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Design and Development of Cost Effective Clean Rooms For Pharmaceutical Units

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Abstract: *A clean room is an environment, typically used in manufacturing or scientific research that has a low level of environmental pollutants such as dust, airborne microbes, aerosols particles and chemical vapors. More accurately, a clean room has a controlled level of contamination that is specified by the number of particles per cubic meter at a specified particle size.*

As per the regulations specified by regulating authority FOOD & DRUG ADMINISTRATION it is necessary to implement specified norms for all pharmaceutical & food industries. For manufacturers working on small scale in local industrial estate, it is difficult to implement norms in existing infrastructure. Also there was great scarcity of funds, as these funds are to be spared from existing pool of funds. In pursuit of fulfilling the needs of these small scale units we have developed a design for unitary clean room systems using ceiling mounted single skin type ductable split air conditioning units.

Terminology used for clean room systems

1. Particle size: Micron = 10^{-6} m
2. Number of air changes: Integer number indicating ratio of blower capacity of air handling unit to the room volume.
3. Particle count: Number of particles of specified size per m^3 of air inside the clean room.
4. Quality standards for the clean rooms:

a) US FED STD 209E clean room standards. b)ISO 14644-1 clean room standards.
c) BS 5295 clean room standards. d)GMP EU classification.

5. AHU: Air handling units.
6. HEPA: High-efficiency particulate air.
7. Ductable split air conditioning unit: Air conditioning unit having separate condensing unit & AHU which can be fitted with duct.

I. Introduction

Industrial clean room is mainly applied in electronics industry for semiconductor manufacturing. Furthermore, it extends its applications in new material development and fine chemical Industry, pharmaceutical & food industry.

One of the industrial clean room criteria is that, its employment will get the investment capital returned with the improvement of quality and production yield of the products. In short, the investment for industrial clean room is profitable. What level of clean room is necessary for what kind of products is determine by the product requirement.

It is important to design the higher clean room for more important production area and lower and economical clean room for other areas.

II. Clean room classification [1]

TABLE US FED STD 209E clean room standards

Class	maximum particles/ft³					ISO equivalent
	≥0.1 µm	≥0.2 µm	≥0.3 µm	≥0.5 µm	≥5 µm	
1	35	7.5	3	1	0.007	ISO 3

10	350	75	30	10	0.07	ISO 4
100	3,500	750	300	100	0.7	ISO 5
1,000	35,000	7,500	3000	1,000	7	ISO 6
10,000	350,000	75,000	30,000	10,000	70	ISO 7
100,000	3.5×10^{6}	750,000	300,000	100,000	700	ISO 8

TABLE BS 5295 clean room standards

	maximum particles/m³					
Class	≥0.5 µm	≥1 µm	≥5 µm	≥10 µm	≥25 µm	
Class 1	3,000		0	0	0	
Class 2	300,000		2,000	30		
Class 3		1,000,000	20,000	4,000	300	
Class 4			200,000	40,000	4,000	

BS 5295 Class 1 also requires that the greatest particle present in any sample do not exceed 5µm.

TABLE ISO 14644-1 clean room standards

Class	maximum particles/m³						FED STD 209E equivalent
	≥0.1 µm	≥0.2 µm	≥0.3 µm	≥0.5 µm	≥1 µm	≥5 µm	
ISO 1	10	2.37	1.02	0.35	0.083	0.0029	
ISO 2	100	23.7	10.2	3.5	0.83	0.029	
ISO 3	1,000	237	102	35	8.3	0.29	Class 1
ISO 4	10,000	2,370	1,020	352	83	2.9	Class 10
ISO 5	100,000	23,700	10,200	3,520	832	29	Class 100
ISO 6	1.0×10^{6}	237,000	102,000	35,200	8,320	293	Class 1,000
ISO 7	1.0×10^{7}	2.37×10^{6}	1,020,000	352,000	83,200	2,930	Class 10,000
ISO 8	1.0×10^{8}	2.37×10^{7}	1.02×10^{7}	3,520,000	832,000	29,300	Class 100,000
ISO 9	1.0×10^{9}	2.37×10^{8}	1.02×10^{8}	35,200,000	8,320,000	293,000	Room air

TABLE GMP EU classification

Class	maximum particles/m³[10]			
	At Rest	At Rest	In Operation	In Operation
	0.5 µm	5 µm	0.5 µm	5 µm
Class A	3,520	20	3,500	20
Class B	3,520	29	352,000	2,900
Class C	352,000	2,900	3,520,000	29,000
Class D	3,520,000	29,000	n/a	n/a

III. Systems used in conventional pharmaceutical industries

Conventional systems used in industries have double skin type AHU. This AHU consists of an insulated chamber. This chamber has following main sections.

3.1 Blower section: This section consists of a motor & forward curved blower capable of developing static pressure as per design specification (25 mm to 100 mm of water column).It also contains bank of ultra violet lights & pre filters for purification of air. This section is connected to return duct by flexible ducting.

3.2 Air conditioning section: This section consists of HVAC unit useful for controlling temperature & humidity requirements of the room in which controlled atmosphere is required to be produced. This section takes care to maintain the temperature & relative humidity.

3.3 Filter section: This section is instrumental in removal of particles of all sizes, so as to bring the air to required quality. This section is also fitted with micro manometers for measuring the pressures drop across the filter. First filter element is called pre filter. The size of filter progressively reduces in the direction of flow of air.

Other functional parts are supply & return ducts, supply air dampers, return air dampers & volume control dampers.

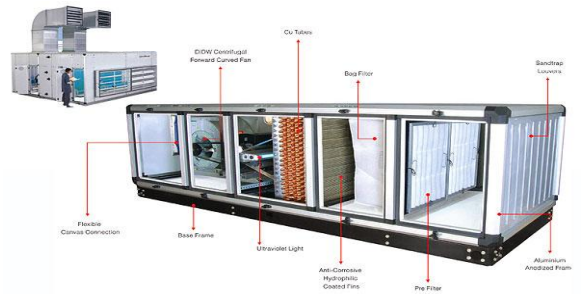

FIG. 1: Typical cross section of double skin roof mounted A.H.U. [2]

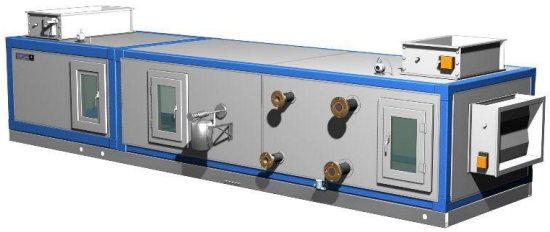

FIG. 2: Typical assembly of A.H.U. commonly used in pharmaceutical units [2]

IV. Clean room requirements for various Industries

Globalization & growth have become key words in present scenario of an industrial development. Along with this various stringent conditions are laid down on food, cosmetic & pharmaceutical industries. These norms are dependent on type of product manufactured and countries to which it is to be exported. Accordingly manufacturer is expected to follow either F.D.A. or G.M.P. or W.H.O. norms. The norms for manufacturing particular product decide design parameter required for particular clean room.

Following are some common products which require clean rooms for their processing & packing.

4.1 Medicines: Clean rooms required for this product is sub classified in to following categories. 1) External drugs 2) Internal oral drugs 3) Betelactum drugs 4) powder & tablets 5) Capsules 6) Saline's & injections (Intravenous drugs) 7) Repacking units of bulk drugs 8) Raw material quarantines 9) Primary, secondary & tertiary packing rooms 10) Microbiology laboratories 11) Chemical analysis laboratory.

4.2 Food & beverages: Requirements for food & beverages clean room is dependent on type of food product being manufactured.

4.3 Electronic Industries [3]**:** Many electronic industries such as, an assembly unit of Camera, cell phones, control equipments, precision medical equipments.

4.4 Painting & surface coating industries: For heat treatment & for providing thin coats of precious metals certain controlled atmosphere is required, which can be provided by specially designed clean rooms.

4.5 Horticulture, biotechnology & agro based products: Agro firms developing advanced agro products are using various methods involving genetic modifications & tissue culture technique. Hence this sector also has wide range of clean room applications.

V. Limitation of conventional Double wall roof mounted A.H.U.

5.1 Cross air contamination: In pharmaceutical industry many drugs are manufactured simultaneously. These drugs may have different chemical compositions. These drugs may have chemical reaction with the chemicals from other product being manufactured. Hence streams of re circulated air cannot be handled by single A,H,U.

5.2 Long ducting length: Long ducting length is evil for clean rooms as, it causes heat loss, pressure loss & cost escalation. It also makes pressure controls difficult for different sections in the building. Chance of air contamination also increases because of increased length of duct.

5.3 Initial cost of the equipment: Initial cost of the equipment is high because of its size, extensive length of supply ducts & return ducts & various accessories needed for pressure control & flow controls in different sections of the building.

5.4 Low part load efficiency: In any process industry all sections may not be working simultaneously. When single A.H.U. of higher capacity is fitted for whole factory building, it may invite for higher electricity bills.

All limitations discussed above prove that conventional double skin A.H.U. used for small scale pharmaceutical industries, repacking units in particular are unaffordable in terms of initial cost & operational running cost. We have devised low cost solution of fitting roof hanging ductable split units with some modifications to offset almost all limitations discussed above, they are working successfully in various pharmaceutical units from last four to five years.

FIG. 3: Ductable split Air conditioning units or roof hanging fan coil units [2]

VI. How ductable split air conditioners can be used in place of conventional double skin AHU?

Ductable split evaporator or indoor units are compact & can be mounted in suspended positions to the ceiling. Hence these units can be placed above false ceiling or on the service floor just above or in the vicinity of the proposed clean room. While deciding the location of these indoor units proper care should be taken for laying ducting, filter section, UV section etc. Proper care should be taken to lay the drains for condensate water as it requires proper slope & it should have minimum obstructions.

TABLE Technical details of Voltas [4] Venture Horizontal Discharge Ductable Split AC

Model	Unit	LB-G0306QC	LB-G0304QC	LB-E0506QC	LB-E0421QC	LB-E0506QC	LB-H0700QC	LB-H0850QC
Nominal Cooling Capacity	TR	1.5 TR	2.5 TR	3 TR (3Ph)	3 TR (1Ph)	5 TR	5.5 TR	9 TR
Power Supply	V-Ph-Hz	230V; 1Ph; 50Hz	400V: 3Ph; 50Hz	400V; 3Ph; 50Hz	230V; 1Ph; 50Hz	400 V-3 Ph-50Hz	400 V-3 Ph-50Hz	400 V-3 Ph-50Hz
Power input at Rated condition	Watts					5600	6000	11000
Maximum Operating Current	Amps					14	16	25
INDOOR UNIT								

Dimensions : W x D x H	mm (inches)	600 x 514 x 388 23.6 x 20.2 x 15.3	1160 x 600 x 298 45.7 x 23.6 x 11.7	1160 x 600 x 298 45.7 x 23.6 x 11.7	1160 x 600 x 298 45.7 x 23.6 x 11.7	1365 x 730 x 370 53.7 x 28.7 x 14.5	1365 x 730 x 370 53.7 x 28.7 x 14.5	1425 x 750 x 460 56 x 29.5 x 18
Weight	kg	30	52	52	52	70	70	105
Nominal Airflow	CMH (CFM)	1189.30 (700)	2718.41 (1600)	2718.41 (1600)	2718.42 (1600)	3740 (2200)	3740 (2200)	5780 (3400)
Fan	Type	Centrifugal	Centrifugal	Centrifugal	Centrifugal	Centrifugal	Centrifugal	Centrifugal
Fan Motor	Nos.	1	1	1	1	1	1	2
	Watts Input	225	254	254	254	700	700	525 (each)
	Rated Voltage	230 V, 1Ph, 50 Hz	230 V, 1Ph, 50 Hz	230 V, 1Ph, 50 Hz	230 V, 1Ph, 50 Hz	230 V, 1Ph, 50 Hz	230 V, 1Ph, 50 Hz	230 V, 1Ph, 50 Hz
Evaporator Coil	Type						Slit fin, inner grooved tube	
OUTDOOR UNIT								
Dimensions : W x D x H	mm	765 x 340 x 540	765 x 340 x 540	900 x 400 x 614	1045 x 421 x 587	1000 x 400 x 1250	1000 x 400 x 1250	

Referring to TABLE 5 horizontal throw ductable split air conditioners are available in the cooling capacity from 1.5TR to 9TR. These cooling capacities are adequate to meet demands of all types of clean rooms, even for clean rooms with heating equipments placed inside it. As these units are placed under the shed only external insulation is sufficient to prevent heat gain from the surroundings. Most important parameter is static pressure developed by the centrifugal blowers. Normally high static pressure ductable split air conditioners develop static pressure of 450 to 500 Pa. This static pressure is sufficient to built positive pressure inside the clean room up to 45 Pa. Here utmost care is needed while designing the system to minimize pressure loss in the system.

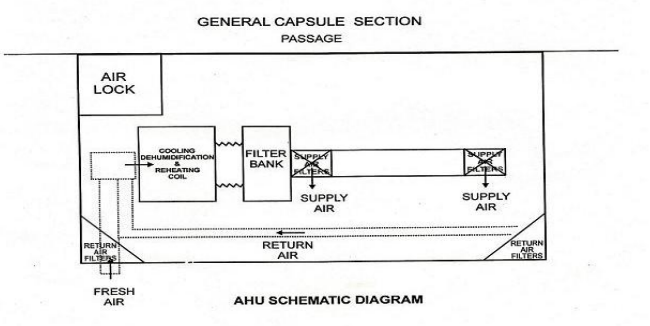

FIG. 4: Typical arrangement for clean rooms using duct able split air conditioning units [5]

Schematic sketch in Fig. 4 is typical plan for single entry, single air lock clean room. It shows two air outlets which supplies filtered clean air to clean room. Air from the room is re circulated through riser & return duct arrangement. Air is supplied from supply air outlets at pressure 25-30 Pa to maintain static air pressure inside the room to the value of 20 Pa. This creates pressure gradient of 15 Pa across clean room & air lock. Air flows back from openings provided at the floor level to the riser. This ensures that dust content at the floor level is minimized. Suction pressure across the opening provided on riser & suction filter ensures continuous circulation and filtration of air in the system. Supply outlets are evenly distributed across the room, where as risers are generally placed diagonally opposite to each other. This ensures that air is distributed uniformly in the room and there is no stagnant air pocket inside the clean room. Cooling, dehumidifying and reheating coils are provided in air stream to supply the air at designed condition. This section also contains centrifugal blower which creates necessary draft to suck the air from the clean room & throw the air across the filter bank inside the room at desirable static pressure. For class A & class B clean rooms mini pleat HEPA filters of standard size are fitted at the air outlets. This controls quantity of air flowing out of air outlet inside the clean room. Another important

feature of mini pleat HEPA filter is that pressure drop across this filter is very low i.e. 15 Pa. This combination is found useful & giving excellent results for class 1000 clean room at M/S ARIHANT SIDDHA PHARMACEUTICALS [5] in Sangli Industrial estate.

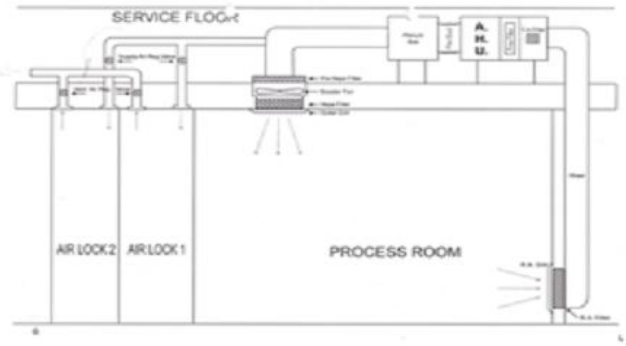

FIGURE 5: Schematic diagram of A.H.U. having double air lock & 15 pa gradients [6]

In case of saline or injections class 10 clean rooms are recommended some times. In such cases two air locks are provided for man & material entry, in addition to provision for separate arrangement for exit. We need to keep 15Pa pressure difference each, across passage & first air lock, first air lock & second air lock and second air lock & clean room. Total 45 Pa pressure difference should be there across passage & clean room. This pressure gradient can be created by using axial flow fans at the terminal filters supplying air to the room. Fig. 5 shows arrangement for creating Pressure gradient across the air locks & passage, consisting of supply air & return air ducts with pressure regulating system. This arrangement is successfully implemented in M/S HEALTHLINE PHARMACEUTICALS LTD. M.I.D.C. MIRAJ [6].

VII. Case Study

BPL Life Science Kavthemahankal[7]: For understanding the concept this case is most illustrious as it covers almost all types of products except inject able medicines. Following steps were taken for the design & cost estimation of the project.

7.1Based on building plan different areas were defined and they were classified in to four different categories, a) production area and testing area b) Raw material quarantines and finished products primary packing area. C) Auxiliary areas such as passages adjacent to production area, gents change room, ladies change room etc. d) External area such as Toilets wash rooms, offices, canteen, passage connecting core area and administrative section etc.

7.2Area, volume, required temperature, relative humidity, number of air changes per hour, class of air required(quality of air), estimated heat load, number of occupants in the room, machinery heat load, air curtain requirement, numbers designated to ventilation equipment etc. is represented in tabular form in TABLE 6.

7.3Detail drawing for location of ducting, size of ducting including cross section, locations of filter banks, air outlets, return air grills, U.V. lamp banks, booster fans and many other accessories is represented on the detailed dimensioned drawing.

7.4Tender document is prepared with all necessary documents including equipment specifications, approved makes, testing standards, testing method, testing norms , validation standards etc.

7.5Tenders are invited from experienced reputed suppliers and contractors.

TABLE Typical DQP (Design Qualification Protocol) summery sheet after testing [7]

Room No.	Name of the Room	Area m²	ht	Vol m³	Cooling Load TR	DBT °C	RH %	Grade	Class	AHU No.	Δ p mm of W.C.	No. of Air Cha-ges/hr	% for Fresh air	F.A. fan mm	Air Curtain	Occupancy		COMMENTS
1	G.C.R	24	3.65	87.60								6.57				20	low	
2	L.C.R	16	3.65	58.40								10.11				10	low	
3	Preparation Solution	27	3.1	83.70	2 x 3 TR	25	51	C	1 LAKH	1 & 2	1.5	24.77	10	N.A.	N.A.	2	low	
4	Bottle Sealing	10.5	3.1	32.55	1 X 2 TR	25	50	C	1 LAKH	3	1.5	27.87	10	N.A.	N.A.	2	high	
5	Solution Filling	18.5	3.1	57.35	2 X 2 TR	25	50	C	1 LAKH	4 & 5	1.5	22.60	10	N.A.	N.A.	2	high	
6	Bottle Washing	23.13	3.1	71.70	2 X 2 TR	25	50	C	1 LAKH	6 & 7	1.5	21.69	10	N.A.	N.A.	3	high	
7	Common Wash.	2.25	3.1	6.98	BLEED OFF	25	50	C	1 LAKH	6 & 7	1.5	23.23	10	N.A.	N.A.	1	low	
8	Ancillary Room	2.25	3.1	6.98	BLEED OFF	25	50	C	1 LAKH	6 & 7	1.5	23.23	10	N.A.	N.A.	1	low	
8a	Ancillary Room	4.71	3.1	14.60	BLEED OFF	25	50	C	1 LAKH	6 & 7	1.5	N.A.	10	N.A.	N.A.			
9	R.P washing	5.4	3.1	16.74	BLEED OFF	25	50	C	1 LAKH	6 & 7	1.5	11.61	10	N.A.	N.A.	1	low	RARE OCCUPANCY
10	Decartoning Room	21.75	3.1	67.43												2	high	
11	Granule store	14.75	3.65	53.84								9.70						NOT IN USE
12	FFS Room	24.11	3.65	88.00														NOT IN USE
13	Deflushing	9.8	3.65	35.77								12.06						NOT IN USE
14	Un-sterilized bottle area	27.69	3.65	101.07								15.90				2	high	
				0.00														
15	Sterilized bottle area	75.63	3.65	276.05								13.19				2	med	
16	**Visual checking**				2.ton Split A.C. voltas vertis											10	high	
17	Finished goods quaranti	162.9	3.65	594.66												2	low	STORE
18	De-dusting	6.6	3.65	24.09	Air Curtain 5 ft 1 H.P. motor											1	low	
19	Raw material quarantine	59.49	3.65	217.14								11.92				1	low	

VIII. Methodology adopted for cost comparison of conventional double skin roof mounted A.H.U. and single skin suspended type ductable spilt air conditioning unit [7]

Following sample specifications are given for the comparison :

a. Class 1000 clean room with single air lock for powder & tablet section

b. Required cooling capacity 5TR

TABLE Cost Comparison

S.N.	Name of contractor	Rate for Double skin roof mounted A.H.U.(Rs.)	Rate for Single skin ductable split a.c.units(Rs.)	Cost saving %
1	Clean room technology Pvt.Ltd.	650000.00	425000.00	35%
2	Sesma Engineers	614500.00	385000.00	38%
3	Himcool technology	860000.00	525000.00	38.95%
4	Swagat industrial engineers	750000.00	450000.00	40%

IX. Conclusion

As a consulting engineer working in the field of clean room technology, we are observing many small scale units being closed down because of non availability of affordable clean room technology. For switching over from existing manufacturing system to the manufacturing system as per mandatory norms development of low cost clean room is the need of hour. This inspired us for carrying out experimentation to design a system using commonly available ductable split units. These efforts were well accepted by the industry & are fruitful to them.

References

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[2] Google image-Illustrations

[3] Clean room wet bench (Clean rooms for) semi conductors-*Vijayraghavan M.N.*

[4] *Voltas Ltd. Technical manual* for ductable split air conditioners.

[5] Schematic sketch *M/S Arihant Siddha Pharmaceuticals*

[6] Schematic sketch *M/S Healthline Pharmaceuticals Pvt.Ltd.*

[7] Schematic sketch & DQP & sample cost comparison chart for *M/S BPL Life Science*