AIR CONDITIONING AND REFRIGERATION Journal
The magazine of the Indian Society of Heating, Refrigerating and Air Conditioning Engineers

Issue : October-December 1998

Air Conditioning for Pharmaceutical Plants

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The pharma manufacturing industry is one of the largest, if not the largest, users of HVACR equipment in India. The present pharma market size is approximately 12,000 crores which is only one percent of the world market size. However our growing population and increasing emphasis on healthcare will be a rapid growth in the industry along with a similar growth in the need for air conditioning and refrigeration equipment.

The emphasis in air conditioning system design in the pharmaceutical industry lies in providing a clean and aseptic environment with controlled relative humidity. The industry in itself is governed by a Good Manufacturing Practice (GMP) The goal of GMP is to provide guidelines for establishing proper environment and repeatable method of producing sterile products free from microbial and particulate contaminants. The GMP embraces a number of issues starting with the selection of building materials and finishes, planning the flow of equipment, personnel and products, determination of key parameters like temperature, humidity, pressures, airflow parameters and classification of clean rooms. It also governs the level of control of various parameters for quality assurance, regulating the acceptance criteria, validation of the facility, and documentation for operation and maintenance.

Various countries have formulated their own GMPs. In the United States it is regulated by several documents such as Federal Standard 209, code of Federal regulations 210 & 211 etc, which are revised and updated from time to time. The European Community has a "Guide to Good Manufacturing Practice for Medicinal Products and in the United Kingdom it is BS 5295, Good Pharmaceutical Manufacturing practice." In India the GMP follows largely the country of the principal technology provider. In addition regulations of the Food and Drugs Administration (FDA) need to be complied with if the products are to be released for sale in the United States.

Building Design

Proper building design and planning of the flow of personnel, material and equipment is essential for achieving and maintaining the design levels of cleanliness and pressure gradients. The building construction itself has to be "tight" with minimum of uncontrolled infiltration of outside air into the building. This is very important in the case of buildings for formulation and sterile production. On the other hand, the bulk drug plants are more open except for some sections for finishing, packing etc. Some of the principles generally followed in the construction and operation in the pharmaceutical industry are:

- Minimum seams and joints
- Avoid crevices and moldings
- Round off all joints
- All material used is non chipping and cleanable
- Wall and floor finishes should not shed particulates and should provide self-cleaning surfaces
- Ceilings are to be flush as far as possible
- Provide airlocks & air showers at the entry points of all important areas
- Operations producing particulates are enclosed and exhausted
- Personnel wear lint-free overalls, head covers etc. And do not wear cosmetics
- Each manufacturer develops over a period of time their own GMP in all these aspects.

Design Goals

Room temperature is not critical as long as it provides comfortable conditions Normal temperatures range between 20 to 25 deg C + 2 deg C, Relative humidity (RH) on the other hand, is of greater importance in all the production areas. While most of the areas could have a RH of 50 ± 5% facilities designed for handling powders need to be at 40 ±

5% Automatic control of he RH is essential for maintaining continued product quality. Of all the design goals, it is the quality of air cleanliness of the space and prevention of contamination which are of utmost importance. All GMP's aim towards achieving a clean aseptic space suitable for production. Currently the normally accepted air quality standards are:

- Manufacturing areas:- 20,000 particles of 5 micron or larger per cum of air - 500 per cum of viable organisms
- Large Volume Systems: - 3500 particles of 0.5 micron or larger per cum of air - 5 particles of 5 microns or larger per cum - 5 viable organisms per Cum

The pressure gradients, roughly are:

Atmosphere	0 Pa
Change rooms	25 Pa
Non-aseptic areas	25 Pa
Aseptic areas	
Cooling corridors	45 Pa
Access corridors	35 Pa
Manufacture laboratory	55 Pa
Filling rooms	55 Pa
Change rooms	25 Pa

(approx. 10 Pa = 1mm wg)

There should be a net airflow from change rooms to the non-aseptic areas even if the pressures are stated as equal. Regular adjustments are necessary to compensate for drift and filter clogging

Good filtration regime is a precondition for achieving the above design goals. For many areas and processes Clean Room facilities must be provided to meet the GMP. Filtration is mainly required to control the atmospheric contamination reaching the production area. It is also used to manufacture of products and also to protect the operator and environment. In dusty production areas such as grinding, granulation, coating, tabletting etc., the filters not only control the atmosphere contamination but also hold the internally generated particulates.

Atmospheric dust is a mixture of dry particles, fibres, mist, smoke, fumes, live or dead organisms. The air-borne particle size varies from 0.01 micron to as much as 100 microns. Less than 2.5 micron particles are considered as fine and particles over 2.5 micron are regarded as coarse. Fine particles are considered as fine and particles over 2.5 micron are regarded as coarse. Fine particles are airborne for a longer time and could settle on vertical surfaces. Coarse particles, products of mechanical abrasion like in grinding and granulation departments, have lower airborne life time and are subject to gravitational settlement. The air conditioning systems in the pharmaceutical industry have to handle both fine and coarse particulates depending on the production pattern and the filter regime has to be appropriate.

Table 1 is a guide line to filter selection.

Table 1 Air Filter Selection

Areas	Efficiency	Arrestance	Type
Non-aseptic Areas			
Pre-filter 1	20-40% dust spot	75 to 85%	Panel or bag
Pre-filter 2	80-85 dust spot	98%	Panel
Final	95% DOP	-	Panel
Aseptic Areas			
Pre-filter 1	20-40% dust spot	75 to 85%	Panel or bag
Pre-filter 2	80-85% dust spot	98%	Panel
Final	99.97% DOP	-	Panel

All filters are dry type with synthetic and glass fiber. While pre-filters could be cleanable, the final filters are disposable.

Filters are distinguished by their efficiency, airflow resistance and dust holding capacity. Filter testing and rating are complicated issues since the performance of a filter varies very the performance of a filter varies very widely on different basis of testing as well as the composition of test dust. Arrestance is a mass fraction of dust removed from a pre-composed synthetic test dust fed into the filter. As the dust is fed, the resistance across the filter increases and the dust holding capacity is determined as the arrestance value when the filter resistance reaches its main maximum specified. Filter efficiency is defined as the ratio of the loaded for pre-filter as per BS 2831 Test Dust No. 2

Other tests are the dust spot and DOP tests. The dust spot test is a measure of the ability of the filter to reduce soiling and discoloration. The DOP test is conducted by counting upstream and downstream particulates through a light scattering photometer or any other particulate counter. Test particulates are of uniform 0.3 micron diameter with a density of 80mg/cum produced by condensation of DOP vapour (Dioctyl phthalate or bis - 2 ethylexyl) or any other suitable substitute British standard 3928 for HEPA filters, and 2831 for other filters and ASHRAE standard 52-1 govern the testing of these filters.

Clean Rooms

Following the development of High Efficiency Particulate Air (HEPA) filters for the nuclear industry, the concept of clean spaces was first developed for the aerospace electronics industry. The same concept was appropriately applied to the semi conductor, pharmaceutical and many other industries where a clean particulate-free environment is essential for maintaining standards of product quality.

A clean room is a defined area where the critical parameters such as temperature, humidity, air changes room pressure, particulates variables etc. are closely controlled to maintain product strength, identity, operator safety and product quality. This may be a requirement of the law or by virtue of the product development data. Clean rooms are divided into several classes based on the particulate concentration limits. The current classification is shown in **Fig.1** & **Fig.2**.

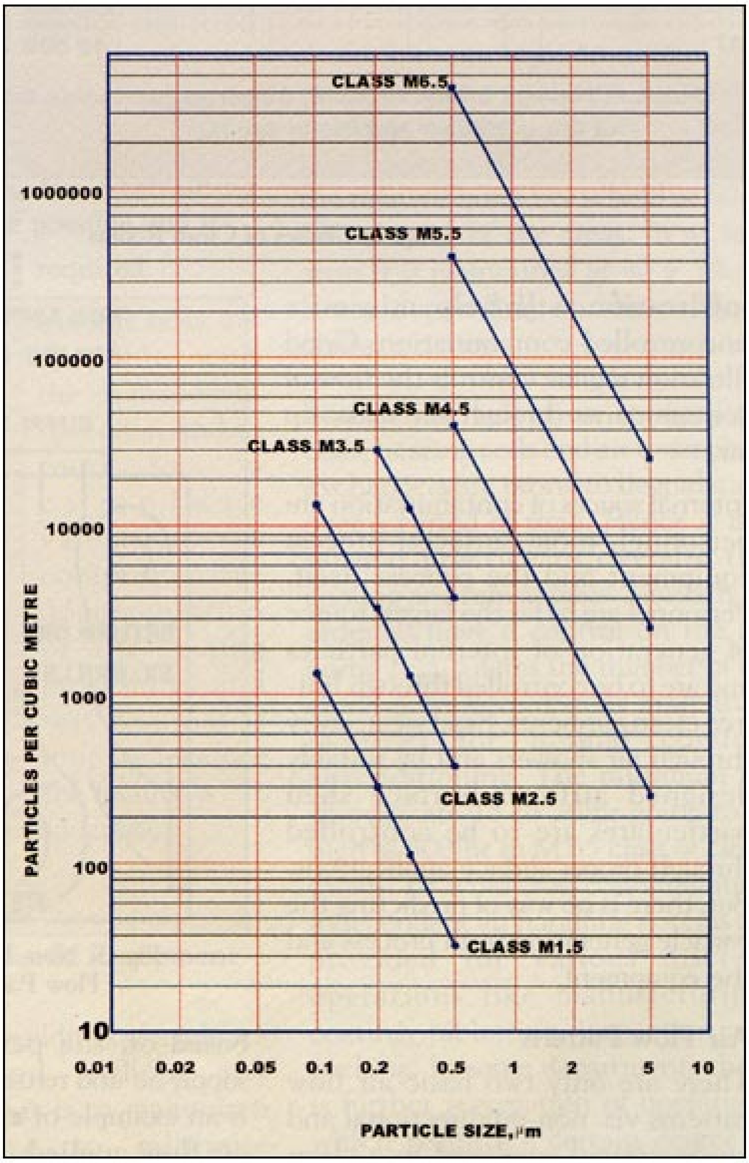

Fig. 1: Air Cleanliness Class Limits

Class Names		Class Limits				
		0.1 um	0.2 um	0.3 um	0.3 um	5 um
SI	**Inch - pound**	**Particles per m ³**	**Particles per m ³**	**Particles per m ³**	**Particles per m ³**	**Particles per m ³**
M1		350	75	30.9	10.0	
M1.5	1	1240	265	106	35.3	

M2		3500	757	309	100	
M2.5	10	12400	2650	1060	353	
M3		35000	7570	3090	1000	
M3.5	100		26500	10600	3530	
M4			75700	30900	10000	
M4.5	1000				35300	247
M5					100000	618
M5.5	10000				353000	2470
M 6					1000000	6180
M6.5	10000				3530000	24700
M7					10000000	61800

Sources : Federal Standard 209E, Airborne Particulate Cleanliness in Clean Room and Clean Zones.

Fig.2: Classes of Clean Rooms

Particle Control

Particle sources in a clean room are either external or internal. External source is atmospheric dust which is a mixture of dry dust particles, fibers, mist, smoke, fumes, bacteria and live or dead organisms. Entry is largely through outside make-up air but could also be by infiltration through doors, windows, wall and ceiling joints and penetrations. Hence a right building with minimum infiltration will help minimize uncontrolled contamination. Good filtration regime controls the flow of contaminants through the make-up air.

Internal sources of contamination are personnel, room surface, process equipment and he process itself. Personnel are by far the largest source of fenestration of internal particles and are to be controlled through lint-free clean garments, head wear, entry through air showers and by suitably designed airflow. Surface shed particulate are to be controlled through proper surface applications. But, there is no way of predicting the particle generation from process and the equipment.

Air Flow Pattern

There are only two basic air flow patterns viz. Non-unidirectional and unidirectional employed in a clean room. Non-unidirectional air flow is clean rooms of class M4.5 and above. In this airflow pattern, there will be considerable amount of turbulence and it can be used in rooms where major contamination is from external source that is the make up air. The contaminants are filtered out in the air handling unit filters and also terminal HEPA filters. If internal contaminants are a concern, a clean work station is provided inside the clean room.

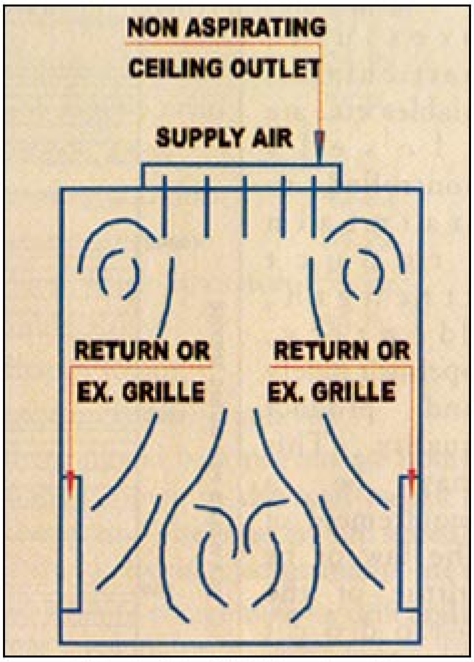

Fig. 3: Non Unidirectional Flow Pattern

The unidirectional air flow patter is a single pass, single direction air flow of parallel streams. It is also called 'laminar' airflow although it is not truly laminar but the parallel streams are maintained within 18 deg - 20 deg deviation. The velocity of air flow is maintained at 0.46 m/s to 0.65 m/s as specified in Federal Standard 209 version B although later version E does not specify any velocity standards.

Unidirectional air flow clean rooms are vertical down-flow or horizontal types. Vertical down-flow type has the ceiling of HEPA filters. In class M3.5 rooms the entire ceiling requires to be covered with HEPA filters with low level returns or solid or perforated floor plenums. The parallelism of streams is maintainable right up to the working height (say 900mm) but stream lined flow gets degraded by obstacles by way of people, equipment and work tables. Thus the room gets divided into an area of stream lined flow and some area of turbulent flow which causes undesirable particle trajectory Horizontal flow systems are same as the vertical except that the airflow is horizontal from a wall of HEPA filters to a receiving wall on the opposite side. In this the parallelism of stream lines of flow is not as maintainable as in the down flow and further the space becomes more and more contaminated towards the return wall. **Fig.4** shows such a clean room. Between the two, the vertical flow pattern yields better results and is more adaptable to pharmaceutical production.

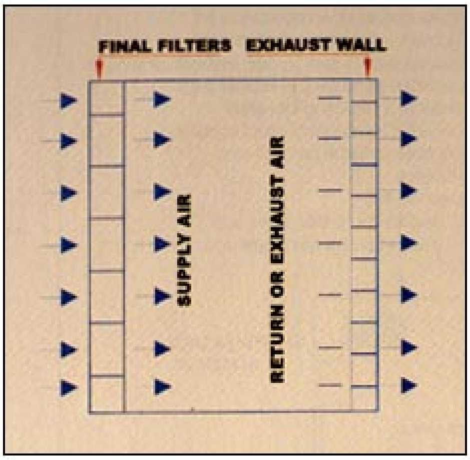

Fig. 4a: Horizontal Unidirectional Flow in White Change Room

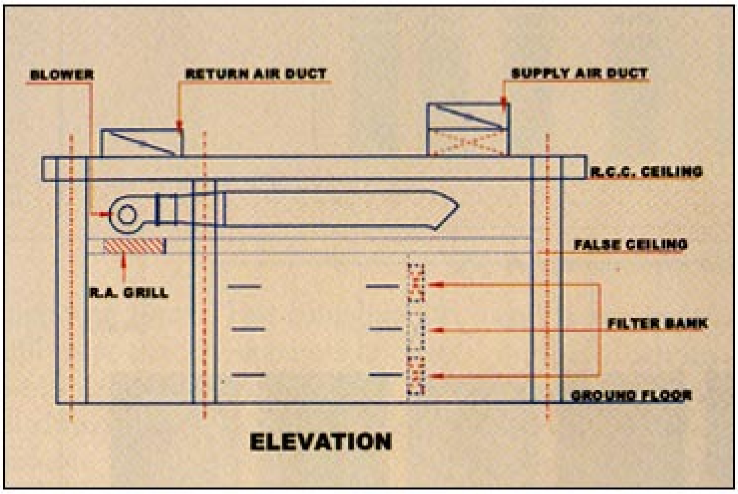

Fig. 4b: Elevation Typical Airflow System for White Change Room

Testing

The air conditioning system for a clean room is tested and validated based generally on US Federal Standard 209 and/or BS 5295 and no production can start until the clean room is validated. For proper evaluation of the facility, the system is tested before commissioning, while at rest, and during production. Pre-commissioning test procedures cover the following parameters:

- HEPA filter integrity by cold DOP testing for pinhole leaks in the filter media, across sealants and frame gaskets, supporting frame and wall. This has to be done on the upstream and terminal filters if two banks are used
- Air stream velocity under each filter panel is to be established
- Establish a spectrum of particulates from appropriate air samples
- Pressure differentials between room to passage to change rooms
- Pressure drop across the final filters
- Room temperatures and relative humidity
- Smoke testing for establishing flow patterns if possible and if required similar test are desirable with the clean room in operation and at rest for a complete

validation. A comprehensive documentation of the testing procedures and test readings is prepared before the facility is handed over for production.

System Design

- **Cooling Loads & Equipment selection**

Pharmaceutical buildings as a rule are totally enclosed without any fenestrations. This is to maintain a 'tight' building to minimise uncontrolled infiltration of atmospheric air. As a result, the room sensible loads are essentially a contribution from process equipment, lighting and personnel. The density of equipment loads is low excepting in the tablet manufacturing facility covering granulation, drying and tabletting. A major contribution of the cooling load comes from outside air entering the air handling unit. There is also considerable diversity in the equipment loads based on the production patterns. All these result in a low room sensible load density varying from as low as 40 Kcal/h/sqm to 100 Kcal/h/sqm. Hence the system design lays emphasis on control land maintenance of relative humidity. The room temperature is normally held between 20 deg. C, whereas the relative humidity is held at 50± 5% in most of the areas. In a few areas it is maintained at 40± 5% or lower depending on the product characteristics.

Equipment selection i.e., cooling coils, hearing coils and air-to-air plate exchangers are prone to degradation over a period of time. Hence it is a normal practice to oversize the cooling and reheating coils. Similarly in order to have a control on the air borne particulates, the number of air changes are considerably more than required for normal comfort air-conditioning. The minimum air changes are 15 to 20/hr going to as high as 300/hr in M3.5 class of clean rooms. To avoid cross contamination independent air handling systems are provided for various discrete operations like manufacturing, coating, tabletting, inspection and packing. In some departments there is further segregation of operations which requires a certain degree of control, if not an altogether independent air handling unit. In other words, the equipment selections and segregation's of the air handling systems needs to be done after through analysis of the process requirements. **Fig.5** is a standard airconditioning flow diagram for a facility without any RH control.

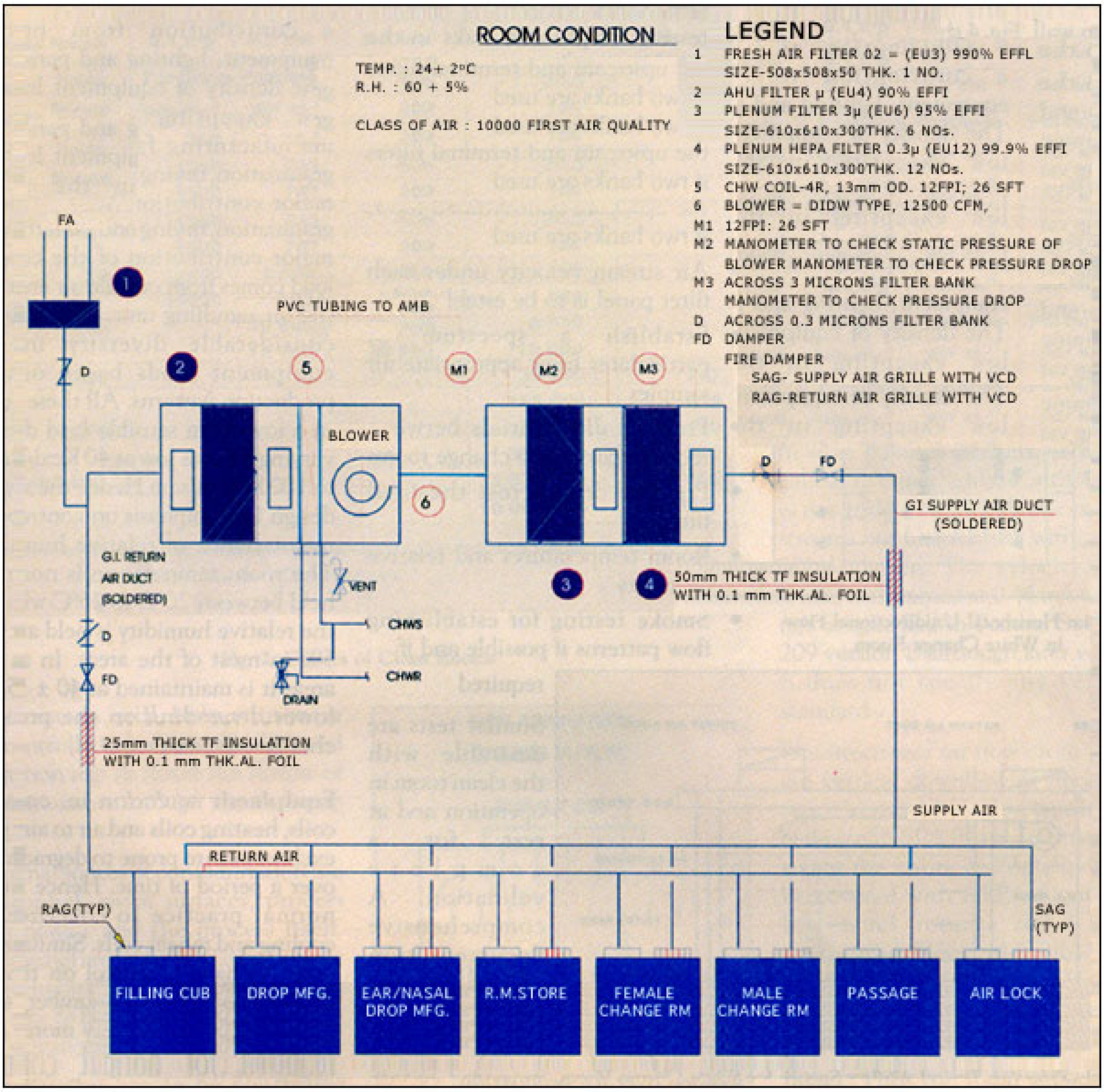

Fig. 5: Air Conditioning Flow Diagram - Filling Facility

- **Relative Humidity Control**

As stated above, pharmaceutical air-conditioning is characterised by low room sensible loads, low and controlled RH and high air changes. All these characteristics contribute to problems of RH control in the industry. A more or less standard configuration of the air handling system is shown in **Fig. 6.1** It consists of a cooling coil, a heater array, return air filters, fresh air filters and supply air filters. This configuration will meet the requirements of clean facilities upto class M 5.5. The modified version using variable air volume is shown in **Fig. 6.2** This system takes advantage of diversity in the air-conditioning air requirements in different departments served by the same air handling unit. In these cases, the fan is driven by a variable frequency drive. Such a system brings about considerable savings in the energy consumption of the fan system and pays for itself anywhere from 1.5 to 2 years.

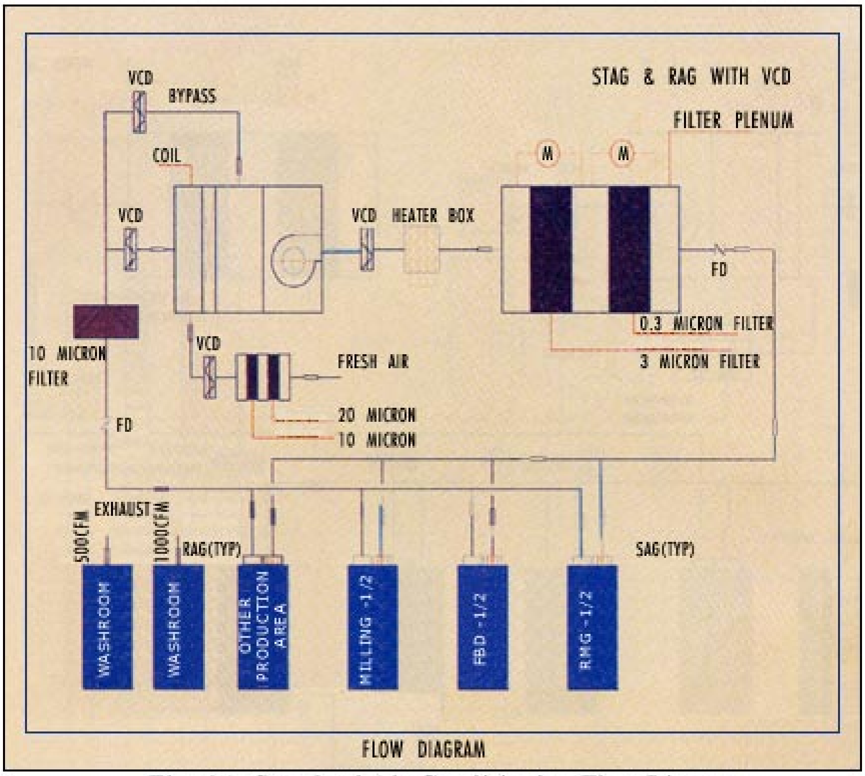

Fig. 6.1: Standard Air Conditioning Flow Diagram

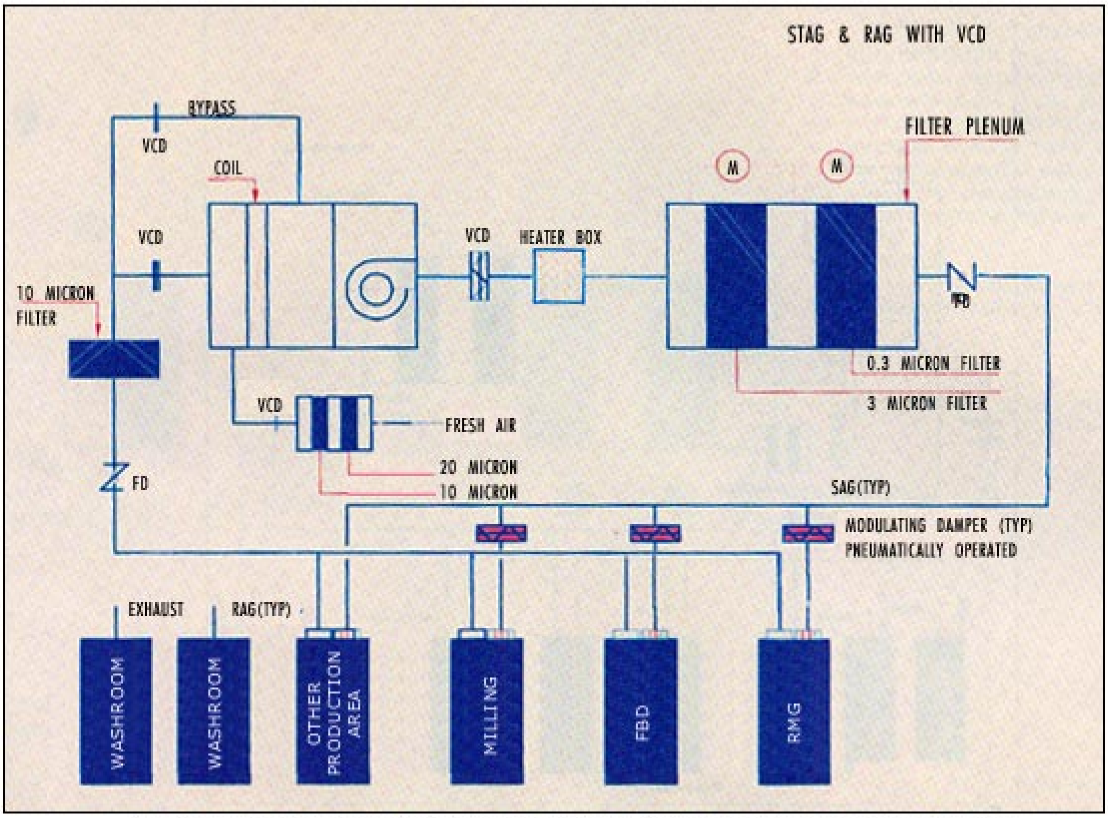

Fig. 6.2: Air Conditioning Flow Diagram with Variable Air Volume System

Spaces where a low RH of 40±5% is required, an additional brine cooling coil is incorporated. **Fig 7** shows a typical diagram using additional brine cooling and hot water coils for a strip packing facility. The brine coil further dehumidifies the supply air which is repeated in the hot water coils for a strip packing facility. The brine coil further dehumidifies the supply air which is reheated in the hot water coil. This is to ensure lower moisture content in the supply air and hence maintain the desired low RH in the space.

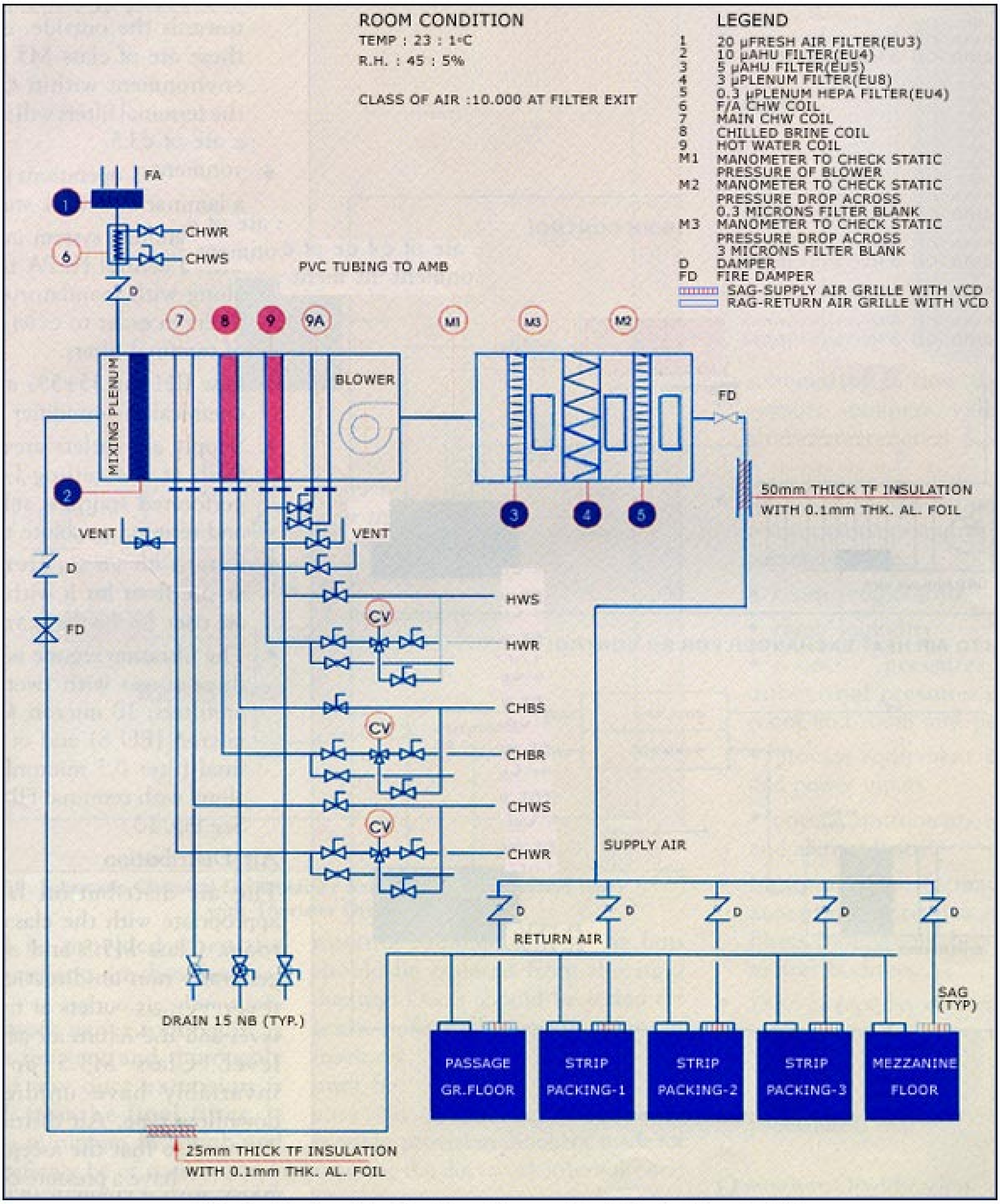

Fig. 7: Air Conditioning Flow Diagram for Strip Packing Facility

Sometimes plate type air to air heat exchangers are interposed between the cold air from the air handling unit and the return air from the room. A part of the sensible heat from the return air (24 deg C) will get transferred to the supply air raising it from 6 deg C to 14 deg. C thus providing free reheat.

Such a system saves the cost of energy spent in reheat coils which is substantial if electrical re-heaters are used. However, one should be cautious in applying a plate heat exchanger for this purpose as the heat transfer capability deteriorates over a period of time. Fig 8 shows the two reheat systems as applied to low RH areas.

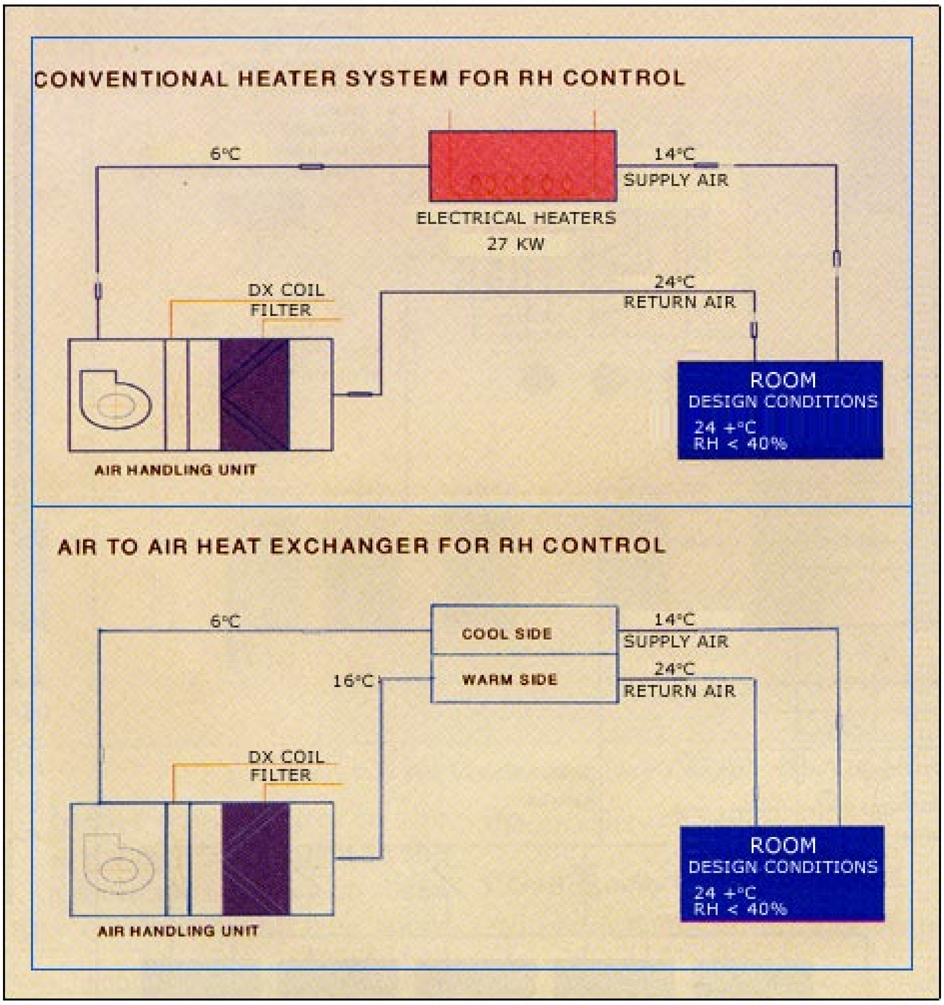

Fig. 8: Reheat systems for low RH applications

Sometimes packaged dehumidifiers are used in rooms where low RH is required. The dehumidifiers are specially designed self contained type air-conditioners which will draw humid room air, dehumidify in the evaporator coil and push back into the room through the condenser coil at a higher temperature. In the process the moisture content in the air is reduced and sensible heat added in the condenser coil. The room humidity will progressively reduce to the desired levels, chemical adsorption dehumidifiers are incorporated for reliable control on the relative humidity. The chemical dehumidifiers are continuously regenerated type. Fig. 9 is an example of an air-conditioning system with the chemical dehumidifier and a thyristor drive to reduce power input to the electric re-heaters on reduction of internal latent load in the production facility.

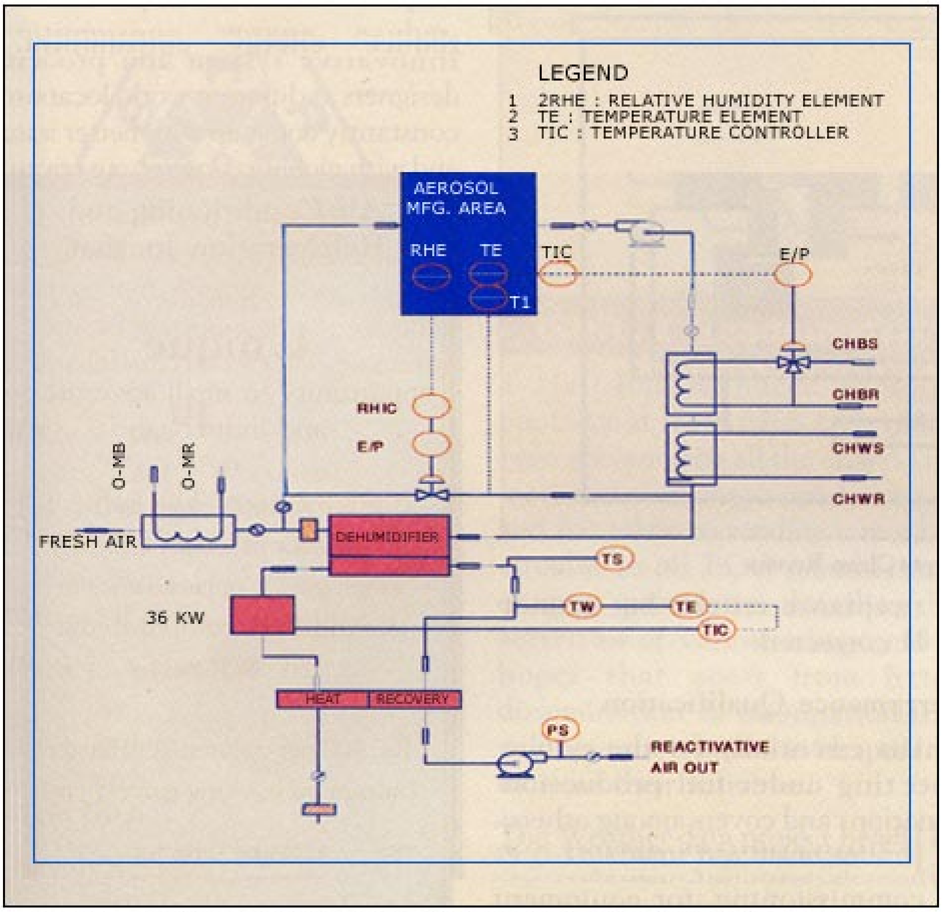

Fig. 9: Schematic Chemical Dehumidifier (continuously regenerated type) with Thyrister Drive

Clean Rooms

All pharmaceutical facilities belong to one or other class of clean room. General acceptance is:

- Tabletting facilities Class M 6.5 (Class 100,000)
- Topical & Oral liquids Class M 5.5 (Class 10,000)
- Injectables Class M 3.5 (Class 100)

Clean rooms are designed for aseptic as well as non-aseptic applications. Pharmaceutical facilities designed for sterile products will have aseptic clean rooms while manufacturing of tablets and oral liquids will have non-aseptic clean rooms. Besides bulk drug plants designed for handling products in finishing suites will also employ non-aseptic clean rooms.

The entrance to the aseptic clean room should be through a regime of change rooms generally designated as black grey and a white change rooms in order of increasing pressures towards the sterile filling facility

Aseptic clean rooms have the following distinct characteristics:

- Highest pressure in the most critical zone is progressively reduced at the rate of 15 Pa towards the outside. Generally these are of class M5.5 but the environment within 600mm of the terminal filters will be as good as class M3.5.
- All Critical operations will be in a laminar flow work station.
- Air handling system is provided with a central HEPA filter bank along with mandatory terminal filters in order to extend the life of terminal filters.
- Low RH say 35±5% is through chemical dehumidifiers.
- Supply air outlets are provided flush at the ceiling level with perforated stainless steel grilles and terminal absolute filters
- Return air grilles are provided at the floor level with a return air riser for better scavenging
- The filtration regime is generally three stages with two stages of pre-filters, 10 micron (EU 4), 3 micron (EU 8) and one central final filter 0.3 micron (EU 12) along with terminal HEPA filter. See **Fig.10**

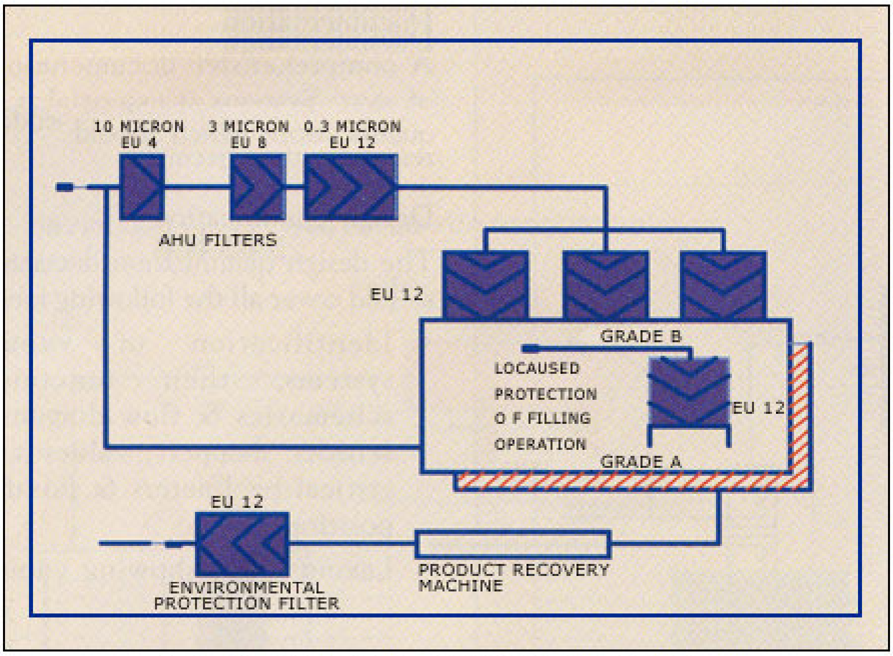

Fig. 10: Filteration in Asceptic Clean Rooms

Air Distribution

The air distribution has to be appropriate with the class of clean room. Class M5.5 and above are generally non-unidirectional with the supply air outlets at the ceiling level and the return air at the floor level. Class M3.5 and lower invariably have unidirectional down flow type. Air distribution is designed so that the aseptic filling room will have a pressure of 50 Pa or above with a gradient of 15 PA to the adjoining area. The pressure gradients are monitored with 'U' tube manometers or magnahelic gauges. Alarm and warning systems may also be provided when the pressure gradients are disturbed.

All duct work must be non-flaking, corrosion resistant and thoroughly sealed. If any duct extension is provided from the final filter, it should be minimum in length and should preferably be of stainless steel upto the finishing suite. Remaining duct work could be of good quality galvanised steel. Round ducting is a natural choice, being self cleaning in shape, wherever space permits. All rotating equipments like the fans should be isolated from the rigid ducting. Ducts should be tested for leaks before the application of insulation. Volume control dampers must be provided appropriately for easy air balancing. Wherever possible, provision should be made for cleaning the duct work internally and externally. Grilles and diffusers should be flush mounted into ceiling, walls or duct work and all such grilles shall be fabricated from stainless steel in the clean areas.

Documentation

A comprehensive documentation of HVAC systems is essential for a proper and complete evaluation. The documentation should cover design, operation and performance qualifications which should and the operation, maintenance and periodic testing of the system.

Design Qualification

The design qualification document should cover all the following issues:

- Identification of various systems, their functions, schematics & flow diagrams, sensors, dampers valves etc., critical parameters & fail-safe positions.
- Layout plans showing various rooms & spaces and the critical parameters like:
  - room temperature.
  - room humidity
  - room pressures and differential pressures between room and room and passages.
  - Process equipment locations and power inputs.
  - Critical instruments, recorders and alarms, if any.
- Equipment performance and acceptance criteria for fans, filters, cooling coils, heating coils, motors & drives.
- Duct & pipe layouts showing air inlets, outlets air quantities, water flows and pressures.
- Control schematics and control procedures.

Operation Qualification

This is a commissioning documentation which shall provide all the details of equipment various points of performance, test readings, statement of compliance and noncompliance with the acceptance criteria. Broadly the features are as follows:

- Installation date showing manufacturers, model no., ratings of all equipment such as fans, motors, cooling & reheat coils, filters, HEPA filters, controls etc.
- As-built drawings showing equipment layouts, duct and pipe runs, control & fire dampers, settings of various sensors and controllers.
- Contractor's rest readings covering rotation tests, megger readings, air quantities, temperatures and RH pressures of each space, dry & wet run of controls, air and water balance, HEPA filter integrity tests at final operating velocities testing of limits & alarms.
- Identification of items spaces, parameters not meeting the acceptance criteria but cannot be corrected.

Performance Qualification

This is essentially for the system operating under full production conditions and covers among others:

- Identification of agency for commissioning, for equipment and instruments and their calibration.
- Test readings of all critical parameters under full operating conditions and full production, modification of readings in the contractors test results, acceptable and unacceptable departures from design qualification and acceptance criteria.

Conclusion

Manufacturing practices, air filtration techniques and air conditioning components are being constantly upgraded in order to improve the finished product and reduce energy consumption. Innovative system and product designers at different world locations constantly come up with better ideas and with globalization serious readers are advised to keep in touch with similar articles in other trade magazines.