1
AN INTRODUCTION TO PHARMACEUTICAL PACKAGING

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Introduction

This chapter endeavours to set out the important role of the pack and the need to consider the total packaging operation as part of any drug discovery and development programme. Although demands on the type of pack (material, style, etc.) will vary according to the characteristics of the product; how it is produced and distributed; where, how and to whom it is sold; how it is used/administered; etc., certain factors are shared irrespective of the product classification (i.e. ethical, over the counter (OTC), veterinary, etc.). Pharmaceutical products generally require a standard of packaging which is superior to that of most other products in order to support and comply with their main requirements, i.e. proven efficacy, safety, uniformity, reproducibility, integrity, purity with limited impurities, minimum side-effects coupled to minimum product liability risks, and a good shelf-life stability profile. Since all these terms tend to be well established, but not always fully understood, it may be useful to emphasise the importance of each and its relevance to product pack development. Thus although packaging technology may be a clearly defined discipline, it must have as its basis a thorough understanding of pharmaceutical products generally, the characteristics of formulations and dosage forms, and the general physical and chemical properties of drug substances. Such background detail must include factors associated with medical and marketing input, the methods of manufacture and packaging, warehousing and distribution, sale, the ultimate customer and product use, coupled to adequate profitability. Quality associated with aspects of good manufacturing practice has to be clearly defined at all stages. This chapter therefore starts with some background information.

Uniformity

Uniformity applies within and between batches and usually refers to the quantification of active ingredients, excipients and impurities/degradation. The term applies to the minimum of variation between items, doses, etc., both as active constituents and excipients and any factors which control dissolution, bioavailability, etc. It may be expressed as a percentage of the initial target figure since in this way any relationship with storage time, temperature, etc. can be quantified. However, changes in uniformity or variable uniformity after storage may relate to variations in the product, the pack or the environment.

Purity

Purity today embraces both the percentage of active ingredient and, when possible, the identity and level of impurities present. If one looks back to pharmacopoeias of say 55 years ago it is quite remarkable that in accepting a purity of 99.0%, 98. 5%, 95.0%, etc., little attention was paid to the remaining percentage which could consist of impurities or degradation of products related to the process of manufacture and the drug entity itself. Today greater emphasis is placed on the ‘other constituents’ as by-products of the manufacturing process and/or degradation of the drug or formulation. In the same way that modern analytical methods have made the quantifications of impurities practical, modern chemical techniques have made it more readily possible to separate major impurities. As a result, purer drug substances are being produced today. Impurity levels of 0.1% or more normally have to be identified and safety detail quantified.

Integrity

Integrity covers any assurance that the ingredients are correct in quality and quantity, the formulation is correctly compounded and exhibits the required bioavailability profile, and the pack is to specification and correctly assembled with the quantity of product and the product-pack correctly labelled and identified. Integrity, therefore, covers all aspects related to quality, quantity and security and is thus a function of production and quality control/assurance. Security against counterfeiting has recently increased in importance.

Minimum side-effects

It is perhaps not always recognised that most drugs have some side-effects. Provided these are minor the drug usually will be accepted. This is generally known as a risk-benefit ratio, and therefore varies according to the severity of the disease. A person using a life-extending drug usually accepts side-effects which would be unacceptable for a milder disease. These side-effects may occur from the drug itself or other excipients in the formulation. In this context any move towards simpler formulations, e.g. the removal of colourants, flavours, preservatives, etc., can reduce some of the risks associated with side-effects. Since packaging, by interaction, extraction, or migration may change, add to or even subtract from the product, this can contribute as a sideeffect factor.

Good stability with a clearly defined shelf-life profile

Occasionally drugs have a limited shelf life irrespective of the pack used, but at the other extreme, some drug formulations are inherently stable and therefore a pack is needed only to prevent direct contamination, i.e. dirt, dust, bacteria, etc. from the outside atmosphere, and for containment. However, few pharmaceutical products can exist without the supporting role of a pack, as many of the above product factors are not only interdependent with the pack, but ultimately represent a compromise between these and other conflicting needs. Traditionally pharmaceutical products have aimed for a 5 year shelf life where practical, or at least 3 years. General stability is currently supported through the International Conference on Harmonisation (ICH) guidelines.

Some factors that may influence the pharmaceutical pack

Pharmaceutical products and/or their packs can be classified under a number of categories, i.e.

- the type of dosage form
- the route or mode of administration or use
- the type of pack
- the mode of sale/marketing area
- the mode of dispensing via a combined device/pack
- administration by a device separate to the pack.

Although a brief explanation is given below of these classifications, it can be seen that all are concerned with the broad product-pack interface, hence no method of approach is of necessity better than another.

The type of dosage form is primarily related to the physical state, e.g. solid, liquid or gas, and whether it is sterile, non-sterile, unit dose or multi-dose.

- Solids may be regular, irregular, free-flowing, cohesive, i.e. powders, tablets, capsules, suppositories, etc.
- Liquid or semi-liquid products may be based on water, alcohol, solvents, oils, gels, etc., i.e. emulsions, suspensions, creams, ointments, solutions, etc.
- Gases may be liquefied, pressurised, volatile, inert, i.e. vapours, inhalations, aerosols.

With each group or sub-group, certain basic properties can be identified which lead to specific packaging requirements in terms of both the packaging processes and the materials to be employed.

Route or mode of administration

The route of administration may make certain packaging features desirable or necessary. Possible routes include the following.

• Oral	dispensing, dosing, with absorption/mode of action occurring between mouth and colon.
• Local	topical applications to the skin, hair.
• Parenteral (large and small volume)	sterile products administered intravenously, intramuscularly, intrathecally, subcutaneously, etc., in single or multi-dose packs.
• Orifice introduction	ear, nose, eye, rectal, vaginal, etc.
• Inhalation	via mouth or nose using a face mask, breathing tube or direct inhalation into mouth or lungs.

Type of pack/material

Type of pack can refer to either the basic materials employed, i.e. glass, plastic, metal, etc. or the pack style/type, e.g. bottle, tube, sachet, blister. Packs may provide single (non-reclosable) use, or multi-use (reclosable). Both groups have influences on the product and have to be considered in terms of the material characteristics and the total packaging concept involving such factors as product compatibility, functional and aesthetic design, production performance, material costs, production costs and user convenience.

Mode of sale or market area

The 'sale' of a pharmaceutical product may be by retail (community pharmacy), wholesale, health centre, hospital, dental, health care centres, special homes, home trade or export, etc. These may be further broken down into ethical and over the counter (OTC) sales. Ethical products are normally available only through or via the profession, i.e. pharmacist, doctor, dentist, nurse, veterinarian, etc. They may be supplied either as a bulk pack which is then broken down into a smaller quantity at the patient-dispenser interface or as an original pack whereby a course of treatment is supplied in the pack as produced by the pharmaceutical manufacturer (also called patient pack or unit of use pack).

OTC or proprietary products, as their name suggests, are products designed for direct sale to the general public. How the sale occurs, i.e. through pharmacies, drug stores, etc., largely depends on legal requirements of the country concerned, and how the drug is classified in terms of the prevailing poison enactments, food and drugs legislation, etc.

Pharmaceutical sales may also include bulk quantities of the drug and the compounded drug for further processing, and/or packing in contractors, overseas countries, etc.

The market may involve and be influenced by how an ethical product is paid for, i.e. privately, by national insurance or by some other form of reimbursement through governmental authorities. Markets are also identified by diseases or illnesses which may vary from country to country, continent to continent and be related to age, ethnic origin, sex, etc., i.e. demographic factors.

Packaging may have to be varied to fulfil any of these various needs—for example, tamper resistance or child resistance.

Administration

The mode of dispensing and the use of packs which act as a device are both related to how a product is administered, and the route or mode of administration. To help the administration, the pack may be required to act as a dispensing aid or a device, e.g. an aerosol, or have accessories which can either be made part of the pack or used as a separate unit, e.g. a dropper assembly.

Finally, the pack may either become part of a device, e.g. a cartridge tube which may be used with a reusable or disposable syringe, or have a separate device which administers the product once removed from the pack, e.g. a hand- or power-operated nebuliser. From this broad introduction it should be recognised that the main objective of most pharmaceutical products is to deliver, introduce or apply a drug of proven stability and safety to a specific site where the most effective activity can be achieved. General investigations to select this dosage form and the dose, by dose ranging studies, must therefore be identified at an early stage in a drug development programme. Prior to formulation of the drug entity, the drug substance should be challenged by a range of factors such as light, temperature range, oxygen, carbon dioxide, water/moisture, so that modes of degradation or physico-chemical change can be established. Formulation then proceeds through a series of stages, such as preformulation studies where any possible interactions between ingredients and the drug entity can be identified, through to formulations which involve feasibility-stability tests and finally to formal stability activities. In the last stage, where the formulation is normally produced on a production scale and packed in the final pack of sale, evaluation is usually carried out on three separately produced batches of the drug, i.e. formal stability. Through all these activities data are gradually accumulated to provide total confidence in terms of the product and the pack, and to satisfy both the company and the regulatory authorities.

Before detailing the broader functions of the pack, the importance of the product-pack relationship cannot be over-emphasised, as it must be considered an essential partnership. Thus any future reference to the pack must ultimately bear some correlation with a product. Most of what follows may appear to be considered in isolation, but in practice this must not occur.

The pack

A pack has a number of functions to perform during its life, including storage, carriage, display, sale, use, etc., all of which require in-depth consideration.

A simple definition of a pack is: a pack is the *economical* means of providing for a *product*

- *presentation*
- *protection*
- *identification/information*
- *convenience/containment/compliance*

until such time as the product is used or administered, paying due attention to any relevant environmental issues.

The term ‘pack’ in the above covers all the components involved, i.e. the primary or immediate pack which consists of those materials in direct contact with the product. The secondary pack and sometimes tertiary components enable the product to be stored, transported and displayed, and possibly assist use. Tertiary components may include ancillary components, e.g. leaflets or inserts, separate dispensing spoons and measures.

As each of the above contributes to the total function of the pack, the separate factors included in the definition are expanded below.

‘Economical’

This term is preferred to that found in some other textbooks—‘minimal (overall) cost’ —since a primary function of a pack in certain circumstances (e.g. OTC products) is to maximise both sales and confidence. It can therefore be seen that a pack of minimal cost that limits sales does not meet the prime requirement of all companies—to achieve the highest return on investment (ROI), i.e. profitability. This may be far more effectively achieved by a pack which costs more but shows a significant increase in sales. ‘Economical’ also covers the total cost, which includes such factors as space used for incoming packaging materials, finished packed stock, handling, labour and distribution. However, as this total costing may vary in the way it is calculated from company to company, material costs, wastage plus production costs, including labour, are widely used for simple initial cost comparisons, i.e. cost as the packed product leaves the production line.

Presentation

Presentation is important in providing confidence and enhancement of the product image. This may be achieved by the aesthetics and/or functional aspects of the pack. The emphasis tends to vary according to the product type, i.e. ethical, semi-ethical, OTC, etc. For instance, an ethical product usually has a high standard of packaging which is relatively simple, elegant, but not over-dressed. On the other hand, an OTC pack which may sell through rigorous advertising may be designed with a view to eye appeal and include a sales gimmick. Pack confidence is often reflected in ‘belief’ in the medication.

Identification/information

The printed pack or its ancillary printed components (e.g. package inserts) serves the functions of providing both identity and information. Much of this information may have to meet the legal requirements of the country of sale. These are likely to cover some of the following points:

- type of product
- product trade name
- official name, i.e. compendium reference
- strength
- quantity
- mode of usage/administration
- batch number
- expiry date or date of manufacture
- shelf-life declaration
- storage instructions
- contra-indications—precautions
- product licence number/manufacturing licence number
- product category (OTC, ethical, etc.) and GSL, P, POM in the UK
- manufacturer’s name and address
- bar code and/or similar security code (UPC, EAN), pharma-code
- warnings (mandatory or voluntary), e.g. ‘keep out of the reach of children’
- product formulation, including excipients, preservatives, colourants, etc.

In a pharmaceutical context, information is likely to become a more important aspect, particularly in terms of the pharmacist-patient relationship. Thus although the primary pack may give only the briefest details, more in-depth information will be available both to the professional person, i.e. the pharmacist, nurse or doctor, and the patient. This may be achieved from published literature (which may be collected, for example, by an information service in a hospital), a computer base or the package insert or leaflet. It is therefore envisaged that the final screen for possible incompatibility between prescribed drugs, making the patient aware of possible secondary reactions which arise either directly from the drug or from other combined sources (i.e. drowsiness arising from alcohol and certain antihistamines), will move more towards the responsibility of the pharmacist issuing the product, as a part of counselling. Patient-friendly leaflets are now an EU requirement.

The legality of other information such as storage instructions, how to use the product, how to open/administer the product and reclose the pack may also need additional consideration.

Convenience

Convenience is normally associated with product use or administration. It may be a feature related to the pack, e.g. a metered dose aerosol, or related to the product-pack, e.g. a unit dose eye drop which both eliminates the need for a preservative and reduces risks associated with cross-infection, by administering only a single dose.

A unit dose pack also offers a number of other convenience factors, i.e. no risks associated with opening and reclosing, a few doses can be more readily carried at a time, size of pack, etc. Most pack devices demonstrate convenience advantages over earlier forms of presentation. However, convenience can also be extended to warehousing and production as well as the end user, i.e. in terms of incoming materials, reel-fed packs need less storage space than glass, metal and plastic containers.

Containment

Containment is probably the most basic aspect of any pack. Whereas it was possible in the past to buy certain vegetable drugs, herbs and spices literally unpacked, this is virtually impossible today. Powders, gases and liquids can only be purchased if they are ‘contained’ in a pack. Remember, a liquid which is not contained is ‘a puddle on the floor’.

Compliance

Compliance has recently times become an ‘in’ word based on the fact that a pack can either detract from or encourage compliance. The advent of the sustained release or delayed release type of product will lead not only to smaller packs, but to a simpler dosage regime that should in theory improve the chances of compliance. This is based on the belief that in taking a product three or four times a day (traditional medication), at least one period could be overlooked. Medication based on delayed or sustained release once or twice daily is currently preferred. This on occasions conflicts with policies which encourage aids aimed at administering the drug to the site where the drug is most effective, giving the fastest response to the symptoms. Thus, rather like packaging, compliance is inevitably a compromise between a selection of factors.

Protection

Protection has been left to last, as it is almost invariably the most important factor and frequently the most complex. Broadly, the pack must afford protection against the following primary hazards:

- *climatic,* i.e. those associated with the surrounding atmosphere
- *biological*—these involve microbiological (bacteria, moulds and yeasts) and biological factors (insects, rodents, human pilferage, etc.)
- *mechanical,* i.e. physical hazards associated with storage, carriage, etc.—general handling
- *chemical*—aspects of interaction and exchange between product and pack, i.e. compatibility, ingress and egress, and combinations of these and the factors above
- *use*—professional and patient, including any possibilities of misuse or abuse.

Many of the individual factors involved tend to be so obvious that there is always a danger that some will be overlooked. The author therefore presents these in a mnemonic form in order to assist memory recall and provide a check list (SCRAP CART MIST MARD).

S—shock	Physical hazards associated with storage and carriage, i.e. during loading, unloading, movement, handling, warehousing, etc.

C—compression
R—rattle (vibration)
A—abrasion
P—puncture
C—contamination/compatibility between pack and product
A—ageing (certain combinations involving several sources)
R—rodents or similar animal sources of contamination
T—theft
M—moisture (relative humidity (RH), rain, sea water)
I—insects
S—sunlight or any light sources
T—temperature (extremes)
M—microbiological
A—atmospheric—gases, pressure differentials, dirt, dust, oxygen, carbon dioxide, etc.
R—reuse/recycling/recovery/reduce, i.e. ‘the four Rs’
D—disposal—indirect hazards associated with ultimate disposal of pack-product including any pollution risks.

Although the above provides a fairly comprehensive check list, each item requires a fuller explanation.

Physical or mechanical hazards

A product-pack system can either be static (during storage) or in a state of motion (during carriage, handling or use). Physical hazards arising from both can occur at any time to the packaging material, the product and/or the packed product. Any material delivered to the site of a pharmaceutical operation also needs to have attention paid to the way it is packed, handled and delivered. This equally applies to in-house intermediate and bulk products stored prior to packing into smaller quantities. Damage is not therefore solely related to journey hazards, although these are likely to be a prime cause.

Physical or mechanical hazards can be identified as follows.

Shock–impact

Shock or impact arises from a change in velocity. The more rapid the change in terms of acceleration or deceleration, the greater will be the shock or impact applied to the object in question. Normally this deceleration is expressed as the number of times greater than the deceleration due to gravity (g). When the article is broken, the number of g thereby derived is called the G factor, or impact load factor. The aim of the pack, particularly where it acts as a cushion, is to limit the shock conveyed to the product-pack to an acceptable level. Knowledge of how, when and where shock can occur is essential for any packaging study, irrespective of the type of product involved. The severity of damage which may occur varies very much according to the handling facilities and the type of distribution media used in each country. The fragility factor is the maximum force an item (and pack) will withstand before it is damaged to a point where it becomes unusable or non-saleable.

Loads which are distributed in their entirety, e.g. lorries or trucks with fully palletised loads, containerised loads, etc., where movement is minimal during transportation, providing stacking strength is adequate, invariably incur the least risk. Mixed or part loads, items despatched individually or where transhipment occurs, are likely to suffer more damage and hence require a higher standard of protective packaging.

Examples of where shock or impact can occur are as follows:

- drops from tops of pallets, back of trucks, during stacking, loading or unloading, etc.
- impact from slings, hooks, shunting, rapid braking, forks of lifting trucks, etc.

Drops and impacts can usually be visualised from a study of warehousing and the main modes of sophisticated transportation, i.e.

- inland—road, rail, inland waterways
- sea—cargo, tramp, container ships, etc.
- air—cargo, passenger.

However, other forms of transport such as mules, donkeys, camels, horsedrawn cart or bullock cart with solid wheels may be all that is available in less developed countries, and these are less easy to visualise and quantify.

An assessment of drop-impact damage risks can be made by direct observation, self-contained instruments (within packs), and special recording instruments to identify how simulated laboratory tests can ultimately be substituted for travel tests. Data loggers are now capable of recording temperatures, RH, impacts and vibrations.

Compression

Compression is usually associated with stacking. Compression, as with shock, can be approached on a scientific basis by hydraulic compression tests equated with stacking loads. However, other factors may influence what happens in practice, i.e. the evenness of the floor, the type and style of pallet or stillage and, where paper-based outers are used, the temperature and RH of the surrounding atmosphere. In some instances, shock and compression may both be involved.

The height to which items can be stacked will depend on both the outer packaging and whether the item contained therein is rigid or collapsible. Articles such as sachets or plastic containers may require higher strength outer packaging than those containing glass or metal products which will accept high stacking stresses. However, certain points should be borne in mind:

- a pallet of glass containers may be significantly heavier than plastic
- for the same volume of pallet, the plastic container is likely to be 25–30% smaller, hence a greater weight of product can be stacked on the same pallet volume.

Whether a pack suffers from compression depends on both the design of the primary pack and the way it is positioned in the final pack. For instance, blister and strip packs afford little protection to the product if they are placed in a horizontal position, as all the top weight tends to be taken by the product. However, on-edge positioning not only maximises the strength of the packaging material, but also eliminates direct compression of the product.

Top weight or compression which is transmitted through the pack to a primary pack may cause changes and subsequent failure in function of some closuring systems. In turn such compression may provide the necessary stress to cause environmental stress cracking (ESC) should the product contain a stress cracking agent and the packaging material used be prone to ESC. Cracking or damage due to pure physical stress can also occur.

Although compression is obviously a serious hazard, there is a tendency for most pharmaceutical companies to over-pack on the outer packaging. Subsequent reappraisal of the outer packaging may therefore offer substantial cost savings. This is not taken advantage of by many companies.

Vibration

Vibration is defined by frequency and amplitude. At the extremes it can be a ‘bump’ or a high-frequency vibration. A bump may be a rise and fall of say 1–3 cm, such as may occur when a vehicle travels along a rutted or bumpy road.

Under certain circumstances vibration may cause direct problems with the product, independent of the pack, i.e. segregation of powders, separation of emulsions, surface dulling of tablets, settling down of product, etc. Vibration will also act in combination with compression forces and thereby possibly accelerate the weakening or distortion of board outers, cartons, etc. It can also lead to the distortion of flexible packs such as strips or sachets.

One significant vibratory effect is associated with abrasion or rub, particularly where printed or decorated surfaces are involved. This effect is likely to be more severe on round containers which will revolve (clockwise and anti-clockwise), and move side to side and up and down in either a carton or a divisioned outer. Rectangular or square containers under the same circumstances will usually show less movement. Thus unless the label is recessed, superior rub resistance is usually required for a label on a cylindrical pack.

Vibration, in conjunction with compression, may also cause loosening or leakage from closures. Distortion of flexible materials, i.e. plastic bottles, cartons, etc., which can produce ‘high spot’ areas where the item bulges, may lead to excessive lateral rub.

Puncture

Puncture, where a pack is penetrated by an internal or external object, is a fairly rare occurrence in the pharmaceutical industry. Although the problem is ever-present from such objects as fork trucks, sharp corners of pallets, slings and hooks, mixed loads inevitably present the more serious risk. The resistance of a pack to penetration can be measured by burst and puncture (swinging pendulum) tests.

Damage caused by the primary pack or a component of the pack on its outer packaging should not be overlooked (i.e. penetration from within the pack).

Climatic hazards

Before proceeding to how the product-pack may have to stand up to certain hazards, it is reasonable to assume that the drug entity, the ingredients associated with the formulation, and the final formulation have been challenged to a range of conditions prior to full packaging investigations being started. It can therefore be expected that the susceptibility to temperature, pressure, oxygen, carbon dioxide, heavy metals, bacteria, mould, pH, etc. has provided guidelines on the sensitivity of the product and its ingredients. This information provides a broad indication of what 'protection' is required. It is essential that the packaging technologist has access to such reports.

Temperature

Let it immediately be said that temperatures cannot strictly be broken into such simple categories as were once envisaged, i.e. 'home' and 'export' markets. The fact that many pharmaceuticals will finish up in the kitchen or bathroom invariably means that extremes of temperature and humidity may be worse in the home than in export-type conditions. Companies should also note that goods transported in the boot or trunk of a representative's car may occasionally reach temperatures in excess of 60° C. If outdoor arctic or antarctic conditions are included, then products may be exposed from −60°C to +60°C depending on the circumstances. As temperature scales used for test conditions frequently bear some relationship with the past, those selected for testing may tend to be related to a rather arbitrary selection or even what manufacturers of cabinets have available. The pharmaceutical industry therefore, until recently, tended to operate to no particular standard and selected from the following conditions for testing purposes:

- −18°C to −22°C — deep freeze conditions (arctic, antarctic conditions)
- freeze-thaw — recommended for drug substance
- 4°C — i.e. refrigeration 0–8°C
- 10°C
- 15°C — (lower temperate)
- 20°C
- 25°C — (upper temperate/lower tropical)
- 30°C
- 37°C or 38°C — (tropical, body temperature)
- 40°C — a preferred condition for certain Japanese tests
- 45°C or 50°C — upper maximums for medium-term storage, i.e. 3–6 months
- 55°C, 60°C, and 80°C — usually short-term upper challenge conditions

The phrases in parentheses, other than body temperature, have evolved by tradition rather than on any scientific basis and should be interpreted accordingly.

Recent investigations based on kinetic mean (km) temperatures have divided the world into four zones:

zone I	km temperature 21 °C mean RH 45% (lower temperate Europe)
zone II	km temperature 26°C mean RH 60% (upper temperate Europe)
zone III	km temperature 31°C mean RH 40% (tropical dry)
zone IV	km temperature 31°C mean RH 70% (tropical humid)

These temperatures are usually 'rounded' to 25°C (zones I and II) and 30°C (zones III and IV) for stability-type programmes.

40°C 75% RH is now being widely adopted as an accelerated condition where practical. It has been used in Japan for many years. The above forms the basis of harmonisation (ICH) investigation carried out by Europe, Japan and the USA.

The use of a series of conditions at 10 °C intervals has some advantage, in that chemical changes which follow Arrhenius plots can clearly be identified. However, with the ever-increasing cost of tests there is a tendency either to reduce the range of storage temperatures or, if product-packs are stored over a range of conditions, to limit full analysis to, say, one or two conditions until such time as a change is identified or suspected. Accelerated tests may not proceed to the expected rules, especially where certain plastics are under strain. In these circumstances the strain may be increased by lowering the temperature and reduced (by cold flow) by raising the temperature. In addition, quite a few packaging materials will weaken, break down, or not function properly if consistently stored at temperatures of 45°C and above. Thus certain higher

temperature testing may accelerate product degradation through pack breakdown, hence even short-term storage at higher temperatures cannot always provide a scientific means of predicting a shelf life. It should also be noted that testing at an accurately controlled temperature condition does not compare with any actual climate where tem perature fluctuations can lead to dimensional and pressure changes which may encourage exchange between the product and the outside atmosphere. Long-term formal stability which uses controlled conditions can therefore be fully justified only if the true effects of temperature, RH and pressure differentials are evaluated in the investigational or feasibility stage of a pack-product assessment. Most formal stability work also involves static conditions, i.e. it does not include effects due to handling, warehousing and distribution.

A few cases where variable conditions may cause changes other than arise from storage at a controlled temperature are:

1 the pack 'breathes'—exchange may be in or out, or both
2 the closure loosens or tightens
3 laminates separate or delaminate, usually starting at the edges.
4 materials 'age' faster.

Declared storage conditions (temperature)

Serious attempts have recently been made to clarify the storage statements used for pharmaceutical products, with a view to eliminating such vague phrases as 'store in a cool dry place'.

Single label statement (no storage temperature statement) is acceptable if product has the ability to withstand temperatures to 30°C (based on support data). Below 30°C, storage statements are necessary, e.g.:

- up to 25°C
- 2–8°C—refrigerate, do not freeze
- below 8°C—refrigerate
- below−5°C—freeze
- below −18°C—deep freeze
- protect from light
- store in a dry place.

These statements formed part of ICH harmonisation discussions, hence there are currently variants on these, i.e.:

- 8–15°C (USA)—a cool place
- 30–40°C (USA)—warm
- above 40°C (USA)—excessive heat.

Controlled room temperature (USA) refers to an expected control between 20 and 25°C with excursions which allow a total range of 15–30°C.

Moisture

There is perhaps a tendency to challenge packs, particularly during storage tests, to higher conditions of controlled RH which may be difficult to equate with a lower 'norm'. Suffice it to say that if the product and pack pass a stringent test, then any subsequent risk may be small. However, failure may make decisions difficult, particularly where a combination of conditions is involved. For instance, the author has experienced a number of occasions where deterioration at 25°C 75% RH has been greater than at 37°C 90% RH storage. It might be suggested that higher vapour pressures in the pack at the higher temperatures are playing a different role.

Moisture can exist as either a vapour or a liquid. The latter can be associated with rain, sea water, flooding, etc., or occasions where a reduction in temperature causes dew point to be reached and, literally, a 'shower' within the pack or the surrounding packaging materials. Although water vapour ingress and egress may occur from a variety of causes, the product changes which may result can be extremely diverse, e.g.:

- hydrolysis
- weight gain, e.g. stickiness with sugar-based products
- weight loss—note the increased concentration effect when water or solvent is lost; loss of more volatile constituents can also occur (flavours, alcohol, etc.)

- chemical interaction (e.g. effervescence)
- drying out, caking, hardening, softening
- changes in dissolution, disintegration times
- changes in microbial growth or microbial effectiveness
- dimensional changes, swelling, contraction (packaging and product)
- change in appearance—dulling, loss of gloss
- organoleptic change in flavour or odour
- changes in electrostatic effects—under dry conditions many plastics become more highly charged, and collect dust and dirt.

Exchange of moisture between a pack—product and the surrounding atmosphere may occur for a number of reasons.

1 The closuring system is not fully effective (some moisture exchange is likely to occur with most closure systems, even heat seal systems involving foil laminates may allow low permeation via the edge seals).
2 The materials used are permeable—this occurs to some degree with all plastics.
3 The pack may 'breathe'—not a truly scientific form of terminology but a means of indicating that loss or gain will be increased or reduced by external influences such as changes in temperature and pressure (i.e. where capillary channels may exist in creased heat or cold seals—see (6) below).
4 Increasing or reducing the pressure within a pack, e.g. a reduction of pressure within a pack can occur if a warm or hot fill is employed or if a flexible container is compressed during capping.
5 Changing the atmosphere surrounding the product by absorbing the moisture (e.g. a desiccant or substance which is hygroscopic in nature) or the emission of moisture whereby an equilibrium moisture level between the product and air space is set up. Both absorption and emission may be temperature-dependent.
6 Capillaries and capillary attraction: if folds occur in areas where seals are made, exchange may occur by capillary channels. Similar surface effects can occur with bottles employing an internal plug system. Sinkage or furrows in bottle bores, which may arise from shrinkage at the thicker thread section, crizzles or hair lines, etc. may all act as an encouragement to capillary-type leakage or seepage.
7 Wicking: this is an expression originally applied to strands of cotton wool which straddle the sealing surface of the bottle. As a result moisture enters (or leaves) via the raw ends of the strands, which literally act as a wick. However, the term has now been extended to any material which will transport moisture via an exposed end. For instance, reels of regenerated cellulose may expand or shrink due to moisture uptake or loss via the raw cut edges (this in turn can change the tension of the reels, whereby machine running performance is drastically impaired).

Whether a product gains or loses moisture depends on its affinity to water, the nature of the pack and the seal, and the RH (or water) in the area which surrounds it. Packs which are basically impermeable, i.e. metal, glass and most types of foil, largely rely on the effectiveness of the seal or closure. The torque of screw closures, for example, may vary according to the temperature and the relative expansion and contraction of differing materials. Increasing the RH differential gradient between the inside and outside of the pack will increase the rate of loss or gain.

The above should further indicate why moisture must be considered as a serious hazard. It should also clearly establish that moisture constitutes a far more critical hazard than the simple effects associated with loss or gain.

Moisture both in the product and in the environment in which the product is produced, processed, packed or used may also be relevant. Thus in some circumstances the apparently simple action of opening and reclosing a pack under an adverse atmosphere may lead to product deterioration.

The atmosphere and atmospheric gases

Although a simple analysis of the atmosphere identifies the main gases as oxygen, carbon dioxide, nitrogen, etc., traces of localised gases cannot be ignored. Oxygen invariably gives the most problems due to oxidative type interactions. In the case of oils and fats, oxidation will lead to rancidity and unpleasant off odours or flavours. Volatile oils are also subject to oxidation to a point where resinification may occur with the production of light brown to black, viscous, possibly odorous, residues. Oxygen can also be absorbed by certain types of product with the result that a headspace may be reduced into a partial vacuum, and materials which are flexible will partially collapse (for example, panelling in low-density polyethylene bottles). Chemical degradation by oxygen may be sometimes avoided or reduced by minimising the headspace (e.g. vacuum packaging), gas flushing with an inert gas such as nitrogen, plus an effective closuring system and correct barrier materials. Oxidative effects may be accelerated by the presence of light, higher temperatures or the presence of catalytic substances. The degradation of Vitamin B_1 is a typical example of an oxidation process that can be accelerated by the presence of copper.

Carbon dioxide, although less of a hazard than oxygen, can act as a weak acid and cause either a pH shift or a reaction with alkaline substances (possible precipitation as carbonates). A pH shift is most likely to occur with non-buffered aqueous solutions stored in materials (e.g. low-density polyethylene bottles) which are highly permeable to carbon dioxide.

Nitrogen, by its inert nature, is not likely to cause any problems. However, it should be recorded that the simple act of nitrogen flushing does not overcome all problems, particularly if the material used is permeable to oxygen and carbon dioxide.

Under this general heading of the atmosphere, it should be noted that a pack has two atmospheres which need consideration, i.e. those internal and external to the pack. Exchange both within the pack and between product and the external atmosphere is usually related to a 'gradient' based on concentration, and pressure differentials between the two.

Changes of internal pressure within a pack, irrespective of whether they are created by the processing (accidental or devised), the product or the environment, therefore need to be carefully monitored. The following are examples.

1 Hot-filling leading to product and airspace contraction/condensation causing a partial vacuum, assuming that significant exchange does not occur via the closure. Flexible containers may show a state of partial collapse, especially if hot-fill is followed by storage under colder conditions.
2 Terminal autoclaving.

- Changes in closure efficiency during autoclave cycle whereby the closure may seal less or more effectively at some stage.
- Dimensional changes which, due to differential cooling, may lead to pack distortion, i.e. in cooling of pack, hot contents extend pack. Can contribute to the 'dimpling' of plastics.
- Pressure in pack (liquid and air space expansion) which is not sufficiently counteracted by over-pressure so that the pack distends and distorts (due to content pressures—airspace and product). Can contribute to the 'dimpling' of plastics.

3 External changes in atmospheric pressure.

- Packs filled at sea level then transported to higher altitudes (negative pressure). Can apply to both non-pressurised and pressurised aircraft.
- Packs filled at high altitudes then transported to lower altitudes (positive pressure). Can apply to both non-pressurised and pressurised aircraft.

4 Capping a flexible container whereby the container is compressed, flexed or distorted (i.e. squats) to an extent that the content momentarily occupies more volume in the container. Thus if a good seal is then obtained, a partial vacuum can then be created in the pack. This type of operation may be extremely sensitive for plastic containers which show changes in wall thickness and compress (e.g. concertina) easily.
5 Inadequate ullage in the container. This is especially relevant where ingredients either exert high vapour pressures or have high thermal coefficients of expansion (e.g. alcohol).
6 Vacuum packaging—degree and efficiency of vacuum retention.
7 Product change leading to pressure changes (acid/alkali interaction, metal acid/alkali reaction, leading to release of hydrogen or the absorption of oxygen or CO_2 from container headspace etc.).
8 Efficiency of nitrogen flushing—frequently an operation which is difficult to monitor and control. Flushing an empty container then filling tends to be more effective than trying to nitrogen-flush the headspace once filled.
9 Extremes of temperature, particularly when unexpected, e.g. non-insulated vehicle caught in subzero temperatures, warehouses where goods are stacked near heat sources, may cause pressure changes.
10 Filling to incorrect weight, volume, number, whereby product to ullage ratio is adversely altered.

Sunlight/light

Sunlight covers a range of wavelengths from infrared (IR) through the visible spectrum to ultraviolet (UV). While certain packaging materials, e.g. metals and foil, will reflect the IR rays, some colours will absorb IR (e.g. amber glass bottles) and show a corresponding temperature rise. UV offers the most serious risk as it can cause photochemical changes to both the product and the pack. These changes can be visible (discoloration) or invisible. Whereas the effects of light can be accelerated by the use of light sources which intensify all or certain wavelengths (e.g. UV) it is somewhat difficult to divorce such effects from higher temperatures, particularly if IR wavelengths are also involved. Tests using certain accelerated light apparatus (e.g. xenon test), although providing excellent comparative data, are frequently difficult to interpret in the degree of protection from light actually required. It should, however, be noted that most products spend a significant part of their shelf life in a

carton surrounded by secondary packaging. Adequate protection from light may therefore be necessary only in the latter or final exposed stages of storage or use. For total exclusion of light it is not sufficient to use opaque materials since thinner papers and board, most plastics except those pigmented with carbon black, and coloured glasses (even amber and actinitic green) do allow the passage of some light waves. Metal-based materials, aluminium, tinplate and aluminium foil provide an absolute barrier.

Selected amber and actinitic green glasses provide substantial protection against the short UV wavelengths provided the glass is of adequate thickness (usually 2 mm or more).

The Japanese recommend that a light test use 1.2×10^6 lux hours as a drug substance-product challenge (now part of the ICH Guidelines).

Ageing

Ageing is used as a general term when either the cause cannot be clearly identified or a combination of climatic effects is involved. Natural rubber materials suffer from ageing, which can be accelerated by the combined effects of light, higher temperatures, oxygen, ozone and moisture in that the elastic properties are lost and the rubber can ultimately become tacky or surface-crazed to a point where it splits or disintegrates when stretched. Many companies now put re-examine dates on packaging materials so that any long-term ageing can be established.

Contamination

Contamination may arise from chemical interaction, organoleptic effects, exchange of ingredients between product and pack, or from particulates or biological-microbiological causes. Further details of some of these are given below.

Particulate contamination

Under the broad terminology of atmospheric contamination, both microbiological and particulate airborne contamination can be considered. These two aspects should partly be considered together, especially as microbial contamination will frequently increase or reduce according to the ‘cleanliness’ of both the product and the pack, i.e. particulates can be a bioburden carrier.

Particulate contamination, although mainly airborne, can also arise when materials are cut, torn, rubbed, fractured, punctured or penetrated. In these cases any airborne phase may be either short or non-existent, i.e. direct contamination can occur. However, for the purpose of this preview, particulate contamination will be related to how it may arise.

Airborne environmental sources

Dirt, dust, fibres, grit and hairs are ever-present in a non-filtered atmosphere and vary from submicrometre, invisible particles to visible, clearly definable units. Particles of below 50 μm are not easily seen by persons with normal eyes. Contamination from the environment is also dependent on the prevailing atmospheric conditions and any electrical charges carried by the particles and the materials which may become contaminated. Such charges are usually increased by dry, low-RH conditions and lessen as humidity rises.

Environmental sources—not airborne

As above but with the inclusion of larger particles or agglomerates which contaminate by direct contact, i.e. placing a product or component onto a precontaminated surface. Particles may adhere initially by gravity, electrical charges, or due to the adhesive nature of the surface or particle.

Contamination arising from physical actions

Examples are as follows.

- Fracturing, breaking, e.g. glass fragments arising from the opening of a glass ampoule.
- Sawing, cutting, tearing, e.g. paper fibres from paper (cellulosic) based products.
- Abrasion/vibration—between the same or different surfaces; aluminium, for example, is particularly prone to abrasion from both a raw edge and a flat surface.
- Rubber also suffers from a form of abrasion when a needle passes through it, i.e. fragmentation.

- Removal of surface acting substances from plastics, e.g. lubricants, slip additives, such as stearamide, stearates, anti-static agents.

Contamination arising from the fabrication processes

Although fabrication processes may involve some of the examples in the above list, certain processes may further encourage contamination, e.g. trimming metal, paper, board, etc.; flash from trimmed and untrimmed plastic components, flash from residues from tumbling or freeze tumbling operations; friction-generating processes, shaping, swaging, seaming, extruding, cutting dies, grinding, polishing, excessive handling.

Contamination arising from in-house production and processing (including packaging) operations

For example, excessive rubbing of plastic materials may induce high static charges, thereby increasing the attraction of particles. Unscrambling and printing can also be a source of particulates.

Chemical contamination

For example, a partially corroded metal surface from which particles of corroded metal can become detached.

Avoidance or elimination of particulate contamination

Minimising particulate contamination is obviously related to the product—pack form, the type and source of contamination, and the environment. Although adequate control of these will produce a relatively particle-free situation (i.e. prevention), either the introduction of processes to eliminate contamination or a combination of relatively clean materials plus limited processing may be equally acceptable. The latter may therefore involve a number of cleaning type activities, i.e. dry oil-free air blowing of components plus vacuum extraction. Alternatively, washing with water or water plus detergents with an adequate rinsing procedure followed by drying may be used. Drying may vary between air drying, hot air drying with or without filtered air, etc. As hot air drying tends to produce high levels of static, recontamination at the drying stage represents a high risk unless the area and atmosphere are reasonably particle-free. This risk is particularly significant with plastics. Producing sealed preformed containers which are opened immediately prior to filling and resealing, e.g. closed ampoules, is a further option that is becoming increasingly available.

Solvent washing

Provided materials are compatible with solvents, solvent washing is a useful alternative to water, especially where surface residues (oils, greases, lubricants, release agents) may either act as an adhesive bond for particles or give rise to a form of chemical contamination.

Ultrasonic washing

An effective cleaning process can, under certain conditions, create particles. Ultrasonic energy usually detaches particles into a liquid, thus diluting the particle population.

Fixing particles

This can be done by annealing or firing (i.e. fixing glass particles on to glass), burning off organic matter (glass), lacquering or coating.

Avoidance of electrostatic build-up

This can be achieved by neutralising charges, i.e. use of ionised air, raising the humidity or using material incorporating anti-static additives (plastics).

As indicated previously, the alternative to cleaning is producing a material/product and/or pack under clean conditions. To achieve this in totality means that all operations must match those of a sterile or aseptic type of process in terms of cleanliness. However, as this is not totally practical, attention to special detail, such as filtered air to feed plastic moulding equipment,

production under laminar flow and positive air pressure, avoidance of draughts, minimum of handling by operators and good housekeeping goes a long way towards cleaner manufacture.

Before any efforts are made to reduce contamination, knowledge of the materials, the processes by which they are made, the packaging materials in which they may be packed, how such packs may be opened, removed/unscrambled, etc., are an essential part of total control. Basically these are all part of good manufacturing practice (GMP). However, before this can be done some agreement must be reached on what constitutes contamination and how it may be detected.

Detection options

1 Visual observation—largely dependent on the eye sight of the operator; tends to be very subjective.
2 Visual under low magnification, i.e. 2–10 times magnification, including use of hand lenses with and without graticules.
3 Polarised light—with and without magnification.
4 Microscope—low-to high-power magnification.
5 Counters, which operate on a number of principles:

- electrical resistivity, e.g. Coulter counter
- light scattering, Royco
- light blockage, Royco, HIAC
- lasers, e.g. Malvern.

These may require the particles to be suspended in a solution, hence in terms of containers and components results are dependent on how the particles are removed from the surfaces to the solutions.
There is no obvious standardisation on levels of particulate matter permitted in a product.

EXAMPLE 1.
EYE OINTMENT—TEST ON PRODUCT

British Pharmacopoeia (BP): this takes an approximate 10 mg smear on a microscope slide with the following acceptance limits. Number of particles:

- not greater than 25 µm–20
- not greater than 50 µm–2
- not greater than 90 µm–none.

BS 4237 applies limits to metal fragments in collapsible tubes.

United States Pharmacopoeia (USP): This takes the contents of ten tubes which are melted in separate Petri dishes, cooled and inverted. Examined under 30×magnification, and particles of 50 µm and more measured. The test is passed if particles do not exceed 50 for ten tubes and not more than one tube has eight particles. If test fails, twenty further tubes are taken. The test passes if the particles do not exceed 150 for thirty tubes and not more than three tubes have eight or more particles.

EXAMPLE 2.
IV SOLUTIONS

The USP uses a filtration technique whereby the particles are retained by a membrane filter and then measured under 100×magnification. Particles are gauged by their effective linear dimension. Limits are:

- not more than fifty particles equal to or greater than 10 µm
- not more than fifty particles equal to or greater than 25 µm.

The BP 1980 test permits the use of an instrument based on either:

1 electrical zone—sensing principle, i.e. Coulter counter, or
2 the light blockage principle.

Different limits are specified for each method. These limits are:

1 not more than 1,000 greater than 2 µm and not more than 100 greater than 5 µm
2 not more than 500 greater than 2 µm and not more than eighty greater than 5 µm.

Both estimated per ml of undiluted solution.

Finally it should be noted that whatever the methods of particulate detection employed, each remains a somewhat subjective judgement and is constantly being updated.

Biological contamination

Under this heading the following will be considered:

1 insects, including termites
2 animals, including rodents
3 human pilferage, adulteration, etc.
4 moulds, bacteria and yeasts, i.e. microbiological aspects (bioburden).

Insects

While drugs are still obtained from vegetable and animal origins, some contamination risks from insects etc. will remain. The frequent gassing of stores and warehouses has done much to reduce the general level of infestation.

The types of insect that create the most damage are moths and small beetles. Moths and flying insects in general can be minimised by control of doors, windows, etc., or through use of 'Insectocuters' etc. Termites are of minute size and usually exist in very large colonies, in total darkness, attacking paper, board and wood-based materials, and require specialist attention. Traps for crawling insects are also available.

Animals

Damage caused by animals in general and rodents in particular may relate to penetration (leading to possible product spillage) or general fouling leading to an unhygienic situation.

Bulk stored and transported items tend to be more prone to infestation by insects and animals. Attention to properly maintained storage conditions is essential if infestation and general fouling is to be prevented.

Pilferage

As the pilferage of pharmaceutical products can be a profitable business, particularly with highly priced items in countries of either high unemployment or low wages, the use of tamper-resistant (a preferred term to pilfer-proof) closures or packs may be advised. Such systems may also be used and are indeed a mandatory requirement with certain sterile products to indicate that the container seal has not been disturbed and the product has not been subjected to contamination from external sources.

Tamper resistance and adulteration

The Tylenol incidents of 1982 caused serious concern to governments and the pharmaceutical industry in particular. The USA immediately brought in legislation (5 November 1982) to ensure that OTC products had some form of tamper evidence, with 1984 as a deadline for virtually all OTC and certain cosmetic and toiletry products. Tamper-evident seals at that time included glued or taped cartons (provided a fibre tearing seal was achieved), carton (film) overwraps (clear material had to be printed with a recognised design), diaphragm seals, various closure break systems, shrink seals or bands, sealed tubes (i.e. collapsible metal tube with a blind end), pouches, blisters, bubbles or strips, etc. All had to show some distinct form of evidence of having been tampered with or opened. Each pack also has to indicate (in print) the primary means by which tamper evidence had been achieved. Although as part of a pharmaceutical image the legislation may appear ethically sound, virtually all systems can be circumnavigated by a skilful and dedicated person via an alternative route to the main closure system. The customer opening the pack may not always observe the state of the tamperevident seal, particularly if it is carefully and cunningly replaced.

Microbiological aspects

Microbiological aspects of pharmaceuticals are of importance not only to sterile products but to all products, in that gross contamination should be avoided irrespective of how the product is used or administered. Although bacteria, moulds and yeasts constitute the major sources of contamination, pyrogens are also included under this heading.

Bacteria are widely distributed in all surroundings unless special precautions are taken to eliminate or partially exclude them. Bacteria can be pathogenic (disease-producing organisms), non-pathogenic or commensals (i.e. bacteria which occur naturally on or in the body without doing any obvious harm). Some bacteria may produce dormant forms of spores which are very resistant to heat and disinfectants, hence are more difficult to destroy.

METABOLISM OF BACTERIA

Bacterial cells are nuclear structures bounded by a cell wall. Although as with other cellular structures the moisture content is high (75–90%) other constituents may include sulphate, silica, sodium, phosphorus, potassium, magnesium, calcium, chloride, carbohydrates, fats and lipids.

In order to survive, bacteria require water (free liquid water), food (usually in the form of organic substates with a supply of nitrogen and carbon), particular temperature conditions and certain atmospheric gases.

Some bacteria will only grow in the presence of oxygen and are known as obligatory aerobes. Those which will grow in either the presence or absence of oxygen are called facultative anaerobes; those which will only grow in the absence of oxygen are obligatory anaerobes. A few bacteria will only grow in the presence of relatively large amounts of carbon dioxide. pH is also critical for the survival and growth of most bacteria with the optimum range being pH 7.0–7.8 for many and pH 5. 0–8.0 covering most pathogenic types. However, some bacteria will flourish at abnormally low or high pHs. As with human beings, bacteria have a definitive life cycle.

TEMPERATURE

The normal growth temperature for most bacteria is 15–40°C, with pathogenic organisms growing best at 37°C. A few bacteria, called thermophilic, can live at temperatures of 45–70°C. Bacteria can, however, generally withstand low temperatures and remain viable. Bacteria can be killed by exposure to high temperatures which can be quantified as a time-temperature reaction: the higher the temperature, the shorter the kill time (see ‘Sterilisation’ below).

LIGHT

Light frequently inhibits the growth of bacteria, although there are species which readily survive in the light (UV light has surface sterilising properties).

MOULDS AND FUNGI

Moulds and fungi consist of filaments or masses of filaments of one cell in width which initially extend as hyphae, branch and grow and form a readily visible colony mass known as mycelium. This in turn produces spores on the surface either by sporangium or conidiospores, or by a process of reproduction. Moulds can produce enzymes which break down surrounding substances, which can be then adsorbed as a food. Some acids can be made by fungal fermentation. Such acidic excretions can lead to corrosion of metal-based materials. Moulds require similar conditions of growth to bacteria, except that high RH is necessary rather than liquid water. Properties of moulds are as follows.

1 Best growth condition is around 25°C; moulds are less resistant to low and high temperatures.
2 Moulds do not need liquid water but will use atmospheric moisture. An RH of 75% and above is usually necessary.
3 A source of organic food which includes fairly simple chemical substances is required.
4 All moulds require oxygen, although some will grow under relatively low concentrations.
5 Some moulds will grow under both light and dark conditions. Others will be either inhibited or stimulated by one of these conditions.
6 Moulds will tolerate wide ranges of pH, with a preference towards acid medium. Some not only produce acidic substances but will survive in a relatively low pH (e.g. in vinegar).

YEASTS

Although yeasts are basically closely aligned to moulds and fungi, they frequently exist in an unicellular form. Yeasts ferment sugars forming alcohols, and will grow in high CO_2 concentrations.

The above outline on the characteristics of bacteria, moulds, fungi and yeasts is necessary to understand:

1 the requirements of sterile products and aseptic packaging
2 the need to minimise microbiological contamination and the involvement of GMP and good laboratory practice (GLP)
3 how these organisms can survive and hence be controlled
4 the special pack characteristics associated with the above.

An obvious way of controlling organisms relates to aspects of cleanliness, good hygiene and the removal or control of those factors which are necessary to the survival of viable organisms, i.e.:

- removal of moisture
- removal of oxygen (note that certain organisms can still survive)
- removal of nutrients (unless product itself provides a nutrient base).

It should be immediately seen that the pack must be an effective barrier to moisture and gases so that entry does not support growth or, if the product is made sterile, re-entry of bioburden is prevented. Control can also be exerted by the use of preservative systems. These may involve disinfectants, germicides, bactericides (kill bacteria), fungicides (kill fungi, mould or yeasts) and bacteriostatics (inhibit growth but do not necessarily have a significant rate of kill). The activity of any preservative system is influenced by concentration, temperature, time in contact, the test organisms (or the contaminating organisms), the pH, presence or absence of organic matter, and surface tension (wetting power) of the solution. Other factors may be involved, e.g. effects related to the drug entity, the presence of other ingredients such as EDTA, which can increase the effectiveness of certain preservative systems, etc. (e.g. benzalkonium chloride). Typical preservatives include:

- mercurial compounds—inorganic and organic
- medicinal dyes
- phenols and chlorophenols, i.e. phenols, cresols, chlorocresol, chloroxylenol
- anionic and cationic detergents.

Product changes which may be related to the pack characteristics can reduce (or increase) the microbial effectiveness of a product. Examples include adsorption and absorption of preservatives with plastics, and the change of pH due to the passage of carbon dioxide through certain plastics.

Sterilisation

Sterilisation is the finite method for microbial control and can be achieved either by sterilising each component (product and packaging materials) followed by assembly, i.e. aseptic processing, or by a terminal sterilising process which involves both product and pack. The latter is the preferred method as it entails less risk of a non-sterile product being produced.

These processes of sterilization are used in pharmaceutical production:

1 dry heat (160–180°C) for 1 h or more
2 moist heat (autoclaving) 115–118°C for 30 min or 121–123°C for 15 min or an appropriate temperature/time cycle; high-pressure steam is also employed
3 filtration (of liquids) by use of a 0.2 μm filter
4 irradiation, either gamma irradiation or accelerated electrons (beta irradiation)
5 gas treatment (ethylene oxide)
6 heating with a bactericide
7 UV (non-official).

Heat and irradiation

Each of these processes imposes different demands on the packaging materials. Dry heat (temperatures of 160–180°) can only be withstood by glass, metals and a few selected plastics. Glass often uses 320°C or slightly higher for 3–4 min.

Autoclaving by moist heat involves the effects of temperature, expansion and contraction, pressure differentials and moisture. Gamma irradiation of 2.5 Mrad (25 kGy) can be used to sterilise materials and filled packs. Packaging materials sterilised by this process are normally double-sealed in a polythene bag, in a second sealed polythene bag within a fibre board outer. This enables the outer bag to be removed in a non-sterile area; the inner bag and contents may then be passed through a hatch to a sterile area where the inner bag is removed. Gamma irradiation normally uses a cobalt 60 source of 2.5 Mrad. The rays will penetrate most materials. Caution is, however, required as many of the possible effects have not been fully identified or quantified. Glass, for example, is darkened to the extent that white flint glass becomes a smoky grey-brown and amber changes to almost black. Although this discoloration tends to fade with time, the appearance remains unsightly and variable from container to container. Paper-based materials are reported as not being affected, but as these are usually only used for the secondary packaging operation, any change is less critical. Rubber, other than certain synthetic grades, is generally listed as suitable for gamma irradiation. With the increase in the use of plastics, many of which are aseptically processed, the question as to whether irradiation can be employed is very important. For example, certain polymers pronounced as suitable have been found to have some grades which are either unsuitable or suitable only for certain products. Thermosets, thermoplastics and their suitability for each process of sterilisation are more fully covered in Chapter 7. Suffice it to say, at this stage, that as the use of gamma irradiation is extended, further detail as to possible packaging material changes will be identified. To approve the irradiation of a filled pack requires additional attention to safety and the identification of any possible degradation compounds associated with the product.

An alternative method of irradiation sterilisation is the use of accelerated electrons, i.e. beta irradiation. This generally has a milder effect on both the product and the packaging material than gamma irradiation. Although it has less penetrating power than the latter, it is equally effective in terms of sterilisation. The cycle time is short (seconds) whereas gamma irradiation takes hours. UV rays have been used to control microbial growth in liquids flowing through narrow tubes, e.g. water.

Gaseous sterilisation

Although several gases will kill bacteria (ethylene oxide, formaldehyde, propylene oxide), ethylene oxide is the one which has been most widely adopted for pharmaceuticals, instruments, and dressings. Sterilisation by ethylene oxide involves either a gas concentration of 10–20% with an inert gas such as carbon dioxide or nitrogen, or the gas in a pure state. The dilution method is usually preferred, particularly as ethylene oxide can form an explosive mixture with air.

For the lower concentrations of ethylene oxide a temperature of 50–60°C is employed, together with a degree of humidification, as moisture assists the penetration of the gas. The exposure time for the above is normally around 16 h. Degassing can be achieved by forced aeration, vacuum cycles or storage for a period (7–14 days) in a well-ventilated area to allow natural degassing. However, the material being sterilised must be permeable to the gas.

Virtually all sterilisation processes impose some hazard or risk of adverse effects on the packaging material, and they all need study before they can be pronounced as com pletely satisfactory. Those processes which may be critical to a particular material will be reviewed in great detail in the respective material section.

Pyrogens

Pyrogens are mainly liposaccharide components of dead gram negative bacterial cell walls which can cause disease and temperature increase. They are difficult to destroy (dry heat temperatures of 250°C and above are required) and are detected by either the rabbit injection test or the LAL test (Limulus amoebocyte lysate), the latter now being the preferred test. Keeping microbiological contamination low is an essential part of reducing pyrogens to a minimum. Preventing such contamination (microbial entry or re-entry) therefore partly relies on the type of pack employed.

Chemical hazards and compatibility

Compatibility basically covers any exchange which will occur either between product and pack or between pack and product. Incompatibility may be associated with interaction, migration, leaching, adsorption, absorption, extraction, whereby ingredients may be lost, gained, or chemically or physically altered. Such exchanges may be identified as organoleptic changes, increase in toxicity/irritancy, loss or gain of microbial effectiveness, precipitation, haze, turbidity, colour change, pH shift, degradation, etc. Again other external influences may catalyse, induce or even nullify chemical changes. Chemical changes may also be followed by further chemical reactions.

Chemical interaction or contamination can also arise from impurities in the ingredients, accidental ingredients arising from the production processes, or abrasion between contact surfaces. Examples of these are, respectively, as follows.

1 An oxidative reaction accelerated by the presence of low levels of copper.

2 Contamination arising from the extraction of plasticisers from PVC pipelines.
3 A bulk product involving a clarity of solution test was packed in a low-density polyethylene bag inside a metal drum. On reaching its destination the product failed the clarity of solution test. This was traced to a lubricant in the polyethylene which achieved its effect by being present at the surface of the film. During transportation the lubricant was physically removed from the film surface, by vibration with the solid product.

Other examples of incompatibility or partial incompatibility are as follows.

- Adsorption of chemical entities onto component surfaces which are frequently related to the surface areas involved—losses of EDTA and certain preservatives have been known to occur due to surface adsorption.
- Absorption and surface evaporation. The more volatile preservatives, e.g. chlorbutol, phenol, 2-phenylethanol, show fairly rapid loss through low-density polythene. If an external overwrap which is not permeable to the preservative is used, the loss can be restricted to relatively low levels, i.e. less than 10%.
- Other surface active ingredients which may be found in plastic materials and suffer loss into product by solution, surface abrasion, etc. include anti-static additives, slip additives, mould release agents, etc.
- Detachment of glass spicules may occur when alkaline solutions of citrates, tartrates, chlorides or salicylates are stored in soda glass containers. It may occasionally occur when treated glass is autoclaved in the presence of similar alkaline salts.
- Organoleptic changes—permeation of volatile or odorous substances through plastic materials (conversely to loss of perfume through plastic containers).

Environmental issues

To complete this introductory chapter, attention must be drawn to certain environmental issues. These are receiving increasing publicity, and include:

- conservation of the earth's natural resources (renewable and non-renewable)
- conservation of energy and minimum use of energy
- minimising pollution, from raw material production to pack disposal
- disposal of packaging materials following fulfilment of purpose
- modes of material disposal and recovery, including recycling, reuse, and chemical recovery
- packaging as a prime cause of litter.

These have recently been emphasised under the 'four Rs' of recovery, recycling, reuse and reduce (the materials involved).

As the packaging technologist of the future will certainly be required to have a basic understanding of these and life cycle analysis (LCA), some explanations are offered. All processes involve the use of energy irrespective of whether the energy can be related to a mechanical, chemical, biological, electrical or environmental activity. Thus any packaging material can be quantified in terms of total energy arising from the processes associated with obtaining the raw material, conversion into a finished container and the auxiliary activities related to storage, transportation, etc. One early estimate on the energy involved for a range of material/containers is given later. However, figures will vary considerably for individual containers depending on size to weight ratio, the conversion process employed, the distance materials are transported, etc., and therefore figures may have to be continually updated as new data become available, usually as part of life cycle analysis. They do provide a broad guide and readily reveal the more energy-intensive activities in the life span of a packaging material.

Once a packaging material has completed its function, i.e. the product has been removed or administered, the next critical question is the disposal or recovery of the material(s). This may appear to be the simple act of placing the materials in the dustbin or garbage can. However, consideration must be given to whether the material is best recycled, reused, used in part or whole to generate some form of energy, or broken down into a reusable chemical form. Until recently, disposal in a dustbin subsequently led to one of the following means of disposal. In Europe this is covered by The Packaging and Packaging Waste Directive 94/62/EC.

Open dumping—a rather primitive method for solid waste disposal whereby the material is left to break down naturally or deliberately fired to reduce volume. Since both constitute health hazards (rats, mice, etc. and noxious fumes), open dumping is not encouraged.

Sanitary landfill—this mainly uses large holes in the ground and prepared areas where the top soil has been set aside for reclamation. Once the holes are filled, the surface can be covered with the top soil and eventually reused. However landfill can still generate undesirable gases, e.g. methane.

Incineration—this is a process of controlled combustion (contrast with direct burning) whereby any release of atmospheric pollutants (carbon, noxious gases, etc.) is kept to a minimum. The heat generated in the burning process can be used as an

energy source. Modern sophisticated incinerators are, however, very costly to install and maintain. Experiments continue to establish how energy released in the process can be maximised and costs of running incineration plants minimised. Segregation of certain low-energy materials is now preferred.

Composting—this normally consists of a grinding or breaking down process to give a fairly fine—coarse mixture of compost involving most of the materials found in the dustbin. Although the resulting compost has good agricultural/horticultural applications, the process is again relatively energy-intensive for what is achieved.

In the UK, landfill, incineration and composting are the normal disposal processes (ratio approximately 86:13:1). However, segregation of waste to encourage recycling and reuse (returnable containers) now has more emphasis, with landfill and incineration being seen as poor substitutes (a general but not finally approved opinion).

Reuse—this describes a practice whereby a container is returned, cleaned and used for the same or a similar product over a number of trips, as has been used for such products as milk and beer for many years. Initially this may appear the route to use for many other containers, and attempts have been made within the EU and in Oregon to bring in legislation to introduce deposit systems to encourage the return of the more widely used packs (particularly glass). However, when the proposition is studied in greater detail it becomes less clear how the advantages and disadvantages can be further quantified. For example, the UK milk bottle only remains economical if the trippage is above fifteen and the bottles are collected on a regular basis. Once the milk bottle reaches the dairy, energy is involved in the cleaning process (hot water) and significant quantities of detergents, alkalis, water, etc. are necessary to guarantee a clean, hygienic container. These chemicals can be considered as industrial pollutants if they reach the normal effluent systems in quantity, unless they are subjected to further treatment processes. However, it must be recognised that milk bottles (and beer bottles for that matter) are specific products where reuse has been calculated and built into all stages, from sale to return. Return of many food-type containers would mean that retail outlets would not only have to build special storage extensions or reduce selling space, but also allocate staff to the segregation of containers and keeping the areas clean and sanitary, otherwise vermin, moulds and bacteria could produce a most unhygienic situation. One can immediately see that legislation would ultimately be required to control such areas which otherwise could create a hygiene risk to the main selling area. There would be a need not only for capital investment but also for labour resources to return deposits, segregate various types of containers, take stock of types and quantities, arrange returns with invoices, etc., plus other transportation and handling costs etc. No doubt retail pharmacists who have been involved with the simpler return of glass dispensing containers will appreciate the complexities of larger scale reuse.

The above should serve two purposes: establish that the reuse of containers is not as simple as first envisaged, and indicate that the recycling of materials may become a

Table 1.1 Recycling prospects and requirements of basic materials

Material	*Requirements*	*Comments on recovery*
Soda glass	Segregation into colour. Removal of closures (metal). Removal of labels. Removal of more toxic contents! Options: wash cullet; add scrubbing towers to melters.	High temperatures, process burns off virtually all impurities (into the atmosphere). Hygienic process. No known deterioration of properties. Recovery value £40–50 per tonne.
Neutral glass	Has a higher melt temperature than soda glass. Not readily distinguishable from soda glass. Could change properties if contaminated with soda glass or vice versa.	As soda glass, but would need guarantee on material in order to be further used for pharmaceuticals.
Paper board	Can readily be repulped. Requires segregation from plastic, foil, etc. Total removal of contaminants including inks present some difficulties.	Difficult to maintain high-quality, high-purity material, but suitable for slightly downgraded usage. Constant recycling reduces fibre length, hence reduces strength. Recovery value varies from £25 to 100 per tonne depending on quality.
Aluminium	Non-magnetic. Various alloys of aluminium not easily distinguished. Highly energy-intensive, basic material.	High melt temperature, removes virtually all impurities, but possible pollutant source. Recovery value £600–700 per tonne.
Tin plate	Magnetic separation possible. Separation of tin from steel required, otherwise basic characteristics will change.	Recovery of tin from basic steel plate economical provided cost of tin remains high. High temperatures as for aluminium.
Plastics	Suitable for virgin machine scrap where regrind is permitted. Used plastics highly likely to be contaminated. Individual plastic types difficult to identify, unless adequately coded.	Regrind only used when permission is given (pharmaceutically). Increasing use as a middle layer. Certain plastics may be mixed for downgraded usages. Unsuitable for pharmaceutical primary packs. Difficult to remove contaminants. Recovery value varies—mixed £40–60 per tonne.
Composites	May consist of mixtures of paper, board, plastic and metal. Multiple coextrusions present obvious difficulties.	Unless components are easily segregated or separation can be done mechanically, recovery generally is not

Material	*Requirements*	*Comments on recovery*
		economically favourable—may be economic if metal component is aluminium.

more logical way of limiting the depletion of the earth's natural resources. Recycling can be defined as the recovery of a basic material which can be reprocessed into a further usage. The ability of a material to be recycled varies considerably. Glass, which is most readily recyclable, is the least energy-intensive of the packaging materials. Aluminium is the most energy-intensive material, therefore may more readily justify recovery. Table 1.1 provides a summary of the recycling prospects of the major materials.

The future packaging technologist may therefore have to consider disposal as part of the brief and even design the pack from materials with the most effective disposal or recovery in mind. To this end, the material factors which have to be considered may include the following:

- energy used to obtain the basic raw material
- waste value
- weight/density
- volume
- crushability
- separability
- combustibility
- risks relative to material contamination (from product)
- material changes (physical and chemical) which may result from reuse or recycling, i.e. whether the material will be downgraded by reprocessing, impurities, contaminants, etc.

These factors are relatively complex, and as yet no simple approach is obvious nor have the factors been fully evaluated and quantified.

Energy used in container production is given in the Table 1.2 by the kind permission of the Metal Box Co plc (now Carnaud plc). Although this data is 'old', it does indicate some of the factors which need considering on an ongoing basis.

The above has provided a broad introduction to the environmental issues associated with packaging. These issues although more obviously applicable to the higher volume users in food, beverages, etc., may in the longer term influence material usage in other industries. It is important to have a broad understanding, particularly as most information which reaches the general public via the media treats packaging as a villain rather than a necessity. It must therefore be recognised that few of the public understand the role of packaging and that packaging technologists in industry should be well versed to challenge some of these adverse comments. Table 1.3 quantifies what was found in the average London dustbin in (1935–36, 1968 and 1980) and is often quoted

Table 1.2 Energy used in container production (tonnes of oil equivalent, TOE)

	Aluminium	*Plastics*	*Paper*	*Tinplate*	*Glass*
Raw material production	6.00	2.30	1.45	1.00	–
Conversion to containers	0.20	0.40	0.05	0.10	0.35
Heating and lighting factors	0.08	0.16	0.07	0.04	0.02
Transport to user	0.06	0.06	0.02	0.02	0.01
Total	6.34	2.92	1.59	1.16	0.38

Table 1.3 Contents of London dustbins

	Year		
Item	*1935–36*	*1968*	*1980*
Dust and cinders	57.0	22.0	12.0
Vegetables	14.0	17.5	17.0
Paper	14.0	37.0	43.0
Metal	4.0	9.0	9.0

	Year		
Item	*1935–36*	*1968*	*1980*
Rags	2.0	2.0	3.0
Glassware	3.0	9.0	9.0
Unclassified	6.0	2.0	2.0
Plastics	–	1.1	5.0

to show how growth in packaging has occurred, with suggestions that packaging must be greater than the actual need (i.e. that a large number of products are overpacked). This has not significantly changed since 1980, when domestic waste still represented only about 4% of the total 'solid waste' in the UK.

However, Table 1.3 also gives other social information, such as the swing from coal fires to central heating. It is not surprising that ash has considerably reduced and other materials have as a result changed in proportion. The reduction in coal fires has also meant that the dustbin is filled with materials which had been previously burnt on household fires.

By the early 1990s plastic had increased to around 7% with a marginal reduction in metal and glass. Since then actual amounts have reduced due to the use of various 'recycling banks'. The average dustbin content weight per week in the 1980s was as follows: towns, 16 kg; rural, 13.5 kg; London, 18 kg.

Conclusions

To conclude, it should be emphasised that packaging does go hand in hand with higher standards of living. Maintaining the balance whereby any pack meets an acceptable compromise between all the factors involved is always a matter of judgement. In the case of pharmaceuticals this judgement requires not only a greater in-depth knowledge as identified in this chapter, but a far more critical appraisal than for virtually any other product. This approach to packaging, from the initiation of a new product to ultimate withdrawal from the market after a successful sales period, varies considerably between companies. Even so, the total packaging organisation does not always receive either the overall co-ordination or emphasis required for the most effective and economical operation, even though many pharmaceutical companies spend more money on packaging materials and the storage of packaging materials than on raw drugs or chemicals. The next chapter therefore covers the broader issues of packaging management and the organisation of a packaging function.

Having explored the broad role of the pack, it is now necessary to consider the information required prior to the development of a pack. This needs to be supported by the many disciplines identified in detail in Chapter 2, where one of the first stages may be the creation of a broad 'packaging brief'. This normally includes certain key information in an initial outline form such as the following:

- name of product
- broad purpose of product and likely route of administration
- dosage form and likely dosage regime
- pack size or sizes
- type of pack preference(s)
- territories of launch outline
- predicted quantities per territory for launch and follow-up sales
- competitive products with list of main features including costs
- any relevant cost restraints
- any quality factors
- legal aspects and implications
- distribution factors
- any environment-related issues.

The above will subsequently be expanded under such headings as facts on the:

- product
- market (and medical)
- warehousing and distribution
- manufacture and pack assembly.

How the above information is handled will very much depend on the type of product. For example, detail will be more readily available on an OTC product than on a new ethical product based on a new chemical entity. The more detail is available, the easier it will be to develop the pack rapidly.

To summarise, this chapter has attempted to identify the following.

1 The role of the pack in its broadest context.
2 The fact that most packs are a *compromise* derived from many considerations.
3 The many, sometimes obvious, factors that have to be considered to obtain a satisfactory marriage between the product and the pack (some of which may conflict with each other).
4 The fact that packaging requires a searching mind and a disciplined approach to ensure that these many and often simple factors produce a logical and acceptable answer for both the company and the end user (patient).
5 The fact that the pack helps to optimise sales and increase profits by being economically viable.
6 A realisation that not only must the product and pack be considered as one entity, but good knowledge of the product characteristics is essential to any effective packaging option.

Each factor taken in isolation could be seen as simple, but the possible reactions between the many hundreds of factors involved turn this into a complex function. Unfortunately, most of the older packaging technologists have learnt only from experience (the way much learning starts), hence it is hoped that this book will be seen to start with a wealth of experience from which a more logical and predictable approach can be derived.