8
DEVELOPMENT AND APPROVAL OF A PLASTIC PACK

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Background

As many pharmaceutical products are likely to generate some secondary effects or sideeffects, it is important that the balance is clearly in favour of the effectiveness of the drug and that such secondary effects are kept to a minimum in terms of both the product and its immediate pack. The industry therefore devotes considerable resources to ensure that the pack more than adequately meets its primary function of economically providing presentation and confidence, information/identification, protection against ingress and egress, plus compatibility between product and pack, compliance and convenience, until such time as the product is used or administered. As a pharmaceutical pack is normally required to maintain a shelf life of 3–5 years, in-depth testing is essential. The pharmaceutical industry therefore requires in most instances a level of safety superior to that of a foodstuff. This is of particular relevance when one considers that drugs are normally taken only when a person is exhibiting symptoms of illness, hence any untoward additional side-effects are not only undesirable but against the general interest of public health.

Although glass and metal have traditionally been used for pharmaceutical products, it should not be assumed that they are inert or that they are the ideal packaging materials. Glass, for instance, is particularly hazardous when it breaks and alkaline glass can alter the pH of non-buffered aqueous solutions. The considerable increase in the use of plastic has been associated with user convenience features (e.g. squeezability), the more modern hence psychologically acceptable image, the 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 and the pharmaceutical industry. Thus when it comes to new pharmaceutical products, plastics now stand a high chance of being used in spite of the fact that all are to some degree permeable to moisture, oxygen, carbon dioxide, etc., and are often not as inert as competitive materials such as glass and metal.

Plastic packs have undoubtedly received greater scrutiny than many other types of pack such as metal and glass. Although 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’ and approved in the widest pharmaceutical context.

Aspects which may need consideration in the development of pharmaceutical products can be identified from the following preliminary information.

Product characteristics (drug substance and product dosage)

Good knowledge is required of the physical and chemical properties of the ‘product’, the processes by which it is produced, and how it is used or administered.

Packaging aspects

1 Functional and aesthetic design.
2 Processes of manufacture and any assembly operations.
3 Selection of plastic type—general physical and chemical properties. Ideally food grade approved.
4 Selection of plastic grade—detailed physical and chemical properties, plus knowledge of constituents including any toxicity and irritancy aspects.
5 Compatibility requirements—with product, involving testing stages, i.e. feasibility stages (investigational) and formal stability stages.
6 Any specific performance requirements i.e. during use, including closure efficiency, warehousing, distribution and display, durability of identification/decoration/print, etc.

7 Final studies of development versus production pack to identify any differences to the pack to be sold.
8 Identify additional tests necessary to check differences in (7).

Although certain of the above factors have been listed separately, in practice quite a few have to be considered in combination. For example, the practicability of any design has to be related to the process of manufacture and this may equally apply to the grade of plastic employed and the constituents found in the plastic. It is therefore intended to discuss some of the above factors on a broad basis and then consider the 'safety' and functional clearance of a particular plastic pack in greater depth. Design can be considered as a relationship between size, shape, texture, colour, including opacity or transparency, the type of closure and the functional and aesthetic requirements of the pack.

Functional aspects which must be considered in the broadest context include the following.

1 Efficiency and ease of production for the supplying company, for instance, will production involve wastage due to deficiencies in the design i.e. quality of design?
2 How can container be effectively unscrambled and cleaned if necessary? (Note that trend is to produce clean containers and maintain clean.)
3 Minimum of production line problems during filling, closuring, labelling, cartoning, etc. (production efficiency).
4 Satisfactory stacking, transportation and handling.
5 Suitable for all aspects of patient usage, and general convenience.
6 Effective in terms of opening and reclosing. (Note possible conflicts between child-resistance, tamper-resistance and difficulties for an ever increasing elderly population.)
7 Acceptable to packaging codes of practice, i.e. disposal, conservation of energy, recycling and reuse, minimum pollution risks, etc.
8 Meeting other legal or moral requirements, e.g. child resistance, tamper-evidence, etc., including product liability issues.
9 Compatible and suitable for the product.

The functional aspects of a pharmaceutical pack may range from simple containment, where this is a combined function of a container and its closure, to a pack which acts as a device to aid product administration. Rigidity or flexibility in the design of a container will relate to the type of material and distribution of the wall thickness, which require good radii and the avoidance of square or angular designs. Poor wall distribution, particularly where thin sections are involved, may reduce the product shelf life by increasing the effects of permeation and migration. Since some product constituents will diffuse through a plastic by solution in the plastic, followed by vaporisation from the external surface, rate of loss will largely relate to the solubility/diffusion coefficients and the wall thickness.

Design wall distribution will also be related to the physical strength of the container and its ability to withstand drops (e.g. breakage), long-term stacking (e.g. distortion or spilling), handling during filling, capping, etc. In the last of these the top pressure applied during capping may cause considerable container distortion. This may have to be overcome by alternative closuring methods or supporting the container neck.

The overall effectiveness of most containers relates to the design of the bottle neck and closure and the material from which the closure and container are made. Where a flexible material is used, a buttress thread (BS 5789, 1979) is recommended. However, if the material is substantially harder, e.g. HDPE, PP, or PVC, a conventional type 60° thread (BS 1918, R3/2 and R4 finishes for glass) can be employed.

The aesthetics of a container are of equal importance to ethical and OTC packaging. Ethicals must generally be elegant, simple with clear and concise wording which tones in well with the presentation. Although this may equally apply to some proprietary products, these tend to require greater eye appeal to attract a purchaser's attention.

Process of manufacture

Pharmaceutical containers can be produced by a number of moulding processes, and this may be carried out by a supplier or set up in-house to produce either a preformed container or one which can be formed, filled and sealed as a continuous operation. Often different moulding processes involve different grades of polymer.

Preformed containers can be manufactured by:

- injection moulding
- injection blow moulding/injection stretch blow moulding
- extrusion blow moulding/extrusion stretch blow moulding
- thermoforming by vacuum, pressure, with and without mechanical assistance
- cold forming by pressure or by plug (mechanical means).

All the above processes can also be used in a form fill seal process with, for example, thermoforming and cold forming blister packs. 'Rommelag' type bottle pack systems use an extrusion process where the container is formed by either blowing or vacuum (smaller sizes). Immediately after this, containers are filled, and the pack is sealed (welded) by using the residual heat in an extension to the main body of the container.

Decoration and printing

Decoration and printing are usually a separate process, although in mould transfers/labels or embossing/debossing may be added within the moulding cycle. The extra handling associated with pretreatment (flaming or corona discharge) and the relatively dirty nature of the decoration and printing processes is likely to lead to increased contamination unless very special precautions are undertaken. One option is to seal the containers at the manufacturing stage prior to printing and then later open them prior to filling. Printing or labelling after filling and closing is another way. Printing inks, particularly if plastic- or solvent-based, may also migrate into the product, or product excipients may permeate outwards, weakening the print key or causing changes to ink colours. (Printing inks need to have food grade approval.)

The main processes used on plastic containers, components, films, etc. are as follows:

- paper, plastic or laminated labels
- shrinkable or stretchable sleeves
- dry offset letterpress, gravure, flexography, (silk) screen
- hot die stamping and thermal printing
- transfer processes—therimage, letraset, dinacal, etc.
- cliché print, i.e. tampoprint, tampon transfer, pad printing
- non-contact processes such as inkjet and laser printing.

Materials and their properties

A basic knowledge of the chemistry of plastics, the polymerisation processes by which they are made, and their physical and chemical characteristics or properties is essential. Plastics can initially be divided into two groups, thermosets and thermoplastics. Most believe that thermosets tend to be restricted to wadded closures where there is no contact between the product and the closure, and the fact that certain internal coatings (lacquers) are thermoset-based is frequently forgotten. Thermosets such as urea formaldehyde, phenol formaldehyde (UF, PF), and occasionally melamine formaldehyde, which are used for closures with wood, paper, flour-based fillings, are all produced by condensation polymerisation where during the reaction a state of 'cure' is involved. Inadequate cure or overcure therefore reflects in substandard material and residues will inevitably remain which may occasionally migrate into a product. These residues may be phenol, formaldehyde and ammonia, in the case of phenol formaldehyde caps, if a phenol hexamine reation is used. Thus during the 'cure' both water and ammonia are released, some of which may be retained by the moulding.

Thermoset lacquers are also found in use as adhesive systems (including laminations) and as coatings for metal tins and tubes (i.e. epoxy resin, polyester and polyurethanebased polymers).

As indicated earlier, thermoplastics are far more widely used for containers, films and packaging components. Although a large number of different polymers can be identified, five basic types stand out as more economically viable than the others.

These are:

- (PE) polyethylene LD, MD, HD and LLDPE
- (PS) polystyrene GP and various impact grades
- (PP) polypropylene and its copolymers
- (PVC) polyvinylchloride, plasticized and unplasticized
- (PET) polyester (even though the current price is significantly higher, i.e. around £1,100 per tonne, as it is usually moulded in thinner sections).

The cost of these starts in the region of £650 per tonne (for 10 tonne lots) and rises to around £850 depending on the type and grade. Each has grades approved for use in contact with food.

Price increases occur according to whether a material is natural, white opaque or coloured, or has other additives present. Additives are generally more expensive than the basic plastic.

In the past, equivalency between grades has usually been identified by comparing certain basic properties such as density and melt flow index (the amount of plastic which flows under given conditions of temperature, pressure and time). Although these are quite acceptable for many non-critical usages, further parameters must be considered particularly when the plastic is

used for sterile products. This is because each plastic may contain different constituents and may be polymerised by a different process.

Of the economical plastics mentioned above, GP polystyrene is becoming less popular, as it is one of the most brittle plastics unless it is impact modified. GP or (GPPS) polystyrene has good clarity, is highly permeable (compared with most other plastics) to moisture and gases, has poor heat and solvent resistance. It crazes then disintegrates in contact with isopropyl myristate (which is used in some pharmaceutical formulations). It is, however, an excellent material to mould (low shrinkage)

Impact modified or toughened polystyrene is generally less transparent, more flexible, but poorer in water vapour and gas transmission.

Whereas low-density polythene tends to be used where a flexible pack is desirable, high-density polyethylene and polypropylene are finding a substantial usage where a rigid container with reasonable resistance to water vapour is required. These materials have generally good resistance to chemicals, including those preservatives, which are readily soluble in low density polyethylene. Both HDPE and PP can be steam autoclaved, with PP having around 20°C more latitude. Rigidity, crystallinity (a property related to moisture and gas transmission), chemical and particularly oil resistance, all increase from LD to HD. Low-density polyethylene may be prone to environmental stress cracking, unless a material of low melt flow index, i.e. less than 1.0, is used. Detergents, wetting agents and volatile oils all tend to be stress cracking agents.

Polypropylene can have its clarity and transparency improved by orientation, or by use of clarifying/nucleating agents.

Polyvinylchloride is rigid, transparent and, although it lacks the sparkle of poly styrene, is less brittle. Drop strength can be improved by the use of an impact modifier such as vinyl acetate or methyl methacrylate butadiene styrene (MBS). PVC is moderately permeable to moisture but has excellent resistance to oil and oxygen permeation. Plasticised PVC has high flexibility and is particularly useful when a collapsible pack is required. It is a poor barrier to moisture and a moderate barrier to gases, hence is usually ‘overwrapped’.

Of the five economical plastics, PVC (both plasticised and unplasticised) tends to contain the most constituents and has recently been a prime target for environmentalists who associate its burning with the release of acid gases. LDPE is generally likely to contain the least constituents with PS, HOPE, PP being slightly worse. Identifying, quantifying and clearing these are discussed later. Permissible antioxidants are identified in the EP.

PET is usually the most obvious replacement for glass where oral liquids are involved. It is strong, has high clarity, moderate permeation to moisture, good gas barriers and good retention to certain volatiles such as camphor, menthol and alcohol. Use as a stretch moulding minimises thickness and generally further improves strength and barrier properties.

Other thermoplastics

The use of other plastics tends to be related to specialised needs and whether their advantages justify the additional cost, e.g. Aclar (trade name) may cost twenty times more than PET but is the nearest approach to an inert ‘plastic’ and is approximately ten times less permeable than Saran (PVdC—polyvinylidene chloride) which is widely used as a film coating. However foil, even when thin (0.006 mm and above) remains the best barrier material, with newer techniques of film metallisation, especially where two contact layers are used, coming a close second best.

Plastic grades

Once a plastic type has been broadly selected, the final grade can be decided. Food approved grades are the starting point for most pharmaceutical products. Grades are generally based on density, melt flow index, the fabrication process for which they have been made, final usage, and the additional constituents which they may contain.

These constituents may include additives: antistatic additives, UV absorbers, antislip additives, slip additives, colourants, opacifiers, plasticisers, stabilisers, antioxidants, etc., which may be added at the compounding stage to provide specific or modified properties. However, other ‘constituents’ may be present from the polymerisation and/or the converting processes. The polymerisation process may involve residues and processing aids. Residues (constituents which may remain from the polymerisation process) may include monomer(s), solvents, accelerators, catalysts, initiators, etc. Processing aids are additional substances to aid processing or restrain undesirable effects, e.g. antioxidants.

The converting or moulding process may also include the use of processing aids, e.g. lubricants and mould release agents. Masterbatching may contain lubricants, mould release and a carrier or base diluent which assist the manufacture of a concentrated masterbatch containing colourants.

From the above it is clear that asking the question ‘what additives are included?’ is unlikely to provide the full information related to the polymerisation or converting process. Checking the ‘constituents’ under specific headings provides more detail.

Toxicity and irritancy—safety aspects and organoleptic properties

Ideally no extractive from or loss into a plastic should be permitted, but in most practical circumstances some compromise must be reached. One is thus required to identify not only the level of migration, but whether any risks have been incurred in terms of the product's effectiveness or toxicity/irritancy. In respect of the latter, data is generally more readily available on toxicity aspects than irritancy. Packaging also must not bring about any 'deterioration in the organoleptic characteristics' (critical to many foods but of equal importance to certain pharmaceuticals). Attempts have been made to estimate the TRTC (taste recognition threshold concentration) of certain monomers, e.g. styrene monomer, and other constituents common to plastics. The level of transfer depends on the nature of the product, with oils and fats generally being more susceptible to detectable taint.

Stage 1
in the selection of a packaging material

There is still a certain reluctance for manufacturers, compounders and converters to declare constituents to the pharmaceutical industry, although there may be a reasonable willingness to provide this information to official regulatory organisations, i.e. by reference to a 'drug master file'. This situation is improving but obviously where constituents are not identified, greater clearance difficulties are experienced. Whether such information is freely given or not, it does seem relevant to pose three sets of questions, i.e. to the polymer manufacturer, compounder and converter.

Polymer manufacturer (for each identified grade)

1 What constituents (catalysts, accelerators, antioxidants, etc.) are used in the polymerisation process and what level of residues (particularly monomers) can be expected in the granules? (Note that granules are frequently produced via a multiple rod extrusion process through a 'town' water cooling bath, from which inorganic salts in 'hard' water may evaporate on the surface of the granules leading to contamination in the final moulding.)
2 What toxicity/irritancy data is available on these?
3 What levels of extractive for these residues can be expected using various solvents or simulants?
4 Details of analytical methods and accuracy/reproducibility of the methods, etc.

Compounder

1 What constituents are added, at what level and for what reason, i.e. colourants, dyes, opacifiers, UV absorbers, stabilisers, modifiers, etc.?
2 What toxicity/irritancy data is available on these and from whom (e.g. supplying companies)?
3 What levels of extractives can be expected?
4 Analytical methods and accuracy/reproducibility of the methods, etc.

It must be noted that not all plastics pass through a compounding stage or contain any additional constituents, e.g. possible virgin natural materials. However, constituents may be added by the polymer manufacturer, resin supplier (smaller quantities), via a masterbatching process or at the final conversion stage. Asking where constituents may be added is critical to obtaining information. A masterbatch containing 50% titanium dioxide prompts the question 'what is the other 50%?'.

Converter, i.e. laminate, film, bottle manufacturer

1 What processing aids are used by either direct addition to the granules or onto moulds (e.g. lubricants and antistatic agents)?
2 As 'compounder' above if 'compounding' occurs, e.g. colourants added immediately prior to the moulding operation.
3 What toxicity/irritancy data is available?
4 What levels of extractives can be expected?
5 Analytical method and accuracy/reproducibility of the methods, etc.

In an ideal situation these issues should be resolved between representatives of the pharmaceutical industry and the suppliers identified above, as part of the technical/economic validation.

Finally it should be noted that certain restrictions may have to be incorporated into the packaging material specification, e.g. 'No lubricants to be used', (magnesium and zinc stearate or similar lubricants may be incompatible with either the drug substance or certain excipients).

If the above information cannot be fully obtained then a formal guarantee must be sought that the polymer and the included constituents meet some level of food clearance (FDA, EU, etc.). This is normally accepted as the minimum information required before a plastic is considered further in the development stage of a pharmaceutical product. See Appendix 8.6 for details on EU listings related to plastic contact with foodstuffs.

Stage 2Ð
extractive tests, chemical and biological

This stage is only mandatory for certain types of product. The next testing phase is normally an extractive procedure, using a company in-house standard and/or an externally recognised standard covering chemical extractives and biological tests (toxicity/irritancy), using pharmaceutical simulants under selected conditions of time and temperature. These tests can generally be classified under three categories:

1 national regulations and compendial standards and guidelines (USP/NF extractive tests USA, JP, EP, etc.)
2 standards issued by standards institutions (e.g. BS 5736)
3 international guidelines proposed by the World Health Organisation (WHO).

The main proposals relate to injections and ophthalmic products (see Appendix 8.1), and the interpretation will depend on the product and the product usage.

Differences in approach between the BP 1988 and USP XXIII should be noted. The BP 1988 excludes details of extractive procedures although such tests were included in the BP 80 and are included in the USP XXIII. The BP argues that it only includes test procedures related to ongoing control of materials and products, whereas extractive procedures are intended for use in a developmental phase where a plastic is undergoing selection, i.e. 'extractives' are not intended for routine ongoing tests. It is presumed that once a plastic has been thumbprinted it can be routinely checked by some form of chemical analysis, i.e. IR, DSC.

Because an extraction test may be part of a compendial standard or a mandatory regulatory requirement, it is frequently believed that such a test procedure has total approval for the polymer involved. Although it may be one of the tests available, mainly because there are few alternatives, the usefulness of the procedure is not entirely proven. Therefore a material which passes both chemical and toxicity irritancy type tests is probably safe, bearing in mind that final clearance comes from the following compatibility tests (stage 3). Failing the test may not necessarily establish that a material is unsafe, but rather stimulates additional questions on the polymer, operators, test conditions, etc. Overall one must be reminded that a simulant, even if it appears to be relatively inert (water, saline, sodium bicarbonate solution, etc.) may produce different results to the actual product. Although implantation tests (see USP XXIII) may also provide useful information, this may again create data which are difficult to quantify. One must equally bear in mind the risk to the patient and the company—hence the philosophy that stages 1 and 2, which may be critical in the case of an IV product would involve fewer questions and less investigation for the clearance of a solid oral dosage form. Although extractive tests are not mandatory for all products, they can be a useful part of a databank if a particular grade of plastic is part of a company's inventory. Plastics classified under the USP 6 category, in theory, have the best safety clearance.

Stage 3Ð
product/pack compatibility and investigational testing

The third stage normally covers feasibility or investigational tests, i.e. the initial testing stages which are aimed at establishing the general suitability of a product-pack combination and involve some degree of accelerated conditions. Such tests normally include some cycling conditions, e.g. 15°C 50% RH, 37°C 90% RH with 12 or 24 hourly cycles and temperatures up to 50°C, but be wary of tests using temperatures above 45°C as certain pack properties can change and influence product changes.

One suggested accelerated test is to place an excess of cut-up pieces of the proposed plastic, immersed in the product, in a neutral glass stoppered container which is held at, say, 4°C, 25°C, 40°C for a period of 3 months. The product (and plastic) should be analysed at intervals for change and extraction. However, even a test of this nature is not all-embracing since total immersion eliminates possible change from air to air-liquid interfaces which occur in a pratical situation.

If there is no change in product or plastic, interaction is unlikely. However, if a change does occur it should act as a warning that something may occur under normal conditions in the long term. It is important that investigational tests cover any specially selected challenge conditions (light, cycling conditions, etc.) which it is essential to check but may not be

covered by the formal stability tests. Such additional information has usually to be made available as a standard document and presented as part of any registration documentation (Expert Report under EU).

It is essential that the above tests acknowledge information built from challenges on the drug entity, and the preformulation and formulation stages. This background information should at least indicate the type of protection which has to be achieved by the pack. Compatibility between product and pack is therefore defined at this stage prior to the product-pack entering a formal stability stage. Data generated by feasibility tests may be used to predict an initial shelf life and provide support data for clinical trial supplies. Clinical trials and clinical trial data can also contribute towards the 'total data' which supports the product-pack ultimate shelf life.

Controls

The use of certain control experimentation is of particular importance during initial investigational research into a suitable pack. However, one should be wary of the word 'control' as its interpretation may have to change according to circumstances. If a product shows some deterioration in a plastic pack there must be immediate questions on whether this is pack- or product-related. Having a glass pack with an effective closure as a control will provide useful information, but raises the next question as to whether the glass bottle should be a bottle plus closure or a neutral glass sealed ampoule (e.g. the effectiveness of the closure in the former and an ampoule can become a pressurised system at higher temperatures). Higher temperatures normally accelerate change (all have heard of Arrhenius), and lower ones are less conducive to change. This immediately suggests that a refrigerator is a useful control condition for both the product and the pack. This is generally true, but there are circumstances where 4°C is an accelerated condition, i.e. plastics become more rigid and hence are under greater stress.

Holding adequate retention samples can also be part of control. An example is where a plastic bottle is put under test with a product. On removal of the polypropylene cap a yellow discolouration is found on the bottle neck. The questions asked can be: is it product-related? Is it a reaction between cap and bottle? Could it happen on an uncapped bottle (probably unlikely)? This situation could be resolved by testing bottles capped without product, together with separately stored retention samples of caps and bottles. How retention samples are stored and what they are stored in, etc., are additional questions which have to be asked.

Using effective controls, controlled conditions and well-controlled tests constitutes an important part of all investigational experimentation. It is an often neglected subject. Equally such experimentation should be supported by adequate statistical control. Take a situation where a wadded and a wadless (no liner) closure are to be placed on an HDPE bottle and then stored over a 6 month period in a cycling cabinet which cycles between 15°C 50% RH and 37°C 90% RH each 24 h. Question—devise a statisically controlled experiment to check any torque changes, indicating the number of samples required. Personally I would suggest the use of an induction sealed closure as the experimentation could be complex and costly for the information achieved.

Stage 4Ð
formal productÐpack stability tests

These formal tests are normally scheduled over a period of 5 years, using a range of storage conditions, where the formulation and the pack are analysed at selected periods for changes, degradation, migration, etc., involving statistical evaluation such as regression analysis. The tests may include further biological and microbial challenge procedures, etc., to check that no significant changes have occurred in the product or pack.

Submission of data to regulatory authorities for product registration may commence once 6 or 12 months (ICH guidelines indicate 12 months) of good data has been obtained, on the understanding that this will be supplemented as additional data becomes available. Some authorities will allow a 2 year shelf life to be predicted from 12 months of 'accelerated' data. Guidelines drawn up by the CPMP within the EU, published as III/66/87/EN (now updated by ICH guidelines), identified certain climatic zones. (Table 8.1).

The work described above may be done entirely by the pharmaceutical company concerned or may be partially or fully contracted out. Whichever course is followed, it is important that all test procedures are properly documented and follow the guidelines established by GMP (good manufacturing practice) and GLP (good laboratory practice). This means, for example, that both product and pack components should be clearly defined, specified and identified (QC+type clearance) together with adequate testing procedures and the holding of retention samples, before they are entered into any investigational or formal test programme. Again attention to controls must be advised.

As a result, the data built up from all the stages, and supplementary clinical data, must be sufficient to satisfy:

1 the pharmaceutical company itself

2 worldwide or local regulatory authorities that the product and pack are compatible, that they do not incur any safety hazards, and that they maintain the shelf life declared on the pack and supporting documents at an agreed level of quality.

As pointed out, the above stages to 'clear' a plastic are supported by:

1 information on the pack or device constituents
2 extractive tests/product contact tests etc.

Table 8.1 CPMP climatic zone guidelines

Zone	*Conditions*	*Area*
I	21°C 45% RH	Temperate Europe
II	26°C 60% RH	Sub-tropical
III	31°C 40% RH	Hot dry
IV	31°C 70% RH	Hot humid

Expressed as kinetic mean temperature with recommendations that these conditions should be used in future stability programmes (see Appendix 8.14). Temperatures were subsequently rounded to 20°C, 25°C and 30°C.

3 short- and long-term stability tests between product and packaging/device components.

There are however additional activities (e.g. warehousing, distribution) whereby information is built up in order to establish the total stability/safety of the product, the clinical efficacy of the product/device and the functional acceptance of the product/pack/device in the hands of the ultimate user. (This is particularly relevant where the pack assists product administration: see Appendix 8.9 for further details.)

This total data philosophy covers information accrued from the time a new drug entity is discovered, through preformulation studies to final formulation in terms of physical, chemical, climatic and microbiological challenge so that the product characteristics, deterioration, degradation, etc. are established before it is placed into contact with a pack/device.

Comparison between foodstuffs and pharmaceuticals based on simulated extractive tests is inevitably difficult, because the site and mode of absorption may vary, because of the difference in the pre-storage period and the frequency of use, and the volume/weight of the product taken. With foodstuffs, the contact period between product and pack is usually shorter, but the quantity taken and frequency of use are greater, e.g. daily intake of margarine. Thus any EU extractive procedure may provide useful additional information for the pharmaceutical industry as part of stage 1 involving the screening of the material, but the simulants used may bear little relationship to the final pharmaceutical form. These tests are also more relevant to toxicity aspects rather than to irritancy. For food extractive tests see Appendix 8.6.

An additional fact to consider is that the pharmaceutical usage of any plastic tends to be relatively small when compared with other industries: food, motor, etc. This situation poses considerable problems to both the pharmaceutical industry and the polymer manufacturer or the converter when any information is requested, as invariably the in-depth data required is out of proportion to the profit made. Attempts to overcome this problem have been suggested (the industry pays for the information, or information within the industry is pooled), but so far little progress has been made towards a satisfactory solution.

This general lack of information creates problems between the product and the pack, where on one side considerable analytical resources are put into product identity, purity and impurity (the last of these now being of the greatest relevance) whereas on the other hand the constituents of the plastic cannot be fully identified. This situation inevitably creates an ongoing argument as to whether such in-depth information on the plastic is relevant or irrelevant, particularly if the total pharmaceutical clearance programme does not highlight any cause for concern. Personally I believe that in-depth knowledge can only improve the long-term relationship of suppliers and users. This must also be a two-way process where the pharmaceutical industry must provide more information to the supplier. The fact that many suppliers will provide such detailed information to a regulatory authority (this information is essential in Sweden and the USA) may seem a reasonable compromise, but let us again not forget that the information in total must satisfy both the regulatory authorities and the pharmaceutical company itself (the latter is the more important, since if it has not convinced itself, how can it convince others?!).

Additional discussion

In terms of the differences in attitude towards glass and plastic, glass is generally considered inert and safe as it has been used for thousands of years and proved by time, whereas plastics, being modern, are under constant surveillance. Therefore one

could suggest that if glass had been discovered today, it would have had a more difficult task to establish itself when faced with the more stringent types of tests now applied to plastics.

Another current example of ‘attitudes’ involves thermoplastic and thermosetting resins. The stringent tests referred to previously are invariably carried out on any thermoplastic which forms part of a primary pack. However, thermosets and in particular thermosetting lacquers, enamels and adhesives are rarely exposed to an extractive-type procedure, since they are not always recognised as plastics.

We must also recognise that there is a danger for test procedures to grow to a point where they are either meaningless or unnecessary. This does not imply that every enthusiastic investigator is unscientific, but tries to recognise that the introduction of any new procedure is only based on the facts available at that time and relies much on any subsequent publicity which it receives in order to become established. Procedures once established frequently become far too difficult to replace.

Having made such a comment, it is equally important not to be complacent. Thus any system generally adopted by the pharmaceutical industry must be subjected to constant review, in order that adequate standards of safety can be achieved at a reasonable cost. Although this is likely to mean a need for more in-depth knowledge on the plastic and modifications to the currently recognised extractive procedures, it seems extremely unlikely that the last approval stage (formal stability or shelf life tests) can ever be replaced. However, new computerised data retrieval systems will enable greater confidence to be maintained provided the input of data at all stages is optimised.

It must be reiterated that each use of a plastic, as either a pack or a device, must be carefully evaluated against a background of the product and its use, paying particular attention to the following.

1 Type of product:

- contact phase—volume
- contact area—during storage, transit and in use.

2 Storage conditions at all stages of its shelf life. Note that refrigerator conditions are likely to be far less encouraging to extraction, hence may offer a degree of control.
3 Shelf life and length of time product is in contact with pack. Pack upright, inverted, etc.
4 Mode of administration and the risks of absorption of any extracted constituents via that route.
5 Dosage level, frequency of use and application, i.e. treatment period—continuous, intermittent or temporary. (Is product seasonal, stored partly used until next year?)
6 Misuse/abuse by patient or children, etc.

Finally, the possibility of product migration into the pack (e.g. loss of preservatives) coupled with permeation of oxygen, carbon dioxide and moisture must also be consid ered as a factor which could cause changes in the migratory nature of constituents in the plastic.

Oxygen may cause slow oxidation of a plastic resulting in a slight change in the constituents extracted after storage. CO_2 permeation, being roughly five times faster than oxygen, will frequently cause a pH shift with unbuffered products with an equilibrium value pH of 4.3–4.6. Hence a shift in pH leading to further changes in levels of extraction must not be overlooked. Irradiation can also cause plastic constituent changes (see sterilisation and Appendix 8.11).

General performance requirements

Since the functional aspects may vary according to how a pack or device is used, some general headings will be considered first.

Closure efficiency

Closure design needs consideration for effectiveness during use, i.e. opening and reclosing, problems associated with stacking (top pressure), torque control range if a screw closure, the effects of time and temperature, dimensional tolerances and compliance, etc. Tests to differentiate loss via the closure, or through the main body of the container, are frequently necessary. Even with moderately permeable materials, moisture loss or gain can be greater through the closure system if it is not effectively designed or closed. Plugged bottles systems may be particularly prone to seepage due to climbing film-type effects, and sinkage behind the threads in the bottleneck bore encourages capillary-type seepage. This especially applies to certain extrusion blown bottles. Injection blow moulding may be necessary to overcome this problem, as it provides a better controlled neck finish and can eliminate thread sinkage in the bottle bore.

Decoration permanency

Print and colour may suffer from discoloration (fading or darkening), surface rub or abrasion, print or label lifting due to poor adhesion or key, and lack of product resistance. Various types of test are available to check these. Discoloration may be checked by direct exposure to sunlight or artificially accelerated conditions, e.g. xenon test. With the latter, 'fade' may be compared with changes based on the British Wool Scale. It is advisable to check the temperature as occasionally discoloration is increased by the combined effect of temperature and light. Light may also cause changes to the plastic material itself. ICH Guidelines define tests using specific light sources.

Print key may be checked by the Scotch tape test, where a strip is applied to the surface to be tested and is then removed in a standard way with observation for print lift.

Product resistance consists of applying the product to the print or decoration (controlled temperature), at the end of which the product is cleaned off in a rubbing motion to see whether any decoration is removed.

Solvents in inks may also permeate into the products and occasionally product ingredients may change the permanency of the ink if they pass through the plastic. Similarly, labels adhesives may also contain migratory constituents. (Special checks are essential on pressure and heat sensitive adhesives.)

Environmental stress cracking

Environmental stress cracking is less prevalent today (except in Third World countries) and more readily understood. Stress cracking is a phenomenon related to internal stress arising from the moulding operation or externally applied stress, which in conjunction with a stress cracking agent may lead to a plastic (e.g. low-density polythene) cracking. Most detergents or wetting agents act as stress cracking agents. In the Hedley test the container is filled with the product, the closure applied as normal then stored at 60 °C for 48 h. If no cracking occurs, the test is passed. If the storage is then extended to 7 days the point of cracking (if it occurs) indicates the weakest point(s) in the moulding. Plastics may also be given a stress crack value based on the Bell telephone test (hours taken for a crack to appear). Those with the higher figures are less stress crack prone.

Typical stress conditions may be created by capping (tension between bottle and cap threads), plugging (expansion of the neck bore), top pressure occurring during stacking, etc.

Warehousing and distribution

Warehousing and distribution hazards include impacts, compression and vibration. One or a combination of these may distort the container, loosen or tighten the closure, and cause deterioration to the decoration. Thus any of these aspects may have to be tested by simulated laboratory tests or actual warehousing/travel tests.

Outer or transit packaging can occasionally contribute to changes in the primary pack or the product. External wrapping materials may contain various migratory constituents, e.g. when a shrink or stretch film is in intimate contact with a primary pack or plastic components of a device. Odorous board, adhesives, printing inks on external packaging have also been known to cause flavour and/or odour changes.

Conversely, a laboratory test on single (exposed) primary packs may show a moisture loss or gain which is significantly reduced when the same pack is stored in bulk, i.e. the outer packaging reduces the exchange by adding barrier materials and slowing down the atmosphere circulating around the pack(s), thereby changing the effective gradient between the inside and outside of the pack.

Use and misuse by the patient

Tests necessary to indicate how a consumer uses or misuses a pack or device are critical to total assessment. A point to consider is that air can enter the pack by an increasing amount as a product is used. Occasionally this ingress may give rise to excessive product deterioration, thus proving that either the pack size must be limited or air ingress restricted, e.g. the individual protection offered by a unit dose pack may be the preferred answer. A closure system may occasionally deteriorate or become less effective during use. Returned clinical trials may help in this evaluation, particularly where microbiological contamination may be involved.

Consideration of misuse may challenge the way a product should be stored, i.e. upright, upside down or on its side, and may require testing.

Sterilisation

Sterilisation may give rise to adverse actions depending on the process and the particular grade of plastic, pack, etc. This means that if a pack is to be sterilised, either as a terminal operation or as part of an aseptic process, careful checking for possible changes is essential. Textbooks which make general statements should be treated with caution, as individual grades of plastic may react differently.

The three most likely processes are:

1 steam sterilisation—autoclaving at 121°C for 15 min or 115°C for 30 min
2 gamma irradiation and accelerated electrons (normally associated with aseptic processing)
3 ethylene oxide (normally associated with aseptic processing).

All of these may give rise to changes with the product or pack or both. For example, terminal autoclaving by moist heat may cause physical or chemical changes to the product or the pack. Whether the pack is distorted frequently depends on the product volume to vacuity ratio (i.e. ullage or airspace), since this may give rise to either extension or dimpling of the package. A pack which becomes extended (by excessive internal pressure) puts stress on the closure or seal, or container. A dimpled pack normally results from a negative pressure situation and is particularly likely to occur in packs which have thinner sections. The use of overpressure or balanced pressure autoclaves is essential to control dimpling, when moist heat sterilisation is employed. The overpressure employed will have to be adjusted according to a wide range of variables, i.e. plastic, temperature, pack size, shape, wall distribution, content versus vacuity, etc.

Gamma irradiation of 25 kGy or above and accelerated electrons tend to cause similar changes to the product/pack. These processes are normally used as part of an aseptic process to sterilise the pack components before use, since many products tend to degrade if terminally sterilised. Some contact lens solutions and normal saline products can be satisfactorily gamma irradiated in a suitable plastic or metal pack (aerosols).

Although ‘irradiation stable’ lists of types of plastic and specific grades are sometimes available from suppliers, this in no way clears a plastic for gamma irradiation until a company has satisfied itself that either no change occurs or changes are acceptable. Occasionally chemical changes may be related to either the polymer or the constituents within the polymer. Further details on this are given in Chapter 7 and Appendix 8.11. Note that irradiated samples should be analysed immediately or the samples kept in well-sealed impermeable packs (e.g. glass containers), i.e. avoid containing them in polythene bags to await analysis, as volatile products of degradation can be lost to the atmosphere. Irradiation under nitrogen significantly reduces degradation.

Various attempts have been made to phase out ethylene oxide treatment as a sterilisation process, but it is still used. Ethylene oxide largely relies on the material being permeable to the gas under certain conditions of time, temperature, moisture and pressure. Plastics which do not have a solubility coefficient for ethylene oxide may prove difficult to sterilise or proof of sterilisation may be difficult. The residual levels of ethylene oxide remaining also depend on the affinity or solubility of ethylene oxide for that particular type and grade of plastic. Aeration after sterilisation may be under vacuum or by simple storage with good air circulation for periods of up to 1 month (7–14 days is more normal). Since ethylene oxide degrades to ethylene glycol and epichlorhydrin (when chloride ions are present) and both of these exhibit degrees of toxicity, it is advisable to check for all three products. Any remaining ethylene oxide in the plastic will ultimately partition between the product, pack and external atmosphere. Again, treated containers should be stored in well-sealed impermeable packs when awaiting analysis. As analytical methods become more sensitive to the likely residues, lower limits are likely to be imposed. Since ethylene oxide is not inert, product interactions cannot be ruled out.

It can be concluded that a pack may be affected by most of the sterilisation processes hence thorough testing is essential in terms of possible changes in physical and chemical properties and appearance. Loss of preservatives may also be critical at a sterilisation stage.

Panelling or cavitation

Occasionally plastic packs may show partial collapse or indentation, a phenomenon known as panelling or cavitation. This may be caused by the following.

1 Hot fill plus effective closuring creating a partial vacuum on cooling.
2 Adsorption of a gas (usually oxygen) from the pack headspace.
3 Absorption of a product constituent which causes the inner section of the wall to swell, thus causing distortion.
4 Loss of volatile constituents through the plastic; may be an extension of (3).

5 Pack extension due to incorrect pressure balance during the autoclaving cycle— may be called dimpling if mild. Often associated with uneven wall thickness. The above cannot be predicted and are only discovered after storage.
6 Pack partially collapses during cap application.

The reverse of cavitation can also occur, e.g. on a nitrogen flushed product—gases (oxygen/carbon dioxide) enter the pack causing the bases to be bowed outwards.

Impact resistance

Plastic packs which are likely to crack on impact may be checked by a drop test procedure, e.g. a percentage must not break when dropped from a selected height onto a standard surface. The pack is dropped in a defined way (usually down a tube) onto its base or closure.

Clarity or transparency (light transmission)

May be quantified by the amount of light which passes through the container. Some pharmacopoeia tests require a certain level of light transmission to be achieved in order that particulate contamination can be checked. USP XXIII provides a useful test procedure for light transmission.

Light exclusion

This is the opposite to light transmission in that the greater part of the light must be filtered out. This test may define the wall thickness (i.e. 2 mm in the case of glass). Exclusion of light may be achieved by inclusion of colours, fillers, UV absorbers, or in combination with a carton or overwrap. Only carbon black pigmentation gives 100% light exclusion.

Electrostatic

Most plastics are prone to electrostatic unless special precautions are taken to reduce it. Static is increased by dry product filling, hot filling and operating in a dry atmosphere (more likely to happen when conditions external to the factory are dry, i.e. during freezing weather). Cleaning ‘plastics’ and then drying by heat can create conditions of high electrostatic attraction, and if the air surrounding the materials is not adequately filtered the component can be even dirtier after the alleged cleaning process. Static can be reduced by:

1 moisturing, i.e. using higher conditions of RH
2 earthing, or ionising the surrounding atmosphere
3 washing with the correct detergent, anionic or cationic (i.e. surface antistatic)
4 adding an antistatic agent to the plastic.

(3) and (4) generally work by attracting a layer of moisture to the surface, thereby allowing the charge to be conducted away.

Electrostatic can be measured either directly by sensitive equipment or by checking the dust patterning with a fine carbon cloud under standard conditions.

Pretreatments for printing (and labelling)

Components can be pretreated by:

1 gas flaming
2 high-voltage corona discharge
3 chemical treatment (this may be similar to surface sterilisation as used for some food packaging processes).

Containers are normally pretreated by flaming and films by corona treatment. Pretreatment can be checked by wetting the surface and observing the affinity of the surface to water (untreated surfaces retain the water as droplets) or actually measuring the angle of contact, which is reduced when the surface is oxidised. Pretreated surfaces effectively last for 3–6 months. Surface treatment may also enhance the effectiveness of some of the constituents which operate at the surface of the container, e.g. antistatic slip and anti-slip.

Development versus production pack

Before any pack reaches production, differences between the pack tested and the pack to be marketed must be identified and cleared. It is virtually inevitable that there will be some differences. One of the most likely lies in the labelling, decoration or printing of the pack. If it is subsequently decided to label a pack by, for example, a thermoplastic or a heat seal label, these must be thoroughly checked since all contain constituents (in the adhesive system) which may possibly migrate into or through the plastic. Migration from self-adhesive labels has been reported whereby formulation excipients, including the preservative BKC, can be degraded. Effects from other external influences, even the lacquer used for a collapsible carton, should not be ignored. In another instance, the addition of an overwrap has been known to nullify stability on an exposed bottle in that an ingredient which 'escaped' from the latter was retained when overwrapped and the carton suffered discoloration. Differences often occur between a single impression prototype tool and a multi-impression production tool. It is important to identify any differences and then to ascertain requirements for additional testing.

Conclusion

The ultimate task of the pack is to produce confidence in the product in terms of convenience, preservation and protection from the environment, while ensuring that the product remains satisfactory in the fullest sense, i.e. integrity, identity, uniformity, safety, effectiveness, etc., all at an economically acceptable cost. Undoubtedly pharmaceutical packaging does receive greater attention to detail than any other form of product.

Although the types of test procedure will broadly continue to follow the stages identified in this chapter, the ultimate intensity of the procedure must be related to the type of product and the route by which it is administered, etc. (see Appendix 8.8 for a suggested intensity of testing table). The use of a declared 'food grade' plastic is therefore the minimum standard for a pharmaceutical product. 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 clearance schedules, and to finish with:

1 a product specification including process of manufacture
2 a pack specification covering the pack and its component parts
3 a specified means of bringing the product and pack together, i.e. the packaging process as defined by standard operating procedures.

The future control of the product and pack (and changes) then revolves around these specifications. In the case of a plastic pack or plastic components it may be necessary not only to define tightly certain critical factors in the specification, but to purchase under a certificate of warranty. Regular QC checks are likely to include melt flow index, density and IR identity and the use of DSC (differential scanning calorimetry). The last of these is a particularly useful means of providing plastic identification and an indication that the thumbprint is as per the original clearance tested material. Surface analysis testing is likely to become increasingly necessary with some products. As an additional insurance, a selected number of production batches are placed on an 'ongoing' 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. 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. ICH and EU guidelines provide suggestions.

Note that adequately defining the product, the pack, etc. means that provisional specifications should be written prior to any testing being carried out. Each item should also be thoroughly checked by in-depth QC procedures so that all materials used in investigational and formal tests can be fully identified.

It can therefore be concluded that 'plastic' packs and devices supplied by the pharmaceutical industry normally pass through a thorough and rigorous test procedure, but even so, such procedures will continually improve. If possible, loopholes in the present systems must be identified by more attention to the internal storage containers, piping, filters, etc. 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 'patient'. If these are plastic contact materials, they will require some form of ongoing review.

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

Finally let it be stressed that this chapter has been written to give a degree of both alertness and understanding. It in no way sets out to say that any approach is the ultimate, since test procedures must be constantly reviewed and updated. If a company technologist says 'we have done it this way for the past 20, 10 or 5 years', or 'we have always used this test', it is quite likely that they are not up to date and are not being fully effective. Virtually all stages identified in this chapter must be treated as long-term information gathering. Extractive tests fall into this category by providing the best information available at that moment. To date there are no records of people dying from using 'plastics', but rather from the processes by which they are synthesised (e.g. VCM). However, the industry must remain responsible particularly in terms of product/pack liability and at the same time remain commercially viable. Efforts to push testing to a point where it is carried out for testing's sake, or because someone has devised a test, must be resisted. Finally, tests to clear a pack initially must not be confused with tests to clear component deliveries, i.e. an in-house QA/QC situation. Tests must therefore be reviewed against their applications in a development and/or a QA/QC function.

The appendices

Some appendices are included so that the background on which procedures have been developed can be understood. Developing the future by ignoring the past can rarely be advised. 'Fresh' ways of evaluating pack (device) plastic suitability are essential to the future success of the industry. Five years ago this success as related to plastic and pharmaceuticals was easy to predict. Today, with growing environmental concerns, such predictions are less clear. The sophisticated world continues to be innovative, with emphasis on combination or composite materials (as offered by coextrusion etc.). Reuse and recycling of these mixed materials is certainly far from clear, so how will this apparent conflict be resolved? Who will predict?! Five years ago the author awaited a balance (on plastic testing/investigations) to be achieved between the practical side of industry and the more theoretical side of academia. Today the environmental issues add further complexity to future progress, and may influence a swing back to simple, single materials, or lightly coated materials.

It should be noted that many of the factors which need consideration when a pharmaceutical product is to be launched in a plastic pack share common ground with pharmaceutical and medical devices. Appendices (8.1, 8.3, 8.4 and 8.5) indicate the various proposals on the testing of plastics for pharmaceutical products. Appendix 8.2 provides a typical type of clearance programme for a multi-dose sterile product in a plastic pack.

EU activities on plastics for pharmaceuticals and foodstuffs are covered in Appendix 8.6. The need to extend the principles of GMP to the suppliers of plastic materials, containers and components is highlighted in Appendix 8.7. Appendix 8.8 introduces how the risk related to the product form can be expected to be reflected in the intensity of the tests necessary to approve a product—pack system. Additional factors which may change the level of testing are also discussed.

Appendix 8.9, in identifying how packs are becoming increasingly complex and sophisticated (e.g. to assist in product administration or as special devices), indicates the various types of additional testing which are now essential to approval. Appendix 8.10 lists support papers written by the author with reference to plastics.

Appendices 8.11, 8.12 and 8.13 open up a relatively new topic where a possible technical gap between the information given in polymer supplier data sheets and the properties of the plastic used in the final pack can be identified.

Finally, it is inevitable that some new guidelines will have appeared since this chapter was written. One area of constant advance is the ongoing publication of ICH guidelines, e.g. testing for the effect of light. However, even these guidelines will need review once some experience of their use has been obtained, and this point has been made previously about all test procedures. Testing at the ICH condition 40°C 75% RH provides a severe challenge to many packs, and there are various ways by which this challenge can be addressed (see Appendix 8.14).

Appendix 8.1: WHO guidelines

The World Health Organisation has proposed international requirements for plastic containers for pharmaceutical preparations. These include guidelines on selection of plastics/code of practice, covering the following.

Infusions and injections

- Physico-chemical on aqueous extracts.
- Non-volatile residue, heavy metals, buffering capacity, reducing substances.
- Biological *in vivo.*
- Acute systemic toxicity in mice (aqueous/alcoholic, oily extractants).
- Intracutaneous test (rabbits). Cardiovascular (cat) toxicity—infusions.

- Biological *in vitro.*
- Haemolytic effect of aqueous extract.

Aqueous ophthalmic preparations

- Physico-chemical on aqueous extracts.
- Non-volatile residue, buffering capacity, reducing substances.
- Biological test on aqueous extract.
- Eye irritation in rabbits on repeated instillation (Draize test).

The above is based on the 26th WHO Report and subsequent updates.

Appendix 8.2: Programme evaluation example

The following is a suggested programme for the evaluation of a plastic container for a liquid multidose injection product (not lyophilised).

1 Establish suitable grade of plastic. Determine that the plastic and constituents meet food grade standards. Discuss residues, additives and processing aids, etc. which may be present with relevant parties. Check available safety data. Note—additive content should be low and certain heavy metals absent (Cd, Pb, etc.).

2 Apply physico-chemical tests (on plastic or extract) and biological tests (on extract).

(a) Metallic additives—BP 1980 Appendix XIX A200–202 USP XXIII Containers.
(b) Non-volatile residues, residue on ignition and buffering on purified water injection extract—USP XXIII.
(c) Reducing substances on autoclaved water extract.
(d) Turbidity test (autoclaved) and freedom from froth.
(e) Acute systemic toxicity on sodium chloride injection extract using mice—see USP XXIII Containers.
(f) Intracutaneous test on rabbit. Sodium chloride injection extract—see USP XXIII.
(g) Eye irritation in rabbits—repeated instillation (Draize test) reference possible irritancy effects—USP XXIII.

3 Establish critical product characteristics by preformulation studies followed by challenge test on proposed formulation.

4 Actual injection stored in final plastic pack.

(a) Initial feasibility tests can use a similar plastic container and the product manufactured on a development scale—some accelerated testing may provide relevant data, i.e. temperatures up to 45°C. (May be used to provide stability data for clinical trials—IND stage in USA.)
(b) Formal long-term stability tests.

(i) Usually carried out on up to three batches of product made on a production scale and packed in the container in which the product will be sold.
(ii) Programme to cover 5 years.
(iii) Test periods 0, 3, 6, 9, 12, 18, 24, 36, 48 and 60 months.
(iv) Storage conditions 4°C, 25°C, 25°C 60% RH, 40°C, 40°C 75% RH for full period and possibly 45°C for 3–6 months. Conditions to be humidity controlled (and continuously recorded).
(v) To check product and pack at related intervals for chemical change, i.e. purity/degradation/loss of active ingredients and primary constituents (e.g. preservatives). Preferably by analytically specific methods. Degradation products not to exceed 1% with clear identification of major degradation substances. Recheck microbiological effectiveness (i.e. USP XXIII challenge test EP or BP 88 challenge test) at 0, 12 months, 24 months, 36 months, and sterility. Check plastic for chemical change, absorption, adsorption of ingredients, etc. (by extraction if necessary).
(vi) Physical change (do not overlook the importance of appearance, flavour, odour, colour, etc.).
(vii) At selected intervals and conditions (e.g. 25°C and 40°C after 12 months and 24 months etc.) check for possible changes in toxicity (BP 1980 toxicity test B on A201). Rechecks would also be advised on possible irritancy (Draize test).
(vii i) In cases of pack change, i.e. glass to plastic, it may be possible to use the previous pack as a control. However, a control (i.e. sealed neutral glass ampoule) should always be considered for all stability or feasibility programmes.

Storage of the pack without product may be necessary for comparison purposes in some circumstances. Pack change comparison could use 3–6 months at 40°C 75% RH with four periods of analysis, using previous pack as control, but this would need to be supported by a full stability programme.

5. Write up specifications for plastic, pack and pack components. Agree with suppliers.
6. Carry out ongoing stability on production batches using 25°C plus controlled RH. As per ICH recommendations.

Pack components, products, etc. need to be checked and cleared by QC, using written specifications, prior to use in any test programme. All procedures and activities need to be identified and recorded and fully validated.

These QC/GMP type activities are equally important during any stability programme in that when product samples are removed for analysis, the pack should be checked:

(i) at time of removal from test environment
(ii) when it is opened
(iii) after the product samples have been taken.

This should be a comprehensive examination by a trained packaging technologist. Simply opening a pack without observations may destroy evidence associated with possible pack deficiencies. (Analytical out-riders may be associated with pack deficiencies.)

Appendix 8.3:
Examples of national standards for plastic containers for pharmaceuticals, USA and UK

USA

- FDA: General guidelines; Guideline for the Packaging of Human Drugs and Biologics—February 1987.
- USP XXIII, Containers (currently under review—new draft 1998).
- Biological Tests for Parenterals and Ophthalmics: reference should be made to CFR (Acceptance of Plastics and Constituents for Foodstuffs).

UK

- BP 1988, General Guidelines—Specific Tests for Large Volume Parenterals.
- DHSS (1973) Ref. 008 and 020. Specifications for Blood Bags and IV solutions— with Specific Reference to PVC (updates scheduled).
- BS 1679 (pt IV) Plastic Containers for Tablets and Ointments (currently under revision).
- BS 5736 (1979–1989) Parts 1–9, Evaluation of Medical Devices for Biological Hazards.
- EC/EP 1989—then 1999.
- EP: Polyolefines.
- LDPE: See monographs.
- PVC/PP/HDPE etc., EP 1989.
- 9090/111: see summary in Appendix 8.8.

Appendix 8.4:
Examples of national standards for plastic containers for pharmaceuticals, Europe and Japan

France (Pharmacopoeia Francaise Xth edn 1982)

- General Statement of Interaction.
- Parenterals—Biological and Physico-chemical tests.
- Ophthalmic preparations—Transparency and Neutrality.

Japan (Pharmacopoiea 10th edn 1982)

- 500 ml (or larger) aqueous infusion containers only apply.
- Physico-chemical and water permeability tests.
- Biological tests.
- Note—Japan Pharmaceutical Affairs Bureau Notification covers ophthalmics.

Nordic Pharmacopoeia

- Transfusion tubing
- Containers for blood, aqueous solutions, infusions, injections, irrigation solutions.
- Biological (pyrogenicity, acute toxicity, haemolytic) and physico-chemical tests.

National Swedish Pharmaceutical Laboratory

- Submission on standard form.
- Composition and properties of plastic and constituents.

Switzerland (Pharmacopoeia Helvetica)

- Must meet food requirements.
- Parenterals and ophthalmics—colourless, translucent, chemical tests, permeability to water and micro-organisms.

Note: The European Pharmacopoeia has now replaced many of the national ones.

EU—General rules covering medicinal products

- Directives 65/65/EEC, 75/318/EEC, 75/319/EEC, 89/341/EEC, 89/342/EEC, 89/343/EEC, 89/381/EEC.
- There are further CPMP guidelines issued as ‘The Rules Governing Medicinal Product in the European Community’, found as volumes I, II, III and IV

See Chapter 3 for updated information.

Appendix 8.5: Bibliography

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20 Guidelines for Submitting Documentation for the Stability of Human Drugs and Biologics, Feb. 1987 (FDA). Currently being updated and expanded.
21 *Contemporary Biomaterials* by Boretos and Eden, published by Noyes. References: Acute safety tests, Acute toxicity tests, Implants and histopathology.
22 Some biological clearance references (packaging and product): BP 1980/1988/1993; EP 1989, various sections on plastics (constantly being updated); BS 5736 pts 1–9, Evaluation of Medical Devices for Biological Hazards.

Appendix 8.6: The pharmaceutical industry, plastics and the EU

A European committee (under the EU) has introduced monographs on plastic for certain pharmaceutical packaging applications as part of the European Pharmacopoeia. These identified certain plastics, and their ingredients which could be 'permitted'. It is now becoming increasingly evident that a 'permitted' list is possibly restrictive to free trade and biased towards the grades of plastics and their associated ingredients which have been 'approved'. A view that the information is advisory rather than mandatory is being seen by some countries as a means of either accepting the broad principle or circumnavigating the original intentions. The UK BP commission maintained that some form of performance standard would be preferable, i.e. an approach which is generally adopted by most UK-based companies.

Although it is generally accepted that only plastic materials and their associated constituents declared as 'food grade' should be used for pharmaceutical products, the 'global migration' approach currently being adopted in Europe has also come in for criticism. The aqueous extractive procedure causes little concern, but the rectified olive oil extractive procedure is not only difficult to carry out but relatively poor in terms of reproducibility. In addition, olive oil, being a naturally occurring product, is difficult to control.

In defence of this approach it must be noted that dependence on FDA approved materials is not foolproof, since many substances included are based on a committee consensus of opinion rather than detailed toxicological evidence. However, records of deaths from using plastics (excluding the polymerisation or compounding process) are virtually non-existent and reports of adverse affects relatively rare. The latter tend to be related to toxicological and pharmacological work on ingredients where mutagenicity, carcinogenicity, etc. have been shown, and such ingredients were excluded from use even though the risk of these being extracted may be nil. In general quite a few of the recorded adverse affects tend to be related to the plastics used internal to the body (implants, catheters, tubing, etc.).

It therefore can be concluded that there is considerable confusion in Europe associated with the use of plastics for pharmaceutical applications generally. The following 'food' legislation has been introduced:

- 90/128/EEC: Details of limits (10 mg/dm^2).
- 82/711/EEC: Details of tests.
- 85/572/EEC: Details of simulants.

These, together with various amendments in each case, cover the extractive test procedures, based on an upper limit of 10 mg/dm^2. Plastics and the constituents which they may contain are partly covered by a list system as mentioned earlier.

Appendix 8.7: The plastics industry and GMP including traceability

The extensive testing carried out by the pharmaceutical industry to clear a plastic and identify the constituents is of no avail if the polymerisation, compounding and fabrication processes are not controlled by some code of practice. The *Orange Guide on Good Manufacturing Practice (GMP)* and the recent EU guidelines could equally be applied to the plastics industry. Some of the more basic aspects would relate to the following.

1 Clear batch identification of all materials (polymers and constituents).
2 Documented control on materials received/issued incoming and outgoing materials (i.e. traceability).
3 Identification of what batch is used in what process to allow trace-back to an original 'supply' batch.
4 Clear flow paths from raw to finished materials with 'hold' and quarantine areas.
5 Materials and finished goods to be identified by name, batch number, date, etc., and to pass through a 'hold' or quarantine area (while under inspection) to a clearly defined storage area when status is confirmed.
6 The QC operation identified above in (5) would also include status labelling which indicates the various stages, e.g. green (pass), red (failed).
7 All materials to require a specification by which they can be identified, ordered and controlled.

8 Materials used in any process must also undergo checking operations to ensure that (a) materials are correctly labelled, (b) correct materials are issued, (c) the correct quantity is issued.
9 Retention samples should be kept for specific items and any change (process or materials) should be carefully monitored, and referred to customer.
10 Material segregation to be organised and controlled to prevent admixtures. (Particularly important for regrind.)
11 Item segregation to be organised and controlled to prevent admixtures from adjacent machines.
12 Machines to operate under acceptably clean conditions to minimise airborne contamination.
13 Items emerging from machine to be exposed for a minimum of time, i.e. direct feed into suitable (clean) PE bags etc.

It should therefore be concluded that the pharmaceutical industry will ultimately require a reasonable guarantee that the material tested, approved and specified remains identical in terms of formulation, purity and general quality. Buying under warranty may be an acceptable way of achieving this, coupled with a good GMP approach by the plastics company.

Note: In the UK the Pharmaceutical Quality Group (Institute of Quality Assurance) have devised Supplier Codes of Practice which link GMP to ISO 9002 Quality System certification.

Appendix 8.8:
Risk versus intensity ,of testing

It is logical that the risk (to patient/user and company) should bear some relationship to the intensity of the tests involved in the clearance of the materials from which the pack is made.

Intravenous (IV) solutions head Table 8.2, as with the large volumes involved even a small level of ‘extractive’ will be rapidly in contact with the most sensitive body organs, i.e. heart and brain, e.g.

1000 ml extractive 0.1% = 1 g (IV solution)
20 ml extractive 0.1% = 20 mg (nasal spray)

Table 8.2 Intensity of testing required (in reducing order)

Group A
- Sterile products
- Large volume parenterals (LVPs)
- IV solutions
- Irrigation solutions
- Dialysis solutions, etc.

Group B
- Small volume parenterals (SVPs)
- IV additives
- Intravenous
- Intramuscular injections
- Subcutaneous injections, etc.

Group C
- Implants
- Ophthalmic products (multidose and unit dose)
- Nebulisation solutions
- Wound care products
- Non-sterile products, i.e. transdermal patches, vaginal-rectal products, local and topical products, liquid oral products, solid oral products

This example confirms a need for different intensities of testing according to the product category/route of administration. This will also be influenced by:

- the product-to-pack contact area
- the nature of the product (chemical-physical characteristics)
- the contact time and temperature (etc.).

Table 8.2 suggests a product 'intensity of testing' order, which is headed by sterile products. However, the position in this order may change according to any special product characteristics, contact area, contact time, temperature, etc. The table is therefore given to create a greater awareness of how 'risks' to 'benefits' might be considered. Some 'other factors' are given as a separate list below.

Intensity of testing: other factors

1 Patient type, i.e. elderly, adult, child, neonate.
2 Treatment—position in general may vary according to nature of treatment, i.e.

- pre-operation
- post-operation
- intensive care.

3 Size of product-to-pack contact area.
4 Nature of product, e.g. oils tend to be more extractive than water-based materials (e.g. rubber/plastics). See also EN 9090/III (Appendix 8.13).
5 Storage conditions/period (temperature, RH, time, etc.).
6 Processing factors (terminal versus aseptic processing etc.).

Appendix 8.9: Pharmaceutical packaging with emphasis on administration aids and separate medication aids/devices

Introduction

An increasing trend towards 'drug delivery systems' has meant that packs which assist product administration, separate devices which aid medication, and the use of implantations have been steadily growing. Examples cover squeeze packs, pump systems, aerosols, dermal patches, lung inhalation systems involving powders and solutions, etc. These sophisticated and complex designs to aid drug administration have brought a need for a new level of knowledge associated with their production, efficiency in use, cleaning techniques and procedures, etc., coupled to the overall product stability. For example, although a product may be chemically stable, it will possibly only remain effective if its physical form and the performance of the device do not change throughout storage and use. Analytical test procedures therefore have to be supplemented by either 'user' assessments or simulated laboratory tests, in order to establish that the dose delivered remains in the right form (e.g. particle size distribution in the case of inhalations), the right concentration and quantity, etc.

In certain instances, this work becomes part of the stability programme so that 'drug delivery' parameters can be checked at the various time/storage intervals and conditions. This is also likely to involve the hygiene side of medication, i.e. whether there are any microbiological risks to users, how are these minimised (usually by cleaning) and, if a disinfecting agent is advised, whether it is safe, particularly if residues cannot be avoided, etc.

Although less complex, products which are reconstituted may also fall into a similar category, particularly as the pack may have to play two roles, e.g.

1 Retaining a dry powder or crystalline product in a stable form for the main shelf life.
2 Providing limited shelf life—usually as a liquid product, from reconstitution to completion of the medication period.

Subtle changes to plastic packaging components (e.g. swelling or shrinkage due to temperature or solvent absorption) may also influence the 'dose' dispensed (e.g. top pressure on a dropper plug has been known to reduce the orifice size, thereby changing the size of the 'drop'). See also Chapter 2.

The elderly patient

In this area there is already a conflict between tamper-evidence/resistance; child resistance; and packs which require easy access and reclosure by those who are infirm, elderly, arthritic, poor of sight, etc. This conflict also extends to OPD (original pack dispensing) and the increasing use of controlled dosage packs (i.e. special packs for the elderly population). Since many of these packs place several products in a common area, identifying those products to be taken at, say, 8.00 a.m., 12 noon, 5.

00 p.m., 9.00 p.m., etc., any possible interaction between the various products must be considered. The fact that these packs have to be made up by a dispensing activity conflicts with the concept of OPD (where the original pack reaches the patient) as either original packs have to be broken down or bulk packs of products become a necessity.

The fact that monitored dosage packs are useful to elderly compliance does not appear to be in dispute. However, there are certain question marks against the direct admixture of several products, e.g. whether checking this is a development, clinical, medical, stability/analytical function has to be decided. Most of the packs used are based on plastics.

This also raises questions on the suitability of dispensed packs and their shelf life.

The fact that a pharmaceutical company spends significant costs, time and effort in establishing a product-pack shelf life and that this can be put at risk by transfer to a different pack (the pharmacist thereby accepting responsibility) appears questionable in terms of modern 'product liability'.

Patient usage

As packs, administration aids, and separate medical application devices become more complex, the possibilities of misuse or abuse obviously increase. This in turn brings increasing demands for good clear instructions and assessment, either as part of a clinical trial or by special user/laboratory programmes capable of identifying misuse and/or abuse.

Under such programmes even packs or systems which do not assist administration may need some form of assessment (e.g. blister packs and the elderly). However, with reclosable packs, the user may never replace the closure properly, hence a different question may have to be addressed, i.e. whether the product will be adequately protected during its use period! Opening and reclosing a pack under an adverse atmosphere is a further possible 'risk'. Syrup-based products often cause closure sticking problems, hence may need special tests.

Some initial conclusions

One initial conclusion is that storing a packed product under a static climatic condition and chemically analysing any change is no longer an adequate test for 'fitness for purpose'. This is particularly true where the pack may 'change' under the conditions of storage or use, or where the pack assists in the administration of the product, or where the product is administered via a separate device. In the last case, subtle product changes may alter the dose delivered to the patient, or the device may also change with use and time (e.g. wear) and cause dosage problems. Product and device therefore have to be assessed together and independently, and hence may require shelf-life limitations.

Support documentation for company and regulatory clearance (of products, packs and devices)

It should be increasingly evident that the total data required to clear a product, pack and device is becoming more and more complex from both a company and a regulatory point of view. Boundary areas, as associated with previously apparently welldefined disciplines, are also becoming less easy to define. What is becoming more important is that there is an overviewer who can see the total picture and can make certain that all pertinent tests and procedures are identified and adequately carried out, with the results recorded and signed by an authorative person. This type of background is particularly important where the 'risk to user or patient' is high, e.g. large and small volume parenterals, implants, eye products, sterile unit doses, wound care products.

Although less information and testing may be necessary where the risk to patients is lower (topical application, oral products), it has already been indicated that the need for further 'tests' in this area may also increase.

Finally, it should be stressed that 'packs' used in all stability trials should be 'examined professionally' both before and after they have been opened and sampled for analysis. Again this may need to be formally written up as an authoritative document.

Documentary support to product registration will therefore increase rather than reduce in the future. Where possible, such documents should follow some common form of layout, for example:

1 what each sets out to achieve (objective)
2 a clearly expressed conclusion
3 adequate support detail free from ambiguity, recording results of tests carried out
4 full details of what product-pack was used
5 comprehensive records of test procedures, conditions, etc.
6 cross-references to book records and person(s) carrying out tests and when
7 authoritative signature (s) of approval with title (s) etc.

A well-presented report will make registration easier and more effective, and improve confidence between company and regulatory authorities.

Some examples of products requiring supplementary testing procedures are given in Table 8.3. The list is not comprehensive, as further examples can readily be added, but it should indicate some of the supplementary types of investigations which may be needed for certain products, both before and after storage and use.

Appendix 8.10: Other articles by author

1 Unit packaging of pharmaceutical preparations, *Institute of Packaging Symposium,* 27 September 1973.
2 *The Pharmaceutical Industry—Plastics and Packaging,* BPF, 1975.
3 *Blister and Strip Packaging,* Institute of Packaging, 1977.
4 Foil in pharmaceutical packaging, *BAFRA 77 Symposium,* published in *Manufacturing Chemist and Aerosol News,* February 1978.
5 The unit dose packaging of liquids and semi liquids, *Interphex Conference,* 1978.
6 The Pharmaceutical Clearance of a Plastic Pack/Device. *GMP Conference— Powder Technology,* October 1980.
7 Quality control and pharmaceutical packaging, *British Journal of Pharmaceutical Practice,* Vol. 2, No. 10, March 1981.
8 Plastics and the pharmaceutical industry, *Frost and Sullivan Symposium,* 1981.
9 Polyethylene—pharmaceutical and medical applications, *PRI Polymer Conference,* June 1983.
10 Plastics for toiletry and cosmetic products, *Toiletry and Cosmetic Journal,* 1983.

Table 8.3 Products requiring supplementary testing procedures

Product	*Test*	
Multidose injections (vials)	•	Multiple piercing of rubber bung, e.g. fragmentation, coring, resealing.
•	Volume extracted (how).	
IV solutions	•	Check against ‘giving sets’ for fit, flow, removal of particulates, leakage, collapse (if collapsible), air ingress, etc.
Inhalations (generally)	•	Particle distribution, blockage, losses by impaction, changes in dosage throughout pack.
•	Influence of different inhaler systems, if relevant, etc.	
Metered dose pump systems, e.g. nasal spray	•	Actuations to prime.
•	Retention of prime.	
•	Dose variation (device).	
•	Number of doses per pack.	
•	Particle size range.	
•	Blockage.	
•	Drying-out of solution.	
•	Non-available residue	
•	Microbial risks—contamination.	
Eye drops, i.e. multidose/unit dose	•	Variations in drop size.
•	Drops per pack.	
•	Efficiency of closure in use.	
•	Drying-out of product.	
•	Drop size change in use/after storage.	
•	Loss of preservative during use.	
•	Non-available residue.	
•	Microbiological ‘grow back’.	

11 Packaging and product stability, CPA *Conference,* Holland, November 1983.
12 Design of powder inhalers (Newman, Dean and Young), *The Practitioner,* November 1983.

13 A new era in unit dose packaging, *Unit Dose Conference,* IOP, 8 October 1986.
14 Stability aspects of packaging, *Drug Development and Industrial Pharmacy,* Vol. 10, Nos 8 and 9, 1984.
15 Sources of particulate contamination in sterile packaging, *Pharm. Technology,* August 1985.
16 Assessment of performance, testing and quality of conventional screw (plastic) closures , *PRI Conference,* 28 April 1986.
17 Handling and performance characteristics of plastic screw closures (production lines), *PRI Conference,* 28 April 1986.
18 Tamper evident and tamper resistant packaging, *TEPCON Conference,* April 1987.
19 The manufacture of clean materials, containers and components for the packaging of pharmaceuticals, *IOP One-day Conference,* 2 December 1987.
20 Historical survey on the use and growth of plastics in the pharmaceutical industry, *PRI Conference on Update on Plastics,* 7 December 1988.
21 *Combination materials, flexibles., laminations, etc.,* March 1989.
22 *Closures and closure systems for rigid plastic packs,* IOP, July 1990.
23 *Overcoming permeation and diffusion problems by the use of overwraps,* 1990.
24 The sterilisation of plastics. An introduction and overview, *IOP Conference on Sterilisation of Plastics,* 4 December 1990.
25 *Pharmaceutical packaging with emphasis on administration aids and separate medication devices,* ECEC, 1991.
26 *Assessment of closure efficiency,* PRI/IOP, January 1991; IOP, January 1991.
27 *Making an effective seal, heat sealing,* IOP, January 1991.
28 *Pack—material selection for the packaging of toiletry and cosmetic products,* CPA, USA, August 1991.
29 *Package printing and decoration,* Version VI, February 1991.
30 The expanding role of the pack (and the test procedures associated with registration), *BIRA Conference,* September 1991.
31 An introduction to the filling of liquid pharmaceutical products, *IOP Conference,* December 1991.

Appendix 8.11:
Possible processing effects on plastic materials, containers and components

Plastics subjected to processing procedures, either as part of a conversion operation or at a subsequent stage associated with product manufacture and packaging, may incur temporary or permanent changes. Whether these changes are critical to the product will depend on the product and the risks incurred. In the case of pharmaceuticals, toiletries, cosmetics, etc., some in-depth investigations may be required to quantify the significance of any deviations from the chemical, physical or physico-chemical properties of the preprocessed material. Examples of possible changes are indicated below.

Plasticised PVC 'bags' undergoing steam autoclaving

When autoclaved under pressure in a steam autoclave, plasticised PVC interacts with moisture/heat and becomes quite hazy and milky. After cooling down, the PVC reverts to its normal clarity. There is, therefore, a temporary period during which the PVC has different physical and possibly physico-chemical properties.

It should therefore be noted that a number of plastics may change during a steam autoclaving process where temperatures of 100–135°C (achieved by pressure) can be reached. This applies to both single and multilayer material, and includes adhesive layers. Overpressure autoclaves are usually essential to prevent physical distortion during cooling.

Gamma irradiation

Irradiation (usually at 25 kGy) can have various effects on plastic including physical and chemical changes which may be permanent, temporary, or ongoing. Physical changes are most frequently associated with cross-linkage, which usually reduces flexibility and increases rigidity (slightly).

Chemical and physico-chemical changes can be related to both the polymer and the constituents in the polymer (residues, additives, processing aids, etc.). Chemical degra dation to any of these may be identified as colour changes, surface changes, odours, taints, as well as by chemical analysis. For example, certain grades of LDPE have been known to generate both formaldehyde and formic acid (as end breakdown products) when subjected to 25 kGy gamma irradiation. Antioxidants can also be degraded.

Since gamma irradiation may modify the surface of a plastic, initial stress lines (due to molecular chain fracture or cross-linkage) may become a propagation point for long-term cracking, particularly when stored under 'hotter' conditions. This surface modification or change usually depends on the presence of air or oxygen. Carrying out irradiation in a nitrogen atmosphere, or having an oxygen impermeable layer on the plastic surface, reduces the above problems.

Surface treatments

A major application of surface treatments is for print key or adhesion related to printing, labelling, etc., by oxidative-type surface treatments. These include corona (films), flame treatments (containers), each of which can give a marginally different effect.

Surface treatment can also affect the amount of 'bloom' or surface migration of various active surface agents (lubricants, slip and antislip additives, etc.) and either subsequent 'migration' into a product by surface abrasion or chemical removal, solubility, etc.

Electron beam or beta irradiation

As a generalisation, electron beam treatment creates similar effects to gamma irradiation, but usually on slightly reduced scale, since depth of penetration is less.

Changes—crystalline versus amorphous

Processing involving heating and cooling may influence the ratio of crystalline to amorphous material, thereby modifying the characteristics of the polymer involved.

Conclusions

The above examples are only the tip of the iceberg. There are many process procedures that can modify the properties of plastic. The more obvious ways in which plastic performance can be influenced include:

1 changes in the solubility of the absorbing materials in the polymer
2 changes in the solubility of the absorbing materials in the surface layer
3 changes in the surface conditions
4 opening-up of molecular structure by swelling (increases permeation)
5 movement of internal constituents to the surface (or vice versa)
6 changes in mass or density
7 molecular changes due to degradation, including chain fission.

If any of the above (or combinations) occur, changes may arise to physical, physicochemical properties, e.g. in terms of diffusion, permeation and migration/leaching. Thorough retesting is therefore sometimes essential to detect changes between the 'processed' and 'unprocessed' (as supplied initially) plastic.

Appendix 8.12: Pharmaceutical supplement

Summary—plastics and pharmaceutical packaging

Since the worldwide need for pharmaceuticals is still steadily expanding, there is a continuous growth of pharmaceutical packaging with a particular emphasis on plastics. This growth is especially vigorous where packs also act as administration aids or devices, in special blow/form fill seal operations and in general areas where innovation is involved. Coupled to these activities are gradual changes in the intensity of testing, together with a greater interest in traceability, effective validation, safety, efficacy, quality, etc. As the knowledge requirements also have to increase in order to meet the above demands, it may be useful to have a check list on what problems can arise between pharmaceuticals and plastics as seen 'today'. The following list is not in any order of importance, as problems will change according to the product and circumstances involved.

1 Permeability to moisture.
2 Permeability to normal gases, oxygen, carbon dioxide, nitrogen.
3 Absorption of moisture/solvents.
4 Physical and chemical changes due to processing activities (conversion, pretreatment, sterilisation, etc.).
5 Changes due to ageing/exposure against time and the environment (light, oxygen, temperature, etc.).
6 Potential for environmental stress cracking.
7 Absorption and adsorption of product constituents, e.g. certain preservatives.

8 Constituents' migration from the plastic to the product.
9 Exclusion of light.
10 Removal of constituents present at the surface of the plastic, by physical abrasion.
11 Shrinkage/sinkage—related to plastic, thicknesses, design, etc.
12 Dimensional and visual assessment.
13 Level of electrostatic charges.
14 Evaluation of closure efficiency.
15 Total compatibility with the product.
16 Material cleanliness, i.e. material bioburden/particulates.
17 Aroma/flavour.
18 Identification, i.e. checking supply of correct materials, by chemical or physicochemical analysis of the bulk material, or the surface of containers.
19 Constituents identified in terms of residues (from polymerisation process), processing aids, additives, masterbatch constituents.
20 Identification of process(es) of manufacture/conversion, as these may influence properties.
21 Food grade approval via any relevant food regulations.
22 Colour measurement to obtain a reference standard (usually light and dark limits) for pigmented (opaque) and dyed (translucent/transparent) materials.
23 Resistance to pH changes—may arise from pH shift or changes.
24 Resistance to impact forces (drops, forces, puncture resistance, etc.).
25 Resistance to vertical forces—top compression as experienced during capping, stacking, shrink wrapping.
26 Heat softening and heat deflection/distortion temperatures—reference hot processing etc.
27 Flame/fire-resistant—relevant to electrical instruments and devices.
28 Resistance to creep or cold flow—materials may change in shape, dimensions, etc., related to a pressure force (stress) and temperature/time.
29 Resistance to sterilisation process (dry heat, moist heat, irradiation, UV, etc.).
30 Degree of orientation (may influence percentage of shrinkage on heating).
31 Extractives. Tests may be derived from directives, compendial standards, World Health Organisation, etc., with limits/standards based on chemical or biological test procedures. Such tests can provide useful comparisons but final approval can only be based on tests where contact between product and pack is involved.

The above list indicates a range of factors to be considered when developing a plastic pack for a pharmaceutical product. The level of in-depth testing required will inevitably vary according to the risks to both the user/patient and the company, e.g. product liability.

Each factor identified can be expanded as a topic in its own right. A few examples are given below.

Absorption and adsorption of preservatives

Certain preservative systems can be lost from certain plastic packs by 'sorption' and solubility in the plastic and, if they are also volatile, by evaporation from the external surface which is in contact with the atmosphere. Reports, particularly as references in textbooks, often suggested that phenol could not be used as a preservative in lowdensity packs. Subsequent work, many years later, established that the solubility of phenol in polyethylene was relatively low and that sufficient phenol for adequate preservative efficacy could be retained by a number of methods, i.e. coating LDPE internally or externally, or enclosing the pack in an additional barrier overwrap (e.g. paper/foil/PE or similar foil-bearing barriers).

Other preservatives which suffer from sorption in LDPE include benzyl alcohol, chlorbutol, chloroform, chlorocresol, 2 phenyl ethanol. Sorption also occurs with HDPE and PP but usually to a lesser extent. PVC is less prone to preservative absorption and has been employed to retain certain volatile preservatives (2 phenyl ethanol).

Adsorption, where the preservative attaches itself to the surface of a plastic, tends to vary according to the type of plastic, constituents in the plastic, surface treatment, surface area of the plastic. Adsorption has been found with most mercurials, including Thiomersal, benzalkonium chloride and bromide, etc. Small amounts of chlorhexidine, benzoic acid and hydroxybenzoates have also had losses reported for certain plastics.

It should be noted that although preservative loss can be quantified by chemical analysis, the microbial effectiveness of the preservative remaining can usually only be evaluated by a preservative efficacy challenge test.

Absorption of moisture

Since all plastics are to some degree permeable to moisture it is inevitable, particularly at higher humidity levels, that plastics may contain traces of moisture. Certain plastics, especially those based on OH groups, e.g. polyvinyl alcohol, ethylene vinyl alcohol and others (some nylons), can absorb sufficient moisture to cause problems during moulding. Such polymers need to undergo a predrying operation prior to moulding. In general, the higher is the moisture content the higher the permeability to moisture, gases, and odorous vapours. EVOH, for example, is an excellent barrier to gases and moisture when very dry, but these barriers significantly reduce as the moisture content in the polymer increases. As a result of this EVOH is usually sandwiched between two moisture barrier polymers such as LDPE or PP. Plastics which absorb moisture are less prone to electrostatic problems.

Sinkage and shrinkage

Plastics show a much higher coefficient of expansion (and contraction) than metals. This means that the material contracts during the cooling cycle of a moulding operation, hence most moulds have to be made larger than the component drawing dimensions if the defined size is to be produced. The level of shrinkage typically varies from around 0.5% to 5%, e.g. the polystyrenes (PS, HIPS, SAN, ABS) are in the lower level while HDPE/PP tend to be towards the upper level with the other plastics somewhere in between. Calculating shrinkage becomes increasingly complex with difficult threedimensional objects which exhibit many changes in thickness. For simplicity of design an item of uniform section is far easier to produce than a complex three-dimensional design. Thicker sections may typically show areas of sinkage as found within the bottle neck bore of many extrusion blow moulded bottles, i.e. behind the thicker sections of the external thread. In complex designs this sinkage, coupled to changes in section thickness, can lead not only to sinkage, but to distortion and possible twisting of the component. Although this might be overcome by putting the component in a jig which restrains movement during final cooling, this can be an expensive, labour-intensive process. Although the ‘pressures’ employed in injection moulding can reduce sinkage and distortion, good effective mould design is essential to quality mouldings. However, the final quality will also depend on the machine cycle (pressure, time, temperature, etc.), hence this must ultimately be equated with cost.

The level of sinkage/shrinkage is also influenced by other factors such as fillers, pigments, melt flow index, density and cooling rate. It should be noted that materials which are oriented, either purposely or accidentally (e.g. in a moulding, operation), will shrink significantly if they are heated above the temperature used for the orientation process. Amorphous materials show less shrinkage than crystalline polymers.

Extractives and general compendial tests

Extractive tests based on various simulants are offered in such compendial standards (past and/or present) as USP, EP, JP, WHO, and BP. These tests, in which extracted solution(s) are subject to chemical analysis and biological assessment, give information on the materials extracted and the general safety of the extracted solution. Although attempts are being made to standardise methodology worldwide, there are currently differences between the requirements in the USA, Europe, Japan, etc. Some of these are summarised in Table 8.4; in the EP 1989 they are covered under V1.1.2. etc.

Table 8.4 Requirements for plastic materials

V1.1.2.1. pages 1–8	Materials based on poly (vinyl chloride) i.e. materials based on plasticised poly(vinyl chloride) for containers for human blood and blood components and for containers for aqueous solutions for intravenous infusion. (1989) Covered by V1.1.2. (1–7)
V1.1.2.1.2 pages 1–5	Materials based on plasticised poly(vinyl chloride) for tubing used in sets for transfusion. (1991)
V1.1.2.2.	Polyolefins
V1.1.2.2.1. pages 1–3	Polyethylene—low density, for containers for preparations for parenteral use and for ophthalmic preparations. (1992) Note—no additives.
V1.1.2.2.2. pages 1–5	Polyethylene—high density, for containers for preparations for parenteral use. (1990)
V1.1.2.2.3. pages 1–5	Polypropylene for containers for preparations for parenteral use. (1990)

Covers homopolymer and copolymer.

Limit of not more than three stabilisers (antioxidants) from a list of nine.

V1.1.2.3. pages 1–6	Ethylene-vinyl acetate copolymer for containers and tubing for total parenteral nutrition preparations. (1993)
Limits level of vinyl acetate –25% maximum containers, 30% tubing.	
Limit of not more than three stabilisers (antioxidants) from a list of five.	
Identifies limits for oleamide and erucamide, calcium and zinc stearate, calcium carbonate, potassium hydroxide, silicone dioxide.	
SILICONES	
V1.1.3.1.	Silicone oil as a lubricant. (1985)
V1.1.3.2.	Silicone elastomer for closures and tubing. (1985)
V1.2.3.	RUBBER CLOSURES
V1.2.3.1.	Rubber closures for containers for aqueous preparations for parenteral use. (1989) There are two basic types—Type I: meet strictest requirements
Type II: offer certain requirements but cannot meet all the requirements of Type I.	
V1.2.2.	PLASTIC CONTAINERS
V1.2.2.1.	Plastic containers and closures
V1.2.2.2.	CONTAINERS FOR BLOOD and BLOOD COMPONENTS
V1.2.2.2.1.	Sterile plastic containers for human blood and blood components.
V1.2.2.2.2.	Empty sterile containers of plasticised poly (vinyl chloride) for human blood and blood components.
V1.2.2.3. pages 1–2	Plastic containers for aqueous solutions for intravenous infusion. (1990)
V1.2.2.4 pages 1–5	Sterile single use plastic syringes. (1991)

Appendix 8.13
(based on EN/9090/III): Typical pack/packaging information normally required

Primary or immediate packaging

1 The nature of the packaging material, indicating the qualitative composition.
2 Description of the closure (nature and method of sealing).
3 Description of the method of opening and, if necessary, safety devices.
4 Information on the container (single or multidose) and dosing devices.
5 A description of any tamper-evident closure and child-resistant closure.

The above has to be supported by supplementary data, i.e. development pharmaceutics which justify the choice of pack and include:

1 tightness of closure
2 protection of contents against external factors
3 container/contents interaction
4 influence of the manufacturing process on the container (e.g. sterilisation conditions).

Packaging material (primary or immediate packaging)

Specifications and routine tests, covering:

1 construction, listing components
2 type of materials identifying nature of each

3 specifications, which may vary in detail according to product nature and route of administration.

Routine tests are likely to include:

- identification, appearance, dimensions, performance, bioburden, etc.
- scientific data listed under general and technical information
- plastic (general information)

1 name and grade as used by manufacturer
2 name of plastic manufacturer (parenterals, ophthalmics)
3 chemical name of material
4 qualitative composition
5 chemical name(s) of monomer(s) used.

Material should have food grade approval, otherwise additional toxicological data will be required.

Plastic (technical information)

1 Characteristics: general description, solubility in various solvents.
2 Identification usually by infrared for the material, the main additives, any dyes.
3 Tests including general tests, mechanical tests, chemical/biological (extractive procedures using suitable solvent).
4 Name of manufacturer/converter.

Appendix 8.14: Summary of ICH guidelines on stability and possible influences on the `pack'

Although the ICH guidelines make reference to ‘stress conditions’, involving low and high temperatures, low and high humidities, freeze-thaw, varying light intensities, including cycling conditions, storage at a fixed temperature and humidity may not fully challenge the pack (and the product). A pack may therefore withstand continuous storage at 25°C/60% RH, 30°C/60% RH, 40°C/75% RH, etc., but fail under cycling or higher temperature stress conditions. However, packs are more likely to change if exposed to a multiplicity of challenges, e.g. temperature and RH changes, vibration and compression (on a production line, in storage or distribution), the influence of oxygen, light. Changes arising from these challenges may subsequently be reflected in the stability of the drug substance or the product dosage form.

It is therefore important to bear in mind some of the differences between fixed static climatic conditions and the real world where fluctuations in temperature, humidity, light, etc. may be further influenced by such physical challenges as varying degrees of vibration and top compression, as identified earlier. The author therefore believes that the ICH guidelines put additional emphasis on the role of the packaging technologist who must more thoroughly investigate any deficiencies which may arise in the pack and possibly jeopardise the shelf life of the product. Information detailing such challenges will likely need to be presented as a formal document as part of the regulatory submission, rather than being included in any formal stability programme.

Packs which are to some degree permeable to moisture (as are most plastics) will lose or gain moisture according to whether they are exposed to a high or low relative humidity respectively. 40°C/75% RH may be particularly severe on a fully exposed blister pack and give an artificially low shelf-life prediction. The same condition may offer little challenge to moisture loss as the vapour pressure inside the pack may virtually be at equilibrium with the external atmosphere (plastic containers).

Packs removed from a simulated climatic condition also need to be checked for any signs of change/deterioration

1 prior to opening
2 during opening (peel strength, closure, torque/force, etc.)
3 after product removal.

This is particularly relevant where extremes of temperature and cycling conditions are involved since closure efficiencies may vary according to the storage temperature. This can be critical where a product in its pack is allowed to equilibriate with bench conditions before it is subjected to analysis, so a trained packaging technologist is essential to these examinations.

Finally, it is likely that the severest ICH conditions will imply that more effective barrier packs will be essential for certain products (some blisters). As the guidelines only test the primary pack, the fact that the secondary (transit) packaging can contribute to the total shelf life has not been considered. Although a packaging technologist might argue with this, it seems unlikely that the guidelines will be changed in the near future. As a result trends may be towards better barrier materials, coated materials or the addition of various overwrap options. This is yet another challenge to tomorrow's technologist.

It is therefore important to be aware of guidelines but at the same time to be 'wary' of any deficiencies that may be associated with them.

Appendix 8.15: Future polymers for pharmaceuticals

Needs for improved properties may involve the use of coatings for the well-established economic polymers, the additional use of protective overwraps, or the use of new potential polymers. The last of these are likely to include:

- PBT (polybutylene terephthalate)
- COC (cyclic olefin copolymer which includes Resin CZ from Daikyo Seiko and Topas from Ticona Mitsui); use for the former has already been found for vials for expensive lyophilised biotechnology products
- LCP (liquid crystal polymers) used either on their own or as blends with other materials (PE and PET)
- PEN (polyethylene napthalate) currently being used with PET to achieve hotter fills.

Another alternative is the use of Metallocene catalysts to produce polymers with improved control of MFI and chain length distribution.