Process Validation Lifecycle and Sterility Assurance

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Day: Thursday
Time: 15:00-15:45

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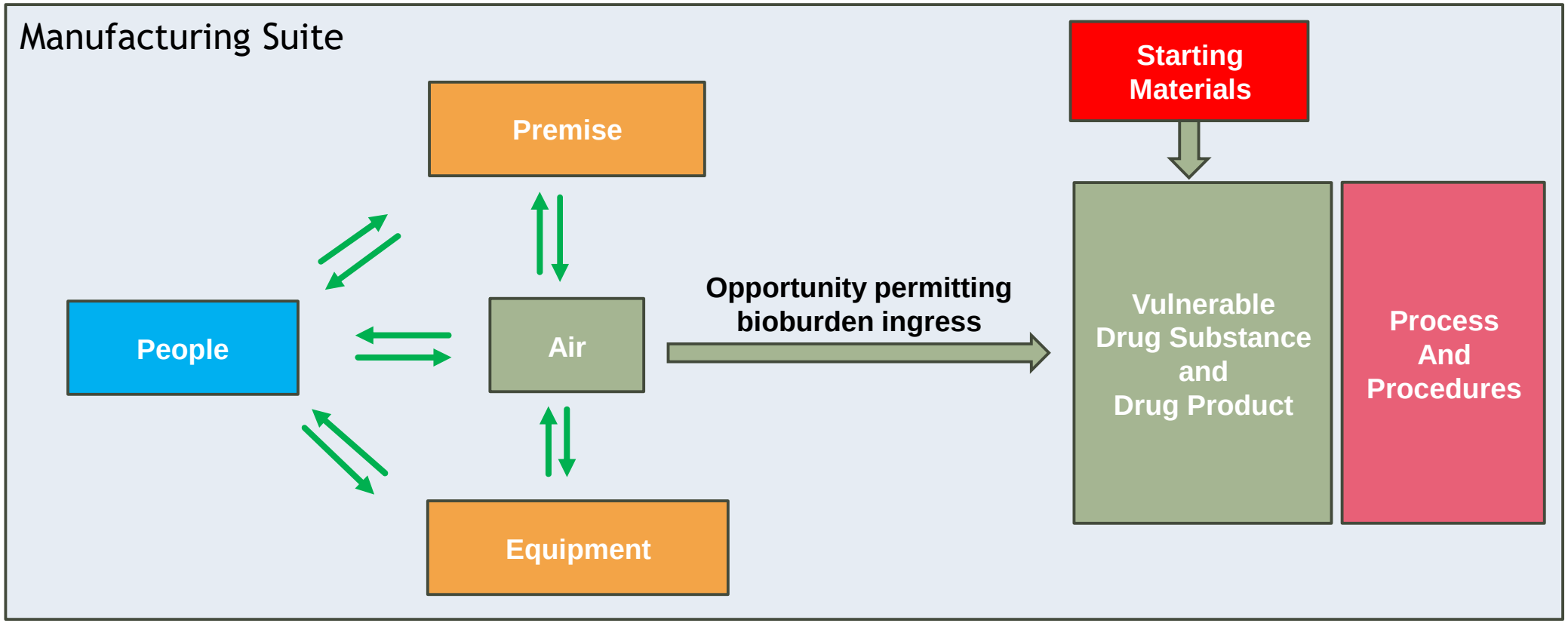
Agenda

- Contamination
- Sterility/Sterilization
- Process Validation Lifecycle
- Process Validation Lifecycle and Sterilization Assurance

Contamination

Model for Bioburden Ingress



Conceptual model for air-borne bioburden ingress into aseptically manufactured product

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Five Principles of GMP, Schematic Overview.

Sterility/Sterilization

Sterilization Process Controls

1. Confirm that the sterilization process was validated by reviewing the validation study

2. Review the specific procedure(s) for the sterilization process selected and the methods for controlling and monitoring the process; Verify that the process is controlled and monitored

3. If review of the Device History Records (including process control and monitoring records, acceptance activity records) reveals that the sterilization process is outside the firm's tolerance for operating or performance parameters:
   a. Determine whether the nonconformances were handled appropriately; and
   b. Review the equipment adjustment, calibration and maintenance

4. If the sterilization process is software controlled, confirm that the software was validated

5. Verify that personnel have been appropriately qualified and trained to implement the sterilization process

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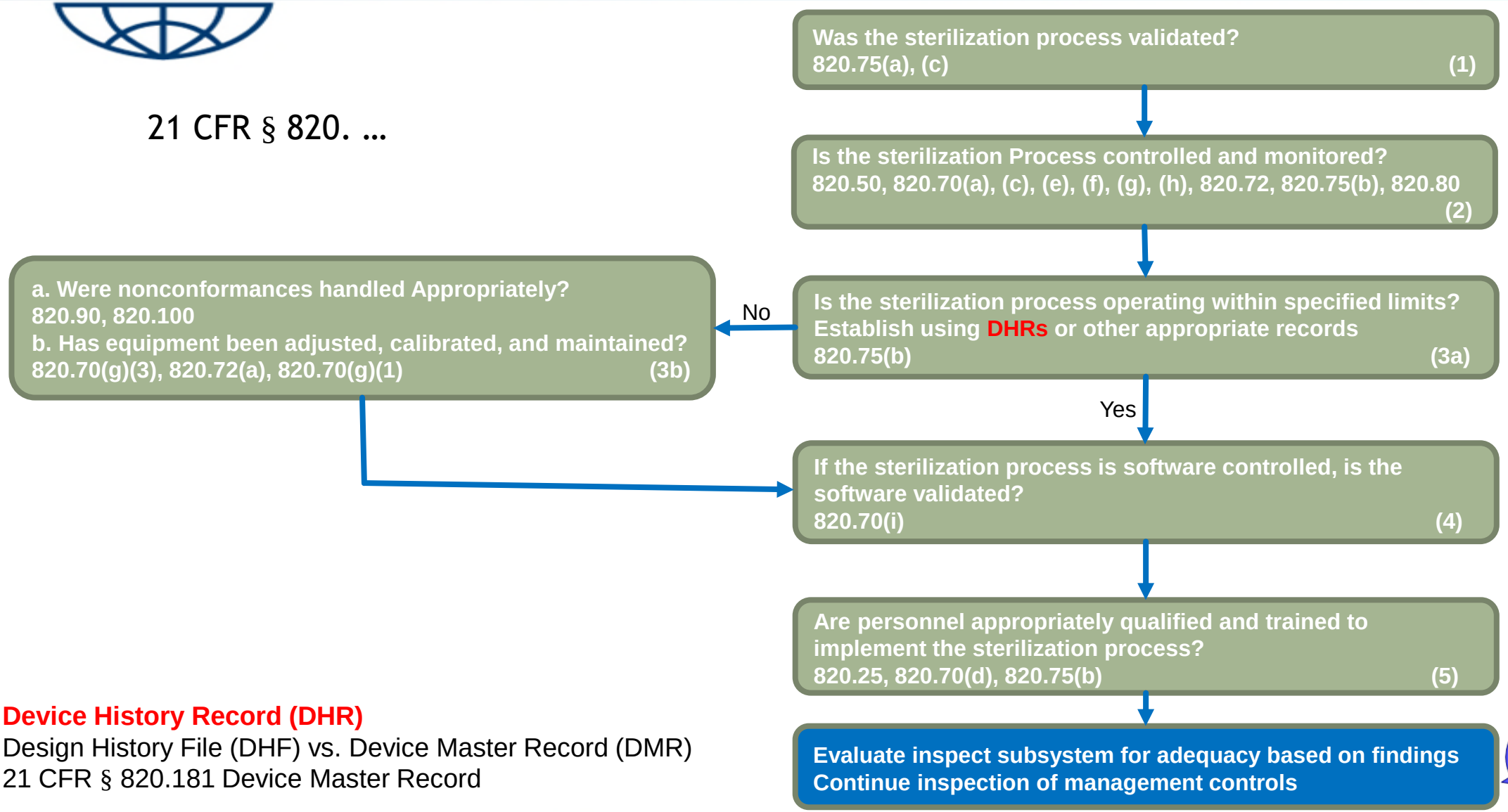
Sterilization Process Controls Decision Flow Chart

21 CFR § 820. …



Device History Record (DHR)

Design History File (DHF) vs. Device Master Record (DMR)

21 CFR § 820.181 Device Master Record

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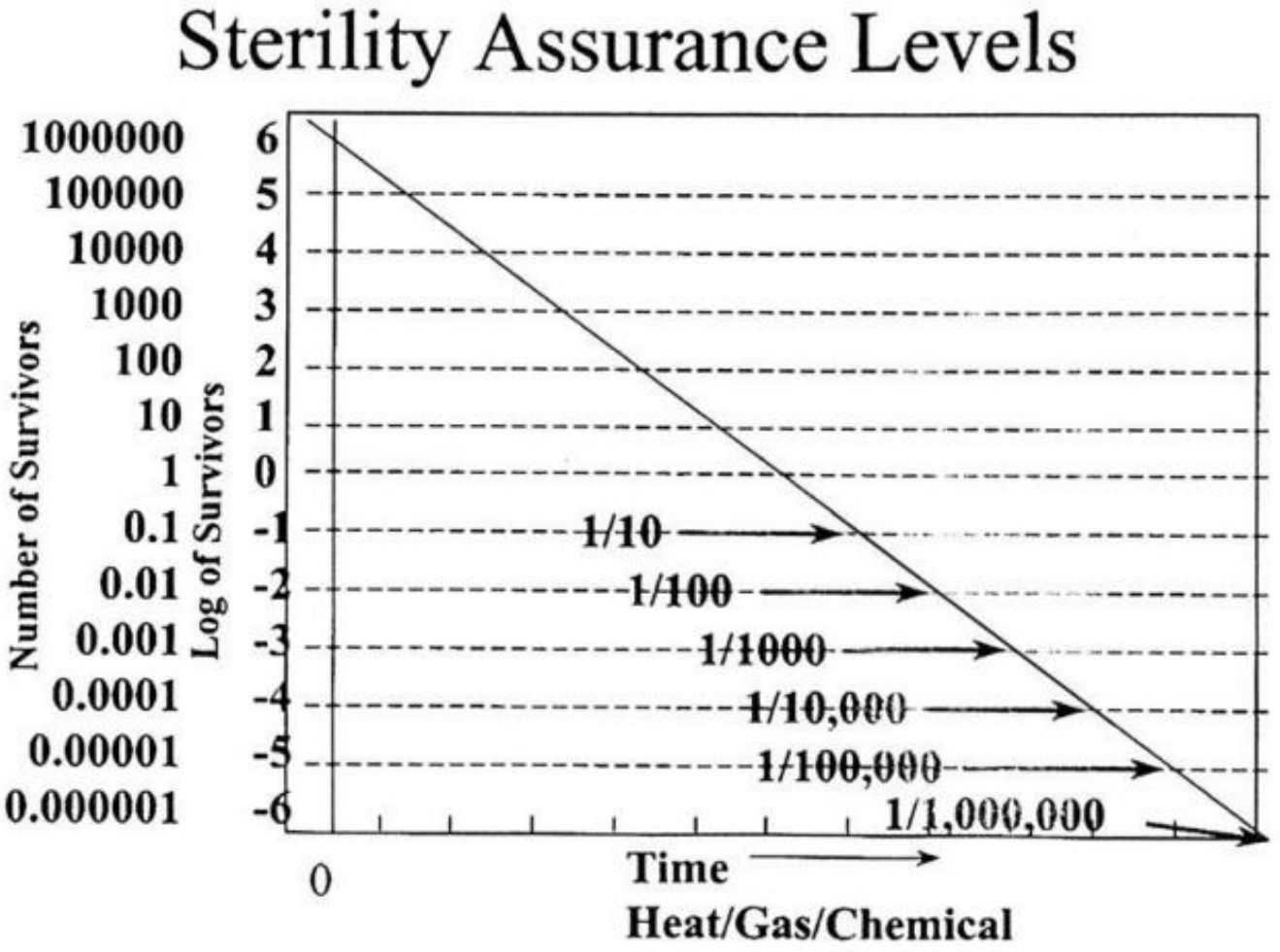
Sterility Assurance Level



Sterility Assurance Levels for heat, Gas, or Chemicals.

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Process Validation Lifecycle

Process Validation Concept – EU-EMA vs US-FDA

EU Annex 15 2014

Process Validation:

1. General
2. Approach to PV
    1. Concurrent PV
    2. Traditional PV
    3. Continuous PV
    4. Hybrid approach
3. Ongoing process verification (OPV)

Annex15 2014

FDA Proc Validation guidance 2011

Process Validation:

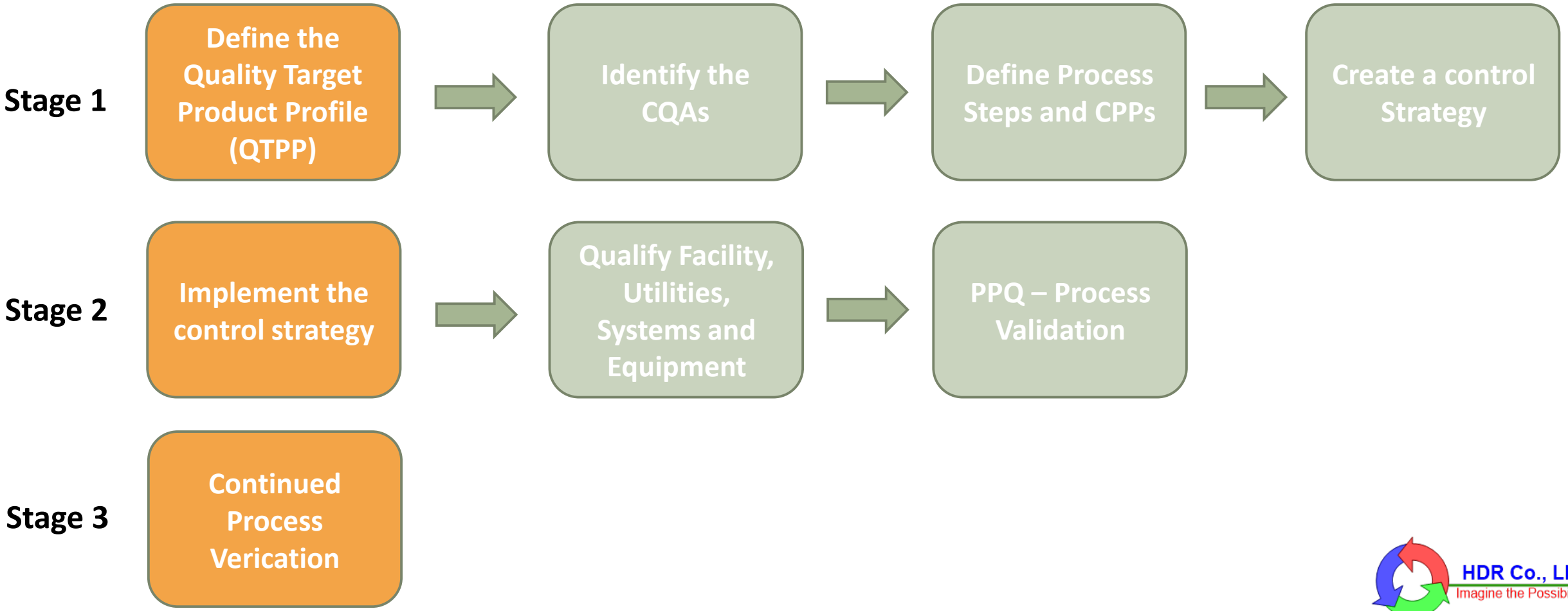
1. Process Design (stage 1)
2. Process qualification (stage 2)
    - C&Q Facility/Utilities/Equipments
    - Process Performance Qualification (PPQ)
3. Continued Process Verification (CPV) (Stage 3)
    - Heightened testing
    - Routine process monitoring

FDA PV 2011

Apparent different approach and terminology, in reality much more aligned than it looks:

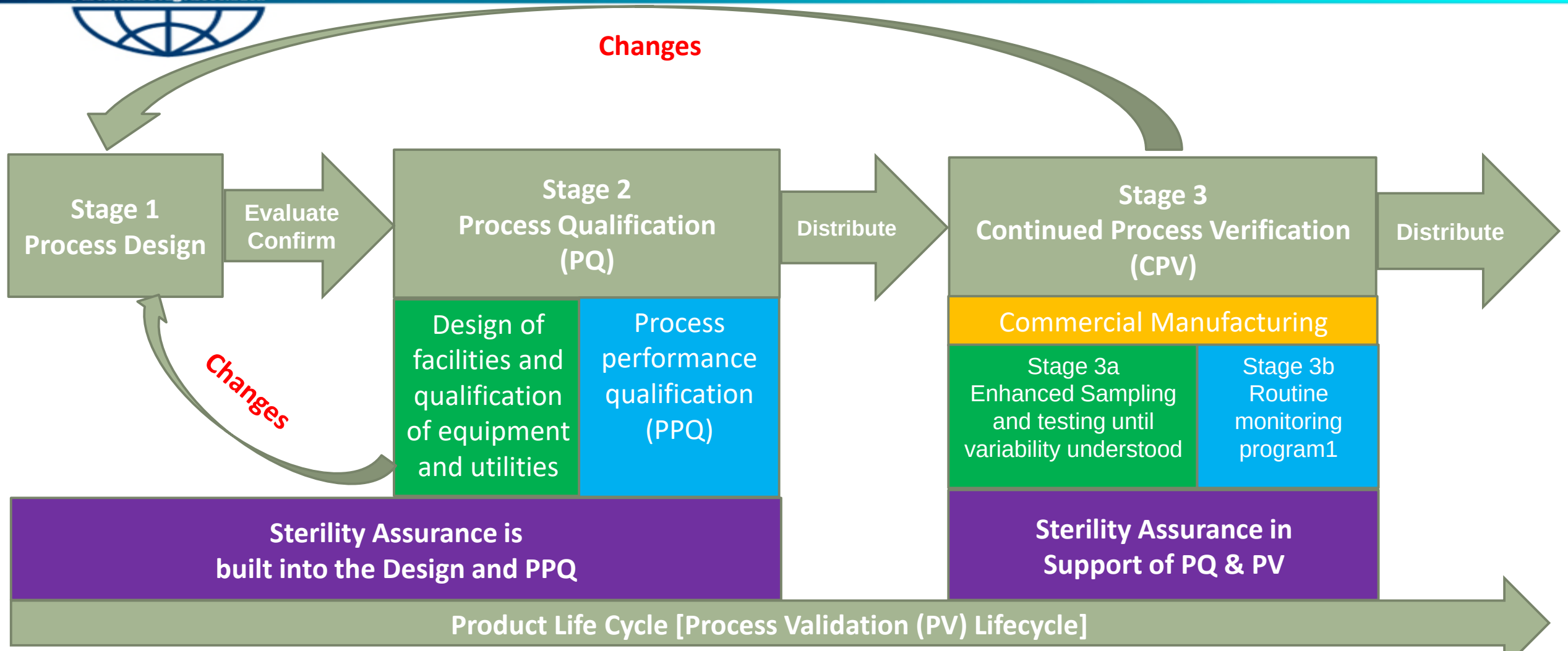
- **Both requiring Quality Risk Management approach**
- **Both referring to development studies which should take place prior to routine manufacturigng**
- **Both are not allowing any more retrospective validation**
- **Both requiring Process validation Plan and Protocols**
- **Both requiring a surveillance period after PPQ/PQ/PV but using different terms (OPV vs CPV)**

Process Validation Lifecycle



Process Validation Lifecycle and Sterilization Assurance

Process Validation Lifecycle and Sterility Assurance



During the **process qualification** (PQ) stage of **process validation**, the process design is evaluated to determine if it is capable of reproducible commercial manufacture. This stage has two elements: (1) design of the facility and qualification of the equipment and utilities and (2) process performance qualification (PPQ). During Stage 2, CGMP-compliant procedures must be followed. Successful completion of Stage 2 is necessary before commercial distribution. Products manufactured during this stage, if acceptable, can be released for distribution.

Process validation: The collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality products.

Sterility Assurance and PPQ

Sterility assurance can not be seen as something independent from the product validation. Sterility assurance is generally a prerequisite to PPQ, however the process should be designed not just taking into consideration the drug substance/drug product, but also the combination sterility assurance/product.

- Quality [Q]
- Safety [S]
- Efficacy [E]
- Purity [M???]

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PV is well defined by the regulations

(for a parenteral drug products)

For a parenteral drug products, It means ensuring a product is sterile, with

1. **Very low endotoxins**
2. **Very low foreign particles**
3. **The entire manufacturing process shall be designed to fit the characteristic of the product**
   a. **Excipients**
   b. **Drug Substance**
   c. **Container**
   d. **Platform**
   e. **Administration route**
4. **This process can be divided in steps, and for each shall have as minimum control of bioburden, endotoxins and particles at some point in time for the main product components:**
   a. **Formulation**
   b. **Equipment in contact with product**
   c. **Container closure**
   d. **Environment where product is exposed**

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Enhanced Approach:

A development approach where risk management and scientific knowledge is used to identify and understand the material attributes and process parameters which influence the critical quality attributes of a product.

https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-process-validation-finished-products-information-data-be-provided-regulatory-submissions_en.pdf

Sterility Assurance Impact on CQA

1. There are situations where the Sterility assurance requirements may be in conflict with the product CQA;
   a. Use of oxidizing disinfectants
   b. Generation of particles due to sterilization process
   c. Degradation of product due to heat exposure
   d. Radicalic reaction triggered by product preservatives
   e. Wet sterile parts impacting lyophilization products
   f. Radicalic reactions due to interactions of materials with radiation sterilized materials
   g. H2 antagonist was “partially” terminally sterilized at 100 ºC, it would not tolerate 121 ºC.
2. There are situations where the product process may impact sterility assurance, e.g.:
   a. Sterile powder residue on edge of vials does not ensure gas tight closure
   b. Formulation with residue may impact sterile filtration

H2 Antagonist; H2 antagonists (Histamine Type-2 Receptor Antagonist) are used by clinicians in the treatment of acid-related gastrointestinal conditions.

Radicalic reaction; A radical substitution reaction is a reaction which occurs by a free radical mechanism and results in the substitution of one or more of the atoms or groups present in the substrate by different atoms or groups.

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Aseptic Processing?

Essential Elements

1. **Facility**
2. **Process**
3. **Equipment**
4. **Personnel**
5. **Control & Verification**
6. **Finish Product & Testing**
7. **Documentation**

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Design Space:

The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval. (ICH Q8)

https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-process-validation-finished-products-information-data-be-provided-regulatory-submissions_en.pdf

Sterility Assurance in Aseptic Processing

Sterility assurance in aseptic processing requires contributing elements such as;

- **Heating, ventilation, and air conditioning (HVAC) system**
- **Clean-room environment**
- **Material transfer**
- **Equipment**
- **Manufacturing process steps**
- **Sterilization processes and sterilizing filtration**

to be qualified and validated as applicable and for personnel to be trained and qualified.

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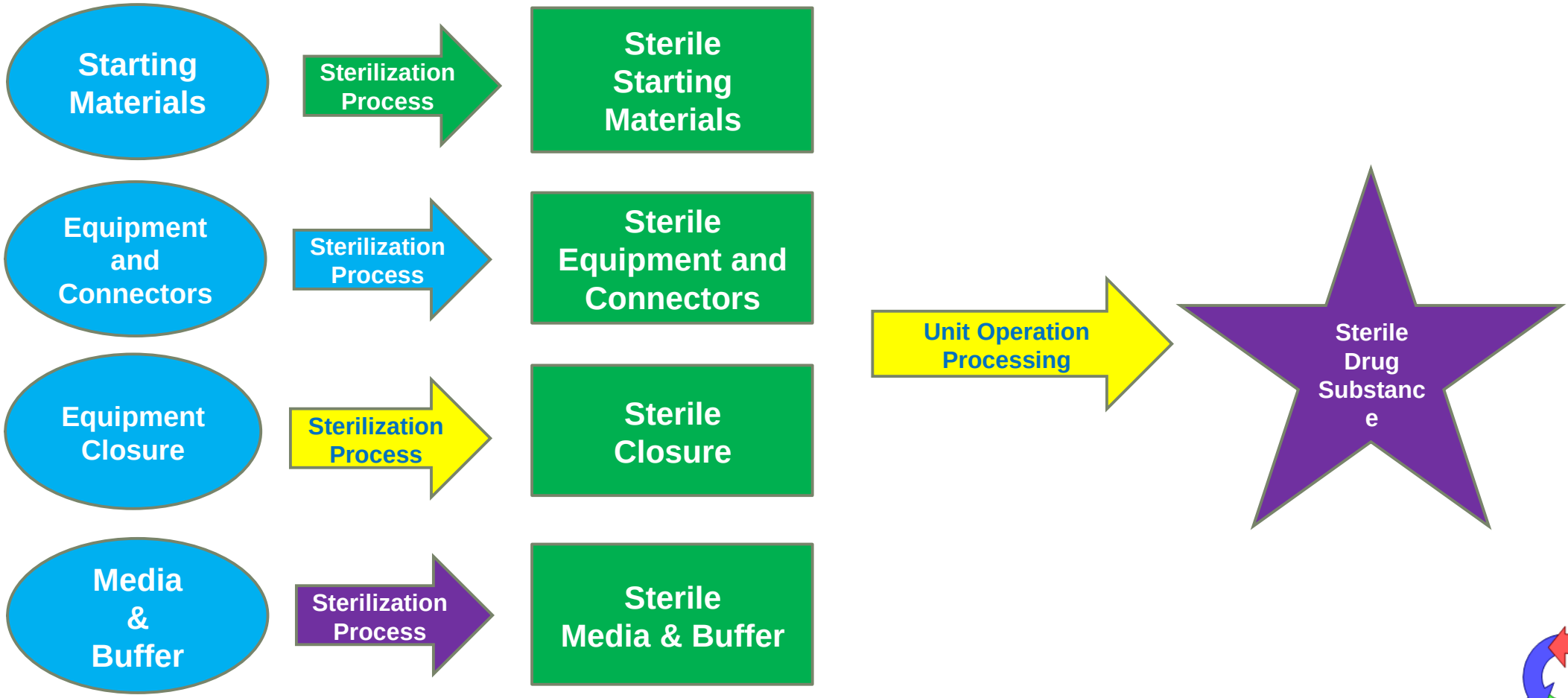
Multiple Sterilization processes

Drug Substance



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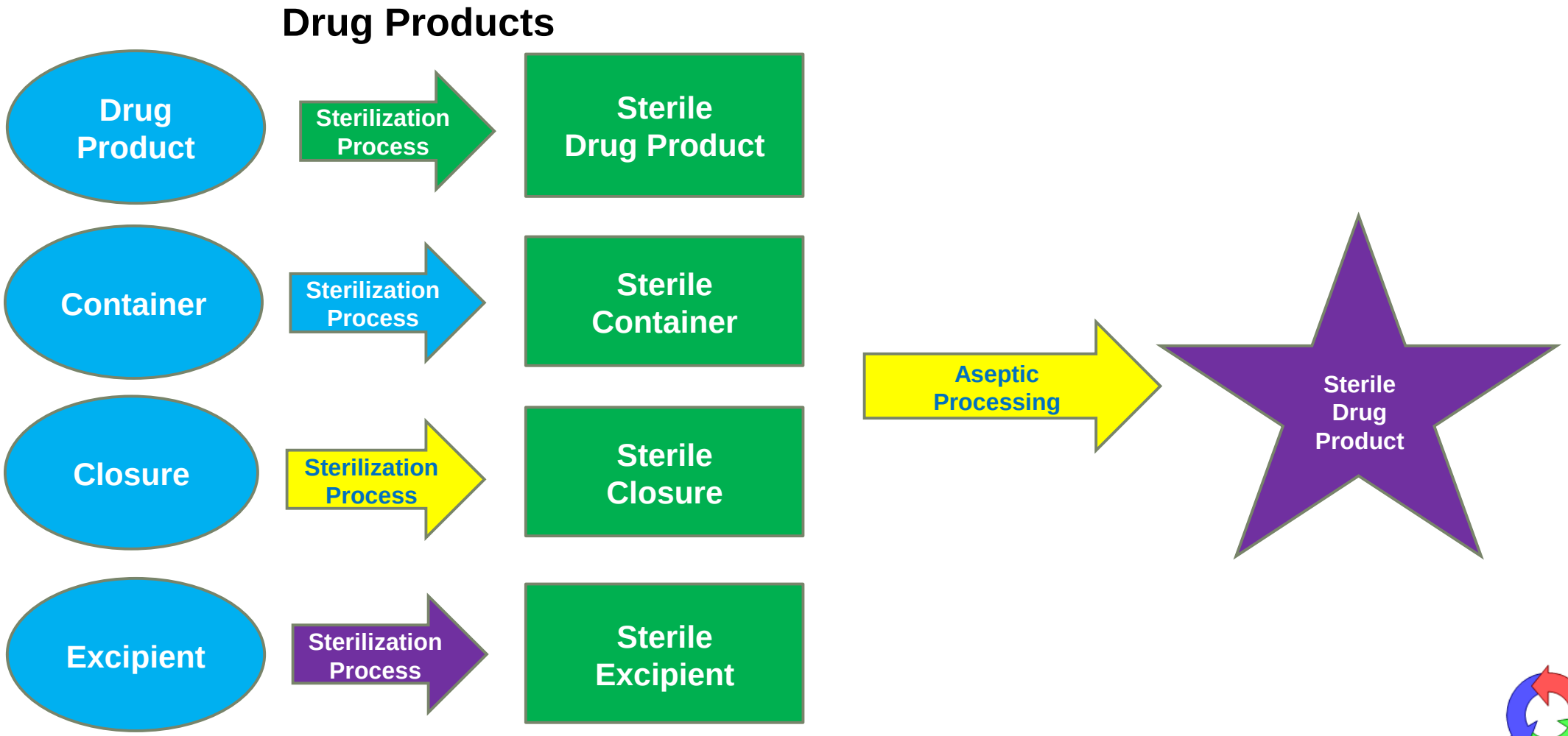
Multiple Sterilization Processes



What sterility assurance level should demonstrate?

A sterility assurance level of 10^{-6} or better should be demonstrated for a sterilization process. For more information, please also refer to the FDA guidance entitled Guideline for the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products.

Aseptic Process Simulation (APS)

Aseptic process simulation (APS) is a study that simulates the aseptic filling process by using growth media instead of the actual product. It is required by regulators* to demonstrate the sterility confidence and the aseptic capability of the process. It involves qualified or validated elements such as HVAC systems, cleanroom environment, material transfer, equipment, sterilization processes, and sterilizing filtration. It also requires operator training, skills, supervision, quality assurance, and microbiological monitoring. It is performed as closely to the actual production procedure as possible.
It consists of a minimum of three initial media simulations and repeat media simulations at six-monthly intervals.

Key Words:

- Aseptic process simulation
- Media fills
- Aseptic process qualification
- Aseptic process validation
- Risk assessment

*This guidance pertains to current good manufacturing practice (CGMP) regulations (21 CFR parts 210 and 211) when manufacturing sterile drug and biological products using aseptic processing. Although the focus of this guidance is on CGMPs in 21 CFR 210 and 211, supplementary requirements for biological products are in 21 CFR 600-680.
https://www.fda.gov/media/71026/download#:~:text=This%20guidance%20pertains%20to%20current%20good%20manufacturing%20practice,for%20biological%20products%20are%20in%2021%20CFR%20600-680.

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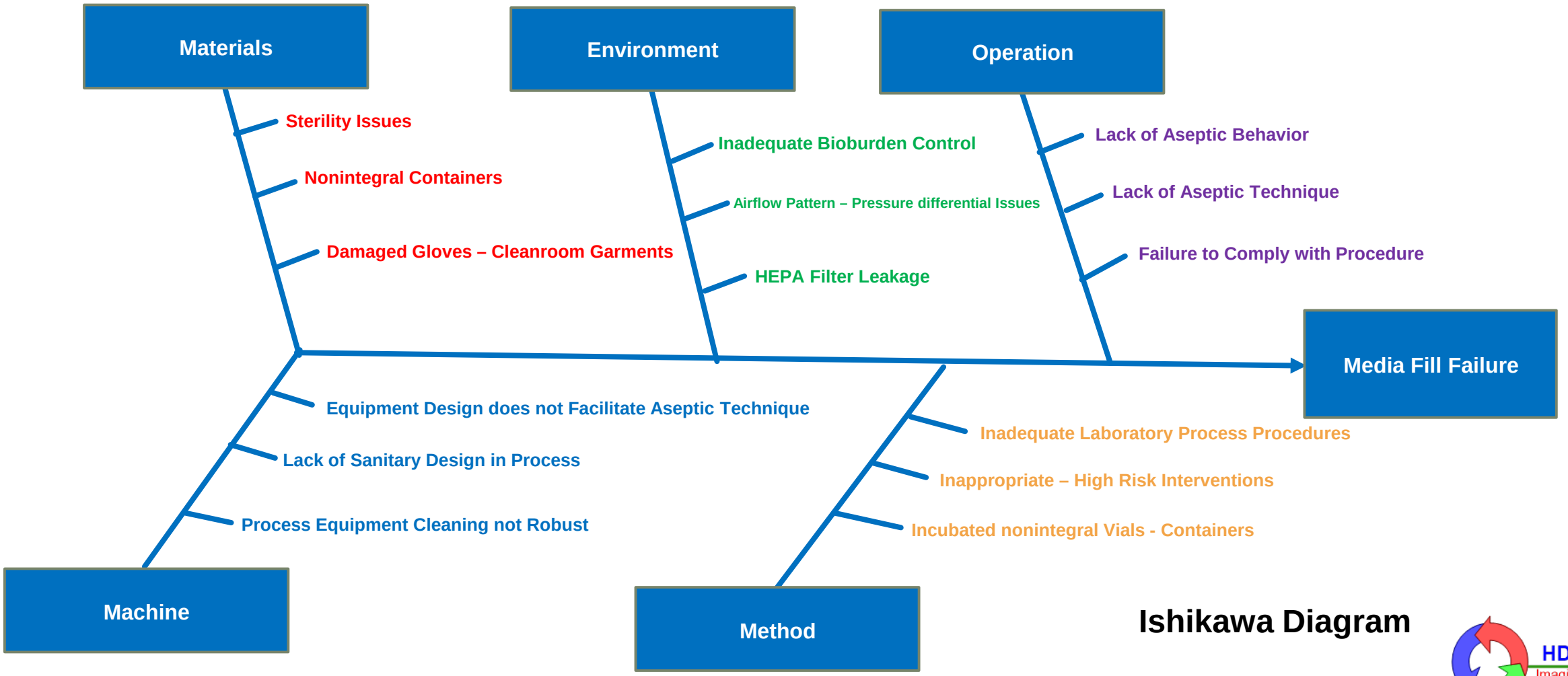
Media Fill Failure Root Cause Investigation and Identification



Ishikawa Diagram

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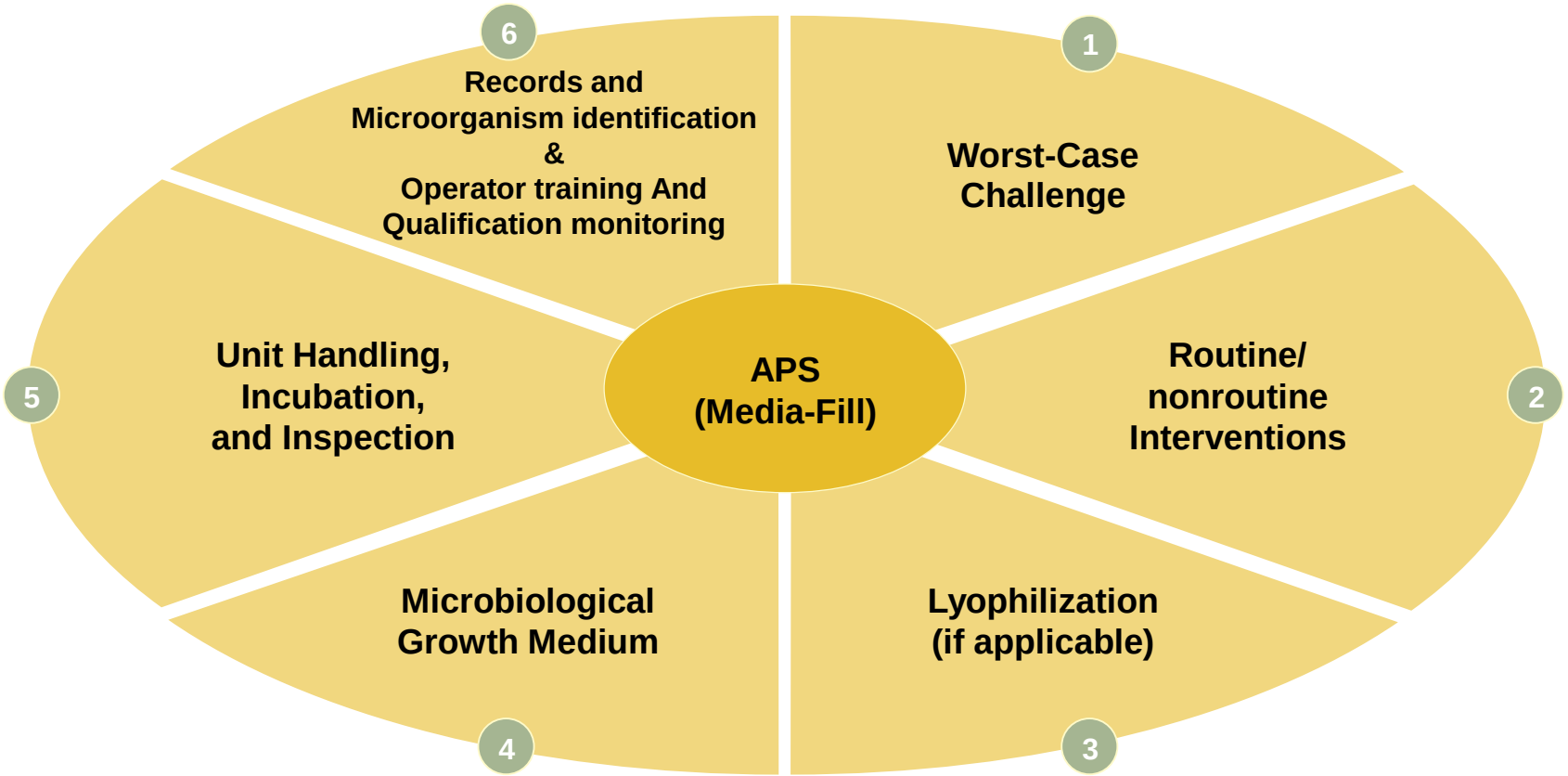
Points to Consider when Designing APS Study



Q & A

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