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THE PACKAGING FUNCTION: MANAGEMENT, DEVELOPMENT AND PRODUCT SHELF LIFE

D.A.Dean

Packaging management

It must first be stressed that the packaging function cannot and should not be separated from the product, particularly as the pack primarily serves as a means of selling and protecting the product. The functions within a company which are either directly or indirectly associated with packaging become more diverse in terms of individual job responsibilities as a company increases in size. Whereas in a small company one person may cover every activity and probably not realise that one is involved in packaging, many specific jobs can be identified with larger companies. Although the job titles may vary, the list below covers most of the major activities. These are not listed in any particular order of importance, and a study of various companies will establish that the authority endowed in a specific function varies significantly, depending on whether the overall activities are marketing, purchasing, development, engineering-oriented, etc. Any one of a number of areas could therefore have the responsibility of leading a packaging co-ordination function. The following job titles or activities are frequently found in the pharmaceutical industry:

- marketing and sales
- packaging supplies buying, packaging buyer or package purchasing
- supplies manager, warehouse supplies, warehouse manager, finished stock manager
- package development, packaging technology, pack or package research or engineering
- production, product manufacture and packaging
- production engineering, machinery purchasing, spare-part supplies and maintenance
- analytical method development for product and ‘pack’
- pack design, packaging design—graphical and functional; design purchasing
- legal aspects of packaging; legal department
- works technical, technical support—usually based as a support function to production
- quality control (QC), packaging
- quality assurance (QA), packaging
- specifications, pack assembly details, general documentation associated with packaging (may be seen as an administration/clerical function)
- transportation manager
- project management and packaging co-ordination management
- market research—user opinions/attitudes
- clinical trials—particularly relevant where pack is administration-oriented
- costing, package costing
- regulatory affairs (product—pack registration)
- medical—advising on dosage regime, method and site of administration
- formal stability testing and ongoing product stability testing.

The functions which these disciplines broadly cover can be expanded as follows.

Marketing and sales

This area is usually involved in defining the product and pack marketing requirements; identifying competition; stressing the importance of the dosage regime; maximising compliance, optimising the mode of administration; considering marketing strategies in conjunction with medical support and clinical evidence; assisting with instructions for leaflets and publicity for both OTC and ethical products; establishing prices and profit levels; calculating initial launch quantities and predicting future

sales for all the markets in which the product will be sold; deciding a target date for launch; and dealing with initial launch strategy, sample packs for the profession, prelaunch publicity, training of representatives and, in particular, how to introduce and 'pitch' a new product image. Instruction on product administration may also be advised, in conjunction with medical opinions.

Packaging supplies buying, package buyer, package purchasing

Responsibilities are likely to cover purchasing of packaging supplies; identifying possible suppliers; evaluating suppliers commercially and technically; inspecting suppliers' premises and noting documentation; evaluating ability of suppliers to meet delivery dates in terms of quantity and quality (auditing of suppliers or contractors is usually a joint function with QA/QC, sometimes with assistance from development staff); keeping abreast of new packaging developments and obtaining samples/supplies; co-ordinating technical liaison between internal and external expertise as it affects commercial activities; and advising on suitable contract packers.

Supplies manager, warehouse supplies, warehouse manager

This usually involves the planning of deliveries, the warehousing of both raw materials and finished stock, covering possibly ordering (supplies management), storage and movement from and to the warehouse and all closely related functions; defining how materials must be handled to prevent damage, stacked in a suitable manner and under suitable conditions, held in quarantine until cleared by QC; organising proper and effective identification with consideration being given to re-examination should materials be stored for prolonged periods or subjected to adverse conditions; stock keeping, correct rotation of stock, cleanliness and environmental control of premises, maximising use of space, controlling revenue and capital budgets related to warehousing and the movement of stock; knowledge of handling methods, stacking systems (automated or otherwise), types of pallets, stillages, etc. and their maintenance, etc.; introducing and operating computerised systems where these are cost-effective and relevant to stock control.

Packaging development

This may be called packaging engineering, packaging research, packaging technology, etc. in some companies. Package development is normally closely related with product development. The function covers knowledge of packaging materials; investigations into basic materials, packs and packaging systems; carrying out feasibility/investigational programmes on primary (immediate) and secondary packs with the product, devising test procedures for product and pack; establishing packaging procedures for formal stability tests; creating provisional and completed (verified) specifications in liaison with QC, engineering, etc.; providing, proving and updating test methods for materials and finished packs; recommending pack assembly methods; assisting in the selection of packaging equipment; considering cost saving exercises. It may have its own analytical support activity and an internal QC type unit.

Production function

Production covers the manufacturing of the pharmaceutical formulation, the holding of the product under bulk storage until cleared, and the carrying out of the packing of the product. The last of these involves the organisation, training, safety, maintenance and control of packaging lines covering the primary and secondary packaging operations. Since line efficiency and output depends not only on the machinery but on maintenance and the quality of the materials, close liaison is essential with those involved in specifications, QC, development, machinery, safety, engineering, etc.

Production engineering, maintenance and machinery purchasing

Production engineering is likely to be associated with the purchase of packaging machinery, the life expectancy of machinery, the care and maintenance of equipment, the training of maintenance fitters and basic production line training of management, supervisors and line operators. To achieve these functions effectively, good knowledge is required on materials, pack components and pack specifications. As a result, engineering is usually involved in the pack specification clearance to indicate that the specification is compatible with the machinery requirements.

Works technical, production support

Production support and works technical type functions are frequently operated as a support activity to production and may cover chemical and formulation processes, packaging, etc. concentrating on product—pack introductions, including scale-up operations and cost savings which are broadly related to any part of the 'production' process. Many of these activities require a technical and scientific support group covering, in the case of pack changes, packaging operation changes, further evaluation of both the primary and secondary packaging and related equipment technical 'qualification' (i.e. validation) and efficiency. Such a unit may operate a similar packaging operation to the initial packaging development area, covering production line assessment, feasibility testing of new and changed packs, including packaging materials, which is supported where necessary with full stability testing. Some companies may limit such tests to, say, a year or six months until equivalence is established with the previously cleared pack. Although this approach may be quite suitable for minor changes, it is essential to generate actual long-term stability data where significant product or pack changes are involved. Placing the first production batches (usually three) on stability test following a proposed change is one way of confirming that the change was acceptable, assuming initial judgement recommended this from earlier evaluation investigations.

Production support activities may also fall under packaging development (related to initial drug discovery of new products), engineering or production.

Pack design

Pack design can be divided into graphics/aesthetics and function. The latter cannot usually be divorced from development and therefore is part of the initial product—pack activities prior to the launch of a new product. Graphics is closely linked with the market, sales, publicity and legal requirements of the product and pack. It is therefore possible to have a separate graphics department or a graphics buyer whereby designs are carried out by external agencies. Alternatively it may be found as an internal activity under one of the other main disciplines (i.e. marketing, general purchasing, packaging development, etc.). Both functional and aesthetic design may involve market research so that external (or internal) opinion is sought on how best the product can be presented and administered. In total, pack design must provide a suitable marriage between graphics and pack performance and consultation with production on where and how variable detail such as batch coding and expiry dating is added. DAR (digital artwork and reproduction) or DTP (desk top publishing) can be used to assist graphic design.

Legal aspects (see also Chapter 3)

The legal aspects of packaging are always broadening. They cover a wide range of legislation which may include product (and pack) liability—general function including accuracy of dosage administered (where relevant) and risks associated with the product, any hazards associated with pack usage, etc.; and correct description and wording as per labelling legislation. In the UK up to fourteen pieces of information are required on most packs. Fewer are required on smaller packs where the area limits what can be legibly achieved. Legal aspects also include type of sales category (e.g. prescription only), permitted phrases (e.g. 'keep out of the reach of children') and general medicines and poisons regulations.

Quality control and quality assurance, and specifications

These two 'quality' titles are not synonymous, although they are occasionally used indiscriminately. QC can be defined as the function responsible for the maintenance of quality to an agreed standard. QA covers the activities and functions concerned with the attainment of quality, i.e. building quality into processes by broad association with GMP, GLP, etc.

The control of quality may be covered as a central function where incoming raw materials, intermediate and manufactured chemical entities, intermediate and bulk formulations, packaging materials, the packaging line, the packed end product, complaints, etc. all undergo some form of check or analysis. The same function may also be responsible for the analysis of development work (on new products or modifications to product-pack of an established product), the checking and validation of new methodology/equipment, supplier audits and the formal stability programme. Close liaison between packaging QC and packaging development has distinct advantages and these two functions may sometimes be under the same management. Specifications are always a common link to both, as these activities tend to be the basis of any project. A provisional specification is essential for any material before it is subjected to a test procedure, irrespective of whether it is related to feasibility, stability studies or subsequent ongoing production. Specifications are also built up over a period of time (tentative, provisional, agreed or verified). As a result of this, specifications are likely to be initially established via a development operation and then handed over to a QC function. This transfer is the most important part of any liaison link and it should be likened to baton change-over in a relay event, and not one where responsibility ends when the other receives the specification. Best motivation is frequently achieved where the QC operation is involved in the stages of development, and 'development' has a

responsibility with a new product—pack until it has been 'successfully launched'. This latter phrase has been deliberately selected since the time scale to define when a product is successful may vary with each launch, i.e. usually the first *x* batches or 3, 6 months of a new production operation.

'Specification' must be looked on as a word which can be used to describe a number of activities whereby a process, an assembly or a material is defined and agreed between a number of parties. The ultimate success of any product is therefore related to having:

1 a specified product including the processes by which it is manufactured, with individually specified ingredients
2 a specified pack including the materials and components from which it is assembled
3 a specified method of assembly of product-pack and the processes involved, e.g. standard operation procedures derived via a product manual.

Where relevant, process detail should include environmental conditions (humidity, temperature, time, duration, etc.); documentation of procedures, tests, etc.; details of records to be kept (GMP); written instructions for operators; reference to machinery to be employed; etc. It can therefore be concluded that an effective level of specification is required for any pharmaceutical product and the appropriate detail must be similarly treated for the packaging function. As specification detail and tests associated with specifications frequently show a tendency to expand with time, it is important that these are constantly reviewed in terms of both the quality level necessary and the procedures by which materials are judged as satisfactory. Although the setting-up of a specification system is relatively simple, maintenance and updating frequently cause problems. It is therefore recommended that any specification distribution system have the absolute minimum of recipients.

The tendency to have a pack component specification which is all-embracing is also changing. A simpler procedure utilises a series of information documents which lay out the procedures that a supplier has to follow for selective package forms, i.e. glass bottles, plastic bottles, laminates, labels, collapsible tubes, etc. It is then possible to have an abbreviated specification document which covers critical, major and minor defect classifications, advice on delivery and identification, and basic information on the material to be employed, etc. The specification therefore cross-references to its respective information (component manual) document and becomes considerably simplified in terms of both layout and detail. This is particularly important now that specifications are being computerised in conjunction with stock control and purchasing.

The main areas of packaging/pack specification are as follows.

1 Basic packaging materials and components (possibly divided into purchasing and performance specifications).
2 Finished pack specification:

- normally requires an agreement between user and supplier, i.e. acts as a purchasing specification; occasionally there may be a separate 'performance' document
- an in-house standard which will be acceptable to marketing, sales, medical, development, production, QC, etc.

QA/QC plays an important link role in the above. However, there are no hard and fast rules on the area that should create, issue and control any specification system. With the advent of computerisation, the 'control' may arise from those who are most competent to initiate and maintain computer programs.

Transportation—direction and control

This involves the safe movement of goods to agreed time schedules supported by adequate documentation. Since no pack can be expected to meet every rigour of transportation, packs are normally produced to withstand certain handling conditions plus a safety factor. Studies are therefore required of transit conditions irrespective of whether own transport, contractor's transport or nationalised transport is used. Actual conditions will vary between air, road, rail, sea and inland waterways. Knowledge is equally essential of intermediate storage/transhipment points which may be encountered on a journey. As products move from home trade to export the supportive documentation becomes increasingly important. Since the cost of transportation may relate to either size or weight, the economies of transportation may vary significantly according to the materials of the primary pack, the size/weight of contents and the secondary protective materials. For some export markets the use of containerised loads is likely to be more economical.

A study of warehousing arrangements external to the producing company, the handling facilities, types of pallet and stacking systems is also required as part of the total evaluation. Due attention must be given to hazardous goods, in terms of safety and adequate labelling.

Project management and package co-ordination

Project management operating across the hierarchical systems by a matrix approach is being increasingly used within the pharmaceutical industry, particularly where new products are involved. This usually brings together all the major company packaging disciplines previously identified. However, as the role of the pack becomes increasingly important, a separate packaging co-ordination role may be required to bring together all those who can contribute to the successful launch of a product.

The costing of projects both before they commence and during progress is an essential part of project management. There is also the costing of the product—pack so that the sale price can be worked out at an early stage, covering the various stages of profitability, i.e. pharmaceutical company, wholesaler, retailer, etc. Methods of costing covering production, materials, direct and indirect costs, etc. tend to vary between companies, hence the most important feature is to compare like with like. Fully effective cost comparisons are sometimes difficult to achieve as, depending on how a product is packed, significant costs (or cost savings) may be incurred in warehousing and transportation. How materials are warehoused and whether transportation relates to weight or volume, partial or full loads, etc. is frequently a neglected aspect of the total packaging operation. The difference between the production cost (into the company's warehouse) and the cost sold on is normally referred to as the 'contribution'. Profit is the part of the contribution remaining after various other costs such as warehousing, distribution, etc. are deducted. Since warehousing has become a costly operation, longterm storage reduces profitability, hence the justification of 'just in time' philosophies (JIT) which improve cash flow.

Final thoughts on packaging management

A company's reputation depends largely on how it is seen by the outside world. Part of this outside world includes those who supply to the company. Too much diversification of job responsibilities may make it difficult and confusing for such supplying companies, especially when they are contacted by a large number of persons, i.e. works technical, engineering, project management, production, design management, development, purchasing, etc. Although two levels of contact between users and suppliers are obviously desirable, i.e. commercial and technical, some central coordination is required to monitor all levels of information exchange. The initial choice of supplier for a new product concept tends to be particularly difficult, as a number of functions within a company may consider it their responsibility. There are dangers if the QC-GMP type operation of an external company is judged too critically at this early development stage, as quite a number of projects are not likely to reach fruition. Choosing a company because it operates an excellent QC system may therefore be fruitless if the expertise within the supplying company is insufficient to meet the design demands of a new concept. The author argues that it is easier to teach quality man agement than innovation, since experience has shown that entrepreneurial innovative companies have been condemned because of a lack of initial investment into quality standards.

Packaging management ideally should involve the total co-ordination of all direct and indirect packaging activities. Once a company has recognised that packaging is an essential activity, then any of a number of systems will undoubtedly satisfactorily control this function. In fact many companies simply leave these contributory factors to reach their own level, relying on individuals to compensate for any over- or underemphasis of specific areas. However, the most effective system must be where there is some centralised control, probably through a packaging co-ordinator.

A check on the total cost of all incoming materials may frequently reveal that incoming packaging materials cost more than those ingredients which are 'product'-oriented. Although this may be overlooked, added value ultimately becomes the main yardstick by which cost-effectiveness is measured.

Finally, no management system can be considered without the support of a planning operation with various types of bar charts, PERT (Program Evaluation and Review Technique) charts and full critical path analysis. Although these systems are a useful tool for management, occasionally there is a risk that the system takes over management.

Product and pack development

Following the above introduction to total packaging management it is necessary to revert to the main aspect of the pharmaceutical industry, i.e. the development of new products and packs. For this part of the exercise the technical detail will be defined, rather than the management system by which the end-point, i.e. the successful launch of a product, is achieved.

The first requirement for any development programme is to identify the type of development involved, i.e.

1 new product—new pack (note that a new pack may be a modified existing pack since all new pharmaceutical products must pass through a full development programme)
2 existing or established product in a new pack, i.e. a major pack change

3 major product change (reformulation of a product) associated with a major pack change or no pack change; could be a product extension e.g. a new disease treatment
4 minor product change-no pack change (possibly limited testing required)
5 existing product-minor pack change (possibly limited testing required)
6 special pack with existing product or new product for promotional purposes, usually distributed to professional people or used by representatives for demonstration purposes
7 pack either acting as an administrative aid or being used in a device (note that this can apply to any of the above).

The next and probably the most important stage is the defining of *objectives*. This includes what is generally known as a packaging brief, covering the more important packaging aspects listed below.

1 Product name/identity, i.e. project title.
2 Route of administration, likely dose, dosage frequency, etc.
3 Detail of product characteristics, i.e. physical, chemical and biological properties.
4 General pack requirements:

- type of pack suggested
- pack sizes, primary and secondary; warehouse versus distribution number for transit pack
- product strengths
- any special requirements, e.g. tamper-evidence, child resistance, administration aids.

5 Estimated sales, against initial launch and follow-up quantities; territorial sales, initial and follow-up.
6 Suggested launch date; initial launch (which territories?); other territories—priorities.
7 Tentative cost schedule for product-pack.
8 Any special legal requirements, e.g. product category, poison schedule, weights and measures, labelling.
9 Customer requirements—may be unknown initially, but simulated usage is essential as pack is probably more likely to fail during use than when it remains unopened.
10 Similar products on market, i.e. competitors' products and costs.
11 Safety hazards if relevant, i.e. internally and externally, including pack—product liability.
12 Any environmental issues, restraints.

If it is assumed that most pharmaceutical companies will have some form of pharmaceutical/packaging development operation, then the activities which stem from the above brief are likely to involve the following.

Keeping up to date on materials, components and innovative packs in terms of physical and chemical properties—note that pharmaceuticals use virtually all materials offered and therefore this field is not only as wide as in any other industry (food, confectionery, etc.) but requires greater in-depth knowledge and background investigation. Most companies will therefore need to do some type of research investigation on components, materials, packs and test procedures on an ongoing basis. The above serves to strengthen the information base line within any company. Note that certain pack innovations can be patented, hence extending the patent life of product.

Assisting in or actually specifying the packs to be used for any R&D investigation, i.e. covering safety, animal and human studies (clinical pharmacology), clinical trials, as well as formulation development and package development. These activities also provide a useful source of early information on product-pack compatibility which can be supported by pack observations and general stability-type studies (see Chapter 3).

Feasibility or investigational tests

This phrase normally covers any tests carried out between the areas of formulation, drug substance, and packaging to establish the suitability of possible packs and materials. It is important that any material used is covered by a provisional specification and then cleared through a formal QC process prior to being used for a test. The indiscriminate use of unidentifiable materials (e.g. testing in 100 ml plastic bottles where grade and type of material cannot be identified and/or bottles which have not been cleared by a closure test) serves virtually no purpose. It should be noted that challenge tests carried out on chemical entities, preformulation studies and formulation studies should provide excellent knowledge of how a product is likely to deteriorate, i.e. through moisture, oxygen, carbon dioxide, losses due to migration, etc. Packs with the required protection characteristics can be readily selected once compatibility studies (part of the feasibility programme) have been covered. Developing test procedures to evaluate materials and packs is also part of the development programme. Where suitable, such tests may

ultimately become part of a more formal QC clearance procedure. This stage needs the services of an analytical unit, certainly for the full identification of plastics.

Formal stability tests

The final stage of any product—pack clearance is usually a formal stability test. Although this is basically an analytical programme, packaging examination and pack analysis should also form an important part of the procedures. The final assessment of shelf life should therefore be agreed by a number of interested parties, i.e. analysts, microbiologists, formulators, packaging technologists, etc. Any use of accelerated testing in either the feasibility or the stability programme also needs careful evaluation, as changes in the pack may occur that will lead to incorrect interpretation of results. For example, a closure on a pack may loosen and/or tighten under broad cycling conditions due to dimensional changes associated with temperature and relative humidity. Similarly, in a static condition test where samples are prepared at, say, 18°C and then stored for a prolonged period at a higher (e.g. 40°C 75% RH) or lower temperature (refrigerator), differential expansion and/or contraction between container and closure may cause loosening or tightening of the closure. Measurements are essential at all temperatures as too often packs are allowed to equilibrate with the laboratory environment before being checked. The use of temperatures above 45°C or 50°C also tends to cause some changes, both physical and chemical, with many packaging materials, any of which may subsequently lead to product deterioration.

It is therefore important that all packaging support work is meaningful, as inadequate attention to detail can totally invalidate even the most technical and scientific stability programmes. When stability work is carried out by an area well divorced from packaging development there is an inherent assumption that packaging work has been adequately and effectively done. A list of this work, taken from the introduction to packaging development given earlier, therefore bears some expanding, since this clearly identifies further areas of possible weakness where a 'company' may be caught out.

Packaging and stability (the formal estimation of shelf life)

Companies frequently see a 'formal stability test' as the ultimate stage which confirms that there is a satisfactory product-pack with an established 'shelf life'. It must therefore be stressed that this approach is only relevant if all the supporting activities have been adequately covered. Although the stages identified below make major reference to plastics, similar detail is essential for the approval of any (primary) material. This is particularly relevant when ICH and EU guidelines are considered, as these make assumptions that the activities listed in the remainder of this section have been effectively carried out.

The formulation and packaging disciplines have carried out adequate investigation or feasibility support work to establish the functional and aesthetic aspects of the pack, both primary and secondary. The primary pack (US terminology—immediate pack) may be defined as the pack which is in immediate contact with the product, and the secondary pack as the ancillary materials required for presentation, information, warehousing and distribution purposes. Feasibility or investigational work may involve information-gathering on the pack and its components, etc. (i.e. basic research into materials, packs and processes) and compatibility studies, accelerated or otherwise, on the product and pack.

The materials used for the primary (and secondary) pack, even if constituents are non-migratory, are non-toxic and non-irritant and this information can be adequately supported by the study of:

1 the constituents in the materials (the material itself)
2 toxicological data on the constituents
3 the availability of adequate analytical methods to detect migration, or surface removal should it arise.

It should be noted that constituents in terms of plastics could include *residues* (from the polymerisation process), *additives* (ingredients added to enhance or modify certain properties), *processing aids* (ingredients added or used to assist in a fabrication or conversion process, e.g. mould release agents, lubricants), and *master batch* constituents (if a master batch is used).

Sufficient in-depth extractive and compatibility investigations have been carried out to establish likely level of extractives with conventional simulants and the actual product(s). Note that exchange between product and pack may occur in either direction (and with materials other than plastics).

Note also that although EP, USP and WHO extractive procedures (see also BS 5736 parts 1–10) give only limited information and are usually mandatory only for eye products and injectables, this type of test may be useful for company assessment of various types of plastics. Compatibility tests at the feasibility stage may involve so-called accelerated or stress conditions. It should be recorded that higher temperatures may in some way either destroy the pack or make it less effective,

with the result that the product is no longer fully protected by the pack. Thus, unless these higher temperature conditions are to be found in practice, some accelerated tests may not provide realistic extrapolations.

Provisional specifications have been created for all packaging components, and these are subsequently used to clear all materials through a QC plus type operation prior to use in any tests, irrespective of whether these are feasibility or formal stability studies. Procedures should include (for plastics) material identification (by IR, UV, differential scanning calorimetry (DSC), etc.), physical assessment including dimensions and functional tests, and should be of greater technical and scientific depth than the QC procedures used for subsequent regular incoming production materials (hence the use of the phrase 'QC plus').

Repeat the previous paragraph creating a provisional product specification and in particular have complete and comprehensive records of how the drug entity was produced and the formulation processed into a product. Note that any subsequent changes may not only require monitoring but possibly lead to further stability work to support the product stability profile (i.e. scale-ups).

Accurate details are kept and recorded on how the product—pack was processed and assembled. This detail should include reference to environmental conditions, machine types, speeds and settings, heat seal strength, cap torque, fill volumes, etc. and where, when and by whom the operation was performed, etc.

One should constantly recall that a static stability test does not cover those effects likely to be associated with warehousing (in bulk), handling, transportation, display or use. It is essential that other tests cover these aspects to ensure that stability data is not invalidated. This may be done by the use of either laboratory simulated tests or actual 'field trials'. Top pressure (compression) and/or vibration is likely to present one of the more serious hazards.

One should ensure that packaging evaluation work where possible includes 'control' packs and involves recognised test procedures in order to provide good comparative type data, e.g. tests to show moisture loss or moisture gain, changes in closure torque and heat seal strength on storage. Test procedures should involve adequate analytical and instrumental support. Remember that, even in a scientific society, the use of observation to detect visual and organoleptic changes is still invaluable (e.g. touch, sight, taste and smell). This work should cover not only the primary pack but the secondary packing (effects of storage, stacking, vibration, etc.).

One should ensure that in use testing, patient acceptability and possible abuse and misuse aspects are adequately covered and interpreted, since most formal shelf-life testing does not involve any 'use' of product and pack. It is possible that the product—pack may have a restricted shelf life once the pack is opened and is in use, i.e. it may occasionally be necessary to have two shelf-life periods, e.g. for reconstituted and/or overwrapped products:

- for the unopened pack, e.g. 3 years plus
- for the opened pack, e.g. 'use within 4 weeks' or 'the contents should be discarded after one month', etc.

There may be differences between the product—pack formally stability tested and the pack to be sold. It is essential that all 'differences' are considered and, where relevant, investigated. Although there may be a firm intention to test the pack to be ultimately sold, there are frequent (and almost invariably subtle) differences either from the primary pack or arising from the fact that the primary pack is rarely tested together with the secondary (warehousing, transit or display) packaging materials. A typical example is where an entirely new pack is to be produced and the 'economics' do not permit the laying down of production moulds until the initial concept has been proven. The options then are:

- to test in the 'same materials' using a similar design of pack
- to test in the correct design using packs produced from a single impression prototype tool (using the materials of choice)
- to test in similar materials using the nearest size which may in fact be significantly different in design (i.e. product to pack surface area to ullage is different).

If tooling is required for both a bottle and a closure, then the situation is further complicated by even higher tooling costs. Also, if a pack either acts as or incorporates a delivery system, often tooling may become even more complex and costly, particularly as the number of components involved increases. However, as the pack becomes more complex there is a greater need to complete stability work on the pack to be ultimately used, as this decreases risks associated with possible anomalies.

Stability samples and any samples used in evaluation programmes (including clinical trial supplies) should be subjected to QC evaluation inspections:

1 at commencement of programme
2 at various stages during any lengthy storage period (e.g. roving inspections)
3 on removal from test condition for assessment
4 during opening
5 after use or evaluation of product.

An adequate number of additional samples should be included in each programme to allow for 'destructive testing'. In the case of samples withdrawn for analysis, these should be examined visually, any critical parameters recorded (e.g. cap torque, if relevant), and then examined in detail prior to disposal.

The data generated from any programme, whether formal or otherwise, should satisfy both the company and the regulatory authorities. It is therefore important that all testing procedures leading to a 'decision' be well recorded in notebooks (GLP) and then, when written up as a formal document, checked and signed by a responsible person. These will form part of the 'Validation' archive.

The data leading to final product and pack specifications, with accompanying standard operating procedures, should support all the work earlier carried out to approve the product and pack.

All companies should work towards a total data philosophy, whereby all data, literally from inception of drug to ultimate discontinuation of product, should be used to justify not only stability, but also safety, efficacy, quality and integrity, in order to safeguard both the position of the company and the ultimate patient/user.

Drug substance

There is one important stage which must occur prior to the start of any work where stability on the drug entity, now referred to as the 'drug substance', must be performed. This work, carried out by a research or development function or an external laboratory, is now likely to follow the guidelines issued by the EU or ICH (harmonisation), which provide details on scale of batches, number of batches, environmental storage conditions, information on packs, etc. Since this work also needs input from 'packaging', a further check list is advised along the previous lines to make certain that nothing is overlooked. It must be noted that the pack, although not destined for a patient and not primarily for sale, may in the long term be sent to another factory, a contract packer or another company.

In the case of established drug substances (as used for OTC products), the formulator must be satisfied that adequate stability data exist (by reference searches) prior to using it in a formulation. These data also become part of any regulatory submission, independent of the source. It is too easy to assume that every other company's product has been thoroughly tested. Some examples of where problems have occurred, with reference to the above, are given below:

Example of inadequate monitoring between the pack tested and the pack adopted

(See the paragraph commencing 'There may be differences' (p.45).) A device (separate to a pack) which used a rubber bulb was stored under a range of conditions and observed for deterioration (visually and performance). None was detected. It was subsequently packed in a dark-coloured carton, marketed, and no problems occurred. It was later packed in a printed white carton with a polypropylene film overwrap (to give a degree of tamper evidence). The white carton changed slowly to a yellow-orange colour as a volatile organic copper ingredient from the rubber bulb, retained by the polypropylene film, caused carton discoloration. This was lost through the previously non-overwrapped carton, without detection, partly due to the printed dark colours and partly because it escaped into the atmosphere.

Example of where low temperatures gave an accelerated effect

Zinc and castor oil cream was tested in a polystyrene jar using a four start lug finish to simplify removal of the closure (mother holding baby). Samples were stored at 4°C, 20°C, 30°C and 37°C. Jars cracked at the four stress points created by the four lug closure, first at 4°C then at the higher temperatures in ascending order of temperature (i.e. 6 weeks, 3 months, 7 months, 10 months). The subsequent use of an impact modified polystyrene with the return to a conventional continuous screw thread and screw cap ultimately provided a satisfactory pack.

Example of use of incorrect material and lack of initial specification detail

A strip pack using an aluminium foil/low density polyethylene laminate was used for a tablet containing volatile oil constituents. Delamination between foil and film subsequently occurred as the volatile constituents passed through the polyethylene and softened the adhesive bond. It was not known that the bond was an adhesive at the time, and subsequently an extrusion-coated laminate provided a satisfactory answer.

Example of insufficient investigation prior to formal stability

A neutral unbuffered aqueous solution was stored in a polyethylene bottle. The pH reduced on storage to 4.3–4.5 but reverted to 6.5 when the solution was heated. The change was identified as carbon dioxide permeation with the formation of carbonic acid. Possible solutions include change of plastic, an overwrap or possibly a buffered formulation.

Example of adequate investigations prior to formal stability (problems discovered then overcome by pack choice)

It was required that a veterinary iron injection be packed in a collapsible (for withdrawal of multiple doses) flask, and LDPE was chosen as a possible contender as this gave good collapsibility. However, the product was susceptible to oxygen permeation and a pH shift, and the phenol preservative system was apparently readily lost through LDPE. This information, given in a literature search, challenged the use of LDPE. Subsequent investigations showed that phenol loss into LDPE was very low and that the loss of the volatile phenol had been judged by the nose (external aroma). The flask, when packed in a paper/foil/polythene sachet, which restrained phenol loss, prevented oxygen permeation/degradation, pH change, etc., and subsequently provided a 3 year plus shelf life.

Example of ineffective monitoring of environment

(See the paragraph commencing ‘Accurate details are kept and recorded (p.45).) A part of a batch of an effervescent tablet packed in a foil strip pack subsequently ‘ballooned’ due to release of CO_2 within the pockets. A searching investigation showed that the dehumidification of the room where the product had been packed had not functioned properly for a short period, and that a reaction had resulted from the introduction of moisture to the product via higher RH. Although this change had been recorded on temperature—humidity charts, these had been filed as a record rather than read (reason: previous charts had not shown problems).

Lack of process monitoring

A sterile product was prepared for stability using a hand plugging, capping operation due to the non-availability of automatic equipment. The team doing the plugging and capping used rubber gloves, lubricated with a sterile glove powder based on starch. Examination of the product prior to placing under test revealed a ‘haze’ in some samples which was subsequently identified as grains of starch that had become detached from the gloves. Procedures to clean gloves prior to use had not been followed. The batches had to be remade, thereby causing delay in registration and launch.

Although these examples clearly identify some of the risk areas associated with packaging and the need for good laboratory practice (GLP) and GMP covering adequate records of all activities, this type of thinking may well have to be extended outside the true development area. For example, many companies tend to assume that bought-in materials are adequately packed and are stable for, frequently, an indefinite period. This assumption needs to be questioned and if an ingredient is to be stored for prolonged periods some allowance for re-analysis is always advisable, particularly as some products and packs may never have been subjected to any formal assessment (now being advised in guidelines). Equally, data produced 10 years ago may be inadequate.

Most companies have systems involving retention samples of ingredients, intermediates, completed formulation, etc. which are sometimes based on the assumption that all retention packs are perfect. The author has on a number of occasions discovered totally unsuitable packs being used, i.e. small polyethylene bags, polystyrene tubes and PVC bottles or glass with an unsuitable closuring system. Even such packaging systems therefore need monitoring, if reference to an analysis of retention samples is to be meaningful should complaints arise. One further aspect is the handling of materials in house. It has been noted that ingredients may occasionally be transferred and stored in polyethylene bags, or formulations or intermediates in a process stored for unexpectedly long periods, in containers which have not been shown (or proved) to be suitable. Instances have also been known where changes to equipment (e.g. the introduction of plasticised PVC tubing or the use of non-approved filters) have introduced migratory ingredients or particulate matter into the product. Validation procedures should prevent such occurrences in the future.

Shelf life

The ultimate shelf life of any product may, in certain instances, depend on and be influenced by how and in what containers and materials the ingredients and the intermediates are stored, prior to and during processing, including bulk storage of the product, until the time when it is packed into the pack for sale.

It can therefore be inferred, having identified some of the possible areas of weakness/risk associated with establishing a product—pack shelf life, that no company has yet found the ultimate means of estimating and approving the 'best' pack which will guarantee optimal shelf life for all times and conditions. The latter part of this chapter will enhance this point in that all packs finish up as a compromise of a number of often conflicting factors.

However, before moving on to these aspects, the converse of the above examples of 'risk' could be counter-balanced by asking how realistic is your predicted shelf life as identified by initial investigative tests.

Shelf life based on moisture loss or gain

The rate of moisture transfer via a pack by permeation or the seal/closure depends on a number of possible variables, including the following.

1 The vapour pressure gradient between the environment inside and outside the pack (the greater the gradient, the greater is the potential for moisture transfer detected as loss or gain).
2 Whether the external environment is 'static' or has a constant air circulation (which encourages maximum gradient conditions).
3 The presence or otherwise of temperature changes which will cause changes in vapour pressure and gradient, plus such other factors as:

- material gauge or caliper
- effectiveness of the seals
- nature of the barrier material and how it absorbs moisture (i.e. whether it has a low or high moisture content at equilibrium)
- nature of the product and level of moisture content (which again will reflect on the vapour pressure exerted for a given temperature).

Although each of the above (and other) factors will contribute to how a product in a pack may lose or gain moisture, factors (1) and (2) will have a major influence. This is supported by the following example.

Example

If a moisture-sensitive product is packed in a UPVC blister pack lidded with 18–20 µm hard foil, it is likely that this pack will be 'proved' unsuitable if samples are exposed, naked in a climatic cabinet, at 25°C 75% RH or higher conditions, e.g. 38°C 90% RH, using a fan-driven environment. Therefore let it be assumed that the product shelf life under say, 25°C 75% RH conditions is 6–8 weeks. (Note that using more protective PVC 4+ barrier combinations might give 24–30 weeks with 100 g/m coating of PVdC and years with an Aclar/PVC combination.) However, this does not take into account

1 the fact that the environment transfer can be slowed down by considering various 'overwrap' options
2 the fact that placing blisters in a carton, twelve cartons in an outer, four outers in a shipping outer, 240 outers to a pallet and then adding a shrink hood could extend the shelf life to over 2 years (even at 25°C 75% RH), if held for that period as a full pallet load.

The additional overwraps which might be considered could include:

- a PVdC coated PP flow wrap for *x* blisters
- a carton with a PVdC/PP overwrap
- an outer pack of *x* units (e.g. six or twelve) fully shrunk or overwrapped
- a pallet load of outer packs fully shrunk or stretched wrapped.

Basically each overwrap changes the gradient around the pack (between the inside and outside of the pack) and adds an additional barrier through which moisture has to permeate. Theoretical calculations for a multiplicity of barrier layers need a fairly complex mathematical appreciation and practical estimates may be equally difficult, as either a pallet will not enter a climatic cabinet or the cost of samples could be prohibitively high, with an expensive product kept on test for a prolonged period.

Table 2.1 must inevitably raise some queries, e.g. how does continuous exposure to 25°C 75% RH equate with actual *fluctuating* conditions, i.e. is it an accelerating or decelerating effect? How does 25°C 75% RH equate with 48 months under

normal warehouse conditions where both the mean temperature (say 14–17°C) and the RH (40–55%) will be significantly lower? How effective are the overwraps, particularly with reference to seals and as a barrier to moisture? This will also depend on tightness of wraps and airspace therein. How does one know the period that each (1–5 in Table 2.1) will be stored for, and the climatic conditions involved?

These unknowns can partly be covered by shelf-life declarations, particularly when the final blister is removed from its last overwrap, e.g.:

- 'This product should be used within *x* months following removal from…'

Table 2.1 Variation of shelf life with packaging and conditions

	Pack A (with flow wrap)		*Pack B (no flow wrap)*		*Storage*
	Description	*Shelf life*	*Description*	*Shelf life*	
1	PVC blister foil lid	6–8 weeks	PVC blister foil lid	6–8 weeks	at 25°C 75% RH
2	+Flow wrap	25–30 weeks	Excluded		at 25°C75%RH
3	+Overwrap in carton	80–90 weeks	+Overwrap in carton	25–30 weeks	at25°C75% RH
4	+Overwrapped outer pack	3½–4 years+	+Overwrapped outer pack	2½–3 years	at 25°C75% RH
5	+Shrink wrapped pallet	4½–5 years+	+Shrink wrapped pallet	3½–5 years	Normal warehouse conditions
		(no change detected after first 60 months' storage as a full pallet)		(no change detected after first 48 months' storage as a full pallet)	

- '*x* will normally be either equal to the 25°C 75% RH shelf life (tropical, subtropical conditions) or greater than this, e.g. 2*x* (for temperate markets).'

It can be concluded that a series of overwraps will significantly extend the shelf life of, for example, a moisture-sensitive product as moisture permeation is considerably reduced and/or a low barrier primary material may give adequate protection. This counters any need for an improved pack as found under the ICH 40°C 75% RH conditions.

Thus if one tests blister packs in a carton (possibly overwrapped with a protective film) and from this predicts a shelf life, under actual conditions it could be expected that a much longer life could be achieved, i.e. the prediction has probably built in a significant 'safety factor', e.g. 6–8 weeks (no shelf life) has been extended to up to 60 months.

It should be noted that formal shelf predictions can be checked in the long term by withdrawing samples for analyses from various marketing conditions (home, export, warehouses, hospitals, etc.) and from home storage points. This is usually considered to be part of an ongoing stability activity.

Under the earlier definition of packaging as the *economical* means of providing *protection*, *presentation*, *information/identity*, and *convenience/containment/compliance* for the full life of the product during storage, carriage, sale, display, and use and until such time as the product has been used, or administered or simply disposed of, most packs inevitably finish up as a compromise. Since no compromise can ever be considered as perfection, it has to be recognised that in a human judgement reached by humanly devised evaluation (tests), some risk of failure (even if by misuse by the ultimate user), however small, is invariably present. It can, therefore, be concluded that even the apparently 'best' pack may not guarantee the optimal shelf life at all times.

For example, in this context, any pack which involves multiple opening and reclosuring almost always evoke the question, 'how often is the pack effectively reclosed during use?'. Since the answer may at least be 'not always', this can immediately create a case for an alternative unit dose pack which provides individual protection right up to the time of use, albeit in some instances at a higher cost per dose. There has also been a tendency towards introducing microbial limits for many types of product, and any support for these limits may be difficult to substantiate if gross contamination can occur during the product in-use period. Although it may be relatively easy to justify the absence of certain pathogens, it is more difficult to accept, for example, an argument for a sterile nasal preparation, especially as we do not continuously breath 'sterile air'. The *protective* aspects of the pack will therefore vary from product to product with differing emphasis on chemical (including compatibility), biological, climatic and mechanical protection.

With many pharmaceutical products the protective aspects of the pack may be both critical and diverse. It is therefore essential to identify clearly a range of hazards against which some products may require *protection*, especially as those of an obvious nature can easily be overlooked on the basis that 'familiarity breeds contempt'. The author therefore advises even the most

knowledgeable to use some form of check list under the headings given in Chapter 1. It is also important to remember that hazards tend to work in combination rather than in isolation.

The above should clearly establish that the many important functions of the pharmaceutical pack can be variable and complex. To emphasise this point, two further examples are given.

A sterile product incorporated a preservative system to cover withdrawal of a multidose liquid product. The product passed the USP XX microbial challenge test when first made and packed. After six months it was noticed that the level of ethylenediamine tetra acetate (EDTA) had significantly reduced, possibly by chelation with heavy metals + surface adsorption onto the plastic. A repeat microbial challenge test was not passed. It was 'theorised' that this was due to slight preservative loss coupled to the loss of EDTA which tended to enhance the preservative efficacy, i.e. a chemical + physical change (preservative adsorption) had created a drop in preservative efficacy. Changing the EDTA/preservative levels was subsequently necessary in order to meet the microbial challenge test over the full shelf-life period.

A powder formulation, diluent plus active of differing particle sizes designed to give an accurate dose when dissolved in water, was packed in a sachet. Immediate analysis indicated no problems. Subsequent analysis after transportation to a different site showed a drop in the active drug by approximately 5%. This was traced to preferential adhesion of the drug of the finer particle form (not the excipient) to the inner plastic layer of the sachet. The situation was corrected by an overage whereby the full dose could then be delivered at the drug solution stage. Sachet vibration tests could have established the above at an earlier stage, and avoided a new packing operation, which delayed the product launch.

If the phases covered above are considered as normal development procedures, then it is necessary to state that any packaging development operation has recently had to consider two newer aspects, i.e. patient compliance and the pack's relationship to such environmental issues as pollution, disposal and conservation of energy and the world's natural resources. It is obvious that a pack can either assist or deter patient compliance, and therefore greater emphasis may be placed on this by investigational research in the long term. The environmental aspect will also need more consideration in the future, particularly as some patients will see this as an additional emotional issue if the antipackaging lobby continues to be publicised, without the advantages which packaging contributes to today's society being fully explained, to the public in general. The EU Packaging and Packaging Waste Directive, 94/62 will apply to pharmaceutical packaging.

It must be re-emphasised that a company, in generating data to satisfy itself and the regulatory authorities, should consider the former to be initially more important. A company must therefore try to stand back and ask whether the data generated can withstand challenge; only then should the data be submitted externally to the authorities. The use of experts and expert reports should assist such needs. Frank, early discussions with regulatory authorities may also help to give confidence that a likely successful and acceptable approach is being adopted and followed.

The total data philosophy approach mentioned earlier, which embraces information collected from product inception to final withdrawal from the market (cradle to grave approach), is receiving greater regulatory attention and acceptance. To achieve this, monitoring, validation and co-ordination are essential both at the initial research and development phases and during subsequent ongoing production and sale. The activities leading into this total accumulation of data will usually cover the following.

1 Full knowledge of the drug entity or active substances (from initial research phase) related to identity, purity, process residues, degradation routes, crystal structure, polymorphism, etc. and changes which may occur when challenged by light, oxygen, moisture/water, acid, alkali, carbon dioxide, temperature, etc., plus interrelated safety and toxicological (toxicity/irritancy) studies. The above is now frequently covered by preformulation work. (See (3) below)
2 Initial drug entity scale-up and a recheck leading to a comprehensive provisional specification, which is likely to be used for the activities below.
3 Preformulation studies including interaction, challenge (similar (1) above), dissolution studies, polymorphic form, release, bioavailability, etc.
4 Stability studies on drug entity (i.e. drug substance) in various packs are now strongly advised under EU guidelines and international harmonisation programmes.
5 Clinical trial supplies which include full QC and supporting stability studies to show that product-pack is satisfactory for issue (i.e. IND stage in the USA). See also (8) below, paying usual attention to GMP, effectiveness of standard operation procedures (SOPs), etc.
6 Formulation studies/feasibility investigational work which are part of or an extension to clinical supplies, leading to final formulations. Accelerated stability and longer term stability tests on pharmaceutical development batches and scale-up batches, leading to a full product specification.
7 Packaging studies—investigational work usually carried out in conjunction with (5) above. Provisional pack specifications, backed up by in-depth recording of all information and data.

8 Formal stability, preferably using three production scale batches (or initial semi-production scale) in final pack where possible, using internationally acceptable protocols. ICH requires 12 months at 25°C, 60% RH, 6 months at 40°C, 75% RH or 12 months at 30°C, 60% RH prior to submission.
9 In-use tests with patients. May be part of clinical evaluation or an extension to it. Most important with devices or where pack acts as an administration aid.
10 Initial production batches for first launch supplies—additional stability work on first three production batches, using ICH storage conditions to verify shelf life if formal stability batches were not representative of final production scale.
11 Ongoing production, ongoing stability tests. Batches representative of production placed on confirmatory stability tests at regular intervals.
12 Warehousing inspections (own and wholesaler's), drug store inspections and end user checks (professionals and patients).
13 Monitoring all complaints—product and pack, adverse reactions, etc.
14 Updating records, leaflets, specifications by constant review of accumulated data.

At all stages attention must be paid to GLP, GMP and validation. Having surveyed the broad functions of the pack, further emphasis should be placed on the role of the packaging specification and the method of pack assembly. Attention to these two factors is highly important to both the development and the ongoing production situation.

The packaging specification (purchasing)

One ultimate purpose of a specification is an agreement document between purchaser and supplier. A provisional or outline specification is, however, essential, even when initial development samples are being surveyed, since it provides both a disciplined approach to the examination of materials and components and a record of exactly what was received, used, etc. A specification is usually documented under the following layout headings:

- standard title (bottle, cap, laminate, etc.)
- specification reference number and date written
- previous edition/specification ref. no.
- general description of item.
- materials of construction—types, grade, colour, etc.
- construction, the process by which constructed; size/weight/capacity, with tolerances (may be under a drawing reference)
- drawing ref., date, details of dimensions and tolerances
- decoration, detail of print, method of decoration, colour target(s), artwork reference, etc.
- performance tests (with reference to test method, number, etc.)
- how to be delivered and identified
- signatures of approval: supplier/purchaser.

Inspection procedures, and acceptable quality levels (AQLs) related to critical, major and minor defects may be part of the specification document but are more likely to be in a general information support manual, unless these are specific to the item concerned.

An alternative approach involving a master manual which contains the basic features for a selected type of component, i.e. glass bottles, plastic bottles, collapsible metal tubes, etc., has much to recommend it. This, together with a simpler description-type document, then becomes an agreement specification between the supplier and the user.

It is therefore advised that prior to the commencement of any product-pack tests, materials should be clearly identified, quantified, measured and checked for performance, etc. In this way the components used for any test can be employed more confidently and better comparisons can be achieved between a series of tests irrespective of whether the tests are investigational, feasibility, formal stability, travel test, etc. If materials, product and pack cannot be properly quantified, then obviously test results may verge on being meaningless. Aspects of quality are further explained in Chapter 4.

Performance specifications

Some companies have specifications which define the performance of an item, rather than specifying it in full detail (e.g. this could apply to shipping outers). However, in the pharmaceutical industry, certainly for primary packs, it is normal and often essential to follow details established in pack approval tests exactly.

Pack assembly detail (assembly procedures for packing operations), i.e. (SOPs), works instructions (WIs), etc.

Full pack assembly detail follows the philosophy of knowing what you are testing and what is to be ultimately produced in a final production situation. The establishment of comprehensive records of both how a pack was assembled and the tests performed to show that the pack was recorded as satisfactory is likely to cover the points detailed below, most of which can be related to GLP or GMP. Data obtained from this initial pack assembly detail ultimately lead into the documents which cover the final product in a production situation. These must, therefore, cover any assembly operations in sufficient detail to ensure that a consistent quality of output is achieved.

Some pack assembly features

The points to consider in activities prior to the final production operation so that a pack assembly detail can be derived include the following.

1 Batch references and batch numbers of the components and product used. Any previous history of components and product, previously unrecorded traceability.
2 Date assembled, where assembled, how assembled, responsibility for assembly.
3 Quantity of material/components issued, used and recovered, i.e. accountability and reconciliation.
4 Equipment used for assembly operations (assembly speed/output). Product—pack specification.
5 On-line target figures associated with fill (volume, weight, number), cap torque, heat seal strength, etc. Figures achieved.
6 Problems encountered during assembly.
7 Environmental conditions etc. in assembly area(s).
8 Results of any special functional tests applied to finished pack.
9 Judgements on visual appearance (i.e. attributes which may be critical to ongoing production).

Only when detail such as that given above is recorded and studied can ultimate confidence be expressed in any test results and the pack assembly document created from them. This becomes particularly relevant when responsibilities become split, i.e. production packed, QC tested, third party evaluated, where each may adequately perform their own functions, but no one area accepts full responsibility for co-ordinating and assessing the total data.

Although emphasis has been placed on specifications and the examination of all test materials prior to the initiation of any tests, the more formal QA/QC approach in a continuing production situation also needs a mention. Records acquired from such ongoing examinations may yield valuable data on changes to incoming materials, process modifications, changes in pack assembly procedures, which in turn may result in a modification to the product shelf life. It is therefore important that QC records are constantly monitored so that any trends may be recognised, as even in today's climate technologists can be overcome by the simple pass or fail syndrome rather than using data to sense change. For instance, one company introduced an apparently impressive supplier or vendor rating system which ultimately graphed each supplier on a points system every few months. Suppliers at the top of the table were naturally considered good and those at the bottom bad, with constant efforts being made to upgrade the latter through a more rigorous and critical approach to defectives. However, a quick assessment by an outside consultant immediately indicated that some of the top suppliers had items of good design and those at the lower end of the scale had poor or difficult designs. The table, therefore, gave a general design rating in addition to being a vendor rating system. Technical discussions which concentrated on the design were able to upgrade the ratings of some of the poorer suppliers. As suppliers occasionally introduce minor or even major modifications which they regard as improving the process or the item being produced, it is essential to insist that any change is notified to the user company. A phrase to cover this is normally incorporated into the specification. Once a company has been notified of an impending change, judgement has then to be made as to whether any further tests are required to establish whether the change has any significance.

As indicated earlier, formal stability work is only of relevance if it is backed by an effective team which studies the project and the product-pack in total. Within this team there must be a high level of packaging expertise and effective co-ordination between formulators, analysts, engineers, statisticians, packaging technologists, etc. Even when a shelf life has been initially established, this must be supported not only by ongoing stability, by sampling production batches, but also by a monitoring system that ensures that the product and pack continue to meet the requirements essential to guarantee efficacy, safety, integrity, uniformity, etc., and confidence of the ultimate user. Only by this approach can a product and the industry as a whole be assured of consistent quality. The need to improve quality constantly is also essential to the industry.

It can therefore be concluded that those carrying out formal stability work must not only be supported by an effective pack examination system but also have adequate knowledge of the total supportive role which the pack plays.

Clearance of a pharmaceutical pack or device

In order to provide a greater appreciation of the in-depth knowledge required for the above packaging development operation, it would perhaps be useful to look at the steps involved in the clearance of a pharmaceutical pack/device. This type of activity is becoming increasingly important in terms of both the expertise required and the need to support the significant growth in the use of plastic. This growth has frequently been associated with user convenience features (e.g. squeezability), a more modern hence psychologically acceptable image, a greater ability to produce packs and devices in functional and complicated shapes involving less weight and frequently lower volume, at competitive and economically acceptable prices. New concepts, which would not be practical in glass and metal, have also assisted the progress of plastics for both packs and devices in the pharmaceutical industry. Thus plastics now stand a high chance of being used for new pharmaceutical products in spite of the fact that all are to some degree permeable to moisture, oxygen, carbon dioxide, etc. and may not be as 'inert' as the other longer established competitive materials such as glass and metal.

The fact that plastic packs have undoubtedly received greater scrutiny than many other longer established types of material has to be noted and accepted. Although the author would stress that in many instances this might be considered unfair, plastic can at least be used as an example of how a material can be thoroughly 'cleared' in the widest pharmaceutical context.

It is for this reason that Chapter 8 traces the development of a plastic pack, covering:

- functional and aesthetic design
- process of manufacture, as this may influence the grade of plastic required
- selection of plastic type—general physical and chemical properties
- selection of plastic grade—detailed physical and chemical properties, plus knowledge of constituents including toxicity and irritancy aspects
- compatibility requirements, involving both the feasibility and formal stability stages identified previously
- performance requirements associated with warehousing, distribution, display, use, including closure efficiency and durability of identification/decoration/print.

Differences between development and production packs need to be recognised, plus any possible special test requirements for such deficiencies as environmental stress crack resistance, surface changes and static charges, panelling/cavitation, etc., which should be established at an early stage.

Although the above items have been listed separately, in actual practice several have to be considered in combination. For example, the practicability of any design has to be related to the process of manufacture, the grade of plastic employed and the constituents found in the plastic.

The early part of this chapter indicated a number of different scenarios where package development activities might be involved. These are now expanded.

Changes to product and pack (after initial launch)

The means of proving product or pack equivalency when either the product or the pack is altered or modified in terms of size, materials, shape, closure, etc. is a constant discussion point. Of these a change in pack size using the same container, materials and closure size should be the easiest to prove in equivalency, particularly when the product has been shown to be highly stable. Products sensitive to moisture (or gases) can be evaluated against the moisture (or gas) lost or gained per product (i.e. per item, volume or weight) and, provided this is similar or not significantly greater than the previously used pack, a case could be made for a change in pack size, even if the closure was also altered. Although similar reasonings could be put forward for changes involving different pack types and packaging materials, additional factors such as compatibility have to be considered. This may be covered by short-term, possibly accelerated studies which can then be backed up by longer term formal stability tests. The time at which change can be released must largely depend on the complexity of the alterations. Arguments have been put forward that provided a series of packs has been proven equivalent and the product has good stability, interchange should be readily acceptable to both the company and the regulatory authorities. This approach, although very dependent on the phrase 'proven equivalent', goes back to a philosophy that if a company is satisfied with the data and is thereby happy that a commercial risk is justifiable, this should prove adequate, with discussion if necessary, for clearance by any regulatory authority. In virtually all cases any change will have to be supported by longer term stability tests (possibly covered by established product/ongoing product stability procedures) which in certain instances can be carried out in parallel with production and 'sale' of the product-pack change. Internally within a company, any proposed alteration should involve all those who could possibly be affected, i.e. purchasing, development, production, quality control, warehousing, customers, etc., as occasionally a change which seems excellent to one area may have significant disadvantages to another. Each proposal should, therefore, be fully reviewed in its own right before any resources are allocated to the more expensive

testing procedures which 'prove' equivalence. More formal guidelines are provided by Japan, where 40°C 75% RH is offered as a condition under which both the existing and new/modified pack are compared. Provided both packs can be shown as equivalent (or better) over four analytical periods during 6 months (e.g. 0, 2, 4, 6 months), a change may proceed. Some examples of the more usual types of change are provided, with discussion, below.

Pack change examples

Example

The current pack of 100 tablets is an 80 ml rectangular amber glass container fitted with a 28 mm metal screw cap with pulp board/PVdC faced wadding. An additional pack size is required involving a 125 ml cylindrical amber glass pack holding 150 tablets. At this size the screw neck is increased to 33 mm but has identical wadding. Points to consider are as follows.

1 Glass and closure system use identical materials, hence there should be no major compatibility issues.
2 Moisture (gas) ingress/egress is likely to be proportional to circumference of the screw finish provided a proportionately similar torque is used (i.e. higher torque for larger bottle orifice). The effectiveness of the closure seal can be quickly checked by desiccant tests, or other tests which are coupled with confirmation of screwing-on and screwing-off torques. (Note—28 mm:33 mm in circumference are of the ratio 1:1.5 (i.e. ratio of 100:150 tablets), hence in this example moisture ingress/egress should be similar per tablet assuming sealing surfaces are of similar quality.)
3 A cylindrical bottle will rotate (due to vibratory effects) in transit and therefore has a greater chance of label rub or loosening of the closure than a rectangular pack. Some form of assessment of this factor is therefore advisable.
4 Checks should also be made on ullage volume, i.e. whether headspace to content volume is similar or whether product could suffer greater physical change if differences occur.

Likely conclusions

Any risks are very much related to the physical nature of the product and journey hazards; otherwise 'equivalence' should be relatively easy to establish.

Example

Rectangular glass bottle 80 ml with 28 mm closure and 100 tablets as above. Change is required to high density polyethylene bottle involving a similar size (capacity) and the same closure.

1 HOPE is permeable to both moisture and gases, hence exchange via the container walls may be more relevant than the closure, dependent on container wall thickness and uniformity of distribution (including desiccant tests).
2 Closure may react differently on plastic, i.e. change of torque, back off, under variable conditions of temperature and humidity (humidity less significant). Thread form may not be ideal for a metal closure, e.g. buttress thread form is preferred for a plastic-to-plastic closure fit and is more likely to be used on an available stock container. Additional tests necessary to confirm suitability of metal to plastic fit and effectiveness of closuring systems. Cycling conditions useful. Tests may show that a closure change, including an addition of a foil diaphragm might be advisable. This may involve another potential contact material.
3 Dimensional assessment of drawings essential—particularly bottle-to-closure tolerances.
4 Detail of plastic and constituents. Incompatibility unlikely unless volatile constituents are present, but some form of accelerated test probably essential if there has been no previous experience with the material. Check odour and taste, plus degradation.
5 Moisture ingress tests—use glass as a control to establish combined closure and container permeation differences.
6 Light penetration may be greater with plastic (compared with amber glass). Additional checks advised, both with and without a carton.

Likely conclusions

Decision largely dependent on the stability of the formulation and whether any degradation, physical/bioavailability changes related to moisture, oxygen, light, carbon dioxide, etc. could occur. Long-term stability data on pack appears essential and could be part of procedure prior to agreed release, i.e. check via the above tests, then do 3–6 months of a formal stability test

prior to release. A change in closure may become necessary, as a metal cap on plastic container has certain limitations. A plastic cap incorporating a diaphragm induction seal may provide an ideal solution.

Example

Change from an amber glass bottle to a foil strip pack. An aluminium foil strip (i.e. paper/foil/polyethylene or foil/polyethylene) should, in theory, give as good or superior protection against moisture ingress to a glass bottle with an effective closuring system provided machine problems are absent (i.e. good heat sealing, no excessive extension of pockets by size or location of item in the pocket, etc.). There will, however, be a new contact material with the product, namely the heat sealing ply. Product headspace (air) may differ from that of a glass pack. The factors to consider include the following.

1 General machine efficiency—delivery and location of product in pocket, extension of pocket area, strain on seal area, etc.
2 Does heat sealing operation raise any product problem with heat retained by pack and transferred to product?
3 What is material in contact with product (heat seal material)? Query compatibility against material specification including any constituents in plastic.
4 What are seal requirements etc.?

- Elimination or avoidance of capillary channels in seal margins (possibly due to creases in seal area).
- Peel strength of seal (i.e. related to temperature, dwell and pressure).
- Vacuum testing requirements, or alternative leak detection.
- Moisture ingress/egress (weight change on product or desiccant tablets).
- Does heat seal pattern avoid perforation of pack?

Likely conclusions

Not so simple to prove total equivalence—some stability advisable prior to acceptance. Strip pack should, in theory, be superior. Flavoured type tablets need additional checks. Formal stability tests essential.

Example

A product (aseptically produced and filled) in a multidose vial (20 ml) uses a natural rubber stopper through which the volatile preservative system is lost. As a result a 3 year shelf life (predicted and assumed previously) cannot be achieved. An alternative rubber stopper is advised. The supplier recommends a chlorbutyl synthetic rubber stopper. Actions advised are as follows.

1 Check new stopper for fragmentation, resealing (following multiple penetration) and force for needle to penetrate—note that synthetic stoppers are generally inferior in these properties. (Repeat after ageing period.)
2 Check extractives before and after autoclaving of stoppers—chemically and toxicity.
3 Check preservative absorption and moisture loss via stopper (synthetic stopper should be significantly superior with regard to both).
4 Check if washing and sterilisation process (i.e. autoclaving of stoppers) generates any particulate matter.
5 Consider stability test parameters, including analytical methodology (if product has been marketed for a number of years methodology may be out of date and non-specific).
6 Make up necessary batches for stability and place on test (check stopper insertion and subsequent seal); 12 months' data advised prior to submission.

Likely conclusions

Formal stability-type tests essential before clearance can be given. Release most likely after a 6 month or longer period, depending on quality of previous product data. Even if certain accelerated conditions are used, there is no room for error on an injectable product. Level of testing likely to be intensified when compared to programme used to achieve a launch on the same product previously.

Note

The number of batches required for formal stability data to support changes varies between regulatory authorities. In certain cases there may appear to be good reasons to support a one or two batches approach rather than the more conventional three batches. The latter provides a higher confidence level and is essential according to ICH guidelines.

Having provided a number of examples of specific roles of the pack, the hazards which a product may face and how the pack may cope with these factors can be further expanded under a check list. Such a list is essential as frequently the risk of errors is associated with the most obvious observations.

The expanding role of the pack (e.g. where pack acts as an administration aid or is used in a device)

In an early definition, packaging was defined as the economical means of providing protection, presentation, information, identification and containment of a *product* during storage, distribution, display and use. Today this definition is changing as the role of the pack expands with more emphasis on factors of convenience, compliance, improved drug delivery, associated with use as an administration aid, or as a component within a device, etc. Although this trend produces more sophisticated forms of pack, and a need for greater innovation makes the clearance procedures for a pack more complex, the future environmental issues will need additional consideration.

Before discussing examples of the more sophisticated forms of pack which are involved in improving 'compliance', brief mention should be made of increasing emphasis on user—patient protection which may be included under the broad heading of 'product liability'. This other protective role can include aspects of integrity and security associated with such factors as tamper-evidence, tamper-resistance, childresistance, etc. However, as with innovation and the environmental issues, these safety aspects may conflict with other issues, i.e. concern for the increasing elderly population. As a result, the latter may experience difficulty both in gaining access to and reclosing their medication and in coping with infirmities, rheumatism, weakness of grip, poorness of sight, etc. when using these more complex administration systems. This all means that the tests necessary to establish pack acceptability have to be extended beyond basic product-pack compatibility into areas of use, long-term performance, misuse, abuse, interpretation of instructions, general hygiene, cleaning procedures and their microbiological significance, etc. As an aid to working out the intensity of testing necessary to achieve this, the author offers in Chapter 8 a league table based on the product, the route of administration, and the risk to patient. The products at the top of the list, which include IV preparations followed by injections, involve significantly higher 'risks' than those at the foot of the table, e.g. oral solid products, particularly in terms of compatibility between pack and product. However, no position in such a table is fixed, as the 'risk' will vary due to a number of factors (see Appendix 8.8, Chapter 8).

Defining the type of tests which may be required will depend on the types of material involved, i.e. glass, metal, plastics, etc. However, as packs become more complex and more innovative, plastic becomes the more favoured material for sound economic reasons (frequently associated with fewer components which provide simpler assembly procedures).

The types of test to be applied may be influenced by the role of the pack, as follows.

1 Pack where administration component forms part of the primary or immediate pack and where some components are in intimate contact with the product (examples: aerosols, pumps, etc.).
2 Pack where some of the administration components are in contact with product only during in use period (i.e. possibly act as a transfer system, e.g. IV transfer of additives).
3 Pack that is used in a device but is otherwise separate from the device in which it is used (e.g. Glaxo Diskhaler system).
4 The actual type of test(s) are likely to be selected from the following.

(a) Identifying that the plastic, meets food, toy, FDA, etc. approval requirements.
(b) Identifying constituents covering polymer residues, additives, processing aids, and master batch components, together with toxicological/irritancy risks, methods of analysis, etc.
(c) Carrying out extractive-type tests to USP, BP 80, WHO, EP, BS 5736 procedures, etc. and establishing chemical and biological acceptance.
(d) Carrying out investigational tests on device/packed product using accelerated and normal conditions to indicate suitability/compatibility.
(e) Carrying out formal stability tests using control, EU climatic and accelerated test conditions to meet EU and international/national standards with emphasis on Europe, Japan, USA, etc. including ICH guidelines.
(f) Carrying out preservative efficacy challenge procedures, i.e. test initially, and at appropriate condition—time intervals to check that preservative efficacy (chemical v. microbiological change) still provides adequate protection against microbiological challenge, i.e. if preserved.

(g) In tests (e) and (f) check that product when dispensed via 'device' does not significantly change or remains acceptable (i.e. combined product—device tests).
(h) If device is separate to pack, check storage against accelerated and typical conditions to ascertain that performance does not change. This may be covered by batches of product (as initially produced), some derived physico-chemical test procedures, etc. and involves batches of product from (d) and (e) above to ascertain whether changes in performance have occurred.
(i) Clinical trial assessments or special user tests (actual patients or simulated laboratory tests) to check how:

- effective are the proposed instructions
- abuse or misuse may occur, and the effect on product—device efficiency.

(j) Check microbiological contamination risks of device:

- in use
- by grow back experimentation
- from recommended cleaning procedures, where applicable.

(k) Check safety aspects of cleaning, particularly where cleaning solutions are recommended (i.e. using chlorine, peroxide or other antimicrobial systems), i.e. do residues occur; are residues a hazard; can residues affect or inactivate drug actives? etc.
(l) Where devices and product are critical to the particle size delivered (i.e. inhalation-type drugs), check initial and ongoing particle size distribution as affected by storage of product and device.
(m) Check 'dose' delivered from device:

- initially
- during storage tests on product and device
- and define any losses which may occur due to

  (i) impingement/impaction
  (ii) environmental conditions, e.g. temperature and RH
  (iii) air flow velocity (e.g. inhalation rate 15 to say 120 l air flow per min)

- under specific environmental and user conditions (humidity can affect powder particles which attract moisture).

(n) Identify likely 'dose' to patient and confirm whether this can be quantified via urine, blood, plasma, breath analysis, etc. Check (d), (m) above by mass balance estimations to ascertain whether total device output has been explained. (This also involves any residues remaining both in the pack and in the device components.)
(o) Having established (d), (m), (n) above, total dosage delivered can then be quantified:

- as—
- with a dosage range in standard deviations etc., paying attention to whether this varies according to storage of device/product/pack and at beginning, middle and end of pack use together with any residues remaining (as losses).

(p) Quantify expected 'doses' delivered from each pack, taking due allowance of fill accuracy and variations of fill.
(q) Carry out accelerated usage tests—to define shelf life of device using likely, actual, and excessive usage, checking performance, appearance, wear, at all stages, etc., i.e. can device performance change?
(r) Sterile products—involve the validation of the process of sterilisation, and sterility of components. Validation of maintenance of sterility of closure system(s), retention of sterility during storage and use, including any grow back tests (see also (j) above).
(s) Measurement of loss or gain via the total system, i.e. by permeation or seepage-leakage via the closure system or the container.

Note that in the case of aerosol valves, the effectiveness of the valve system is likely to depend on how the propellants cause swelling (or shrinkage) of the rubber components, i.e. gaskets. Initial loss and steady loss may therefore have to be quantified, with loss usually reducing after the rubber components have expanded. Since all plastics are to some degree permeable to

gases, solvents, moisture, etc., the significance of these losses or gains will probably have to be checked to establish relevance to shelf life.

Note that although plastics are emphasised in the above list, some of the tests are equally relevant to other materials (metal, lacquered metal, glass, etc.).

Some historical device-oriented products

Packs acting as devices began many years ago in relatively simple ways. The author recalls menthol cones in thermoset plastic cases, lip salves in special push-up cases and spirally operated godets, smelling salts in special glass-stoppered bottles, rubber-teated dropper screw-necked glass bottles for eye and nasal drops, which date back over 50 years. The Second World War encouraged the invention of some early innovative packaging. One of these items was a collapsible metal (tube) syringe fitted with a metal needle used for injecting morphine (Omnopon). The dental syringe which took a glass cartridge tube, with a rubber diaphragm fitting at one end and a rubber plunger internally, is an early example of a pack used in an administration device. Following initial use in dentistry anaesthesia, its use was extended to a range of injectable medications (e.g. Boots' 'Viule' range). Medicated dusting powders, with sprinkler-sifter type tops, are another example of administration aids within a pack.

At that time, other than syringes and a few spray systems for throat usage (based on the Bernoulli principle as used in the 'Flit' fly spray) and the Rybar inhaler, separate device systems were virtually non-existent.

These early examples of pack-product device systems were made from glass, rubber, metal and thermosetting plastics such as urea and phenol formaldehyde. As mentioned earlier, a steady growth of pack administration systems was not possible until the arrival of thermoplastics in the 1950s.

Since the first thermoplastics on the scene involved polyethylene (and to a lesser extent polystyrene), it was the soft, flexible nature of the former that was initially exploited. Squeezee bottles, dropper plugs, followed by nasal spray packs, therefore appeared. These passed through a fairly traumatic learning period which lasted for nearly 10 years as various adverse effects related to the use of plastics were identified and overcome. These included poor closure systems (leakage, seepage, overriding of threads, loss of torque, etc.), changes in drop size due to orifice closure or distortion, plugs flying out when bottles were squeezed, stress cracking, dust patterning due to electrostatic build-up, constituent degradation due to oxygen permeation, moisture loss or gain due to water vapour permeation, preservative loss due to absorption and adsorption, loss of other volatile and permeable constituents, etc., and the disintegration of polystyrene caps when in contact with isopropyl myristate. Virtually all these problems, together with others, were identified in the period up to the late 1960s. At one time it appeared that the exciting predictions on the use of thermoplastics would never be fulfilled. However, the adage that a problem identified is the first stage to finding a solution proved true. These problems were not only overcome, but the positive features of plastics were identified and then further exploited. Unfortunately much of this historical information is not always in textbooks, and a visit to Third World countries can frequently show that the problems are happening once again. Those who believe that the above list of negative features is purely historical and that 'I don't need to know either the problem or the solution' may therefore be caught out if other parts of the world are visited.

Having briefly given the historical background, the development of pack-device systems can be brought up to date and the current state of the art considered. This will indicate that as systems have progressed, with many having a high degree of complexity, a greater level of testing has become necessary to satisfy both the company and the regulatory authorities as a safeguard to the ultimate user, i.e. the patient.

This growth into modern technology has seen new product and pack trends, involving both sterile and non-sterile products. These include developments in multidose and single (unit) dose product forms covering both preserved and non-preserved products. The latter has brought a growth in sterile products for such preparations as oral liquids, eye drops and nasal preparations, where preservative systems are possibly undesirable due to sensitising effects.

Typical examples of product-pack 'devices' and packs which are used in devices include:

- aerosols (delivering a range of product forms)
- pump systems (delivering a range of product forms)
- powder insufflators (nasal, wound care, etc.)
- powder inhalation systems for delivery to the lungs
- nebulisation systems for delivery of liquids to the lungs
- multi-port IV packs
- IV additive systems
- dermal patches
- pump systems including electronics to provide a timed delivery
- insulin 'pens' and other automatic injection systems

- prefilled syringe systems
- enema (large volume and 'micro')
- intra-uterine devices etc., and recently needle-less syringes.

It should be immediately apparent that this is only a starter list, and a few of these options will therefore be expanded as an indication of the total complexity, remembering that the additional influences of the environmental issues, use by an ever-increasing number of elderly people, needs for tamper-evidence/resistance, child-resistance, etc. still have to be considered.

At this stage there may be some difficulty in defining what is a pack. Is a soft gelatin capsule containing vitamins in an oily base—a pack? Is a hard gelatin capsule containing a fine powder for lung inhalation, e.g. spincaps and the Spinhaler (Fisons), Rotacaps and the Rotahaler (Glaxo), a pack? In the author's opinion these are open to interpretation either way.

At the other extreme are aerosols, where neither the product nor the pack can exist without the other. Aerosols can be used to dispense powders, liquids, sprays, gels, true aerosol clouds, etc., either as a continuous delivery or as a controlled or metered dose. The main container component can be fabricated from metal (aluminium or tinplate), glass or plastic coated glass, or plastic (e.g. polyester), and the valve components from combinations of plastic, metal and rubber. Depending on the product usage, the majority of the tests listed earlier may have to be involved in the clearance of an aerosol, particularly if it is a metered dose aerosol for administration of a product to the lungs (a critical administration route).

Since certain aerosols can be sterile and non-preserved, microbiological risks may have to be checked at the dispensing orifice, including the possibility of 'grow back'. Special double valve systems and other alternatives are being continuously evaluated for such applications. Innovation related to aerosol adaptors for nasal, ear, eye, etc. applications are typical examples of evolving technology.

For aerosols delivering products to the lungs, patient compliance associated with firing and breathing has brought about the introduction of 'spacers' (yet another component needing investigative procedures) and breath-activated aerosols (e.g. 3M (Riker)— Autohaler).

The virtual condemnation of CFC propellants has put new challenges to aerosols in general and to the pharmaceutical industry in particular, when cloud break-up into small (less than 10 μm) particles is critical to product success. The latest date for the withdrawal of CFCs for pharmaceutical products is 2005, with HFAs 134a and 227 being the main replacement candidates.

Powder inhalation devices

The mid-1960s saw the first development in fine powders destined for the lungs, with particular emphasis on the invention of the Spinhaler (Fisons/Aventis) and its successful use with sodium cromoglycate (Intal—Fisons). Investigations into actual devices and ideas (patient searches) will indicate that there are now over 200 options available for powder delivery systems. Successful examples include the Rotahaler (Glaxo), Turbohaler (Astra Zeneca), Diskhaler (Glaxo), Accuhaler (Glaxo), etc.

As with aerosols, the effective dose to patient is difficult to quantify and validate, as this depends on a range of factors. Although when questioned patients generally prefer the apparent convenience of metered dose aerosols, the dose is very much dependent on the use of correct techniques and procedures. Since powder inhalation systems more readily couple 'synchronisation with use', the more complex operating procedures may be more than compensated by a more effective dose guarantee.

A continuing competition between aerosols and powder inhalations can therefore be predicted.

Small and large volume parenterals

Both SVPs and LVPs have been subject to an active area of innovation to improve administration and compliance. LVPs have offered packs with a range of 'ports' either as preformed containers or as packs produced as a form (blow)-fill-seal operation (e.g. as equipment offered by Rommelag and ALP). Modifications to giving sets and transfer aids (for the production of IV 'cocktails') also fall into this category. Examples of the latter include the Abbotts system (ADD-Vantage) and the Kendall McGaw (Add-A-Vials) transfer device.

SVPs are meeting similar challenges, e.g. plastic ampoules via form-fill-seal (Braun Mini-plasco), prefilled syringes (using single or bicompartmental systems), etc.

Closures

Closures have for the past 30 years been a major area of innovative changes either to improve product removal administration or to meet some specific challenge to safety. The options related to the former are enormous and could constitute a book in their own right.

Safety challenges have, since the introduction of the Poisons Prevention Act (1970) in the USA, seen a steady increase in the use of child-resistant closures (which meet BS 6652 1989 in the UK or DIN 55559 in Germany or ISO 28317). The Extra Strength Tylenol poisonings of 1982 also put new emphasis on tamper-evident and tamperresistant packaging, and, it is hoped, the disappearance of the word 'tamper-proof or 'child-proof from any of the packs just mentioned. For example, a CRC may actually be less safe if it is not properly or correctly reapplied. As mentioned earlier, many of these safety features cause difficulty to the elderly population either in the opening of the pack or in the correct replacement after use. Providing elderly user-friendly packs is therefore a recent trend. Among these one finds the monitored dosage systems and medical event monitored systems (MEMS).

Other systems and examples

The above examples have only scratch the surface of the expanding role of the pack. What about dermal patches, implants, insulin pens, pump systems, suppository and pessary delivery systems, nebulisation, puffer packs, 'Ocuserts', a review of unit dose applications, etc. Systems are now so numerous that doing a paper search and review would take several weeks. However, they do indicate the new roles which are being undertaken by the pack. Each new system challenges new sets of tests in order to evaluate performance and efficiency.

Conclusion

The information given in this chapter, together with that in Chapter 8, should provide a good basic understanding of the broad role of a packaging development activity, and the supporting role associated with other relevant disciplines. All activities must support the ultimate task of the pack, i.e. to provide confidence in the product in terms of convenience, presentation, protection, etc. while ensuring that the product remains satisfactory in the fullest sense, i.e. in terms of integrity, identity, uniformity, safety, effectiveness, etc., all at an economically acceptable cost. Undoubtedly pharmaceutical packaging does receive and demand greater attention to detail than any other form of product. With the advent of product liability and the expanding administrative role of the pack, investigations will not relax but rather will intensify.

Although the types of test procedure will broadly continue to follow the stages identified in this and other chapters, the ultimate intensity of the procedure must be related to (and vary with) the type of product and the route by which it is administered etc. The use of a declared 'food grade' plastic is usually the minimum standard that would be used for a pharmaceutical product, either for a secondary packaging component or where extraction between product (solid items) and the plastic may seem unlikely. Reference to toy regulations may also provide useful information, especially where coloured materials are employed.

As the cost of clearing any product-pack combination is inevitably high, it is extremely important to define adequately the product, the pack and the processes involved in these original clearance schedules and to finish with a total clearance programme which is ultimately supported with full specifications.

The future control of the product and pack then revolves around these documents. In the case of a plastic pack or plastic components, it may be necessary not only to define certain critical factors in the specification tightly, but also to purchase under a certificate of warranty, as exhaustive QC procedures (particularly biological tests), which might be necessary to detect change, could involve prohibitive costs. Regular QC checks are likely to include melt flow index, density, IR or DSC identity, etc. The last two are a particularly useful means of providing plastic identification, with DSC now more widely used.

As an additional insurance, a selected number of production batches are placed on an 'existing' product stability test annually. This monitoring system ensures that the stability profile (and shelf life) of the product does not change with the passage of time. Any changes in product, pack or process inevitably involve some form of retesting schedule, the intensity of which varies according to the nature of the change. In all such support programmes it is still important to thoroughly re-inspect all packs before, during and after chemical and biological analysis.

It can therefore be concluded that packs and devices supplied by the pharmaceutical industry which utilise plastics (and any other material) normally have to pass through a thorough and rigorous test procedure, but such procedures must still be improved upon with progress. If possible loopholes in the present systems are to be identified, more attention will be required on the internal storage containers which are usually found in factory production areas and the bulk containers used to supply the industry with drugs and other excipients, as these receive far less attention than the pack destined for the patients. Validation and traceability are current key words, but undoubtedly others will arise.

The work related to the clearance of the pack, the establishment of total integrity and GMP cannot be isolated into apparent water-tight compartments such as product development, pack development, production, marketing and QC, as all must operate as an effective team with a high degree of communication and co-ordination. A packaging co-ordinator with an ability to give an overview is virtually essential to success but to date this has been recognised by only a few companies.

It should be stressed that the latter part of this chapter has been written in such a way as to encourage a degree of both alertness and understanding. It does not set out to say that any one approach is the ultimate. Test procedures must be constantly reviewed and updated. Virtually all the stages identified must be treated as long-term information gathering. Extractive tests fall into this category; they provide the best information available at this time and therefore must not be treated as the ultimate. To date there are no records of people dying from plastics, but rather of deaths from the processes by which they are synthesised (e.g. the vinyl chloride monomer saga). However, the industry must remain responsible, particularly in terms of product—pack liability, and at the same time remain commercially viable.

To complete this chapter a final section is required, i.e. consideration of tests and test schedules which may be used for the evaluation of materials and completed packs. This represents the area where information tends to change the most, and the subject is so diverse that it would only be effectively covered by a full textbook. It is therefore not practical to cover all tests and methods in detail but only to provide broad reference to possibilities. Tests can be applied to materials (e.g. water vapour permeability), on components or completed packs. Tests generally fall into three categories, i.e. those required:

1 to gain information where no previous information exists or information is scant
2 to control quality—usually fairly simple tests that can be carried out rapidly, giving numerical results which can be readily interpreted and compared
3 to predict performance—used where some relationship has clearly been established between field performance and a laboratory test.

The standard of these tests may be related to in-house company standards, industrial or national/international standards.

Typical standards bodies include:

- ISO (International Standard Organisation)
- BSI (British Standards Institute, which issues British Standards)
- ASTM (American Society for Testing and Materials, which issues ASTM Standards)
- FEFCO (Federation Européenne des Fabricants de Carton Ondulé (test methods))
- BPBMA (Technical Association of the British Paper and Board Makers Association)
- TAPPI (Technical Association for the Pulp and Paper Industry (USA), which issues TAPPI Standards).

Standards are generally applied to the following applications:

1 dimensional standards
2 performance or standards of quality
3 standard methods of testing
4 standard technical terms and symbols
5 standard codes of practice.

Table 2.2 Tests on plastics (general) (see various parts of BS 2782)

Test	*Standard*
Melting temperature (°C)	BS 2782 part 1
T_m (crystalline)	BS 2782 part 1
T_g (amorphous)	BS 2782 part 1
Specific gravity/density	D792, BS 2782, ISO 1183
Tensile strength	D638, BS 2782, ISO 527
Elongation (%)	D638, ISO 527
Compressive strength	D695
Flexural strength	B790
Impact strength (Izod)	D256, BS 2782, ISO 180/1AR
Hardness (Rockwell)	B785
Impact strength (Charpy)	ISO 179/1
Vicat, softening point	D1525, ISO 306
Modulus of elasticity	D790, BS 2782, ISO 527
Thermal conductivity	C177
Thermal expansion	D696

Test	*Standard*
Refractive index	D542
Transmittance	D1003
Haze	D1003
Water absorption	D570
Flammability	D635
Water vapour transmission	ASTM C355, BS 3177
Melt flow index (g/10 min)	D1238, ISO/R 1133
Stress cracking	ASTM D1693–70, BS 2782–832A

Table 2.3 Tests on plastics (films)

Test	*Standard*
Specific gravity/density	D1505
Tensile strength	D882
Elongation (%)	D882
Bursting strength per 0.001 inch thickness	D774
Tearing strength	D1922 (Elmendorf), BS2782 360A–360C
Tearing strength	D1004
Folding endurance	D2176
Water absorption (24 h/%)	D570
Resistance to acid/alkali	D543
Resistance to grease/oils	D722
Resistance to organic solvent	D543
Resistance to heat and cold	D759
Change in linear dimensions	D1204
Flammability (burning rate)	D1433, CS192
Rate of water vapour transmission	E96 ASTM, BS2782–820A/822, DIN 5312L, BS 3177
Oxygen permeability	DIN 53380, BS2782–821A, ASTM D1434

Table 2.4 Tests on plastics (optical)

Test	*Standard*
Gloss	BS 2782 520A, ASTM D2457 (Gardner 45°)
Haze (wide angle) (%)	ASTM D1003
Haze (clarity)	ICI test (Gardner), BS 2782 521 A
Coefficient of friction	ASTM D1894, BS 2782 824A
Dart impact	D1709

Table 2.5 Tests on plastic containers and mouldings

Test	*Standard*
Screw-neck finishes	BS 5789
Environmental stress cracking	BS 2782–832A
Permeability (moisture)	BS 3177

Table 2.6 Standards related to other specific containers

Item	*Standard*
Collapsible tubes	BS 2006
Glass bottles	BS 1133 section 18, BS 1918 glass container finishes, drop test, impact, thermal shock, hydrostatic pressure
Fibreboard	BS 1133 section 7, FPCMA
Timber and plywood cases	BS 1133 section 8

Item	*Standard*
Aluminium foil	BS 1133 section 21
Metal containers	BS1133 section 10
Metal collapsible tubes for eye ointment	BS 4230
Printing inks, resistance testing	BS 4321

Table 2.7 Tests on sterile products

ISO 8362:	Injection containers for injectables and accessories.
Covers:	hardness, fragmentation, self-sealability, needle penetration, seal integrity, etc.
ISO 8536:	Infusions
ISO 8871:	Elastomeric parts
Covers:	extractive tests including chemical and biological assessment, UV, reducing substances, ammonia, non-volatiles, pH, zinc.

Tables 2.2–2.7 provide some ‘lists’ on the types of standard tests available. None of the lists are anywhere near inclusive of all the tests which are available. Tests are particularly useful for the comparison of materials, usually to assist the selection of a material or materials for further evaluation. The ultimate selection phase usually stems from the investigational tests in contact with the product, and is finally supported by formal stability programmes. In all these data must be adequately detailed, properly recorded and, where necessary, relevant conclusions must be drawn.

Examples of tests for specific materials

For tests on paper and board, see Chapter 5.

Tests other than those quoted in this chapter can be found as ISO, ASTM, TAPPI and BSI standards. In most tests on paper and board, the materials have to be conditioned prior to testing, otherwise compatible results will not be achieved. See Tables 2.2–2.7.