Process development facilities and pilot plants 10

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10.1 Introduction

Process development facilities and pilot plants are an integral part of research and development operations for all major pharmaceutical companies seeking to provide new products for the future. Their design, construction, commissioning and validation have their own special problems arising out of the individual company's traditional research methods, the class of compounds to be developed and the regulatory requirements.

These facilities are frequently multi-purpose and/or multi-product and the processes used are constantly under development. The design requires a degree of 'crystal ball gazing' because future requirements usually need to be included in the specification.

The full range of pharmaceutical processing needs to be covered by process development facilities and pilot plants from chemical synthesis to production of the active pharmaceutical ingredient, through physical manipulation to formulation, production of the final dosage form, filling and packaging.

The problems for chemical synthesis facilities are often different to those for other facilities. In the case of chemical synthesis facilities, the large number of chemicals used exacerbates the difficulties. In the other facilities it is often the problems of cross-contamination and the variety of machines required that dominate.

Pilot facilities for primary and secondary manufacture require a greater degree of flexibility for the reconfiguration of equipment compared with general production operations. This is easier for secondary operation than for primary as the reactors and other items of chemical apparatus are more difficult to reposition and link into each other.

For secondary operation, although it is necessary to have a dedicated sterile unit, all other operations are usually self-contained.

This chapter summarizes the main design requirements that are necessary in these facilities for development and small scale manufacture. The detailed

requirements follow the principles for primary and secondary operation in earlier chapters.

10.2 Primary and secondary processing

The division between primary and secondary processing is to some extent arbitrary and different manufacturers place the dividing line at different places in the total manufacturing process. In general all the chemical stages up to and including the manufacture and purification of the active pharmaceutical ingredient are part of primary processing. In some cases, physical manipulation processes such as milling are also included. All the steps after purification (except in some cases milling) are usually included in secondary processing.

The decision of where to place the dividing line is often based on:

- the type of purification and physical manipulation processes that are required;
- the chemicals used within the purification and physical manipulation processes;
- the need for the primary process to stop at a point where meaningful samples can be taken;
- the type of building and facilities available to the manufacturer.

10.3 Process development

There are a number of stages in the development of pharmaceutical products. These stages are driven by the regulatory process, which is summarized in Chapter 2. The initial research that involves searching for new chemical entities is usually carried out at the laboratory scale and is not discussed further in this chapter.

Once a promising new chemical entity (NCE) has been discovered, tests will begin on the compound to confirm that it has the required activity, stability, and low toxicity. It will also be necessary at this pre-clinical stage to identify that the compound can be synthesized by a practical route and that it can be purified and formulated.

Much of this pre-clinical trials activity will be carried in the laboratory but it may be necessary to carry out some work in a small-scale pilot facility. Once this work has been completed, the clinical trials themselves start. These are carried out in three stages with increasingly large quantities of material. For the first stage, a small-scale pilot facility (in the order of one-hundredth of

production scale) will usually be sufficient, whereas normal scale pilot facilities (one-tenth production scale) are usually required for stage three clinical trials.

During process development the whole manufacturing process will need to be both scaled up and optimized. Initially, this will be carried out in the small-scale pilot plant, followed by the normal scale pilot plant. The final scale up work will be carried out using production scale equipment and this may take place some time after the product launch since it is often possible to produce launch quantities of material using the pilot plant.

Process optimization needs to take place early in development because the regulatory authorities require the stage three clinical trials to be carried out using material produced by the same manufacturing process as is used for the full scale.

Stage three clinical trials are usually carried out at one-tenth of production scale because the regulatory authorities expect the scale up from the development scale to the product scale to be no more than ten fold.

10.3.1 Good manufacturing practice

Once the clinical trials start it is necessary to produce all the material required based on the GMP requirements detailed in chapter 3. Although the regulations are directed primarily at the stages after chemical synthesis, the principles should be applied throughout the whole manufacturing process.

Contamination by operating staff

The operating staff in a pharmaceutical facility is likely to be the main source of product contamination. Body particles are continually shed as people move around. Microbiological contamination is always a problem and all stages of production, apart from the early stages of chemical synthesis, will require a hygiene regime. The operating staff can cause cross-contamination between different products and/or different intermediates by material spilt on their clothing. Clean clothing needs to be regularly supplied.

Small-scale facilities involve a large number of manual operations, so contamination by the operating staff may be greater than on a production scale. For particularly sensitive products, this may require a high level of protective clothing for the operators and/or the use of laminar flow booths or glove-box isolators.

Cross-contamination

Cross-contamination between different products and/or different chemical intermediates is a major source of drug adulteration. Since small facilities can be used to make a large variety of products and/or intermediates, the

possibility of cross-contamination needs to be addressed at the design stage. Issues to be considered include:

(a) Easy to clean equipment
Small-scale chemical synthesis equipment is cleaned either manually, by using mobile cleaning rigs or by refluxing with solvents. Equipment will need to be accessible and may need to be disassembled to allow access. This is a design requirement.

Mobile cleaning rigs using high-pressure hot water jets with or without the use of detergents can be useful for cleaning. However, these rigs can only be effective if all contaminated surfaces can be accessed. It can be used to clean large bore pipework. Careful consideration will need to be given to the possible safety hazards. Hot water can easily lead to scalding of operating personnel and some strong detergent solutions are particularly corrosive.

Refluxing with solvents can be useful for reaction equipment fitted with a condenser.

Other small-scale equipment will almost certainly need to be stripped down for cleaning.

In all cases, it is important for the equipment to be constructed without crevices that hold chemical, particulate or microbiological contamination and to have a surface finish that is inherently easy to clean. Glass, electropolished stainless steel and PTFE are common easy to clean finishes.

(b) Primary containment
Primary containment is based on the actual equipment used to do the processing, for example, reaction vessels should have a closed top and a seal on the agitator. Full primary containment can be achieved when solids are charged via glove-box isolators and liquid connections are made via hygienic dry break connections.

Primary containment minimizes the need for secondary containment and reduces the building standards required.

(c) Secondary containment
Secondary containment involves placing the manufacturing equipment in some form of ventilated enclosure resulting in a number of conflicting issues:

- segregating flameproof areas from safe areas;
- protecting the product from contamination by the operating staff and the environment;
- protecting the operating staff from highly active materials.

These three requirements can be resolved by the use of air locks, the correct pressurization routines and correct extraction and ventilation regimes. For more details see Chapters 6 and 8.

Some enclosures are large enough for the operating staff to enter via air locks. In other cases the equipment can be enclosed in a down flow booth with an open front that allows the equipment to be operated with sufficient air velocity to protect both the operator and the material being produced.

With the smallest scale equipment, it is possible to place the equipment inside an isolator with equipment being operated via gloves or a half suit. Such a system offers a high level of protection and is frequently used when the material being produced is highly potent or highly active.

(d) Ventilation

Ventilation can be used in laminar down flow or cross flow booths to protect the product from cross-contamination and the operating staff. Also an increase or decrease in pressure in different areas prevents the flow of air into or out of the room.

Ventilation systems require careful design because they can be the cause of cross-contamination themselves, particularly if one ventilation system is used to serve more than one area.

(e) Cross-contamination by the operating staff

This is minimized by making efficient use of the containment system, by ventilation, providing clean clothing at regular intervals and appropriate changing facilities.

Materials of construction

The materials of construction for pharmaceutical equipment are covered by both European and American guidelines and regulations.

Paragraph 3.39 of the European Guide to Good Manufacturing Practice states: 'Production equipment should not present any hazard to the products. The parts of the equipment in contact with the product must not be reactive, additive or absorptive to such an extent that it will affect the quality of the product and thus present any hazard.'

Section 211.65 of the Code of Federal Regulations title 21 states: 'Equipment shall be constructed so that surfaces that contact components, in-process materials, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.'

To meet these regulations, it is necessary to specify materials of construction that are corrosion resistant, easy to clean, do not release material into the process by leaching of the material or absorb any of the process materials. The most commonly used materials are glass and stainless steel. These are corrosion resistant and easy to clean if constructed correctly. However, it is possible for glass to absorb ions from some chemicals, which can lead to cross-contamination, and materials can be leached out of stainless steel unless the surface is correctly treated.

Polymeric and elastomeric materials need to be chosen to have the widest range of chemical resistance as well as being able to withstand the range of temperatures likely to be encountered. These materials are particularly problematical with respect to chemicals being leached out of them because they generally include a range of plasticizers to improve their stability or flexibility.

Whatever materials are used, documentation will be required to demonstrate that the specified material has been installed.

Surface finishes
To ensure that equipment is easy to clean, liquids drain easily and solids do not adhere to walls, it is necessary to consider the surface finish of both the inside and outside of equipment.

Metals normally need some form of treatment such as polishing. Mechanical polishing of metals requires the use of grits that are held together by soaps and grease and these can become embedded in the surface and lead to product contamination. At the small scale this problem is best overcome by having the metal surface electro-polished. Mechanical polishing is suitable for the external surface of metal.

Non-metallic materials such as glass and PTFE have an inherent smooth and easy to clean finish both on the outside and the inside. However, other non-metallic materials are much less smooth. Lining these with PTFE may be required. An external finish will need to take into account the likelihood of damage due to manhandling the equipment.

Material storage and handling
Systems to ensure that intermediates and products are not confused are of fundamental importance to good manufacturing practice. At the small scale there is likely to be a large number of materials to be stored, made by different processes. The storage handling system must be able to prevent different materials from being incorrectly identified and must prevent the same material made by differing processes from being mixed.

10.4 Small-scale pilot facilities

10.4.1 Chemical synthesis – primary manufacture

Reaction equipment

Small-scale pilot facilities with capacities ranging from 20–100 litres are generally required for the chemical synthesis stage of the manufacturing process. To provide a high level of corrosion resistance such facilities usually use glass equipment that can be configured for the particular processes taking place. In some cases the whole rig is built from scratch and then dissembled when it is not required. This type of rig is often called a 'kilo-lab'.

Solids handling equipment

Simple filters, centrifuges and dryers will be required since most pharmaceutical intermediates are solids. The solids handling equipment will be corrosion resistant and mobile so that it can be connected to the reaction equipment.

Depending on the quantities of material used, stage three clinical trials material may be produced by this equipment, which will replicate the type of equipment that will be used on a production scale and have a similar modus operandi. This solids handling equipment can be hired from equipment vendors.

Small-scale solids handling equipment suffers from the problem that much of the product may be held up in the equipment and consequently the yield is very low.

Multi-purpose equipment

Some specialist vendors provide multi-purpose equipment that can be used for reactions, filtration and drying. These units have the advantage that they reduce handling and, thus, reduce the exposure of the operators to the chemicals. However, as this equipment is complex it is usually a compromise and the result is not cost effective and less than optimal for each unit operation.

Solvents

Most chemical syntheses use flammable solvents which means that the small-scale facility will need to be a flameproof area. Since these facilities are often located within laboratory complexes it is necessary to separate flameproof areas from safe areas. This can be achieved by the use of pressurized air locks and in some cases the pressurization of the safe areas.

Small-scale facilities make use of a large number of solvents usually handled in drums requiring a flameproof drum handling and storage area, outside the building to reduce ventilation needs. A method of safely transferring the solvents from the drums to the manufacturing equipment is required. One method involves moving the drums from the drum store to a dispensary area, where the required quantity is decanted into a safe solvent container that is used to transfer the solvent to the reaction area. In other cases intermediate containers may be used to transfer the liquid from the drum store to the dispensary.

Since a large number of solvents are used in small-scale facilities it is unusual to find solvent recovery facilities included in the area, unless one or more solvents used in larger quantities can be recovered using the equipment used for the chemical processes. The recovery of solvents prevents cross-contamination and enables them to be disposed of safely.

Toxicity

Although the final drug product manufactured may have a low potency, the chemical intermediates that are made during the synthesis of the active pharmaceutical ingredient are often highly potent. The design of the facility must ensure that the operating personnel are protected. This in part may be covered by the building design, but also it will require the use of fume cupboards, local extract ventilation, glove-boxes, rapid transfer ports, contained transfer couplings and air suits.

Environmental considerations

The chemical synthesis route of many pharmaceuticals is highly complex (see Figure 1.1, page 3). In many cases more than 20 intermediates are made before the active pharmaceutical ingredient is prepared. Even if every stage has a high yield the overall yield can be very low. This means that facilities must be provided for all the waste streams to be handled.

The large variety of chemicals produced in low volumes usually precludes the use of an on-site effluent treatment plant for handling all the waste streams. Liquids and solids must be put into groups that can be mixed together for disposal; for example, halogenated solvents will need to be separated from non-halogenated solvents.

Depending on the quantities involved and their toxicity, vapour and gaseous emissions will be treated. Vapours can often be condensed using a low temperature system — the use of a liquid nitrogen cooling system is economical at the small scale. Solvent, acid or alkali scrubbing systems may be

required for the gaseous emissions. The choice of equipment will depend on the chemicals used and the flexibility required.

10.4.2 Physical manipulation

Physical manipulation is a process not involving a chemical reaction that changes the purity of the material. It usually involves crystallization, filtration, chromatography, milling, drying or blending for example. This type of process is frequently required to achieve one or more of the following requirements:

- crystal morphology;
- moisture content;
- specific particle size;
- particle surface physico-chemistry.

Depending on the product, the equipment for crystallization, filtration and centrifugation may be the same equipment as is used in the chemical synthetic process, and so most of the comments made in Section 10.4.1 are relevant. However, other equipment is used to carry out a particular operation, such as milling, micronization or granulation.

To achieve maximum flexibility this equipment needs to be mobile. In some cases developers may hire this equipment from the vendor when it is required.

Many organic solids are explosive when finely divided and require explosion protection and it is likely that the most appropriate method will be to use inert gas blanketing.

10.4.3 Manufacturing the final dosage form – secondary manufacture

The first stage of the manufacturing process is formulation. This is the process of adding the drug(s) to one or more excipients (see Chapter 6 for more details of excipients) to provide the correct mixture for the final dosage form. These may be solids or liquids depending on the final dosage form.

Liquids, gels, creams and syrups

If the final dosage form is a liquid, gel, cream or syrup then the equipment used for chemical synthesis may be suitable for the required blending operation. However, some formulations such as those required for aerosols require specialist formulation equipment because the propellants used are pressurized liquids with vapour pressures in the region of 3 to 4 bar g.

Conversely it may be advantageous to use equipment located close to the filling equipment, which may require dedicated formulation equipment, so that it is possible to run the formulated product directly to the filling machine. If this is not then the product would be transferred into one or more intermediate

vessels and moved to the filling area. Rapid transfer between formulation and filling is a particular requirement with terminally sterilized products, as these must be formulated, filled and sterilized within 24 hours.

The choice of whether to use equipment directly connected to the filling equipment is determined by the nature of the product and overall facilities available to a company.

Solids

When the final dosage form is a tablet or pellet a solids mixing system is required. Small specialist solids mixing equipment is usually provided for formulation. At the smallest scale this equipment may be hand operated and similar to a modern version of a pestle and mortar.

Solid dosage forms, such as tablets, capsules, suppositories and solid dose inhalers require a second manufacturing stage beyond formulation for their production.

The machinery required is highly specialized and designed to carry out a particular task. Whilst hand operated bench scale equipment exists, this is usually only used to test the formulation and demonstrate that the required final dosage form can be produced. Such equipment is suitable for use at the pre-clinical stage.

Once material is produced for clinical trials, small-scale automatic machines is required. Since these materials are designed to make specific final dosage forms, pharmaceutical companies often specialize in a small range of dosage forms. This reduces the number of machines required.

10.4.4 Filling

Filling is the process of putting the finished pharmaceutical product into its primary container, which may be a bottle, vial, ampoule, tube, aerosol can, or blister pack.

In the early stages of clinical trials, automated filling machines may not be used for tablets and capsules as these can be filled and packed by hand.

Suppositories are filled by machine as they are easily damaged, and solid dose inhalers will almost certainly be filled by machine due to their complexity. However, they will only be simple semi-automatic machines.

For liquid products, the filling operation produces the final dosage form. When only small quantities of these are required hand operated bench scale machines may be used, larger quantities will require automatic machines. These are specialist machines and, as with solid dose machines, companies tend to specialize in a few dosage forms.

With liquid filling it is usual to connect the formulation equipment to the filling machine so that the liquid can be transferred directly. In production facilities it is common to have completely integrated filling lines with filling, check weighing and washing connected together. At the smaller scale flexibility can be increased by keeping the individual machines separate and manually moving the filled packs from one unit to another.

10.4.5 Packing

Most pharmaceutical products are sold in some form of secondary packaging. This gives protection to the primary packaging and allows detailed instructions to be included with the product. Packing is the process of putting the product already in its primary packaging into its secondary packaging.

At the early stages of clinical trials, this can be carried out by hand. However, once the required quantities increase to more than a 1000 containers, a semi-automatic packing machine is usually necessary. If it is expected that the product will be packed by machine during the production process, then the chosen pack(s) will need to be tested on the packing machine during clinical trials to prevent a delay to the product launch.

There are several stages to packing:

- labelling the primary packaging;
- putting the primary packaging and instructions into the secondary packaging;
- printing lot specific information on the secondary packaging;
- fastening a tamper evident label to the secondary packaging;
- over-wrapping the secondary packages into collated parcels;
- packing the over-wrapped parcels into cases.

Maximum flexibility can be achieved by using semi-automatic operations with each machine separated and fed by hand. The placing of the primary package and the instructions in the secondary packaging is usually a manual operation. The machine then folds and closes the secondary packaging, carries out any external printing and attaches the tamper evident label. Case packing is usually carried out by hand at this scale. Hiring the machines from the vendor or using contract packing-companies may be an option.

10.4.6 Building design

To handle the large number of processes reaching the pre-clinical trials stage, the building layout must be flexible and allow the use of mobile equipment. Often the buildings for small-scale facilities consist of a number of processing rooms on the ground floor with a service floor above providing all the required

services such as air conditioning. The process rooms may have technical spaces for other general purpose equipment, such as hydraulic power packs, vacuum equipment, or condensers. The rooms can also be used for access to some of the pipework as it enters the process space.

The rooms are fitted out with a minimum amount of furniture and process equipment so that mobile equipment can be moved around and equipment set up.

In some instances, one part of a specialized fixed equipment item is designed to be placed in a clean environment while other parts are designed to be installed in a technical space. Examples of this are horizontal dryers and centrifuges. The materials being handled are fed into the machine in the clean area and discharged in the clean area whereas the mechanical parts of the machine and the solvent handling equipment are located in the technical space. This is achieved by siting the equipment in the wall of the room.

Depending on the level of instrumentation and control, it may also be appropriate to have separate control rooms away from the processing rooms. It is usually advantageous to have the control room adjacent to the processing rooms to be able to observe the operations.

Changing rooms

Changing rooms are an integral part of any pharmaceutical facility. For small-scale facilities these will need to be designed to ensure that the operators can be dressed in suitable clothing, that cross-contamination does not occur and that any highly active materials are not carried out of the building on clothing.

A number of different changing rooms might be required to allow access to different parts of the building.

Equipment store

With small-scale facilities making use of mobile equipment, consideration must be given to the clean equipment store. It must ensure that the equipment is not damaged during storage.

Equipment may need to be stored on GMP pallets so that it can be moved easily and so that multilevel staging can be used to save space.

Each unit should be numbered and have a log book which clearly identifies its status (clean/dirty) and the processes for which it has been used. There should be an appropriate place for signatures of the operators and supervisors.

Access for potable equipment

To be able to move equipment around a building safely, sufficient access for movement should be designed. Consideration should be given to:

- the width of corridors;
- turn areas;
- size of doors;
- size of lifts;
- size of transfer hatches.

Office/write up areas

Experimental work generates large quantities of data and reports. Some writing areas will be required within the development areas adjacent to the equipment. In other cases it is necessary to have an office and write up area out of the main development areas but within the same building. This is because some processes run for a considerable time and only need to be visited for short times but at regular intervals. Often it is necessary to go through several different change areas, one after another, in order to arrive at an area of a higher or lower status within a building and this can take some time. Offices between the changing areas allow this time to be reduced.

Environmental control

Pharmaceutical products need to be handled in controlled environments to prevent contamination. With small-scale, flexible, frequently manually operated equipment, it may be difficult to provide primary containment and, therefore, high quality secondary containment is required. (See Chapter 8 for more details of room environments).

To achieve the required flexibility, it may be necessary to provide the equipment to supply many of the rooms with high quality air. To prevent cross-contamination it may be necessary to provide each room with its own stand-alone system.

Fume extraction and the use of flammable solvents will have an impact on the choice of equipment to be used for environmental control.

Laboratory

Since development requires many experimental tests to be carried out and adjustments are made to the process on the results of these tests, an in-house laboratory is necessary. In some cases this may be close to the process and, to reduce testing time, may be inside the area controlled by the innermost changing area.

Airlocks/pressure regimes

The pressure regime within a building must ensure that air flows in the desired direction. The pressure regime along with the air locks between each area must be designed to prevent the following arising:

- product contamination;
- cross-contamination;
- flammable vapour/dust contacting a non-flameproof and non-explosion proof electrical equipment;
- highly active compounds contacting unprotected operators or the outside environment.

Engineering workshop

Small-scale equipment is often built into test rigs and modified frequently as the process develops. With equipment in controlled environments and operators having passed through a number of change areas, it is often appropriate to have a small engineering workshop close to the process rooms. This area must be carefully designed to ensure that tools are not lost and that the area does not become a source of contamination.

Movable walls

Processing areas can be made more flexible if movable walls are used. To achieve this, the services need to come through the ceiling where possible. With the correct choice of materials it is possible to have movable walls even when a very high quality environment is required.

Communication between areas

With the need for operators to be dressed in appropriate clothing for different areas and with need to protect the product, it is not possible to walk around a pharmaceutical facility with ease. This means that communication between areas can be difficult.

Consideration should be given to speech panels, intercom systems, transfer hatches, visual panels and CCTV system to improve communication. Consideration should also be given to the safety of personnel working in areas that may be 'remote' from other areas within the building. This is particularly relevant where hazards exist.

Equipment cleaning

Dedicated equipment cleaning areas will be required. In some cases solvents are used for cleaning and this will require explosion proof electrical equipment.

Automated washing machines can be used and these have the advantage of reducing the labour requirements, producing reproducible results and keeping all the liquids handling equipment in the technical spaces.

Building services

For a flexible small-scale facility it will be necessary to provide a wide range of services to some or all of the process areas. The services will depend on the processes being carried out, but are likely to include:

- water for injection (not usually required for the early stages of chemical syntheses);
- purified water;
- potable water;
- compressed air;
- breathing air;
- nitrogen;
- vacuum;
- air conditioning with temperature and humidity control;
- fume extraction (usually only required for chemical syntheses or where solvents are used);
- steam;
- cooling water;
- single fluid heat transfer fluid;
- services for solvents used in high volumes (e.g. recovery for safe disposal).

10.4.7 Controls and instrumentation

The control and instrumentation requirements for a small-scale facility will depend on the range of products being made and the equipment being used. The following considerations will need to be taken into account:

- the equipment selected will have to be compatible with the environment in which it will be used;
- the instrumentation should be suitable for in-house calibration so that it is not affected by the many processes used;
- control systems loops should be short, simple and flexible.

10.5 Chemical synthesis pilot plants

10.5.1 Introduction

According to a senior executive from one of the pharmaceutical industry's major multinationals, the future of the pharmaceutical industry will be 'moulded by science, shaped by technology and powered by knowledge'. His views would no doubt be shared by the bosses of the other top nine pharmaceutical companies who, in the previous 12 months spent between them over £10 billion on research and development.

Pilot plants are an essential component of the R&D operations of all major pharmaceutical companies seeking to provide new products for the future. The particular requirements for the design of each individual pilot plant will depend very much on the company's traditional research methods, the class of compounds likely to be developed and the regulatory requirements. However, there are some features that must be considered in every case.

A typical pilot plant for primary chemical manufacture will normally be used to transform chemical processes from the original laboratory bench procedure towards practical industrial scale manufacturing facilities. Alternative process routes will be compared and evaluated until the optimum mix of process safety and operability, product quality and manufacturing cost are achieved.

The pilot plant will also be used for the synthesis of samples and supplies to be used for formulation development, clinical trials, safety assessment and stability testing. It will normally comprise facilities and equipment for dispensing, reaction, separation, filtration and drying and finishing and will, therefore, normally include downflow booths, reactors, filtration equipment, a range of different types of dryers, and sieving, milling or micronizing equipment.

When the engineer is asked to produce a design for a new chemical pilot plant, the main challenges will include:

- scope definition;
- multi-product and multi-process capability;
- flexibility;
- GMP operation;
- layout;
- regulatory requirements;
- political aspects.

The following sections look at each of these areas in more detail.

10.5.2 Scope definition

Each pharmaceutical manufacturer has their own ideas on the best pilot plant to suit their needs. For example, when asked their opinion following a tour of a competitor's highly complex fully automated plant, the pilot plant manager from a major pharmaceutical company replied: 'I would be much happier with a glass bucket and a thermometer!'

The point is that it is extremely important to adopt a team approach when working on scope definition. The team must include the ultimate user(s), bearing in mind that these people are normally chemists or pharmacists and are not always aware of the impact of seemingly small changes on the overall engineering design.

When plant facilities to handle novel processes are being designed, it is unrealistic to expect that the user's needs would be fully specified from the start. The process parameters are generally unknown, so the only way to proceed is to develop a capacity model by considering sample processes.

The capacity model can then be reviewed against previous pilot plant activity and the perceived business needs.

The useful life of a pilot plant should be at least ten years, so it pays to spend time at the front-end of the project speaking to the business managers and considering how the company's future products may evolve.

10.5.3 Multi-product capability

The plant must have the capability to permit the handling of future unknown compounds. This may be obtained by:

- using simple (manual) material handling systems;
- using materials of construction for the equipment and pipework that have a high resistance to corrosion;
- providing a high degree of product segregation to prevent cross-contamination;
- providing a high level of containment to protect the operators and the environment;
- providing cleaning systems that allow rigorous decontamination between different product runs.
- using materials of construction that do not react with the product contact parts.

10.5.4 Multi-process capability

In order to provide this capability, the pilot plant will need:

- a speculative range of vessel sizes (typically 50 to 2000 litres) in a suitable mix of materials of construction, based on the capacity model developed earlier;
- vessels with variable volume capability, e.g. double jacket reactors;
- variable temperature capabilities for the reactors, possibly via the use of a single heat transfer fluid system. A typical plant provides heating/cooling in the range of 150°C to −30°C;
- portable/mobile equipment, which allows equipment to be brought closer together avoiding complex piping runs and provides better utilization of available space;
- services such as water, air, steam, nitrogen, heat transfer fluid and perhaps solvents, should be piped to all areas where it is remotely possible that processing will take place, including areas set aside for future expansion. This will allow maximum flexibility and provide a hedge against changes of function due to market forces;
- a high quality de-mineralized water system providing a supply to purified water requirements;
- equipment that is suitable for Cleaning In Place (CIP), in order to reduce downtime between processes.

10.5.5 Uncharacterized products/processes

The very purpose of a chemical pilot plant, i.e. to synthesize New Chemical Entities (NCEs), means that the potential hazards of the processes and compounds involved are not normally known at the time the facility is being designed. It is, therefore, necessary to provide high levels of primary and secondary containment.

The dispensary design will have to allow for raw materials with widely differing hazard potential, which are received in a wide variety of packaging sizes and shapes.

Most pilot plants have down-flow booths for operator protection during dispensing and a local extract ventilation system provided across all other areas. Other containment options, depending on the severity of the hazard, include glove boxes and full air suits.

It is a key part of the design function to classify the types of compound that will be entering the facility and adjust containment levels accordingly.

Another aspect of containment is the need to restrict atmospheric or other emissions of harmful substances to levels that are acceptable to the Environment Agency. For example, releases of Volatile Organic Compounds (VOCs) such as solvents must be prevented and will require the installation of a scrubbing or recovery system.

Good operating procedures in compliance with the legislation require that the volume of all waste materials is kept to a minimum and that all hazardous waste is disposed of in a safe, legal and traceable way.

The multi-function basis and the lack of a defined process, may mean that novel methodology will be required to allow meaningful Safety, Health and Environmental (SHE) reviews to be carried out. Typically, this would involve the development of system envelopes (including control systems), which would be reviewed against guidewords to ensure that the design is sound. Such reviews would be expected to highlight those issues that are chemistry specific. These areas would have to be noted, and then developed in more detail prior to the introduction of each new process into the plant.

10.5.6 Operation

The way in which a chemical pilot plant is operated depends very largely on its designated purpose, but also on the traditions of the client/owner. However, because of the unknown and potentially hazardous nature of the compounds and processes to be employed, many major companies prefer to have the reaction areas of their pilot plant normally unmanned.

This is of course contrary to the chemist's preference for reaction visibility. Typically they like to observe changes of colour or state as the reaction proceeds.

On a smaller capacity plant, which is operated at medium temperatures and pressures, this requirement may be satisfied by using borosilicate glass equipment allowing the operators to observe the reaction areas through windows.

On larger plants where the processes involve more onerous conditions, the use of glass is not tenable. In this situation, some companies have provided the chemists with the possibility to make real time observations of the reactor contents by using closed circuit television cameras.

10.5.7 Layout

As with most of the other topics discussed in this section, the type of layout adopted by the design team will very much depend on the owner's past experience and culture.

Free access is highly desirable to allow easy maintenance and enable the inevitable plant modifications.

Many modern pilot plants have adopted a vertical modular arrangement (see Figure 10.1) which allows gravity feed to be used in processing and is well suited to moving products between the modules via flow stations. However, this type of arrangement is by no means universal. A large number of manufacturers

still prefer the traditional 'reactor hall' arrangement with separate areas for the finishing steps including filtration, drying and particle size reduction.

One point worth mentioning is the high level of HVAC that chemistry pilot plants will require in order to provide the required level of air filtration, pressure differentials and clean environments. This means that the routing of process
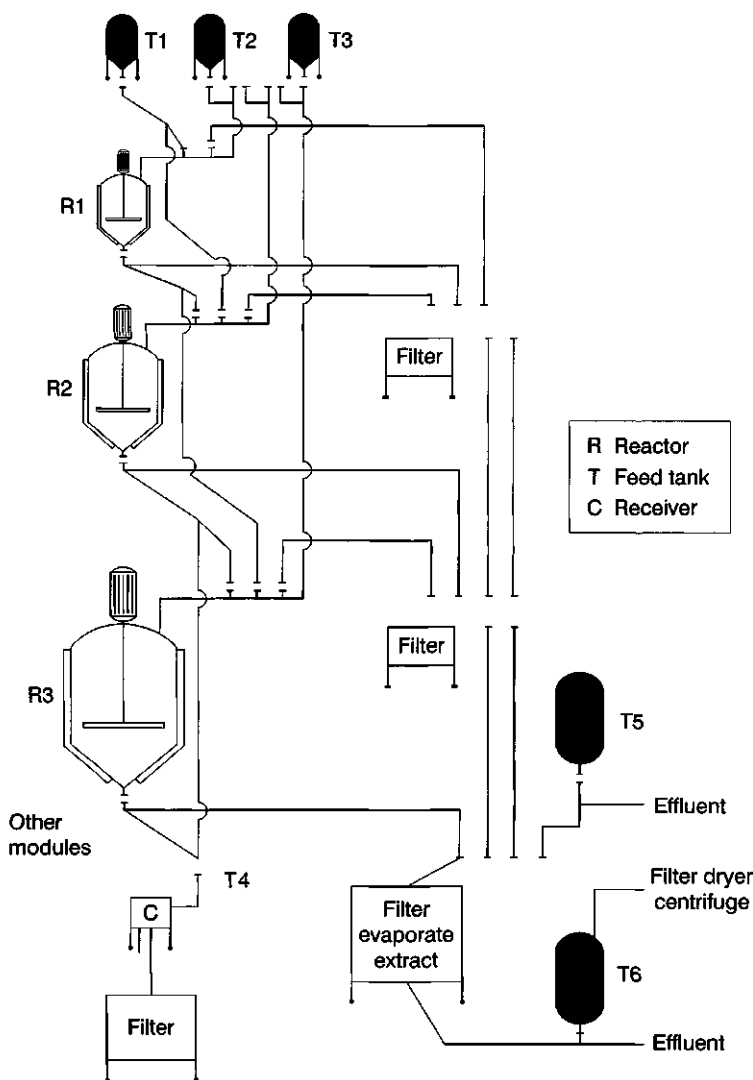

Figure 10.1 Typical module schematic chemistry pilot plant

pipework and building services ductwork will be a critical task. It is wise to decide at an early stage in the project to separate these two major services to avoid possible clashes.

10.5.8 Controls

If you ask a typical pilot plant user what type of instrumentation and control system they prefer, they will invariable reply 'simple!' This is fine when you are working with passive substances and reactions, but totally unsuited to the needs of the modern pharmaceutical research establishment.

The main factors affecting the choice of control system are:

- data acquisition and storage;
- operational safety;
- multi-functional requirements;
- environmental aspects;
- regulatory compliance.

The raison d'être of the pilot plant is to research and develop alternative process routes for the preparation and scale-up of NCE's for pharmaceutical products. In order to achieve this mission, it must have a system for the recording, storage, retrieval and collation of the critical parameters observed during each process run.

Many pharmaceutical products are themselves highly active, or are manufactured from highly active materials. This requires high levels of containment to protect the pilot plant operators. If containment fails, the control system must stop the process and activate a fail-safe alarm procedure to direct uninvolved personnel away from the area of risk.

In addition to highly active substances, the controls will be required to alert the operators to runaway exothermic reactions and possibly detect leakage of flammable compounds.

Some pharmaceutical products have a hydrogenation step in their manufacture. Hydrogen has very wide explosive limits and very low minimum ignition energy. A suitable control package in this case would, include at least hydrogen detectors and a trip system.

The multi-purpose capabilities required of most modern pilot plants can also have a major impact on the choice of control system. If the plant is reconfigurable the control system must allow for these changes. A pilot plant recently completed for a major pharmaceutical manufacturer has around 250 valid equipment configurations. In order to ensure that the configuration set-up is correct, a system of electronic tagging is scanned and checked by the control system for the required 'recipe'. If the arrangement is correct, the system

reveals a password that must be manually entered into the process control computer before process operations can begin.

During the design of the above plant, it was found that one of the most economic ways of providing flexibility whilst still meeting processing and containment requirements was to use mobile equipment that could be installed at various locations throughout the plant. Each item of equipment has its own instrumentation and control requirements, which are identified, powered, controlled and recorded by the control system. When the equipment is correctly located, an umbilical cable is connected using a plug and socket, which provides the necessary signal and control for that item of equipment. At the same time the control system re-assigns the internal address of that equipment item to suit the new location.

It is not always easy to find instrumentation that will operate across the full temperature range of the pilot plant whilst still meeting GMP requirements. Often detailed studies must be undertaken to identify and select the most appropriate type of sensors to be installed.

The control system must monitor and control equipment that is installed to ensure that the emission limits laid down by the Environment Agency are not exceeded. It must take GMP into account and be suitable for validation to meet the requirements of the regulatory authorities.

10.5.9 Legal and regulatory requirements

Chemical synthesis pilot plants for the pharmaceutical industry must be designed to be safe and not pollute the environment. The multi-function basis and the lack of defined process will probably mean that novel methodology will have to be developed and agreed with the legislative authorities prior to Safety, Health and Environmental (SHE) reviews being carried out.

Due to the multi-process nature of the plant, safety reviews need to take place throughout the life of the facility. The initial reviews take place during the engineering design phase, then during commissioning and following that, whenever a new process configuration is required during operation.

As the plant will normally be used to manufacture small quantities of product for clinical trials and potentially subsequent marketing purposes, it must be designed to meet current Good Manufacturing Practice (cGMP) and be suitable for validation by the appropriate regulatory authority.

The pilot plant may also be used to demonstrate the suitability of the selected manufacturing process for industrialization. The normal scale-up factor permitted/accepted by the regulators is 10:1.

10.5.10 Cost

There is no precise guidance on the relative costs of pilot plants when compared to typical manufacturing facilities, other than that the unit cost of the pilot plant will always be higher.

The reasons for the higher costs are simply put down to the wide range of features previously described, which are employed to obtain maximum flexibility and benefit from what normally represents a major investment without guaranteed returns.

It should be expected that the ratio of engineering costs to overall costs would also be higher than for conventional manufacturing units.

The complexity of the pilot plant design to increase as engineering progresses should be expected and allowed for. This will be brought about as solutions are evolved to problems, and by new technology coming available which improve the general usefulness of the plant.

Validation cost is very significant and must be considered from the outset.

10.5.11 Political aspects

A new chemical pilot plant will often be of major strategic importance to the owner, not only because it provides the vital link in developing promising, newly discovered products to market, but also because it demonstrates to investors that this is very much a research-led organization, planning for future growth.

The new facility may often be the only facility of its kind within the company, so the design, layout and its worldwide location may be subject to thorough vulnerability analysis to ensure its security and availability.

10.6 Physical manipulation pilot plants

The equipment used for physical manipulation includes:

- crystallizers;
- filters;
- filter/dryers;
- centrifuges;
- dryers;
- mills;
- micronizers.

This equipment makes use of solvents and gravity flow and is used within the same facility as a chemical synthesis pilot plant. For equipment that falls into this category, most of the detail given in Section 10.5 will be appropriate. However, it should be remembered that physical manipulation is being applied

to an active pharmaceutical ingredient (API) and that the equipment will need to be compatible with the GMP requirements.

In a few cases the physical manipulation equipment does not make use of solvents and gravity flow is of no particular advantage. In these cases this equipment may be included in a final formulation facility and the information contained in Section 10.7 will be appropriate.

10.7 Final formulation, filling and packing pilot plants

The equipment used in this type of pilot plant is a smaller version of the production scale equipment. Facilities are usually built to cope only with certain types of products. For example, a facility to manufacture tablets is likely to be able to cope with a large variety of different products because the processes involved in making tablets are similar even if the active ingredient is completely different. However, this facility would be completely different to one making inhalation products even if the tablet and the inhalation product contained the same active ingredient.

The design of these types of pilot plants is discussed in detail.

10.7.1 Cross-contamination

With the potential to use a large number of products within a pilot plant, cross-contamination is a problem, which means that containment is important. With automatic equipment dedicated to specific purposes it is possible to make use of primary containment to some extent, but with the need to make frequent changes and modifications it is probably wise to provide secondary containment. The secondary containment may be in the form of isolators around the equipment but it may be appropriate to have each piece of equipment in its own room.

To maintain flexibility it will be necessary to have easily cleaned equipment. Some use may be made of Clean In Place techniques, but it is inevitable that equipment will have to be disassembled. This can be one of the greatest sources of airborne particulates, which can lead to cross-contamination, so this need must be considered at the design stage. Rooms and isolation cabinets will need to be designed with easy cleaning in mind.

10.7.2 Material flow and storage

Due to the potential to use many different products and with processes being under development, it is easily possible to mix up materials. Materials flows

need to be simple and prevent incompatible materials coming into contact with one another.

Good housekeeping is a major priority. Storage facilities must have sufficient space for easy access and materials must be readily identifiable. Separate areas for raw materials, quarantine materials and passed finished products are required.

10.7.3 Flexibility

At the production scale, equipment for the final formulation, filling and packaging is often connected directly together. This is good for the high production levels required at the full scale, and it allows a high level of automation and minimizes labour requirements. However, such systems are not flexible.

Flexibility can be increased by having stand-alone machines and moving the output from one machine to the next by hand. This requires a number of suitable mobile containers to be included in the design.

It is also possible that some of the smaller machines can be made mobile, which allows the facility to have a reduced number of processing areas with equipment not in use stored in an appropriate place.

10.7.4 Automation

With filling and packing it is necessary to automate the machines at one-tenth the production scale. However, to enable easy change between different products, the automation should be kept as simple as possible. Changes to the system must be possible without reconfiguring the computer software which would require a high level of documentation to validate software changes.

10.7.5 Building requirements

The building requirements for final formulation, filling and packing pilot plants is similar to that required for small-scale facilities with the following differences:

- fewer rooms are required but the rooms will be larger;
- if mobile equipment is used it will be larger. It may only be possible to move the equipment by having very large doorways or by having removable walls;
- fewer building services will be required and it is likely that each room will only be supplied with the services appropriate to the equipment used in that room.

10.8 Safety, health and environmental reviews

The requirement to carry out a number of different processes makes a SHE review difficult at the design stage. It is necessary to carry out some form of generic review and to examine those processes that are currently known.

The introduction of each new process will require further SHE audits to ensure no new problems have been introduced.

10.9 Dispensaries

Dispensaries are an important part of pharmaceutical processing and are described in Chapter 6. Since small-scale facilities and pilot plants use a large number of products, dispensaries are a major area of risk from cross-contamination.

Dispensaries need to be considered at the design stage and integrated with the operation of the facility. Sufficient space must be allowed to ensure operations are safe and efficient.

10.10 Optimization

Processes carried out within small-scale facilities and pilot plants are not usually optimized, because the facility is multi-functional. It is usually necessary to sacrifice speed of processing and product recovery in order to achieve flexibility.

Equipment should be chosen to ensure that it is:

- quick and easy to change between products;
- easy to clean;
- retains the minimum amount of product;
- simple to operate;
- conforms to GMP requirement.

10.11 Commissioning and validation management

The User Requirement Specification is always difficult to define for these facilities, however once the Design Qualification has been agreed and signed off Installation Qualification is similar to that for production scale commissioning except that it is an ongoing operation as new processes are being continually introduced.

Performance Qualification is more of a problem because data will need to be added to the validation files each time a new process comes on-line.