Validation

4

JOHN WELBOURN

4.1 Introduction

Validation first started in the 1970s on sterilization processes, when it became clear that end product testing alone could not show that every container within every batch of product was sterile and the time and cost associated with testing each individual container was too great, or the testing was too destructive to the product. Validation offered a way of providing evidence that the process was capable of consistently producing a product with defined specifications.

This type of work spread gradually through from sterile and aseptic processes to non-aseptic processes (tablet manufacture, for example) by the mid 1980s. By the late 1980s, the concept of validation was reasonably well established. Regulatory authorities and the pharmaceutical industry have co-operated to define validation requirements and agree upon the definition. The principle is the same for whichever process is being investigated — that is, to provide documented proof of GMP compliance. Validation and GMP go hand in hand.

4.1.1 Definition

Even before the current definitions of validation, industry was operating to the concept in the first edition in 1971 of the British Guide to Good Pharmaceutical Manufacturing Practice (the 'Orange Guide'), which suggested that procedures should undergo a regular critical approach to ensure that they are, and remain capable of, achieving the results they are intended to achieve.

Although the US Federal Register does not contain an official definition, US CFR Part 211 section 211.100 states that:

'There should be written procedures for the production and process control designed to assure that the drug product has the strength, quality and purity they purport or are represented to possess.'

The FDA has issued a 'Guideline on General Principles of Process Validation' which defines process validation as:

'Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes.'

The EU 'Rules Governing Medicinal Products in the European Community' Vol IV define validation as:

'Action of proving, in accordance with the principles of Good Manufacturing Practice, that any procedure, process, equipment, material, activity or systems actually leads to the expected results.'

The EU Rules also define the term 'Qualification', which arises many times within validation work, as:

'Action of proving that the equipment works correctly and actually leads to expected results. The word validation is sometimes widened to incorporate the concept of qualification.'

Validation for the engineer is the act of proving with the necessary formal documentation that something works. It is advisable to create the documentation throughout the design process since it is often expensive and time-consuming to produce retrospective documents.

4.1.2 The need for validation

There are three reasons why the pharmaceutical industry is concerned about validation:

- government regulation;
- assurance of quality;
- cost reduction.

Government regulation

The requirements for validation are now explicitly stated in both the US and European regulations (US Code of Federal Regulations US CFR Part 211, subpart L, 211.220 and 211.222 and within the EU 'Rules Governing Medicinal Products in The European Community' Vol IV, Part 5.21, 5.22, 5.23, 5.24).

In CFR 211.220 it says:

'The manufacturer shall validate all drug product manufacturing processes . . . '

and:

'... validation protocols that identify the product and product specifications and specify the procedure and acceptance criteria for the tests to be conducted and the data to be collected during process validation shall be developed and approved ... '

and:

'... the manufacturer shall design or select equipment and processes to ensure that product specifications are consistently achieved. The manufacturer's determination of equipment suitability shall include testing to verify that the equipment is operating satisfactorily ....'

Similar requirements are stated in the EU Rules.

Assurance of quality

Without process validation, confidence in the quality of products manufactured is difficult to prove. The concepts of GMP and validation are essential to quality assurance. Frequently, the validation of a process will lead to quality improvement, as well as better consistency. It may also reduce the dependence upon intensive in-process and finished product testing. It should be noted that in almost all cases end-product testing plays a major role in assuring that quality assurance goals are met, i.e. validation and end-product testing are not mutually exclusive.

Cost reduction

Experience and common sense indicate that a validated process is a more efficient process that produces less reworks, rejects, wastage, etc. Process validation is fundamentally good business practice.

In summary, validation should be applied to all aspects of the process, including the equipment, computer systems, facilities, utilities/services and in-process testing (analytical methods). From the above discussion, the following key points have developed:

- documented evidence must be written down (if it's not documented it's not done);
- formal documentation — all design documents should be signed off. Signatures, page numbering, control copies, storage/retrieval, etc., should be installed;
- acceptance criteria — decide what is acceptable before testing;
- repeatable — one-off results are not acceptable;

- validation and qualification — processes are validated whereas the equipment used within the process is qualified.

4.2 Preliminary activities

Prior to embarking on a validation project, it is necessary to establish an organizational framework in which validation resides. This must start with the commitment and sponsorship of the senior management within the company, for without this commitment to validation any validation project is likely to fail.

4.2.1 Establishing policies and procedures

One of the first steps is to establish the policies and procedures that will govern the validation project — for example, the development of policies to define general concepts involved such as:

- how validation 'fits' within the overall QA structure and its relationship with cGMP;
- commitment to cGMP and its reinforcement through validation (i.e. the pharmaceutical company's commitment);
- definition of key terms such as critical process step, critical equipment and instrumentation, the various qualification activities including DQ, IQ, OQ, PQ (more about this later);
- how validation is structured and applied with respect to plant, processes, computer systems, analytical methods, etc. (how is it organized, what steps are performed in each case and how does it all fit together).

More specific procedures will need to be generated later for:

- validation documentation preparation (including house style, standard document sections, document numbering);
- validation documentation review and approval process;
- validation document change control system;
- validation master plans and final validation reports (preparation, content and structure);
- pre-qualification activities;
- cGMP reviews of design;
- vendor assessment and auditing (especially computer systems);
- equipment/computer system protocols and reports (i.e. DQ, IQ, OQ, PQ) preparation, content and structure;
- instrumentation and calibration;
- execution of field work;

- set-up and operation of validation test equipment;
- cleaning validation;
- process optimization and experimental work;
- process validation protocols and reports;
- analytical methods validation;
- documentation filing and management systems.

Note that it is particularly important at an early stage in the project to agree aspects such as document format, structure, content and numbering. This agreement needs to be recorded in the project quality plan.

At this early stage it is a good idea to establish the key validation team members and prepare an overall organizational chart.

Some of the first activities for the validation team to address will include:

- process evaluation to determine validation requirements;
- identification of systems and system boundaries;
- preparation of user requirement specifications;
- development of the validation master plan.

4.2.2 Process evaluation to determine validation requirements

Process evaluation involves a review of the process to identify the process steps and process variables, to determine how they are controlled/monitored and to identify what processing, equipment, utilities, instrumentation and control systems are associated with these steps. This should identify which systems need to be qualified and which parameters and instrumentation are important to the process and will need to be evaluated in the validation study or will become 'critical instruments.' As part of the development work done on the process, much of this should already have been defined, however, the documents where this is recorded need to be collated and reviewed.

The specification and procedures required for the process such as equipment operation and maintenance, calibration, set-up, cleaning and in-process testing should be identified, since these will need to be prepared for the new facility.

The various components used to manufacture the product should be reviewed to establish that all items have been specified and are under control. This may then point to requirements for analytical methods, validation or supplier audits, for example.

Based on an evaluation of the process a decision can be made as to what does and does not require validation. To perform such an evaluation requires a thorough understanding of the process and may include process components, process chemistry, plant (equipment, automation systems, etc.), specifications and procedures, in process controls and analytical testing methods.

User requirement specifications (URS)

These should be prepared by the user to formally document the requirements for each system to be qualified in terms of the final process requirements. A URS should typically include specific, but non-detailed information relating to, for example, quantity, quality, compatibility, performance, environment and finishes, in terms of:

- materials of construction;
- cleanability requirements;
- maintenance requirements;
- operator interface requirements;
- performance criteria;
- critical parameters;
- essential design criteria;
- requirements of computerized/automation system;
- training and documentation requirements.

It should make reference to relevant in-house standards and regulatory documents. It is essential that input to the URS includes persons with 'hands on' knowledge of the system and persons with a wider knowledge of the overall project.

4.2.3 Identification of systems and system boundaries

In parallel with process evaluation, systems and system boundaries need to be defined. The objective is to break the facility down into logical, manageable-sized packages of qualification work, and concentrate the validation effort in the most important areas to allow structured qualification.

A system may be an area of the facility (group of rooms), a group of functionally related process items, a utility or part of a utility, a HVAC, a computerized/automation system or any combination of these.

Determination of system boundaries involves the evaluation of the proposed facility design to establish the boundaries and break points for each package of qualification work. It is important that at the earliest stage practicable any 'grey' areas are removed, such as overlaps between areas of responsibility, missing areas, break points, IT systems interfaces.

Systems may then be categorized as 'Primary' or 'Secondary', (it may be appropriate to develop several more intermediate categories, such as in the case of IT systems). For example, primary systems could be defined as large, complex, purpose built or configured, generally fixed in place units. Examples include an aseptic filling suite, low temperature hot water system, water for injection system, electrical power distribution system, a piece of

automated manufacturing equipment or a plant supervisory control and data acquisition system (SCADA).

Secondary systems could be defined as smaller, simple, 'off the shelf', generally portable items with no or minimal unique features or configuration, such as a bench top balance, filter integrity tester, a pallet-bailing machine and a 10-litre standard holding tank. Typically these systems may be bought direct from a supplier's catalogue.

Systems may be further categorized as 'critical' or 'non-critical.' Typically the following criteria are used to evaluate if a system is critical:

- stage of the process — is it used before, during or after a critical process step;
- effect on product quality;
- contact with product or product components;
- monitoring or controlling elements related to product quality.

Examples of primary critical systems are an aseptic filling suite, a water for injection system, a piece of automated manufacturing equipment, or a plant supervisory control and data acquisition system (SCADA).

Examples of primary non-critical systems are a low temperature hot water distribution system or an electrical power distribution system.

Examples of secondary critical systems are a bench top balance, filter integrity tester, and a 10-litre standard holding tank. An example of a secondary non-critical system is a pallet-bailing machine.

All critical systems should be validated. For primary critical systems this may involve the development of detailed plans, protocols, reports, certificates; for secondary critical systems, however, the use of simple, standard, check-sheet type documents may be more appropriate.

Non-critical systems do not require qualification — standard, well-structured project documentation is adequate.

4.3 Validation master planning

The initial activities described above can be formalized and consolidated into a validation master plan (VMP). This is a formal, approved document that describes in clear and concise wording the general philosophy, expectations, intentions and methods to be adopted for the validation study. Everyone involved in a project will have their own interpretation as to what validation is and what should be done. The VMP is an agreed document acting as a road map or guide for all team members to follow.

Once complete, it becomes a useful tool to show regulatory bodies that compliance with regulations is being sought and that there is a plan describing

in detail the steps and programmes to be implemented to assure a validated and compliant facility.

To prevent the VMP becoming too unwieldy, it is common practice to develop separate validation plans for various parts of the overall project such as process equipment, utilities, computer systems, process and analytical methods. On large projects it may be necessary to have several levels of plans.

In terms of when to begin to develop the VMP, this will vary from project to project but it should normally be in place by the early part of detailed design. The VMP will then be a living document, updated regularly and amended during the course of the project. At the end of the project the VMP should define how the validation was actually performed.

The VMP, as with all formal validation documents, should be prepared, reviewed, approved and controlled under pre-defined company policies and procedures with final approval by QA. It must have a document number and a document revision history and page numbering must pass the 'drop test' (i.e. it is possible to reassemble the document from the page numbering and know that all sheets have been accounted for). The number of copies should be controlled.

4.3.1 Contents of the VMP

This will differ slightly from project to project and company to company, but the following items should usually be included:

(1) approval page;
(2) introduction;
(3) the aim;
(4) descriptions of:
    - facility;
    - services/utilities;
    - equipment;
    - products;
    - computer systems;
(5) validation approach:
    - overall;
    - detail (matrix of validation documents);
(6) other documentation.

Approval Page

The approval page is the title page to the entire document and should contain the name of the company, the title and a space for approval signatures. Usually the author and three approvers sign the approval page. The approvals should come

from the people affected by the validation project, such as production, QA and engineering functions related to the facility. A development signature may be necessary if the project relates to the manufacture of a new product.

As a general rule it is not a good idea to have too many approvers as there is a danger that scrutiny and understanding starts to suffer because each approver will be expecting others to have checked certain items. It is important that the approvers know what they are signing for. As with all validation documentation, the continuity of the dates from the signatures is important. The author should sign first, followed by the others, with QA input last.

Introduction

The introduction should explain why the project is being undertaken, where it is going to be located and the broad timetable.

Aim

The aim should explain that this is to be a formal validation study on a specific project and show that the approach conforms to cGMP. The aim may point to the various company policies and procedures under which the VMP is to be prepared and controlled.

Description

This section should describe the main features of the project in concise terms, picking out particularly critical features or acceptance criteria.

Facility

This section of the VMP should outline the facility's intended use, briefly discuss how it is to be built and state whether it is an entirely new facility or an expansion of an existing one.

For example, it could describe the size of the facility, the number of floors the facility occupies, the processing areas and, if necessary, the segregation for contamination; how many HVAC systems there are, and what the classifications are; any special gowning procedures or other procedures to be followed. Some simple outline drawings will generally be included with the description — typical drawings to insert are:

- facility location in relation to site;
- cross section of the facility (if relevant);
- floor plan (one for each floor) with equipment locations;
- HVAC zone identifications;
- personnel flow;

- component flow;
- raw material flow;
- product flow.

Services/Utilities

This section may consist of a list of plant utilities and services, such as cold potable water, purified water, water for injection, plant air, instrument air, nitrogen, chilled water.

In addition to this listing, there should be a brief description with simple line diagrams for each system, which should include any key performance criteria such as minimum flow rate or pressure, and quality. However, detailed requirements of the systems can be written into individual protocols — this helps keep the VMP to a sensible size and makes it easier to control.

Equipment

As with the previous section, this could start with a list of all the major items of equipment that are going to be installed into the facility, for example, porous load steam sterilizer, bench top balance, or powder mixer. It is a good idea to divide up the list by facility area or stage in the process. The list that is generated should include a unique plant item number for each major piece of equipment for reference purposes. For the most important items it is a good idea to include a brief description with a simple line diagram with any key performance.

Products

In this section, information should be provided about the products that are going to be manufactured in the facility in question. For each product this may include:

- batch size;
- ingredients:
  - quantities per unit dose;
  - quantities per batch;
- the steps by which the product is manufactured:
  - process flow diagrams;
  - summary of manufacturing method.

Computer systems

This section lists all the computer systems associated with the facility, process equipment and utilities as well as IT systems to operate the plant such as LIMS, SCADA and MRP systems, and provides descriptions of each system picking out any important performance.

Validation approach – overall

This section of the VMP is used to describe how the validation work is to be performed and documented (see Figure 4.1 on page 49).

It gives the design engineer's viewpoint of the Validation Master Plan. Note that it starts with the User Requirement Specifications (URSs), which is usually prepared by the user in discussion with the design engineer. This document forms the basis for the design.

This flow chart forms an excellent checklist for the validation process and underlines the importance of preparing validation documentation right from the issue of the URS to the performance qualification of the plant built to the final design. The main aspects of this flow chart, which provide the design engineer with a good background to the validation process, are detailed.

Process evaluation and validation systems

This section should explain how the facility has been divided up into separate systems and how the process has been evaluated to determine what aspects are critical to product quality. It should introduce concepts such as 'critical parameters' and 'critical instrumentation' and relate these to the validation requirements, in line with the method described in Section 4.2.2 and 4.2.3.

Validation team

This section defines the role and responsibilities of key personnel involved. It is often a good idea to use job titles rather than names since individual personnel may change, and to include a project organization chart. In particular, it is important to explain the role of QA in the approval processes.

Validation methodology

The validation methodology should describe what types of documents will be generated within the project (protocols and reports — Design Qualification (DQ), Installation Qualification (IQ), Operational Qualification (OQ), Performance Qualification (PQ), and Process Validation (PV)) and how they will be prepared, reviewed, approved and controlled. This section should draw on company policies and procedures, which should define each part in more detail. In addition, as appropriate, the methodology should discuss cleaning validation, analytical methods validation and computer systems validation (there will be more about the various validation activities later in this chapter).

The section should then describe the execution strategy for the protocols including, for example, how results are recorded and how any problems encountered are dealt with, and the role of equipment vendors in validation

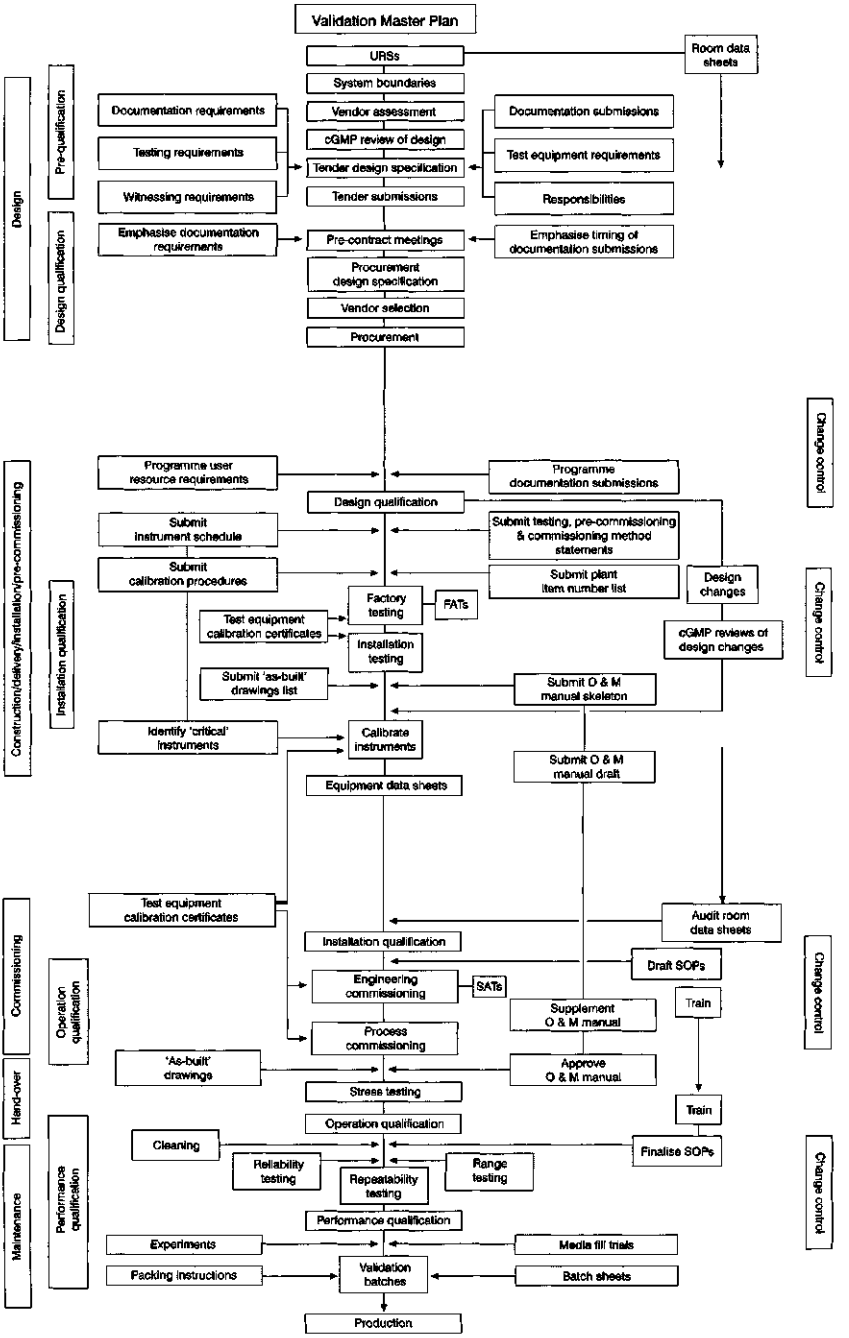

Figure 4.1 Validation flow chart (By kind permission of Validation in Partnership).

(i.e. utilize vendors as much as possible in the preparation and execution of validation work or do as much of the work as possible 'in-house').

This section can also be used to describe the organization and management of project documentation, including document flow and filing (for example, documentation filing structure, use of document management systems, IT).

Validation schedule

It is often useful (although not obligatory) to include a time schedule in the plan. It is probably best to keep this relatively simple, as schedules tend to change frequently during a project. The VMP is not intended as a document to convey this type of information.

Validation approach – detail

This section includes details of which types of documents are going to be produced for each system to be qualified and which processes are to be validated. This is often done by a validation matrix (see Table 4.1).

Other documentation required

This section should establish links to other types of documents that could be required at regulatory authority inspections. The type of documents which come under this heading include:

- batch production records;
- packing instructions;
- training;

Table 4.1 Example of a validation matrix

Item	Item no.	Document type				
		DQ	IQ	OQ	PQ	PV
Utilities						
HVAC	ABC123	✓	✓	✓	–	–
WFI	ABC456	✓	✓	✓	✓	–
Equipment						
Tablet Press	XYZ789	✓	✓	✓	–	–
Autoclave	XYZ123	✓	✓	✓	✓	–
Product						
Tablet A		–	–	–	–	✓
Tablet A, cleaning		–	–	–	✓	–

- SOPs;
- maintenance and calibration records;
- organizational charts and CVs;
- change control procedure;
- drawings.

4.4 Development of qualification protocols and reports

The VMP defines which systems are to be qualified and how the work is to be organized and controlled. The next step involves the preparation of qualification protocols and the generation of associated reports.

4.4.1 Qualification protocols

There are various different approaches to the format and content of qualification protocols — for example, protocols can be developed as stand-alone documents or can cross-reference other project engineering documentation. They can be designed so that results are recorded within the body of the protocol or that all the detail is left for recording in the reports. The former results in bulky protocols but brief reports, whereas the latter results in slim protocols and bulky reports. As with all validation work the protocols should be developed in accordance with company policies and procedures. There should be SOPs for protocol preparation, execution and reporting.

Whatever approach is taken, there are certain key features that the protocol must have. These can be summarized as follows:

- **formal documents:** The protocol must go through a review and approval process with final approval by QA; this must be numbered, the number of copies must be controlled and have a document revision history, page numbering must pass the 'drop test' (see Section 4.3);
- **defined scope:** The protocol must define what area, equipment, etc., it addresses. This may be achieved by, for example, a system description, diagram or list of items;
- **objective:** The protocol should describe the purpose and how this relates to the overall validation activity and scope of the protocol;
- **test structure:** Each test must describe the objective and purpose of the test, the test procedure and the method of recording results. This should be in sufficient detail so that it could be understood by a third party, and repeated if necessary;

- **acceptance criteria:** Each test must have acceptance criteria as to what constitutes a pass or a fail. The acceptance criteria must be approved before execution of the protocol.

A typical table of contents for a qualification protocol would consist of the following:

- title page;
- revision history;
- table of contents;
- introduction/background;
- purpose;
- scope;
- reference documents;
- system description;
- prerequisites;
- personnel performing the qualification;
- test equipment details;
- method;
- acceptance criteria;
- list of attachments.

4.4.2 Qualification reports

Once the protocol has been executed the results should be documented in a qualification report. At least one report should be written for each protocol. A typical table of contents for a qualification report would consist of the following:

- title page;
- revision history;
- table of contents;
- purpose;
- scope;
- executive summary;
- results;
- deficiencies and corrective actions;
- assumptions, exclusions and limitations;
- conclusions;
- appendices (depending on the protocol style adopted, one of the appendices may be the complete protocol).

The reports are also formal documents and should follow a similar preparation, review and approval process as protocols.

Deficiencies

As a general rule the report should be prepared by exclusion; that is, if a test was successful with no problems then only a brief mention is required in the report. The report should concentrate on the tests that failed and describe what remedial action was necessary and what retesting or further work was/is required. Examples of deficiencies include:

- conflicts with specifications — for example, the pump seal material was viton rubber not EPDM rubber as specified;
- information which is unavailable or incomplete;
- documentation discrepancies (incorrect reference number, issue number).

Each deficiency should be given a unique identification number and a complete list of deficiencies encountered during the execution of the protocol should be included in the report. An audit trail should be established to show how the deficiency was resolved.

4.5 Design qualification (DQ)

The purpose of design qualification is to ensure that the final design:

- accords with all relevant specifications and design intentions;
- meets the requirements of the process, product and user;
- adequately specifies all necessary supporting documentation;
- complies with the requirements and principles of GMP.

DQ is providing documented evidence that quality is built into the design. DQ is an auditing function to provide formal documentation that the facility has been designed to meet the requirements of the user and the GMP guidelines. DQ activities may include:

- GMP reviews of overall facility design;
- establishing the suitability of vendors and vendor deliverables through vendor assessment and auditing where appropriate;
- review and approval of equipment specifications and design documentation to ensure user requirement specifications (URS) have been adequately interpreted in the design process and that the design is in compliance with GMP.

DQ comes down to carrying out a formal comparison of what is required against the proposed design. There should be DQ documentation for:

- the overall facility;
- each system within the facility.

4.5.1 GMP reviews of overall facility design

The GMP review of the overall facility/project design can be defined in the same terms as an audit, that is a formal documented review of the design of a plant (including facilities, equipment, utilities, computerized/automation systems and procedures) to give assurance that:

- it complies with the applicable statutes and associated published current Good Manufacturing Practices;
- it complies with applicable regulatory licence(s) and registrations submitted for the particular process(es) or product(s) to be manufactured, held or stored.

Note that because of the confidential nature of the process, including licensing application details, the second point may be considered separately from the first.

Typically, topics to be dealt with include:

- facility (construction, finishes of walls, floors and ceilings, corners and crevices, cleanability, durability, access control, pest control, etc.);
- environment (area classification, temperatures, humidity, air pressures, air change rates, viable and non-viable particle levels, etc.);
- personnel flows (access authorization, change regimes, gowning requirements, occupancy levels, cross-contamination, etc.);
- materials flows (solids, liquids, gases, toxicity, hazard risk, containers, transportation, storage, cross-contamination, etc.);
- equipment flows (size, weight, mobility, cleaning, method of handling, cross-contamination, etc.);
- general equipment design (proprietary, purpose built, materials of construction, finishes, cleaning, change parts, control systems, etc.);
- automation philosophy (monitoring or controlling, level, protection, environment, access control, archive storage and retrieval, electronic signatures, disaster recovery, etc.);
- maintenance/servicing (access, space, tools, diagnostic equipment, materials, power, lighting, authorization, training, etc.);
- documentation (SOP's, permits, history records, training, log books, etc.);
- waste management (liquids, solids, gases, packaging materials, cleaning, etc).

4.5.2 DQ of each system

Vendor assessment

Vendor assessment is the documented evaluation of the suitability and capability of the vendor to provide the 'system' to be procured to the quality required to fulfil user and cGMP requirements, including all necessary supporting documentation. Where appropriate this may include vendor auditing.

Vendor assessment may stretch over several stages including assessment of the vendor's suitability to tender, assessment of preferred vendor and follow up vendor audit(s). Vendor assessment would generally involve, for each primary critical system including primary critical computer system, sending out self-assessment questionnaires and then, where appropriate, auditing vendors prior to placement of orders. Subsequent audits may be required throughout the design and construction/implementation process depending upon the nature of the system and the findings of the assessments and audit.

DQ of system plant

Design Qualification (DQ) of system plant (in other words, equipment, piping, valves and in-line fittings, field instrumentation, ductwork, insulation etc., or combinations of these) is the documented evidence that quality is built into the design of the system. It should include verification that the 'system' design incorporates the requirements of the user and of cGMP. Typically the DQ activities will include.

- cGMP review of design;
- specification review (URS/design specification(s) review);
- compilation of design documents;
- QA/QC review;
- facility acceptance testing (FAT).

4.6 Installation qualification (IQ)

Installation qualification is the documented evaluation of the equipment or system to establish that it has been installed in accordance with design specifications, cGMP requirements and manufacturers recommendations. Typically it will consist of various static checks, which may include for example:

- **system completion:** Check that the system is mechanically complete and all critical punch list items have been cleared. Check that all work which should

have been completed and documented during the construction and installation of the system has been performed. This will involve checking through the various construction check sheets and certificates;

- **security/utility connections:** Check that the correct connection of utilities has been made and that, where appropriate, utilities have been IQed;
- **documentation inventory:** Check that all necessary supporting documentation such as specifications, operation and maintenance manuals are available and have been reviewed and approved;
- **equipment inventory:** Check that installed equipment name plate data complies with specification and record equipment serial numbers;
- **materials qualification:** Check that, where appropriate, contact part materials, surface finishes and lubricants are in accordance with the specification. This may involve a review of material certificates, chemical data sheets etc., or performing physical inspection and testing of materials;
- **drawing validation:** Perform a P&ID walk-down to check that all main components are as shown and in the sequence indicated. Where appropriate check pipework slopes (is it free draining?), measure pipework dead legs and drainage air gaps, check accessibility of manually operated devices;
- **main equipment features:** Check that each main component is in accordance with the construction drawing, check critical specifications such as filter grade, perform any static checks required prior to start up, such as checking lubricant levels, drive belt tension and torque settings;
- **instrument calibration:** Check that all critical instruments have been calibrated and that the calibration is traceable to national standards;
- **spares and maintenance:** Check that adequate spares provision has been made and maintenance requirements have been considered. This may involve, for example, getting a copy of the spares list reviewed and approved by the maintenance department and then checking that all spares have been supplied, and checking that the maintenance and calibration programme for the system is in place and that equipment log book(s) have been prepared.

4.7 Operational qualification (OQ)

Operational qualification is the documented evaluation of the system to show that it operates as intended throughout the anticipated operating ranges. Typically it will consist of various functional checks on the equipment, generally performed using inert materials such as water or compressed air and in the absence of real product.

Tests should be designed to show that the equipment would perform as intended and to specification. The tests should encompass upper and lower processing limits and circumstances, including those within normal operating conditions, which pose the greatest chance of process or product failure compared to ideal conditions. These conditions are widely known as 'worst case' or 'most appropriate challenge' conditions.

For utilities it is important to show that the utility can be delivered within the requisite parameters (such as flow rate, temperature, quality, etc.) under conditions of maximum diversity (i.e. with the greatest or least preserved normal operating demand on the system from the most or least users of the system).

It is difficult to provide typical examples of tests conducted during OQ because they will be dependent upon, and specific to, the system under test, but for example the tests on a dispensary area downflow booth could consist of:

- air supply system:
  - downflow and bleed air velocity (check that when correct velocity is achieved inside the booth the volumetric flow rate is within range);
  - green zone velocity test (to ensure that the green zone of safe airflow is set to correspond to an average filter face velocity of between 0.45 and 0.55 $msec^{-1}$);
  - filter pressure differential test (to ensure that the pressure drop across each filter is within the correct operating range and to provide a baseline clean filter reading);
  - dirty filter simulation test (to ensure that the airflow rate is controlled to maintain correct downflow velocity with dirty filters);
- control and indication system:
  - temperature control and indication system (to demonstrate the functionality of the temperature control and indication system and show that booth temperature can be maintained with specified limits with maximum heat load generated in the booth);
  - dehumidification control and indication system (to demonstrate the functionality of the dehumidification control and indication system and show that booth humidity can be maintained with specified limits with maximum moisture load generated in the booth);
- containment systems:
  - HEPA filter integrity testing (check that all HEPA filters are integral and pass the DOP test);
  - smoke containment test (to demonstrate using smoke that the booth contains emissions generated within the safe working zone at both the minimum and maximum safe airflow setting, and that fresh make-up air

drawn in from outside the booth is drawn in and maintained below bench top height through to the back of the booth);

- light and sound levels:
  - light levels (to confirm that the lighting levels are within range for an industrial working environment);
  - sound levels (to confirm that the sound levels are within range for an industrial working environment);
- safety systems:
  - air flow alarm (to demonstrate the functionality of the unsafe flow alarm system);
  - emergency stop (to demonstrate the functionality of the emergency stop system and check that all devices move to fail safe condition).

OQ and commissioning

OQs demonstrate the functionality of the installed system and are often carried out as part of commissioning. Engineering commissioning is normally undertaken by a 'system' vendor and is geared to starting up the 'system.' OQ work is more concerned with the operating parameters of the 'system' and with the identification and independent measurement of operating variables over their normal operating ranges.

However, depending on how contracts are let and the responsibilities for the 'system' testing are specified, the vendor or installer may be requested to carry out certain OQ activities as part of commissioning work. For instance, in the case of the commissioning of a HVAC system, it may fall within the scope of the engineering activities to stimulate certain 'worst case' conditions such as the effects on the air pressure regime of a power dip.

The OQ protocol should require verification of the satisfactory completion of all such commissioning activities.

4.8 Handover and process optimization

Most projects undergo a period of plant handover following completion of OQ. This is normally the time that 'ownership' of the facility is transferred from the engineering function to the user function. If a main process contractor is running the project then this is often the point that completes their contractual responsibilities.

Generally, before the next stage of the validation can begin, a period of time is spent optimizing the process. Process optimization can take various forms depending upon the nature of the process and facilities. For example in BPC plants this may encompass 'solvent trials', where solvents to be used in the

facility are first introduced. This may require re-tuning of control loops that have only previously operated with water. The nitrogen system may now switch from running on compressed air over to running with nitrogen. Plant safety is clearly of primary concern during this phase.

Typically during this period operator training will be underway and the SOP's required to operate the facility, run the process, and maintain the equipment will be finalized.

4.9 Performance qualification (PQ)

Prior to commencement of PQ all operators involved must be trained and the procedures that will be required during production must be available, since they should be used during the PQ.

Performance qualification is the documented evaluation of the system to show that the system operates as intended throughout the anticipated operating ranges, under conditions as close as possible to normal production. Typically it will consist of various functional checks on the equipment, generally performed using actual product.

PQ work should be performed on systems whose performance or process parameters are critical and could affect the quality of the product. Examples of the systems requiring PQ work are pieces of process equipment such as a production sterilizer and critical utilities such as a WFI system.

As with an OQ, the critical parameters and acceptance criteria of the system under consideration should be defined. Once these have been defined, the test that is required to show the parameters are met can be designed. To successfully complete PQ work it is necessary to examine a number of consecutive batches or runs. One should also consider the variability to be expected to show that it does not affect product quality — i.e. 'worst case' conditions.

Normally any samples taken during PQ testing work will be taken by the user's personnel, not by vendors or outside contractors responsible for installing and commissioning of the system.

The contents of a PQ protocol may include for example:

- approval page;
- system description;
- purpose;
- sampling regime;
- testing regime;
- acceptance criteria;
- deviation and corrective action.

4.10 Process validation (PV)

Process validation is defined as:

'Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes.'

In essence, a PV is a PQ of the manufacturing process. As with a PQ, the critical parameters and acceptance criteria of the process steps should be defined. The parameters can be associated with the raw materials used in the process, with the equipment used, or with process variables (time, pressure, temperature, etc.). Identifying the critical parameters and understanding how each of them can adversely affect the finished product is the first step in the validation cycle.

The second step is to examine the effect of each of the critical parameters on the process to ensure that the variability in the parameter anticipated during routine production does not adversely affect the quality of the product. This procedure of examining the practical limits of the critical parameters is often referred to as 'worst case' validation or 'most appropriate challenge' conditions. It is essentially examining the robustness of the process.

The third step to successfully complete PV work is to examine a number of consecutive batches (usually three). The sampling and testing of these batches should be designed around the critical parameters. This step is what many companies have traditionally undertaken to validate their process. It is essentially examining the reproducibility of the process, and is acceptable if the process being validated is robust; but this is often not the case — hence the need for the first two steps.

The process should be considered as a series of functional steps. Each step should have a recognizable end point, or deliver a significant change to the material such as an increase in bulk, change of identity, change of physical or chemical form, change of container.

Process validation is associated with the process and not with the product. It is the list of instructions that is being qualified. An alternative process that produces the same product will be subjected to a separate process validation. Each functional step must be examined three times. In many instances a batch will comprise a number of sub-lots — it is not necessary to examine every functional step in all sub-lots of the three subject batches.

The protocol is often based on demonstration batches or manufacturing batch records. The contents of a typical PV protocol should include:

- approval page;
- system description;

- purpose;
- sampling regime;
- testing regime;
- acceptance criteria;
- deviation and corrective action.

Process validation data is presented as a report. It is important to note that it is the review of all the batches involved together, not a series of separate individual reviews.

4.10.1 Retrospective process validation

When a product has already been manufactured successfully for at least three years (and at least twenty batches have been made), a statistical review of all the data pertaining to at least the last twenty batches can be carried out.

No batches may be omitted from this review unless documented reasons are included to explain each individual case (examples would include equipment failure, or contamination not associated with the process). If more than 20% of past batches are omitted, the retrospective process validation should be abandoned, as it is likely that influencing systems are not under control. Only when these are identified and addressed should the validation project recommence.

4.10.2 Sterile products

Process validation for sterile products can be considered in two parts:

- validate the process to gain assurance that the system can deliver a sterile product. This would include, for example, themal mapping, thermal commissioning, filter integrity testing and control systems testing;
- validate the manufacturing process of the actual product including process technology and biological testing.

4.10.3 Bulk pharmaceutical chemicals (BPC)

For BPCs process validation starts at the point where the drug substance is chemically formed or where other impurities will not be readily removed.

4.11 Cleaning validation

The creation and implementation of effective cleaning processes is an essential part of any pharmaceutical production process. The two main reasons for this are:

- to ensure that the appropriate level of general cleanliness is maintained in order to prevent the accumulation of dirt and microbial contamination which could affect the quality of the product;

- to minimize the risk of cross-contamination from one active product into the subsequent product, which could lead to serious adverse effects on patients. Cross-contamination could also result in degradation of the main product and loss of potency.

4.11.1 Choice of cleaning method

Various approaches can be taken to ensure that cross-contamination levels are minimized between two different products.

The simplest approach is to dedicate a complete facility, its building, services and equipment, to a single product. Obviously this is a very expensive approach, unless the product is required in sufficient quantity to justify a dedicated facility. For very active products such as penicillin, cephalosporin and hormones, where cross-contamination at very low levels is not acceptable, this is the safest option and is a regulatory requirement.

In dedicated facilities effective cleaning procedures still need to be developed and validated, although the stringent cross-contamination levels that are usually applied to multi-product facilities can be relaxed somewhat and the emphasis placed on general levels of cleanliness in accordance with GMP.

In most circumstances though, facilities are multi-product and effective cleaning processes must be developed and validated by means of sampling and measuring the levels of cross-contamination.

The most common type of cleaning process involves the full or partial dismantling of equipment, followed by solvent washing and subsequent drying of the separate parts. Water/steam (with or without added detergent) is the most common cleaning solvent, but organic solvents can also be utilized.

Manual cleaning is still used extensively in the pharmaceutical industry but 'clean-in-place' (CIP) systems are rapidly expanding and 'sterilization-in-place' (SIP) is also being introduced.

It is quite common and also highly desirable to dedicate specific parts of the equipment which are difficult to clean, thereby reducing the overall time and cost of the cleaning process. Examples of this are the woven fibre filter bags used in fluid bed dryers or the rubber/plastic o-rings found in pipework.

These examples illustrate the importance of designing an effective cleaning process using a variety of techniques before embarking on any validation work. Remember, successful validation will only confirm that the cleaning process is effective, it will not make an ineffective one effective!

4.11.2 Measuring the level of cleanliness

As part of the overall validation programme the actual level of cleanliness that has been achieved by the cleaning process must be measured. This involves a three-stage process:

- a sampling method to detect and pick up the remaining contaminants;
- a method of analysis to quantify the amount of contaminant remaining;
- a calculation to extrapolate the results.

The usual sampling methods are:

- swabbing;
- aqueous/solvent rinses;
- non-active product follow through.

(a) Swabbing

Swab testing involves the use of dry or solvent impregnated swabs, which are wiped over a known area of the processing equipment. The contamination picked up is extracted in the laboratory by soaking the swab in a suitable solvent, and the solvent is then analysed to give a quantitative result. The total quantity of the contamination is calculated by multiplying the total area of the equipment by the swabbed area. In practice, the swab is unable to pick up 100% of the contamination, but it is possible to run a laboratory test beforehand to estimate the percentage pick up. This is done by deliberately contaminating the stainless steel plates (or sample of whichever material is in contact with the product) with a known quantity of contaminant, usually letting a solution evaporate on the plate. The plate can then be swabbed and the swab analysed to demonstrate the percentage of the contaminant that has been picked up. The analytical method must also be checked to ensure that the swab itself does not interfere with the result by running blank swab tests.

(b) Aqueous/solvent rinses

Aqueous/solvent rinses are commonly used in areas where it is difficult to swab (such as pipework or a sealed reactor in a bulk chemical plant). The method involves rinsing with a known volume of water/solvent and then analysing a small quantity of the rinse. The total amount of contaminant is simply:

$$\frac{\text{Quantity in sample} \times \text{Total volume of rinse}}{\text{Volume sample}}$$

The solvent used must provide sufficient solubility to pick up the contamination effectively but must not degrade the contaminant. The contact time must be controlled.

The main drawback of this method is that only material dissolved in the rinse water/solvent would be analysed and it would not be possible to find out how

much was left inside the pipework, vessel, etc. The solubility of the contaminant, contact time and physical force of the rinse will all affect the final results, and it may not be possible to ensure all the areas have been adequately rinsed.

(c) Non-active product follow-through

The non-active product follow-through is sometimes used, and involves processing a non-active substance through the whole process and then analysing samples for the contaminant. The calculation is analogous to that used for the rinse method, but this method has the advantage that it mimics the real situation of a subsequent batch being processed, and that it covers all the equipment involved. However, as with the rinse method, only the contaminant that has been picked up can be measured, and not the contaminant left behind. Also, in the case of solid dosage forms, the contaminant may not be uniformly mixed throughout the non-active substance.

The swabbing method is generally preferred because it permits the areas likely to be most heavily contaminated to be targeted more thoroughly and also makes allowance for contamination not recovered, provided the laboratory tests are undertaken. Despite all this, it is still prone to variability since no two samplers will swab in exactly the same manner. The inherent variability in any of the sampling methods is one of the reasons for the use of a 'Safety Factor' when calculating the acceptable contamination limit.

4.11.3 Setting limits

When a cleaning process is used only between batches of the same product (or different lots of the same intermediate in a bulk process), it is normally only necessary to meet a criteria of 'visibly clean' for the equipment. Such between-batch cleaning processes do not normally require validation.

Chemical cross-contamination limits

One of the basic concepts of validation is that a process is proven to be capable of performing to a *pre-defined limit*. There is no exception with cleaning validation and although agreeing a pre-defined limit can be difficult, it is essential to establish one prior to commencing the validation work itself.

As there are often no obligatory legal or regulatory limits, manufacturers have come up with their own viable methods for setting limits.

The simplest of these methods is to set a blank limit to all products. A typical limit would be 1 to 10 ppm. This approach has been used in the bulk pharmaceutical chemical production and product development areas where a large number of compounds are processed and for many of them relatively little is known about their properties. The scientific rationale for limits in the region of 1 to 10 ppm is that this is somewhere near the limit of detection for suitable

analytical methods for many compounds, and pharmacopoeia limits for heavy metals and other adulterants tend to lie in this region. The problem with this approach is it makes no allowance for the different pharmacological effects of different compounds. This will lead to excessive cleaning and wasted time and resources in some cases, whilst in other cases it may leave patients exposed to potentially hazardous levels of contamination.

Several companies have adopted a limit where the maximum amount of contaminant (A) that can be ingested by a patient taking the product B, manufactured immediately after product A, is one thousandth of the minimum normal therapeutic daily dose. The figure 1000 is used as a safety factor, which not only reduces the daily dose below pharmacological activity level but also allows for the errors inherent in the sampling and testing methods used.

Finally, the limit of detection for the assay method must be considered. Setting a limit of 0.001 mg per swab when the assay limit is 0.01 mg is pointless. Either the assay method needs developing, or the limit of assay will have to be the acceptance criteria.

Microbiological cross-contamination limits

Most cleaning validation protocols do not include sampling and testing procedures for microbial contamination. This is because the sterilization itself is validated for processes where minimization of microbial contamination is important (sterile and aseptic).

It is important that the cleaning procedure does not actually increase the level of microbial contamination. This requires the cleaning agents to have a low level of microbial contamination, and the drying procedures to adequately remove all traces of water. Storage of equipment is also important — it should be kept clean and dry and well covered or wrapped. There should be a maximum storage time defined, after which the equipment is cleaned again.

Where it is felt necessary to confirm that a particular level of microbial contamination has been achieved, swabs can be impregnated with a suitable growth media. The use of media impregnated swabs or media solutions will itself contaminate the equipment, which must be cleaned thoroughly before routine use.

4.11.4 Validation of CIP systems

For CIP systems there are several steps to be undertaken before any actual sampling and testing is carried out.

CIP validation cycle

- Assess design of CIP system including analytical method development;
- Experimental work to optimize cycle and cleaning agents and including analytical method validation;

- Change control system;
- Operational qualification;
- Cleaning validation protocol;
- Cleaning validation report for three successive cleaning cycles.

CIP systems are usually fitted to large immovable pieces of equipment, such as dryers and coaters. Often the CIP system will adequately clean the large flat surfaces of the equipment, but will leave excessive amounts of material in the corners, crevices, inlet/outlet ports, and around and behind seals and flaps. Therefore, before starting with validation protocols, the design of the CIP system should be assessed to eliminate (or at least minimize) any obvious weak areas. For example, one simple test often performed to determine coverage involves coating the item to be cleaned with an appropriate dye, then operating the cycle to determine if all the dye can be removed. If alterations to the CIP system itself are impractical, then it may be possible to remove part of the equipment for separate manual washing.

The main advantage of a CIP system is that it should provide a reproducible cleaning process. This process needs to be effective and optimized to provide the best chance of successfully validating the cleaning process. Experimental work can be performed using different wash cycles, rinse cycles, detergent types, drying conditions, etc. to establish the most effective conditions. If a range of products is to be cleaned then experiments should be performed on the most difficult to clean product.

Having established the most effective conditions, the CIP system and cleaning cycle should form part of the formal OQ for the equipment, to demonstrate that the critical parameters used in the cleaning cycle can be satisfactorily achieved and reproduced.

In parallel to the experimental work and OQ activities, analytical methods will have to be established and validated.

Finally, the cleaning validation/PQ protocol can be written and executed. This protocol can be either a stand-alone document or part of the general PQ protocol. Either way, the cleaning validation protocol is specific to a particular changeover between two products on a specific set of equipment.

The protocol should include the following sections:

- definition of equipment being used;
- definition of the product(s) being cleaned from the equipment, and the product that will subsequently occupy the equipment;
- explanation of the parameters being used in the cleaning process (temperature, times, pressures, detergent types and concentrations, etc.);
- sampling regime (sampling method(s), number and location of samples);

- testing procedures (description of tests to be performed on samples);
- acceptance criteria (acceptable maximum levels of contamination in each of the samples).

The validation protocol should be performed on at least three successive occasions to demonstrate reproducibility.

When the analysis of the samples is complete, the data should be collated, summarized and presented in a validation/PQ report. Comparison of the data to the pre-determined acceptance criteria will form the basis of the conclusions. Any missing data or data that is outside the acceptance criteria should be accompanied by an explanation. If the validation has failed then the cleaning process will have to be altered and the work repeated.

On completion of a successful cleaning programme, the validated cleaning procedure must become subject to the plant's change control system.

4.11.5 Validation of manual cleaning

Manual cleaning validation cycle:

- Experimental work (optimize cleaning method, drying cycle, etc.);
- Change control system;
- Prepare standard operating procedure (SOP);
- Operator training including retraining/re-evaluation;
- Evaluation of training;
- Cleaning validation protocol;
- Cleaning validation report.

Most equipment is relatively small, easily dismantled and portable to facilitate frequent and rapid cleaning. Operators often dismantle, clean and reassemble the equipment.

Operators are people and are therefore variable. Whilst it is virtually impossible to totally eliminate this variability, it can be minimized to an acceptable level by the use of clear and concise instructions (SOPs) together with regular training and assessment of the operators. Part of the validation of any manual cleaning method should involve the evaluation of the process to determine the level of variability — a high variability (even if within acceptable limits) suggests a process that is poorly controlled.

The actual validation protocol will be very similar to that used for the CIP system validation, but it must refer to any SOPs associated with the cleaning procedures.

4.12 Computer system validation

Automated or computerized systems are validated using the same general validation approach identified for equipment and utilities. However the nature of computer systems means that certain activities become particularly critical. A software programme is not a tangible thing and cannot be tested exhaustively (i.e. with large programmes it is impractical to prove the code) since to test every possible path through the code under every possible set of circumstances would take an inordinate length of time. For this reason the quality and confidence must be 'built in'. Software development must be carefully planned and controlled under a quality assurance system following a life-cycle approach. It should be noted that the term 'computer system' refers to the computer hardware and software as well as the interface between the computer and the machine/plant/environment.

Various models have been developed for the validation of computerized systems such as that proposed by IEEE (IEEE Standard for Software Verification and Validation Plans); the PDA report on the validation of computer-related systems or the GAMP (Good Automated Manufacturing Practice) Supplier Guide for Validation of Automated Systems in Pharmaceutical Manufacture. All these models are fairly similar. This section will not cover in detail the 'engineering' associated with the design, development and testing of computer systems but will concentrate on the validation activities associated with each stage.

4.12.1 Assessment of computer systems to determine validation requirements

The necessity for computer system validation is based on several criteria. The first of which is that the element in question is to be classified as a computer system (for example, some instruments may be programmable and may or may not be treated as a computer). The following criteria should help determine whether the element is a computer system:

- **inputs and outputs (I/O):** The presence of physical channels (digital, analogue, pulse, serial, etc.) for importing or exporting data that is used or has been calculated by the element;
- **memory:** A means of storing executable code is used;
- **Central Processing Unit (CPU):** Use of a device for interpreting executable code using data accessed from inputs, and presenting the result via outputs.

If all the above criteria are present then the element can be assumed to be a computer system and should be treated as such from a validation point of view.

The next step is to determine if validation is required. This involves a process of evaluating the role that the computer system plays. Assessment criteria include:

- **GMP implication:** Generally any computer system with GMP implications should be validated. This includes for example critical operations such as controlling or monitoring operations that can affect product quality;
- **system functionality:** If the computer system is only used for supervisory tasks, with no computer-generated information being used by or forming part of the batch record information then generally the computer system does not require validation;
- **safety critical systems:** Although GMP does not cover safety critical systems, there is a good argument for them being treated in the same way;
- **system configuration:** Although a computer system may be involved with critical operations, it might be that another independent system provides a full check of the operation of the computer system. In this case the computer system does not generally require validation;
- **system operability:** Although the system may be computerized, the corresponding operating procedures may introduce so many manual operations and checks that all computer controlled operations are duplicated by the way the system is operated. In this case the computer system does not generally require validation.

Once it has been determined that computer system validation is required, the detailed validation activities will need to be determined. The extent of computer system validation depends upon two main factors — the level of standardization and the complexity of the system. A standard system has been largely validated by its wide use, so most of the validation effort should go into validating the system with respect to the user's particular circumstances. The issue of system security (prevention of modification or reconfiguration) must also be addressed. Generally the simpler the system, the less validation effort is required. There is a risk that because simple systems are easier to understand they tend to be more 'fully' validated. Instead increased emphasis should be placed onto more complex systems.

These two criteria should be applied to both the computer hardware and software.

Hardware

The hardware can be classified as either standard hardware (produced in large quantities over an extended period) or application specific (mainly produced for the applicable project only). Both will require validation but the approach to

standard hardware is simpler, mainly being concerned with the configuration, installation and functional testing aspects. The design and design process must also be considered for application specific hardware. This may involve assessing the methods employed, critical components, compatibility between units, standards used for design and testing, type testing carried out, etc.

Software

There are generally three types of software that can be identified for computer systems:

- **system software:** This is the software required to run the computer system itself. It includes all the operating systems (the software controlling the CPU, memory, I/O, operator interfaces, etc.) as they are configured for a particular computer system. Normally this software does not require validation because it is classified as 'standard software' (see below).
- **configurable software:** As the name implies, this type of software would normally be standard software, which can easily be adapted to an applicable project, such as Lotus 1-2-3 for example. The software purchased from Lotus is classed as standard software, which does not require validation (because of the wide use of this software), but its use with formulae applicable to a specific project must be validated. Configurable software is also sometimes referred to as 'canned software'.
- **application software:** This software is produced or configured specifically for the applicable project and must be validated.

The term 'standard software' is often used as a reason for not performing validation. The following criteria may be used to determine if a piece of software is standard:

- **the supplier's QA system:** Ideally this should be a recognized system such as ISO9000 or similar and it should demonstrate that development and testing of the software is controlled and documented;
- **the product being widely used:** This is generally interpreted as meaning more than 100 similar units. It is of further advantage if the software has been applied to a wide range of applications, and thus more thoroughly exercised and tested;
- **product age:** Product history and experience including knowledge of 'bugs' will increase with age. Standard software is usually expected to have been in wide use for a minimum of twelve months.

- **version control:** Software is usually developed and corrected during its life-cycle. The number of software versions can be great, so a system of version control must be in place to be able to take all versions into account with respect to product age and usage;
- **user feedback:** The vendor must be able to demonstrate that feedback from users is handled and acted upon;
- **not application specific:** The software cannot be classed as standard if parts of it are specific to the particular application.

If all the above factors are fulfilled then the software can be classed as standard and does not require validation. However the computer system may still require validation including functional testing.

The results of the above assessment should be documented and included in the Validation Master Plan.

4.13 Analytical methods validation

Analytical methods can be validated in a number of ways. Compendial methods such as methods appearing in the USP are generally considered validated, but it is important to demonstrate that the method works under the actual conditions of use. If a compendial method exists but a company elects not to use it, they must demonstrate that the in-house method is equivalent or superior to the official procedure.

Validation data from repetitive testing should be consistent, and varying concentrations of test solutions should provide linear results.

4.14 Change control and revalidation

4.14.1 Change control

All process and plant subject to validation should be covered by a change control system that enables formal reporting and recording of changes, reviews the impact of a change on the validation status and permits revalidation requirements to be identified.

Change control standard operating procedures should define which changes do and do not require change control. Generally, items subject to change control include:

- procedures that contain validated activities or processes (for example, cleaning, equipment operation, sterilization);

- process equipment and plant;
- facilities;
- utilities;
- production processes;
- commodities (primary packaging components, filters, sterile clothing, disinfectants, cleaning agents);
- raw materials;
- computer systems;
- test methods and specifications.

Standard operating procedures and change control forms should allow all proposed changes to be considered, commented upon and approved or rejected by relevant experts. These experts generally represent Quality Assurance (whose authorization is always required), Production, R&D, and Engineering, though other experts may be consulted as necessary. Reviewers should identify whether the change needs to be validated and, if so, outline the nature and extent of validation required.

It is recommended that change control forms reference qualification protocols in those cases when revalidation is necessary. The date of re-introducing the process or plant subject to change into operation should be recorded so that it is clear that revalidation, when required, has been completed before use.

On occasions, where an emergency situation occurs, an unplanned change may have to be implemented without prior formal consultation. In such cases details of the change should be introduced into the change control system as soon as possible.

Where a planned change is not approved, it must not be implemented. Where an unplanned change is not approved, the process or plant must immediately be returned to its original state.

4.14.2 Revalidation

In order to maintain the plant, facilities, systems, procedures, methods and processes, once initially qualified, in a state of validation throughout their life-cycle there should be continuous review of the need for revalidation and implementation of revalidation whenever it is agreed to be necessary.

Revalidation requirements should be defined based on a technical review of the initial qualification(s), change control data and documentation supporting the performance of the item subject to validation. Revalidation will be undertaken if a change is likely to affect the validated status or if the

performance of the validated system is seen to have deteriorated. Revalidation exercises should be built into the Validation Master Plan.

The need for revalidation may be identified via several mechanisms:

- through a change control procedure;
- by regular review of the performance of a validated item to a predetermined schedule;
- by the use of a plant certification system;
- through annual product reviews;
- through internal audits.

Critical items of the plant are frequently covered by a routine certification and re-certification programme. Revalidation intervals and the test to be conducted are normally specified at the time of certification.

Summary

The key points from this chapter are as follows:

- validation is required to provide documented proof of GMP compliance. Validation activities should be organized as a scientific study that follows a life-cycle approach;
- validation activities should be conducted in accordance with pre-defined company validation policies and procedures under a validation master plan;
- the validation master plan(s) should define what will be validated, describe the validation approach to be adopted (this will reference the policies and procedures developed) and explain how the validation work will be organized and related documentation will be controlled;
- the validation activities should be lead by a validation team, which should consist of members from relevant disciplines participating within the project including members of the QA/QC function. The team will be responsible for organizing the validation activities and reviewing and approving associated documentation;
- the processes should be evaluated to determine what aspects are critical and require validation. This may include determining critical process steps, critical parameters and critical instrumentation and systems;
- in parallel with process evaluation, systems and system boundaries should be defined. This allows validation work to be broken down into logical, manageable sized packages and concentrates the validation effort in the most important areas;

- cGMP reviews should be performed at key points in the project life-cycle to confirm that the design complies with cGMP requirements and the specification;
- User Requirement Specifications (URS) should be prepared by the user for each system to be validated to formally document the final process requirements. These will form a key part of the basis for subsequent validation activities;
- validation activities should be documented and controlled through the use of qualification protocols and reports, typically these will fall into categories including DQ, IQ, OQ, PQ and PV.