Primary pharmaceutical production

5

ROGER SHILLITOE, PHIL MASON and FRED SMITH

This chapter considers the production of the bulk active ingredient or bulk pharmaceutical chemical (BPC) that is subsequently converted by physical means into the final drug's presentation form.

This area of the pharmaceutical industry has much in common with fine chemical manufacture. The unit operations carried out are similar and many fine chemical and speciality chemical manufacturers also manufacture pharmaceutical intermediates.

Traditionally, the bulk production was carried out on a different site to the R&D and secondary processing. The style of operation, attention to cGMP and culture of a primary site, was more associated with the type of chemistry or operation carried out.

Three main influences are changing the face of the BPC industry:

- regulators, particularly the FDA, are putting greater emphasis on reviewing BPC production, and recognize the effect that failure in quality can have on the finished dosage form;
- major pharmaceutical companies are focusing on 'Research and Development' and 'Marketing and Selling of the finished product'. Secondary manufacture to a limited extent, and primary or BPC manufacture to a greater extent, is being sub-contracted out to third parties;
- BPCs are becoming more active and tonnage requirements are dropping as a result. Linked with this, the size of the equipment used in the manufacture is reducing. The increased activity also brings increased handling considerations and limits for exposure, which in turn drives towards closed processing operations, which is also consistent with improvements to cGMP.

5.1 Reaction

The production of the BPC is by three main methods:

- **chemical synthesis**: Examples of synthetic conversions include aspirin, diazepam, ibuprofen. This method produces the largest tonnage;

- **biotechnology or microbial action**: Examples include antibiotics, vaccine production, blood plasma products. This method produces the high value products;
- **extraction**: This can be by extraction of natural materials from animal or plant material such as the opium alkaloids, dioxin, heparin, insulin (pigs pancreas), thyroxine (animal thyroid gland).

This chapter will concentrate on the first two methods. The extraction method for naturally occurring materials was the main source of drugs up to the 1930s but was being gradually replaced with synthetic routes to products. There is resurgence now in extraction techniques linked to the biotechnology area, where specifically developed or altered organisms are allowed to grow and produce a desired product that is harvested and extracted. This is discussed in Section 5.1.2.

5.1.1 Synthetic chemistry based processes

Various general synthetic chemical reactions are utilized in the synthesis of BPCs. These include simple liquid/liquid reactions, complex liquid reactions with catalysis such as Grinards, Freidel Craft, reaction with strong reagents such as phosphorous oxychloride, thionyl chloride or elemental halogens such as bromine or chlorine. Gas reactions with liquids are common for example with hydrogen, hydrogen chloride or phosgene.

Most reactions in the pharmaceutical industry are carried out on a batch basis, in non steady state operation. Continuous processing is occasionally used for a few generic tonnage commodity BPCs or where safety can be improved by the benefits continuous processing can bring by inventory minimization.

Conventional batch reactor systems

The batch reactor is the workhorse of the synthetic BPC industry. Typically made from stainless steel or glass lined mild steel, capacities ranges from 500 litres at the small scale to 16 m^3 at the large scale. Some processes employ reactors of even greater capacity but this is becoming unusual as the activity of new drug substances increases.

The reactor is typically fitted with an external jacket or half pipe coils so that the temperature of the contents can be adjusted. Occasionally if a high heat duty is required, further coils can be placed inside the reactor.

Typical operating conditions are from $-25°C$ to $+160°C$, and full vacuum to 6 bar g. Generally, reactions at elevated pressures above 1 bar g are uncommon, with the exception of specific gas reactions such as hydrogenation. However, more processes are now being developed where working at an

elevated pressure brings benefits — for example, it can allow the selection of the ideal solvent for a reaction that could not normally be used at the ideal reaction temperature because this would be above its atmospheric boiling point.

The temperature is normally adjusted by indirect contact with a heating or cooling medium circulating through the coil or jacket, but direct heating with live steam or quench cooling with water or other materials is possible. The medium used for the heating and cooling fall into two main areas:

- **multiple fluids**: typically steam, cooling water, refrigerated fluid such as ethylene glycol or brine. These are applied in sequence to the coil or jacket as required;
- **single fluids**: typically some form of heat transfer oil, heated or cooled by indirect contact with steam, cooling water or refrigerant, and blended to provide the correct fluid to the coil or jacket.

Agitation is provided to the reactor to ensure good heat transfer and good mixing for reaction. Depending on the process requirements, various agitation regimes can be set up using different agitator profiles, speeds and locations.

Connections are made to both the top and bottom of the reactor to allow material to be charged into the reactor, material to be distilled from the reactor, and liquids to be drained out.

Reactors are normally fitted with a manway to allow entry for maintenance purposes. Historically, this was also the way in which solids were added to the reactor and samples were extracted, but this practice is becoming less common.

Alternative reactor systems

Other types of reactor systems exist with each having their own specific advantages for specific processes. These include the loop reactor that specializes in gas-liquid reactions at elevated pressures, such as hydrogenation, and the batch autoclave reactor that specializes in high-pressure reactions of 100 bar g and higher.

Materials of construction

Reaction modules can be constructed from other materials dependant on the chemistry being employed and requirements for heat transfer. These include glass, plastics and exotic metals such as hastelloy or titanium.

5.1.2 Biotechnology based processes

The processes in biotechnology are based on cultivation of micro-organisms, such as bacteria, yeast, fungi or animal and plant cells. During the microbial process the micro-organisms grow the product, which is either contained within

the cell or excreted into the surrounding liquor. The micro-organisms need carbon substrate and nutrient medium for growth and the microbial process is normally performed in water.

There are essentially three steps to biotechnology processing, namely:

- fermentation;
- recovery;
- purification.

The equipment in which the microbial process is carried out is called the fermenter and the process in which micro-organisms grow or format product is called fermentation.

Once the product is formed it is recovered from the biomass or the liquor by downstream processing, e.g., centrifugation, homogenization or ultrafiltration.

Purification of the recovered product is then required. Two differing techniques are required depending on whether it is for bulk large-scale or for small-scale genetically manipulated organisms. Large-scale recovery can be likened to bulk chemical organic synthesis operation.

Fermentation

The fermenter is the equipment used to produce the micro-organisms. Biotechnology applications of fermentations divide conveniently between microbial types and mammalian cell culture. Microbial fermentation, which can encompass very large-scale antibiotics as well as smaller scale recombinant products, is characterized by fast growth rates with accompanying heat and mass transfer problems. Mammalian cell culture is characterized by low growth rates and high sensitivity to operating conditions. Both techniques have common design principles.

Several different types of vessel are used for large-scale microbiological processes, and their degree of sophistication in design, construction and operation is determined by the sensitivity of the process to the environment maintained in the vessel.

The following is a brief description of the main types of fermenters:

(*a*) *Open tank*

The simplest type of fermenter is an open tank in which the organisms are dispersed into nutrient liquid. These have been used successfully in the brewing industry. In the anaerobic stage of fermentation, a foam blanket of carbon dioxide and yeast develops which effectively prevents access of air to the process. Cooling coils can be fitted for controlling temperature during fermentation.

(*b*) *Stirred tank*

Stirred-tank fermenters are agitated mechanically to maintain homogeneity, to attain rapid dispersion and mixing of injected materials, and to enhance heat-transfer in temperature control and mass-transfer in dissolving sparingly soluble gases such as oxygen. The extent to which these are achieved depends mainly on the power dissipated into the medium by the agitator, so that the agitator is essentially a power transmission device. The effectiveness of the power input depends on the configuration of the agitator and other fermenter components.

For aerobic fermentations, air is injected through a sparger, a single nozzle or a perforated tube arrangement, positioned well below the lowest impeller to avoid swamping it with gas. The sparger should have provision for drainage so that no culture medium remains in it after the vessel is discharged.

The rate of air supply must be sufficient to satisfy the oxygen demand of the fermentation after allowing for the efficiency of oxygen dissolution achieved.

Instead of a rotating stirrer, some systems obtain the mechanical power input by using a pump to circulate liquid medium from the fermenter vessel through a gas entrainer and then back into the fermenter. This separates the liquid movement and gas dissolution functions into separate specialized units. Two designs have evolved using this principle — the 'loop' fermenter and the 'deep jet' fermenter. In the loop fermenter, the gas dissolution device is a subsidiary vessel into which gas is injected, and the gas-saturated liquid is recirculated to the main growth stage. In the deep-jet system, gas is entrained into a high-power jet of liquid injected into the liquid in the fermenter, re-entraining gas from the vessel headspace. Exhaust gas is purged partly from the vessel headspace and partly from the specially designed circulation pump, from which the degassed liquid passes through a supplementary cooler before passing to the gas entrainer. This system gives high gas dissolution rate, but has correspondingly high power consumption compared to conventional systems. The liquid and entrained gas can also be introduced into the fermenter through a 'bell', which holds the gas bubbles in contact with the recirculating liquid to enhance gas utilization.

(*c*) *Gas-lift and sparged-tank fermenters*

This design has no mechanical stirrer and the power required for mixing, heat-transfer and gas dissolution, is provided by the movement of gas through the liquid medium. The gas is, therefore, the power transmission system from the gas compressors into the vessel. While the relatively low efficiency of gas compression seems to make this design unattractive, it has some important advantages compared to the stirred-tank system. Firstly, the absence of a rotating agitator shaft removes the major contamination risk at its entry point

to the vessel. Secondly, for very large vessels, the required power input for agitation is just too large to be transmitted by a single agitator. Thirdly, the evaporation of water vapour into the gas stream makes a small contribution to cooling the fermentation. The fermenter interior does, however, need careful design to ensure that the movement pattern of the gas through the system produces satisfactory agitation.

The various designs of non-mechanically agitated fermenters can be grouped broadly into sparged vessels and gas-lift (including air-lift) fermenters. Sparged-tank fermenters are usually of high aspect ratio, with gas introduced at the bottom through a single nozzle or a perforated or porous distributor plate. The gas bubbles rise through the liquid in the vessel and may be redispersed by a succession of horizontal perforated baffle-plates sited at intervals up the column. In the gas-lift fermenters, internal liquid circulation in the vessel is achieved by sparging only part of the vessel with gas. The sparged volume has a lower effective density than the bubble-free volume, and the difference in hydrostatic pressure between the two sections drives the liquid circulation upwards in the sparged section and, after gas disentrainment, downwards in the bubble-free section. The two sections may be separated by a vertical draught-tube.

Important design considerations for good fermenter operation

The following are important design considerations in fermenter operation:

(a) Aeration and agitation

Animal cells are shear-sensitive (mild agitation is therefore required) and they are often sensitive to air bubbles. These considerations impose significant constraints on oxygen transfer design. One way in which this problem has been addressed is by the use of gas exchange impellers. Another strategy is to circulate medium through the reactor while simultaneously oxygenating it in an external loop. A third method is to use silicon tubing through which air diffuses into the liquid medium.

Cell culture medium often contains serum, which has a tendency to cause foaming. Since defoamants may inhibit growth, agitation and aeration systems must be designed to minimize this potential problem. However, care must be taken in the amount of agitation applied because, although it provides good oxygen and heat transfer characteristics, it can result in mechanical degradation of the cells. Usually systems with gentle agitation also minimize foaming. The type of impeller, baffles, and tank dimensions influences the degree of mixing. Note that mammalian cell cultures are more easily damaged by these mechanical forces than microbial cultures.

(*b*) *pH*

The internal environment of living cells is approximately neutral, yet most microbes are relatively insensitive to the external concentrations of hydrogen and hydroxyl ions. Many organisms grow well between pH 4 and 9, although for any particular organism the required pH range is small and accurate control is essential. Note, however, that there are exceptions where growth outside this range can occur.

(*c*) *Sterile design*

The importance of sterile design cannot be over emphasized; even the presence of a single contaminant will be disastrous. The fermenter must be designed to be easily cleanable (smooth surfaces and no crevices), after which it must be sterilized. The most effective form of sterilization is to utilize clean steam to kill both the live micro-organisms and their spores. This is usually defined as maintaining 121°C for 20 minutes. Shorter times and higher temperatures can be used but not vice versa. The quality of the steam supply is important; clean steam is required for mammalian cell culture, whereas, plant steam with approved additives can be used for large-scale antibiotics.

If the fermentation design calls for sterility, the following special precautions are required:

- air should be provided by an oil free compressor;
- Clean in Place (CIP) and Sterilize in Place (SIP) systems should be incorporated into the design;
- the fermenter and all associated piping and vessels should be designed to allow sterilization initially by 1.5 bar g steam. Branch connections should be minimized. All lines should be free draining and have minimum dead legs with the correct type of valves specified. Selection of internal surfaces, piping design, and valves is critical in ensuring effective removal of unwanted organisms during sterilization and preventing subsequent ingress of contaminants from outside the sterilized system;
- many fermentation media, at the large scale, can be sterilized continuously by heat. Economies can be achieved by incorporating heat recovery exchangers in the system to preheat the feed;
- all seals and instruments must be designed to withstand steam sterilization;
- the equipment should be designed to maintain sterility e.g. to include the use of steam seals on agitator inlets, double O-rings for probe insertion and steam blocks on transfer lines;
- piping should be stainless steel;
- an integrated approach should be taken to the physical layout, the piping and instrumentation (P&ID) flowsheeting and the sequencing to ensure that sterility is an integral part of the design;

(*d*) *Temperature control*

The temperature for organism growth ranges from approximately −5°C to 80°C. However, the actual temperature is important, particularly for cell cultures, so temperature control is critical. The lower limit is set by the freezing point of water, which is lowered by the contents of the cell. The upper limit depends on the effect of temperature on the vital constituents of the organisms — for example, protein and nucleic acids are destroyed in the temperature range 50° to 90°C.

(*e*) *Media sterilization*

Medium ingredients should be controlled through a careful quality assurance programme. However, sterilization is also required and there are essentially three methods used:

- continuous sterilization for large scale. The time and temperature of the continuous sterilizer should be optimized based on the most heat resistant contaminant. The hold section of the continuous sterilizer should be designed for plug flow to prevent back mixing;
- in-situ batch sterilization by heat for smaller batches;
- sterilization by filtration for heat sensitive products such as cell culture.

Recovery and purification

The product separation and purification section is critical to the design of a fermentation plant; indeed, the bulk of capital and operating costs for a typical plant are often connected with this area. The design of product recovery systems encompasses both intracellular and extracellular products from both microbial and mammalian cell fermentation broths:

(*a*) *Large-scale extracellular products*

Technologies for recovering the simpler extracellular products consist of conventional unit operations such as vacuum filtration, crystallization, liquid-to-liquid extraction, multi-effect evaporation, precipitation and distillation. These are similar to the basic organic synthesis processes detailed earlier in this section.

(*b*) *Recombinant products*

Recombinant therapeutic products can be intra- or extracellular depending upon the host micro-organism. Recovery facilities for the more complex intracellular protein products involve cell harvesting, debris removal, pellet washing and recovery, product concentration, desalting, purification and sterile product finishing operations.

The recovery and purification of protein products from fermentation broths involves rapidly-evolving, state-of-the-art unit operations. The complexity of

these operations is increased due to the heat and shear sensitivity of the proteins being recovered.

The use of recombinant-DNA organisms can also affect the design of the cell recovery area. If the organisms are not killed in the fermentation area, the recovery area handling the live organisms must be designed in accordance with applicable guidelines for containment.

Typical methods for recombinant product isolation and purification include:

(*a*) *Cell disruption*

For intracellular products the product of interest is inside the cells. The objective of cell disruption is to release this product for further separation. Cell disruption is usually carried out by mechanical means. This can be by use of homogenizers, grinding by beads or by high pressure liquid jet impacting. Other methods are use of sound, pressure changes or temperature changes and chemical methods. The separation of product from the cell debris after cell disruption is usually done by centrifugation.

(*b*) *Centrifugation*

Centrifuges are commonly used for cell harvesting, debris removal, and pellet washing operations. Cells can be separated using disc-stack or scroll decanter centrifuges. The latter allows cell washing prior to subsequent processing. The arrival of steam sterilizable, contained designs have made the use of such machines more suitable.

(*c*) *Ultrafiltration*

Ultrafiltration is widely utilized in the recovery and purification of protein products. The main uses of ultrafiltration are as follows: concentrating protein products; desalting product solutions by diafiltration; exchanging product buffer solutions by diafiltration; and depyrogenating of buffer solutions used in the process. Ultrafiltration is also finding increasingly wider use in the cell harvesting operation. It has an advantage over centrifugation in this situation since it subjects the protein to less heat and shear effects. Ultrafiltration is excellent for processes using cell recycle and in particular for mammalian cell applications.

(*d*) *Electrodialysis*

Electrodialysis is sometimes used to remove salts, acids and bases from fermentation broths. A unit will consist of compartments separated by alternate anion and cation exchange membranes. A direct electric current is then passed through the stack to effect the separation.

(e) *Chromatography*

Chromatography is the main technique for final purification of the product protein. Chromatographic separations take various forms depending on the driving force for the separation. There are essentially two basic forms of chromatography; partition chromatography (such as gel filtration) and absorption chromatography (for example, ion exchange and affinity chromatography).

Gel filtration, also called molecular sieving, separates molecules based on size. It is sometimes used to desalt protein solutions. In this method the product and impurities travel at different speeds through the bed effecting the separation. Gel filtration is essentially a low capacity technique and not suited for high volume processes.

Absorption chromatography is where the product binds to the matrix in the bed and is subsequently eluted by a change in the buffer composition. Common forms of separations include ion-exchange chromatography (which separates proteins based an electrostatic charge) and affinity chromatography (which separates a product or removes an impurity by means of a biospecific attraction between the molecule and a liagand attached to the gel or resin).

In order to achieve the required purity it is necessary to run the chromatographic units in series to reach the purity needed.

Automated programmed chromatography controllers are recommended for the reproducibility of their operation and reduced labour requirements. Once initiated, the programmed chromatography controller automatically loads the product on to the column, washes and elutes the product.

Scale up of chromatographic systems is reasonably straightforward and follows well-documented guidelines.

Solutions for purification operations

Solutions required during purification are generally prepared in solution preparation areas. Smaller volumes can be filled into portable containers or mobile vessels whereas larger volumes are generally piped to the user point. An important aspect of buffer preparation is to identify where Water for Injection (WFI) is required. In cell culture systems, where endotoxins are not produced by the culture, WFI is generally recommended for all buffer solutions so as to prevent the introduction of endotoxins, which would then need to be removed in a later chromatographic step. In microbial systems where endotoxins are produced (such as *E. Coli lipopolysaccharides*), WFI may not be needed until a later stage where the pyrogens are reduced to low levels or effectively eliminated. For very large volumes, storage of diluted buffer solutions is impractical. One approach is to make up concentrated solutions and dilute as required — this approach can result in significant space and cost savings.

5.2 Key unit operations

5.2.1 Liquids materials handling

Materials to be added to a reaction system can come in liquid, solid or gas form. However, the easiest to handle are liquids and consequently materials are used in the liquid form where possible. If not the natural state at ambient conditions then the material can be made liquid either by melting or more commonly by making a solution by dissolving in a solvent.

Liquids can fall into three categories when used in a reaction:

- **solvent**: this allows the reactant to mix and react and to create a mobile mixture that can be controlled for temperature by heat transfer with surface contact. Solvent liquids generally form large quantities in a batch make up;
- **reactant**: the active compound used to react with another material to synthesize the desired intermediate or final molecule stage. Use of liquid reactants is generally desirable as they can easily be transferred and added to the reactor system under controlled conditions;
- **catalysts**: these are usually required in small amounts. Handling small quantities can bring difficulties; it is easy to dispense the correct quantity in a laboratory or fume cupboard, but getting it safely into a reactor system needs to be carried out via an air lock or charge flask arrangement.

Liquids are usually handled in drums if the quantities are small or the duration of production is short — this typically applies to reactants, particularly where there is no source for bulk deliveries. If the material is used in larger quantities then bulk delivery in road tankers and storage in a bulk tank system is preferred as it minimizes the manual handling requirements, and hence, reduces the operator inputs.

Liquids delivered in bulk quantities from road tankers must be shown to be suitable for use in the process — that is they are of the correct purity, strength or even the correct chemical composition. This may be by reliance on the supplier's audited quality control/assurance system and certificates of conformity, or by sampling the road tanker and then analyzing the contents before offloading. Alternatively where analysis is lengthy and would incur waiting time charges from the delivery company, special quarantine bulk storage tanks can be used which allow a segregated offload of the material and then the appropriate testing prior to release for use or reject and return.

With the increasing legislation on Volatile Organic Compound (VOC) emissions, it is common to vent the bulk storage tank back to the road tanker during offload to avoid release of VOC.

Liquids are charged to the process either by direct pumping from the bulk tank or drum into the reaction system or to an intermediate addition vessel such as a head tank which allows more accurate determination of quantity and greater control over rate of addition. Alternatives to pumping include closed vacuum or pressure charging, although these methods are not commonly used now because of the safety issues associated with them.

5.2.2 Solids materials handling

Solids are most commonly used in processes as reactants but can also be used as catalysts, purification agents such as activated charcoal, or seed for crystallization process stages.

One of the main sources of solid is as an intermediate stage in a lengthy multi-stage synthesis production operation.

Solid material is most commonly stored in sacks, plastic drums or lined fibreboard kegs. The most important consideration during use is the safe, contained dispensing of the required quantity and the charging of this into the reactor system.

Open manway charging used to be the main transfer method but this is now considered unacceptable because of the risks of exposing the operators to the chemicals inside the reactor. Similarly the risk of exposing the process to cross-contamination from surrounding activities is also unacceptable in many circumstances.

Current methods involve creating a protected area for charging, either directly to the reactor via a weigh hopper or charge lock, or to an intermediate bulk container (IBC). This IBC can then be moved to a docking station to allow enclosed charging to the reactor system. The protected area involves controlled clean air flows to minimize risk to product and operator by reducing contamination and exposure within a purpose designed charge booth.

The use of split butterfly valves or contained transfer coupling systems is now a very popular way of making the connection between the IBC and the process system, as it allows the handling of very active materials with increased safety and ensures minimal contamination of the reaction process.

The use of solids in bulk is not very common unless for large tonnage products where a dedicated plant with silo storage and transfer techniques such as pneumatic transfer, screw feeders or conveyors can be used.

5.2.3 Liquid/liquid separation techniques

As part of either the reaction stage or purification stages of the synthesis, it is often necessary to separate one liquid from another. There are two main types

of technique available for this, those involving heat and those using other properties of the liquids to achieve the separation.

Thermal processes

Thermal processes are commonly used for removing materials, such as an inhibiting by-product formed during a reaction, typically water, or operations where evaporation techniques give an effective and efficient method of separation. These can be either single stage such as a flash distillation or involve the use of fractional distillation by utilizing distillation packing materials in a column.

Batch distillation is not an easy process to perform due to the unsteady composition of the still vessel and the fall in efficiency as volumes drop, and therefore, so does contact with the heat transfer surface. A supplementary heat transfer surface can be provided by pumped or thermo-syphon circulation through a heat exchanger.

Another problem with thermal processes is that they can result in the degradation of product if it is sensitive to heat. To minimize this, the pressure at which the distillation is carried out can be reduced by vacuum pump systems to allow evaporation at lower temperatures. In the event of particularly sensitive or labile materials this can be carried out in small continuous units operating at extremely low vacuums known as short path stills.

An alternative extractive technique is azeotropic distillation. Here an additional material is added to create an azeotrope, which will preferentially be distilled out achieving an otherwise impossible thermal separation. The entrainer is then separated from the removed material and recycled if possible.

Non-thermal processes

It is a relatively common process to add a liquid to the process into which impurities or even the product is preferentially soluble. The added liquid is immiscible with the process stream and forms a separate phase, which can then be separated by various techniques. This process is commonly carried out with water or aqueous solutions and is known as washing.

The immiscible phases can be separated by allowing the layers to settle in the reactor vessel and then running the lower layer out until the interface is seen. It is common to run this layer to a receiver; it could be the product layer or if it is the waste layer it could be held prior to discharge.

Interface detection can be difficult. Automatic detection devices have mixed success and generally an illuminated tubular sight glass and trained operator is the most successful technique.

In large production plants, mechanical techniques such as decanter centrifuge, multi-plate disk centrifuge or counter flow liquid–liquid extraction devices can be used to increase the efficiency of the separation.

Techniques that were previously used mainly in the biotechnology field are now becoming more available to achieve difficult separations and purifications in the synthetic process arena. These include chromatography techniques and selective membrane processes, which are becoming more feasible with the developments in membrane technology.

5.2.4 Crystallization

Most synthetic processes involve the isolation of a solid stage. This can be an intermediate stage, a byproduct or most commonly the final active BPC. The formation of the solid form can be carried out in several ways:

- crystallization by cooling;
- crystallization by evaporation/concentration and cooling;
- precipitation by reaction or pH change;
- precipitation or crystallization by solvent change.

This operation can be carried out in the standard or slightly modified batch reactor described earlier. The allocation of a specific or dedicated reactor for crystallization use is becoming more common and provides a way of avoiding contamination of the final product. The need to provide controllable agitation with gentle profiles to avoid crystal damage and good heat transfer are the main areas addressed along with the rate of addition of precipitant or cooling profiles to allow for optimal crystal form and size. In order to promote the desired crystal form, seed materials of the desired crystal type can be added at the correct stage to initiate crystallization of the appropriate form.

The crystallization activity is becoming increasingly sophisticated. Known as crystal engineering, it is of growing importance especially in tailoring the product form of the final BPC to suit the demands of the secondary operations, avoiding comminution or granulation to achieve desired product form.

Most crystallizations are carried out on a batch basis. However, if production quantities demand or specific product form/size distribution profiles are required then continuous crystallization arrangements can be used. New developments involving the use of ultrasound to form a nucleus for crystallization (known as Sonocrystallization) have been developed. They can produce mono-size distributed slurries accurately engineered for the desired property and are of particular interest for sterile production where seed introduction is more difficult.

5.2.5 Solids isolation

Once the solid form has been produced, it needs to be isolated from the liquid or mother liquor.

Separation of solid from liquid generally involves some form of filtration since techniques such as sedimentation are not routinely applied in the pharmaceutical industry. Filtration involves creating a medium through which the liquid can pass but the solid is retained. Once the medium has been formed, a driving force to cause the liquid to flow is needed; the way in which the driving force is generated is the main area where differences in technique or equipment occur and can be created by vacuum, gas pressure, mechanical pressure or centrifugal force.

The other main area which differentiates the filter type is the quantity of solid involved and whether it is a by-product to be removed or a product.

Filters

Solid impurities in small quantities up to 10 kg can be removed using cartridge, bag or multi-plate filters such as the calmic filter.

The single sheet, nutsche filter is a common unit that has developed greatly. The original form was an open box filter that used vacuum in a lower section of the box to draw filtrate through a filter medium or cloth. The disadvantage with this type is that they offer little to protect the general plant area, contain the process to protect the operator or prevent cross-contamination. The other main disadvantage is the level of vacuum that can be generated limits the driving force.

The first development of the nutsche filter was the agitated pressure nutsche filter. This unit has an integral pressure chamber above a filter media, typically a cloth element. The unit is fitted with an agitation arm that can be used to smooth the cake and discharge the damp solid. The driving force for separation is generated by either applying vacuum to the filtrate receiver and sucking the filtrate out of the slurry to leave a damp cake, or by applying pressure above the slurry and forcing the filtrate out to leave a cake.

Occasionally both pressure and vacuum are used to generate the driving force, but it is commonly found that increasing the driving force above 3 bar has little benefit on filtration rate due to compression of the cake and the closing off of the route by which filtrate can flow out. The pressure is most commonly generated by nitrogen and because the materials are typically flammable solvents, nitrogen also provides an inert atmosphere. It can be provided either once-through from a mains supply leaving via the filtrate receiver or recycled taking low pressure nitrogen from the receiver, increasing the pressure, then putting it above the cake to displace more filtrate. This has the advantage of minimizing the amount of nitrogen used and reducing emissions

to the atmosphere as the nitrogen entering the receiver is laden with solvent vapour. The recirculated nitrogen can also be heated prior to entering the filter to aid drying of the cake. The nitrogen is then taken directly from below the cloth to the compressor package where it is chilled to remove the solvent, then repressurized and heated before recirculating back above the cake.

The cake can be washed in the filter to remove soluble impurities. This is done in two ways, either a displacement wash or a reslurry wash. In the displacement wash the wash fluid is sprayed onto the cake surface whilst vacuum or pressure is applied to cause the wash fluid to quickly pass down through the cake, taking out the impurities and out to a receiver. This is commonly used where the impurities are very soluble in the wash and can be easily removed or where the product cake itself is soluble in the wash so that residence time is minimized to avoid losing product with the wash. With a reslurry wash, a volume of wash fluid is added to the filter and the agitator is used to mix the cake with the wash fluid to form a slurry. By this process the impurities can then dissolve into the wash fluid. The resultant slurry is then filtered again to remove the wash fluid and the impurities. The wash filtrate is often collected in a separate receiver to allow for recovery of product that may have been dissolved and lost as well. This is known as second crop recovery.

Discharge from the filter can be in one of three ways. Most commonly the product is discharged as a damp cake; here the agitator is lowered to the cake surface and rotated to start to break up the cake. By altering the direction of rotation, the cake can be drawn to the outside edge of the filter where an outlet hatch is opened to allow discharge of the cake out of the filter to the next process unit. As discharge proceeds the agitator is lowered gradually to the bottom of the filter to ensure all the cake is discharged. The nature of this operation results in slugs of damp cake being discharged as the arm goes past the discharge hatch, which may cause problems for the next processing module. An alternative approach is to have a central opening in the middle of the filter element and dig the cake and bring it to the middle. This provides a continuous flow of solid out but reduces the area for filtration and can give problems of sealing the central outlet. The other methods of discharge involve either making a slurry or solution of the cake in a solvent and charge as per the wash fluid. This is then agitated and discharged via a valve and pipe arrangement from the side of the filter above the filter cloth.

The nutsche pressure filter has also been developed into a filter dryer. Here heat can be applied to the cake once filtration has occurred via coils on the side and top of the filter body and via heating passages through the agitator. A single fluid heating medium, often hot water, is circulated through these coils and this provides heat to the product to remove the remaining solvent to give a dry solid.

At the same time as the heat is applied, the space above the cake is subjected to a vacuum pulled on the system normally via an integral dust filter to avoid any losses of product solid with the evaporated filtrate. The filter dryer has proved a very successful item of plant and minimizes the exposure of the product during its transfer from the filter to another dryer. The disadvantage of the unit is that the time taken to filter, wash and dry a batch in the filter dryer is overall rate limiting for batch time cycles.

Other types of filters exist which provide different methods of presenting a filtration element and a driving force of pressure to separate solids and liquids and then discharge the solid. These include rotary vacuum filters, tube filters, disc filters and belt filters, but they are not common in the pharmaceutical industry and are used for specialized applications only.

Centrifuges

These devices generate a centrifugal force to drive the liquid through the separating medium leaving the solid. There are four main types:

- **vertical axis — top discharge by basket lift out:** This is the traditional type and is not commonly used now except in small sizes. The main problem is the exposure of the operator when emptying the basket and the risk to the product of cross-contamination in the open process;
- **vertical axis — bottom plough discharge:** This allows contained discharge of the solid from the basket by a movable knife or plough that cuts the solid out of the basket and down a chute at the bottom of the machine;
- **horizontal axis — peeler discharge:** This unit has advantages over the vertical axis machine in that it can spin at higher speeds, and hence, create a higher G-force or driving force for separating the liquid. Discharge of the solid is carried out in a similar way by a knife or peeler blade, which is used to channel the solid into a chute and away from the machine;
- **horizontal axis — inverting bag discharge:** This is the most current development. It has the benefits of the higher G-force for separation but the cake is removed by inverting the filter cloth. It also has the benefit of being able to remove the entire heel to ensure ease of further separations and minimize batch-to-batch contamination. Most modern centrifuges are automatically controlled. This covers inerting and purging cycles, filling, spinning, washing and discharge.

5.2.6 Drying

The final step for most BPC processes is to dry the intermediate or final product. This removes any residual solvent from the solid. Often this is done to

produce a fine free-flowing powder that can easily be handled in the secondary processing. Alternatively if the solid is an intermediate then subsequent processing often involves the use of a different solvent. Drying reduces the moisture level of solvent to an acceptable level, usually to below 1% w/w of the solvent present.

Dryers can be classified into two main types — direct and indirect. With a direct dryer, air or more commonly nitrogen is heated and passed through the solid. An example of this type of dryer is the batch Fluid Bed Dryer (FBD). This unit uses a basket that would be filled either by hand or by gravity from the filtration or centrifugation unit. The basket has a perforated base and when placed in the fluid bed dryer, the heated air or nitrogen flows up through the solid, fluidizing it and evaporating the solvent. The off-gas stream is filtered, usually by a cyclone or a bag filter system to prevent loss of product. The filtered stream can be cooled to remove the evaporated solvent, then reheated and passed back through the basket. Whilst the units are relatively cheap, they are not favoured for the following reasons:

- VOC losses are high without the high additional cost of a nitrogen gas recycle system;
- there is a high risk of static discharge;
- effective filtration of the heated air stream is required to avoid introducing contamination;
- open handling of the cake does not provide a contained system, particularly for very active products.

For these reasons, indirect or enclosed dryers have replaced the direct dryer. Many pharmaceutical products tend to be thermally sensitive and as a result most are dried under vacuum, since this allows for solvent evaporation at lower temperatures. Jacket temperatures of typically 40–100°C are used with hot water or a single fluid system as the heat source. A dust filter is installed on the dryer body or in the vapour line to prevent loss of product with the vapour stream. A vacuum is generated by liquid ring pumps, once-through oil lubricated pumps, dry running vacuum pumps or more rarely ejectors. Solvent condensing is carried out either before or after the vacuum pump depending on the capability of the pump to handle liquids and condensation of the solvent. Often this is not desirable for corrosion reasons and all the condensation is carried out after the pump. The ideal solution is to use a liquid ring pump with the same or compatible solvent, chilled, as the ring fluid, then condensation can occur directly into the ring fluid.

The fundamental principle of the indirect dryer is to provide a heated surface and a means to ensure good heat transfer from that surface to the solid, whilst

maintaining a vacuum above the solid to efficiently vaporize the solvent. Various designs for achieving this exist and can be categorized by the means used to achieve the heat transfer, as follows:

(*a*) *No agitation*

The vacuum tray dryer is the only example still in routine use under this category. Here, solid is laid in thin layers onto trays and placed onto heated shelves in a vacuum chamber where heat and vacuum are applied to evaporate the solvent. The dryer is not very efficient as it takes a long time to dry the product due to the lack of agitation, and hard dried lumps can form because there is no agitation to break down agglomeration during drying. The biggest failing with the dryer is that it is messy to load and unload the trays, requiring a high degree of containment and equipment to protect both the operator and the product. It is, however, very popular in R&D environments where its flexibility is a benefit, and in instances where mechanical work on the product will damage crystal size or shape or cause safety problems such as detonation of a shock sensitive solid.

(*b*) *Horizontal axis agitated vacuum dryers*

This type of dryer, the 'paddle dryer', is most widely used in BPC manufacture. It consists of a horizontal cylindrical chamber, the outside of which is fitted with heating and cooling jacket or coils. Inside, the dryer is fitted with a slow rotating paddle that moves the solid to give good mixing and allows replacement of the solid in contact with the heating surface, aiding drying. Horizontal axis dryers have high jacket surface area to volume ratios and are efficient dryers giving low drying times. Vapour is withdrawn via a dust filter fitted to the top of the body, allowing collected powder to be routinely shaken or blown back into the batch. They also have low headroom and can be fitted into process buildings without adding a full floor whilst utilizing gravity in the isolation train. They can be difficult to clean particularly because both shaft seals are immersed in the solids. Some designs allow for easy and complete removal of the end plate and agitator shaft.

(*c*) *Vertical axis vacuum dryers*

There are a number of variations of vertical axis, agitated vacuum dryers; the main difference between them being the ratio between diameter and depth of dryer. Short large-diameter dryers, often referred to as pan dryers, are popular. A variant of this utilizes a specially designed agitator that provides a very efficient mixing regime giving good heat transfer and efficient drying. This type of dryer has been termed a turbo dryer. Some designs allow the lid to be

hydraulically lifted for internal inspection and cleaning. High-speed impellers known as lump breakers can be fitted in addition to the main stirrer to break up any agglomeration. The drive can be either top or bottom mounted. The bottom drive has the disadvantage of requiring a seal in the product contact area, whilst the top mounted drive takes up a lot of space on the dryer lid, reducing the opportunity for additional nozzles and restricting the opening of the lid. The top mounted drive allows for the agitator to be raised and lowered through the solid, adding to the range of agitation profiles for drying. A variant of the vertical axis vacuum dryer is the filter dryer, referred to in the previous section, which combines the functions of a pressure nutsche filter with a vacuum pan dryer. The compromise tends to be due to the retention of the filter cloth during the drying process and the design of the agitator.

When the depth of the dryer exceeds the diameter, the dryer is referred to as a cone dryer. Deep cone dryers have a double rotating screw inside, which performs three functions: wall to centre solids movement for heat transfer by horizontal and vertical turning; delumping of solid initially and during drying; assisting bottom valve discharge by reversing the screw direction.

This design is favoured by a number of companies since it offers reasonably efficient heat transfer, delumping, relative ease of cleaning by refluxing with solvent and caters for variable batch sizes. Top and bottom drive mechanisms are available. From a GMP viewpoint, internal drive mechanisms must not shed particles. The one disadvantage of these dryers is that they are relatively tall compared to the other types and can add a floor to the isolation area, although protruding the discharge cone region into the clean pack-off room can compensate this.

5.2.7 Product finishing

Historically, BPC products were simply packed off from the dryer into fibre-board kegs and shipped, via a QC sample and check stage, direct to the secondary plant. Here finishing operations such as mixing, comminution or milling and granulation were generally carried out.

However, with the change in the profile of the BPC manufacturer, the end user for the BPC is often a different business or group within the same pharmaceutical manufacturer, or the BPC manufacturer is a different company to the pharmaceutical secondary company. In these instances there is an increasing need to provide some of the finishing operations to produce a product with specific physical characteristics in addition to the correct chemical composition. The increasing demands of 'speed to market' have also caused a blurring of the activities traditionally seen as 'secondary operations' and have increasingly come to be expected as part of the BPC manufacture.

Milling, sieving and granulation

Milling is an operation to reduce the particle size of a solid down to an acceptable profile or range of sizes typically below a certain maximum size. It is best carried out in-line after the dryer to avoid double handling, particularly since dryer discharge is often a low rate, semi-controlled process. If carried out off-line after quality approval, then a separate milling line in a clean room suite is needed. Intermediate bulk containers (IBCs) are usually used for solid transfers and act as feed hoppers to the mill feed system.

There are various types of mill used in the BPC industry, including pin mills, hammer mills and more commonly jet mills and micronizing mills. Further details are given in Chapter 6 covering secondary processing.

Sieving is an operation to classify the solid into a range of particle sizes. The equipment is often used in-line with the discharge from the dryer. The sieve operation consists of passing the solid through a series of screens. The first screen removes particles that are larger than the specification; these are discharged and recycled to the mill. The second screen then retains particles of the minimum size and above. The solids passing through the screen 'fines' is too small and may be recycled to the crystallization stage. The material is encouraged to pass through the screens by either vibration or by the use of rotating arms. The material that does not pass through the screen is removed from the sieve in either a batch or a continuous method to be packaged. Oversize and fine material can be reworked in some cases, but sometimes has to be destroyed.

There are some cases where more than two screens are used. This provides a series of size fractions that can be used for products that require specific drug related release profiles or for filling directly into hard shell gelatin capsules.

5.2.8 Packaging

The final packaging of a BPC is carried out in a controlled environment to protect the product from contamination by external sources and also to protect the operator from exposure to the active material. Most BPCs are solid powders and are packaged in sacks, drums or IBCs. A small number of products are liquids and these are packaged into the appropriate containers in either a manual or automated filling system.

5.2.9 Solvent recovery

Solvents are widely used in the production of BPCs and, as previously stated, provide several functions including dilution of the reactant concentration and mobility to allow good mass and heat transfer. Solvents are important in obtaining the correct final product form and in washing the product in isolation equipment. When used in a reaction, the solvent generally does not

react or break down to other components. In order to maximize the efficiency of the process, solvent remaining after a processing stage can be recovered for use in the same process from which it originated.

Solvent recovery can be either a batch operation or, more commonly if larger volumes are involved, a continuous recovery plant.

The type of recovery used largely depends on the contamination present and the properties of the solvent being recovered. Flash stripping is the simplest operation and is often sufficient. Fractionation, often by the use of random or structured packing, is used where complex mixtures require separating.

Pre-treatment is often used to allow a simpler recovery. This can involve crude solids filtration to more complex precipitations or pre-stripping.

Most solvent recoveries result in a residue, which will then require further treatment or handling — most commonly incineration or landfill.

5.3 Production methods and considerations

5.3.1 Production

Pharmaceutical production is mainly carried out on a batch basis for a number of reasons. The main reasons are normally linked to the traceability of the product, validation and regulatory issues, but others include the scale of operation, the flexibility of operation required, inventory optimization or even technology development.

Production is arranged into three main types of facility:

- dedicated — the facility is designed and built for one specific process;
- multi-purpose — the facility is designed and built to carry out a number of known and defined processes, potentially with a minor amount of modification to configure the plant to the next process;
- General purpose — the facility is designed to handle a variety of processes, both known and envisaged for the future.

Batch chemical processes with cycle times typically of 16 hours or more are most commonly carried out on a 24-hour a day, seven days a week operation.

5.3.2 Automation and control issues

Any automation system must provide tangible benefits to justify the investment. In general, the benefits of automation will derive from:

- higher levels of safety;
- the ability to apply sophisticated control strategies;

- consistent product quality;
- higher levels of plant utilization for a given manning level;
- more efficient usage of materials and reduction in waste;
- provision of timely and relevant information.

The logic and numerical processing capabilities of modern process control systems enables operating conditions to be tightly regulated to the specified profiles, optimizing processing time, delivering consistent quality of product and providing a higher level of safety.

While the use of properly designed and implemented process automation systems enhances the safety of the plant (by improved control and reporting/notification of potential risks) these systems should not be relied upon to ensure plant safety. The recently published international standard IEC 61508: Functional Safety of Electrical/Electronic/Programmable Electronic Safety Related Systems addresses the requirements of safety related systems.

The key issues to be considered when embarking on automation projects include:

- the functionality required;
- the level of automation required;
- the types of systems employed.

Most primary pharmaceutical manufacturing processes can be classified as being either 'continuous' or 'batch' with a few, if any, being categorized as 'discrete' processes. This section focuses on the requirements of batch type operations.

The requirements of batch operations can generally be considered more onerous than those for other types of processing. Batch processing involves the sequential modification of process conditions through a predefined regime rather than maintenance of established 'steady-state' conditions.

Batch operations essentially consist of a series of phases that are executed sequentially. The execution of a phase is usually dependent on process conditions established in a preceding phase; therefore any fault that interrupts the execution of a phase may require the processing to be resumed from a point in the operation sequence other than that where it was suspended. The process automation system must be capable of executing sophisticated exception handling procedures. It may require the provision of facilities that enable the operator to intervene and manually adjust the point in the sequence at which processing is to resume.

System functionality

The functionality required of the system will principally depend on the processing objectives and the method of operation proposed. The plant equipment and its connectivity also affects the functionality; the following are some possibilities:

- single batch, single stream (one batch at any given time);
- multi-batch, single stream (more than one batch being processed at any given time);
- multi-batch, multi-stream, dedicated equipment trains;
- multi-batch, multi-stream, common equipment.

On plants where a variety of products are regularly manufactured, some form of automatic scheduling functionality may be desirable. When equipment is required to undergo Clean In Place (CIP) or Sterilize In Place (SIP) routines at regular intervals or at product changeover, the CIP/SIP operations may be considered as a 'product recipe' and scheduled accordingly.

The sophistication of the scheduling systems available vary from the basic, where queued operations (or batch recipes) are initiated when the necessary processing units become available (or predefined constraints are satisfied), to others which are capable of developing a production schedule from demand data transferred from ERP (Enterprise Resource Planning) or MRPII (Manufacturing Resource Planning) systems. The sophisticated systems are capable of queuing recipes, calculating the optimum batch sizes to complete a campaign, and making changes dynamically as 'demand' changes. (Some form of 'gateway' to control the transfer of data from ERP systems is recommended to prevent disruption of manufacturing operations by sudden changes in demand). Other factors that complicate scheduling include the following:

- resources that can be simultaneously allocated to more than one process (e.g., cooling fluid circuits, ring-main fed utilities);
- number of streams in the system;
- selection of the best resource to use when several (shared) non-identical units are available (requires knowledge of what will happen next);
- operations that are dependent on activities/equipment controlled by external systems (which may result in the duration of the operation being unquantifiable).

The recipe handling requirements of the process control system are affected by the type and configuration of the plant. The recipe system may also need to be able to cater for variations in the properties of raw materials, which may result in a requirement to modify the processing parameters. Any variation in

the processing parameters/formulation, whether for a campaign of batches or for an individual lot, needs to be recorded and the appropriate mechanisms and facilities need to be provided to enable this.

As well as the quantity and complexity of the recipes that need to be executed, the number of recipes that can be simultaneously active in the system (on the plant) needs to be considered. In 'multi-batch' situations, the process control system needs to be able to report the impact of a malfunction or process deviation on other concurrent activities.

The exception is handling facilities that are critical to the successful operation of a batch plant. In the event of a deviation from the expected pattern of occurrences, the operator should be informed and appropriate action should be taken promptly. A minimum of three categories of operator message are recommended:

- critical alarms generated when there is risk to equipment or personnel;
- process alarms caused by deviations from the expected conditions;
- events which keep the operator aware of actions being performed.

In the case of critical and process alarms, the process control system will normally be expected to take action to put the plant in a safe condition automatically. Facilities are also needed to enable the system to restore the plant to its prior state as effectively as possible. A good understanding of both the process and the control system are required in order to develop the necessary procedures and phases.

The production data, exception reports and alarm information generated need to be associated with the appropriate batches and stored to satisfy operational as well as regulatory reporting requirements. As in the case of the process control software, the definition of the reports requires knowledge of operational procedures and company standards.

The recording and storage of data should be clearly differentiated from the reporting function. Justification should be provided for all data that is to be recorded because, while it is true that data not recorded is lost forever, recording excessive quantities of data can have severe drawbacks. Some systems enable data recording to be triggered by events; this enables data collection to be restricted to critical phases of an operation (such as during an exothermic reaction).

It is important that the recorded data is stored in a format that allows it to be manipulated in the manner required. While the control systems use a variety of data compression algorithms to facilitate the storage of large quantities of data, this can prevent data export and restrict the processing and manipulation of the information to the control system with the consequent limitations.

Interfaces and communication facilities with other systems also need to be evaluated when identifying the functionality required of the system and this is addressed in a later section.

Automation levels

In a processing environment automation should be aimed at removing the mundane and repetitive tasks from the operators, freeing them to add further value. The numerical processing capabilities of modern control systems enable advanced control strategies to be employed to improve efficiencies.

All areas of the plant will not require the same level of automation. There is also a trade-off between the manning level reductions available through automation and the flexibility available from lower levels of automation. In certain areas, such as raw material tank farms, a 'basic' level of automation can result in a far more effective system, while other areas benefit from all the sophistication available. In the main processing area, manual intervention may be restricted to critical operations where heuristic judgment is required or those aspects where the necessary facilities to allow automatic execution have not been provided.

As part of the development of the control philosophy, each area of the plant should be reviewed and the required automation level established. The basis of the justification for automation will vary and could include conditions within an operating environment such as physical aspects of the nature of the task to be undertaken, the need for an automated record of activities performed, etc.

5.4 Principles for layout of bulk production facilities

Many examples of unplanned developments can be seen on pharmaceutical sites throughout the world. Production facilities have grown in many cases in a totally uncontrolled manner with decisions made based on the priority of the moment with no regard for the future. This has happened due to lack of thought, concern for cost and lack of information on the company's future marketing plans. The result is a totally random 'hotch potch' of buildings leading to inefficient operation, potential hazards, questionable use of land, and expensive future development of the site.

Two types of development will now be considered. Green field development involves the use of land on which there has been no previous commercial developments. Plans for such sites will not generally be restricted by previous

buildings and existing operations. Brown field development may, however, have some restrictions due to past or existing operations and freedom of design may be curtailed.

In both instances however, at some stage of design, it is necessary to review the impact of the new development on the future use of the site. All these principles equally apply to secondary production facilities.

5.4.1 General considerations

In the pharmaceutical industry, sites may be laid out for primary production, secondary production, research and development, warehousing and distribution or administration and head office activities. A single site could cover any number of these functions. There is considerable dialogue on the advantages and disadvantages of multiple use sites, which will not be discussed in this guide, except to point out that all the above activities do not necessarily sit well together. Here the guide is aimed at bulk drug primary production site layouts only.

5.4.2 Green field sites

Site location

It is assumed in this guide that the new site will consist of multiple production units; the first of which is to be built at the time of developing the site infrastructure, with others following on at some later time.

When selecting the site, due consideration will have been given to its geographical location with specific attention to road systems, communications, ports and airports, availability of skilled labour and adjacent developments. Any special environmental requirements and full information on the availability and capacity of public utilities will also have been investigated. Discussions with all appropriate planning and statutory bodies will have been carried out to determine if there are any requirements that would prevent the development of the optimum design for the site. It is also necessary to ensure that any adjacent developments in the planning stage are compatible with a bulk drug operation. For example, an open cast mining site adjacent to a plant manufacturing high cost pharmaceuticals would not be ideal.

It will be necessary to carry out full topographical and geotechnical surveys to determine the surface contours and the load bearing characteristics of the land. These surveys will provide information on underground obstructions, mine-workings and geological faults. Such information could influence the positioning of buildings or indicate the need to carry out specific rectification work. The land should also be checked for ground contamination. Information

on the ambient climate of the site, including prevailing wind directions, is also necessary at this stage. The majority of the above data should be obtained prior to the purchase of the land. The above requirements are not exhaustive but do indicate typical actions which are required prior to finalizing on a particular site.

Conceptual design

The project may be divided into two parts. The first part covers site infrastructure, including:

- offices and administration buildings;
- operator and staff amenities;
- control and test laboratories (if not in the production plant);
- engineering workshops and stores;
- central warehousing;
- on-site utility generation;
- gate house and security fencing;
- utilities and services distribution;
- roads, road lighting and car parks;
- underground utilities;
- site grading and landscaping.

The second part will cover production facilities. This, as mentioned previously, may be the only production unit or may be the first of a number. In this guide it is assumed that the site is to be laid out to accommodate a phased development and the design must ensure that future construction will not cause interruptions to production. This second part typically will include:

- the main reactor and process facility;
- special hazard production units;
- environmentally controlled finishing units;
- bulk raw material tank farm and drum store;
- effluent treatment final conditioning unit;
- control room for the production processes;
- production offices;
- on plot generated services;
- switch rooms and transformers.

The split of the project into two parts can be advantageous commercially. The infrastructure is mainly civil and building engineering and the production

unit is mainly process engineering. More suitable contracts can be negotiated if this difference is understood.

Based on these various elements, it would be normal to look at a number of possible layouts to finalize the overall concept before proceeding with detailed design.

Generic production plot layout

Before proceeding with the layout of the site, it is advantageous to give some consideration to possible plot layouts. It is anticipated that the production units, which will eventually be constructed on the site, will produce a number of products that may benefit from a custom design approach. If the plants are to be of a multi-product design then consideration should be given to the maximum numbers of reactors to be included in one plant.

Regardless of the style of production unit, the fully developed site is likely to have a number of production buildings each with associated control rooms, on-site utility generation, offices and tank farm etc.

Based on the first production unit to be developed, it is advantageous, before considering overall site layout, to develop an outline plot layout that can be the basis for all plants on the site. This does not mean that all plots will be identical but the main principles will have been identified at this early stage and will have some influence on the ongoing development of the site. Typically control room positioning, spacing of on-site tank farms, policy for facilities for hazardous operations, position of on-site switch room and electrical transformers should be identified.

Whilst the brief for the first production unit may be well defined, subsequent developments may be unknown at this stage. It is essential to recognize this and to incorporate flexibility into the eventual site layout and to identify which production plot parameters could possibly change. Site master plans should not be written in tablets of stone but should be reviewed with each new development. They should not, however, be changed by default.

Site layout – master plan – zoning

The term 'Site Master Plan' has been introduced in the previous paragraph. In green field development this is likely to start with an area of land that has no structures or building on it. It could be a cornfield, an area of heath land or a cleared and level site recovered from some defunct industry. There are likely to be several ways to lay it out and the first exercise is to decide on a concept. As stated before, there may only be information on the first production unit but the positioning of that unit will have a critical influence on the success of the site in the future. It is essential to look ahead and prepare a conceptual image of how

this site could look when fully developed to allow a logical expansion of the site in future years.

The first consideration of the master plan is associated with zoning of the site — which areas will be allocated to offices, amenities, warehousing, utility generation, workshops and production plants. Zoning plans also contribute to solutions for the most efficient utilities distribution design and are the first stages of development of site logistics.

Master plan – landscaping

Having zoned the site, the overall site landscaping strategy can be developed. This will be very much dependent on company policy and any particular need to screen the plant. The outline site contours will have been decided and any necessary planting schemes can be worked out.

The master plan

Once the site has been zoned, a generic plot plan has been developed and outline landscaping has been decided, it is then appropriate to proceed with the overall master plan. The purpose of master planning is to look at how the site could be when it is fully developed and then only build the part that is required in the first instance — this ensures that what is actually built will fit into a logical site development. The master plan should be revisited at the time of each future project and modified if necessary to keep in line with changing requirements.

On-site roads

Discussions with the statutory authorities will have already identified the approved entrance and exit from the site, but the on-site road system should be developed based on the zoning plan. This must take into consideration gate house procedure, off-loading facilities, car parking, restricted access areas, emergency access, road vehicle access, forklift truck access and pedestrian circulation. The road system must also be capable of progressive development as the site expands without disruption to operations.

Car parking policy can often present major problems. By the very nature of the site operation, the site is likely to be away from built up areas and operator car parking space is therefore essential. The safest practice is to provide it outside the main operational site boundary, but this may not be a popular choice on large sites in geographically exposed locations. The main emphasis must however be to ensure that private vehicles cannot get within recognized safety distances of operating units. Road system designs must recognize this requirement.

Public utilities and site generated utilities

Public utilities are likely to include towns water, electricity, natural gas and sewage. Earlier discussions with the supply companies should have identified where, on the site boundary, these utilities will be available. It is now necessary to decide on the appropriate site interface. In most cases a control booth is constructed for piped utilities and a transformer house and switch room for electricity is constructed adjacent to the boundary.

On-site centrally generated utilities will normally include steam and compressed air. Refrigeration and recirculated cooling water is normally generated on each production plot.

Utilities, liquid raw material and interplant transfers can be distributed in several ways:

- **above ground:** this will normally involve a pipe bridge and is possibly the most convenient way of distribution in that it does not interfere with traffic and pedestrian circulation at ground level. An access platform should be fitted to the bridge for maintenance purposes;
- **below ground (in an open culvert):** the culvert walls may be inclined or vertical. This has the advantage of easy access for maintenance, but has to be bridged at each road crossing and is difficult to keep clean;
- **below ground (in closed trench):** this is not favoured for bulk drug sites because of possible hazards to operating staff and difficulty in maintenance;
- **surface run:** this method causes problems to traffic and operator circulation.

The design of the distribution system must allow for future expansion in both layout and capacity. The question of ring main capability, which may be required in the future if not initially, must be examined. The master plan must reserve space on the site for the extension of possible bridgework in the future. This design will require an estimate of peak and average usage of utilities when the site is fully expanded. This, together with forward assessment of future marketing forecasts, will allow an informed decision on the initial sizing of the distribution system.

Site offices, gate house, amenities, laboratories, warehouses

It is assumed that the site being discussed is for production only. Based on this, the general administration offices are likely to be small and can possibly be sited in the same building as catering and possibly laboratories, although this will depend on the nature of work being carried out in the laboratories. The building should be sited adjacent to the entry gate to the site, thus limiting the need for visitors and office staff to go through any operational areas. The catering facilities are likely to be used by day staff as shift staff associated

with production operation are likely to have their own facilities within the control room building of the production unit. The office building will be positioned in an unclassified area of the site.

The procedures for receiving road transport arriving at and leaving the site will determine the layout of the gate house area and the final positioning of the gate house. Appropriate lay-bys for lorries and weighbridge facilities may need to be incorporated in the layout.

It will always be good practice to minimize vehicular access to the vicinity of the operating units. The site warehousing policy will influence this considerably. Each production plot can have its own warehouse for raw materials and finished goods. This would of course require road transport to have access to loading and unloading docks near to operating units. In addition the storage of high value, finished products adjacent to chemical reaction operations could give rise to a potential financial risk in the case of a hazardous incident occurring. It is not possible to generalize on recommendations for positioning warehouses but if possible the main warehouse should be positioned in the unclassified area of the site and the specific production units could have a small storage capacity for finished goods under test and possibly one or two day raw material storage. The production plant stores would be supplied by on-site forklift trucks.

Engineering workshops

Engineering workshops may be directly associated with each production unit or may be a site centralized facility — the size of the site will influence the choice. In medium to large sites it would be normal to have both a central workshop and satellite workshops on each of the production units. Certain engineering operations can only be carried out under flame permits or in workshops in unclassified zones.

The production unit

The discussion on generic production plot layouts identified a number of considerations for the individual production plot. The plot will generally house the buildings and facilities identified above, but there are no hard and fast rules and the requirements for specific products may differ greatly. For the purpose of this guide, it is assumed that automated batch reactor plant are being dealt with that carry out potentially hazardous processes. Processes that could result in explosions and/or use or produce highly active chemicals should be housed in a special hazard unit in an isolated area of the site.

The site layout

With due regard to the above considerations, it is possible to draw up a site master plan based on typical processing requirements and information from marketing and research and development departments. This can entail some guesswork but it gives more logic to the development and hopefully prevents, for example, the construction of the site boiler house on the area that might be required for a future production unit. The data for the plot layout for the first production unit should be available but maybe not those for future units. It is normal, however, for a company to be involved in specific types of chemistry and this may allow the concept of a typical plot layout to be developed, although the concept is unlikely to satisfy the detailed requirements of the next factory. The flexible parameters of this master plan are discussed in more detail in the next section.

The master plan suggests that on the area of land under consideration it is possible to construct up to, say, five separate production units of a size applicable to normal bulk drug facilities. Each unit would have the necessary on-plot facilities including a bulk liquid tank farm, the relevant on-plot utility generation, a control room and management offices. Depending on the design of the main reactor building there could be reactor capacity up to 96,000 litres using a variety of reactor sizes. The site infrastructure possibly includes central site generation of steam and compressed air and space has been identified for engineering workshops, special hazard operation and effluent treatment and conditioning. A number of these buildings may be developed in a phased manner as the site expands.

The plan gives a basis for future expansion and allows a logical development that is not too restrictive.

5.4.3 Brown field sites

There is a wide range of brown field projects — it could begin with a cleared area within an existing production site that can be fenced off from adjacent operational areas or an area of an existing building that has been cleared for a new production unit or it could even be the installation of additional equipment in an operating factory. They all have one thing in common — they will all be influenced by what is already there. The cleared plot will have to take into account the existing site infrastructure; the cleared building will have to take into account the potential limitations of the existing structure; the additional equipment project will have to recognize the existing utilities and the impact of ongoing production operations within the building. For the purposes of this guide the discussion will be limited to the cleared site.

It is likely that the brown field project will be equivalent to the production plot concept described in green field section. The site boundary will be equivalent to the green plot boundary and it should be anticipated that the necessary public utilities and centrally generated site utilities would be made available at the boundary. The project may or may not include the augmentation of these utilities. Considerations for the layout will include:

- process buildings;
- control rooms;
- on-site utility generation;
- tank farm and drum stores;
- switch rooms and transformers;
- warehouse;
- offices and operator amenities.

In most cases the approach will be similar to a green field production plot except for the impact of the surrounding existing site and the restrictions it might introduce, both to design and construction activities.

In some instances integration with the existing site road systems might require substantial modification to the existing system. In other examples, the new production facility may be required for operation under GMP standards when the rest of the site is manufacturing a non-pharmaceutical product.

The overall approach to the layout of brown field site should follow the same general principles as described for green field sites. The overall picture should be considered before settling on the layout for the specific plot in question.

5.4.4 Layout specifics for biotechnology facilities

Personnel and material flows have to be carefully designed to allow an orderly progress of product from fermentation through purification to finishing whilst minimizing the risk of cross-contamination. Other factors that are important to facility design include constructability, operability and maintainability. The latter covers accessibility to equipment for maintenance purposes especially in clean rooms; services access can be provided via the interstitial space above ceilings or via voids in the walls connecting onto corridors. All these factors should be optimized to maximize space utilization and minimize facility cost.

Due to the changing nature of the biotechnology field, it is important to incorporate features into the design to enable expansion, re-use of existing space and re-use of equipment. Some of the methods available include:

- mobile vessels that can be moved easily to provide flexibility;
- centralized buffer solution preparation areas;

- centralized cleaning areas for mobile vessels, etc.;
- centralized kill systems for liquid/solid wastes.

However, these methods would have to be reviewed carefully to obviate any possibility of cross-product contamination.

5.5 Good manufacturing practice for BPC

5.5.1 Regulatory framework

The manufacture of any pharmaceutical product is subject to regulations dependant on the country in which the product is sold. In the case of BPCs, the main regulatory body is the Food and Drug Agency in the US. They expect BPCs to be manufactured in accordance with the rules laid down in the Code of Federal Regulations title 21. Within the EU the manufacture of pharmaceutical material is regulated by EU Rules for Pharmaceutical Manufacture, Volume IV.

Current thinking from the FDA is that they expect manufacturers to 'control all manufacturing steps, and validate critical process steps'.

A critical step is not necessarily the last step in manufacture but may be one which:

- introduces an essential molecular structural element or results in a major chemical transformation;
- introduces significant impurities into the product;
- removes significant impurities from the product.

Further information on this topic can be found in Chapter 3.

5.5.2 Good manufacturing practice (GMP)

The manufacture of BPCs in accordance with GMP ensures that the product has a high degree of assurance of meeting its predetermined quality attributes. GMP for a BPC is concerned with the manufacturing process, the equipment and facility in which it is carried out.

GMP is all about protecting the product from anything that can cause harm to the patient. This covers the processing itself and the avoidance of any contamination.

Modern BPC manufacture is generally carried out in closed process equipment so the potential for contamination is greatly reduced. Special attention is paid to activities that involve exposure of the product or its raw materials or intermediate stages. This involves protection of the operator and the process when dispensing, reactor charging, sampling and product packing.

GMP is also concerned with cross-contamination from other sources and linked systems. Special attention is paid to hold up within process systems, cleanability and the use of Clean In Place techniques, interactions with shared systems such as nitrogen and vents.

GMP is involved with the operating method. Any instruments that record critical data have to be calibrated and validated to ensure the integrity of the data. The process must be well understood and capable of being controlled.

5.5.3 Validation

The validation for BPC follows the same concepts and requirements to those detailed in Chapter 4. The main difference for BPC production is the concept of a critical step, and the point at which validation and pharmaceutical quality assurance have to be applied.