Good manufacturing practice

3

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3.1 Introduction

This chapter explains what is meant by current Good Manufacturing Practice (cGMP) and, in particular, how it applies to the engineering aspects of pharmaceutical production. The chapter also shows how it is possible to develop the GMP requirements to allow the facility to be engineered, and looks at the GMP design review process.

3.1.1 Definition

A key part of the control of medicinal products and facilities relates to GMP.

The EU Guide To Good Manufacturing Practice and Good Distribution Practice defines GMP as 'the part of Quality Assurance (QA) which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by marketing authorization or product specification.'

'Engineering for cGMP' may be defined as those activities performed throughout the project life-cycle, which ensure that it will be easy and natural to operate the completed facility in accordance with current Good Manufacturing Practice.

The 'Project Life-Cycle' means from project inception through feasibility studies/conceptual design, engineering, construction, installation, start-up, operation, maintenance to final plant decommissioning or modification.

GMP is controlled by the US Code of Federal Regulation (CFR) 21 in the USA. European pharmaceutical companies wishing to supply this market must also comply with these regulations.

The various regulatory authorities produce different types of applicable documentation, which broadly fall into two categories:

- directives, rules, regulations, including for example:
  - US Code of Federal Regulations CFR 21 Parts 210 and 211 (Drug products) and CFR 21 Parts 600 to 680 (Biological products);

- EU GMP Directive 91/356/EEC, Commission Directive Laying Down The Principles and Guidelines of Good Manufacturing Practice;
- Rules Governing Medicinal Products For Human Use in the European Community, Volume IV; Guide to Good Manufacturing Practice for Manufacture of Medicinal Products.

- guides, guidelines, points to consider, including for example:
  - FDA Guide to Inspection of Bulk Pharmaceutical Chemical Manufacturing;
  - FDA Guide to Inspection of Validation of Cleaning;
  - FDA Guide to Inspection of Computerized Systems in Drug Processing;
  - FDA Guidelines on General Principles of Process Validation.

Although not necessarily in a strict legal sense, the first category is mandatory and must be complied with. The second category, although classed as guides or guidelines, is also very important and generally must be complied with.

The US Food and Drug Administration prepares guidelines under 10.90 (b) of the regulations (21 CFR Part 10) to help with compliance. A comprehensive listing of potentially relevant guidelines, guidance and points to consider is provided by Center for Drug Evaluation and Research, 'Guidelines for Regulations that are applicable to the Center for Drug Evaluation'.

As well as the formal documents outlined above, there are other ways that cGMPs have evolved. These include the interpretation of the various rules and regulations and what is generally considered to be good practice by the industry. For example, the US Food and Drug Administration, through the freedom of information service, produces reports on inspections and inspection failures. These reports are in effect 'legal rulings' or interpretations of the regulations, e.g. Form 483. It is important to keep up to date on these requirements through publications such as GMP Trends or QC Gold Sheet. As a rule of thumb in terms of good practice, if more than 50% of the industry is moving over to something then it becomes cGMP.

In addition to the codes laid down by the various regulatory authorities, there are parallel industrial quality standards that are deemed to apply to all industries. In Europe these tend to be grouped around ISO 9000, and the US equivalent are ANSI standards grouped around Q90. It is obvious that common standards should be applied and to this end the International Committees for Harmonization of Standards have published relevant recommendations as ICH guidelines.

3.1.2 General GMP requirements

When first embarking on a new pharmaceutical facility, consideration will need to be made as to what cGMP requirements will apply to the project and how they will impact on the project life-cycle. These may vary. Although the words differ, there are common general requirements that run through virtually all the cGMPs worldwide. Common elements are:

- the establishment and maintenance of an effective quality assurance system;
- control of the process;
- personnel that are suitably qualified, trained and supervised;
- premises and equipment that have been located, designed, installed, operated and maintained to suit intended operations;
- maintenance of adequate records of all aspects of the process so that in the event of a problem being identified, an investigation can trace the complete history of the process, including how, when, and where it was produced, under what conditions and by whom (i.e. an audit trail);
- the prevention of contamination from any source, in particular from components, environment, premises and equipment by the use of suitable premises and equipment and through standard operating procedures.

3.1.3 Project assessment to determine applicable standards

Whilst the objectives of most cGMPs are generally the same (i.e. to safeguard consumers), the nature of pharmaceuticals dictate that different sets of specific requirements have evolved depending upon the type of product, its stage of development or manufacture, and where it will be manufactured and sold. In addition the different regulatory authorities have prepared slightly different sets of standards, and apply them in different ways. One of the first steps when preparing to undertake a new project is to establish under what cGMP regulations the plant will operate. An assessment should be made to determine the:

- stage of product development;
- stage of production;
- category of the product and production processes employed;
- facility location and location of the markets that the facility will serve.

Based on these factors a judgment can be made as to applicable standards that need be applied.

Stage of product development

For the purposes of this book, the stage of product development may be divided into three parts:

- laboratory trials (pre-clinical animal trials);
- clinical trials;
- routine production.

Generally speaking, cGMPs regulations do not apply during laboratory trials, 'Basic cGMPs' apply during clinical trials, and 'full cGMPs' apply during routine production. cGLPs (Current Good Laboratory Practice) may apply during laboratory trials and cGCPs (current Good Clinical Practice) may apply during clinical trials.

Essentially GLP is concerned with the organizational processes and the conditions under which laboratory studies are planned, performed, monitored, reported and recorded. The UK GLP regulations (Statutory Instruments No. 654) came into force in April 1997 and are monitored by the UK GLP Monitoring Authority, which is part of the Medicines Control Agency (MCA). Currently about 150 test facilities are registered under the scheme and are inspected on a two-year cycle.

GCP is 'a standard for the design, conduct, performance, monitoring, auditing, recording, analysis and reporting of clinical trials to provide assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected' (Definition from the ICH Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95)). In the UK the GCP Compliance Unit was established within the Inspection and Enforcement Division of the MCA in Autumn 1996. GCP inspectors assess compliance with the requirements of GCP guidelines and regulations, which involves conducting on-site inspections at pharmaceutical sponsor companies, contract research organizations investigational site and other facilities involved in clinical research.

Stage of production

The stage of production means what the facility is used for. The stages of production can be divided into the following four parts for the purposes of this book:

- Bulk Pharmaceutical Chemicals (BPCs) manufacturing;
- finished product manufacturing;
- packaging;
- warehousing/holding.

Different regulatory authorities apply certain specific cGMPs to different stages of production. In some cases facilities may be used for more than one stage of production, and in such cases more than one set of cGMPs may apply.

Category of the product and production processes employed
Broadly speaking most active ingredients are manufactured by one of the following routes:

- chemical synthesis;
- biotechnology;
- blood derived;
- animal or plant extraction.

By the nature of these routes certain methods of production to produce dosage forms have evolved, and in each case specific GMP requirements have been developed. From a GMP point of view regulatory authorities categorize products as following:

- sterile medical products:
  - terminally sterilized products;
  - aseptic preparations;
- biological medical products:
  - microbial cultures, excluding those resulting from r-DNA techniques;
  - microbial cultures, including those resulting from r-DNA or hybridoma techniques;
  - extraction from biological tissues;
  - propagation of live agents in embryos or animals;
- radiopharmaceuticals;
- veterinary medicinal products;
- medical gases;
- herbal medicinal products;
- liquids, creams and ointments;
- metered dose aerosols;
- products derived from blood;
- tablets and hard gel capsules;
- soft gel capsules;
- transdermals;
- implants.

Clearly some pharmaceuticals represent a combination of these types.

Facility location and market location
cGMPs regulations are produced by a number of different countries or groups of countries world-wide, in addition to the World Health Organization. The key

regulations are from the USA, the EC and, to some extent, Japan. However no assumption must be made that these are suitable standards to apply. Clarification should be sought from the pharmaceutical manufacturer before the design commences.

3.2 GMP design requirements

Based on an assessment of the regulatory requirements (as described above) we can begin to define the GMP requirement for the project. Generally, issues and areas to be considered during the conceptual design phase will include:

- **process** issues:
  - closed or open (Is it to be completely contained with piping and equipment at all times or will it be exposed to the surrounding environment? In which case, what measures are to be taken to prevent/minimize contamination?);
  - level of batch to batch integrity required (Is simultaneous filling and emptying of vessels with different batches in known proportions or limits to be permitted? Do systems need to be engineered to be self-emptying? Will process systems need to be subject to cleaning, drying or sterilization between batches?);
  - level of segregation or containment required (Is it acceptable to manufacture product A in the same facilities as product B? Will processes be campaigned?);
  - level of production required.
- **layout** issues:
  - site location and layout (including existing site, brown field, green field, overall site layout and its suitability in terms of space, general layout);
  - facility layout (including cored versus linear layout; use of transfer corridors, segregation of areas, environment, containment strategy, modularization/expansion, security and access control).
- **automation strategy** issues:
  - level of technology, use of design tools and models, number of layers — hierarchy;
  - availability/redundancy/maintainability, modularization/expansion;
  - instrumentation/cabling/field devices;
  - paperless batch records, electronic signatures.
- **flow** issues:
  - people (security, access, occupancy level, shift patterns);

  - equipment (mobile or fixed, use of hard piping, flexible piping or disposable transfer bags, cross-contamination/mix-ups);
  - components/materials (materials handling systems, cross-contamination/mix-ups).
- **regulatory** issues:
  - stage of product development, stage of production, category of the product and production processes employed, facility location, and location of the markets that the facility will serve.
- **validation strategy** issues:
  - validation required, validation team(s), validation plan(s).

These basic requirements can then be refined for the various aspects of the project to allow the facility to be engineered. The following categories are suggested for guidance:

- facilities and environment;
- services and utilities;
- personnel flows;
- material flows;
- equipment flows;
- equipment design;
- computerized systems;
- maintenance and services;
- waste management;
- procedure and documentation.

The following sections provide guidance to the type of criteria that will need to be considered. It may be appropriate to formulate these (and other applicable criteria), into a checklist for use during the development of the design and the design review.

3.2.1 Facilities and environment

These are the buildings, rooms and environment containing the production processes. They are of prime concern wherever the product or product components may be exposed. Typical criteria include the following:

General considerations for the entire facility:

- local environmental considerations (including pollution and security);
- suitability/acceptability of physical segregation of processes for manufacturing and holding products, (such as segregation of production stages of the same, similar and different products and the use of dedicated or shared facilities);

- overall layout of the facility (including use of cored environmental layout, position of technical and other non-production areas with respect to processing areas);
- general layout of production processes (logical flow through the facility with no/minimal cross-over of processing streams);
- pedestrian and vehicular access;
- pest control.

Specific considerations for each area:

- available space and ergonomics for operators, equipment, materials and products;
- cavities/penetrations and how they are sealed;
- surfaces of walls, floors and ceilings (they should be easily cleanable, low particle shedding, minimal dust traps);
- materials of construction of the walls, floors and ceilings and their suitability for the intended operations;
- types of doors, windows, light fittings and void closures (for example, flush fitting, methods of sealing);
- provision and location of support utilities (both for production and maintenance/housekeeping purposes);
- provision of suitable electrical outlets and communications systems (electrical sockets, telephones, speak through panels, network termination points, intercoms);
- furniture (quantity, suitability for the operators, surfaces, cleanability).

Environment:
This is of prime concern wherever the product or product components may be exposed. Typical criteria include:

- assessment of the environmental classification of the various areas against the level of quality required by the product (including non-viable particulate and microbiological contamination in both the unmanned and manned conditions);
- airflow regime and types of processing operations (turbulent or laminar, horizontal or vertical);
- air pressure differentials between areas;
- air change rates per hour;
- location of ventilation ducts relative to processing points and other equipment;
- emissions within the area (water vapour, compressed air, toxic fumes);
- humidity (comfort level, static hazards, growth promoting);
- environmental control at point of access to area;

- illumination levels (relative to operations performed);
- adverse operating conditions (start-up/shutdown, dirty filters/blockages, power failure, redundancy);
- methods of monitoring, recording and controlling the environment (including temperature, pressure, humidity, air flow/velocity, particulate and microbiological);
- maintenance and cleaning of environmental systems (such as routine maintenance, safe change systems, redundancy).

GMP requirements may generally be limited for external areas such as administration buildings, canteens, plant rooms. Staff will be able to access these areas in street clothing or working garments unrestricted by GMP, but there may be other reasons why specific garments are required. Personnel access should be controlled to all areas within a pharmaceutical facility (by access cards or pass-codes, for example). Pest control measures must be employed to prevent insect and rodent infestation.

For areas such as packaging, warehousing, technical areas or where the product is fully contained in pipework, typical GMP requirements would include that:

- clothing consists of general factory overalls or lab coats and hats, with personnel to enter these areas via cloakroom facilities (primary change);
- environment air should be filtered to Eu 3 or above. Air pressure should normally be ambient;
- surfaces should be easily cleanable, finished flush and sealed. Equipment should be readily accessible for cleaning;
- measures should be taken to minimize the risk of cross-contamination.

For areas where specific environmental control is required such as in secondary pharmaceutical manufacturing where products or ingredients are exposed, or for the preparation of solutions and components for terminally sterilized products, and in BPC plant areas handling exposed products or critical step intermediates, GMP requirements may include the following in addition to the above:

- personnel must enter the area via a secondary change and the area must not contain toilets or eating areas;
- process materials and components should enter via an airlock;
- filtration and air circulation should achieve EU GMP Guide Grade D or equivalent;
- drains should be sealed during normal operation with air breaks provided between sink or equipment outlets and floor drains;

- compressed air exhausts should be vented outside the area;
- the preferred material of construction for process equipment is generally stainless steel and pipework lagging should be avoided where possible. Operators should be protected by mechanical guarding. Separate belt conveyors should be in different grade rooms, with dead plates at the wall opening.

Where tight microbial control is required, such as areas used for the preparation of solutions to be filtered before aseptic filling, GMP requirements may also include that:

- filtration and air circulation should achieve EU GMP Guide Grade C or equivalent with pressure positive (typically 15 Pa) to adjacent lower grade areas;
- strategically located local environmental protection, such as positive pressure Grade A LAF units, should be in place for exposed operations.

For areas where specific microbial control is to be exercised continually, such as for aseptic preparation and filling operations, additional GMP requirements will need to be applied such as:

- all operations should be performed aseptically with filtration;
- air circulation should achieve Grade B (EU GMP Guide, Annex 1) at positive pressure to lower grade areas;
- any process or equipment drains should be sealed and fitted with a sterilizable trap;
- strategic Grade A protection should be provided at all points of product exposure.

3.2.2 Services and utilities

Services and utilities that come into direct product contact (or form part of the product) are of particular concern. Some typical criteria for commonly used critical utilities include:

High purity water systems such as WFI systems:

- assessment of the proposed water quality against the level of quality required by the product (in terms of chemical quality, microbiological, pyrogenic, and physical particulate contamination);
- materials of construction (including piping, gaskets, valve diaphragms);
- internal surface finishes (Ra ratings, use of electropolishing, passivation);
- water pre-treatment and control (adequacy);
- system sizing (minimum and maximum demand);

- key design considerations such as minimum flow rates, minimum deadlegs with no cavities, vents and how they are sealed/filtered, drainage air gaps and backflow prevention devices;
- use of security devices, such as 0.2 micron sterilizing grade filters, UV sterilizers, ozone injection;
- instrumentation and control of critical process parameters (for example, temperature, velocity, flow, conductivity control limits and alarms, use of dump valves and recirculation of bad quality water, monitoring, recording and controlling systems);
- storage (such as storage temperature, maintenance of circulation and wetting of all internal surfaces, vent filter integrity and sterilization);
- methods and adequacy of cleaning and sanitization;
- adverse operating conditions (start-up/shutdown, power failure, redundancy, etc.);
- proposed method of construction (including procedures, control and inspection of material stock, fabrication, welding, field installation, passivation, preservation).

Clean steam systems:

- similar considerations to those described for high purity water systems can generally be applied to clean steam systems.

Gases (such as compressed air, nitrogen, hydrogen and oxygen):

- assessment of the proposed gas quality against the level of quality required by the product (in terms of chemical quality, microbiological, pyrogenic, and physical particulate contamination);
- materials of construction (including piping, gaskets, valve diaphragms);
- internal surface finishes (Ra ratings, use of electropolishing, passivation);
- system sizing (minimum and maximum demand);
- use of security devices, such as 0.2 micron sterilizing grade;
- instrumentation and control of critical process parameters (for example, temperature, pressure and dew point, monitoring, recording and controlling systems);
- methods and adequacy of cleaning and sanitization;
- adverse operating conditions (start-up/shutdown, power failure, redundancy, etc.);
- proposed method of construction (including procedures, control and inspection of material stock, fabrication, welding, field installation, passivation, preservation).

Typical GMP criteria for Water for Injection (WFI):

- quality to conform to compendia requirements (such as USP and/or Ph.Eur Monographs);
- production to be by distillation (also reverse osmosis allowed in some regions) from purified water and to conform to USP and/or Ph.Eur Monographs;
- WFI to be sterile and pyrogen free with an action limit set to less than 10 CFU/100 ml (Colony Forming Units) with a sample size of between 100 and 300 ml and an endotoxin level of less than 0.25 EU/ml (endotoxin units).

Design of WFI systems:

Firstly it is important to ensure that there is adequate pre-treatment and control of feed water, using methods such as deionization, ultrafiltration and reverse osmosis. Pre-treatment by deionization alone may prove to be unsatisfactory.

Key features of the WFI system itself include:

- still to be of multi-effect type, heat exchangers of double tube sheet design and holding tank employing tube type external jacket;
- WFI system to be fitted with a hydrophobic sterilizing grade vent filter to protect system from ingress of non-sterile air;
- vent filter to be jacketed to prevent condensate blocking the filter and to be steam sterilizable and integrity tested in place;
- provision for continuous ring main circulation at temperatures over 70°C at velocities sufficient to achieve a Reynolds number of >25000;
- provision for periodic sterilization of the system;
- provision for sampling at all loop take-offs (the start and end of the loop) with take-offs design to prevent re-contamination of the system by air-drying, steam locking or trace heating;
- WFI to be stored in a nitrogen atmosphere where appropriate to minimize the absorption of oxygen;
- product contact materials be supplied with material certification and PMI (Positive Material Identification) and stainless steel contact surfaces to be <0.5 μm Ra and passivated;
- pipework joints and couplings to be minimized with pipework being orbitally welded where possible. Detailed weld records to be supplied with weld logs and NDT reports on specified minimum proportions of all welds. Couplings and equipment to be crevice free — clamp fittings IDF couplings or similar are preferred. Deadlegs in vessels and pipework be minimized, by for

example use of zero deadleg diaphragm valves. System to be designed to allow for periodic complete flushing or draining such that all lines will slope to low drain points at a slope of greater than 1 in 100.

3.2.3 Personnel flows

This includes the influence personnel have on the quality of the product that might be caused by their contact with the product. Typical criteria include:

- clothing requirements (suitability of proposed plant clothing against the types of operations being performed within that area);
- changing regimes (stages of changing);
- changing facilities (adequacy of changing and washing facilities, doors, step over barriers, provision of adequate space for clothing, use of vision panels and their position relative to/from production areas);
- security and access control including potential short cuts and back doors;
- types of movements within the area (including passing through, local operations, supervisory support);
- occupancy levels;
- shift patterns (what supervisory and maintenance support is available);
- potential points of cross-contamination between personnel (such as transfer hatches, changing rooms — gowning/ungowning, finger streak stations);
- activity levels (i.e. sedentary or active and how this compares to the required room environment, occupancy level and clothing regime).

3.2.4 Material flows

This includes all the movement of materials. Typical criteria include:

- general flow of materials through the area (for example, linear flow through with no cross-over of production streams);
- methods of handling and prevention of cross-contamination;
- frequency of movements and available space;
- possible points of cross-contamination between materials (for example, temporary storage points, processed and non-process materials, bulk containers);
- identification and segregation of materials;
- storage conditions (refrigerated, toxic, hazardous, filtered).

3.2.5 Equipment flows

It is important to consider that not all equipment may be fixed in one position; it may either be moved routinely as part of the production process, or at least be

capable of relocation for plant maintenance or reconfiguration. Typical criteria include:

- methods of handling and prevention of cross-contamination;
- frequency of movements and available space;
- physical size and weight of equipment against room construction (heavy equipment may damage welded sheet vinyl floors or fracture gyprock walls — trowelled on epoxy cement or blockwork may be more appropriate);
- possible points of cross-contamination between equipment (such as temporary storage points, washing machines and bays);
- identification and segregation of mobile equipment;
- storage conditions (refrigerated, toxic, hazardous, filtered);
- provision of non-routine access, such as removable wall or ceiling panels.

3.2.6 Equipment design

The examination of the GMP issues within a machine or system is a 'micro' version of those for a facility, and includes many of the same questions such as surfaces, flow of materials and personnel issues. The amount of detail will vary with the complexity of the equipment and its effect or potential effect on product quality. Typical criteria include:

- pedigree of the machine (established for pharmaceutical use, 'off the shelf' or specially developed prototype);
- pedigree of the manufacturer (specialist supplier to the pharmaceutical industry who manufactures more than 50 identical units per year or first development machine by a new manufacturer);
- materials of construction and surface finishes of primary and secondary contact parts (i.e. primary — direct product contact, secondary — contact with local environment);
- equipment sizing (minimum and maximum demand);
- key design considerations (minimum deadlegs with no cavities, all critical surfaces accessible and cleanable, drainage air gaps and backflow prevention devices);
- instrumentation and control of critical process parameters (temperature, pressure, speed control limits and alarms, monitoring, recording and controlling systems);
- methods and adequacy of cleaning and sanitization;
- adverse operating conditions (start-up/shutdown, power failure, redundancy);
- proposed method of construction (including procedures, control and inspection of material stock, fabrication, field installation);

- maintenance (access for maintenance during and outside production, use of maintenance free items, requirements for special tools/no tools).

For equipment and pipework that does not come into contact with the product or product components, there are no specific GMP requirements.

For process pipework and equipment there is no need for sophisticated Clean in Place (CIP) or Steam in Place (SIP) but plant washing and flushing with water or chemicals may be used. Typical requirements include the following:

- dismantling and inspection should be easy and involve minimal use of tools;
- all pipework should slope towards the drain points;
- product contact materials should be supplied with material certification and stainless steel surface finishes in contact with the product should be $<1.0\ \mu m$ Ra and passivated. Pipework couplings and equipment should be crevice free. Clamp fittings, IDF couplings or similar are preferred and deadlegs in vessels and pipework should be minimized.

For areas where CIP and SIP effectiveness is critical, GMP requirements may include, in addition to the above, that joints and couplings are minimized with pipework being orbitally welded where possible and that stainless steel product contact surfaces are $<0.5\ \mu m$ Ra electropolished.

For certain types of equipment, specific GMP requirements have been issued — one example of this is for sterilization equipment. Typical criteria for porous load moist heat sterilizers include:

- the complete chamber space should achieve a uniform temperature distribution of less than $\pm 1°C$ at the sterilization temperature for the complete sterilization period, and the equilibrium time to achieve this distribution should be less than 30 seconds;
- the chamber should be resistant to corrosion and the leak rate of the chamber should be less than 1.3 mbar per minute;
- monitoring instrumentation and recording charts should be independent of control instrumentation and utilize an independent time/temperature and pressure chart or equivalent of a suitably large scale to record the sterilization process;
- an air detector should be fitted such that a difference in temperature of greater than 2°C between the centre of a standard test pack and chamber temperature at commencement of equilibrium time is detected;
- drains should be trapped and vented and not connected to other drains which could cause a backpressure or obstruction to flow — an air break is necessary;

- steam used for the sterilization process should have a dryness fraction of not less than 0.95 and the superheat measured on expansion of the steam to atmospheric pressure should not exceed 25°C with the fraction of non-condensable gases not exceeding 3.5% by volume. The steam generator should be designed to prevent water droplets being carried over into the steam and should operate so as to prevent priming. The steam delivery system should be fitted with a water separator and traps to virtually eliminate condensate build up, and be resistant to corrosion with minimum deadlegs to reduce the risk of water collection and biofilm formation.

3.2.7 Computerized systems

The amount of detail will vary with the complexity of the computerized system and its effect or potential effect on product quality. In particular the pedigree of the manufacturer, type of hardware and type or category of software to be used need to be carefully considered. The systems manufacturer is generally responsible for providing the validation documentation and ensuring that the system complies with GMP. Typical criteria include:

General:

- up to date specifications, including principles, objectives, security measures and scope of the system and the main features of the way the system will be used and how it interacts with other systems and procedures;
- the development of software in accordance with a system of quality assurance;
- system testing including a demonstration that it is capable of achieving the intended results;
- procedures for operation and maintenance, calibration, system failure (for example, disaster recovery, restarting), recording, authorizing and carrying out changes, analysis of errors, performance monitoring;
- pedigree of the machine and manufacturer;
- type of hardware (for example, standard 'off the shelf' components from reputable suppliers operating a recognized quality system, installed in a standard system such as a PC or fully bespoke hardware developed specifically for the system);
- type/category of software (operating system, can be configured, bespoke software);
- adequacy of system capacity (in terms of memory, I/O, etc.).

Control/access/security:

- built in checks of the correct entry and processing of data;
- suitable methods of determining unauthorized entry of data such as the use of keys, pass cards, passwords and restricted access to computer terminals;
- control of data and amendments to data, including passwords. Records of attempts to access by unauthorized persons;
- additional checks of manually entered critical data (such as weight and batch number of an ingredient during dispensing);
- entering of data only by persons authorized to do so;
- data storage by physical and electronic means. The accessibility, durability and accuracy of stored data. Security of stored data;
- data archiving, remote storage of data;
- recording the identity of operators entering or confirming critical data. Amendments to critical data by nominated persons. Recording of such changes;
- audit trail for system;
- change control system;
- obtaining clear printed copies of electronically stored data;
- alternative arrangements in the event of system breakdown, including the time required to recover critical data;
- positioning of the equipment in suitable conditions where extraneous factors cannot interfere with the system;
- form of agreement with suppliers of computerized systems including statement of responsibilities, access to information and support;
- release of batches, including records of person releasing batches.

Personnel/training:

- personnel training in management and use;
- expertise available and used in the design, validation, installation and operation of computerized systems.

Replacement of a manual system:

- replacement of manual systems should result in no decrease in product quality or quality assurance;
- during the process of replacement of the manual systems, the two systems should be able to operate in parallel;
- reducing the involvement of operators could increase the risk of losing aspects of the previous system.

3.2.8 Maintenance and servicing

This applies to all the facility and everything within it. It is important to consider that not all equipment may be fixed in one position, it may either be moved routinely as part of the production process or at least be capable of relocation for plant maintenance or reconfiguration. Typical criteria include:

- methods of handling and prevention of cross-contamination;
- frequency of movements and available space;
- physical size and weight of equipment against room construction (heavy equipment may damage welded sheet vinyl floors or fracture gyprock walls; trowelled on epoxy cement or blockwork may be more appropriate).

3.2.9 Procedures and documentation

In order to support the facility, adequate procedure and documentation are required. During the design stage many of the documents required for normal operation of the facility may not yet be available. At this stage, it is probably too early to consider exactly what documentation will be required, but it is possible to begin to consider how documentation will be accommodated and organized. Typical criteria include:

- adequate workspace, storage capacity and personnel to control stored documentation;
- security of documentation (including access control, fire protection, additional remote storage capacity);
- adequate, rapid access to stored data, including suitable provisions for the local retrieval of data stored electronically.

3.3 GMP reviews of design

To ensure that the project remains in compliance with cGMP as it progresses through its life-cycle, periodic GMP design reviews must be undertaken.

3.3.1 Organizing the GMP design review team

Reviewing a design for compliance to cGMP requirements can often be a daunting prospect. It requires a range of knowledge that no single person is likely to possess. For this reason it is often more effective if the review is performed by a small team that has an understanding of the basic requirements and works methodically. The team should consist of persons selected for both their depth of knowledge in a particular area and for general knowledge of

cGMP principles applicable to the project. A good mix for a suitable team would be:

- cGMP compliance/validation specialist (knowledge of regulatory, QA, validation, etc.);
- architect (knowledge of finishes, layout, personnel/materials flows, etc.);
- process engineer (knowledge of process, equipment, utilities, etc.).

Depending upon the nature of the facility the architect or process engineer could be substituted for more suitable disciplines. For example, the design review of an automated high bay warehouse may be better performed using a materials handling specialist and an automation specialist. The team would normally be lead by the cGMP compliance/validation specialist who would organize the team, co-ordinate the review and prepare the report(s). It is recommended that the team be kept as small as practicable, since it will be able to operate more efficiently and flexibly and be easier to co-ordinate. If issues arise that are beyond the combined knowledge of the team then they can be referred for further investigation by specialists in the particular subject.

3.3.2 Information required to perform the review

Two basic types of information are required to perform an effective review:

- specification of the pharmaceutical product and manufacturing process;
- specification of the equipment and facility.

Note that some facilities are used for a variety of products that may utilize different processes. In this case a separate review of each process may be performed. However, often it is possible to base a review on a 'typical' product that runs through the entire process.

As part of the cGMP review all information sources used must be documented. Regulatory authorities always demand to see original information. It is, therefore, essential that a good record keeping system be established — for example, original design calculations must be retained. All engineering drawings must be authorized and signed off.

Specification of the pharmaceutical product and manufacturing process

General details of the process are required rather than exact details of, say, a particular chemical reaction involved. Sources of information may include:

- regulatory documents such as:
  - New Drug Application (NDA), Product Licence Application (PLA), Investigational New Drug Application (IND);

  - manufacturer's licences such as Product Licence, Wholesale Dealers Licence;
  - Drug Master File (DMF);
- technology transfer documents;
- batch manufacturing documentation prepared for similar facilities;
- process description;
- process flow diagrams (PFD).

The type of information required will typically include:

- description of processing operations including:
  - manual operations such as loading, sampling testing, adjustments;
  - automatic operations such as process unit operations, cleaning cycles and materials handling;
- quantities and throughputs;
- components and processing chemicals;
- critical parameters such as temperature, pressure, time and volume;
- batch size and frequency;
- regulatory requirements in original product licence/regulations;
- technical requirements identified during laboratory/pilot scale production.

Specification of the equipment and facility

Clearly the review will utilize the GMP design philosophy as a key document, but this should be compared with what has actually been specified. General details of the equipment and facilities are required. Sources of information may include:

- architects/facility engineers;
- process engineers;
- engineers from the various technologies as appropriate — for example, mechanical, electrical, civil, control, instruments;
- R&D;
- QC/QA.

The type of information required will typically include:

- process description, materials and personnel flow diagrams;
- general arrangement drawings, axiometric drawings and room layouts;
- process and instrumentation diagrams (P&IDs);
- HVAC basic layouts, specifications and area classification drawings;
- main equipment items list with specifications;
- utilities list with specifications;

- user requirement specifications;
- control system functional design specifications.

3.3.3 Divide up the facility into manageable sized areas

The best way to divide up the facility for the review largely depends on the type of facility and nature of the process. The following approach is suggested for guidance.

Bulk pharmaceutical chemical manufacturing

Typically for BPC manufacturing the process is contained within closed vessels and pipework arranged as an integrated/interconnected process. In this case it is probably easiest to break the cGMP review up into a series of reviews of each main P&ID. Each P&ID is then considered by the review team along with any associated equipment and utility specifications, control system descriptions etc., as a package.

Secondary manufacturing

Typically for secondary manufacturing, the process is carried out in a series of discrete stages in separate areas such as:

Goods in.	Weighing.	Services and utilities.
Warehousing.	Mixing/blending.	Goods out.
Amenities.	Filling.	
Changing rooms.	Sterilizing.	
Equipment preparation.	Labelling.	
Dispensing.	Packing.	
QC testing laboratory.	Administration area.	

The best method here may be to perform the review on each area of the facility. The review will centre on the room layout drawings along with associated environmental classification drawings, equipment and utility specifications and control system descriptions, as a package. It may also be possible to identify specific areas that have no cGMP implications — these can be considered to be 'outside the GMP area' and need not form part of the review although any decisions made to include or exclude particular areas should be documented.

In some cases, a combination of both the above methods may be the most appropriate. The key point is to break the task down into logical, manageable-sized portions, which can then be reviewed.