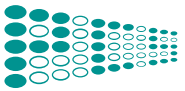
PHARMACEUTICAL
CONSULTANCY
SERVICES

ASEPTIC FACILITIES

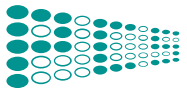
Jaap Koster

ZONING



HYGIENE ZONING … GENERAL PRINCIPLES

1. All manufacturing activities must take place in the appropriate class of environment (A, B, C, D or ISO 4.8, 5, 7, 8).
2. Different classes must be segregated from each other to reduce contamination (airlocks, changing rooms etc.)
3. Each class of environment has its own design criteria to meet the required level of performance.
4. Each class of environment has its own disciplines and practices to maintain the level of cleanliness.
5. Each class of environment has its own monitoring requirements to demonstrate that the desired performance is actually achieved.



ENVIRONMENTAL CLASSIFICATION IS NOT ONLY BASED ON AIR (HVAC) REQUIREMENTS, BUT REPRESENTS A HOLISTIC APPROACH, COVERING…

Design Features

Facility to be correctly designed for clean/sterile operations

Facility Monitoring

Facility monitored to demonstrate class requirements

HVAC Specifications

Air system to supply appropriate environmental conditions

Operations

Facility operated in compliance with current expectations

ENVIRONMENTAL CLASSIFICATION IS NOT ONLY BASED ON AIR (HVAC) REQUIREMENTS, BUT REPRESENTS A HOLISTIC APPROACH, COVERING…

Design Features

- Walls/floors/ceilings
- MALs & PALs
- Material/people flows
- Equipment
- Hatches
- Drains
- Gases

Monitoring

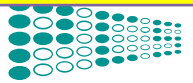
- Particles
- Viables
- Surfaces
- People
- Pressure/temperature/RH
- Requalification

HVAC Specifications

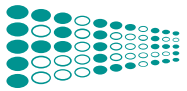
- Filters
- Pressures/RH/°C
- Air velocity
- Air changes
- Air flows

Operations

- Clothing
- Disinfectants
- Cleaning
- Material supply
- Training



REQUIREMENTS



CLASS A

Definition	Aseptic filling zone. Must be surrounded by Class B area.
Air flow	Laminar under the filter. Practically unidirectional at work station.
Air velocity	0.45 m/s ± 20% @ 15-30 cm below filter face (WHO-2011). NLT 0,36 m/s @ working level (WHO-2011)
Design features	No drains, sinks. Smooth impervious surfaces.
Non viable air count	3520 @ 0.5 µ and 20 @ 5 µ /m^3 in operation and at rest.
Particle monitoring frequency	Continuous
Clean up period	N/A
Viable air count	< 1 cfu/m3 in operation (and at rest if tested). <1 cfu/4 hr settle plate (90 mm).
Surface counts	<1 cfu/55 mm contact plate (no recommendations for swabs).
Gloves counts	< 1 cfu/5 fingers during normal operations.
Gowns counts	No recommendations. Company to define strategy and specification.
Gown type	Full, sterilised, low particles, specially laundered, goggles, gloves.
Disinfectants	Sterile prior to use.
Supply of material	Only appropriately wrapped, sterilised materials via adjacent Class B area.
Personnel qualification	At least annually with a media fill in addition to “normal” training requirements for on-the-job skills.

CLASS B

Definition	Aseptic area surrounding the Class A filling zone.
Air flow	Away from critical points. Turbulence minimised.
Air velocity	0.45 m/s ± 20% at filter face.
Design features	No drains, sinks. No differences to Class A.
Non viable air count	3520 @ 0.5 µ, 29 @ 5 µ /m^3 at rest and 352 000 @ 0.5 µ , 2900 @ 5 µ /m^3 in operation.
Particle monitoring frequency	Continuous recommended but not mandatory
Clean up period	15-20 minutes
Viable air count	10 cfu/m3 in operation (and at rest if tested) and/or <5 cfu/4 hr settle plate (90 mm).
Surface counts	5 cfu/55 mm contact plate.
Gloves counts	5 cfu/5 fingers during normal operations.
Gowns counts	Also called: Exit count No recommendations (company to define strategy and specifications).
Gown type	As for Class A.
Disinfectants	Sterile prior to use.
Supply of material	Through double ended sterilisers or multiple wrapping strategy, or "spray and pray" with validation data.
Personnel qualification	As for Class A.

CLASS C

Definition	High grade clean room.
Air flow	Away from critical activities. Some turbulence.
Air velocity	0.45 m/s ± 20% at filter face.
Design features	No sinks. Closed drains permitted. Water supply permitted.
Non viable air count	352,000 @ 0.5 µ and 2900 @ 5 µ /m^3 at rest. 3,520,000 @ 0.5 µ and 29,000 @ 5 µ in operation.
Particle monitoring frequency	No recommendation on frequency.
Clean up period	15-20 minutes.
Viable air count	100 cfu/m3 in operation (and at rest if tested) and/or 50 cfu/4 hr settle plate (90 mm).
Surface counts	25 cfu/55 mm contact plate.
Gloves counts	No recommendations.
Gowns counts	No recommendations.
Gown type	Single or two piece. Sterilisation not required. Low particulates.
Disinfectants	Regularly monitored.
Supply of material	Through MAL as needed. Sterilisation not required to protect environment but determined by process requirements.
Personnel qualification	Normal training requirements.

CLASS D

Definition	Clean area.
Air flow	No requirements.
Air velocity	No requirements.
Design features	Basic hygiene. All equipment permitted. Local LAF protection if needed.
Non viable air count	3,520,000 @ 0.5 µ and 29,000 @ 5 µ /m^3 at rest. No specification in operation.
Particle monitoring frequency	No requirements.
Clean up period	No requirements.
Viable air count	200 cfu /m3 in operation (and at rest if tested). 100 cfu/4 hr settle plate.
Surface counts	50 cfu/55 mm contact plate.
Gloves counts	No requirements.
Gowns counts	No requirements.
Gown type	Head/foot cover, general protective garment.
Disinfectants	Regularly monitored.
Supply of material	Through MAL as needed. Basic hygiene rules apply.
Personnel qualification	Normal training requirements.

EN/ISO 14644-1
CLASSIFICATION OF AIR CLEANLINESS

Selected airborne particulate cleanliness classes for clean rooms and clean zones.

Classification by formula
Illustrated by a table

ISO 4.8 =
Class A

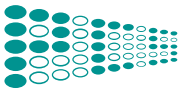
Classification numbers Numbers (N)	Maximum concentration limits (particles/m^3 of air) for particles equal to and larger than the considered sizes shown below					
	0.1µ m	0.2µ m	0.3µ m	0.5µ m	1µ m	5.0µ m
ISO 1	10	2				
ISO 2	100	24	10	4		
ISO 3	1 000	237	102	35	8	
ISO 4	10 000	2 370	1 020	352	83	
ISO 5	100 000	23 700	10 200	3 520	832	29
ISO 6	1 000 000	237 000	102 000	35 200	8 320	293
ISO 7				352 000	83 200	2 930
ISO 8				3 520 000	832 000	29 300
ISO 9				35 200 000	8 320 000	293 000

EXAMPLE OF OPERATIONS VS. CLASSIFICATION

Grade	***Examples of operations for terminally sterilised products (see par 17-EU, 4.7.9 WHO)***
A	Filling of products, when unusually at risk
C	Preparation of solutions, when unusually at risk. Filling of products.
D	Preparation of solutions, when unusually at risk. Filling of products.
Grade	***Examples of operations for aseptic preparations***
A	Aseptic preparation and filling.
C	Preparation of solutions to be filtered.
D	Handling of components after washing

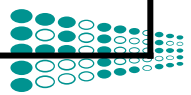
*) *See for further reading: WHO, November 2012,* ***Environmental Monitoring of Clean Rooms in Vaccine Manufacturing Facilities***

DESIGN CRITERIA



HVAC DESIGN CRITERIA

Issue	Notes
Constant volume or pressure	No preference if adequately validated
Air inlet/outlet strategy	No preference if adequately validated
Prefiltration configuration	No preference if adequately validated
Humidification	Preferably steam injection – 55% ± 10%
Temperature	23° C ± 5%
Prefilters HEPA filters	EN779 EN1822, H13 (D/C) H14 (B/A)
Position of HEPAs	Class A-C: Terminal, Class D: central
Air change rates	No specification – guidance values only
Air pressure differentials	• Minimum 10-15 Pa Guidance value • Practically: 12.5 Pa ± 2.5 Pa • Required at class interfaces only (“interclass” ΔP) • “Intraclass” pressure differentials not specified • Continuous monitoring at class interfaces by either manual or automatic means (minimum daily) • Positive pressures for all areas <BL3 and below (no containment) • Negative pressures for all areas BL3 and above (containment) • Negative “sink” concept for all other applications.



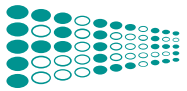
HVAC DESIGN CRITERIA

Issue	Notes
Air velocity	• 0.45 m/sec (± 20%) at the filter face (design specification). • 0.45 ± 20% at working height for guidance only. If laminarity is demonstrated at higher or lower velocities this can be accepted. However, velocities should be homogeneous. • Velocities checked twice per year for Class A/B. Annually for Class C.
Air flow patterns	• Smoke studies in Class A/B areas only. Should show even flow of air in predicted direction. Workstation should show "practically" laminar flow. • Studies repeated only after breakdown/change.
Zoning concept issues	• Class D → Class B: 3 chamber changing area (PAL) 2 chamber airlock (MAL) • Class C → Class B: 2 chamber PAL 1 chamber MAL • Unclassified → Class B: Not permitted (2 changing rooms required)
Air clean up rates	• After challenge, class should be re-established in 15 minutes • Test in Class A-C only • Test performed at IQ, OQ stage only and after breakdown or change.

CRITICAL PERFORMANCE PARAMETERS

These are the key items about cleanrooms in the GMPs:

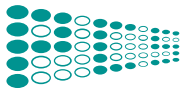
- Particle classification
- Biocontamination control (if required)
- HEPA filter selection
- Filter testing
- Room pressurization
- Uni-directional airflow (UDAF) system velocity
- Dynamic Passboxes
- Performance monitoring
- Clean room validation



ROOM DESIGN CRITERIA

Principle of an airlock

- Physical separation between the areas
- Pressure differential
  - 10 - 15 Pa
  - Continuous monitoring
  - Be aware of special processes!!
- Doors must not be open simultaneously
- Sufficient air changes for the operation



ROOM DESIGN CRITERIA

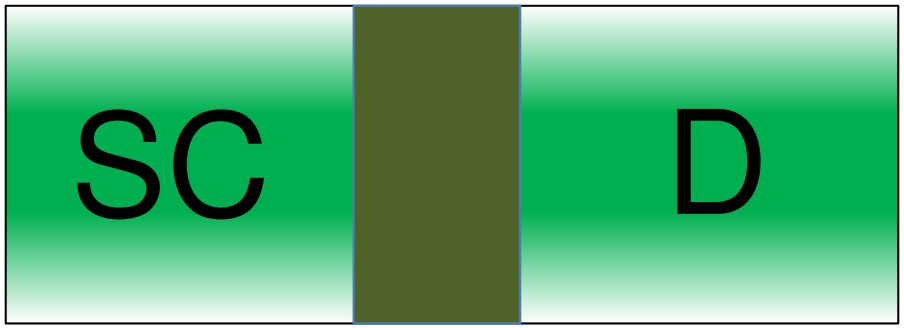
Principle of an airlock

- Cleanroom clothing – changing principles for each step
- Incoming and outgoing materials flow
- Incoming and outgoing people flow
  - Changing principle for cleanroom clothing
- Disinfection for each step
- Final step at rest equivalent to the production area

AIRLOCK CRITERIA

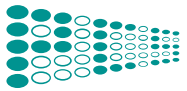
EU-51 (Annex 1) comparable with WHO TRS961 (11.7)

- **Changing rooms: airlocks providing physical separation.**
- **Flushed with sufficient air**
- **…..The final stage of the changing room should be in at-rest state, be the same grade as the area into which it leads….**
- **….In general hand-washing facilities should be provided only in the first stage of the changing room…..**

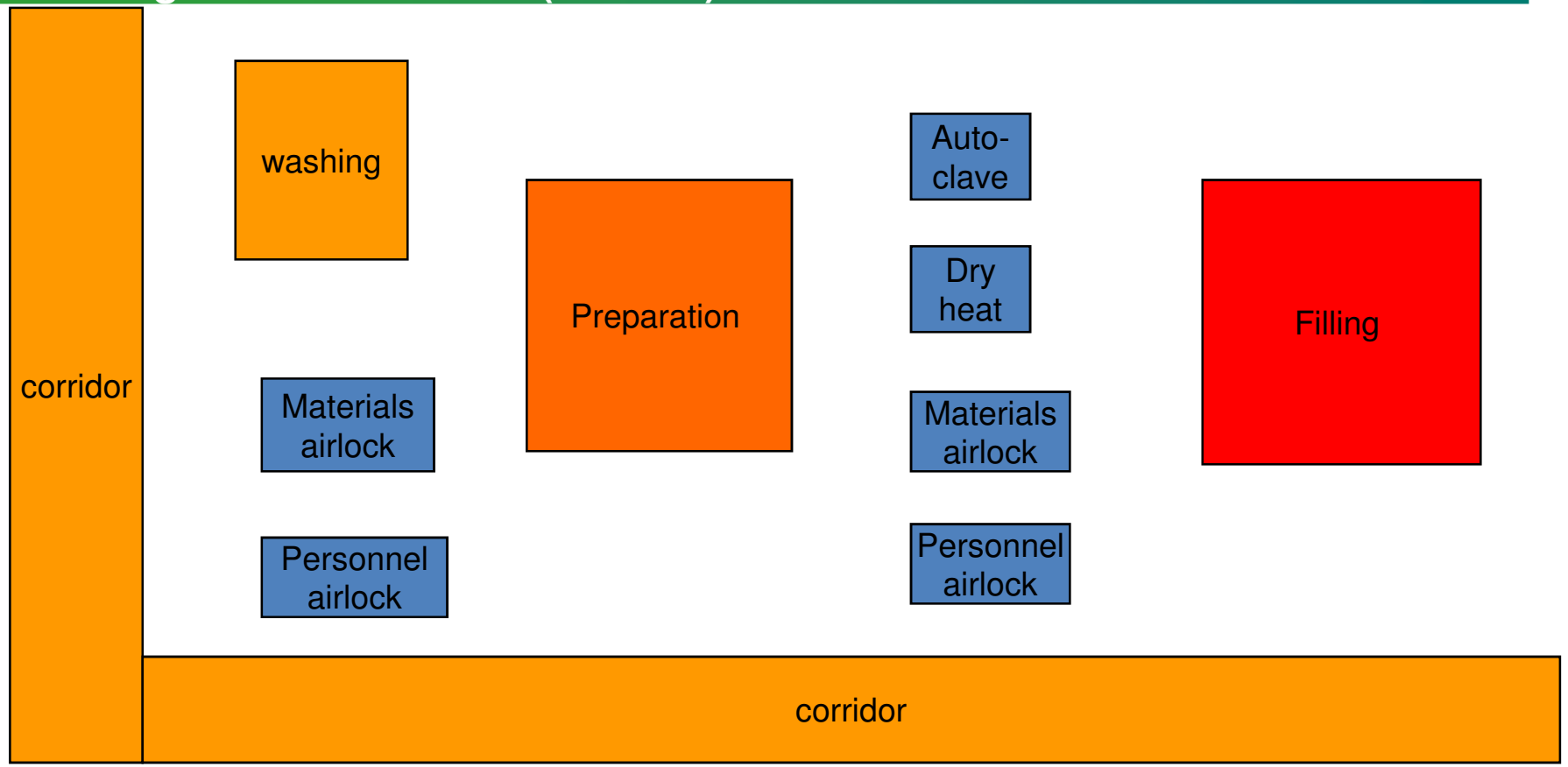


SC = Social Clean (unclassified but clean)

OPERATIONAL ASPECTS

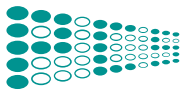


ROOM DESIGN CRITERIA
Design of a clean room (Class A)



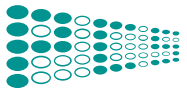
ROOM DESIGN CRITERIA
Design of a clean room (flows, Class A)

- Process Flow Diagram and/or Manufacturing Diagram to be prepared.
- Mapping of:
  - Personnel Flow
  - Raw Material Flow
  - Flow of utensils/devices
  - Finished Product Flow
  - Waste Flow
  - Cleaning Utensils
  - ……
- Checks/Reviews on Cross-flows and



OPERATIONAL ASPECTS

1. Operator gowning
2. Operator training / qualification
3. Cleaning and sanitisation practices
4. Material movement across clean zones
5. Operator behaviour / attitude



GOWNING REQUIREMENTS

EU-43 (Annex 1) comparable with WHO TRS961 (10.8)

- **Grade D:** Hair and, where relevant, beard should be covered. A general protective suit and appropriate shoes or overshoes should be worn. Appropriate measures should be taken to avoid any contamination coming from outside the clean area.

- **Grade C:** Hair and where relevant beard and moustache should be covered. A single or two-piece trouser suit, gathered at the wrists and with high neck and appropriate shoes or overshoes should be worn. They should shed virtually no fibres or particulate matter.

- **Grade A/B:** Headgear should totally enclose hair and, where relevant, beard and moustache; it should be tucked into the neck of the suit; a face mask should be worn to prevent the shedding of droplets. Appropriate sterilised, non-powdered rubber or plastic gloves and sterilised or disinfected footwear should be worn. Trouser-legs should be tucked inside the footwear and garment sleeves into the gloves. The protective clothing should shed virtually no fibres or particulate matter and retain particles shed by the body.

GOWNING REQUIREMENTS

EU-44 (Annex 1) comparable with WHO TRS961 (10.6)

- **Outdoor clothing should not be brought into changing room leading to Grade B AND Grade C rooms. For every worker in a Grade A/B area, clean sterile (sterilzed or adequately sanitized) protective garments should be provided a each work station. Gloves should be regularly disinfected during operations. Masks and gloves should be changed at least every working session. Operations working in Grade A and B areas should wear sanitized goggles.**

MINIMUM PERSONNEL

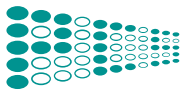
EU-36 (Annex 1) comparable with WHO TRS961 (10.1)

- **Only the minimum number of personnel required should be present in clean areas; this is particularly important during aseptic processes. As far as possible, inspections and controls should be conducted from outside such areas.**

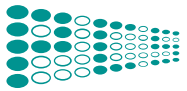
MATERIAL MOVEMENT ACROSS CLEAN ZONES

- Double ended sterilisers
- Multiple wrapping
- Spray and pray
- Active airlocks
- H_2O_2 airlocks
- UV lights

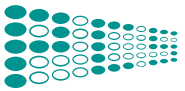
ALL DESIGNED TO ENSURE THAT CONTAMINATION IS NOT TAKEN INTO CLEAN AREAS



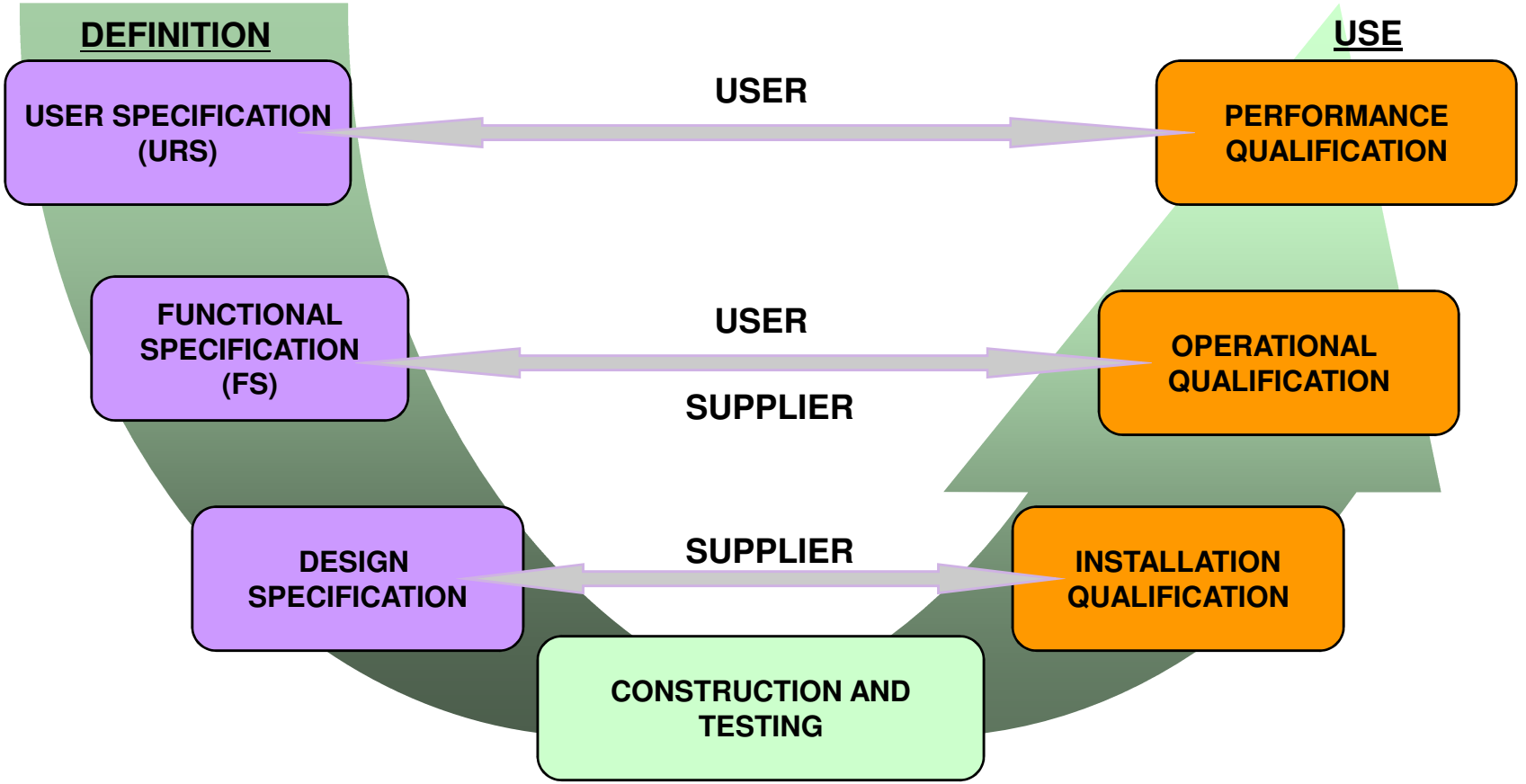
QUALIFICATION



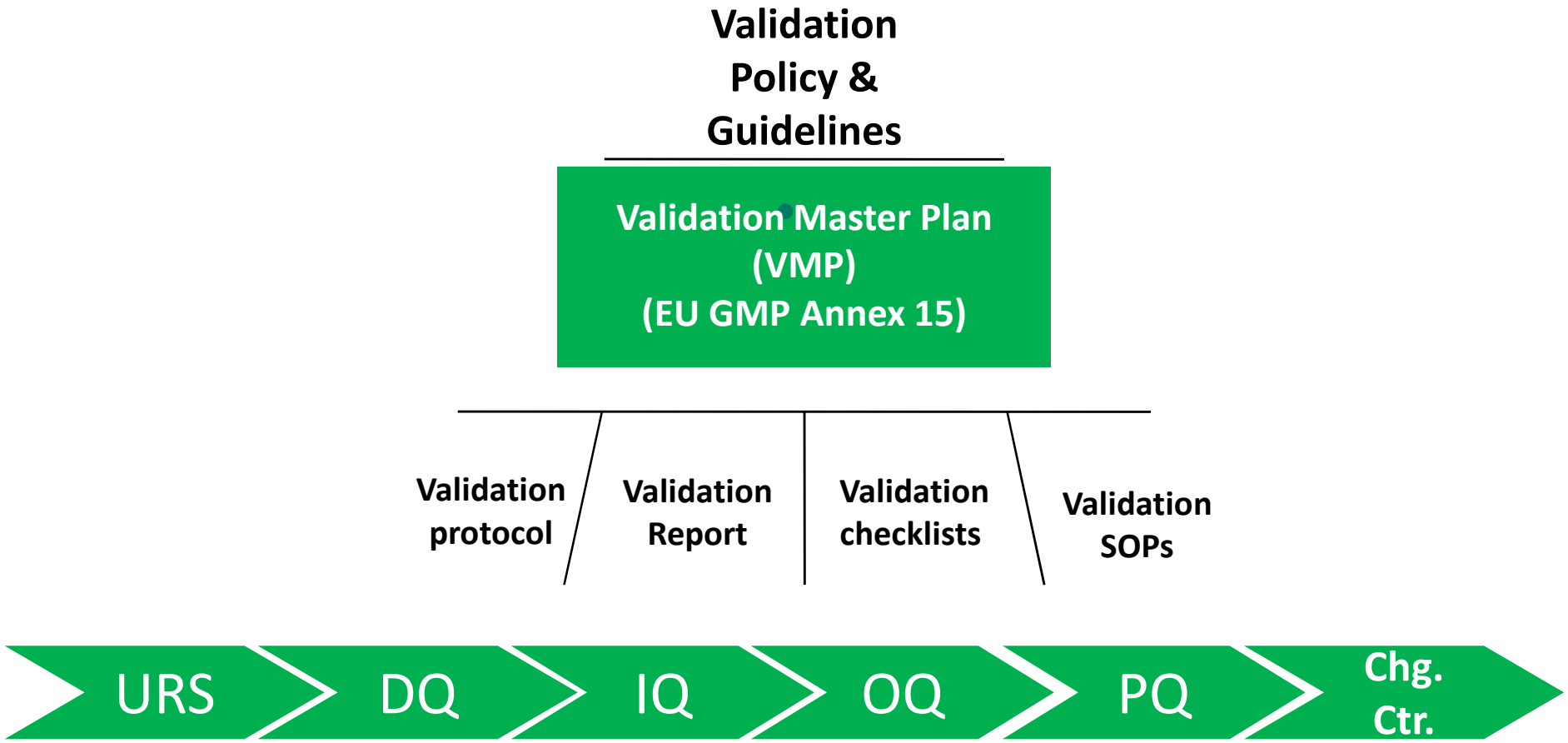
MODELS



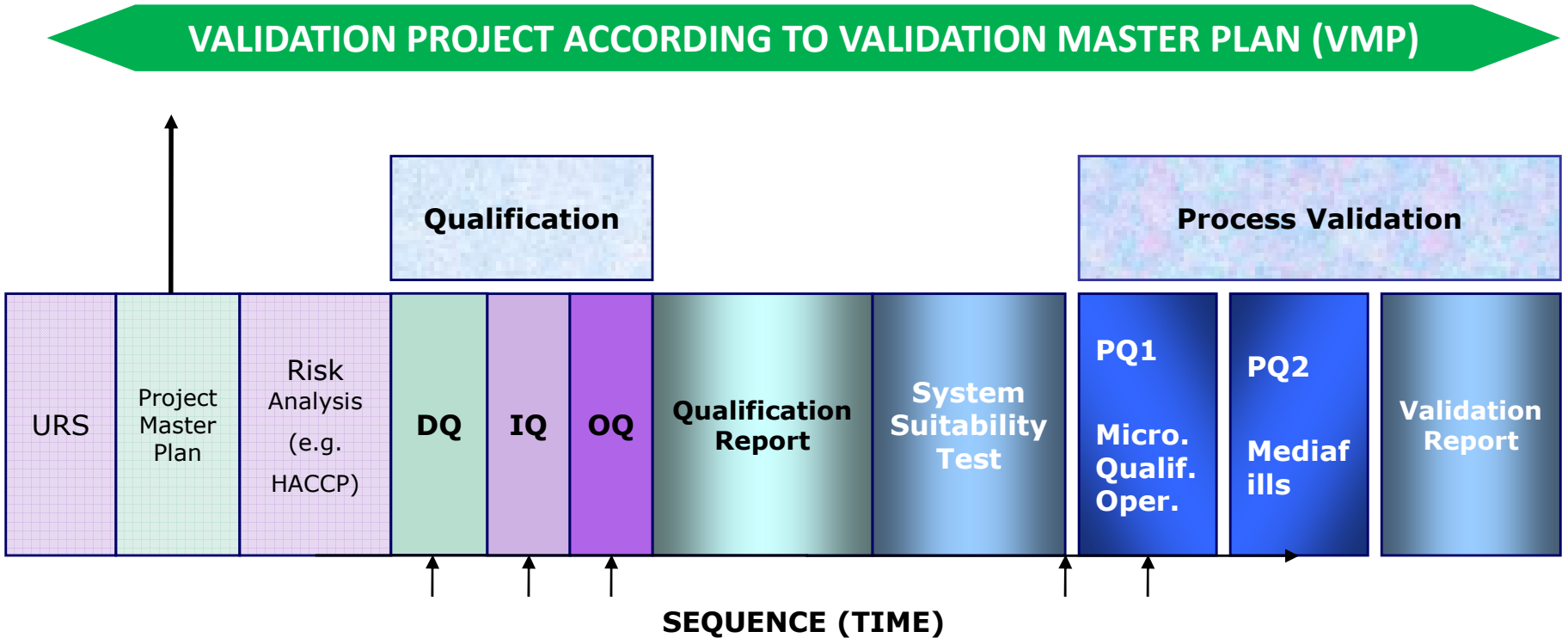
THE "V MODEL": A THEORATICAL FRAMEWORK



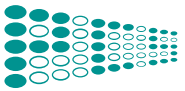
VALIDATION DOCUMENTATION



SEQUENCE OF QUALIFICATION STEPS AND VALIDATION ACTIVITIES



DESIGN

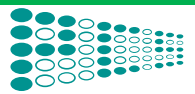


USER REQUIREMENT SPECIFICATION

A URS document clearly defines what the user(s) of a clean room expect :

- ✓ Aseptic/terminal sterilisation
- ✓ Bulk/finished products
- ✓ EU/US compliance
- ✓ Product types
- ✓ Production volume and mix
- ✓ Production Processes
- ✓ Sterilisation processes
- ✓ Number of operators
- ✓ Single/multiple shifts
- ✓ Monitoring requirements
- ✓ Automation requirements
- ✓ Safety/environmental issues
- ✓ Waste management
- ✓ Logistical issues
- ✓ Multipurpose/dedicated

ALL THE ABOVE WILL IMPACT ON DESIGN SPECIFICATIONS



FUNCTIONAL SPECIFICATIONS

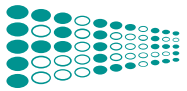
The Functional Specifications are a technical interpretation of the URS. For clean rooms, they should typically include :

- ✓ Room conditions (temperature, humidity, light, noise)
- ✓ Room classification (A,B,C,D and/or 100/10.000/100.000 or ISO)
- ✓ Room pressurisation
- ✓ Recirculation versus fresh air
- ✓ Filter specification
- ✓ Layouts
- ✓ Airlocks
- ✓ Changing rooms
- ✓ Construction details
- ✓ Walls, floors, ceilings
- ✓ Drains
- ✓ Garment types
- ✓ Monitoring :

SOME TYPICAL OFFICIAL FUNCTIONAL SPECIFICATIONS APPLICABLE TO CLEAN ROOMS

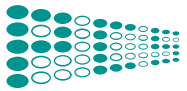
- ISO 13408 — Chapter 5: Facility Design Features
  Chapter 6: Aseptic Processing Area (APA)
  Chapter 7: Support Areas outside APA
- BS 5295 — Environmental cleanliness in enclosed spaces, Parts 1-4
- ISO 14644 — Clean rooms and associated controlled environments

- US Pharmacopoeial Chapter <1116> — Microbiological Evaluation of Clean Rooms
- US FDA — Guideline on aseptic Processing
- EU Annex 1 — Manufacture of Sterile Products
- WHO TRS 961 — GMP for Sterile Pharmaceutical Products



DESIGN QUALIFICATION

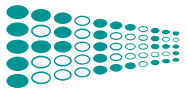
- A qualification milestone in which the URS and the Functional Specifications are formally approved.
- Change Control applies after DQ to manage changing requirements or functional specifications as the project proceeds
- DQ forms the basis for all following qualifications (IQ/OQ) and validation (PQ) requirements
- DQ often regarded as the first official GMP document (in conjunction with URS).



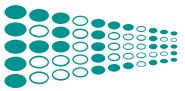
DESIGN SPECIFICATIONS

- Often referred to as Detailed Engineering
- Converts the Functional Specifications into specific requirements for each component
- Calculates air requirements
- Defines materials of construction
- Provides technical specifications on all components

DESIGN QUALIFICATION ALSO POSSIBLE AFTER THIS STAGE



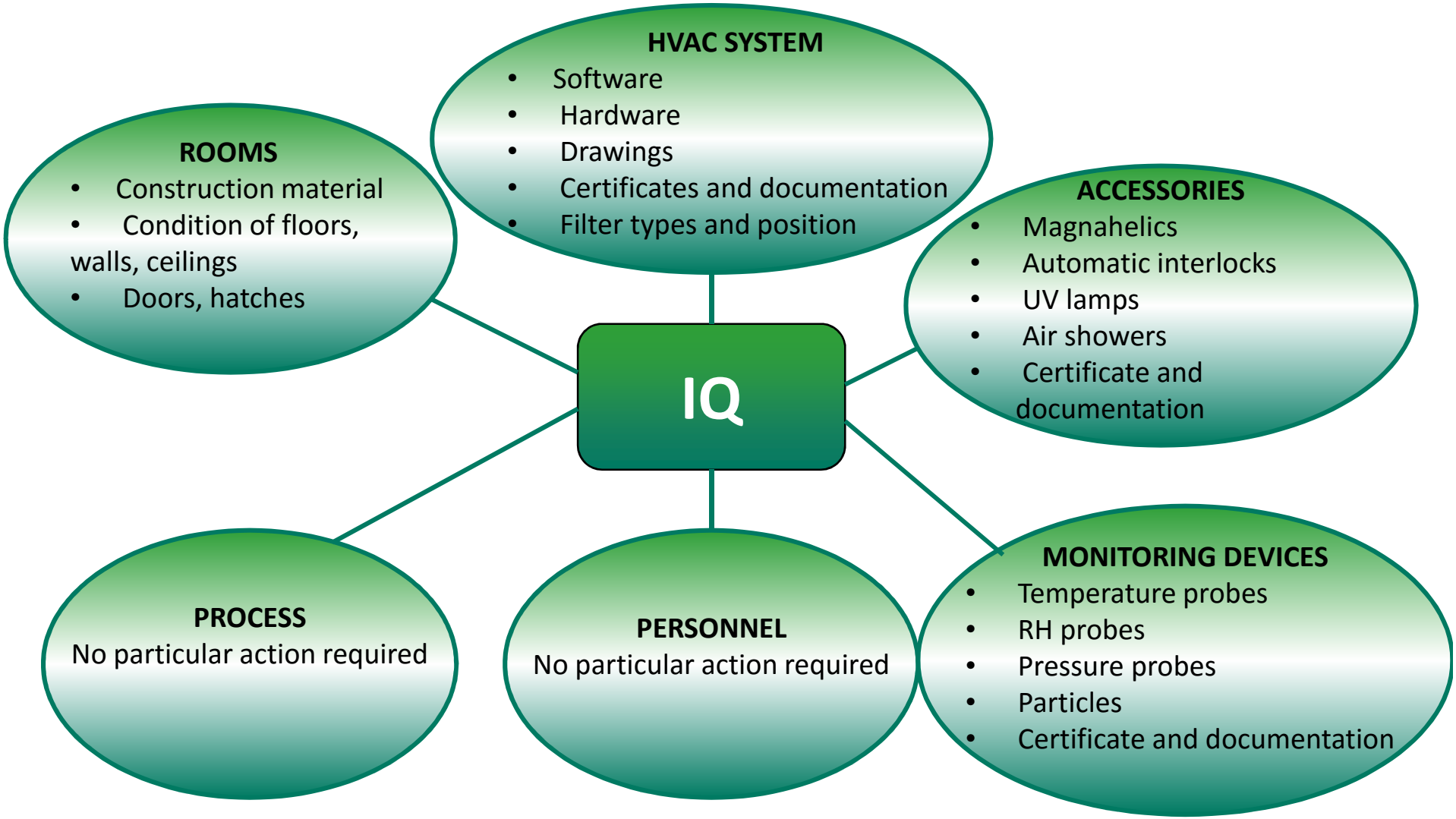
IQ/OQ/PQ

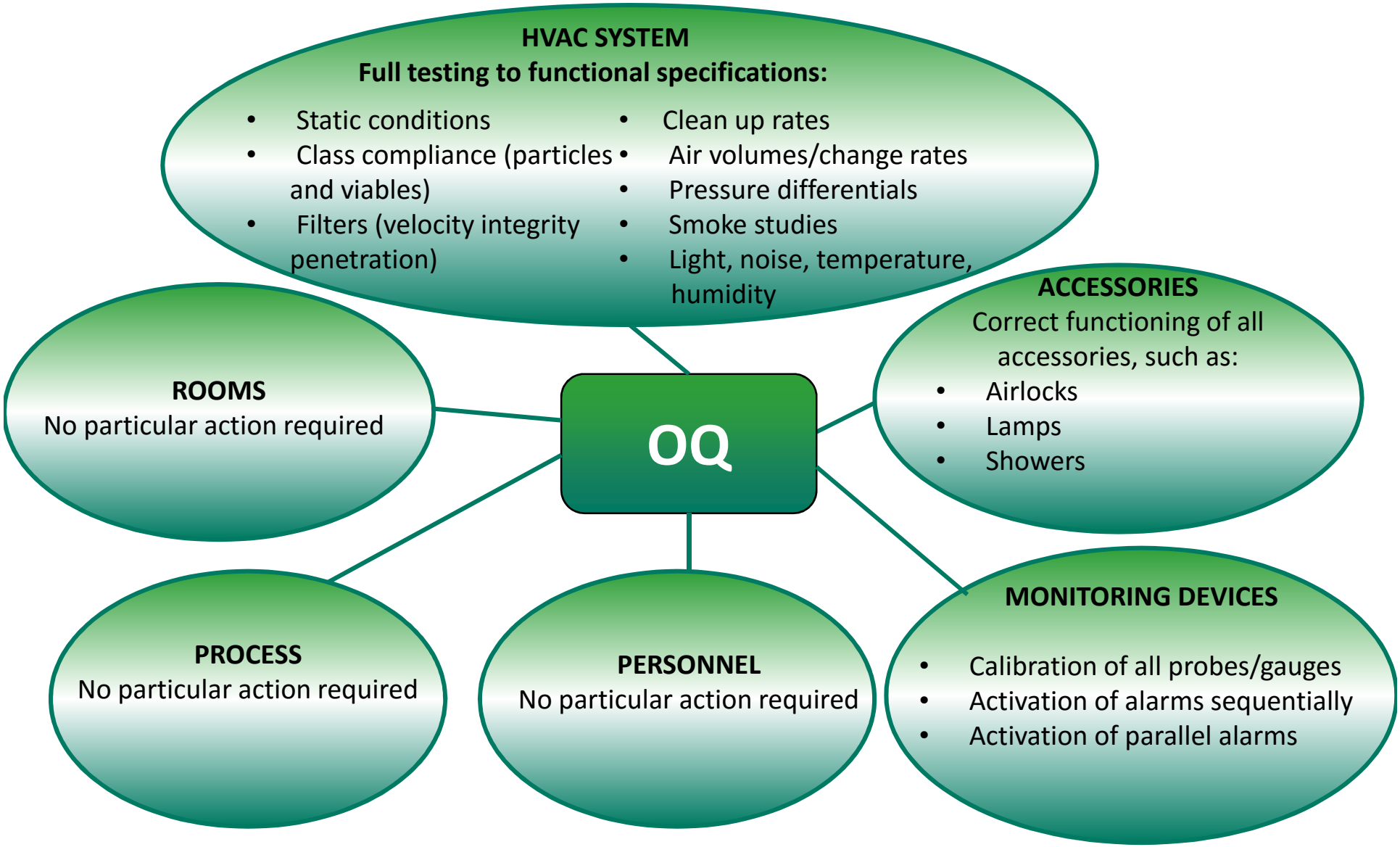


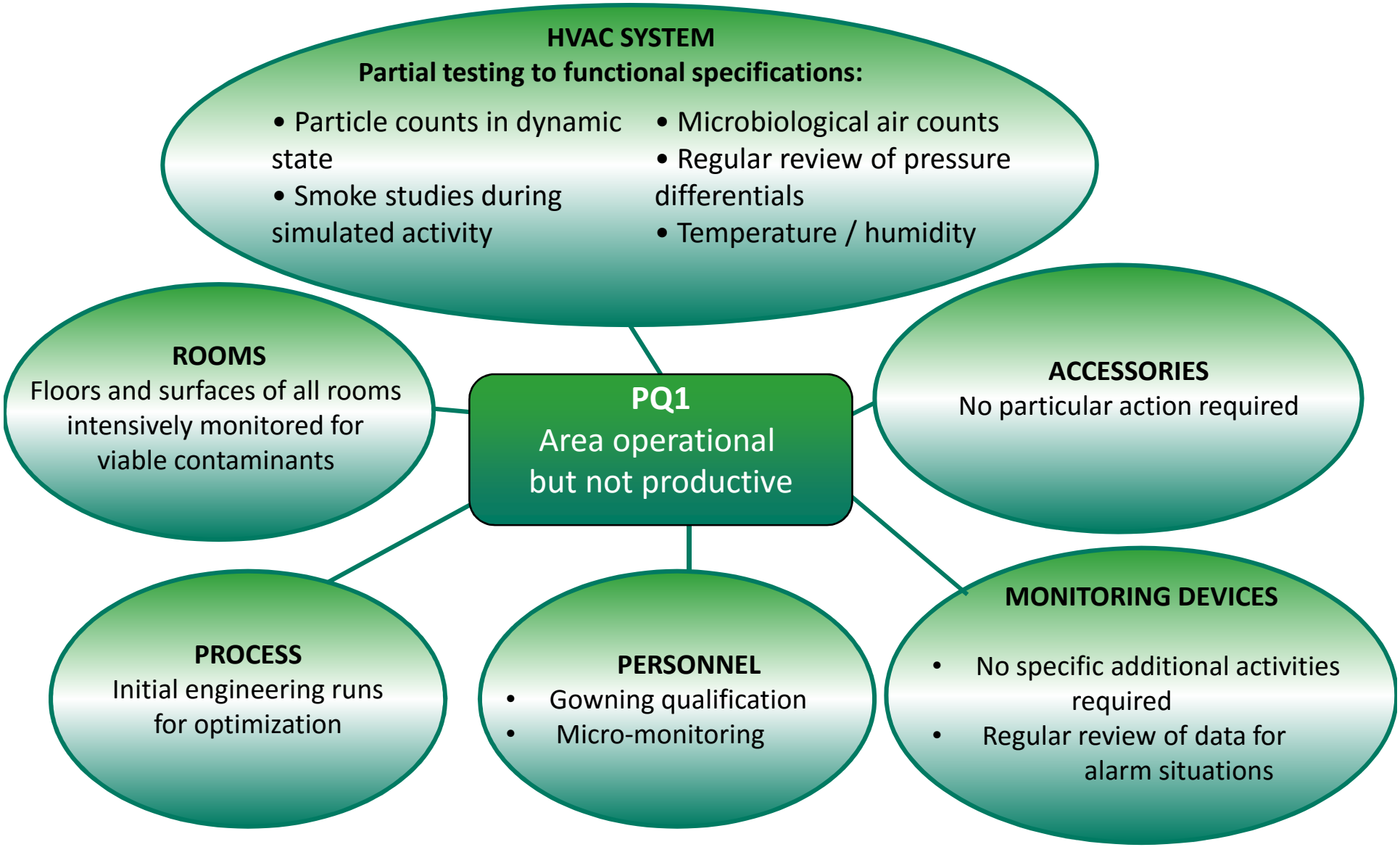
FAT/SAT

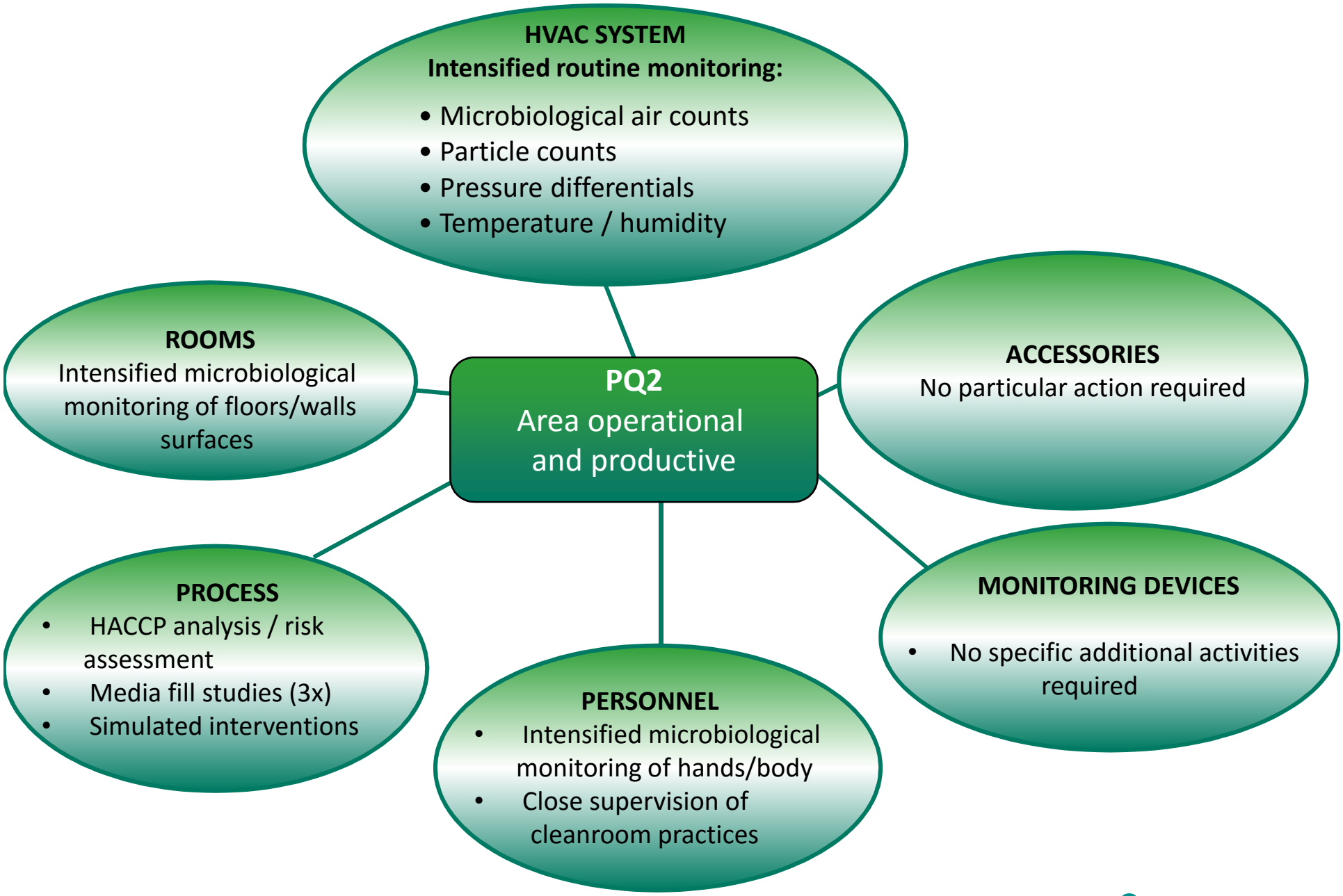
- FAT: Factory Acceptance test (at site of vendor)
- SAT: Site Acceptance test (at site of vaccine-facility)

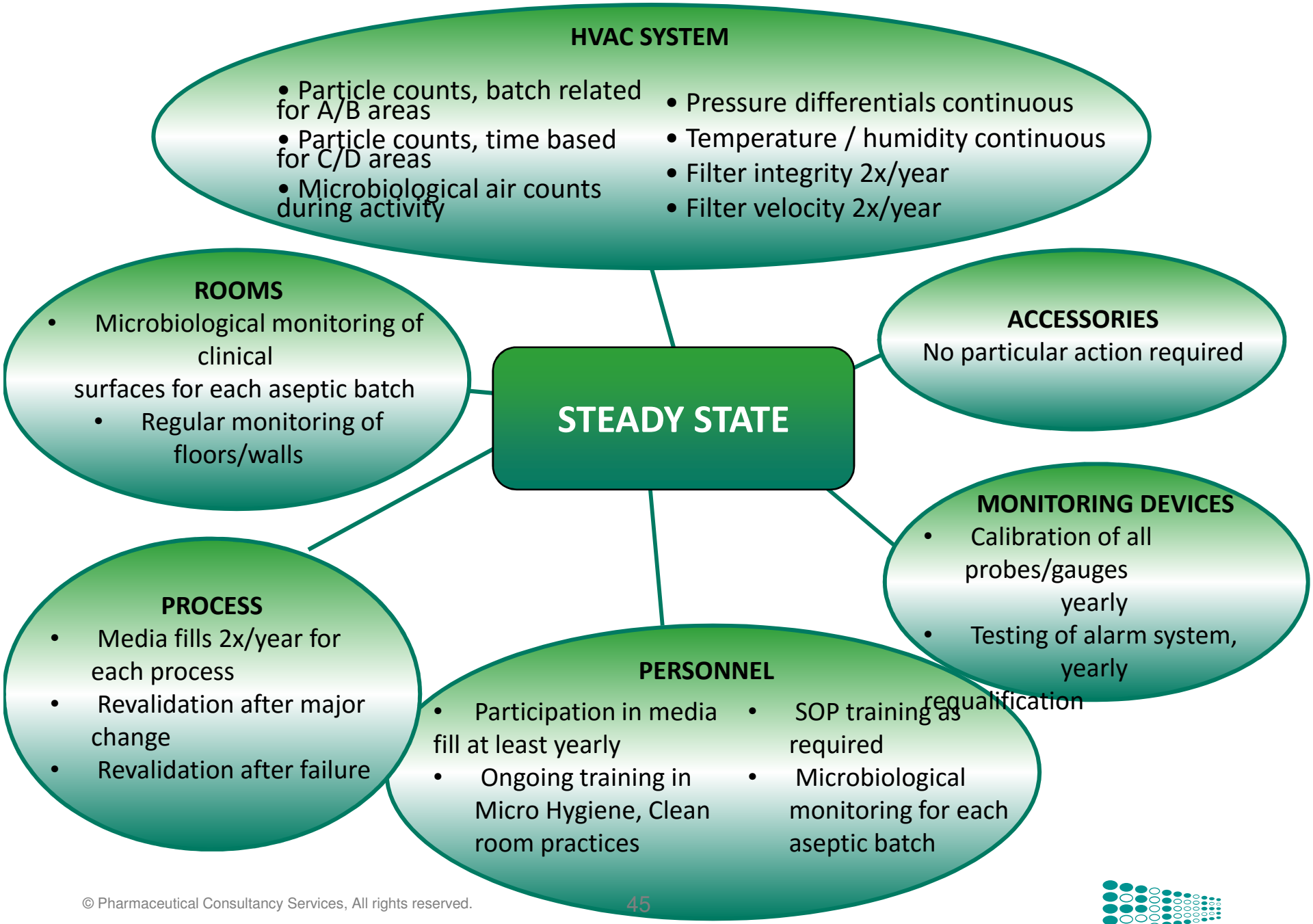
- Newly introduced d in Annex 15 EU as precursor for IQ/OQ
- In general, if qualified, information in FAT/SAT maybe used for IQ/OQ



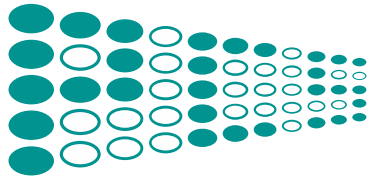








THANK YOU FOR YOUR ATTENTION



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