Design of utilities and services

8

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8.1 Introduction

The design engineer may ask why this book covers the design of utilities and services and their maintenance, as these are common throughout industry. However, these systems have become important parts of asset management and should no longer be an afterthought following the completion of the 'pharmaceutical' part of the design. Consideration throughout the design makes the validation stage so much easier.

The impact on the design of engineering workshops for maintenance and servicing of production and the utilities is outlined in this chapter and aspects particularly relevant to the pharmaceutical industry are emphasized.

Regulatory inspectors spend a lot of time looking at the design of water supplies, air conditioning systems, their operation and cleaning, and how they impact on pharmaceutical processes. They also want to know how the business is run and organized and who is responsible.

The ideal pharmaceutical facility (using the USA convention to mean the entire building, services plant, services distribution and production equipment) is:

- simple;
- has accessible plant and services;
- reliable;
- does not breakdown, go out of adjustment or wear out;
- fully documented.

The engineer wants the information on the plant in a form that his people can understand, to enable them to maintain it easily and find a quick solution to a problem. The production department wants a flexible plant available at all times, while the quality assurance department wants a plant which performs to design, with written procedures that are always followed and documented and where all changes are recorded and validated. The company wants all this at minimal cost.

Engineering has moved from being a service to becoming an essential part of overall profitability and is now spoken of in terms of asset management. Asset management is the consideration of the activity as the ownership of a major company resource, i.e. the plant and equipment rather than as the 'fixer' connotation normally appended to maintenance.

Maintenance is now using fault analysis, more sophisticated monitoring of the equipment and methods to assess performance to concentrate effort where it is needed. Less maintenance, correctly performed, can be shown to give increased up time.

There are two aspects to achieving trouble free operations:

- management and organization;
- engineering design and specification.

Management requires a clear understanding of the objectives of the engineering function to enable organization and planning and to ensure people are available when required. Clear objectives enable the choices to be evaluated and selected.

Organization requires a clear statement of responsibilities and functional relationships of staff and contractors, selection and training of people, setting up external contracts, followed by a system to measure the performance of the engineering department and make improvements.

Planning ensures the information is fed into the design at the right time, the facility is designed, built and tested to the design, the people and systems are in place when the plant is in use and the facility is maintained.

The design of the engineering space and content of workshops and offices is a subsidiary design exercise based on all the above.

Engineering design requires use of all available engineering knowledge, analytical skills and design experience, by a systematic questioning of the design for operability and maintenance throughout the design and construction.

8.2 Objectives

The engineering function in a pharmaceutical facility is a cost centre (it has a direct impact on the costs and profitability of the company) and, therefore, must be justified. Engineering costs, as with all costs in the industry, are constantly being reviewed. 'Downsizing', 'internal customers', 'process re-engineering', 'delighting the customer' and 'core activities' are terms in common use in the pharmaceutical industry. The emphasis is on trouble free

operation for the customers and they expect no breakdowns, the lowest cost and to be able to plan production without concern over availability of the equipment.

No longer is a new facility designed with a clean slate to set up the maintenance department. A greenfield site does not automatically have an engineering complex with all the essential functions of machine shop, welding and fabrication, instruments, design office and a full set of satellite workshops throughout the production areas. The objectives and measures for the engineering function, therefore, need to be determined with the customers. These will depend on company policy, the location and the type of operation in the facility. For example, the following may have different objectives:

- 'Over the Counter' (OTC) facility;
- 24-hour freeze drying operation;
- handling cytotoxic products;
- a local packaging operation.

8.3 Current good manufacturing practice

The attention of the inspecting bodies is moving from the process and production operations to the research and development activities before production and to the services plant and maintenance during production. Increased importance is being placed on validation of the plant and equipment and maintenance of the validated state. For a new product, the pre-approval inspection will require a fully validated plant. Subsequent inspections will examine production records and follow these through the maintenance routines.

FDA guidelines cover these principles (see Chapters 2, 3 and 4). They require:

- appropriate design of facilities;
- equipment history and records or database;
- written procedures and evidence that procedures are followed;
- a maintenance programme.

This enables engineers to set up systems to ensure control of their activities. It places a requirement to know the plant and equipment and to be able to show that it is receiving the correct maintenance. It requires method statements of the maintenance and the description of the tasks.

To do this requires planning, systems and records. There is only one good time to start this — at the inception of the project.

8.4 Design

During design, decisions are made which affect the maintenance and operation of plant and equipment. Maintenance considerations are as important as the process, the production capacity of the facility or the tests to be performed by a quality assurance laboratory. Access and routes for maintenance are as important as those for production and quality assurance staff and for supplying materials to the facility.

Maintenance requirements must be considered during the design stage, as the cost at this stage is minimal compared to the costs after completion and the consequential costs of poor performance.

The maintenance strategy should be part of the initial design study and will determine action during design and installation. The maintenance staff should be part of the project team. The engineer responsible for maintenance should be appointed and be responsible for design decisions and acceptance of the plant and facility. The validation master plan will have been formulated and an essential part of validation is the clear trail from design intent to finished facility.

Co-ordination of the services and the structure are critical. The question to ask of every service line and connection is 'Why do I need access and how do I check it?'

8.4.1 Building

The materials of construction and general size and shape of the building are important. Heights of floors and size and location of plant rooms are part of the design process. The service loads should be calculated in the front-end design to size the main elements of the plant and an allowance made for the inevitable increase in these during design development. This determines the area for services and the location of main plant areas.

Separate engineering floors can be justified. Floor to floor heights should be generous. The increase is in structural cost of floors and envelope. The floors are needed to support the plant, so are not extra and the increase in envelope cost is minimal. The cost of services plant and its controls can represent up to 60% of the total project and the civil structure up to 10%.

All ducting requiring inspection should be on the plant floor and not hidden in false ceilings. This leads to structural slab ceilings in parenteral areas. Where services are run above a false ceiling (such as an office suite) there are beams supporting the floor and, if it is a reinforced concrete structure, there are caps on the columns, which will reduce the space locally.

The structure must allow for access for services. The increasing electrical power and controls require co-ordination and affect the structural design. A reinforced concrete structure can become complex when many conduits pass through an area.

Thought must be given to future service requirements, for example, in an analytical laboratory additional services may be required or the bench layout may be changed to suit new methods. The floor must be designed to permit these changes without affecting the strength and a grid of soft spots may be required.

The trend is to locate the drives and services of production plant in service areas. These should be designed with good access and enough space for maintenance.

Inlet and exhaust should be located to suit the prevailing wind and may require a special study on a multi-building site.

Details such as the design of windows or atria for cleaning are important. A glass stair tower may look good but will be costly to clean. It may need specialist contract equipment, which will require steel reinforced concrete pads. Building expansion joints should not run through critical areas and should be kept away from heavy traffic routes. Parenteral production areas should be on a good slab to minimize floor cracks.

Wet services should not run over critical areas. If this is unavoidable there should be no joints and all items requiring maintenance should be located away from the area. Inspection points and clean-outs for drains should be located in service or plant areas. Particular attention should be paid to the design and construction of service penetrations to process areas.

8.4.2 Maintenance access routes

Movement of engineering personnel should be part of the overall people and materials movement study. Separate engineering floors allow separate access routes for staff, which reduces contamination of the production space; fire escape routes or separate external entrances can provide access, for example. A WFI plant may require a specific changing area and decontamination for parts to be fitted to the plant.

8.4.3 Plant access

The structure and the openings to the plant areas must be designed to allow removal of the largest maintainable item without affecting the integrity of the production facility.

Adequate access for maintenance of the plant and services should be provided. Any valves requiring maintenance must be accessible even if this

means locating them away from the heater batteries. Test points should be accessible. With conventional design tools basic decisions such as location of pumps, motors, valves, traps, filters, etc. can be made.

The mechanical, electrical and control services in a modern pharmaceutical plant area need co-ordination to ensure that there are no clashes and that a normal-sized person can reach all areas of the plant requiring access. Drawings to 1:20 scale in plan and elevation of plant areas are required to check this. Alternatively, modern design software using 3D could be used.

8.4.4 Storage of consumables

As part of the strategy, a decision is required on the storage of spare filters and other consumables that are used infrequently. If they are held on-site then dry, safe storage is needed.

Solvents

In this context solvents are considered as organic liquids that provide a vehicle for bringing reactants together, moderating reaction conditions, preferentially extracting one component from another, or cleaning equipment, but are not themselves reactants.

Most solvents are flammable, often with low flash points, usually of low reactivity and generally non-corrosive.

Bulk, drum or IBC storage and distribution

In any design, one of the early decisions must be the choice between bulk, drum or IBC storage and distribution. In the absence of other factors, bulk storage is the preferred option since it usually provides advantages in terms of economics, minimized labour involvement and more effective integration in automatically controlled processes. Despite the greater inventory, bulk storage also has the better safety record.

In practice, this early decision will be made primarily on the basis of the individual batch quantities combined with estimated campaign or annual consumptions. The choice may be influenced to a lesser extent by the existence or otherwise of a tank farm, site space considerations, capital versus operating costs, or occasionally the package availability of the solvent involved.

Bulk storage is the method of choice for much primary production but for pilot plants with reactors of say 0.2 to 1 m^3 capacity, drummed solvents often provide an appropriate solution where one-off batches or very short runs are common.

In secondary production, solvents are frequently needed only for equipment cleaning and in such relatively small quantities that supplies in drums or even smaller containers often suffice.

Bulk storage siting

One of the initial decisions relates to the location of storage tanks; whether in a dedicated tank farm serving a number of buildings or by placing alongside the production units they supply.

In laying out a greenfield site, space could be set aside for a tank farm specifically able to meet the initial site needs but capable of expansion to cater for bulk solvent demands as the site develops. However, the benefits of centralized control, minimized space and facilities for tanker unloading and sampling and reduced vehicle movements on-site must be weighed against higher first costs for set-up and piping distribution to production buildings. Once established the marginal costs of adding further solvents or destinations are likely to be small in comparison with the alternative approach of siting storage tanks adjacent and dedicated to individual production units as and when the need arises.

The majority of new designs will, however, be applied to existing plants where choices between centralized versus local storage are not applicable and location will be dictated by the site philosophy and space availability.

When decisions are taken to locate tanks adjacent to the buildings they serve, conscious recognition must be given to the additional restrictions imposed, particularly in ensuring the safety of the facilities in the event of fire. Such limitations can affect the total quantities stored against the proximity of building walls, the nature and fire resistance of their structure, location of doorways, windows and fire escape routes.

Wherever tanks are located a prime requirement is good road tanker access, not only to allow safe docking for unloading but also to facilitate rapid vehicle exit if required by a serious incident. Siting should minimize or avoid obstructing site roads during unloading which, with quality control checks can occupy several hours per visit.

For the most part storage tanks should be located above ground. Although below ground installations provide some advantage in terms of fire protection, environmental concerns and the costs of providing satisfactory protection and leakage detection often prove prohibitive.

General

Having located the storage area and associated tanker bay, facilities are needed to allow safe sampling of the cargo before discharge, often in the form of a height adjustable overhead gantry. Occasionally, weather protection is provided

by canopies, usually without sidewalls, which inhibit ventilation and dispersion of flammable vapours.

Over recent years pumping has become the preferred method of emptying road vehicles, in contrast to the increasingly rare use of compressed air discharge with its attendant drawbacks of formation of flammable atmospheres, potential for solvent contamination and unnecessary emission of vapours. Though some road tankers are equipped with pumps, one forming part of the storage facility itself will give greater assurance of cleanliness especially if dedicated to one material.

Provision of static earthing, safety showers, self-sealing hose couplings and vapour balance connections (between tank and tanker head spaces) are safety or environmental features of an almost mandatory nature.

In sizing storage vessels the main factors will be the annual consumption together with individual batch and campaign requirements. Consideration should, however, also be given to ensuring that tanks are sized to contain a full tanker load plus a margin to allow for order lead times as well as unexpected late deliveries (caused by inclement weather, for example). Typically 10% ullage is applied once the actual storage volume has been determined.

The normal practice is for tanks to be installed within bunds, mainly to protect the environment against leakage. More than one tank can be located in a single bund provided its capacity is adequate to accommodate the capacity of the largest one plus 10%. Good bund design should allow adequate access between bund and tank walls for maintenance and to ensure ease of escape in an emergency. For similar reasons, wall heights need to be limited. Low walling has the additional benefit of promoting vapour dispersion. Since bunds collect rainwater, arrangements are needed for its periodical removal.

Where several tanks are located together or single tanks are located close to buildings, drench systems can provide cooling in the event of fire in adjacent vessels or buildings. The need or otherwise of such protective devices is determined in conjunction with insurers, the Health and Safety Executive or similar authorities.

Most storage tanks for highly flammable solvents (flash point below 32°C) are blanketed with an inert gas as a safety precaution. For some materials, excluding oxygen and moisture helps to maintain solvent quality and for this reason it is also applied to less flammable situations. Nitrogen is the most common inerting gas, but carbon dioxide is an occasional alternative with typical blanketing pressures of 10 to 20 mBar.

Distribution

From the storage tanks, solvent will be distributed via a system comprising pumps, distribution pipework and usually metering devices and filters.

An appropriate control will be built into the scheme. Distribution pumps are generally located outside the tank bunds on plinths arranged to drain away any leaked fluid. The pumps (duty plus standby for critical situations) and distribution main are sized to support the number of vessels that need to be filled simultaneously. Branches to individual users will be based on the desired filling time for that vessel. With non-water miscible and hydrocarbon solvents, particular emphasis should be placed on reducing fluid velocities to minimize static build up. This applies especially where the presence of moisture may create two phases.

Pump differential heads are determined using standard calculations accommodating pipeline, filter and instrument losses and static heads including pressure in receiving equipment. Calculations should cover the full operating envelope of the system. Centrifugal pumps provide low cost, reliable service with packed glands or single mechanical seals suitable for the majority of installations. Magnetic drive pumps eliminate the leak potential of rotating seals.

To minimize leakage and avoid establishing unnecessary zoned areas, welded lines are preferred with the minimum of joints for maintenance purposes. Solvents do not usually need to be distributed through ring mains — continuous circulation wastes energy and can cause unwanted heat and static. Long pipe runs especially where subject to temperature variations (for example exposure to direct sunlight) require protection against hydrostatic overpressures, most commonly in the form of a small relief valve returning to the source vessel.

Protection of pumps with inlet strainers is good practice as is end-of-line filtration, largely to remove rust scale and similar particulates. Where higher standards are demanded, micron filters can be fitted usually alongside a downstream piping specification change to stainless steel to avoid potential recontamination from lower grade materials.

Batching meters are a common and economical means of metering solvents into receiving vessels with satisfactory levels of volumetric accuracy for most purposes. Versions are available with output signals suitable for integration into computer and other control arrangements. Load cells, level gauges and transmitters and other devices on either source or receiving vessels provide alternative means of metering with varying degrees of applicability, accuracy and cost.

Most bulk distribution systems are connected to many destination vessels so that the final shut-off valve will be exposed to its internal conditions. This final valve must, therefore, provide positive shut-off to ensure no back contamination; where circumstances are more critical, the final solvent valve can be

mounted on a manifold with other services, with double protection being provided by another valve between the manifold and vessel.

To eliminate risks from static, it is vital that all metal components of flammable solvent systems are checked for earth continuity both before bringing into use and after modification. Arrangements to allow entering solvents to run down vessel walls helps to eliminate 'free fall' static generation.

Materials of construction

Most solvents are produced in plant fabricated from carbon steel. Hence, this material is adequate for many pharmaceutical grade solvent storage and distribution systems. For certain solvents or where absence of colour is important, stainless steel is an alternative constructional material.

Carbon steel is similarly suitable for the majority of distribution pipework although it may well be upgraded to stainless steel downstream of final filtration. Such upgrade avoids pick-up of particulate downstream of the filtration, minimizes internal corrosion where the tail end of the solvent pipe may be exposed to reactor contents and provides cleaner, maintenance-free piping within the process areas. The latter point is particularly important for ensuring GMP in secondary manufacturing plant.

Plastic and glass-fibre are rarely, if at all, employed for flammable solvent handling. Difficulties of static elimination, potentially inadequate chemical resistance and above all their lack of fire resistance make them unsuitable. Solvent suppliers are always willing to offer advice on suitable materials of construction and their advice should be sought if there is any doubt over the suitability of one material over another.

Recovery

Most plants have some form of solvent recovery plant to reduce the costs of purchasing new solvent and disposing of contaminated solvent waste. Steam stripping is usually used for this application, so non-polar solvents with low boiling points are preferred.

Recovered solvent is usually stored separately from new solvent, with the facility to top up with new solvent as required. It is common to use the recovered solvent in the initial stages of production with the new solvent being used for the final filter washes. New solvent is always used for cleaning.

8.5 Utility and service system design

There is a temptation to specify spare capacity and duplicates of plant for run and standby. Care should be taken with this approach, as over-sizing fans and pumps can lead to control problems.

Run and standby may require more control. For example, do you alternate between the two or have 'run' installed and 'standby' unbelted or as a non-installed spare? On WFI a simple system with no dead leg is required. Duplicate pumps require more valves and give dead areas unless complex controls are provided. Standardized flange spacing and a non-installed spare can replace duplicate steam reduction sets.

A risk analysis or Failure Mode Effect Analysis (FMEA) may need to be carried out to decide the strategy.

Shut off valves should only be used sparingly. Breaking a complex service into many sub-sections with shut off, in the hope of being able to carry out selective shutdown, is expensive and you will have to prove that the flows in the part plant are still within design limits. It may be better to shut down the whole system for repair work.

Multiple-use HVAC plants should be avoided. They are difficult to keep in balance and prevent cross-contamination.

Table 8.1 shows the type of system categories that may be required and the areas of utilization.

Table 8.1 Utility system categories

Utility category	Type of system	Possible area of utilization	
		Plantroom	Packing
Compressed	Service comp air	✓	✓
Gas and Vacuum	Process/instrument comp air	✓	✓
	Breathing air	✓	
	Special gases		
	Vacuum-cleaning		✓
	Vacuum-service		✓
	Vacuum-process		
Water	Domestic H&C	✓	✓
	Purified		✓
	WFI		
	LTHW	✓	✓
	Condensate	✓	
	Chilled water	✓	✓
	Cooling water	✓	
Steam	Service	✓	
	Clean		

Some examples are discussed in this section. The intention is not to provide prescriptive solutions, but to indicate factors that will influence the design and to suggest sources of information that may be useful to the designer. It is important to achieve a clear understanding of the requirements of the system under consideration, in terms of quantity and quality, at the outset of the design process, as this will allow a proper assessment to be made of the best methods available for meeting the requirements of the system. Of particular importance when specifying the quality will be the likelihood of contact with the product, i.e.:

- part of final product, e.g. water;
- direct contact, e.g. solvents;
- indirect contact, e.g. Clean In Place;
- no contact, e.g. thermal fluids.

For fluids with no contact with the final product there are many similarities with standard chemical manufacturing facilities, but these areas will also be discussed for the sake of completeness. This chapter will also discuss the effects of forthcoming regulatory requirements, allowing for any future expansion and systems to prevent cross-contamination of utilities with process uses. Table 8.1 gives a checklist for determining possible requirements for utility systems in various types of pharmaceutical facilities.

Possible area of utilization				
Laboratory	**Creams liquids**	**Tablets oral**	**Aerosols**	**Sterile bio**
✓	✓	✓		
✓	✓	✓	✓	✓
		✓		✓
✓		✓	✓	✓
		✓		✓
✓	✓			
	✓			✓
✓	✓	✓		
✓	✓	✓		✓
				✓
✓				
	✓	✓		✓
✓	✓		✓	
✓	✓		✓	✓
✓	✓	✓		✓
✓	✓			✓

8.5.1 HVAC

The types of HVAC systems commonly found in secondary pharmaceutical facilities are extremely diverse and are selected mainly on the basis of the required environmental conditions and the specified level of product contain-

Table 8.2 HVAC system designs

Description of HVAC system objectives	Possible applicable areas
1. Natural ventilation only	Plant rooms, warehouse
2. Mechanical ventilation	Plant rooms, warehouse, changing
3. Mechanical ventilation with heating and/or cooling	Warehouses, receipt and despatch, changing, bin floor, dry products, creams/ointments, packing hall, corridors, offices.
4. Air conditioning i.e. heating and cooling and humidity control to meet a specified band of temperature and humidity	Warehouses, receipt and despatch, changing, bin floor, computer rooms, dry products, creams/ointments, packing hall, corridors, offices
5. Full air conditioning i.e.: heating and cooling and humidity control to meet a specified condition of temperature and humidity	Offices, stability rooms special stores, computer rooms, dry products, creams/ointments, packing hall, offices.
6. As 4 or 5 below but including a low humidity set point (i.e. below approx. 50% RH)	Dry filling, capsule manufacturing, aerosols, dry products.
7. As 4, 5 or 6 below with specified clean room conditions	Creams, dry products, aerosols, steriles.
8. As 7 below but with Class 100 laminar flow distribution	Steriles, dry products (for dust control)
9. As above but recirculation in lieu of Total Loss	As above
10. Separate systems for each work centre and total loss systems to minimize risk of cross-contamination. Terminal HEPA filters on supply and extract. Sterile (positive) or containment (negative) pressure cascades. Low humidity. Dust extract. Specified classification of clean room	Sterile, dry products, aerosols, cytotoxics, vaccines, clinical trials, bio pharms.

ment. As the degree of control associated with these factors increases, the complexity, and therefore, cost of the HVAC system increases proportionately. Table 8.2 details the main types of HVAC systems commonly used in secondary pharmaceutical facilities.

Associated plant	**Temp and humidity control**	**Filter standard**	**Clean room class**
As 6 below + terminal HEPA Filters + Dust extract. ***Note: Total loss demands the highest possible plant loads***	As 6 below	HEPA	100–100,000
As above but reduced plant loads	As 6 below	HEPA	100–100,000
As 7 below	As 4, 5 or 6 below	HEPA	100–100,000
As 4, 5 or 6 and HEPA filtration	As 4, 5 or 6 below	HEPA	100–100,000
As 5 below and dehumidification	Any manufacturing conditions with low RH i.e.: 19°C 30% RH or 18°–22°C 30% RH Max.	EU3 to EU9	NIL
Input/extract fans, heating and cooling, filters and humidification. *Note: Requires greater plant capacity than 4 below*	Specified manufacturing conditions (not lower than 50% RH) i.e.: 21°C 50% RH summer and winter	EU3 to EU9	NIL
Input/extract fans, heating and cooling + filters and humidification	Comfort conditions usually a specified band for summer and winter i.e.: 20°C–24°C 30%–60% RH	EU3 to EU9	NIL
Input/extract fans + heating and/or cooling + filters	Max or min temperature control only i.e.: Max 25°C	EU3 to EU9	NIL
Input/extract fans + filters	5°C–10°C above external temperature in summer	EU3	NIL
High and low level louvres	10°C–20°C above external temperature in summer	NIL	NIL

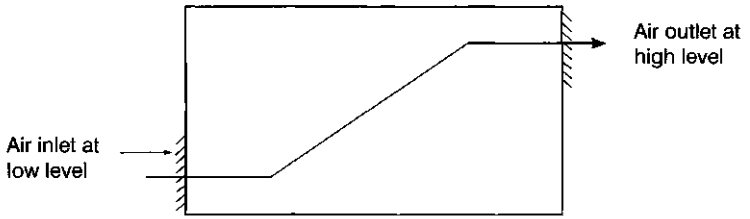

Figure 8.1 Natural ventilation

Figure 8.2 Mechanical ventilation

These systems are shown in schematic form in Figures 8.1 to 8.10.

8.5.2 Air

Compressed air is used in pharmaceutical applications for driving pumps and back flushing bag filters. Atmospheric air is passed through a 50 μm or smaller aperture filter to remove insects, dust and pollen before it enters the compressor. Care should be taken to ensure that the air intake is not immediately adjacent to sources of solvent vapour or combustion fumes.

The air is compressed to an appropriate pressure for the system, taking into account the maximum required design pressure and distribution system pressure drop.

The air is then filtered again using a 0.1–0.5 μm filter and dried to remove any compressor oil and condensed water. The pipework is usually carbon steel or galvanized carbon steel.

A general specification for air for these duties is:

- particulate filtration to 0.1 micron;
- pressure dew point at 7 Bar g + 3°C;
- oil filtration to 0.01 ppm;
- normal operating pressure 7 Bar g.

Instrument air is used for actuating valves. Compressed air is filtered to remove dirt and oil mist, which can clog the actuator. The pipework is usually carbon steel or galvanized carbon steel. The specification of the air varies according to

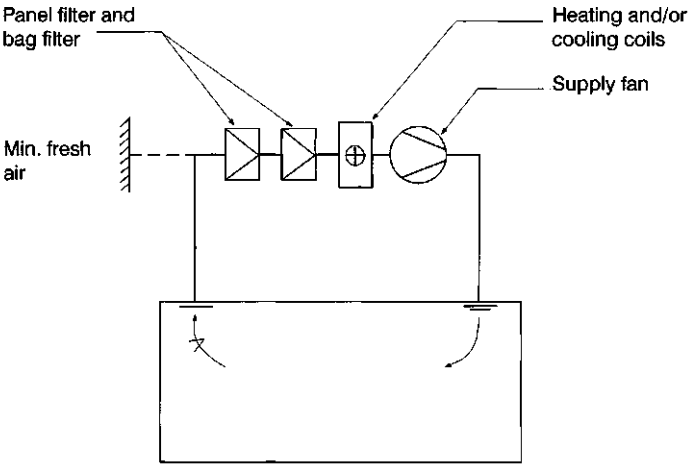

Figure 8.3 Heating and ventilation

user requirements and guidance should be sought from valve suppliers. A general specification for instrument air is:

- particulate filtration to 0.01 micron;
- pressure dew point at 7 Barg −40°C;
- oil filtration to 0.003 ppm;
- normal operating pressure 7 Barg.

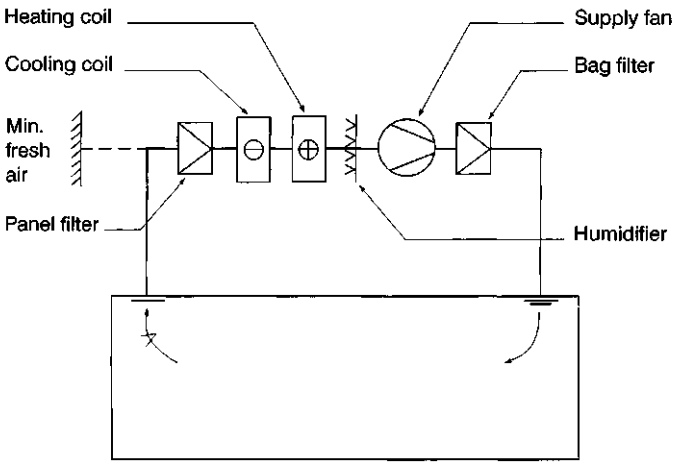

Figure 8.4 Air conditioning

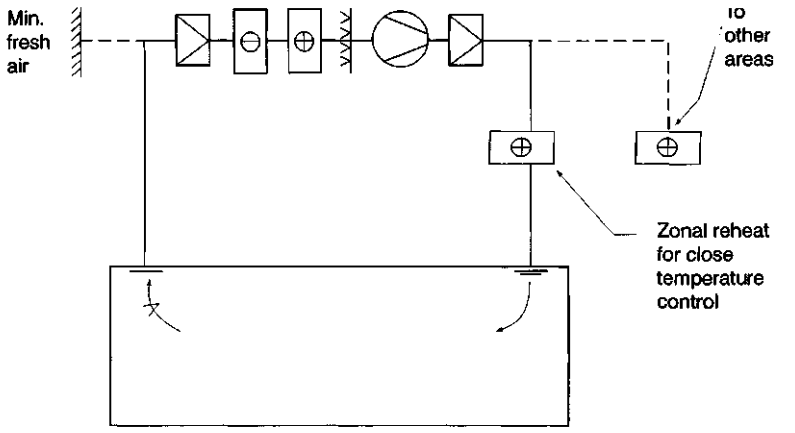

Figure 8.5 Air conditioning with zone reheat

Breathing air is used to protect personnel from dust and toxic fumes by supplying air to hoods or full suits. British Standard BS4275 covers the design of distribution systems for breathing air.

The breathing air system is usually supplied from the compressed air system. The air is then filtered, purified and dried before distribution to the end users. The use of compressed air for breathing means that the location of the compressor air inlet is especially important to prevent toxic fumes from entering the breathing air system.

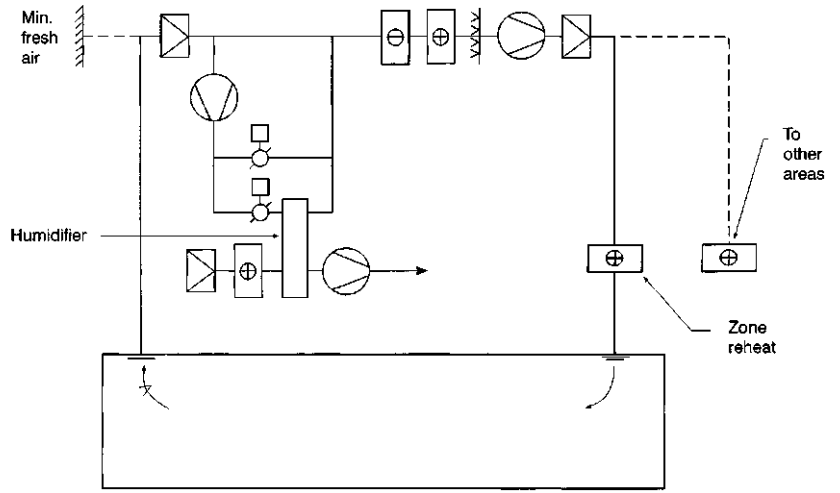

Figure 8.6 Low humidity air conditioning

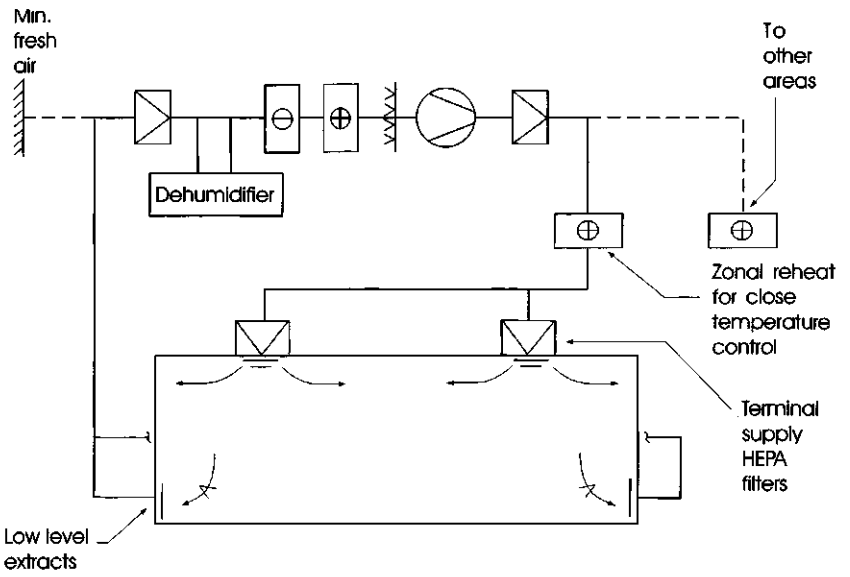

Figure 8.7 Low humidity clean room air conditioning

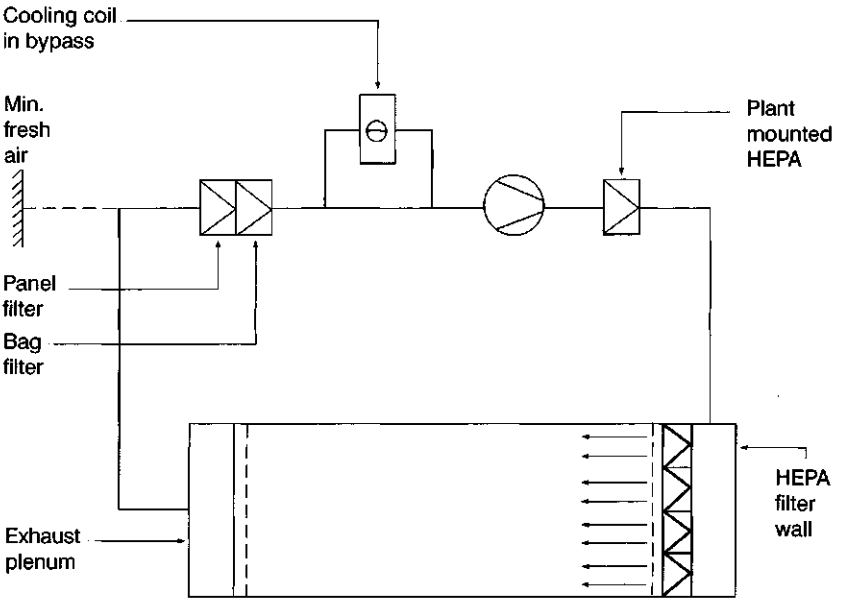

Figure 8.8 Laminar flow clean room

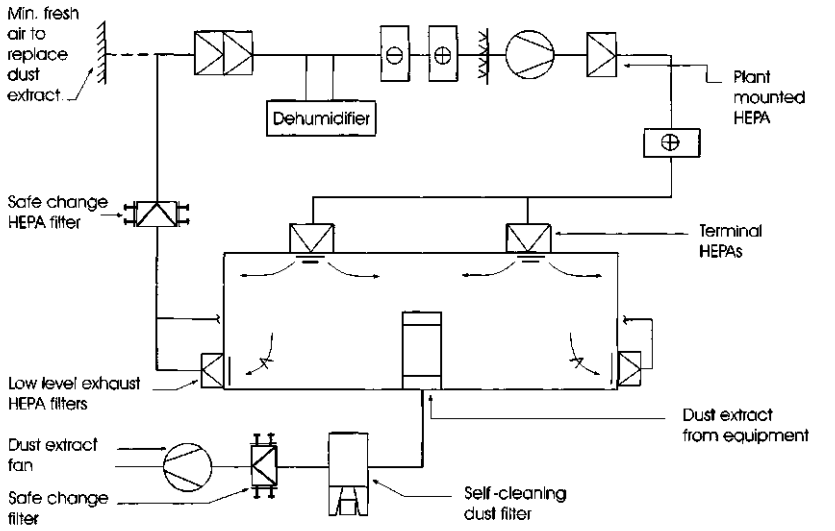

Figure 8.9 Low humidity containment clean room

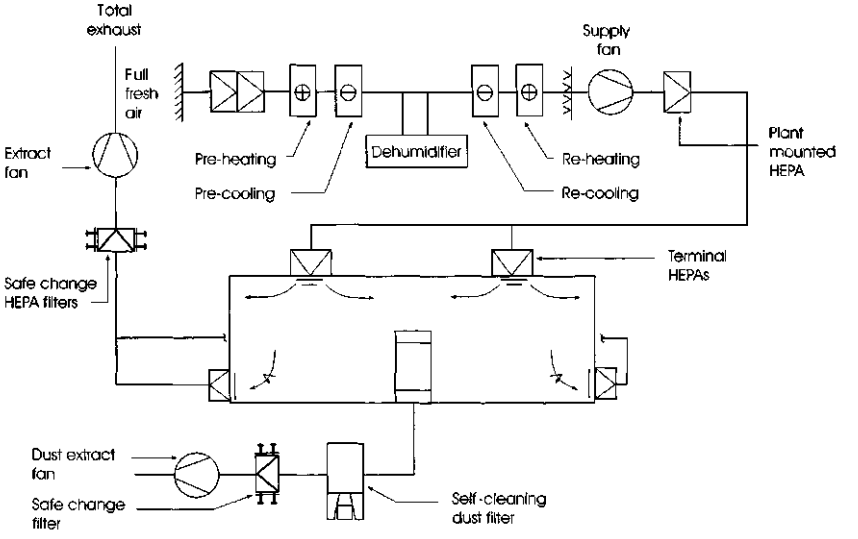

Figure 8.10 Low humidity total loss containment clean room

Air purification units may contain the following equipment:

- 0.01 micron pre-filter to remove solids;
- activated carbon adsorption bed to remove hydrocarbons;
- desiccant drier to remove water;
- catalytic element to remove carbon monoxide;
- final filter;
- carbon monoxide monitor alarm;
- flow meter;
- low pressure alarm.

BS4275 states that provision must be made to warn operators if the system fails. An emergency supply facility is usually provided in the form of a storage tank or cylinder.

There should be a minimum number of manual isolation valves in the distribution system due to the possibility of these valves being mistakenly closed whilst the system is in use. The materials of construction for pipework can be galvanized carbon steel or degreased copper. The distribution system ends in self-locking fittings that feed directly into the PE air hoods or suits.

Process air is used for feeding to fermenters or for processing equipment for parenterals. Process air is sterile, i.e. filtered to 0.2 micron. For fermenters, the air may have other gases added such as carbon dioxide; the gas used being dependant upon the cell culture being grown. Materials of construction are usually stainless steel and the pipework and fittings must be suitable for occasional steam sterilization. As a guideline, the general specification for instrument air (see page 275) is also applicable as it is the basic source of air for this purpose.

8.5.3 Vacuum

General vacuum systems are normally connected to a number of process vessels through a common pipeline and are used for evacuating process equipment prior to nitrogen blanketing, filling head tanks from drums and transferring from one vessel to another. The actual vacuum achieved is not critical, but is of the order of 200 mBar g.

For filtration, a vacuum pump is normally connected to a single filter via a receiver. The vacuum is connected to the liquid outlet of the filter and used for transferring filtrate from the filter to the receiver. The vacuum is applied to the receiver and the receiver is usually fitted with a vent condenser to prevent the vapours from reaching the vacuum pump. The pipework is commonly stainless steel as a minimum, as the filtrate is often reused either directly or after distillation.

For drying, the vacuum may be used to dry the solid on the filter by applying to the top of the filter or dryer. There will be a vent filter on the dryer to prevent the solids from entering the vacuum system. The solvent vapours will be condensed using a condenser supplied with refrigerant and collected in a receiver. The vacuum used for drying will depend upon the maximum temperature which can be applied to the product balanced against the likelihood of pulling solids into the vent filter causing a blockage.

The use of vacuum in distillation systems on pharmaceutical facilities is common, in order to depress the boiling point of distillation mixtures where some component of the mixture is sensitive to heat. Since depression of boiling point is inversely proportional to the system pressure, this duty gives the greatest demand for high vacuum with requirements for system pressures of 1–2 mbar g being commonplace.

There are two main types of vacuum pump:

- liquid seal;
- dry running.

Liquid seal pumps use fluid to provide a liquid seal between the pump casing and the central impellor. As the maximum achievable absolute vacuum is the vapour pressure of the seal fluid at the operating temperature, the choice of sealing fluid is important.

The seal fluid can be run on a single pass or on recirculation. A single pass type is the most appropriate choice for vapour streams containing solids, condensed solvent vapours or corrosive gases. This is due to the flushing action of the sealing fluid preventing the build-up of contaminants to corrosive concentrations leading to pump damage. The downside to this, however, is the increased amount of effluent produced, which is costly in terms of sealing fluid. Recirculating seal fluid systems require additional equipment such as a cooler (to remove heat from the condensing process vapours and the power of the pump motor) and a pot that can be topped up with fresh sealing fluid and which has an overflow to drain. The recirculating system produces less effluent but if not correctly maintained or cleaned can become blocked with solids or the seal fluid can be completely displaced by solvent. A further downside is that if the cooler is not effective, the exhaust gases may also contain a greater amount of solvent and the pump may produce a poor vacuum due to the increase in vapour pressure of the seal fluid at the higher operating temperature.

Dry running pumps are similar in operation to liquid ring pumps but use oil for the lubricating fluid. The tolerances within the pump are much smaller and, therefore, much less oil is required. The choice of lubricating oil is important as this can react with the process vapours and choke the pump.

Dry running pumps are also intolerant to some corrosive gases but, unlike single pass liquid ring pumps, they do not have the protection of the flushing action. These pumps are capable of very high vacuums and in clean process conditions, are superior to liquid ring pumps, with less effluent produced.

Multistage units can produce very high vacuums required for purification of primary product from close isomers by distillation.

Vacuum pumps are usually fitted with an inlet condenser or small vessel to receive any liquid carryover or condensate. All pipework should fall towards the catch pot to prevent back flow of condensed vapour to the equipment item. If the vacuum pump is used for more than one vessel, care should be taken that vapours and condensate cannot reach the other vessels. The pipework should be arranged to minimize pressure drops and pipelines should have long radius elbows or pulled bends to prevent erosion due to solids carryover. There should be the lowest possible number of in-line devices to avoid blockages.

A condenser that uses a refrigerant can be used, but care should be taken if water is being removed from the vapour and gas stream. The discharge of the pump is fitted with a device to remove entrained liquid prior to discharge to atmosphere. Care should be taken to ensure that discharge pipework has a low pressure drop as this will control the absolute vacuum the pump is capable of achieving.

The pipework is suitable for the process but care should be taken, in the case of a reduced specification at the receiving vessel, that no dirt or corrosion products could back flow to the vessel.

Care must be taken when cleaning, especially in the case of filter failure on a dry vacuum line, that any change in pipework specification occurs after the high point, in order to ensure that no corrosion products can back flow in the condensed vapour. If the condensed solvent is to be recycled, the use of stainless steel pipework throughout is recommended to ensure cleanliness.

8.5.4 Clean steam

Clean steam is used in pharmaceutical applications where steam or its condensate is in direct contact with the product. The end use of steam demands that it is supplied dry, saturated and free of entrained air. The requirement for chemical purity is primarily what differentiates clean steam from plant steam. The prohibition of corrosion inhibitors and anti-scaling additives influences generator design and materials of construction. Clean steam and plant steam systems should be completely separate.

The requirement to use clean or pure steam is governed by the cGMP to avoid contamination of the product.

The major use for clean steam is in the sterilization of process and specialist water systems. Clean steam is also used in autoclaves and sometimes for the humidification of clean rooms. Pure steam is used in processes producing parenterals, which demand the use of WFI and here the steam must not be contaminated with micro-organisms or endotoxins (pyrogens). The steam must be of the same specification as the WFI (to BP or USP standards for WFI) and is also used for the sterilization of WFI systems.

The uses of clean steam in pharmaceutical plant are fundamentally different from the uses of pure grades of water, as steam is rarely used as part of the product and only traces come into contact with the final product. It could be argued that the steam need not be to such a high specification, but it is generally used in the final stages of production where precautions against contamination are most stringent.

Clean steam and pure steam are usually produced in a dedicated steam generator. The generator is heated using plant steam. The heat exchanger is double tubesheet with an air gap between plant and clean sides which prevents contamination.

The generator is fitted with a device to remove entrained liquid droplets that may contain bacteria or endotoxins from the vapour stream. This may take the form of a demister pad or some sort of baffle arrangement.

The generator is usually manufactured in stainless steel 316 L or possibly titanium due to the corrosive nature of pure water. It is important not to let too much non-condensable gas (0.5% by volume) into the steam distribution system, as this will form a coating on the vessel surface and prevent efficient heat transfer. There is normally an aseptic sampling device before and after the generator to allow for sampling for endotoxins. The feed water to the generator is purified and free of volatile additives such as amines or hydrazines. As generators will only usually reduce the endotoxin concentration by a factor of 1000 whatever the quality of the feed material, it is important to control endotoxins in the inlet water to minimize the chance of spikes of high endotoxins in the pure steam system.

Steam is a sterilizing agent so although the materials of construction are required to be 316 or 304 stainless steel for reasons of corrosion resistance, the pipelines do not require special internal finishes and can be connected using flanges. The main consideration for distribution systems is their ability to remove condensate. Condensate poses the risk of micro-organism growth and reduces the effectiveness of sterilization. To ensure effective removal of condensate there should be steam traps at all low points and at 30 m intervals of pipework. The pipelines should incline towards the point of use by 1:100 and be properly supported to prevent sagging. Any in-line fittings should be

designed to prevent condensate collection. Any lines not used continuously should be fitted with their own steam trap arrangement to prevent the build up of condensate above the isolation valve.

Condensate should not be recovered for use as clean steam. It could be returned to the plant steam boiler if not heavily contaminated, although the small quantities of condensate involved make this impractical and it is therefore usually sent to drain. There should be an air break between the condensate lines and the drains to prevent back flow of condensate. The drains should be suitable for dealing with hot corrosive water. The steam traps should be 316 stainless steel, free draining, with the minimum number of internal crevices i.e. thermostatic type. Condensate quality for clean steam systems should comply with the USP or BP specification for WFI.

For fermenter systems growing recombinant or pathogenic organisms, where there is a possibility of contamination, the condensate should be fed to the kill tanks (see Section 8.9).

8.5.5 Inert gases

Nitrogen is used to blanket vessels, for liquid transfers, filtration, cleaning bag filters, and for blowing process lines clear. It is also used for inerting explosive atmospheres in solids handling equipment and for pressure testing vessels.

Nitrogen can be produced in pressure swing absorption systems from air, by other means from air, or from liquefied nitrogen in storage tanks and cylinders. Pressure swing absorption can produce nitrogen at a reduced specification if the unit is undersized and, therefore, should not be used for critical applications such as inerting of mills. Liquid nitrogen can be produced in many different grades and, therefore, it is important to select the correct grade for the application. It must be remembered that the grade must be for the highest requirement if the system is for site wide nitrogen supply. Some grades of nitrogen contain hydrocarbons (dependant upon the manufacturing route) and these would be unacceptable for flammable environments. cGMP requirements normally specify nitrogen to be filtered to 0.1 micron when in contact with the primary product, i.e. once the bulk pharmaceutical chemical has been produced.

The material of construction for pipework is usually carbon steel. The highest pressure required and the maximum line pressure drops set the pressure of the main. The back flushing of filters is usually the highest pressure and is of the order of 6 Bar g. Normal maximum operating pressures for systems of this type are of the order of 10 Bar g.

Hydro fluoro alkanes (HFAs) are a group of gases that have been developed to take the place of the old CFC refrigerant gases. They are used as propellant

for pharmaceutical aerosols and their main property is their degreasing effect, which means that diaphragm pumps are usually used for transfer. They are expensive and, therefore, leakages in the system should be kept to a minimum. In the interest of cleanliness the materials of construction are stainless steel for HFA systems.

8.5.6 Specialist water supplies

This section offers an overview of the main aspects of water and steam production and use in pharmaceutical facilities. This area is covered in far more detail in the ISPE 'Baseline Pharmaceutical Engineering Guide Volume 4: Water and Steam Guide'.

There are many types of water to be found in pharmaceutical facilities. A few of the main types are as follows:

- *towns water* is usually straight from the mains and may vary in quality throughout the year. The specification can be obtained from the local water company and is usually given as a yearly average. There may be two or more water sources for a given plant, and the characteristics of water from these different sources may vary widely;
- *process water* is normally towns water that has passed through a site break tank;
- *de-ionized/demineralized and softened water* has passed through some form of water softening process to remove calcium and magnesium ions that can cause scale on heat exchanger surfaces and in reactors;
- *purified water* has usually been softened and passed through a UV source to remove bacteria. There are various specifications for this as discussed later in the section. The most suitable of these depends upon the market for the final product but generally the water is soft and contains a reduced number of bacteria;
- *water for injection/pyrogen-free water* has been softened and has a low bacterial count and a reduced endotoxin loading. There are a number of different specifications for this type of water. The USP and BP specifications are the most commonly used for WFI.

Towns and process water is treated to give all the other types of water by using the following processes (amongst others):

- organic scavenger — removes organics (may be naturally occurring);
- duplex water softeners — removes calcium and magnesium salts on a continuous basis;
- coarse filtration — removes dirt and debris;

- break tank — protects water supply and protects against short-term failure of supply. Often a mandatory requirement under water bye-laws;
- reverse osmosis unit — removes solids, salts and bacteria;
- electrical deionization — removes the ions present, effectively softening the water;
- UV sterilization — kills a significant number of the remaining live bacteria.

Potable water is used widely in the pharmaceutical industry as a solvent, a reagent and a cleaning medium.

Purified water is used in the preparation of compendial dosages. While Water for Injection is generally used for sterile products, it is also used for cleaning equipment used to make such products.

Specifications for specialist waters are laid down by British Pharmacopoeia (BP), European Pharmacopoeia (Ph.Eur.) and United States Pharmacopoeia USP. These documents also describe the tests that must be carried out to prove the water is to specification.

Historically these specifications were much the same. Recently however, there have been moves to harmonize the BP and Ph.Eur. specifications but the USP specification has changed. This change has lead to a drastic reduction in the number of tests required and specifies only Total Organic Carbon (TOC) and conductivity, both of which can be measured continuously using online monitoring equipment. It would also appear that the specification of the water has been tightened by change.

At present there is some confusion about the specification of WFI and purified water mainly because of the wide differences in requirements between the USP and BP/Ph.Eur. water specifications. The main problem is that WFI must be produced by distillation in the BP and Ph.Eur. specifications, but can be produced by reverse osmosis in the USP specification. Although it would appear that the BP and Ph.Eur. will probably follow the USP at some point in the future, it has left manufacturers who market their products in both the Europe and America with something of a dilemma. With this in mind, it is important to be clear of the desired final product specification when initially specifying a new water system.

After treatment to produce purified water or WFI, the water is collected in a receiver, which is either jacketed or has an in-line heater. The vessel is normally a cylindrical dished end vessel designed to withstand the vacuum that may occur during steam sterilization. The vessel is 316 stainless steel to prevent corrosive attack by the hot purified water.

The tank is fitted with a relief device and possibly some sort of relief monitoring device. The vent is fitted with a HEPA filter to prevent the ingress of

microorganisms and is normally heated, to prevent blockage of the hydrophilic filter packing with water. The vent is fitted with a drain via a steam trap to allow any condensate in the vent line to be drained off.

The water is pumped from the vessel through a heat exchanger and then to the distribution system. The heat exchanger can be a shell and tube or plate variety but must be of the double wall type. The water is maintained at 80–90°C by heating with steam. The distribution system can be a ring main or closed line. Ring mains are favoured as the hot purified water continuously cleans them, but single lines are acceptable to the Food and Drug Administration (FDA) as long as they are regularly cleaned and validated. The pump must be fitted with a casing drain to allow drainage after sterilization.

8.5.7 Heat transfer fluids

Hot oil is used for reaction temperatures greater than about 180°C and is dedicated to a small number of reactors.

The system consists of an electrically heated element, pumped loop, distribution pipework and expansion tank. The tank may be vented to atmosphere or nitrogen blanketed. The latter increases the life span of the oil by reducing oxidization of the hot oil at the surface. The system will need periodic draining and cleaning to prevent build up of carbon on the heat transfer surfaces.

The type of oil specified is dependant upon the desired operating range, but the oils are normally silicone based and, therefore, have high boiling points and are highly stable at sustained high temperatures.

Heat transfer oils may also be used where it is critical to prevent water reaching the reagents, for example, if this produces an explosive reaction. The vessel will then be heated using a pumped loop with the normal services (steam, cooling water, refrigerant) on a heat exchanger in the loop. This system will also need an expansion tank.

8.5.8 Refrigeration systems

'Fridge' systems are used to cool reactors, in batch crystallization or as vent condensers on volatile solvent tanks. Glycol is usually used as the heat transfer medium with ethylene glycol being used for nonfood use and propylene glycol for food use.

There are usually two tanks, with one to hold the chilled glycol supply and the other to receive the refrigerated glycol return. The glycol in the return tank is then passed to the supply tank via the chiller or may overflow to the supply side via a weir system.

The concentration of glycol is specified by the desired minimum operating temperature of the process vessels, so care must be taken to ensure that the

glycol concentration remains at the required level. Low glycol concentrations may cause freezing of the line's contents, whilst excessive concentrations of glycol may cause problems in the pump due to its viscosity exceeding the pump specification.

The heat removed from the glycol in the chiller is either discharged to the cooling water or to the air via forced draft coolers.

8.6 Sizing of systems for batch production

The sizing of utilities requires a good knowledge of all the operations in the plant including the other utility operations and HVAC requirements. A large amount of information is required and the processing part of the plant needs to be designed before the utilities are designed.

Information required includes:

- mass balance;
- energy balance;
- batch times;
- mode of operation i.e. 24 hr, 5 day etc.

The first step is to produce lists of users for each utility with some assessment of the mode of operation, i.e. continuous/intermittent. The next stage is to attempt to assign a quantity to the users for each operation. Some trivial requirements can be ignored.

Electricity

A motor list is usually made which details power requirements and whether the power requirement is intermittent or continuous. Depending upon the electrical zoning of the plant, it may be necessary to construct a switch room for housing the MCC panels and control equipment.

Cooling water

Using the mass balance and batch times it is possible to calculate the cooling requirements of the process. The summertime cooling water temperature should be used to give a worst case. The cooling requirements of utility systems, for example HVAC and refrigeration equipment, need to be included here. If the process has more than one stage running concurrently a Gantt chart needs to be constructed and the heat loads for a day/week should be considered. From the data, a graph of duty versus time can be produced from which the peak requirements can be ascertained. The designer should also look at the worst possible case and at situations which are not part of standard operation i.e. start-up and shutdown. Future expansion requirements should also be considered. It

should be noted that cooling towers come in a limited range of sizes, which vary between suppliers. The final choice of actual size is, therefore, constrained by the supplier chosen. As with all design sizing there is a balance between capital cost and flexibility of operation.

Steam

The method for sizing steam-raising systems is as described above, but an additional consideration is the required pressure. This can either be standard site steam pressures or an individual consideration of the desired final temperature within the process vessel. The flow rate of steam at the desired pressure can be calculated for all the duties and from the above the overall heat duty for the system can be ascertained. Allowance should be made for heat losses in the distribution system and for future expansion of the system.

Nitrogen

The flow rate for purging can be calculated but care must be taken in designing these systems for plant including filtration operations, as these are batch operations. Using the batch cycle time (or an estimate of this), the volumetric flow rate for this duty can be found. Some flow rates will be specified by suppliers, such as backflushing of bag filters. From the volumetric flow rate at the user pressure, the volumetric flow rate at the distribution pressure can be calculated. Again using a graph of duty versus time for the process the overall flow rate at the supply pressure can be found. The supply pressure will depend upon the users' maximum requirements.

The system will normally have an accumulator depending upon the critical nature of the uses to which it is put and the method of producing nitrogen. The supply pressure will be reduced within the plant to give the variety of pressures required. There is usually a relief valve after the pressure-reducing valve to protect downstream equipment from an overpressure within the nitrogen system. The main criteria are:

- pressure required at end user and supply;
- quality;
- quantity;
- temperature at user;
- application e.g. tank blanketing, reaction control.

Compressed air

The ratio of the maximum to minimum capacity of the utility is known as the turn down ratio. All systems should have the capacity to be turned down if part

of the plant is under maintenance or if the process is changed for any reason. To allow for future expansion, new systems should not be designed to be operating at their peak loading for 24 hours a day.

If the ratio of maximum to minimum load is greater than about 10, consideration should be given to the use of two or more smaller units, which increases the flexibility of the utility. This would increase initial capital cost but would, if properly controlled, reduce the running costs of the plant. Multiple units may also reduce down time, as the plant may be able to operate on a single unit when not under peak loading.

Duty/standby

Critical systems should have a duty standby facility such that some of the equipment is not run continuously. This allows time for maintenance without the necessity for shutdown periods.

If there is a single duty of short duration with high flow rate, capital costs can be reduced by having some sort of accumulation system to allow a smaller unit to be installed.

8.7 Solids transfer

For charging biologically active solid materials into reactors, it is important to determine:

- the quantity to be added;
- the sizes of kegs to be used;
- the Occupational Exposure Limit (OEL);
- whether the material is explosive;
- whether contact with air is acceptable;
- whether waste bags and filters can be removed safely?

Glove-boxes are used for solids input and kegging of primary product. The requirements in primary production are usually controlled by the characteristics of the product, i.e. the particle size range, the explosive characteristic of the material and whether it is necessary to exclude air or moisture.

8.8 Cleaning systems

All reactor systems require cleaning if a batch has failed or for period maintenance. Some items of plant are also used for different processes and cleaning between these is required, and often this must be validated.

In batch reactor systems, cleaning can be carried out by boiling either water or solvent in the vessel to give the degree of cleaning required. Validation of the cleaning procedure will be necessary.

8.8.1 Clean in Place (CIP)

The first thing to consider for CIP is what is to be achieved by this process and what is to be removed. The systems themselves are very simple, consisting of a tank filled with the correct concentration of cleaning medium, heated by recirculation to the required cleaning temperature and then introduced in the pipework or vessel. This is pumped through the lines and back to the tank or to a drain. The lines are then flushed with water and may be blown with nitrogen before the system goes back to production. The important consideration here is the superficial velocity of the cleaning medium.

8.8.2 Steam in Place/Sterilize in Place (SIP)

Cleaning of lines and vessels using steam can be broken into two main types — Steam in Place or Sterilize in Place, with the main difference being that Steam in Place does not have a quantitative check on the microbial content of the lines after cleaning and that the procedure is not validated. If the requirement is to minimize the biological loading of the system without the total removal of the biological population then Steam in Place is the most appropriate choice. Sterilize in Place is used in biotechnological processes to clean the vessel between batches and for periodic cleaning of Water for Injection (or purified water) storage and distribution systems. This process requires validation to ensure that the cleaning process can be repeated with confidence.

Steam to be used for cleaning must be pure steam (see Section 8.1.4) and is usually reduced down to 1.2 Barg at the point of use, corresponding to the usual sterilization temperature of 121°C, which is the temperature at which *Bacillus Stereothermophilis* spores are destroyed. The vessel is normally cleaned by CIP first, as the steam will only sterilize the surface, and the vessel internals are checked to ensure cleanliness. Steam is injected into the highest point and collected at the lowest. The time taken for sterilization is determined by the initial bacterial loading and the final bacterial loading required and is governed by the exponential equation:

$$N = N_0 e^{-Kt}$$

where: N is the number of colony forming units (cfu/ml) at the end of the sterilization;

N_0 is the number of colony forming units (cfu/ml) at the start of the sterilization;
k is an empirical constant for the organism in question at the sterilizing temperature;
t is time in seconds.

Clearly, the same percentage level of reduction in biological loading can be achieved by sterilizing for longer at a lower temperature.

The actual time is usually determined during commissioning by covering the vessel or pipework with thermocouples, and timing from when the coldest spot reaches the required sterilization temperature and then relating back to the vessel temperature probe reading.

Vessel requirements

The vessel must be capable of withstanding any vacuum produced by the sudden condensation of the steam. Care must be taken in the design of any vessel that is to be cleaned in this manner to minimize crevices in the vessel and any connecting pipework. The vessels are normally dished end design.

Care must be taken that the condensate produced by the cleaning process can drain away as pockets of warm condensate will not adequately be sterilized. The process is validated by swabbing or by strips impregnated with a substance that changes colour when exposed to a given time/temperature combination.

8.9 Effluent treatment and waste minimization

The following section is a brief overview of a broad area of knowledge. More detail can be found in the standard texts on the subject. All chemical manufacturing processes produce waste streams and, as all treatment and disposal costs money, it is sensible to reduce waste wherever possible. Waste minimization can save money but all effluent treatments have costs. The chosen waste disposal strategy is based on economics, regulatory compliance and commercial secrecy. Health and Safety has a part to play in any decision, as legislation requires pollution control to follow an integrated approach. It is unacceptable simply to move pollution from one form to another, for example, air stripping of ammonia from a liquid effluent to produce a gaseous discharge.

8.9.1 Types of effluent produced by process

Pharmaceutical processes do not tend to produce large amounts of solids but produce large amounts of waste water contaminated with solvent, reaction

products and inorganic salts, some waste solvents, tars from solvent recovery, scrubber liquors, and contaminated gaseous waste streams.

This tends to produce small amounts of high Chemical Oxygen Demand (COD) waste broth, large amounts of wash waters and some gaseous effluents, all of which may be contaminated with microorganisms. There may be commercial reasons as well as environmental to prevent the organisms leaving the site, such as if the organism is novel or genetically engineered.

In general, most waste streams pass to a jacketed vessel known as a kill tank. Periodically the vessel contents are heated to the temperature required to kill the organism. Here the costs of any treatment process (capital, operating, maintenance, disposal) must be weighed against the present cost of disposal.

8.9.2 Options for effluent treatment (in order of expense)

- direct recycling;
- sell to waste processor, for example, waste IPA is used in car screen washes and waste aluminium hydroxide (from Friedel Craft's reactions) is used in antacid tablets;
- recovery and reuse with some form of clean up, such as solvent recovery;
- to the foul sewer with simple gravity separation and pH modification;
- incineration, although some materials such as iodine based contaminants cannot be incinerated because they form acid flue gases which corrode the incinerator;
- landfill is becoming increasingly expensive due to the reduced number of suitable sites, pressure by local populations and the substantially increased Landfill Tax.

8.9.3 Regulatory requirements

There are a number of regulations that relate to waste, including the following:

- Control of Substances Hazardous to Health (COSHH) (1994);
- Environmental Protection Act (1990) — the main aspects being that a producer of waste is responsible for knowing where that waste ends up;
- Water Industries Act (1991) — controls operation of water treatment companies, as well as companies delivering waste to them;
- Trade Effluent Prescribed Substances Regulations (1991) — Red List — this determines which chemicals cannot be released to air or atmosphere.

8.9.4 Licensing and regulatory bodies

Water company

The local water company grants consents for discharge of chemical waste to the foul sewer. Here industrial effluent is mixed with sewage and eventually ends up at the sewage treatment works where it is treated by various physical means, before being fed to bacteria and other organisms. If it is an existing site, a consent limit will already be set detailing flowrates and levels of contaminants.

The water company may require information on the toxicity of the effluent to bacteria that break down the sewage and can ask for further information until they are satisfied that the effluent is not a danger to the works.

For discharges from a process the amount, concentration of major contaminants and likely disposal method for each stream are required. The COD load of the process can be calculated and any Red List chemicals identified.

Environmental Protection Agency (EPA)

The Environmental Protection Agency (EPA) grants consents for discharge to the river system. The limits for discharge to rivers are much stricter than to the sewage treatment works, but it is very unusual for a pharmaceutical plant of any appreciable size to be discharging to rivers and not to the sewage treatment works.

EPA regulates Integrated Pollution Control reports for all notifiable processes. A report must be submitted to the EPA which details equipment, process, effluent produced, control strategies.

The EPA has also taken over the duties of the old Her Majesty's Inspectorate of Air Pollution (HMAIP) and consequently grants consents and regulates releases to atmosphere.

8.9.5 Gaseous effluents

The release of gaseous effluents is always controlled by regulation. There are no cost savings other than a reduction in raw materials costs to be offset against the cost of installing and operating abatement equipment.

Characterizing gaseous waste streams

- contaminant characteristics;
- gas stream characteristics;
- design and performance characteristics.

Commonly used treatment processes

- particulate:
  - hydrocyclone;
  - fabric filters;
- vapours:
  - wet scrubbing;
  - biological scrubbing;
  - absorption, adsorption;
  - combustion;
  - condensers.

8.9.6 Liquid effluents

For discharges to the foul sewer, the local water company usually asks for the following information on any aqueous effluent:

- Chemical Oxygen Demand (COD);
- Biochemical Oxygen Demand (BOD);
- Suspended Solids (SS);
- flow rate;
- pH;
- heavy metals;
- contaminants such as cumulative or persistent materials, which will not be broken down at the works, may build up in the water supply system. Phenols are also a problem as they may taint the taste of the final drinking water if water for potable use is abstracted downstream of the sewage works outfall. Many phenols also have a bactericidal effect, and may therefore compromise the operation of biological treatment plants.

The water company treats each effluent on a case by case basis but will give a consent limit for the whole site.

Pre treatment

(1) Equalization

For batch processes, a useful method of reducing loading on the pre-treatment system is to allow streams to mix to a more standard effluent. This optimizes the treatment process and reduces the amount of chemicals added, as some neutralization takes place within the buffer storage. This is normally achieved by a system of sumps or receiving tanks to smooth out the differing streams from a batch process. The pH is then modified to neutrality and suspended solids removed.

Primary treatment processes

(1) Removal of suspended solids

This may be achieved by a number of techniques, including flocculation and skimming or addition of aluminium/iron salts and gravity separation. This process may also remove colour and polar molecules. Turbidity, pH and flow are usually measured at the exit to the foul sewer and there should be some means of sampling the waste stream.

(2) Removal of liquids

Many effluents are contaminated with organic solvents, greases, and the like. These may be removed by means of a simple interceptor, where liquids are separated by means of one floating on the other, or by one of the more complicated systems for enhancing liquid/liquid separation. Lamella plates may be introduced into the interceptor, as in the American Petroleum Institute separator; fine bubbles may carry lighter substances to the surface for skimming, as in Dissolved Air Flotation (DAF); or hydrocyclones may be used to enhance gravity separation. All these techniques tend to decrease the required plan area of plant at additional capital and/or running cost.

Secondary treatment processes

(1) Biological treatment

This uses a number of processes, which are conventionally split into two main groups, based upon whether they are carried out in the presence or absence of air.

Anaerobic processes are carried out in the absence of air — the organisms carrying out the process are actually poisoned by oxygen. These processes carry an advantage over aerobic processes, in that the end products of fermentation include hydrogen, methane, and other flammable substances. These substances can be burned to produce heat, or used in modified diesel engines to generate electricity. The process can, therefore, be a net energy producer if carried out at sufficient scale. The plant required for conventional anaerobic treatment can be very large, but newer techniques are reducing the size of unit operations. The higher the COD of the effluent, the more likely it will be that anaerobic treatment will prove suitable. Far stronger effluents can be treated anaerobically than aerobically, and the total containment of the system that is required to exclude air means that highly odorous effluents can be treated without causing a public nuisance.

Aerobic processes may use passive air, active air, passive pure oxygen or active pure oxygen to provide suitable living conditions for bacteria that degrade organic (and some inorganic) substances, mostly to carbon dioxide, water, and oxidized inorganic salts. There are a great number of techniques for aerobic treatment, differing in how the oxygen is brought into contact with the organisms, whether the organisms are free in suspension, or attached to some media, and whether the process is continuous or batch. There are many other small differences between the generic and proprietary systems on offer, but those preceding have the greatest effect on the important system characteristics, such as resistance to shock loading, running costs, capital costs and unit sizes.

(2) Sludge treatment

All flocculative and biological treatment processes produce quantities of sludge, irrespective of what some manufacturers may claim. Biological treatment sludge is produced in quantities proportional to the total COD put to treatment. There are two main problems with these sludges: their 'instability' (their likelihood to rapidly commence to rot, releasing noxious gases) and their bulk (since most biological sludges are greater than 95% water).

Sludges may be stabilized by means of an additional biological treatment stage, for example aerobic digestion, or by chemical means, such as lime addition. This is another area with a wide range of competing solutions. Having consulted with specialists and decided upon the stabilization strategy, some means of reducing the volume of sludge is usually found desirable, especially if it is to be transported off-site.

The main strategies for volume reduction are analogous to standard dewatering and drying techniques. Not only do they often start in a non-Newtonian state, their characteristics may change with feed conditions to the treatment process, and as a result of continuing biological activity.

The resultant stabilized, concentrated sludges may be in the form of slurries, cakes, pellets, etc. These may be incinerated, landfilled, or sold for soil treatment.

Physical/chemical treatments

As well as conventional biological secondary treatment systems, there are several physical and chemical treatments, removing either specific contaminants, or groups of contaminants with similar properties.

Ozone, peroxides, pure oxygen, air, and a number of other agents may be used. Although these processes tend to take up less space than biological methods, they can be very expensive in terms of running costs, especially with respect to the power costs of ozone systems.

Tertiary treatment

In order to allow recycle or reuse of effluent treated by means of the preceding processes, or in the case of discharge direct to watercourse, it may be necessary to give the cleaned effluent a final polish or moderate its properties in some other way. There are again a number of different techniques for this, with ultrafiltration being common as a good final barrier method to prevent recirculation of undesirable substances.

8.9.7 Solid effluents

The solid effluent such as bags, filter cartridges, etc., are incinerated or landfilled and sludges from primary and secondary treatment processes are treated as previously described. There may be additional constraints on some solid waste, for example laboratory sharps, clinical waste, or waste contaminated with specific biological or chemical agents. These often require separation, marking of containers, and final disposal route.

8.10 General engineering practice requirements

8.10.1 Production area workshops

Space is required in the production areas for:

- storage of change parts for product changes. These should be in purpose built units with clear identification;
- tools for changeover adjacent to the equipment. In the pharmaceutical industry, there are many short runs on packaging equipment and change over time can be lengthy particularly with blister packs;
- diagnostic equipment for fault finding;
- measuring equipment to check the environment and calibrate instruments on the production equipment;
- manuals and records of maintenance, although the latter can consist of a computer terminal. This promotes cleanliness and ensures a single central record is maintained;
- minor repairs and modifications;
- overhauls of equipment.

This can be a combination of local storage units and area workshops and is determined by the working methods agreed in the design brief.

8.10.2 Records

A master plant record — a logical, comprehensive set of information on the facility should be assembled starting at day one of design with the design brief and following design through all stages. Any changes in design intent and design decisions made should be recorded. Engineering change control will ensure this happens and is necessary to show the trail from design concept to completion. It is also a good project cost control tool.

The framework for the record system should be established early. A numbering system for drawings and plant should be agreed. The finance department will want to record the asset value and ideally the same system of numbers should be used. This system will ensure that the required information:

- is available;
- can be found;
- can be updated;
- can be put into systems to monitor, calibrate, and record repairs and use of spares;
- can show that the plant is maintained and performing to design.

8.10.3 Plant numbering

All plant systems, will generally be numbered sequentially from 001. There is a P&I diagram for each system. A system list gives the locations and the areas served, which are shown simply in the P&I diagram. All items on the P&I are numbered sequentially with functions indicated by the symbol and prefix letters e.g., MDM001245 is a motorized damper modulating in system 1 and is item 245 on the P&I diagram. Building management control system outstations sometimes control more than one plant system and this will need to be covered in the BMS system documentation.

A similar method can be devised for electrical panels and distribution boards.

8.10.4 Measurement and calibration

All product significant controls or measuring elements must be calibrated and the calibration traceable to a National Standard. It should be possible to identify the procedures associated with the processes that would detect an instrument problem and, if there are problems, whether the procedures would detect them every time and soon enough. The most serious implications will be associated with critical instruments or instruments in safety-related applications, so a greater margin for error should be used in these cases.

The implications of instrument malfunction are frequently so serious that a cautious estimate of the calibration interval is justified — if an interval is over-cautious, it will soon be revealed as such.

This is an activity that may be desirable to keep in-house. List the types and numbers of instruments to be calibrated and the frequency of calibration to determine the staff and space required. It may be possible to draw on the experiences of calibration from other sites; the same instrument in a similar application may exist, with several years worth of calibration history (e.g. magnehelic gauges) and an optimized calibration interval. This will improve the level of confidence in an estimated calibration interval but must not be used as a substitute for a thorough evaluation of each application; each will be unique in some respect.

Bear in mind that the period between calibrations can be increased if successive calibrations show no deviation. For example, after three successive calibration checks without need for adjustment, it may be possible to double the calibration interval.

8.10.5 Computer systems

Software packages, such as Computer Aided Maintenance Management System (CAMMS) are available but these will only assist with handling the data rather than determining the system. The software package must be validated (see Chapter 4).

The system should be chosen early and records added. The cost and problems of trying to enter the information after the plant has been handed over usually result in incomplete records. If staff who will ultimately use the system enter the data as the work progresses, they will learn the system and the plant. It is essential to manage the quality of this data not only at entry but also throughout its required life. Failure to do this effectively will render the CAMMS system useless and an expensive burden on the operation.

A corresponding reference system for manuals should be set up. Backup copies of all software and records should be made and stored in a secure fire resistant area.

8.11 Installation

8.11.1 Staff duties

The maintenance engineer should be part of the project team.

The technicians should be on-site from the beginning and they should be sent on acceptance trials of major plant. There should be a budget for minor changes, to improve maintenance, and a rigid change control followed.

The technicians should be involved in the IQ/OQ and should ensure that all drawings represent 'as built' and are marked up as the installation progresses.

8.11.2 Training

The core team of technicians may have been selected for their knowledge and experience but they will need further training in analytical skills and fault finding. Involvement in the project is a good training activity and technicians can be trained at suppliers during construction. If it is planned to contract out maintenance, their designated staff should be trained on the equipment. They will also need training on cGMP practices and, if a CAMMs system is in place, they will need training on its use.

8.12 In-house versus contractors

Suppliers of large capital equipment such as refrigeration plant and specialist systems such as fire sprinklers have contract maintenance departments.

In USA and Canada the trend is to contract out facilities management, and consultants and contractors are set up to carry out this service. Major contractors in the UK are now investigating the feasibility of offering this service, as they already have the organization to manage sub-contractors and have established working relationships with preferred suppliers.

An Invitation to Tender or Request for Proposal will be needed, which will specify the requirements and the measures used to compare bids and monitor performance. An Invitation to Tender will typically have the following headings:

- background;
- objectives;
- present situation;
- proposed system;
- company needs;
- nominated staff and qualifications of staff;
- job functions;
- tasks for various job functions;
- reports required;
- confidentiality;
- vendors qualifications;
- timing of proposal;
- format of reply;
- contractors guarantees;
- evaluation of proposal.

The evaluation of proposal lists all the information that is needed to compare bids, such as rates, response times, references, safety record etc.

Partnership is another concept, with agreed performance and profit sharing on improved efficiency.

Contracting out the maintenance is not a simple option. There will still need to be sufficient in-house expertise to effectively control the relevance and quality of the external work.

8.13 Planned and preventive maintenance

8.13.1 Reasons for planned maintenance

- improved equipment reliability;
- reduce lost production time;
- cost avoidance;
- unscheduled repairs and downtime;
- cost control;
- more accurate budgets;
- satisfy FDA and local requirements;
- we deserve a good nights sleep!

8.13.2 Planned maintenance

Planned maintenance, in its simplest form, is applying the manufacturer's routines to the plant at the frequencies they recommend. If done conscientiously and properly, this will reduce breakdowns but it is labour intensive and can result in application with no thought to hours run, duty and environment. Many routines are invasive and can affect the plant if not done correctly. It can result in over-maintenance and rarely can be completed due to pressure to reduce downtime.

Improvements have been made using hours run meters on the starters and BMS systems to log hours run.

8.13.3 Preventive maintenance and reliability centred maintenance

This requires a better understanding of the plant and its use. It involves more extensive examination and review of inspection reports and repair work; an assessment of the potential for failure; emphasis on methods of assessing failure and effort concentrated on those items likely to fail and whose failure has the most significant effect on the facility.

It uses techniques of *condition monitoring*:

- observation and use of analytical skills;
- analysis of oils;
- vibrations analysis;
- Sound/sonic testing;
- Infrared testing.

All the above require a base line of the 'as installed', new condition as a reference.

Good preventive maintenance requires:

- systems (manual or computerized) to track, schedule and record the preventative maintenance;
- system of identifying equipment uniquely;
- good equipment records;
- written procedures;
- following procedures;
- technically competent resources;
- safe working practices and training.

8.14 The future?

More companies will offer contract maintenance and facility management services. The engineering function will reduce in number but increase in engineering and management skill. Plant will be computer monitored and controlled. Confidence and knowledge of computer systems and software will increase and BMS will be used more, removing parallel monitoring and measurement systems. (This is dependent on the BMS software being validatable).

Trouble free operation requires effort. It starts by clearly defining the engineering operating objectives at the beginning of a project and using these to determine the strategy and organization of the engineering department and to prepare a plan to bring this about. Then it requires a lot of detailed effort throughout design and construction on the design and organization.

Then, once this is in place, performance should be measured, reviewed and improved.

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