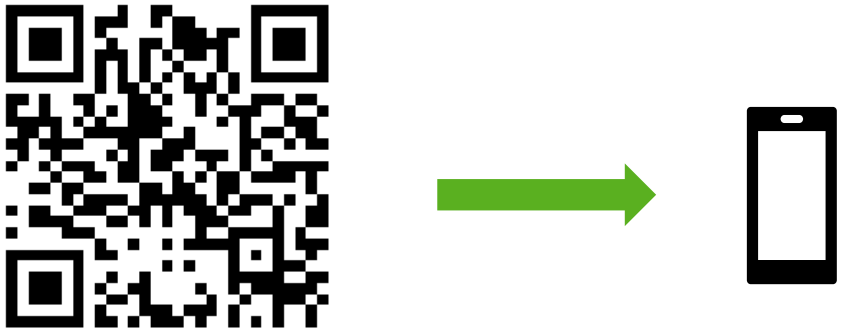
Verbal questions:

Raise your hand to ask a verbal question. A member of the GMP Forum staff will provide a roaming microphone.



Written questions:

Scan the QR code below or click the link in your calendar to access Slido via your mobile device. You can submit your question, and vote on other questions submitted.



Australian Government

Department of Health and Aged Care

Therapeutic Goods Administration