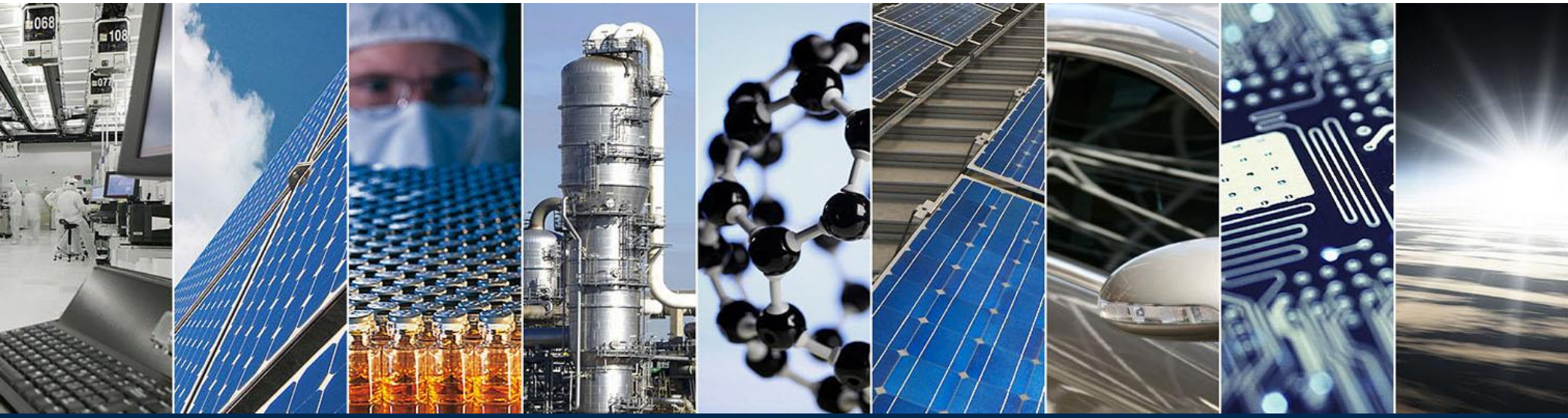
dcvmn
Developing Countries Vaccine Manufacturers Network

M+W GROUP



HVAC System at the Core of the GMP Vaccine Facility

Marcus Beushausen, TV Subrahmanyam
DCVMN – 15th Annual General Meeting
New Delhi, India 30.10.2014

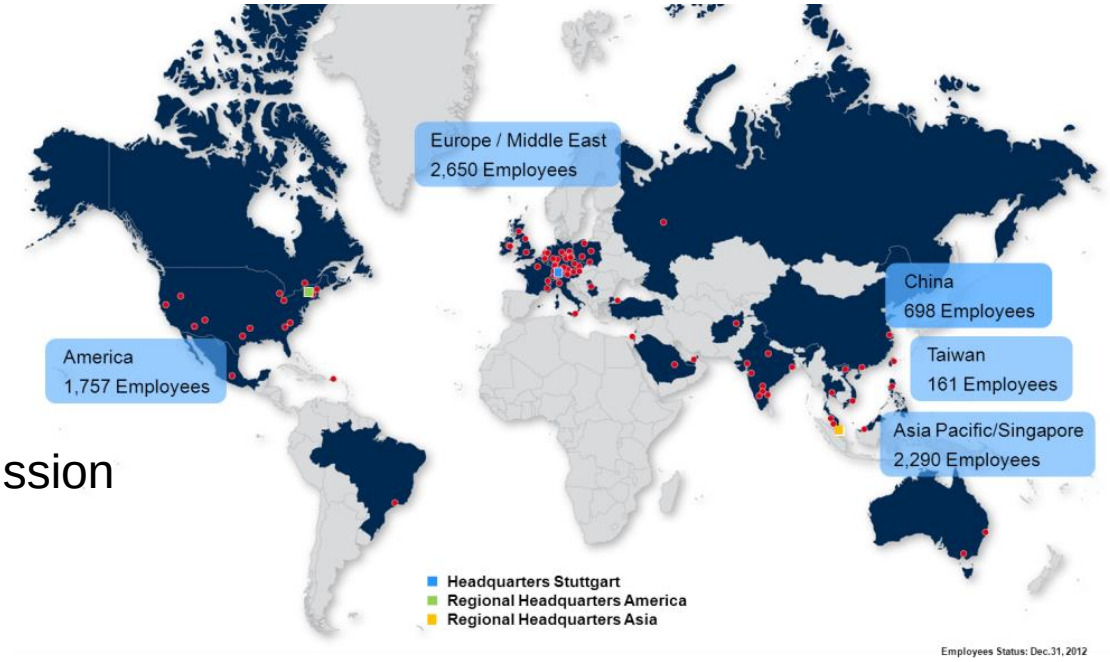
Contents

- Introduction of M+W Group
- Importance of HVAC in GMP Vaccine facility
- Design process of HVAC System
- Installation aspects of HVAC system
- Control Systems and other supporting functions to HVAC
- Commissioning and Validation of HVAC System
- Q & A

M+W Group at a Glance

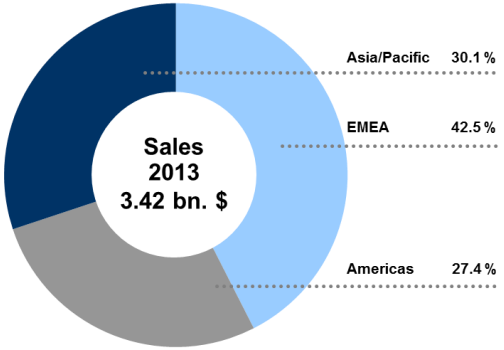
The leading global engineering and project company ….

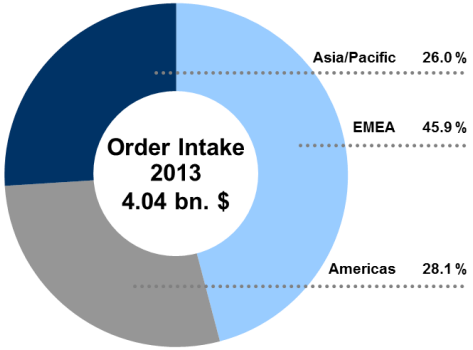
- more than 7,000 employees worldwide
- world class EHS records and awards
- technical expertise in process



…. for high-tech production facilities, mission critical infrastructure and energy & environmental solutions ….

- more than 200 Semiconductor Fabs realized
- LS experience of more than 20 years & 200 facilities
- largest Nanotechnology Research Center built
- over 300 successfully completed turnkey projects





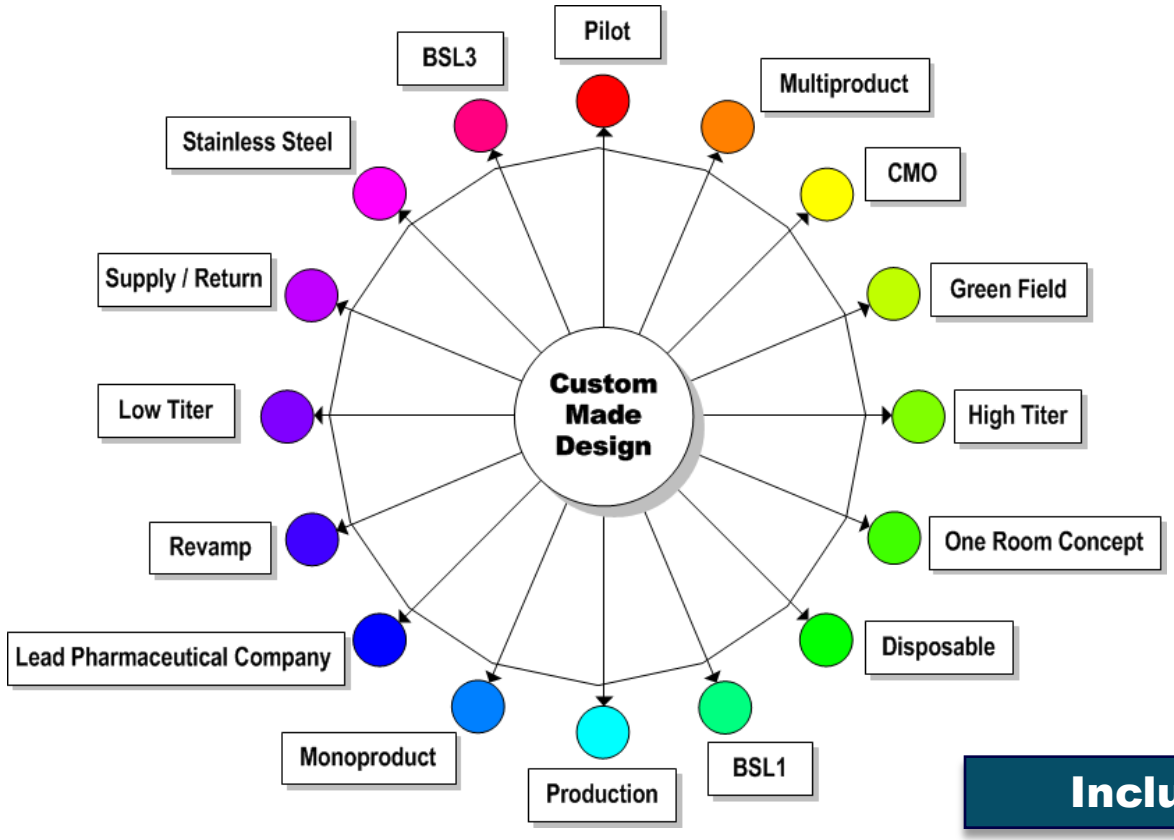
…. committed to deliver customer value

Life Science's Experience in India

M+W GROUP

M+W Group at a Glance for Biopharmaceuticals

- From 1995 designing and constructing bio-pharmaceutical facilities



Including Vaccines

for the Manufacturing of the Bio Active Pharmaceutical Ingredient

M+W World of Life Science
Highly Recognized in the Industry

M+W GROUP

ISPE Facility Of the Year Awards (FOYA)

M+W active part of facility innovation
for world recognized biotech & pharma facilities

FOYA	Company	Project	Class	Country
2014	Patheon Pharma Services (formerly DSM Biologics)	Facility of the Future	Biotech	Australia
2013	F. Hoffmann - La Roche Ltd.	TR&D - Building 97	Pharma	Switzerland
2012	Roche Diagnostics GmbH	TP Expand	Biotech	Germany
2011	F. Hoffmann - La Roche Ltd.	MyDose	Pharma	Switzerland
2011	Novartis vaccines and Diagnostics GmbH	MARS	Biotech	Germany
2008	F. Hoffmann - La Roche AG	Biologics IV	Biotech	Germany
2007	Shanghai Roche Pharmaceuticals Limited	SHIP	Pharma	China

BPA BioPharmaceuticals Australia

Patheon Performance the World Over

DSM BRIGHT SCIENCE. BRIGHTER LIVING.

NOVARTIS

Roche

Vaccine Facilities – One does not fit all
M+W Selected Project References for Vaccines

M+W GROUP

Traditional Egg Based

- 60, 150 TEggs / day
- BSL1,2 or 2+
- Influenza Vaccine

GlaxoSmithKline

GREEN CROSS

Confidential Client

Traditional Specific Processes

- Single processes: cell culture, microbial, etc.
- BSL1,2 or 2+
- Rabies, Tetanus, etc.

NOVARTIS

MERIAL

SHANTHA BIOTECHNICS
Part of the sanofi-aventis Group

CHIRON BIOCINE

Imunološki zavod
Institute of Immunology

New Vaccines Platforms

- "modern biotech"
- No BSL
- VLP, DNA / RNA, etc.

Abbott
A Promise for Life

Rhein Biotech

UreVac

immatics

Confidential Client

Special Applications

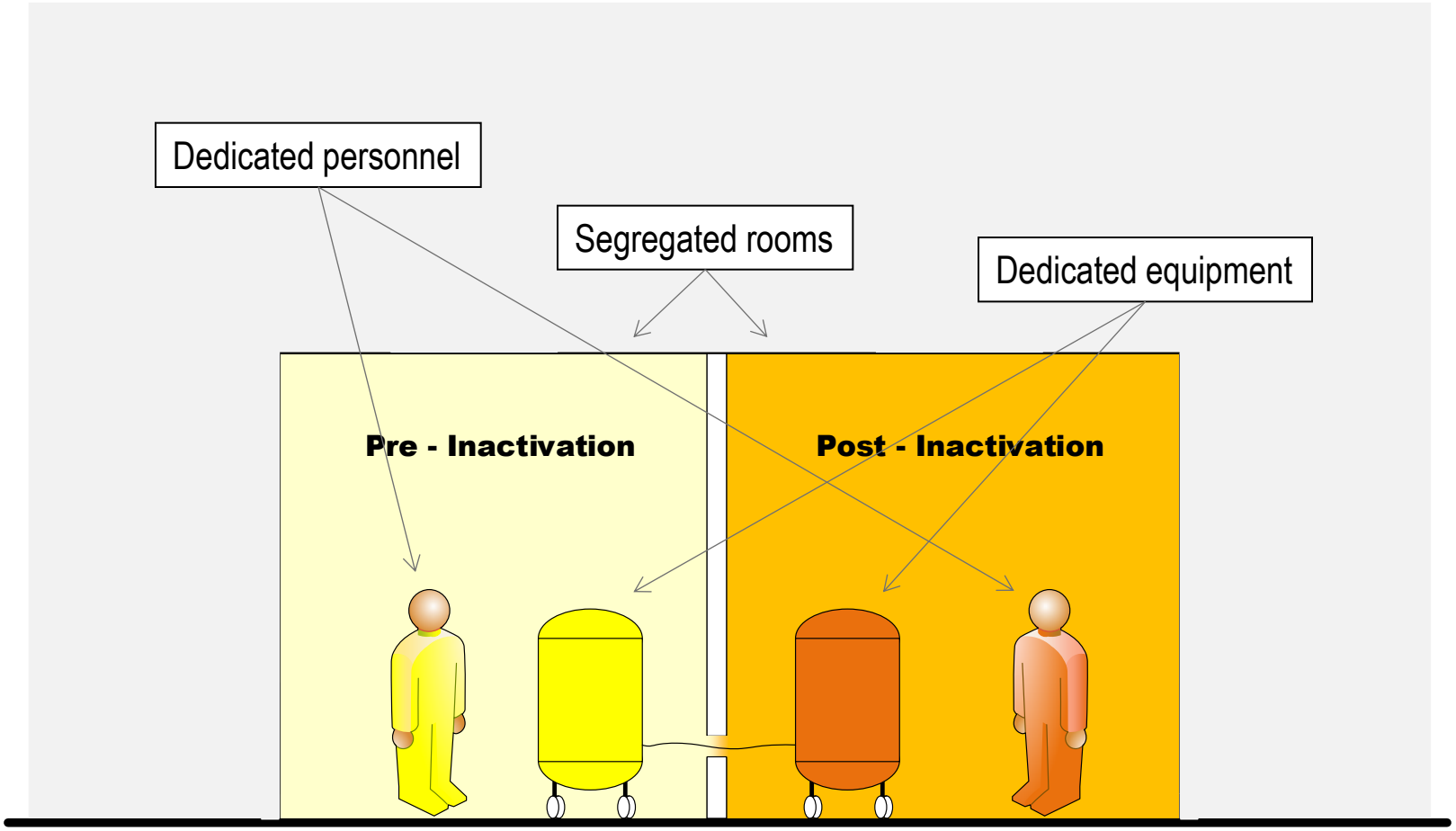
- Dedicated special facilities/R&D labs
- BSL2 to 4
- H1N1

CADILA PHARMACEUTICALS LIMITED

Confidential Client

Understanding Traditional Vaccine Facility

- **What you see is NOT what you get!**



Understanding Traditional Vaccine Facility

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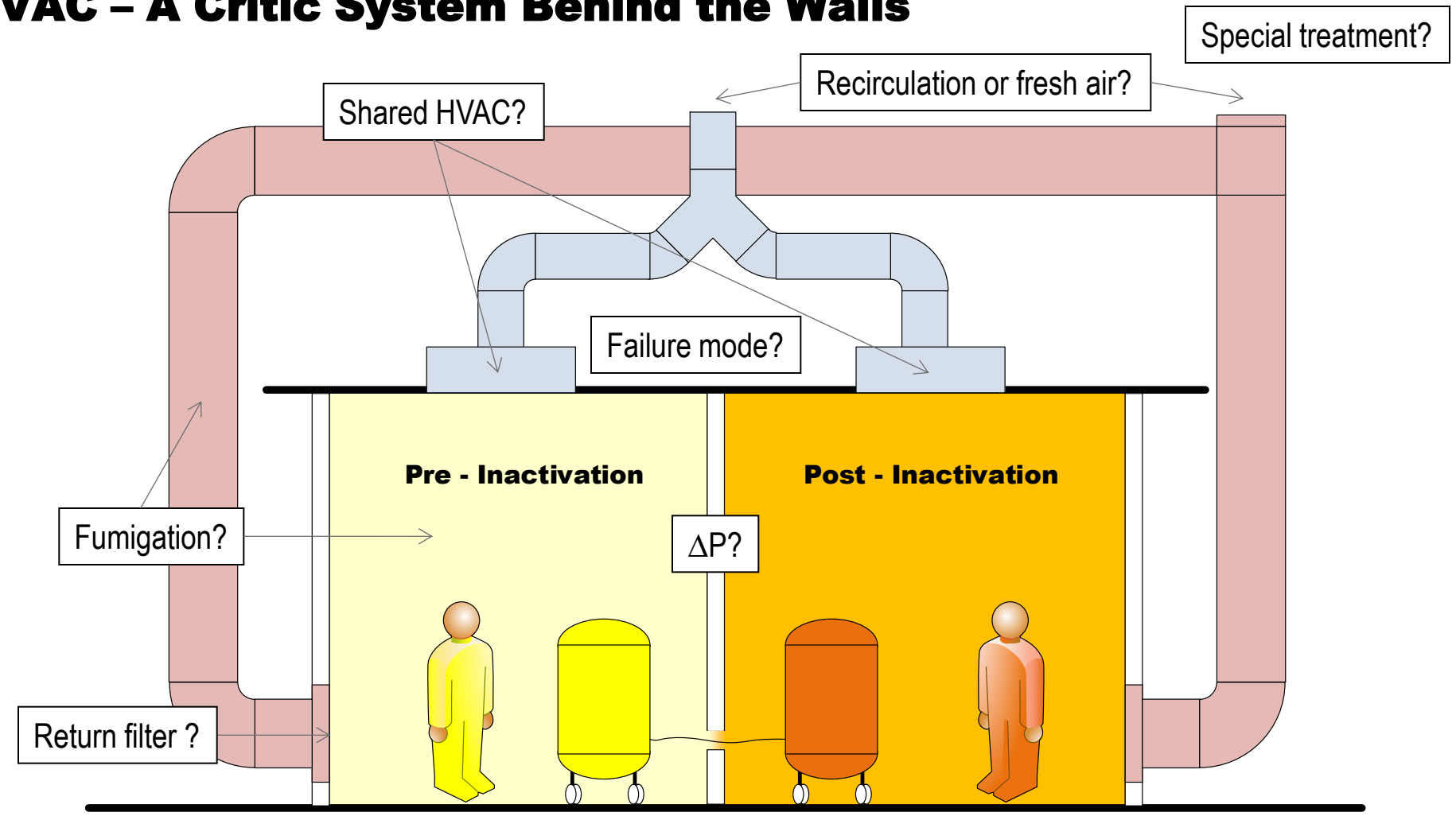
HVAC – A Critic System Behind the Walls



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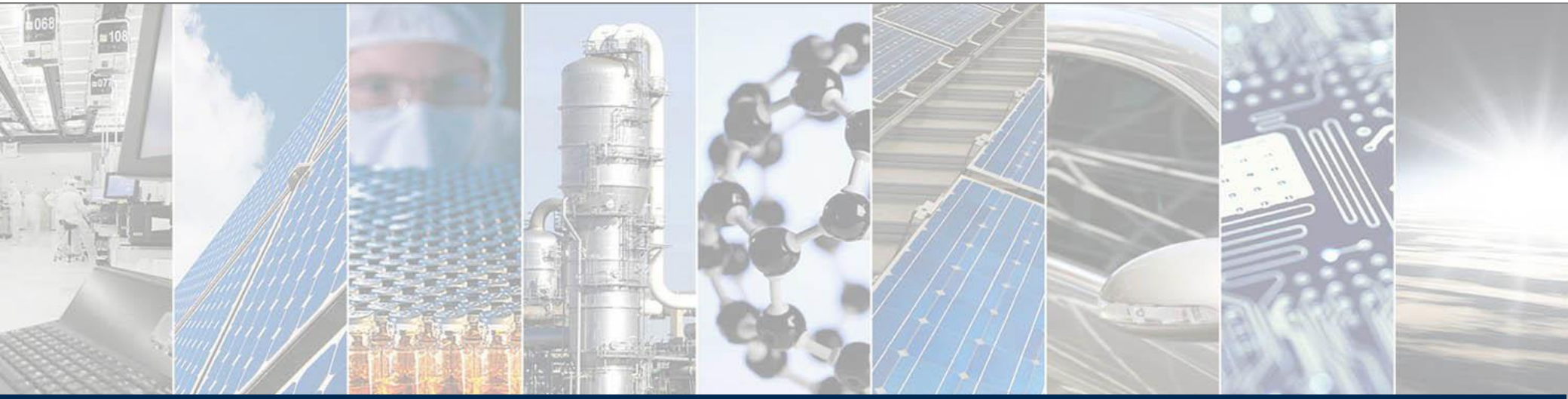
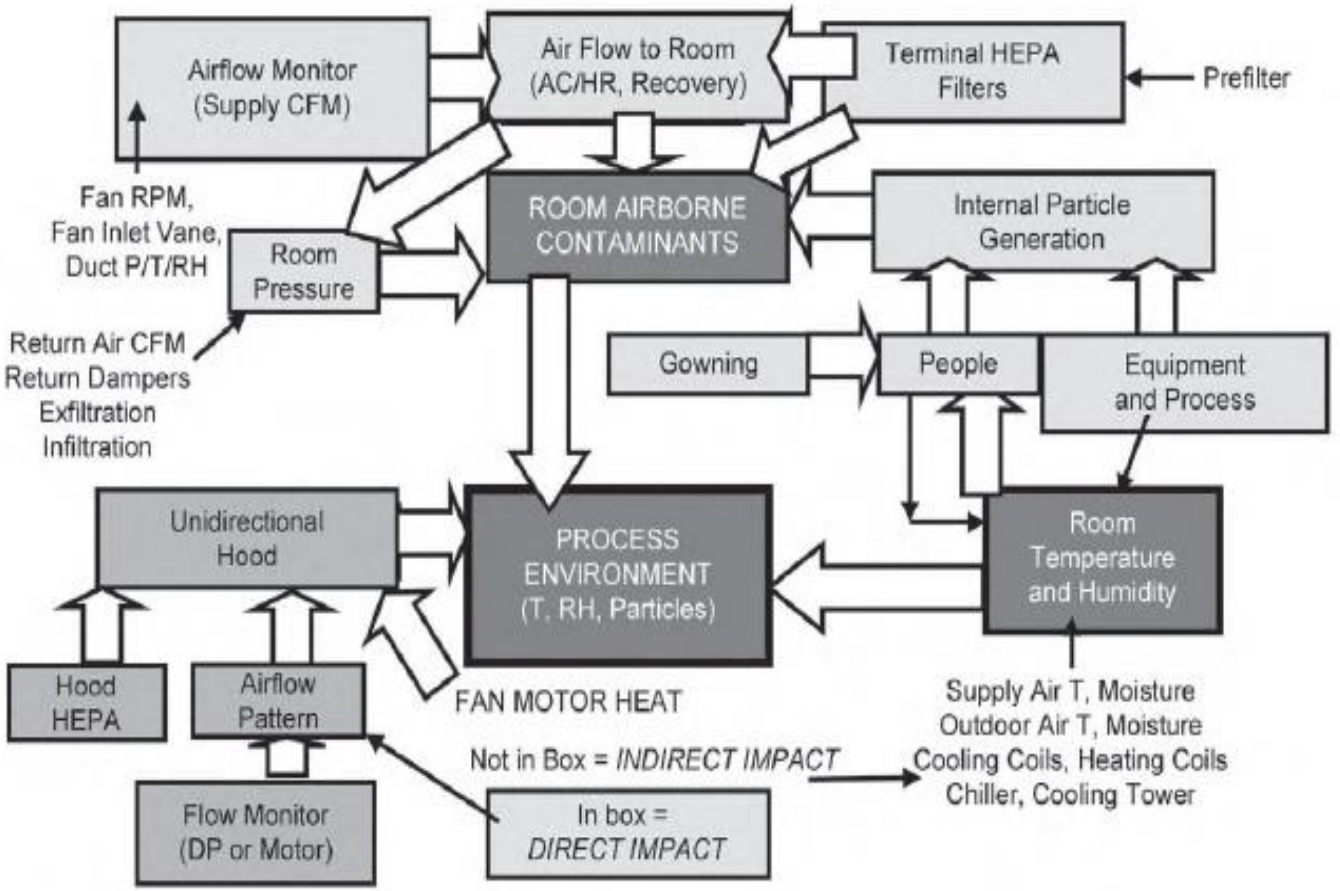


Importance of HVAC in GMP Vaccine Facility

Influencing factors for cleanroom conditions



Importance of HVAC in GMP Vaccine facility

M+W GROUP

- Vaccine facility would be needed a cleanroom environment for manufacturing vaccines to avoid contamination.

- Cleanroom is a room finished smooth finishes with in which the concentration of airborne particles are controlled, and is constructed and used in a manner to minimize the introduction, generation and retention of particles inside the room and in which other relevant parameters, e.g. temperature, humidity and pressure are controlled as necessary.

- HVAC system is contributing a vital role to maintain room classification, temperature and relative humidity in a cleanroom.

Cleanroom Classification/Air changes/Differential pressures

M+W GROUP

Reference	Description			Classification				
ISPE Sterile Baseline® Guide	Environmental Classification			Grade 5	Grade 7	Grade 8	Controlled Not Classifed (with local monitoring)	Controlled Not Classifed (CNC)
European Commission EU EU GMP, Annex 1, Vol. IV, Manufacture of Sterile Medicinal Products (effective 1 March 2009) (similar to PIC/S GMP Annex 1 2007) (References 4 and 7 Appendix 12)	Descriptive Grade			A	B	C	D	Not Defined
	At Rest	Maximum no. particles permitted per m^3 ≥ the stated size	0.5 µm	3,520	3,520	352,000	3,520,000	-
			5 µm	20 ("ISO 4.8")	29	2,900	29,000	-
	In Operation	Maximum no. particles permitted per m^3 ≥ the stated size	0.5 µm	3 520	352,000	3,520,000	Not stated	-
			5 µm	20	2 900	29,000	Not stated	-
		Maximum permitted number of viable organisms cfu/m^3		< 1	< 10	< 100	< 200	-
FDA, October 2004, Guidance for Industry Sterile Drug Products Produced by Aseptic Processing (Reference 9, Appendix 12)	In Operation	Maximum no. particles permitted ≥ the stated size	0.5 µm	ISO 5 (Class 100)	ISO 7 (Class 10,000)	ISO 8 (Class 100,000)	Not Defined	See ISPE Biopharm or Sterile Baseline® Guides
		Action level number of viable airborne organisms cfu/m^3		1	10	100	Not Defined	-

Notes:

- There are small differences in numerical values between the US and European air classes.
- The US particle levels are for the **'in operation'** state only, but it is considered GEP to measure periodic at rest particle levels to monitor the overall health of a facility.
- The US has no equivalent to EU Grade D although the term Controlled Not Classified (CNC) has been used in the pharmaceutical industry and is discussed in the ISPE Baseline® Guides for Sterile and Biopharmaceuticals (Reference 13, Appendix 12). A CNC space may meet ISO 8 at rest without the use of HEPA filters if the airborne challenge is low. For further information on air filters, see Chapter 3 of this Guide. Therefore, a "CNC with monitoring" space could look and perform similarly to a European Grade D space.
- Air quality for facilities that do not require classified spaces, (e.g., oral dosage, packaging, warehousing, closed biopharmaceutical, most APIs (except aseptic processing), and API intermediates) is described in the relevant ISPE Baseline® Guide (Reference 13, Appendix 12).

Air Changes per hour:

Class D: 6 to 20

Class C: 20 to 40

Class B: 40 to 60

Class A: Laminar flow with 0.45 m/s

Differential pressures

Un classified to classified : 15.0 Pa

Change between Different classification: 15.0Pa

Room differential in Same classification:

7.5Pa

Sample Classification Zoning

Sample AHU Zoning

Sample Pressure Zoning

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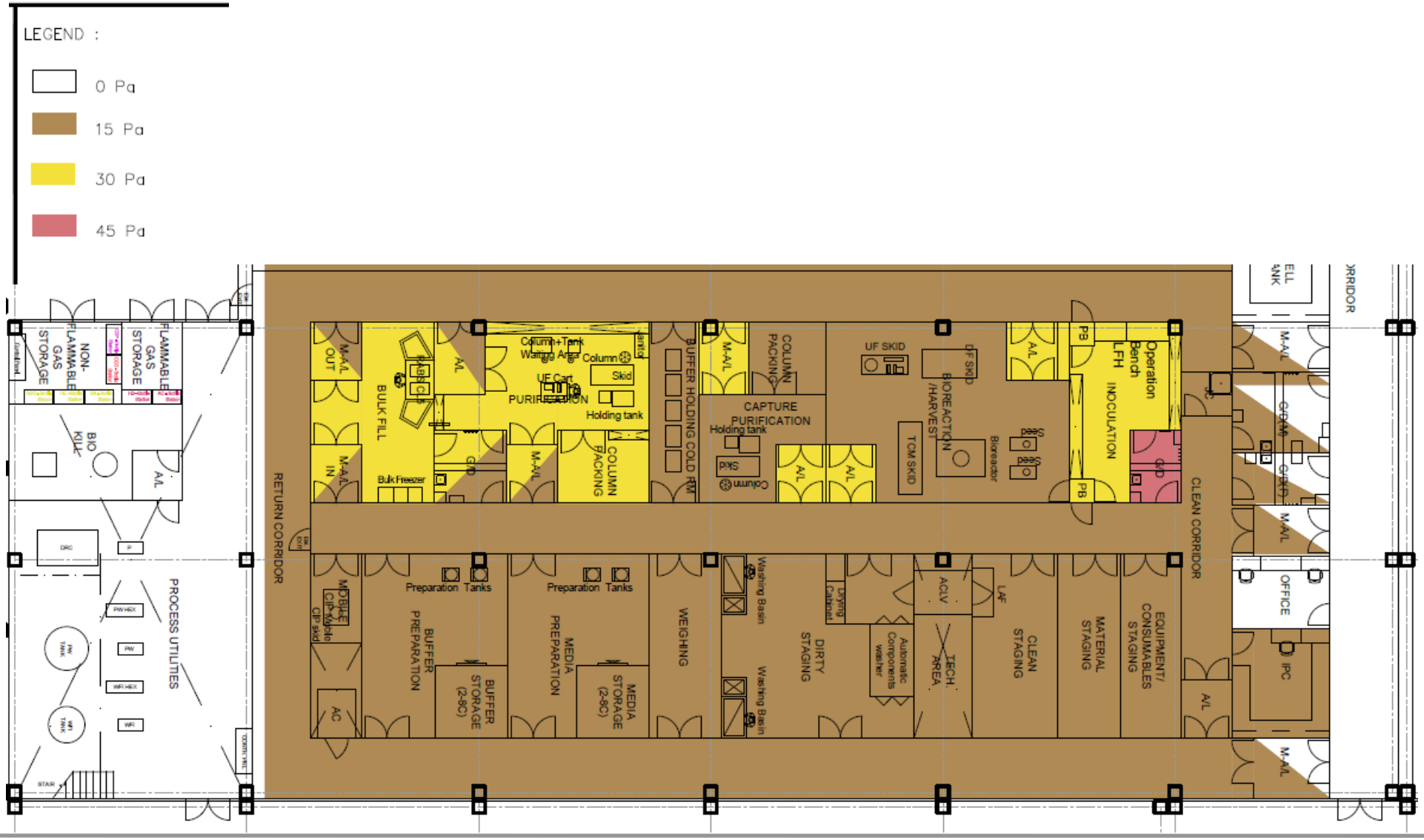
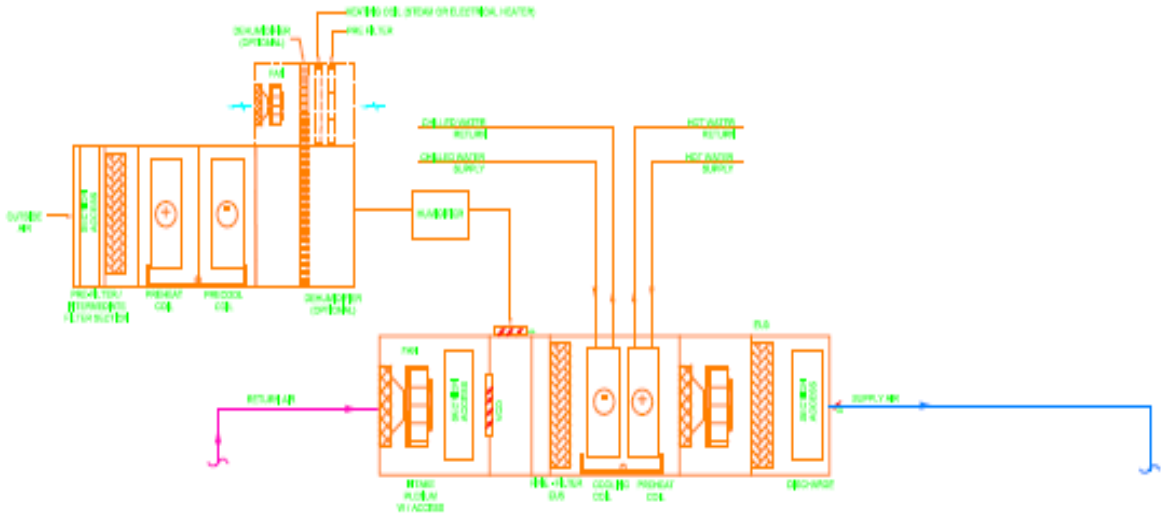
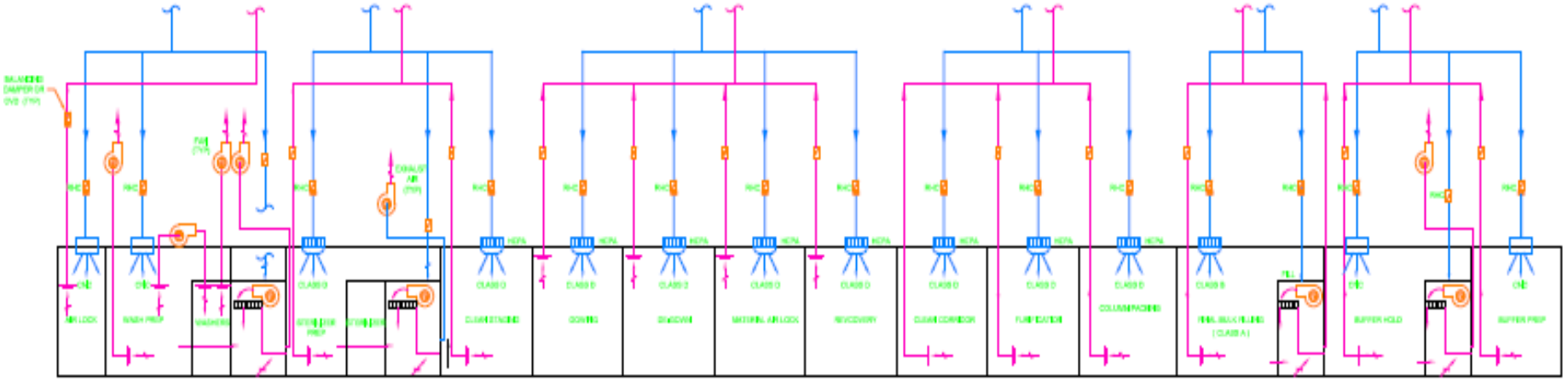
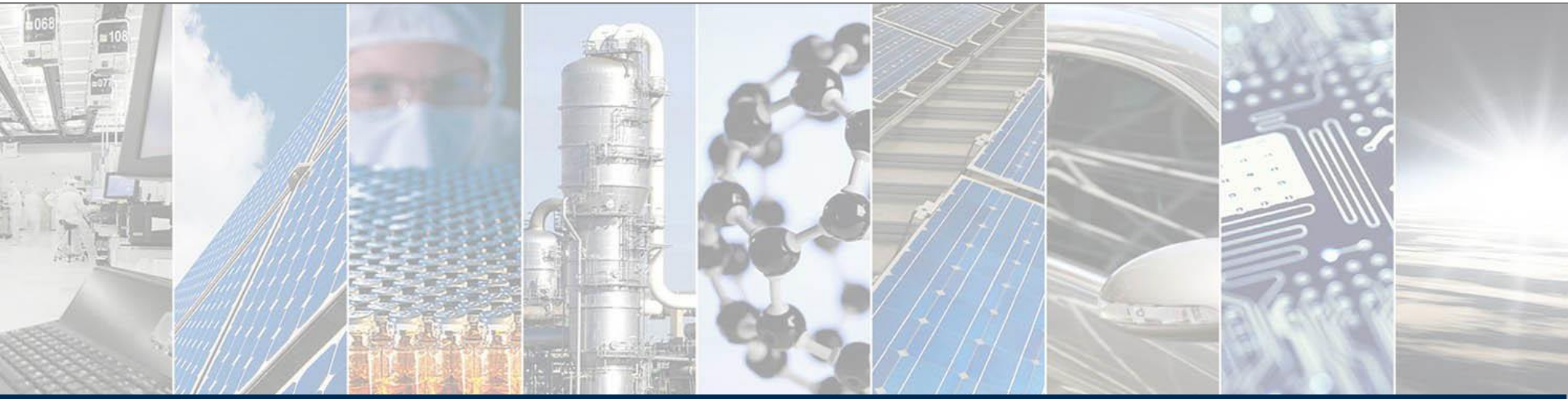


Air Flow Schematics

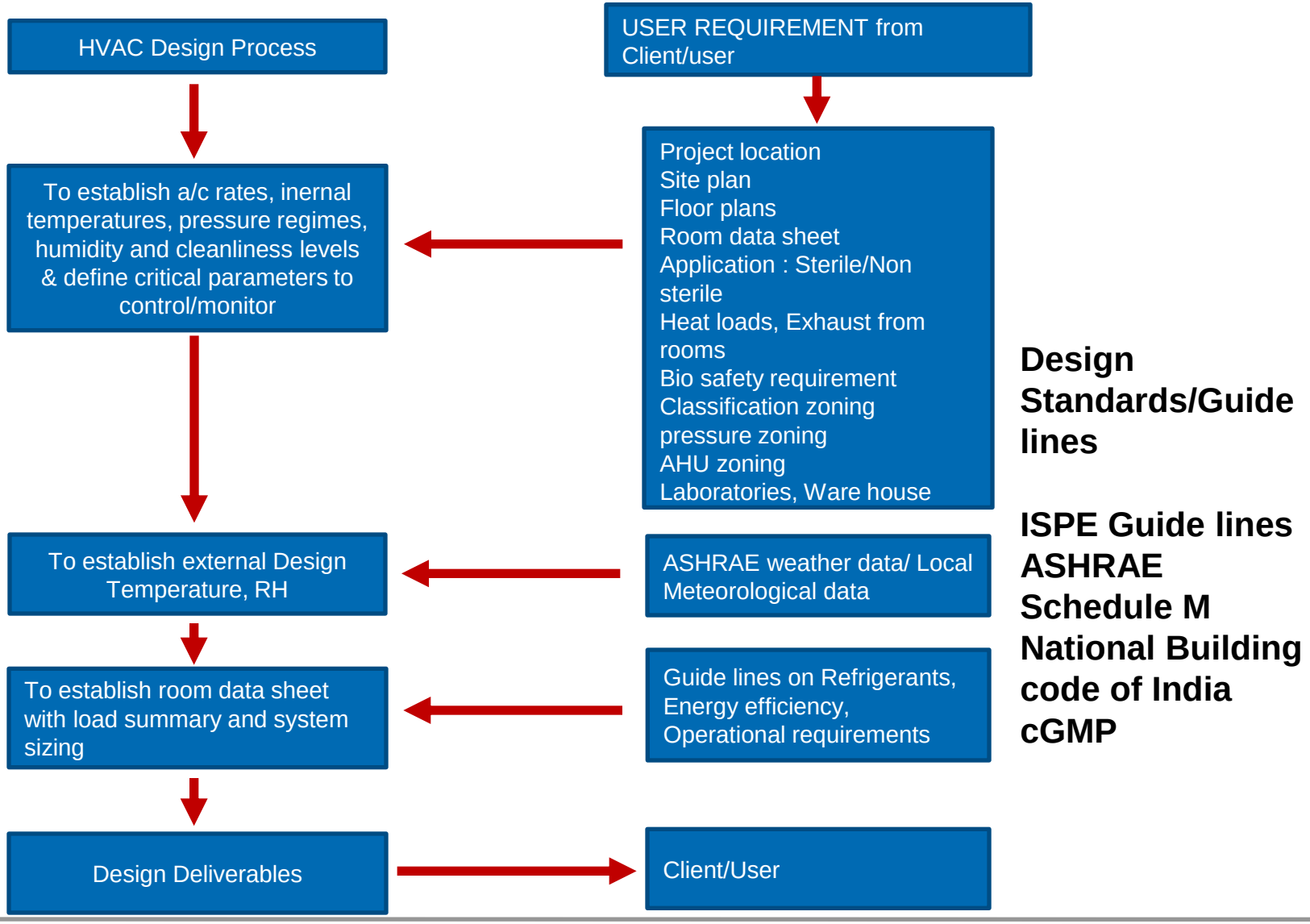






Design Process of HVAC System

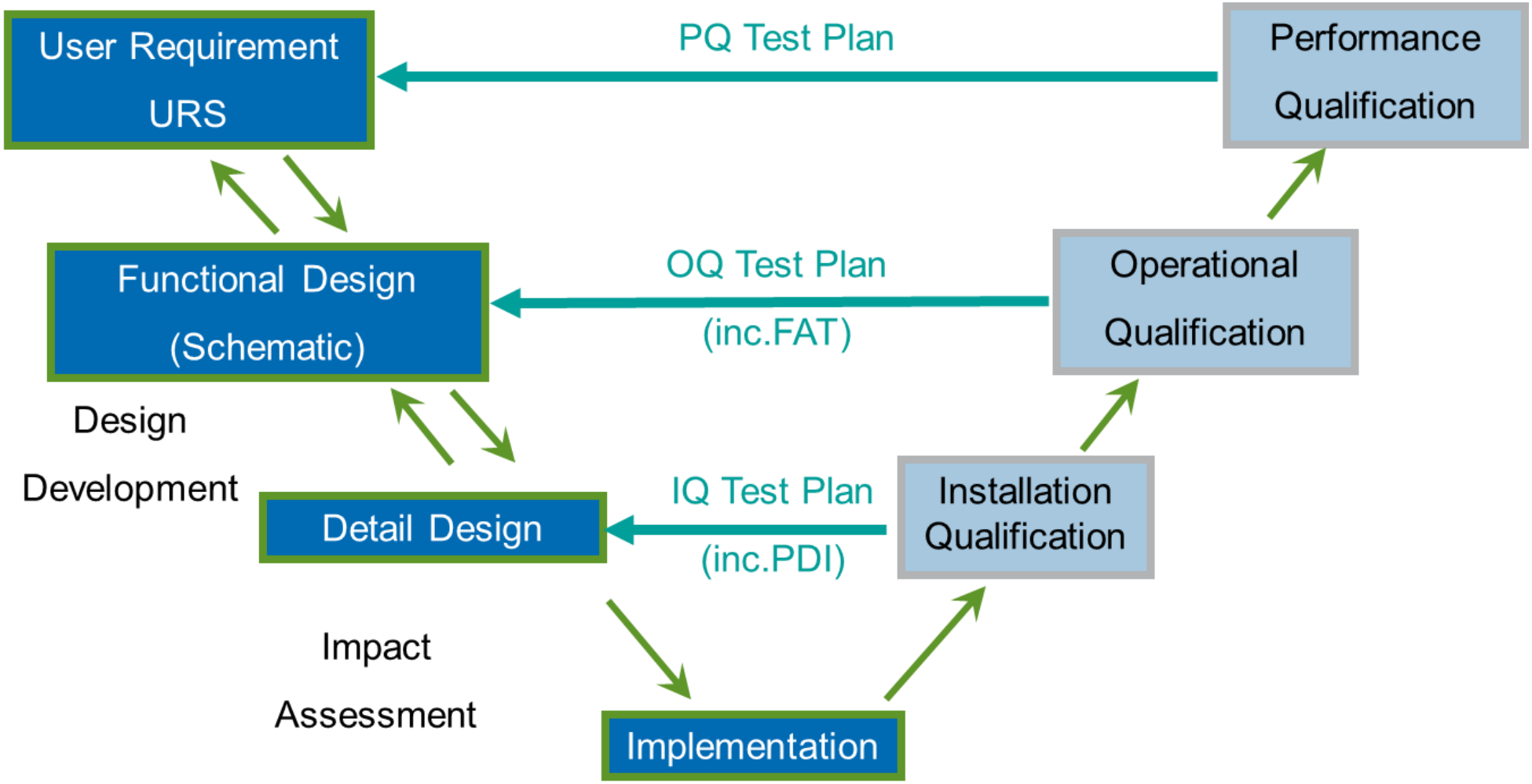
Design & Implementation of HVAC System



Design Standards/Guide lines

ISPE Guide lines
ASHRAE
Schedule M
National Building code of India
cGMP

Design & Implementation of HVAC System



Design Deliverables of HVAC System

M+W GROUP

Design Deliverables

Drawing Number	Description	Submission Design phase		
		Concept	Basic	Detailed
xxx	Mechanical, HVAC - Symbols, Legend & Abbreviations			√
xxx	AHU Zoning Layout	√	√	√
xxx	Pressure Zoning Layout	√	√	√
xxx	Classification Zoning Layout	√	√	√
xxx	RCP Layout		√	√
xxx	Ducting Layout			√
xxx	Sectional Views for Ducting layout			√
xxx	Standard details & typical support details for ducting			√
xxx	Equipment location Layout		√	√
xxx	Chilled & Hot water schematic		√	√
xxx	Chilled water piping layout		√	√
xxx	Hot water piping layout		√	√
xxx	Floor plan for AHUs / Ventilation / Exhaust			√
xxx	Air Flow Schematics	√	√	√
xxx	HVAC P&ID / Plant layout		√	√
xxx	Cooling tower Water Distribution Layout		√	√
xxx	Foundation requirement for mechanical Equipments			√

Weather Data for Indian cities and HVAC Process requirements

M+W GROUP

S.No	Indian City	Dry bulb temperature, ^{0}C		Absolute humidity, g/Kg	
		High	Low	High	Low
1	New Delhi	43.6	4.2	25.2	2.4
2	Mumbai	38.5	14.2	24.3	4.7
3	Chennai	39.5	14.5	25.0	8.0
4	Kolkata	41.2	10.8	28.0	6.0
5	Hyderabad	41.2	11.7	21.0	4.0
6	Bengaluru	36.6	13	21.8	4.2

S.No	Room Temperature	Room Relative humidity	Absolute humidity, g/Kg	Indian City	Cooling & Dehumidification	Reheat	Humidification
1	22	45	7.43	New Delhi	√	√	√
2				Mumbai	√	√	√
3				Chennai	√	√	
4				Kolkata	√	√	√
5				Hyderabad	√	√	√
6				Bengaluru	√	√	√

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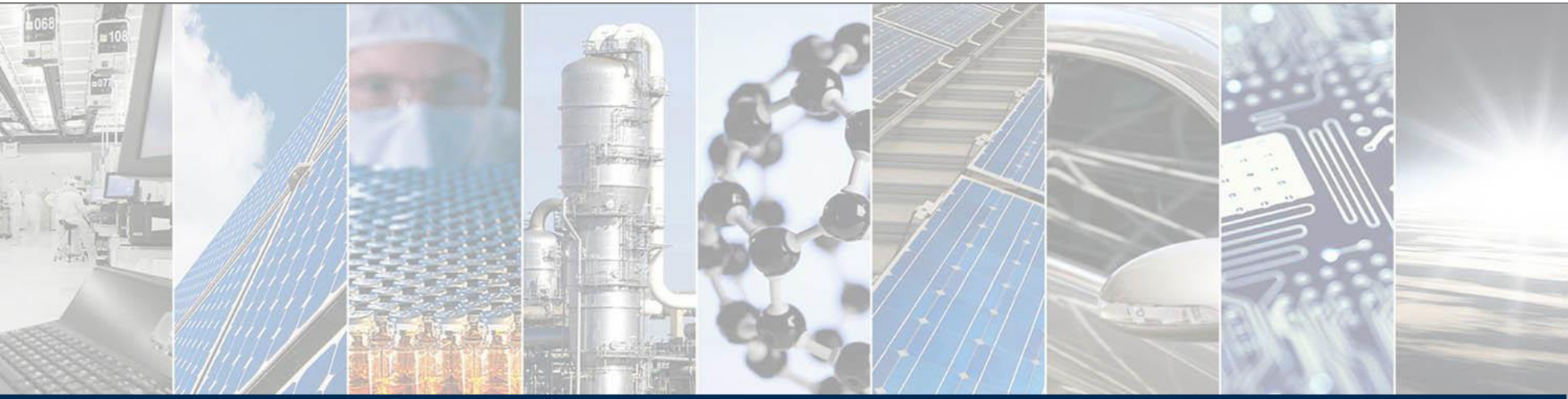

Installation aspects of HVAC System

AHU Service Area

- Vendor selection to deliver the right product with all necessary provisions for maintenance
- Providing necessary service area for attending filters/coil maintenance activity
- Coordination of all the services for proper head room
- Space allocation for Future expansion if applicable
- TAGGING for different services/equipment

Above False Ceiling Area

- Providing necessary height of 1800mm minimum for attending filters/lights/ other maintenance activity above walkable false ceiling
- Cleaning the area after completion of works and maintaining.
- Provision of DOP aerosol injection ports & Terminal filter housing/filter assembly for HEPA installation checks.
- Providing necessary lighting/ventilation to this area
- All services coordination for space/supports

Installation of LAF Systems




- *Installation has to support filter leak test, maintenance and avoid void spaces which can not be cleanable*

System components and their influence on room parameters

M+W GROUP

S.No	Equipment	Temperature	Relative humidity	Room Static pressure	Air flow rate	Air cleanliness
1	Air handling unit	√	√	√	√	√
2	Fan (Supply/return)			√	√	
3	Fume exhaust/extract systems				√	√
4	Heating coil	√				
5	Cooling coil	√	√			
6	Air filter					√
7	Humidifiers		√			
8	Dehumidifiers		√			
9	Duct work			√	√	
10	Damper/louver				√	
11	Diffuser/register				√	
12	UV light					√
13	Thermal insulation	√	√			
14	Chilled water/hot water	√	√			

Installation aspects of HVAC in GMP Vaccine facility

M+W GROUP

S.No	Item Description	Design Clearance	Factory acceptance test	Test certificate for MOC	Installation check	Site Acceptance certificate for performance
	High Side					
1	Chillers/pumps	√	√		√	√
2	Piping/valves/insultation	√		√	√	√
3	Expansion tanks	√		√	√	√
4	Cooling towers	√		√	√	√
5	Hot water generation/pump	√	√		√	√
6	Control system	√	√		√	√
	Low side					
1	Air handling unit	√	√		√	√
2	Humidifiers	√	√		√	√
3	Dehumidifiers	√	√		√	√
4	Duct work/insulation	√		√	√	√
5	Terminal filter module/filter	√	√	√	√	√
6	VCD/VAV/CAV/FD	√		√	√	√
7	Terminal grills/diffusers	√		√	√	√
8	Return air raisers	√		√	√	√
9	Safe change housings	√		√	√	√
10	Ventilation fans	√		√	√	√

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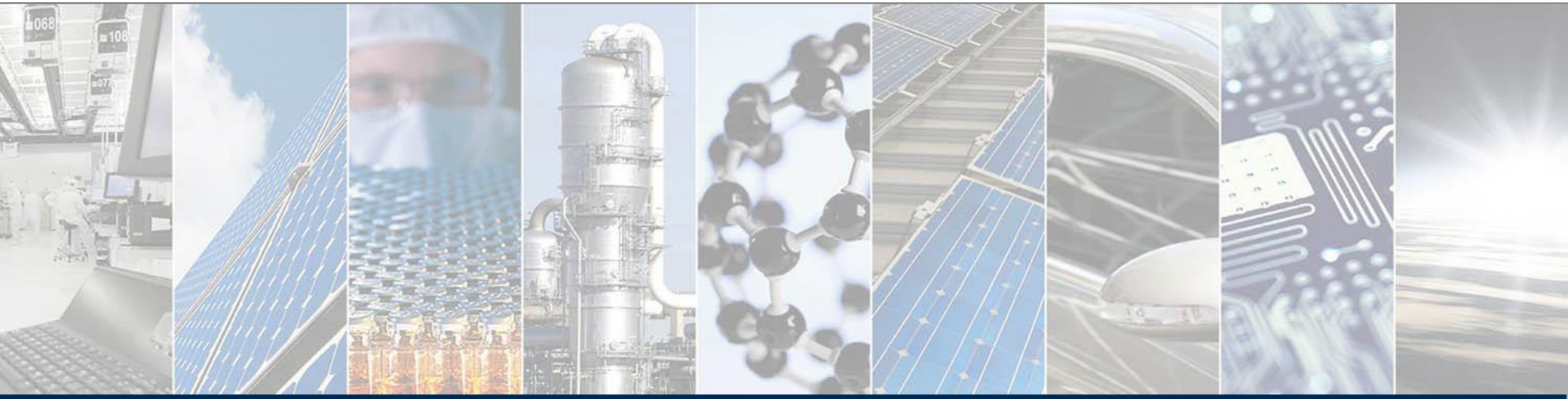

Control Systems and other supporting functions to HVAC

Control System aspects of HVAC in GMP Vaccine facility

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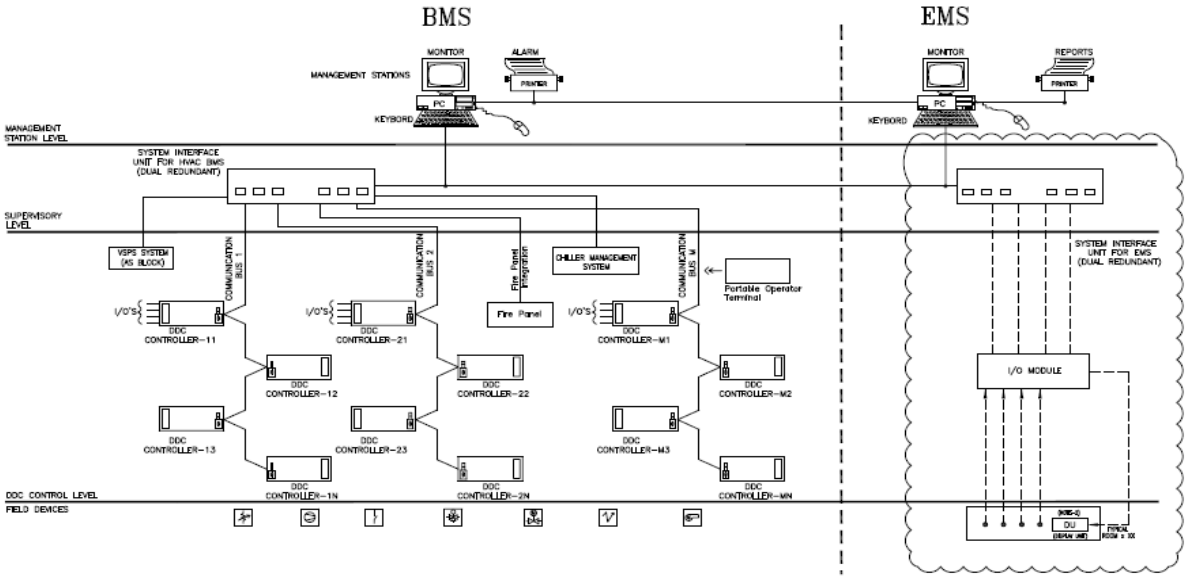

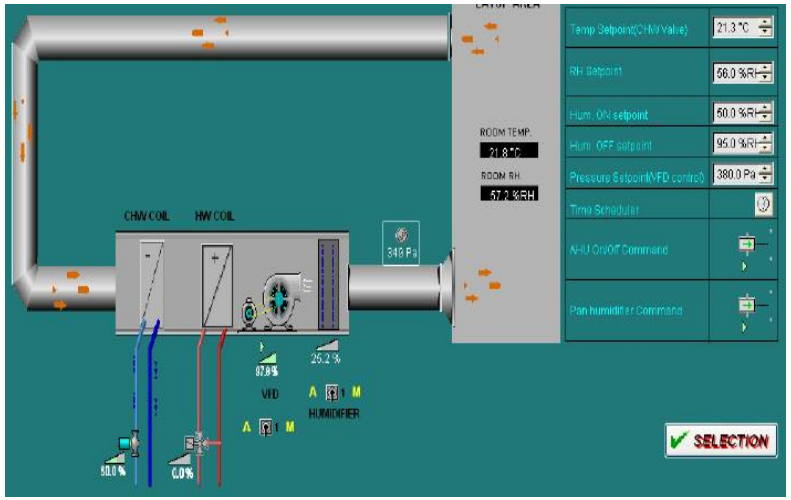

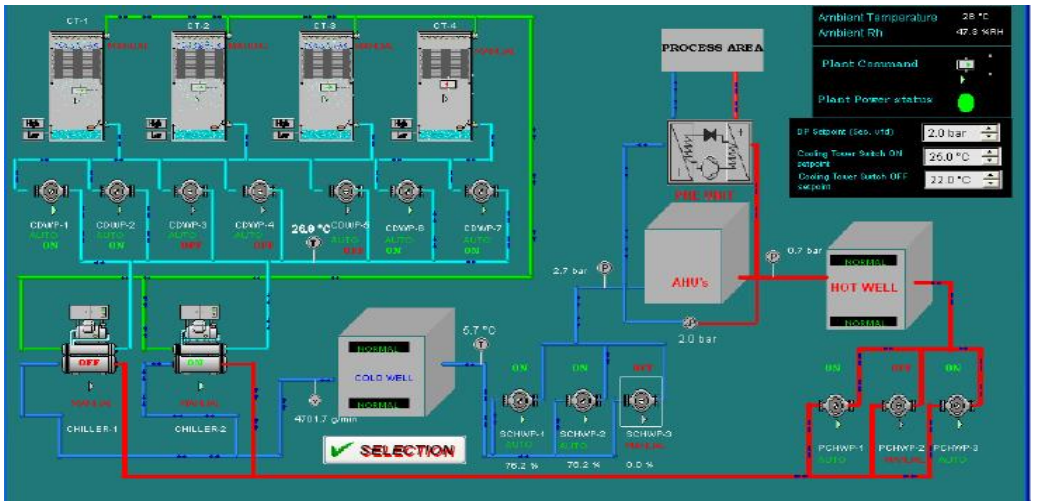

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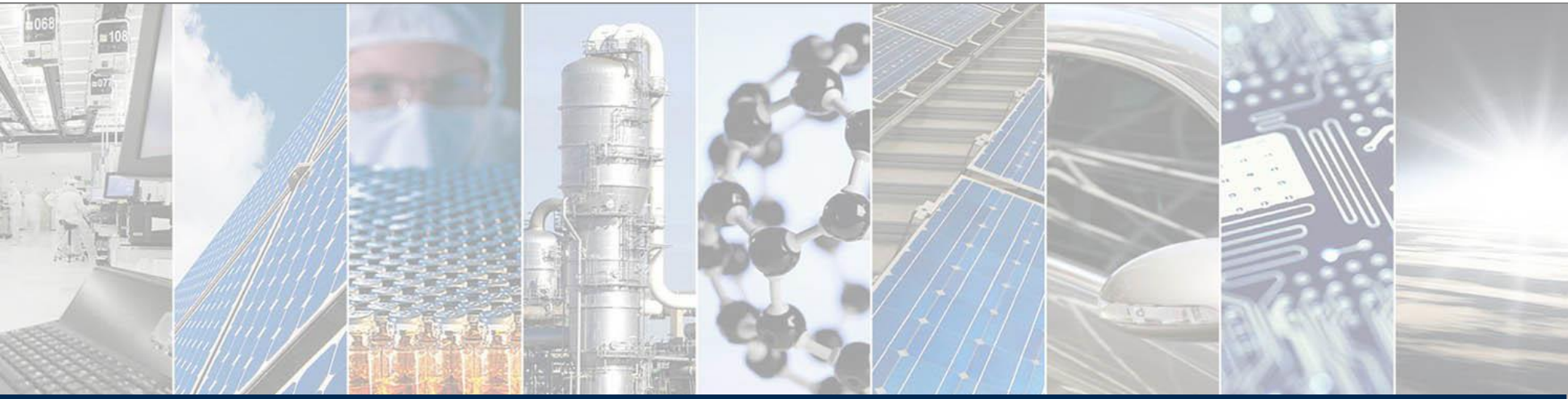

Commissioning and Validation of HVAC System

Commissioning, Qualification & Validation aspects of HVAC in GMP Vaccine Facility

M+W GROUP

- Services Scope

S.No	Commissioning, Qualification and Validation	
	GMP	Non GMP
	DQ/IQ/OQ protocol	Commissioning/Check list/FAT & etc
1	HVAC System low side	Steam generation
2	Cleanroom Interiors	Chilled water
3	Purified water system	Hot water
4	EMS	IBMS
5	Sterile compressed air	Potable water
6	Lab gases	ETP/STP
7		Fire Fighting
8		Electrical system

Legend: W = Write and maintain R = Review A = Witness and Approve E = Execute	M+W Validation Team	User validation Team
Design Qualification for facility systems	W & E	R & A
Installation Qualification for facility systems	W & E	R & A
Operational Qualification for facility systems	E	W, R & A
Performance Qualification for facility systems		W,E, R & A
Commissioning Plan	W & E	R & A
Commissioning Schedule	W & E	R & A
Overall Test Plan	W & E	R & A
Pre-delivery Inspection (PDI) Plan	W & E	R & A
Pre-delivery Inspection (PDI) Report	W & E	R & A
Factory Acceptance Test (FAT) Plan	W & E	R & A
Factory Acceptance Test (FAT) Report	W & E	R & A
Inspection Plan	W & E	R & A
Inspection Report	W & E	R & A
Functional Test Plan	W & E	R & A
Functional Test Report	W & E	R & A
System Test Summary Report(s)	W & E	R & A
Final Commissioning Summary Report	W & E	R & A

Commissioning, Qualification & Validation aspects of HVAC in GMP Vaccine Facility

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Design Qualification (DQ)

- It documents the design of the system and will include :
  - Functional Specification.
  - Technical / Performance specification for equipment.
  - Detailed Schematic diagram.
  - Detailed layout drawing of the system

- A thoroughly executed DQ process ensures the following
  - Compliance with GMP's and other regulatory requirements.
  - Design meets the user requirements.
  - Design details facility airflow and pressure cascade philosophy.
  - Design takes into account process and personnel flow (cross-contamination issues)
  - Design details materials of construction.
  - Design details safety requirements.
  - Full details of the intended construction prior to implementation.
  - Details all equipment that must be ordered.

Commissioning, Qualification & Validation aspects of HVAC in GMP Vaccine Facility

M+W GROUP

Installation Qualification (IQ)

- Design drawings can be marked up and deviations highlighted.
- DQ to be complete and signed off before IQ begins.
- IQ protocols to be written and approved prior to implementation.
- Check lists for components to be installed can be used. Items such as fans, fan motors, cooling and heating coils, filters, temperature and relative humidity sensors and differential pressure gauges can be included in check lists.
- Duct and pipe pressure test reports.
- Filter integrity tests.
- Functionality Loop checks and alarm tests for HVAC control systems.
- Calibration of measuring instruments.
- Calibration of additionally used instruments.
- Initial cleaning records.
- Basic commissioning checks.
- Maintenance requirements.
- IQ process checks that the correct components are installed in the correct location.
- Materials of construction
- Spare parts
- Change controls

Commissioning, Qualification & Validation aspects of HVAC in GMP Vaccine Facility

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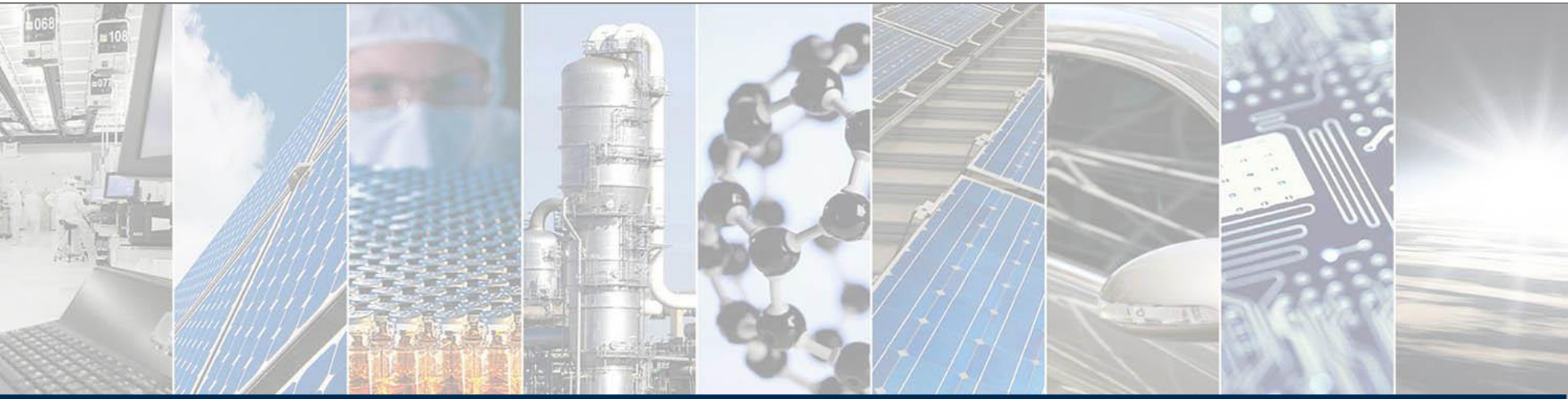
Operational Qualification (OQ)

- IQ reports must be completed and signed off.
- OQ protocols to be written and approved prior to completion.
- Measurement reports are required to demonstrate achievement of critical parameters as detailed in DQ. For Example
  - Temperature measurement report
  - Humidity measurement report
  - Differential pressure measurement report
  - Air flow direction measurement report
  - Room particle count measurement report
  - All drawings etc. – done in ‘as-built’ status
  - All maintenance/ cleaning instructions available
  - All O & M staff to be trained to use and maintain the system.

Commissioning, Qualification & Validation aspects of HVAC in GMP Vaccine Facility

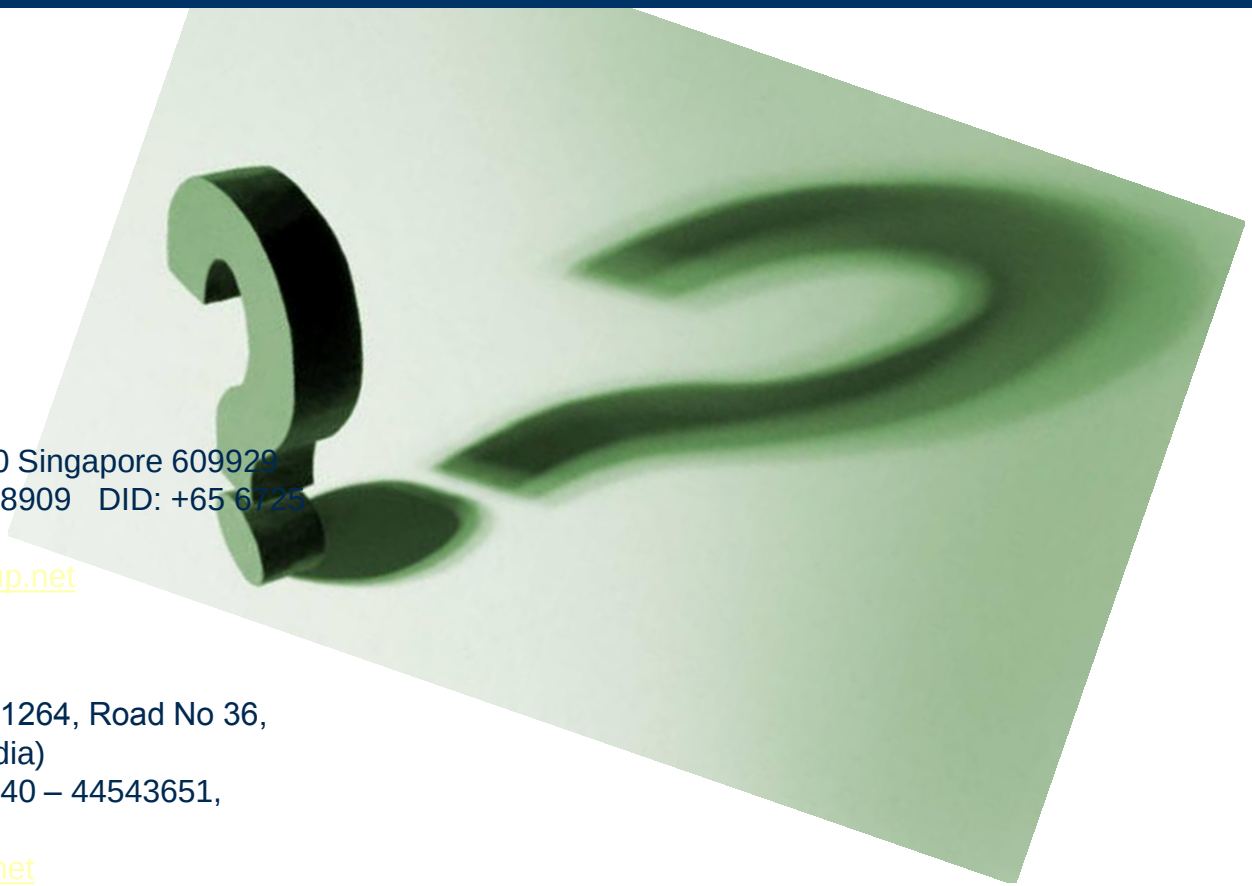
M+W GROUP

S.No	Validation Test	Checks During Design	Checks During construction
1	Installed filter leaks- total leakage, scan test across HEPA filters after installation	HEPA filter selection, filter frame fabrication method	Vendor certificate for HEPA and site inspection for frame installation and DOP test for filter and frame assembly
2	Air flow, velocity and uniformity- for unidirectional air flow spaces, air flow supply from filters and in duct: also air flow to non unidirection spaces	During design, location of the diffusers, selection of diffuser need to be taken care..	During installation testing of duct work, installation checks are to be followed
3	Air differential pressure - used to measure between un classified to classified or lower classified to higher classified room and verify these as per GMP guide lines	During design required exfiltration/infiltration are to be considered	During installation, necessary coordination needs to be done for gap around shutter/frame/floor with cleanroom vendor
4	Containment leakage - This is for the room fabric where potent materials are exposed to environment	Coordination of all the trades of work	Need to coordinate with all trades of work in cleanroom for proper closeout, sealant application along with cleanroom vendor
6	Temperature of the room	During design, heat load from process, exhaust air if any, no of people are to be checked	At final stage of commissioning this also need to be validated against installation, checking chilled water, hot water temperatures & etc
7	Relative humidity of the room	During design weather data of area of the installation needs to be considered for selecting dehumidifier/humidifer.	During installation, Installation of duct work at joints, room partitions, ex filtration/infiltrations, insulations are to be checked
8	Airborn particle counting for room classification	Filter selection as per manufacturer is to be followed and air volume has to be as per air changes	Close out of all the services and completion of filter leak test, air flow and area cleaning to start this



Question & Answers

Thank you for your attention!



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