4
SPECIFICATIONS AND QUALITY

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QualityÐa philosophy

In a cost-conscious world, companies have to be efficient to survive, and products need to be competitive to satisfy the consumer. Where two products compete for the same market, and in the same price bracket, the consumer will search for some advantage to aid the final product choice. Quality is the advantage normally chosen, and this fact is as relevant to the purchasing and selling organisation of the large national and international company as it is to the domestic consumer.

The lesson that quality sells (in particular, realistic quality sells) is, and has been, a hard lesson to learn, particularly when domestic markets become the targets for imports. However, companies that survive the attrition of more quality-conscious competition will themselves eventually develop and exhibit the same superiority in their marketing and manufacturing operations.

The evolution of quality assurance (QA) and quality control (QC) in industry has been a blend of the legally and regulatory imposed standards (since legislation is a quality control over national standards), together with the competition from the occasional far-sighted company, which imposes on the market its own advanced quality standards, leading to imitation by other companies for commercial purposes.

Any examination of the development of QC technology, which now falls under the broad umbrella of QA, will reveal that it closely parallels the history of the mass production industry. This is not difficult to explain, since the simplified, long-running processes that are the efficiency of automation remove the individual craftsmanship and skill that were once required for ‘quality products’. Once this step was taken, the need for an independent responsibility for quality was an obvious reaction, and most of industry now operates with a quality check ‘separate’ from the production process (in the same way, responsibility for machine setting, repair and maintenance has been delegated to specialist departments).

In recent years it has been recognised that it was perhaps impetuous to divorce QC completely from the production process, not because the concept of an independent QC function was itself wrong, but because:

1 QC operates retrospectively to check the quality of what has been made
2 quality cannot be ‘inspected’ into a product after it has been produced (i.e. its immediate actions are limited to the release of conforming product and the recovery and investigation of defective batches)
3 production should be encouraged and organised through formalisation of good manufacturing practice (GMP), proper work training and staff motivation to manufacture to the agreed quality standard, i.e. ‘make right first time’
4 the quality organisation (QC and QA) must be proactively involved in material, product, process and staff development to ensure that quality and process efficiency are not just fully compatible, but are mutually self-fulfilling.

Close liaison between QA and production will more efficiently blend the reliability of an independent QC operation with the higher initial manufacturing standards of the positively motivated manufacturing operator. This degree of motivation has proved achievable using the well-documented techniques of quality circles and company programmes of continuous improvement i.e. parts of ‘total quality’.

The intention and purpose of a correctly organised QA operation must be to aid the company in efficiently producing a specified product which is cost-effective (to the company) and meets the desired requirements (of the customer). This purpose should not be limited by the boundaries of a normal production environment, but be free to co-operate in all phases within the company (development, marketing, etc.) and outside (supplier, sales, customer reports and complaints, etc.).

This approach automatically leads to a quality examination at two levels:

1 quality of design
2 quality of conformance.

Quality of design

This term has been defined as 'the quality specified or required by the customer', and requires active participation between the quality management and the total development function to finalise design standards which will allow and aid manufacturing compliance (with the supplier or sub-supplier organisation as well as with the customer). Additional attention has to be directed to the manufacturing facilities, documentation systems, process and staff training, which together will prevent quality deviations at source.

The quality of design is normally associated with the responsibility of QA, and an important element is the practice of validation and qualification.

Quality of conformance

The assessment of component quality once the manufacturing process is partly or fully completed allows only for a measurement of product conformance and, if a problem is revealed, some remedial action. Limited conformance testing lacks the essential anticipation that prevents problems and does not merely detect them. Therefore, as means of 'controlling' quality, this simplistic regime of QC is a very poor tool.

This does not mean that the role of conformance testing in a practical QC organisation can be minimised, or that effort need 'only' be directed into designing systems. On the contrary, any efficient organisation must employ conformance testing in maximising the quality of production. Close co-operation between production and quality control, with production technicians carrying out multiple scheduled product checks, supported by the QC conformance test, ensures effective process controls, maximises production efficiency, minimises wastage and provides feedback to management and development. However, QC is the final release authority in meeting the standards required by the customer or legislation.

Within a company, QC action is directed at three areas: raw material control, process control, and finished product control. The approach in setting up a system will be very similar in each case, i.e. design into the operation all the parameters that will bear on the manufacture of quality, followed by a means of establishing that conformance has been achieved. (An important element of this is the continuing revalidation that processes continue to perform as specified.)

To generalise by using the examples of raw material/component control: once the product has been made faults either cannot be, or are expensive to, put right or remove by sorting. QC must therefore be involved with the design and development of the raw material/component, the choice of supplier (by evaluation), the pre-production trial of components, the setting of universally acceptable/achievable standards, the testing of components (at the supplier and in-house) and the in-house efficient use of those components with referral to the supplier of any defectives. Unnecessarily highquality components are expensive and wasteful of resources, to the customers and suppliers, while supposedly high-quality components can justify their sometimes higher initial purchase cost by increased in-house usage efficiency and the avoidance of customer complaints.

It is without argument that low-quality components (i.e. those that do not fully meet the desirable requirements), while sometimes being initially cheaper to purchase, will eventually produce lower in-house efficiency, coupled with lower finished product quality.

Priority of the QC resource will usually be directed at the more 'important' component, but this attention should be balanced by consideration of the ultimate usage (see Figure 4.1). The example shown in Figure 4.1 illustrates several points.

1 It is necessary to know the in-house requirements plus the supplier's abilities before setting component standards.
2 A supplier of variable quality can meet the requirements of a customer whose rejection threshold for defectives is high.
3 A supplier that lacks in-process controls or pre-release inspection will invariably fail acceptance by a customer that requires exacting standards for either product or process efficiency.
4 A supplier with in-process controls and/or release inspection sympathetic to the customer requirements will invariably meet expectation.
5 A customer with an approved quality systemised supplier can employ reduced levels of component inspection, supported by low-level supplier audits.

This fairly simple example illustrates the need to review the quality route between design and conformance. Similar examples can be found in the QC role for process quality as well as finished product quality, but the following discourse, in order to be comprehensive, will concentrate on raw material control.

To conclude this introduction, it is perhaps necessary to generalise on a philosophical level.

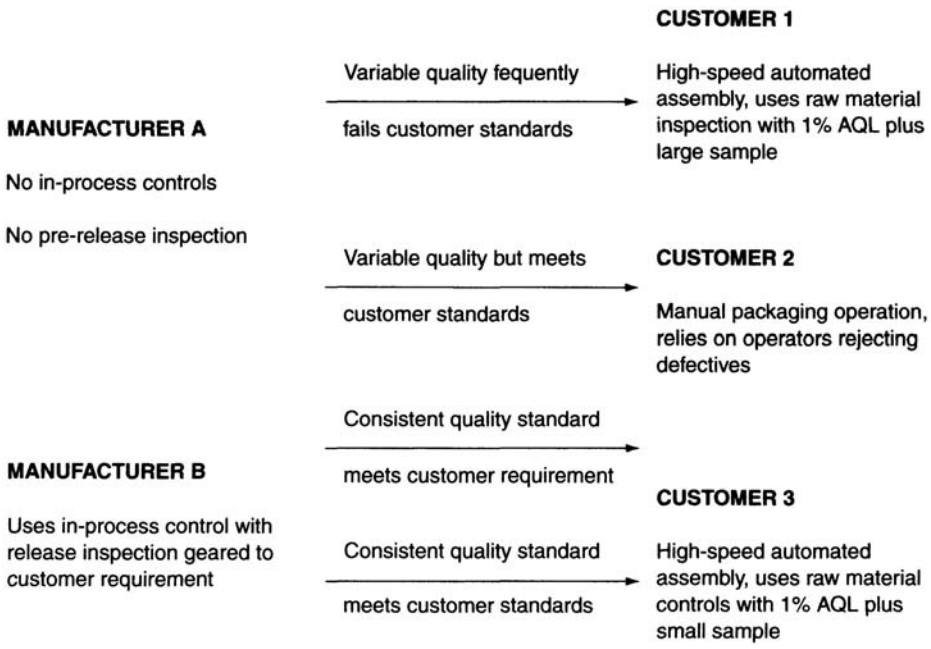

Figure 4.1 Manufacturers' quality policy and customers' standards

1 All personnel employed in a manufacturing organisation will have an impact on product quality. In some areas this is a direct effect, as in production or the support areas of QC and engineering. The impact from the areas of marketing, sales, development, training, purchasing, etc. may be less direct, but it is no less fundamental to the total product quality.
2 All manufacturers are both suppliers and customers and should maintain the same consistency of policy over quality whether they are dealing with internal or external sources.
3 Suppliers and customers must appreciate that they are simply opposite ends, and not opposing ends, of the same quality chain. To achieve the maximum potential of their combined product resource, it is necessary to work together as one development and quality team.

The first part of this chapter therefore concentrates on the QC function and the statistical appreciation required to progress a QC operation successfully. QA, which aims at building-in quality and defect prevention (rather than defect detection), although involving statistics to obtain data (e.g. statistical process control), relies more on regimented procedures and documentation to keep validated processes under control.

Material specifications and quality standards

In discussing packaging quality standards it has to be agreed that no component quality examination can start before construction of the material specification, and the reverse is equally true. The final component specification and the quality inspection procedure must be viewed together, and completed to a similar time scale to realise maximum component potential fully.

In the pharmaceutical industry, while drug research or R&D is formulating the active product, basic packaging presentations will be vetted as primary containers (i.e. for material stability and compatibility). However, once the drug moves into the production development interface, its total packaging design and application for production, distribution, market (and supplier) necessitates close formal liaison between the writers of the component specification and the quality inspection procedure.

Acceptance of this formal liaison introduces the concept of the 'quality project team', in which the original research container can be transformed into the viable component which is designed and manufactured to meet the needs of all parties.

The team should comprise delegates from marketing, development, production, engineering, purchasing and QC. This should be formed once drug research and marketing research have completed their broad packaging brief and have clearly established a viable project.

Responsibility for the final specification must still reside with the specific functional heads responsible for component design and QC test and standards. Hence, if formally required, these functions would provide the project's co-chairmen.

The team activities would concentrate on:

- *aesthetics:* acceptability to ultimate customer or patient
- *component dimensions:* interrelationship with other components, machine, etc.
- *machine requirements and limitations:* line speeds, tolerances, setting ranges, reliability
- *marketing/production:* batch sizes, frequency schedules
- *stock policy:* availability/cost, storage temperature/humidity, shelf life
- *distribution:* unit/collation size, weight, fragility, environmental
- *legislative regulations:* pack size, fill weight, number of items, print labelling
- *supplier:* abilities and limitations.

Although it is not always included as a direct member of the project team, decisions and actions must be agreed with the supplier (see below), since it is the supplier that has the specific technology to make or break the specification.

It cannot be over-stressed that the long-term suitability of the component and the efficiency of the production operation depend on the relevance of the component design. Deficiencies in design can be partially offset by extensive testing and sorting during or after manufacture, but full compensation will never be entirely feasible without redesign. It is for this reason that the importance of design must be recognised and accorded the resources of the project with a realistic time scale concurrent with the actual drug project.

It should be noted that quality audit and vendor rating systems need not only assess the manufacturing capability of a supplier, but may reflect on the quality of its design capability. A poor design, or a design with inherent deficiencies, has a lower chance of achieving high quality. A supplier desperate for new orders has been known to accept knowingly a poor design from an aggressive customer.

The project team should progress design studies through hand-made samples (produced in connection with the supplier) to a first machine sample. Where practical the first machine sample should be used to confirm the supplier's technical ability to quantity-produce the component, as well as the purchaser's design theory. To this end the machine sample for a plastic or moulded glass component should be from a single cavity tool, or for a folding box board carton, from a one-up die (as an intermediate stage to multi-cavity or multi-die production).

Samples should be assessed by laboratory, production, and marketing with the conclusions and recommendations recorded in the minutes of the project team's report.

A useful tool during component design is a failure mode and effect analysis (FMEA). This involves a detailed examination of the design, its uses and application, to determine how it can fail and the consequences of failure. By eliminating potential risks at that stage it is possible to produce a robust design meeting all design requirements, without the eventual need for in-production cures and delays involved in a design revision.

Once all departmental activities are satisfied, with redesign and resamples if necessary, metal should be cut for the full production tool, but on the understanding that further purchaser evaluations must be completed before tool acceptance (or, for example, before a mould is finally plated or hardened).

A component is more likely to complete a satisfactory working life, to the purchaser's and the supplier's benefit, if the project team co-ordinates design study and component trial before commitment to production use, i.e. the purchaser's production use of the first consignment of components should not be the first time that newly developed components have been tried under production conditions.

The component specification

Unlike many commercial operations, most pharmaceutical components are special to each and every pharmaceutical company, although fortunately some commonality will occasionally occur. In fact, distinct technical and commercial advantages exist when a universally common component can be standardised, either by demand or consent of supplier, purchaser or market legislation. These can be to industrial standards (TAPPI), national standards (BS, British Standards; MIL, Military Standards; USP, United States Pharmacopoeia) and international standards (ISO).

For either situation (i.e. of a special or common standard component) the purchaser must document the component specification. The specification must be approved and authorised by the relevant departments of the organisation and accepted by the supplier as the contract specification.

It is now fairly normal procedure to have a general support document, i.e. packaging material manual, issued under specific headings such as bottle glass; bottle plastic; laminations; labels; leaflets. These broadly describe the requirements of the items including reject (defect) terminology and possibly associated AQL. Such manuals provide suppliers with a broader view of the quality expected, and may cross-reference the details of the test procedures, including performance, to be applied (see below).

Quality standards

Policy

No one will argue with the statement that the purchaser has the right to obtain what he or she has contracted for. The initial basis for this expectation must be the agreement between supplier and customer to use the formal component specification. Although the component specification is intended to be contractual, it is sometimes misinterpreted as merely stipulating the intentions, the expectation or the target.

All manufacturing processes have a natural variability, through drift in machine settings, variable raw materials, variable operator standards, etc., and will therefore yield components which also vary. The quality project team, with the supplier, must assess the process capability of the component manufacturing process to ensure that it is capable of producing to the desired quality which always meets the customer's requirements. It is only to be expected that indifferent quality will result if the manufacturing process capability does not match the specification requirements.

The quality control procedure can be viewed as the framework built around the component specification which will translate the development laboratory target (ideal) into the mass production consumables (practical). The quality procedure is devised to achieve consistency of component deliveries by realistically:

1 identifying the total component requirements (of marketing, production, etc.) by correlating practical background experience with the same or similar components against tolerable variability both within and outside the specification, i.e. with relevant defect definitions, AQLs, etc.
2 producing a realistic test regime under which materials can be tested and assessed at both the supplier and the purchaser
3 establishing, and if necessary developing, the supplier's ability (through audits, training programmes, inter-company visits, lists of 'acceptable' suppliers, etc.) to meet the quality demands (see below).

To realise the optimum quality requires a total understanding of the handling and manufacturing processes of supplier and customer. Too high a quality will prove financially expensive to the purchaser, but will also be punitive or restrictive to the supplier that tries to achieve it. Too low a quality can result in purchaser rejections, greater machine downtime and running inefficiency, extra wastage in sorting and in-use complaints.

Optimum quality standards necessitate early involvement between development and QC and close liaison with the supplier (which must be compatible with the full production schedule). A variable-quality product (through design or conformance defects) can interfere with or interrupt the efficient operation of the purchaser's entire production line, possibly leading to variability with associated components (e.g. closures that do not fit containers) and with the pharmaceutical product (e.g. capping difficulties leading to machine stoppages will increase the fill variability of a liquid filling line). This cannot but reduce the ultimate quality of the pharmaceutical presentation as received by the user (hospital/doctor/patient).

Suppliers, particularly of a newly designed component, must be encouraged to participate in fault-finding/debugging of the component, both during the initial trialing period and in early manufacturing batches. This can be greatly aided when a supplier incorporates statistical process control (SPC) into its routine process controls, which relates defects to causes and then removes those causes.

It is to identify and emphasise the fact that, in spite of the efforts of quality project teams, defects can occur, and specification details can be unrealistic, that the first component specification and the first QC procedure must be considered provisional. A review of both documents should be the last operations of the quality project team within an agreed time scale, say after the first five deliveries, or 6–12 months. This will allow practical experience through manufacture, distribution and use to be applied to the final specifications.

The regular review and updating of all specifications and test procedures must be a normal part of the internal disciplines of technical departments. This is separate to the specific responsibilities of the project team engaged on a new component, and tends to expand specification details as specific points arise. Although this may be the inevitable way of quality progress as knowledge grows, the reverse may also be true, e.g. unique quality parameters included in the original specification may be redundant through production, process or market changes. While the review should include opportunities to expand or contract the specification, the updated document must cross-reference all changes.

Procedures/specification

The purpose of QC is to determine compliance with an agreed standard, i.e. whether it passes or fails. Ideally this simple approach maintains the independence of QC and keeps it separate from any commercial expediencies. This does not imply blind adherence to the specification, but simply that if standards are correctly devised, then apart from a 'crisis' any failure against the specification must by definition be unacceptable.

It is for this exceptional crisis that the quality procedure must include a route for concessions, whereby material normally considered unacceptable can (after full inter-or intra-department agreement, possibly involving machine and distribution trials, product functional tests, etc.) possibly be given a qualified release. The decision to release must not be the sole responsibility of QC, but a group decision in which QC is one member (the one with the initial data on the problem).

Following this concession two actions are implied:

1 to determine the causes, with the supplier, of the reason for the defective consignment, and to introduce supplier remedies which prevent repetition
2 to monitor the 'released concession batch' through the company and assess its effects.

If a concessionary batch performs satisfactorily in all areas, this information could allow permanent modification to the specification, or revision to the defect rating of that particular fault. This will not always be desirable when the production requirements are for a 'tight' specification to aid high-speed line performances.

All opportunities presented by defect detection in incoming materials should be taken to monitor the validity of the QC standards. This, as stated earlier, should be a formal procedure, say within 6–12 months or five deliveries of a new component, but can also take place outside this convention.

With the exception of a 'concession', the quality procedure needs to be as precisely defined as the component specification. It will, of necessity, follow a similar format (Table 4.1).

Conformance testing

The QC testing programme for component assessment can be simple or complicated, depending on:

1 the Company's policy on product and market risk (this policy is sometimes qualified by national and international regulatory requirements)
2 the degree of QC resource available
3 the type of material under examination (e.g. moulded glass containers where random samples are feasible versus reel-fed laminate materials where only 'spot' samples can be taken, or sterile versus non-sterile components)
4 the degree of confidence in the supplier (e.g. has it documented systems of process control and quality control?)
5 the production application and required line efficiency, e.g. components for a manual or semi-automatic, low-speed packaging operation need not be as demanding as those for an automated, high-speed one.

The specific requirements of a common component can therefore vary from purchaser to purchaser.

For these and other reasons, it is not always possible to describe a universal system and standards of QC. A basic approach to inspection can, however, be formalised which should ensure compliance with the component specification.

Identification

All batches of components (routine deliveries or trial batches) should on receipt be allocated a unique lot number for future traceability purposes and then subjected to a formal identification on two counts:

1 that the material is as ordered
2 that the material is as specified.

For the first identification, this can amount to a simple comparison with the purchasing order. For the second, identification can be as simple or as complex as procedures demand, i.e.

1 checking the printed identification code on a printed carton or label
2 using IR/DSC techniques to identify the thermoplastic in a moulding or laminated composite.

However tested, the results should record positive component or material identification, as 'does/does not comply'.

Table 4.1 Quality procedure

1.	Title	The term by which the procedure is identified.	
2.	Reference no.	The code number, usually computer-derived, which identifies the procedures. (It should cross-reference the supplier's code number, if different.)	
3.	Sampling details	How the material is packaged. How it is to be sampled, i.e. the system for establishing the number of pallets and containers to be opened, as well as the number of components to be taken. The details for sampling, should call for a visual report on delivery presentation.	
4.	Physical examination	(i)	Component identification.
	(ii)	Visual standard of presentation, e.g.	
		(a)	print defects
		(b)	moulding defects
		(c)	constructional defects
		(d)	contamination defects
5.	Dimensional examination	The critical dimensions to ensure acceptability on:	
	(a)	The production line	
	(b)	assembly and performance with other components	
	(c)	use with the product	
	(d)	distribution handling	
	(e)	patient empathy.	
6.	Functional examination	Tests involving compatibility with production use, product use, distribution, etc.:	
	(a)	assembly tests (e.g. capping torques, scuff-resistance of inks, heat seal strength of lacquers)	
	(b)	capacity tests, whether to shoulder or brim under specified temperature or pressure conditions	
	(c)	leakage tests, moisture vapour permeability of laminates, etc.	
7.	Analytical tests	Tests involving the chemical/physical nature of the component:	
	(a)	glass neutrality	
	(b)	pyrogens/toxicity of rubber	
	(c)	light transmission of glass	
	(d)	heavy metals in glass or plastics	
	(e)	IR/DSC identification of plastic materials.	
8.	Defect classification	Definitions of faults and their significance, i.e.	
	(a)	critical defect—tight AQL	
	(b)	major defect—medium AQL	
	(c)	minnor defect—lax AQL.	
9.	Defect types	Examples which constitute all fault categories: critical, major, etc.	
10.	Defect action levels	Action/reject numbers which relate batch size versus sample size versus AQL.	
11.	Statistical reference	The identification references of the scheme, e.g. BS6001, MIL-STD-105E, normal inspection, inspection level II, Table II A AQL levels, *x, y, z*.	
12.	Defect concession	The basis for using non-standard deliveries.	
13.	Supplier/purchaser obligations	Contractual obligations, e.g. (prior to change)	
	(a)	the supplier to notify the purchaser or any changes to its process/ materials or system of control	
	(b)	the purchaser to notify the supplier of any changes to its process, product application, or system of control.	
14.	Authorisation	•	Signatures of issuing departmental function, e.g. laboratory head, department head, QA director.
	•	Supplier agreement.	
15.	Changes	Reviisions history.	
16.	Date of issue	The date on which the specification was issued.	

When it is considered useful, suppliers should include their manufacturing batch numbers or production dates with each delivery and these should be recorded.

Quantity

Quantity does not usually constitute a QC responsibility, although there are occasions when it may be relevant and require QC actions.

1 Where substance weight of foils, films and foil/film/paper laminates are involved, yield calculations require 'quantity' QC measurements.
2 Where component reconciliation, in warehouse and production, requires a knowledge that labelled 'box quantities' have been QC validated.

Physical inspection (visual, odour, texture, etc.)

Quality control of packaging components does not always require sophisticated measuring equipment to rate variable quality. Detailed visual examination by a trained QC inspector can often identify the unusual or low-level per cent defectives.

Visual inspection is a classical example of quality by 'attributes', where the batch is compared with a 'standard', which can be a quality 'perfect' example of the component or a quality check list. It should be noted that the physical senses of smell and taste, where safe, are often more sensitive than many sophisticated analytical methods, but equally require validation and standardisation.

For attributes, quality training is essential, since the QC inspector (in a pharmaceutical environment) will be challenging the release of material produced by a 'foreign' technology. It can sometimes be advantageous for the QC training programme to acquire, via involvement with the company's own packaging development technologists and visits from suppliers, some specialist technical knowledge of the supplier industry and technology. Additional training, as with testing, can be based on national or industrial testing and safety standards. These points are best clarified by a few examples.

Example 1— printed secondary components (cartons, labels, leaflets, etc.)

The most important characteristic of any printed component is its text, since this provides the user with critical identification of and information on the product. Text is therefore too important to leave proof checking to the time of first delivery, so QC involvement must commence with artwork origination and approval, and be confirmed by batch deliveries.

All printed components should contain a specific artwork reference code, to allow reference between artwork and cylinder or plates. In addition, a general code should identify cylinder/plate positions which will aid QC positional proof checking as well as assisting supplier fault rectification.

Since QC relies on random sampling, complete coverage of every print station in a multi-station cylinder or plate cannot be guaranteed. It is sometimes useful for a printer to supply the customer with a 'first' and 'last' sheet (often termed 'gang' pulls) to show that text did not change between start and finish.

Unless the risk is contractually agreed as acceptable, no printer should print composite sheets, containing examples of several different products, drug strength or one product for different markets. Composite sheet printing introduces the hazard of 'rogue' mixes, and contravenes the basic rule of never allowing two different components to be mixed, since separation (unless automatic with double redundancy) cannot be 100% effective at all times. (Imaging can be used with optical character recognition (OCR) to check automatically the correctness of design and typography.)

For quality checks on colour or graphics, controlled lighting conditions are virtually obligatory. Eyeball colour comparison, by trained inspectors, is still a valid quality tool, although colour comparators or densitometers will provide recordable measurements.

All equipment should be standardised between supplier and purchaser, although some equipment (like electronic code reading) may, because of its sophistication or expense, be delegated to only the supplier.

Example 2— primary components

MOULDED GLASS CONTAINERS

Glass is generally considered to be the oldest form of packaging material, and the glass industry is probably the most quality documented and systemised of component suppliers (e.g. its list and descriptions of defect types are extensive).

As with most technologies, some technical deviations or defects obvious to the 'expert' are sometimes barely detectable to the non-qualified user, and will not present any impairment to use. Alternatively, several defects are liable to affect use on the

purchaser's production line (e.g. capacity variation), while some could hazard product and patient (fragmentation of glass particles from the rim on cap application).

It is essential for QC to acquire the skills to differentiate between grades of defects and to be able to classify their usage implication, e.g. splits in bottles can be significant according to their length or depth as well as their position (in the neck, ring, shoulder, body, base, internal or external surface, etc.) and whether product is hot or cold filled etc.

Most faults should be categorised according to their secondary implication (i.e. 'what it does') as well as its primary rating ('what it is') e.g. lubricants are frequently employed to aid the moulding operations, and components produced immediately after lubricant application will be surface contaminated and usually removed by sorting. Contaminated bottles that reach the purchaser must be considered as visual defectives (i.e. the primary rating). However, since lubricants are normally detectable only on 'white flint' glass (not amber), a normally unacceptable level of defectives could be tolerated if in amber glass and on the outside surface only.

Acquisition of these necessary skills is easier through co-operation with the supplier in an agreed training programme and cross-comparison of defect types and ratings, e.g. purchaser-detected defects to be independently reference-classified by the supplier.

MOULDED PLASTIC COMPONENTS

Plastics have probably changed the packaging industry more rapidly than any other type of material. Their versatility is well appreciated, but limitations such as mould flash, stress cracking and shrinkage can seriously affect compatibility with other components. Fortunately, most defects of the type likely to impair pack performance can normally be visually detected, and then dimensionally and functionally tested before confirming the defect rating.

As described for glass mouldings, training to acquire the necessary specialisation skills must involve the supplier and supplier technology, particularly since the development of plastics is still expanding and the pharmaceutical industry must maintain quality comparability.

A simple disadvantage common to most plastic material is the susceptibility to static dust attraction, and all suppliers should control their manufacturing environment as well as their handling/packaging operation to minimise particulate contamination. Once a component is contaminated, both the product and final process including the operators handling the components can be cross-contaminated and product recovery can be difficult as well as costly. 'Clean' production in a controlled environment is an essential means of avoiding particulates as well as maintaining a low bioburden.

Dimensional inspection

When one is dealing with complex components, or high-speed equipment, it is the subtle dimensional variation between components that can often produce the greatest variability in quality.

Component variation within a batch, or from batch to batch if batches are mixed, can affect compatibility with associated components and lead to reduced running speeds as well as reduced shelf life. Similarly, variability can introduce line running peculiarities which can widen the normal process capability distribution in other machine operations (e.g. the volume range from a liquid filling line can be greatly extended under stop-start operations).

Great emphasis must be placed on the laboratory assessment of dimensional compliance, and the relevant measuring equipment. All measuring equipment should be reviewed in terms of the initial purchase cost, its ease of use (and any training) and its accuracy, precision and reliability. This should then be balanced against the value of the results. The following are examples.

GO/NO GO GAUGES

For basic compliance testing, where there is no requirement to record values, these gauges provide rapid, positive information. Results can be obtained very easily, and training is usually minimal.

The disadvantages are that the gauges are usually one component specific (i.e. they lack versatility) and treat variables (measurements) as attributes (good or bad).

There are several types of go/no go gauges, but the most common are those used on primary components:

1 *ring gauges*—body, neck, ODs
2 *plug gauges*—both IDs, internal depth
3 *combination gauges*—constructed to meet special requirements and often combine diameter and height/length checks.

Non-primary components such as cartons can also employ gauges, although obviously the type of gauge will be somewhat different, e.g. a transparent plastic line drawing of the carton profile, creases and scoring will show specification compliance if simply laid over the test carton. They can also show positional variation of identification and register code bars.

A weakness of gauges is the usual need for further accurate dimensional measurement of components that fail the gauge. The information then provides fuller understanding of the range of the problem and the possibility of a concession to use, as well as feedback to the supplier.

MICROMETERS/CALIPERS ETC.

Most precision dimensional testing procedures utilise micrometers, vernier calipers, optical comparators, measuring microscopes, etc. This equipment provides accurate as well as precise measurements, and offers the versatility to encompass a wide range of component sizes and types. Its disadvantages include the need for perhaps complex training and assessment rating of skills, as well as occasional slowness of obtaining results. The following comparison illustrates the need for understanding the merits of both gauges and calipers.

In testing the body OD of a bottle, a single ring gauge check will confirm whether it passes and, if it fails, the position along the body of the deviation. A single check with a vernier caliper will only establish the dimension of one diameter, at one point of the body. Further repeat measurements are necessary if the maximum or minimum body diameters, and their positions along the body, are required. These manual measurements can, however, be recorded and interpreted statistically (standard deviations) and graphically (histograms) to provide trend plotting.

There is now also equipment that uses electronic gauging, computer controller optical comparators and video image analysers to measure component dimensions automatically. Once this type of equipment is correctly calibrated and programmed, it can relieve pressure on staff operatives while providing an enormous increase in accuracy, statistical data and overall value of examinations. It is only to be expected that it suffers the major disadvantage of being expensive, and probably outside the normal laboratory budget.

As with visual faults, all new dimensional deviations should be functionally tested (in the laboratory where possible, or by machine and process trial under normal operating conditions). Results should be judged as follows.

1 If the components perform normally, and/or to the satisfaction of production/development/QC, they should be accepted. The laboratory results and machine trial should be considered by the component specifying department for possible specification revision, in consultation with the supplier. The supplier should be separately notified, by QC, of the deviation and its consequences, i.e. the concession to accept. The supplier should establish and circulate details of the process variation causes which produced the deviation in order to provide greater process understanding, and the steps taken to avoid recurrence.
2 If the components can only be made to perform normally by extensive line adjustments which cannot be tolerated as a long-term measure (e.g. reduced line speeds/semi-manual handling), a partial concession to use a proportion of the batch may be allowed. This will normally depend on commercial attitudes.
3 If the components cannot be made to run, the batch should be rejected for possible sorting and re-submission.

All ‘failed’ batches should be fully investigated with the supplier, to assess the route of manufacture, with the intention of preventing further deliveries of defective materials. This also applies when problems are identified during production use, or during a patient complaints investigation.

Any use of precision equipment, even simple gauges, requires formal and regular recalibration to ensure that it still meets the performance requirements. The choice of equipment should be discussed with the supplier (and internal colleagues) to ensure commonality of ability as well as fitness for the purpose. Such routines need clear documentation and records as part of site-wide GMP.

Functional/performance tests

Components and component assemblies identified as critical should be functionally tested as part of the QC test operation. This should include compatibility between components (i.e. do they assemble correctly, perform satisfactorily) as well as suiting the production requirements.

To survey all possible functional tests is beyond the scope of this chapter, but the following are examples.

CAPACITY

This measurement must be made under standard conditions (e.g. water at 20°C) using preset rating points (e.g. to the shoulder or to the brim).

RUBBER HARDNESS

Samples can need conditioning (e.g. 20°C/65% RH for 12 h) and be tested according to national or industrial standards using specified equipment and units (e.g. durometer/shore).

HEAT SEAL STRENGTH

Where components include heat seal lacquers or coatings, laboratory tests should subject the material to agreed (supplier/purchaser) sealing conditions of temperature, pressure and dwell time using approved equipment. Once sealed, a section of stated size should be subjected to a strength measurement, again using approved equipment and specified rates. The test, in addition to establishing the strength of the bond, should also (where applicable) confirm the presence or absence of delamination.

PRINT SCUFF TEST

Since patient/market/legislative data have to be incorporated in modern product presentation, it is essential that the text remain legible throughout the shelf life. Printed material should be scuff abrasion tested, under agreed conditions, to meet visual standards of performance.

CHEMICAL TESTS

Compatibility between product and pack is assessed before final component specifications are issued. As a consequence, some materials are coated, or treated, to ensure surface inertness.

1 When aluminium containers are lacquered, the integrity of the coating can be conductivity tested using a copper electrolyte solution. Increased conductivity indicates a poor coating, and results can be referred to standard tables for acceptability.
2 Neutral glass is normally specified when injectable products are involved. Tubular glass neutrality may be affected by the supplier's forming conditions (too hot, too slow, etc.) and chemical testing, to pharmaceutical standards, is a prerequisite of QC acceptance. Failure must result in rejection, with possible supplier treatment (sulphating) to bring the components into specification. (Note that this is only possible with some products in some markets.)

ASSEMBLY

Packs that require mechanical assembly should be tested to assess ease and consistency of fit (e.g. against a maximum force/torque requirement) and to ensure that they function correctly when assembled.

1 A pressurised dispenser (e.g. a material dose inhalation system) should spray the correct quantity versus time, with the correct spray pattern.
2 Hermetically sealed packs should not leak under normal conditions, so laboratory testing could include a vacuum/vibration cycle, in vertical, inverted or horizontal pack modes, if relevant to the product, the market, or the distribution system (e.g. in the pressurised freight hold of an aircraft).

In addition to the normal routine functional/performance testing of components, all deviations which could have an influence on the in-company or in-market use of the product should be similarly assessed.

Defect classifications

Deviations from the specification must be classified according to their effect on patient, product, pack or production operation. This will require laboratory as well as possibly production and market application testing, since it is essential that a defect/defective is accurately defined and quantified.

The normal defect classification is into three categories which are allied to progressively tighter acceptance levels (limits) or AQLs, as follows.

- *Category 1:* minor defect, high percentage AQL.
- *Category 2:* major defect, medium percentage AQL.
- *Category 3:* critical defect, low percentage AQL.

Pharmaceutical packaging, because of the medical risk attached to its products, probably requires a fourth category, possibly termed 'intolerable defect'. This category fulfils the need for the type of fault which, by definition, results in batch rejection and quarantine if one example is found anywhere at any time. It is therefore not necessarily related to any AQL.

- *Category 4:* intolerable defect, 0% AQL (accept 0, reject 1).

This category must only be used for a defect which hazards the patient. For example a 'rogue' printed component mixed within a batch of other products misidentifies and misinforms the user of its contents. This is an intolerable defect and a batch cannot be used until after a 100% fail safe sorting operation (if possible).

It is not possible to include a list of universal defects versus AQLs, since this must be the prerogative of each purchaser and must take into account the ability of its supplier and the requirements of its own production/marketing organisation. This point can be illustrated by the following example.

1 Supplier manufactures and supplies identical closures and bottles to two customers, B and C.
2 Customer B uses these components on a high-speed, automated line, where capping defectives will result in component damage, breakage, contents spillage and line stoppages. Defects which affect capping efficiency (i.e. bottle or closures) are categorised as major defectives with a corresponding AQL of 0.65%.
3 Customer C uses these components on a low speed, manual and semi-automatic line, where capping defectives can be individually rejected and satisfactory replacements used. This results in all unusable components being easily scrapped with minimal loss in efficiency and no line stoppages. For the sake of long-term line efficiency (as well as purchasing standard), a nominal AQL of 4% is applied, and capping defectives are considered as minor.

This example assumes no other functional effect caused by capping defectives (e.g. long-term product leakage), but indicates that identical supply faults need not be rated by two users with the same degree of criticality.

However it is devised, the QC inspection procedure must include:

1 definitions of every defect classification, with corresponding acceptance levels and/or AQLs
2 examples which clearly illustrate each defect classification
3 the route for classifying previously unknown defects, i.e. according to primary definitions in (1) above, plus component trials
4 the possible route and mechanism for component concessions.

Action

Each batch examination calls for a conclusion on the acceptance or rejection status of the materials. The route for establishing this status needs to be simplified into a presentation which immediately relates batch size to sample size and defect AQL to the acceptance number, as shown, for example, in Table 4.2.

The statistical relevance of the action plan should be included for cross-referencing between organisations, i.e. that the plan is based on MIL-STD-105E, Inspection Level II, Normal Inspection, Table IIA AQL 1% (single sample).

All users of the plan should ideally be aware of its derivation and the obligations in following it, i.e. that the agreement to use the plan only allows batch acceptance when the number of defectives found in the sample is less than or equal to the acceptance number. Interpretation outside this constraint is not allowed within the internally delegated responsibility of QC. A batch fails when its acceptance number is exceeded. (As previously explained, the purchasing company can allow a concession, but this is a decision taken by the entire organisation and not independently by QC.)

Records

It is sometimes assumed that QC responsibility for a batch ends once the status has been assigned, and the usefulness of records can be overlooked.

With a pharmaceutical component, inspection can be just the beginning, particularly with modern means of electronic data analysis, storage and retrieval. Records can be used to:

1 build material performance trends into user-supplier relationships (a function of QA)
2 relate in-company production and market performance to the quality specification (e.g. are the quality standards too high/too low?)
3 aid problem-solving during the life of the design/product (e.g. historical data used in future developments of components and component handling equipment etc.), as a part of SPC
4 meet legislative/market requirements.

Records should faithfully represent the tests that have been carried out, and the results that were obtained. They should include all qualification assessments such as repeat samples, machine trials, and batch specific actions by the supplier. The final record should be signed as correct by the examining QC inspector (with his or her numbered stamp, if applicable) and then countersigned by the functional laboratory head. They should be retained for a defined period of time (generally 10 years).

Table 4.2 Establishing acceptance or rejection status

Batch size	*Sample size*	*AQL 1%*	
Acceptance no.	*Rejection no.*		
50,000	500	10	11

Authorisation

The QC procedure is an official company document and forms part of the formal company quality plan (the total company policy on quality). Qualified authorisation is therefore essential and this should ideally include such persons as:

1 the QC laboratory head
2 the QC department head
3 the component supplier
4 persons from the development department responsible for the component specification.

All inspection must be to the approved procedure and temporary revisions cannot be expediently introduced without similar formal approval.

Sampling

It has already been stated that the purpose of QC, in its strictest interpretation, is to determine compliance of a component, a product or service, etc., with an agreed standard. This assessment will form the basis for the decision on acceptability.

When the examination can be restricted to just an individual unit (e.g. examine one item, establish its acceptability, then pass or fail just that one unit) then we can ignore the necessity for random sampling. However, most multiple or mass production involves large quantity batches where the checking of all individual items is not practical. Under these circumstances, sampling of the batch, and a quality status based on the results of that examination, requires some understanding of the peculiarities of sampling.

Most members of the public will have a general understanding of ‘random’ and ‘randomness’, but where QC sampling is involved it is essential that the personnel involved in obtaining the sample are fully aware of its QC significance.

A sample ‘should’ represent all the items or parameters included in the population under examination. Taking a random sample requires the following.

1 Broad coverage of all the batch.
2 No concentration of the sample according to:

- beginning or end of the machine run etc.
- time of manufacture (i.e. not specific on-the-hour plans since these could coincide with natural peaks or troughs in the production cycle)

- speed of manufacture (i.e. not every 100th, 200th, 300th component, etc., since this could also match a production cycle)
- any repetitive predetermined pattern, since this could also coincide with a production cycle.

3 No sampling bias or selection of the items according to any natural senses, i.e. visual, aural, etc.
4 The batch quality should be unchanged on completion of the sampling routine (i.e. sampling a batch should neither improve nor reduce its overall quality standard).

To achieve this, the sampler must firmly understand that random sampling requires that each component has an equal opportunity or chance of being included in the sample. To use a legal comparison, honest, impartial and representative sampling should, like justice, be blindfolded to the peculiarities or characteristics of the item under test.

Table 4.3 gives an example of an ideal but unlikely series of samples, taken from a batch of known proportion defectives (10% bad).

To the non-QC qualified operator, this possibly represents the ideal and hoped for consistently true representation between batch and sample (every sample). In reality, faults randomly distributed in a batch could not perpetually produce the same number/percentage of faults in a sample, since 'chance' decides otherwise (but obviously if enough 'random' samples were taken, the long-term average would eventually equal the batch defect level).

It is at this stage of the consideration of 'sampling' that probability can be introduced to show why samples vary and how it is possible to calculate the likelihood (or probability) of finding a number of defectives in any sample taken from a batch.

This calculation assumes randomness of defects in the batch, and no sampling bias, and uses the binomial distribution to determine the probability levels (the detailed explanation of this distribution, as well as the Poisson distribution, is given later).

Assume:	that batch N	=5,000
that sample n	=100	
that proportion defective p	=10%=0.10	
that proportion good q	=90%=0.90	

Then, according to the binomial distribution, the probability of finding 1 defective or 2 defectives or 3 defectives, etc. can be obtained from the expanded terms of $(q+p)^n$, i.e.

$$\text{probability of 0 defectives} = q^n = 0.90^{100} = 0.00003$$

$$\text{probability of 1 defective} = nq^{n-1}p = 100 \times 0.90^{99} \times 0.10 = 0.0003$$

$$\text{probability of 2 defectives} = \frac{n(n-1)q^{n-2}p^2}{2!} = \frac{100 \times 99 \times 0.90^{98} \times 0.10^2}{2}$$

$$= 0.0016$$

$$\text{probability of 3 defectives} = \frac{n(n-1)(n-2)q^{n-3}p^3}{3!}$$

$$= \frac{100 \times 99 \times 98 \times 0.90^{97} \times 0.10^3}{3 \times 2} = 0.0059$$

Table 4.3 Ideal series of samples

	Batch	*Sample 1*	*Sample 2*	*Sample 3*
Size	5,000	100	100	100
Quality	90% good	90 good items	90 good items	90 good items
10% bad	10 bad items	10 bad items	10 bad items	

The values for 4, 5 defectives etc. are: 0.016, 0.034, 0.060, 0.089, 0.11, 0.13, 0.13, 0.12, 0.099, 0.064…

These values can be plotted as a graph to show the probability distribution for this sample plan (Figure 4.2). This graph shows that the probability distribution peaks with a defect level of around 10 defective, but the figures reveal that there is a very similar probability of finding 9 defectives, 10 defectives and 11 defectives.

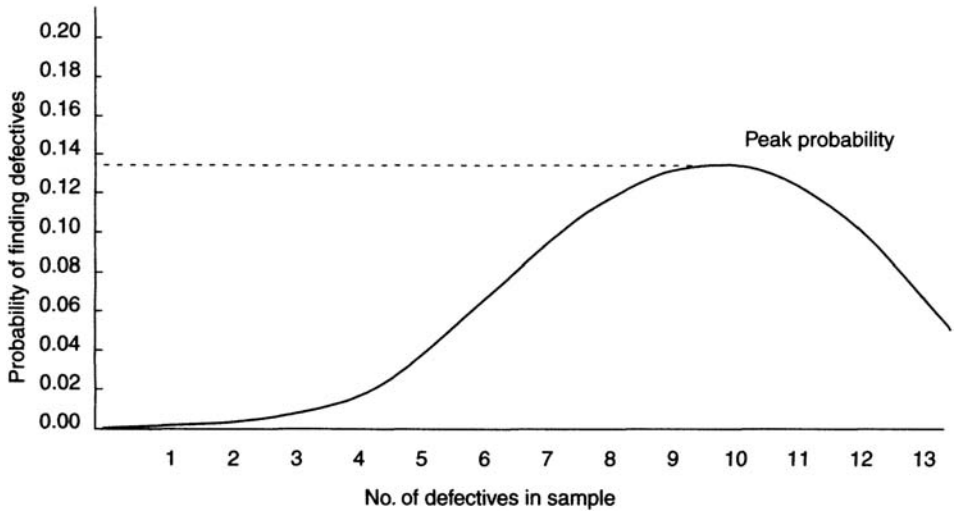

Figure 4.2 Probability distribution for sample plan (defectives)

With this insight into the mechanism of sample plans, we should not be surprised in the earlier example that samples of 100 items, taken from a batch of 5,000, where the 'known' defect level is 10, will not always produce just 10 defectives.

The graph reveals one other useful point: if we sum the total probabilities of 0 defectives through to 10 defectives inclusive (using the probability addition law), we obtain a figure of 0.583. By this calculation we can now say that there is a 58.3% probability that a sample taken from the test population would reveal $\leq$10 defectives. This is the type of calculation on which the recognised sampling tables for inspection by attributes are based, and which is covered a little later.

At this point it is worth reviewing the options available in assessing batch quality.

Not to take a sample

With a batch of unknown quality (e.g. a new supplier or new production unit), the decision not to take a sample does not realistically arise. However, where the supplier or source is known through long-term experience and probably supplier audits, it can be practical to accept a batch on certification release but with the precaution of an identity unit check.

For strict batch statistical quality confidence this option is very rarely considered, but it does have its economic benefits. (Note that the FDA, through the Code of Federal Regulations (CFR), makes no allowance for acceptance on certificate.)

To take a sample

Having decided to take a sample, the type of sample falls into just four categories, as follows.

A spot sample

By this means a batch of many units is released based on the examination of one or two units. This routine does not afford a reliable quality check or allow any precise understanding of the variability of the batch. Its use should be restricted to identity (see above), for example where a supplier manufactures glass containers, a spot check of one unit or one collated group of units could establish that the delivery consists of amber screw neck containers and not a white flint screw neck design.

Fixed percentage/number

It is not uncommon to find historical sampling routines based on the use of a fixed number or percentage of units (Table 4.4). However, it is without argument that decisions can be misleading when coupled to a simple mathematical calculation of quality, e.g. in the earlier example of a 5,000 batch size with a known defect level of 10%. From our previous consideration of this example it is obvious that sampling results can and will vary and should be related to a probability calculation for confidence.

A second important inefficiency of a fixed percentage plan is that as batch sizes increase, what starts as a simple examination of a small number of items can become excessively large and expensive in time and effort for very little appreciable gain in confidence of the result.

100% sampling examination

Sampling, by definition, cannot really be encompassed by a check which involves a 100% examination. This level of inspection is therefore usually disregarded for reasons of expense and/or impracticality, although there are some exceptions, such as the following.

1 Where historical records show that a problem routinely exists at the point of manufacture, it is sometimes feasible to employ 100% in line checking for that defect. The best example of this is in the glass industry where certain dimensions are routinely gauged, and deviations automatically rejected, or during ampoule filling when all production is checked for particulates.
2 During customer receipt checks on reel-fed labels, automatic counting equipment

Table 4.4 Sampling routine based on fixed number of units

Sample	*Results*	*Interpretation*
1st 100	10 defectives	Batch is 10% defective
2nd 100	11 defectives	Batch is 11% defective, i.e. worse than 'known' quality
3rd 100	9 defectives	Batch is 9% defective, i.e. better than 'known' quality

can be combined with electronic code readers to ensure count reconciliation as well as register and identity.

This type of examination is additional to normal statistical checks and can usually be equated with near 100% confidence (assuming the check has been properly validated).

Random statistical sampling

The QC of packaging components for the pharmaceutical industry requires an understanding of the technology of the supplier industry, and uses as a tool multiple sciences and technologies, e.g.

1 chemistry—glass neutrality, plastics analysis
2 engineering—limits and fit gauges.

Statistics, as employed in packaging QC, must be viewed as a further tool to be used where necessary and practical. Before use, consideration must be given to the source of supply, the method of manufacture/assembly, whether multiple components are blended into specific patterns and whether random sampling will identify the variability of each component/assembly.

The main benefits of a statistical random sample include calculable levels of confidence regarding the average, medium and long-term quality standard, as well as an appreciation of the risk involved in the quality decision on any one batch.

It must be stressed that statistical sampling is not infallible and in particular can never reliably detect 'rogue' pockets of excessive variability, since its confidence relies on faults being randomly distributed throughout the batch under examination. This is not always the case, since in any batch process isolated 'rogue' defects can occur which may escape the defect detection system operated by supplier or customer.

To minimise this risk, customers must work with and encourage suppliers to measure their process capability actively, and to carry out routine SPC. By determining the route and frequency by which defectives (and in particular rogue defectives) can occur, effective remedies can be agreed to prevent or minimise their manufacture, or to remove them at a later time.

All processes have a natural, calculable variability, with assignable causes of defects. Initial, perhaps high-intensity, sampling is necessary to determine this variability and remove the causes for the unacceptable 'rogues'. Once a process is operating on a steady state basis, normal random SPC sampling of the batch will provide supplier and customer protection.

Sample size

It must be expected that the size of the sample will vary, primarily for two reasons:

1 not all materials can justify the same QC effort
2 generally, the larger the sample size, the lower will be the sample risk (this point is covered below).

Most countries now have national sampling and inspection tables which relate batch size to sample size and, by using precalculated accept/reject figures for a range of 'preferred' AQLs, allow acceptance of a batch at 90/95% probability levels. In the USA these plans are identified as MIL-STD-105, in the UK as BS 6001 and internationally as ISO 2859.

It is recommended that any intending user of sampling plans should examine these documents closely, since they have the major advantage of being internationally accepted and practised. Procedures are very clearly explained and a knowledge of statistics is not essential to their implementation, although a clearer understanding of their derivation and scope will aid the total quality operation.

For example, a 95% probability that a batch is as good as the AQL does not exclude other probabilities that the batch is worse (for example the 10% probability level, sometimes called the lot tolerance per cent defective (LTPD) or unacceptable quality level, can be several percentage points worse than the AQL). It is the relationship of AQL to LTPD that more closely identifies the quality risk in any statistical sampling plan, and illustrates why the use of national plans as simple accept and reject figures fails to tap their full potential.

Risk is itself related to the chosen AQL and the sample size, and of course the unknown level of defectives, randomly distributed (it is hoped) in the batch. We shall consider the AQL first.

1 The AQL is the maximum percentage of defectives which for sampling purposes can be considered as the process average. With a variable quality of supplies, and over a period of many successive deliveries, the long-term average quality of accepted batches will be equal to or better than the AQL.
2 If several batches considerably worse than the AQL were supplied, the majority would be rejected.
3 It is essential that all manufactured materials have been quality assessed by the supplier. The customer's examination should therefore always start with the confidence that the material has at least 'passed' one quality examination (the procedure for which has previously been mutually agreed).

The customer's examination need not therefore be as detailed as the supplier's, but if it is, and duplicates the supplier's plan, then quality confidence in the accepted batches must be considerably enhanced. For example, the multiplication law of statistical probabilities shows that if there is a 1/10 probability of a batch significantly worse than the AQL being released by an inspection, then if two independent examinations are correctly carried out the probability of release is reduced to:

$$1/10 \times 1/10 = 1/100$$

If we now combine these points, in a comparison of some simple sampling plans, where the batch size is ignored and the AQL is considered to be constant, then it is clear that sampling risk is directly dependent on sample size (Table 4.5). (The theoretical plans used show that, depending on the acceptance of 'special risks', a batch of 20,000 items could be inspected against a 4% AQL with a single sample of from 13 items to 315 items.)

Two points are apparent in this comparison:

Table 4.5 Relationship of sampling risks and sample size

Sample size	*AQL*	*Decision number*		*Defect level at:*	
Accept	*Reject*	*95% probability of acceptance*	*10% probability of acceptance*		
13	4%	1	2	2.73	29.9
20	4%	2	3	4.09	26.6
32	4%	3	4	4.26	20.9
50	4%	5	6	5.23	21.0
80	4%	7	8	4.98	14.7
125	4%	10	11	4.94	12.3
200	4%	14	15	4.62	10.1
300	4%	21	22	4.73	8.95

1 the AQL is never actually 4% at the 95% probability level (since we can only operate with whole number accept/reject figures)
2 as the sample size increases, there is a correspondingly reduced level of defectives potentially acceptable at the 10% probability level.

This can be generalised as:

- small sample=high risk potential

- large sample=low risk potential.

This sample size versus risk dependency is covered in detail below.

One further point in dealing with the size of sample is the choice between single, double and multiple samples. Plans have been produced which allow comparison between these options at the same AQL, and using the same example as above (i.e. a batch of 20,000, AQL 4%) (Table 4.6).

Table 4.6 Comparison of single, double and multiple samples

Type of sample	*Sample size*	*Decision number*		*Total sample*
Accept	*Reject*			
Single	50	5	6	50
Double	1st sample 32	2	5	64
2nd sample 32	6	7		
Multiple*	1st Sample 13*	–	4	91
2nd Sample 13	1	5		
3rd Sample 13	2	6		
4th Sample 13	3	7		
5th Sample 13	5	8		
6th Sample 13	7	9		
7th Sample 13	9	10		

* This sample size does not allow acceptance of the batch, but does allow rejection if 4 or more defectives are found.

Reasons for choosing multiple samples

The obvious first reason for choosing a double or multiple sample plan (and possibly the only real reason) is the opportunity to take a smaller initial sample, i.e. the ability to make a status decision using a smaller sample than if a single plan were used. This reduction in the QC effort is only achieved when the status decision can be made on the first 1 or 2 samples; when a further sample is necessary, the advantage is lost.

The main requirements for double/multiple sampling can therefore be detailed as follows.

1 There must be high confidence that the routine quality standard of the items is high, and can be passed on the preliminary samples. This is often the case with incompany manufacture, or where suppliers have proven/validated and audited QC systems.
2 That the unit cost of the item is high and, perhaps, the test is destructive.

Distributions and operating characteristics

It has previously been stated that the use of national sampling plans does not require a detailed knowledge of statistics, but in practice a working understanding of their derivation will aid the user. All sampling plans are derived from either the binomial distribution or the Poisson distribution, by calculating either:

1 the probability x of finding 1, 2, 3, etc. defectives in a sample (n), where the level of defectives (p) in the batch is known or postulated, or
2 the number of defectives (y) in a batch when the sample size (n) is known and the probability of success is stipulated (e.g. as 95%).

The binomial distribution

This distribution is based on the expansion of the simple equation:

$$(q + p)^n = 1$$

(i.e. the total probabilities). If we use QC terms, then

p=the known proportion of defective items
q=the known proportion of acceptable items
n=the sample size.
Using a simple example, say of a sample of 2 items, the expansion gives us these terms:

$$(q + p)^2 = q^2 + qp + pq + p^2$$
$$= q^2 + 2qp + p^2$$

The individual terms of this expansion are the probability values for 0 defectives, 1 defective and 2 defectives, i.e.
q^2=probability of 0 defectives
$2qp$=probability of 1 defective
p^2=probability of 2 defectives
→ The total probability of ≤2 defectives=1
Extending this example into the full distribution, we obtain:

$$(q + p)^n = q^n + nq^{n-1}p + \frac{n(n-1)q^{n-2}p^2}{2!} + \frac{n(n-1)\,(n-2)q^{n-3}}{3!} \ldots p^n$$

0 def. 1 def. 2 def. 3 def. n def.

This distribution is now in a format which can be used in a QC environment, for example a typical QC sample *(n)* is 50 components, and a not untypical defect level *(p)* in a batch is 1%. (The non-defect level *(q)* is therefore 99%.)
We can then substitute these figures into the binomial:

$$(q + p)^n = (0.99 + 0.01)^{50}$$

and expanding this equation gives

$$p(0\text{ def.}) = q^n = 0.99^{50} = 0.6050 = 60.5\%$$
$$p(1\text{ def.}) = nq^{n-1}p = 50 \times 0.99^{49} \times 0.01 = 0.3056 = 30.56\%$$
$$p(2\text{ def.}) = \frac{n(n-1)q^{n-1}p^2}{2!} = \frac{50 \times 49 \times 0.99^{48} \times 0.01^2}{2!} = 0.0756 = 7.56\%$$

These individual values are not always useful, but if we pose the normal QC question of what probability of acceptance is attached to the above example, when the sample acceptance number is say 1 or 2, we can use the addition law, i.e.:

$$\text{(a)}\ \ p(0\text{ def.}) + p(1\text{ def.}) = 0.6050 + 0.3056$$
$$= 0.9106$$

Probability of accepting on ≤1 def.=91.06%

$$\text{(b)}\ \ p(0\text{ def.}) + p(1\text{ def.}) + p(2\text{ defs}) = 0.6050 + 0.3056 + 0.0756$$
$$= 0.9862$$

Probability of accepting on ≤2 defs=98.62%

The Poisson distribution

This distribution approximates the binomial, and is used as an alternative when:

- the sample is large, $n \rightarrow \infty$ (i.e. >50)
- the level of defective *(p)* is small (i.e. <0.1)
- the form of the distribution used by QC is

$$1 = e^{-m} + me^{-m} + \frac{m^2e^{-m}}{2!} + \frac{m^3e^{-m}}{3!} + \frac{m^4e^{-m}}{4!} \ldots$$

The individual terms of this expansion are the probability value for 0 defectives, 1 defective, 2 defectives, etc.
e^{-m}=probability of 0 defectives
me^{-m}=probability of 1 defective
=probability of 2 defectives
=probability of 3 defectives
By using the same example as for the binomial distribution, we can make the comparison:
n=50
p=0.01

m=mean number of defectives expected in sample
$m=np$
$m=0.5$

$$p(0\ \text{def.}) = e^{-m} = e^{-0.5} = 0.6065 = 60.65\%$$

$$p(1\ \text{def.}) = me^{-m} = 0.5 \times e^{-0.5} = 0.3033 = 30.33\%$$

$$p(2\ \text{defs}) = \frac{m^2 e^{-m}}{2!} = \frac{0.5^2 \times e^{-0.5}}{2} = 0.0758 = 7.58\%$$

and similarly:

$$p(0\ \text{def.}) + p(1\ \text{def.}) = 0.6065 + 0.3033 = 0.9098$$

probability of accepting on $\leq$1 def.=90.98%

$$p(0\ \text{def.}) + p(1\ \text{def.}) + p(2\ \text{defs}) = 0.6065 + 0.3033 + 0.0758 = 0.9856$$

probability of accepting on $\leq$2 defs=98.56%

It can therefore be shown that the two distributions do provide good comparisons, and using the above examples it is not difficult to calculate one's own individual plans, perhaps to meet specific requirements or more realistically just for experience of the construction of documented plans.

It is worth stressing that the AQL is simply the defect percentage level which defines the 95% probability of acceptance. From the example it is obvious that there are other probabilities which can be calculated and, if graphed, provide the operating characteristic (OC) of that sampling plan, i.e.

sample size (n) = 50
acceptance number (a) = 2
proportion defective (p) = 1%, 2%, 3%, 4%, 5% etc. (since we cannot be certain of batch variability)

If we now use the binomial distribution $(q + p)^n$ for each level of defectives, i.e. by expanding

(a) $(0.99 + 0.01)^{50}$
(b) $(0.98 + 0.02)^{50}$
(c) $(0.97 + 0.03)^{50}$
(d) $(0.96 + 0.04)^{50}$
(e) $(0.95 + 0.05)^{50}$, etc.

1 $(0.99 + 0.01)^{50}$ gives p (2 def.) = 98.62% (see $\leq$above)
2 $(0.98 + 0.02)^{50}$ gives the following terms:

$$p(0\ \text{def.}) = 0.98^{50} = 0.3642 = 36.42\%$$

$$p(1\ \text{def.}) = 50 \times 0.98^{49} \times 0.02 = 0.3716 = 37.16\%$$

$$p(2\ \text{defs}) = \frac{50 \times 49 \times 0.98^{48} \times 0.02^2}{2!} = 0.1858 = 18.58\%$$

$$p(0\ \text{def.}) + p(1\ \text{def.}) + p(2\ \text{defs}) = 0.3642 + 0.3716 + 0.1858 = 0.9216 = 92.16\%$$

By the same method, the probability for $\leq$2 defectives can be calculated for batches containing 3%, 4%, 5%, etc. defectives (Table 4.7). These probability values can now be graphed as shown in Figure 4.3.

Several comments can be made from a consideration of the OC shown in Figure 4.3.

1 All sampling plans have an OC in which no matter how low the defect level is at the theoretical AQL, there will be a risk of accepting a batch with a considerably higher level of defectives.
2 The sampling plan cannot be adequately defined by reference to just one point on the curve (i.e. the AQL), but two points will define the plan.
3 The second point usually chosen to define the plan is the 10% probability (risk) of

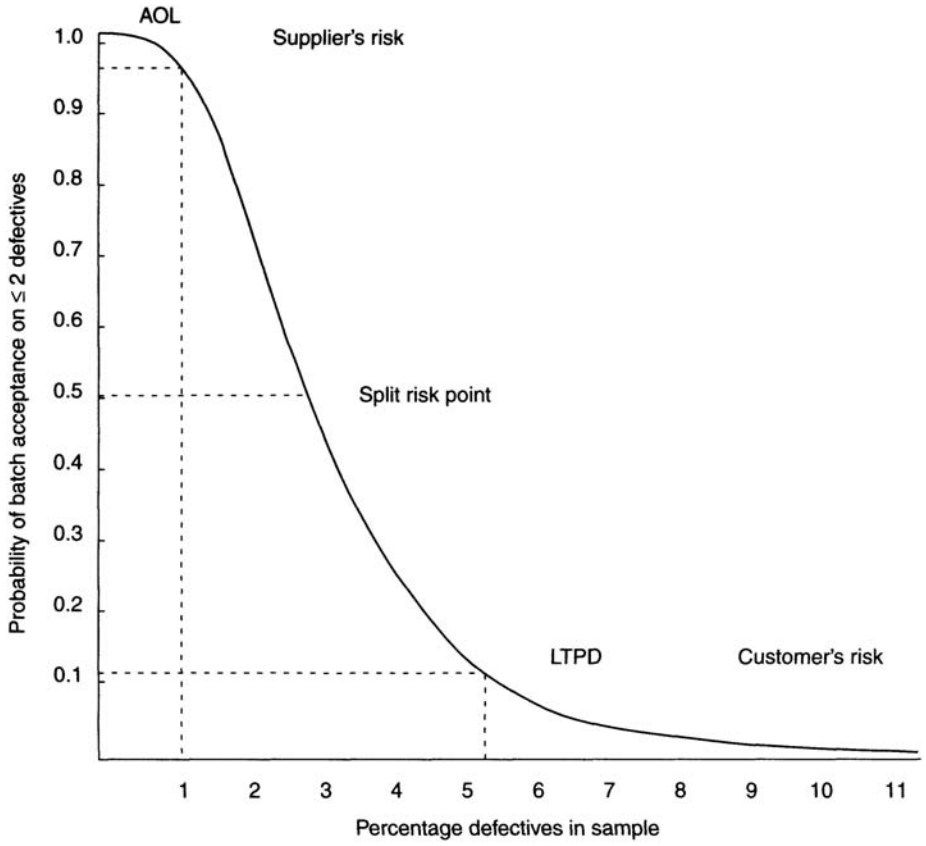

Figure 4.3 Probability of ≤2 defectives for various percentage of defectives

Table 4.7 Probabilities of ≤2 defectives for batches containing various percentages of defectives

No. of defectives	*Probability of finding up to 2 defectives*									
1%	*2%*	*3%*	*4%*	*5%*	*6%*	*7%*	*8%*	*10%*	*20%*	
0	0.6050	0.3642	0.2181	0.1299	0.0769	0.0453	0.0266	0.0155	0.0052	0.0000
1	0.3056	0.3716	0.3372	0.2706	0.2025	0.1447	0.0999	0.0672	0.0286	0.0002
2	0.0756	0.1858	0.2555	0.2762	0.2611	0.2262	0.1843	0.1433	0.0779	0.0013
Total probability of ≤ 2 defectives	0.9862	0.9216	0.8108	0.6767	0.5405	0.4162	0.3108	0.226	0.1117	0.0015

acceptance, and as previously mentioned is termed the *lot tolerance per cent defective (LTPD) or the unacceptable quality level (UQL)*.

4 At the AQL of 95% probability of acceptance, there is a 5% probability (i.e. 100%–95%) of a batch being rejected although it is as good as or even better than the AQL. This 5% probability value is referred to as the supplier's risk.

5 Similarly, the LTPD of 10% probability of acceptance is sometimes referred to as the customer's risk.

6 The mid-point of the OC curve, or the 50% probability level, is sometimes known as the split risk point, since there is an even chance of batch acceptance or rejection.

Comparison of OC curves

All sampling plans have OC curves, and any consideration of a scheme for sampling inspection should begin with an examination of the curve (see MIL-STD-105, or BS 6001). The ambition in examining the curves is to obtain the smallest sample size that provides the greatest confidence of batch compliance with the required quality, i.e. reducing the degree to which the batch may be different from the chosen AQL.

However, it has to be recognised that small samples must equate with a greater chance of accepting a batch significantly worse than the AQL. Larger samples, because they have steeper OC curves, will conversely have a lower chance of accepting a batch significantly worse than the AQL.

In general, very small samples should only be used with a high/lax AQL, and large samples when the AQL is very low/tight.

Supplier evaluation

The supplier plays a key role in the chain of quality events that concludes with the sale of the ultimate final product. This point is sometimes overlooked or consideration and implementation left too late to utilise fully all the potential advantages that can be gained by the correct choice of supplier.

Any realistic QC function must therefore have a policy of supplier evaluation which will ensure that the capability of the supplier matches the requirements of the customer. This is all that can be requested of a supplier, but while assessing the capability it is essential that the customer is equally thorough in stipulating the quality requirements.

Supplier evaluation can usually be subdivided into three categories: new project with existing supplier, new supplier, and new project with new supplier.

New project with existing supplier

This is often the easiest evaluation to monitor since it operates with a full project team and quality objectives can be co-ordinated into the complete design requirements. It is also founded on long-term commercial relationships where the company history will exist to support the actual quality of performance.

A new supplier

This can be more complicated, since it will rely on the assessment of a company's potential ability, separate from the actual context of historical performance. Ideally any new supplier should be certificated to a national or international quality standard (e.g. ISO 9000), with an already audited and proven quality system. (During the 1990s many UK packaging companies have been independently certificated to the Pharmaceutical Supplier Codes of Practice, which are linked to ISO 9002.)

To obtain a realistic assessment, the method and detail of the purchaser's evaluation of a new supplier must be formalised, and the results documented. The opportunity must be taken to view the supplier under normal operating conditions, with the involvement of the relevant technical staff. Systems of working routines must be made available and the operation of quality systems defined. The supplier company should explain its organisation (line/functional disposition), its personnel training policy, and its philosophy and commitment to quality.

The results of the evaluation must be made known to the supplier, and the opportunity presented for comment (to resolve differences, to extend the evaluation or to discontinue the evaluation).

New project with a new supplier

This category will naturally involve a combination of the previous two and, to a great extent, the quality evaluation should parallel the design project team which could itself possibly be involved in the development programme with a research subdivision separate from the manufacturing plant.

Care must be taken with a new innovative company which may initially lack in-depth quality systems, and it may be necessary to help introduce quality procedures compatible with the quality demands. This would be far easier than trying to teach innovative design concepts.

The intention under this title must be to design quality into the component, and to ensure that conformance is achievable.

In general, the evaluation of a supplier will fall into just three categories:

- the supplier's manufacturing capability
- the supplier's quality capability
- the customer's quality requirements.

The supplier's manufacturing capability

The supplier must invite an unconditional tour of its plant, or, at least, of the part that involves or impinges on fulfilling the contract.

This will cover areas of design and development, the production support facility (the tool room for manufacture, refurbishing of moulds, dies, etc.), the manufacturing plant (all the multiphases of the operation including machining, moulding, printing, assembly, packaging, warehousing, distribution, etc.).

Details of normal GMP (perhaps specific to that particular industry) should be highlighted, such as machine layout and space; floor and wall conditions; segregation and separation of material in storage, work or awaiting use; level of lighting; material and work identification; quarantine areas; etc.

Quality capability

The size of the quality organisation and the extent of documented procedures will vary according to the size of company. Independent of size there should be an appreciation that quality systems must be formalised to ensure material consistency. Each manufactured batch must be subjected to the same control, ideally involving pre-running start-up checks, in-process SPC checks and pre-delivery conformance checking.

It is for these reasons that all companies should possess a quality manual which contains the formal policy on company quality. This should be produced by the quality department but have chief executive authorisation. Specific quality procedures should be included in a quality plan, which can be presented as either one complete plan containing a sub-chapter for individual components/component ranges, or a separate plan for each and every individual component/component range.

The assessment of the company's quality capability should review the quality policy, and establish the following.

1 The role, responsibilities and training of staff delegated with the quality function (in both production and QC).
2 The person named as responsible for quality, his or her status and to whom he or she reports.
3 The inspection facilities and equipment must be suitable for the control of manufacture, and able to meet the contract quality specification, i.e. main laboratory and/or line testing areas, measuring equipment, component function testing equipment, sample storage, calibration and validation procedures.
4 Quality procedures must detail the type and route of sampling, inspecting and testing, which will include:

   - raw materials and manufactured products
   - the means for quarantine segregation of defectives, their status identification and the mechanism for sorting and resubmission to QC
   - the action on finding defectives
   - the means of disposal of defectives
   - the production/QC action to remedy the cause of defectives.

5 The degree and type of production-based line inspection, and its relationship to the QC operation. Ideally line inspection should be based on SPC and involve an element of continuous improvement to remove defect causes.
6 The manufacturing process documentation for stipulating the type and amount of materials required per batch; the machines/moulds etc. required for producing the product; the specification details/drawing; the degree of process checking; first-off checks; etc.
7 The documentation system for recording all results obtained by QC (of raw materials and manufactured materials).
8 The means of storing batch data, its accessibility to supplier and customer, and duration of retention.
9 The system for incorporating special customer requirements into production operations, e.g. certificate, special packaging, labelling.
10 The company GMP system covering work practices throughout the plant and warehouse, e.g. in-company audits, line clean down procedures, material identification and segregation, quarantine areas, general traceability.
11 The company system for routine training of operators involved in the manufacturing process.
12 The system for regular review of:

- specification and procedures
- control equipment calibration (in production and QC)
- subcontractor or suppliers
- customer's quality contract
- internal quality systems.

The customer's quality requirements

To be competitive in terms of specification and quality, a modern supplier must have a thorough understanding of its own process capability, its quality ability and its market position. The evaluation must therefore work to the strength of the supplier, by relating that ability to the customer's quality requirements. To that extent, the customer must ensure that its component specifications are complete, that its quality procedures are comprehensive and realistic, and then classify all the details to the supplier's satisfaction. At that point it may be necessary for the customer to use its quality expertise to aid the supplier in improving its quality systems (see above).

Any doubts about the supplier's total ability to meet specific requirements must be resolved before commencing production (machine trials should be utilised to remove doubts, as well as to acquire confidence for either party).

The intention of the evaluation is to ensure that the supplier can control its manufacturing operation and meet agreed standards. It is therefore in the interests of both parties that sufficient time is taken to form the basis for a good long-term commercial relationship.

On completion of the successful examination, the supplier must agree the final component quality procedure since this is an integral part of the commercial contract.

Customer-supplier working relationship

The customer and supplier form the opposite ends of the same commercial chain. To be successful, both must contribute:

1 the supplier must achieve specified standards and service
2 the customer must accept the commercial cost of specified standards.

The arrangements must start with an open evaluation and, through agreement on realistic quality standards confirmed by results on successive deliveries, achieve a steady working relationship.

A review of the quality standards can be initiated by both parties, either because the standards are too low (usually by the customer when problems are occurring in manufacture or market) or because the standards are too high (usually if the supplier is suffering excessive wastage or process downtime).

The quality standard should be automatically reviewed after several consignments or 6–12 months, whichever is more realistic. This review allows performance of supplier and in-use customer data to be incorporated into a more fully validated standard. The longer term ambition of supplier and customer must be to achieve complete inter-company quality trust (evidenced by supply on certificate).

Quality control of material, to be effective, must be close to the point of manufacture. Hence the emphasis on the supplier controlling its process while the material is being produced, backed-up by separate batch testing. The delivery that reaches the customer and is then found to be defective has far-reaching implications on product scheduling, market supply and, eventually, customer confidence.

It is therefore self-evident, as well as cost-effective, that supplier and customer should concentrate most of the QC effort at the supplier's production line, for example by the supplier using strict in-process controls backed-up by a single, large sample, while the customer employs double, smaller samples. The supplier, not the customer, must be responsible for the quality of delivered components.

This system of 'commercial' QC trust should lead to the customer expending more effort in aiding/improving the supplier's quality system (through regular quality audits), and less on routine conformance testing. The supplier has to be aware that a substandard delivery, unknowingly accepted for use, can have serious implications for the customer's production efficiency, but more critical consequences on patient efficacy.

Manufacture and qualification controls

Once a delivery has been received by the purchasing company, and assessed for specification compliance, it is held in a quarantine warehouse awaiting manufacturing use.

The systems required for in-house manufacture are developed as part of the product launch product team, and within the overall time scale. The manufacturing brief will encompass a variety of parameters depending on the type of product and the scale of the manufacturing launch.

Objectives will have to be rationally established, and will probably include:

1 the equipment specification
2 the environmental specification (sterile or non-sterile area, temperature/humidity controlled, etc.)
3 the raw material specification
4 the packaging components specification
5 prestocking for materials and components
6 standard operating procedures
7 staff training (including training in SPC techniques associated with the new process)
8 operator process controls
9 finished product qualification controls.

All these prime activities, and many others, will need in-depth assessment and resolution (usually within a qualification and validation programme) before production can commence, but once production is initiated, confirmation of compliance with the finished product specification depends on the last two activities.

In the modern organisation it is difficult to separate production-operated SPC from QC-operated finished product controls. They must complement one another within the following broad definitions.

1 *Statistical process controls:* manufacturing procedures designed to ensure that process operators 'self-check' their production output (to record results, maintain process variation within established limits, correct the causes of ongoing deviations, detect trends and minimise wastage).
2 *Finished product control:* QC procedures, separate from production operations, to ensure that released product complies with agreed standards (which can be company-based or nationally/internationally imposed specifications).

It must be emphasised that transfer of the 'research product' to the 'manufacturing division' cannot occur in an information vacuum, divorced from the background information and experience of the project team. In many companies it is common for several full-scale 'development' batches to be produced in the manufacturing facility before complete hand-over to production.

This phase-in period allows for better co-ordination of the development technology into the production technology of the detailed product manual. It maintains the skills and expertise of the project team through the difficult learning cycle of the production operators. It enhances GMP and consolidates the process controls necessary to ensure production efficiency combined with 'making it right first time' policies.

Process controls

The degree and type of process controls will vary from company to company and from product to product. Some new products (such as a pharmaceutical drug) may require complicated and new blending/homogenising operations, but then be presented in a standard tablet form. In this example process controls would include routine checks for tablet weight, thickness, hardness and possibly friability and dissolution.

If the process were a large volume liquid filling line, then in-process controls would include measurement of fill levels/weight and, if a screw closure, the release torque.

The following are equally important as determining the type of test to carry out.

1 How many items to check.
2 How frequently the tests should be carried out.
3 At what point of the manufacture the sample should be taken (e.g. checks on label presentation should also be made after cartoning of the container, to avoid over-looking label damage caused by carton insertion).
4 The action to be taken if items are found to deviate from specification. This is the key point and comes from the correlation of defect causes with efforts leading to continuous improvement and the avoidance/prevention of defectives. Answers to these questions can often be found from experience with products of a similar nature (for example, although a liquid filling line may be new, the cap-tightening equipment may be identical to machinery in another part of the plant. Records will show equipment capability and tests can be duplicated).

If, however, the actual filling line is to a new design, fill level testing procedures can only be obtained from first principles, as follows.

1 What is the desired product specification?
2 What is the equipment manufacturer's recommendation? (All manufacturers carry out detailed 'qualification' trials, although not always with exactly the same liquid characteristics.)
3 Carry out detailed trials at the manufacturer to establish consistency standards before the equipment is shipped to the purchaser's plant. Standards will need to be contractual.
4 Once installed in the purchaser's plant, the first three 'development' batches should be used to carry out in-depth process capability trials (with the manufacturer's engineering representative possibly in attendance). The process capability trial is the best opportunity to establish not only the capability of the equipment, but also the in-process checking necessary to ensure batch consistency. The trial will require multi-comparison data:

- frequent but small sample sizes, taken throughout the batch and repeated on later batches
- less frequent but larger samples, covering all filling heads, throughout several batches as above
- repeat testing following batch change-overs from one pack size (of fill) to another, to establish variability induced by engineering adjustment and changes.

The statistical analysis of this data will determine the sample size and frequency of later routine checking by indicating:

- mean fill and range (including standard deviation)
- long- and short-term machine cycling variability
- head-to-head variability
- fill drift (since it is well known that level of fill can drift as the machine 'warms up/settles down' and can require an initial operator adjustment)
- stop/start variability (it is recognised that stop/start interruptions to a process can introduce excessive process variability).

The trials should deliberately investigate the mode for variations and failure route (care must be taken that trial-induced variations in the product are not released for consumer retail unless extensively checked). For example, failure/variation in a vacuum filling line can be caused by loss of vacuum, the result of seal damage from abrasion with the bottle rims. In a piston/cylinder operation, density variations in the product (requiring strict analytical control) are a principal source of fill weight variation.

Although it is not unusual for equipment to cause excessive variations occasionally, defects can often be related to maintenance faults (e.g. seals not replaced at specified times, volumetric adjustment controls not secured after adjustment). One of the most important process checks is at the start of the batch, particularly after a change-over from a different fill quantity or after a maintenance period. This start-up check is the best opportunity to find the gross error and to ensure that all filling heads are set correctly.

Provided that process capability trials have shown process consistency, with only nominal head-to-head variations, only small sample sizes are needed to maintain process control.

Statistical data can be employed to construct control charts (Shewart charts) which provide action limits and warning limits for values of mean and standard deviation. Charts can be used for measurement of variability (size, volume, hardness, etc.) or attributes (good/bad or acceptable/rejectable). Values calculated from routine samples are plotted onto the relevant chart, and provided the results fall within the acceptance area, manufacture can continue until the next sample is called for.

SPC charts have proved their value over many years and no longer need justification or a detailed explanation. They allow for the normal expected process variability, e.g. action can follow a failure at 99.8% probability (1/1,000), with a warning at 95% probability (1/40). They allow easy operator understanding of results, without which data can be misconstrued leading to excessive operator-induced variability (under the impression that the process is out of control).

Where certain process characteristics are important, it is sometimes feasible to incorporate automatic in-process checking of 100% of production. This can remove the risk of low-frequency faults escaping detection and provides virtual 100% quality confidence, as follows.

1 Automatic in-line weight checking programmed with calculated net values of the container weight distribution (provided this is very small relative to the net fill standard). Similar statistical systems exist for the weight-checking of samples, and these can be programmed to indicate whether the fill process needs an increase or decrease adjustment.
2 Automatic code reading and missing label detector. Process control results must be recorded, since the records can be invaluable for later analysis. They will allow immediate action over gross deviations:

- to quarantine current production and re-examine product from the time of the previous acceptance results
- to accumulate daily data for medium-term assessment of line efficiency/wastage levels
- to act as a warning that a deviation is developing which could eventually cause specification failure
- to show long-term process drift indicative of machine wear requiring planned maintenance
- to provide historical data to support customer feedback
- as a means for 'continuous improvement', where causes of deviations are examined and reviewed continually giving an improving quality capability.

One last responsibility after the transfer of a new process/product into the production operation is to institute a review of production records after a set time period or number of batches. This review can be used to consolidate existing limits and test procedures, or to introduce modified or new routines. It should include data from market reports and any customer reactions (good or bad).

The intention of GMP is firstly to design systems, facilities and procedures so as to avoid failure, and secondly to detect at the earliest opportunity process drift that can lead to failure and thereby avoid the manufacture of failures. GMP is dictated by the company need to ensure product constancy within the specifications and to maximise efficiency. For good GMP, process operators must be in control of the production operation and this requires predetermined and relevant process control checks.

Finished product control

Before development of modern QA principles and QC technology, finished product control was the main (and perhaps only) preoccupation of the QC department. Finished products were often sampled at the end of the process and, after inspection, classed as acceptable or not acceptable. Following this decision, it was expected that the 'surprise news' of a quality problem would be investigated and remedial action introduced.

No company can be expected to survive in a competitive market if quality assessments are divorced in time from manufacture. It is for this reason that pharmaceutical manufacturers must believe in production-operated in-process checks where the process operators have the responsibility to self-check. These checks will be complementary to the independent (and legally required) QC assessment.

The finished product control will be based on the finished product specification and will detail the tests, sample size and frequency necessary to ensure compliance. As with the inspection of bought-in components, testing procedures will include details extracted from national and international standards (pharmacopoeias, military standards, etc.). They will however have one major advantage over systems designed to vet bought-in materials, i.e. the higher confidence synonymous with in-house manufacture.

QA/QC will have been involved in the project phase which developed and introduced the new process/product. They will have participated in devising the 'manufacturing specifications' used to produce the product, in particular the in-process production checking. They will have ensured that bought-in materials meet the specification and that all items (components, facilities and process) have been validated in a process capability trial.

With these advantages, the finished product control can be implemented during, or at the end of, the batch manufacturing process, and will include a thorough assessment of the regular documented results of the in-process production checking. (Note that the production in-process checking will normally be at a higher frequency than the QC check, although perhaps not always to the same depth or detail.)

The QC control inspection can therefore justify the economical use of double or multiple sampling techniques (these depend on high confidence of passing on the initial sample(s), otherwise they become uneconomic of sampling effort if further samples are required).

As with in-process production checking, finished product control can employ statistical techniques and control charts or can be derived from national sampling procedures such as MIL-STD 414 (sampling, procedures and tables for inspection by variables for per cent defectives). These sampling procedures are very similar to and complement the sampling, procedures and tables for inspection by attributes (e.g. MIL-STD 105E) and can be used in a similar manner.

The finished product control will be a standard procedure covering primary and secondary pack characteristics such as the following.

1 Primary characteristics:

- weight/volume of fill
- tablet count
- integrity of pack
- efficiency of closure

- functionality of pack assembly.

2 Secondary characteristics:

- presentation of pack
- label details
- carton details
- batch data (lot and expiry).

In general, its format will be similar to that for component inspection.

Validation as part of packaging quality

Validation, in the European Guide *The Rules Governing Medicinal Products in the European Community Volume IV,* is defined as 'Action of proving, in accordance with the principles of good manufacturing practice, that any procedure, process equipment, material, activity or system actually leads to the expected results'.

From this definition it is obvious that packaging components come within the scope of validation (via the 'material' route). In the context of the earlier review of quality of design and quality of conformance, it may seem that the validation concept does not offer a great deal of additional confidence. However, this would ignore the recent history of validation and its expansion into qualification.

While validation has a relatively short technical history, in practice it has largely been directed at aseptic processing (autoclaves and media fill vials, etc.). In recent years validation has been progressively expanded, firstly to cover all manufacturing, then computer systems, analytical methodology and more recently into packaging processes. Coincident with this, validation has itself evolved into qualification, with defined parts:

- SQ (specification qualification, i.e. equipment specified against key requirements)
- PDQ (pre-delivery qualification, i.e. optimised assessment at supplier)
- IQ (installation qualification, i.e. inventory, services, function check)
- OQ (operational qualification, i.e. dynamic assessment against specification, under production conditions)
- PQ (performance qualification, i.e. technical review of first batches).

As was common with validation, qualification can be as broad as an entirely new line, or focused on a new or modified sub-part, e.g. a new capper in a filling line. No matter how large, the important aspect is to ensure that the assessment covers all the possible interactions between constituent parts of the process (i.e. input and outputs), the materials being used and the operation of the process (i.e. operators).

For example, a company which experienced a customer complaint involving a large glass fragment in an aseptically filled powder vial introduced procedural preventive measures but concluded that the issue required automated vision inspection equipment. Once the corrective equipment was identified, a validation master plan detailed the key qualification elements for hardware, software, defect detection system, infeed/outfeed links, but also the specification requirements of the component and component quality, e.g:

1 the specification—supplier, component dimensions, glass type, surface design, etc.
2 the vial quality—particulates, cracks, surface marks, contamination, etc.

Details needed defining with the supplier and the trial components needed to be assessed prior to the trial to document the quality datum, since the whole performance assessment would be based on the components 'as used'. During the trial using laboratory produced 'defectives', false positive/spurious rejects were qualified and assessed in order to determine the true quality performance of the unit. At the conclusion, the unit was certificated in the context of:

1 the inspection unit
2 the process
3 the environment
4 the operational procedure
5 the trained operators
6 the specified components
7 the re-validation schedule.

It is worth stressing that future changes to the process (e.g. a new component supplier or component design) could degrade the operational performance and take it out of 'certification'. Any change must therefore lead to a review, an outcome of which could be re-validation/re-qualification.

A further example of how validation is having an effect on component quality is where regulatory authorities impose new requirements. These are naturally intended to support or expand GMP, and must be viewed positively, but they can create additional quality demands.

The FDA recently confirmed that market feedback showed that mislabelling recalls were not associated with packaging processes with on-line bar code readers. This has led to the relaxation of the need for full component reconciliation, but indirectly upgraded the technical demands on validating bar code readers.

To put this into context, when bar code readers were just one part of an integrated quality system (e.g. supplier count verification, QC count checks on incoming deliveries, line receipt checks, line cleandown checks and reconciliation), only the function of the bar code readers needed to be the focus of attention. As a stand-alone system, full validation/qualification becomes a necessity and takes the issue away from the line and onto technical support (i.e. QA). Just as with the earlier vision inspection equipment, qualification is not just of the bar code reader and the detection performance, but also of the component quality, e.g.

1 the specification—supplier, component dimensions, surface type and finish, colour, print design/coverage, code design, etc.
2 the component quality—colour and surface variation, text location (related to size variation), etc.

Final certification of the unit must relate to specified components and the supplier, with changes, as pointed out earlier, requiring review and possible revalidation.

Validation is not therefore an entirely new requirement for packaging components, but purely an extension of the original 'fitness for purpose' and the desire to ensure that all constituent parts (material and *matériel*) are not only as specified, but also function together as specified, before material is used in a production process. What is possibly new is the interest of regu latory authorities in the combination of packaging component and process validation, which directly increases the need for a fully professional and interested component dossier covering:

- the specification
- the quality standard
- supplier audit
- QC tests
- line and material/process validations
- change history.

This total approach to the integration of quality takes suppliers and users close to a performance guarantee that materials and processes will perform as specified.

Conclusion

It is difficult to write a concluding summary without incurring the risk of paraphrasing the salient features of the main text or simply repeating verbatim. However, product quality, as a topic to manufacturer and lay person alike, cannot be repeated too frequently since it is one of the critical factors that:

- directly affect consumer appreciation
- are directly controllable by the manufacturer or producer
- are cost-effective aids to production efficiency when properly devised and implemented.

All products have a quality horizon. While some are intentionally low, others are intentionally high. This is no different in the pharmaceutical industry, where the 'product' must be considered to be the drug and pack and both will warrant equal quality considerations. Emphasis might vary from company to company or from industry to industry, but whatever the product standard it is essential for the manufacturer to know its market sector and whether quality objectives are being achieved at the right market cost.

Manufacturing costs are important and are always undergoing scrutiny on the basis of reducing costs to improve efficiency. Costs cannot be divorced from quality, but it is wrong to consider that high quality automatically implies high costs, or

conversely that low quality means low costs. In many companies the true 'quality costs' (as opposed to the straightforward cost of QC) are often unknown, and lost in departmental or divisional budgets, e.g. the costs of

- line waste or scrap
- line inefficiency or low running speeds
- line downtime
- defect investigation
- customer complaints
- customer replacement products
- company public relations following up complaints (and cost of 'low' image).

The correct product quality is achieved not by luck or chance but by the consistent application of quality principles to the design of the product, the inclusion of these principles within the GMP of the manufacturing operation, the relevance of the design specification and quality standards, and the follow-up investigation of consumer acceptance/feedback after launch.

Appreciation of the need for real quality standards must therefore be one of the con siderations during the conceptual studies by the product research department of the large multinational companies and by a market research assessment of the potential market slot. It requires an assessment of the market the product is intended to satisfy, followed by the incorporation of these market requirements into the first 'paper' designs.

The initial development phase of the design will primarily involve detailed investigation and liaison between the research and marketing organisation. However, as the design concept 'hardens' and consideration is given to eventual launch, a close relationship is needed with the technical specialists of the manufacturing division (engineering, purchasing, product scheduling, QC, production, etc.).

Control of the multitechnical requirements of these different functions, together with those of suppliers and sub-suppliers, cannot be left to the whims of an *ad hoc* committee, but must be the responsibility of a co-ordinating team. This team (sometimes termed a product launch project team) is ideally composed of delegates from the above specialist functions, and is charged with the responsibility for guiding the new product through the manufacturing operation to its satisfactory launch into the market.

This team will be required to operate at different intensity levels and to differing time scales, i.e. the occasional moderate pressure, but long-term involvement of the research/development group in conjunction with the more intense, short-term brief of the manufacturing division. These different time scales will have to be contained within a critical path network (CPN) once a launch 'window' has been selected, in order to avoid a launch-restricting bottleneck.

Within the CPN different factors will be investigated and actioned, e.g.:

1 research finalisation of the viable design and product specification via in-house assessments, market trials varying from one-off test examples to pre-production trials
2 manufacturing finalisation of

- choice of manufacturing equipment, process speeds, throughputs
- production schedules
- stocking of raw materials, components, etc.
- training schedules
- standard operating procedures
- quality standards for raw materials, components, and intermediate/finished products.
- qualification validation of the process.

These last few points are perhaps the most important in the whole design for quality, since validation provides full objective confirmation that the whole process is fully integrated to achieve the quality specification.

While validation is the final company challenge of the design capability, validation documentation is often the first point of challenge by regulatory inspectors, looking for proof that quality requirements have been built into the design and process.

From the inspectorates' viewpoint, however, quality documentation is critical for all the key stages before and during manufacture. In the event of complaints or referrals from the market or regulatory inspectorates, it is archived batch and test documentation that must provide 'traceability' to the quality conformance history of:

1 the component (in-house and at the supplier)
2 the materials (in-house and at the supplier)
3 the manufacturing process

4 batch and material testing
5 standard operating procedures
6 staff training
7 manufacturing and support equipment maintenance, calibration and validation.

Through unique reference identification of materials, components, products, processes, trials, evaluations, etc., traceability is comprehensively built into the total pharmaceutical process.

It may seem that only immediately prior to commencing the production phase will the word ‘quality’ be commonly documented, and here in the context of QC objectives of measurements, procedures and standards. In practice, quality principles are consciously and subconsciously being viewed, assessed and re-assessed during the earliest product investigations.

As stated previously, marketing must consciously decide the market in which the new product will compete. This will have involved in-market assessments and possibly laboratory studies of competitive product and national standards that govern sale, use and distribution.

Research studies will cross-evaluate the ‘home’ product design against the best of the competition and disregard characteristics which do not exhibit significant advantages. The definitive pharmaceutical product must be subjected to governmental approval using data obtained from laboratory and market evaluations, i.e.:

1 clinical trials—where the test product is clinically assessed for efficacy
2 presentation trials—where the product—pack presentation is tested, initially using ‘one-off or pre-production samples for

- shelf-life expectation
- shelf-life stability
- user acceptability.

Results will invariably be subjected to statistical evaluation before the company decision to proceed is taken, or acceptance by the government’s licensing authority. They must therefore be capable of withstanding independent scrutiny.

The disciplines necessary to ensure registration of a product require the efficient research establishment to follow highly detailed routines of GLP. These routines reproduce in the laboratory environment the procedures, disciplines and systems comparable with the manufacturing operation. They have proved important to industrial research in maintaining consistency of manufacturing standards and product reproducibility.

The inspectorate of most national health organisations devotes equal investigations time to the QC operations and to the manufacturing process. This has been reflected in the corresponding attention paid by the legislature to the control of practices by research and clinical evaluation laboratories. It is essential that in the design stage of new product, the importance of the supplier’s effect on finished product quality is not overlooked. Most modern products are the sum of many different parts and processes, all of which should be equally under control.

Customer and supplier have to agree the raw material/component specification and the associated quality standard. The supplier must be encouraged to operate a system of manufacturing controls to ensure that not only is the material produced in the right quantity and at the right cost, but also to the agreed quality. These manufacturing controls, while perhaps being simpler than those in a pharmaceutical company, should be sufficient to guarantee that standards are achieved.

The launch of a new product, through the manufacturing operation, should be attended by a deliberate but temporary ‘overkill of controls’. The intention must be to measure the quality of the product as it progresses from one operation to the next as well as to establish other performance parameters such as:

- line speeds
- downtime
- wastage
- operation efficiency

As the learning curve is extended for each of these, production efficiency improves while quality is maintained. With this intention, the first batches of a new product (usually three to five) should be under a development jurisdiction to confirm transfer of the design requirements into production conformance (this is often termed performance qualification). Specialist departments other than QC will also be present (training, engineering, O&M, etc.) to ensure the relevance of procedures, systems and performance.

The intention of the quality specialist is not only to confirm the correctness of the quality standards but to ensure that quality monitoring is effective in detecting deviations at the earliest opportunity. Close monitoring by production, through

process controls or through quality control checks, detects process drift before the manufacture of defectives and minimises the risk of rejected product.

The quality system should not be satisfied with the mere release of a conforming batch of product, but should also assess the market response in comparison with the original batch results. Reaction from the market can be invaluable in detecting (and correcting) a minor deviation or trend before it becomes a major complaint. For that reason market opinions should be positively sought rather than passively awaited.

A predetermined time after the launch of the product, or after a specified number of batches, specifications and quality standards should automatically be reviewed to confirm relevance. (This initial review should be the beginning of regular updating and assessment of procedures, specifications and standards.)

To conclude this chapter, quality systems of quality-conscious pharmaceutical organisations can be divided into two categories and summarised as follows.

1 QA (the activities and functions concerned with the attainment of quality). This can take into account the establishment of GLP in the laboratory environment (of research as well as QC), as well as GMP in the production environment. It is concerned with the manufacturing facilities, together with the systems, procedures and disciplines that guarantee that manufacture is right first time. It is equally concerned with the operation of the internal quality assessment systems, which should include efficient self-checking by production of the production process as well as the independent measurement of quality conformance by QC.
2 QC (the function responsible for the maintenance of product quality to the agreed standard). Standards must be documented to show the company's requirements for the consumer (individual, group and/or national regulatory) combined with the economic and efficient utilisation of resources.

QC specialists, or *aficionados,* sometimes engage in technical arguments with specialists from other disciplines over whether QC is primarily concerned with compliance with specification or with suitability for purpose. Consideration of the option of suitability for purpose is sometimes an emotional issue when non-specification/conforming product is quarantined pending detailed investigation. In this scenario the first objective priority of the QC inspector must be to determine defect causes and prevent manufacture of further defectives, in conjunction with assessing the degree of non-conformance to the specification.

As stressed repeatedly above, the setting of a specification or standard must be a realistic technical study which includes all criteria that could affect suitability for purpose. Hence failure to meet the specification must automatically imply non-suitability for purpose (exceptional occasions can occur which necessitate rewriting the specifications).

There is therefore no reason why, provided that:

1 product design encompasses basic quality principles
2 the manufacturing process is correctly chosen and operates to strict GMP
3 specifications and standards are correctly set and implemented

the successful conclusion of the manufacture of a new product should not be summarised by the QA philosophy: 'it came to pass'.

Technical references

BS 6001:1996, *Guide for the selection of an acceptance sampling system, scheme or plan for inspection of discrete items in lots*.
Part 1:1999, *Sampling Schemes indexed by acceptance quality limits AQL for lot by lot inspection*.
Part 2:1993, *Specification for sampling plans indexed by LQ for isolated inspection*.
Part 3:1993, *Specification for skip lot procedure*.
Part 4:1994, *Specification for segregated sampling plans*.
Part 0:1996, *Inspection by BS 6001 attribute sampling system*.
MIL STD-205 E, Military Standard 205 E, *Sampling procedures and tables for inspection by attributes*.
MIL STD-414, Military Standard 414, *Sampling procedures and tables for inspection for product defectives*.
BS 7782:1994, *Control charts: general guide and introduction*.
BS 7785:1994, *Shewart Control Charts*.
BS EN ISO 9001:1994, *Quality systems—model for quality assurance in design, development, production, installation and servicing*.
BS EN ISO 9002:1994, *Quality systems—model for quality assurance in production, installation and servicing*.
Pharmaceutical Supplier Code of Practice (obtained via Institute of Quality Assurance, London.) (i) *The manufacture of printed materials for use in the packaging and labelling of medicinal products (document reference P00021).* (ii) *The manufacture of medicinal product contact packaging materials (document reference P00022).*

The Orange Guide, *Rules and guidance for pharmaceutical manufacturers and distributors* 1997 (London: The Stationery Office).
Code of Federal Regulations, CFR 21 Parts 200 to 299, Part 210—*Current good manufacturing practice in manufacturing, processing, packing or holding of drugs; general*. Part 211—*Current good manufacturing practice for finished pharmaceuticals*.
Rules Governing Medicinal Products in the European Community, Volume IV, *Good manufacturing practice for medicinal products*.
United States Pharmacopoeia and The National Formulary, USP 23/NF 18.