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PRESENT AND FUTURE TRENDS

D.A.Dean

Introduction

Before looking at present and future developments in the packaging of pharmaceuticals, some historical background in terms of products and packs may prove useful. Although certain product forms have existed for centuries, to some it may be difficult to envisage even 50 years ago when the majority of OTC and dispensed products were liquids, usually of a none too pleasant taste, and presented in glass bottles closed with corks. Today solid dosages are the major product form, coupled to a more scientific approach to medication where consideration is given to compliance, bioavailability, dissolution, disintegration, bioburden, mode of delivery, impurities from process residues and degradation, purity, etc. Having been brought up initially on the BP 1932, where purities of 90–100% seemed quite acceptable, it is amazing that one failed 50 years ago to ask the obvious question: what is this other, up to 10%? Today, although we place no less emphasis on purity, we concentrate on identifying the impurities or degradation products to establish that they are both acceptable and safe. In parallel with this change in attitude towards products, there have been significant changes in pharmaceutical packaging. Now there is a highly intense form of investigation where marketing, medical and technical knowledge are brought together to establish the best pack. This 'best pack' is inevitably a compromise of many factors, i.e. how does one balance the need for child-resistance, tamper-resistance, etc. with an increasingly elderly population who survive by their regular medication?

Having set a base line for some 50 years ago, what was the state of packaging art up to yesteryear? Glass and corks were supported by metal cans and tins, metal screw caps, thermoset caps, paperboard boxes and cartons, glassine and waxed papers, composite paper board containers, glass ampoules and cartridge tubes, collapsible metal tubes and the Aspro waxed paper strip.

Real awareness of packaging did not start until after the Second World War, and this intensified somewhat when thermoplastics entered the scene around about 1953. About the same time foil strip packs appeared, followed by pharmaceutical aerosols and squeezepacks, blisters in the early 1960s, pumps in the 1970s, child-resistance in the mid-1970s, elderly patient packs in the early 1980s, to mention a few packaging highlights.

The revolution that has taken place in the allegedly conservative pharmaceutical industry has resulted in greater attention to detail, with high spending on R&D functions in order that product safety aspects are fully covered. Lead times from drug discovery in research to product launch have therefore substantially increased. More sophisticated synthetic products (there were very few in 1938 when most drugs were of vegetable, plant or animal origin) have demanded more and more attention to packaging detail. Thus, although packaging can be described under a definition which equally applies to other packaged products, the emphasis on certain selected pharmaceutical aspects is continuously changing. This initial definition required that packaging should economically provide protection, presentation, identification, information, containment, convenience, compliance and confidence for a product during storage, distribution, display and ultimate use.

The shelf life is the period during which the product remains acceptable in terms of safety, efficacy, conformity and uniformity of content, reproducibility and product liability, with pharmaceutical elegance and acceptable quality.

Since 'standards' associated with the above rarely stand still, upgrading rather than downgrading is an inevitable trend. Under the broad heading of safety, tighter control and/or standards are continually being considered for:

- product-pack security and integrity
- Interaction or migratory exchanges between product and pack
- tamper-evidence, tamper-resistance, child-resistance, child safety, etc.
- dosage delivery etc.

All packs are a compromise, and finding the right compromise is increasingly difficult as the factors which need consideration steadily increase. This is accompanied by expanding facets of control, i.e. by GMP (good manufacturing practice), which start

at product inception, through development, scale-up, manufacturing, packing, warehousing, distribution, sale/dispensing, use, to final disposal of the product and pack.

To meet these demands requires both improved knowledge and a more critical approach to all activities and operations, including packaging.

Present and future trends

These include improving required standards by both the pharmaceutical industry and those companies supplying the industry. This will be reflected in more sophisticated specifications, tighter specifications and the overall stricter control of packaging materials, manufacturing processes and the containers, components, materials which are produced.

Compared with other products, i.e. food, confectionery, beverages, etc., pharmaceuticals are a relatively small user of packaging materials, hence the industry is low in purchasing power. In response to the demand for higher standards, specialist and dedicated suppliers are emerging which give the required quality and security at a premium price. In the case of machinery, specialist machines are built, but often new technology for the food or beverage industry is modified after it has been established, to suit the needs of the pharmaceutical industry.

Changing process trends and changing technology, therefore, tend to follow other established practices but the level of expertise ultimately required by the pharmaceutical packaging technologist is second to none.

Broad policies established via the government, trade associations and the Pharmaceutical Society can have a significant influence on industry. Recent UK policies include the OPD (patient packs) revolution, and the introduction of an ethicals blacklist which has moved certain products into a successful OTC category, and which has also been encouraged by the ‘See your pharmacist first’ campaign. In terms of product trends, there has been a significant growth in packs which aid product administration, packs which act as devices and can be used in devices.

Packaging of pharmaceuticals has been slowly moving away from glass to plastic and is likely, in the long term, to use more combinations of materials. One must, however, remain aware of the environmentalists who see packaging as waste in the dustbin, with criticism of the poor total use of materials and energy. Reuse, recycling, conservation of energy with minimal pollution risks, are becoming well recognised phrases. The professional packaging technologist must therefore be aware of these issues and keep up to date on the activities and responses of the big packaging material users to these ever increasing environmentalist pressures.

Finally, among these broad trends there is the confusing picture caused by cheaper parallel imports. Preventing such imports conflicts with the Treaty of Rome, but it does seem reasonable that a pack should use English text, particularly now that OPD advises the inclusion of user friendly leaflets to better inform the patients.

In the UK, pharmaceutical exports contribute over 5,000 million (1997) to the country’s revenue, and there is still an expanding demand on a worldwide basis. However, this is currently being offset by a steady increase in imports. This growth industry, although expanding in total, could reduce in the UK in the next 5–15 years as many countries are now well advanced in setting up local pharmaceutical manufacture, using expert support from the UK, the rest of Europe, Japan and the USA. The expertise created in the so-called developed countries is an essential factor for the success of less developed ones setting up new industries. One difficulty is to decide the standards to which they should operate, since in many instances one is facing not just a 50 year technology gap but one of 100 years.

Some of the major influences will therefore be discussed under a number of headings, i.e.

- product trends influencing pack trends
- changes and trends in packaging materials
- changes in packaging processes
- other special considerations.

Product trends influencing pack trends

As previously identified, the swing from liquid or semi-liquid dosage forms to the solid dosage form is ongoing. This does not mean that liquid products will disappear, as they are still essential for young children and the increasing elderly population, who either cannot swallow a tablet or capsule or are concerned that it may have a ‘choking’ risk. Paediatric products are, however, changing as emphasis is placed on sugar free (for the prevention of dental caries), freedom from synthetic colourings, which allegedly cause allergies, freedom from synthetic flavourings, the elimination of alcohol, and the avoidance of preservatives which may also give rise to adverse sensitising effects. This trend may slow down at some time, since materials of natural origin are not always free from adverse reactions.

Liquid products are still very popular with many OTC products, so perhaps the apparent inconvenience of measuring it out actually helps to remind the user that a dose should be taken.

Liquids are still an essential form for injectable products both as multidose and unit dose presentations. Unit dose injections which can eliminate the need for a preservative are increasingly preferred. One can therefore predict a steady trend in growth with cartridge tubes, disposable syringes and prefilled syringes. Prefilled syringes include both the single compartmental and the bicompartmental type of syringe, which is useful where the mixing of components, immediately prior to injection, has certain distinct advantages (e.g. due to shelf-life restrictions). In the area of IV solutions there has already been a significant trend away from glass, coupled with a need for administering an increasing number of additives. Prepacked additives with a means of transferring them to IV solutions by injection or via IV pack ports will therefore increase.

Although glass has been holding its own in terms of vials, ampoules, cartridges, tubes, one can predict increasing competition to the tubular glass industry which to date has not suffered in the same way as blown glass containers. Plastic ampoules produced on blow fill seal equipment are gaining in popularity, as are vials which resist breakage, especially for expensive biotechnology products.

Plastic is currently having considerable success with unit dose liquid products, i.e. ear, eye, nasal products, as an addition to the multidose products market which it captured from glass some 25–35 years ago. The unit dose products are usually presented in sticks as either preformed units which are filled and sealed aseptically, or as a form fill seal process such as the Rommelag (Bottlepack) or ALP (USA) blow, fill, seal system. Increasing competition between preformed units and form fill sealed units can obviously be predicted, with emphasis on cleanliness (freedom from particulates), high sterility, confidence/credibility and cost. Unit dose systems without preservatives appear to offer advantages over preserved systems (in fact some consider that 'unit dose' should be synonymous with the absence of a preservative system), but have to be balanced against disadvantages involving higher costs per dose plus greater storage volumes.

Although a few oral products are also emerging in unit dose packs, particularly where the absence of any preservative offers advantages (food allergy conditions), expansion in this area is likely to be limited. For multidose liquid products (oral liquids, emulsions, suspensions, local applications, etc.), plastic continues to make inroads on glass. Whereas it has been relatively easy to find suitable plastics using opaque containers (HOPE, PP, etc.), the clarity and sparkle of glass has been difficult to match economically. Although it has been accepted that no one plastic can offer the inertness of glass, particularly with reference to retention of certain preservatives, flavours and active ingredients, it is relatively easy to find a plastic which is suitable for a specific product—albeit occasionally with a slightly reduced shelf life. Under this category various grades of PETP and PETG (polyester variants) are steadily growing in use. Since under normal handling polyester is much less prone to breakage and is lighter than glass, any cost premium can be readily offset. Polyesters generally show good retention of such volatile substances as menthol, camphor, esters of salicylic acid. Coated and multi-layer plastic containers offer further potential usage for liquid products. Silicon dioxide ('glass') coated plastics are also of interest (SiO_x coatings). These are being closely followed by carbon 'diamond-like' coatings.

Solid dose medication

The past 20 years has seen continuous growth of the hard gelatin capsule. However, the 1982 Tylenol incidents in the USA identified the ease with which capsules could be tampered with, and caused a severe setback for capsule usage in the USA. The discovery of more potent synthetic drugs has also meant that tablets (and capsules) have become smaller. Film coating has partly replaced the use of thicker sugar coatings. Controlled, delayed and sustained release forms have further reduced the occupancy volume for many new products and the frequency of administration. If one adds to this the growing influence of OPD (original pack dispensing), then there is a trend and a need for smaller packs for solid dose forms both now and in the future.

Other medicinal products which influence packaging trends

Although 'targeting of drugs' is a popular phrase, certain newer drug forms are clearly targeted to or via specific areas. These include a whole group of drugs that use the lung and are presented in a fine particle liquid or powder. In these instances the pack may act as a device (e.g. a metered dose powder aerosol), or a separate device may be used, e.g. Spinhaler (Intal), Rotahaler (Ventolin), Diskhaler (Ventodisk), etc.

Dermal patches are another new trend that challenges ingenuity in terms of the material used for the patch and the packaging. In fact it is interesting to note that the theory adopted by the dermal patch, i.e. a drug is incorporated in a polymer matrix from which it diffuses out at a steady rate to penetrate (permeate) the skin, is the converse of that which is normally required for a plastic pack, where no exchange between product and pack is desired.

Growth in biologicals and diagnostic agents are also putting new demands on the pack, especially where—70°C is used.

Changes and trends in packaging materials

As changes to packaging materials occur relatively slowly, the materials which might be considered of historical value are still in wide usage. This particularly applies to the use of glass and metal, which extends back over several centuries.

A slight reduction in the use of glass has occurred in recent years, and it is likely that this will continue as a slow downward trend. However, glass is generally seen as environmentally friendly, hence this trend could reverse.

Metal containers are showing a much more serious usage drop in terms of containers for tablets and capsules, ointments, granules, powders, etc., and even survival as collapsible metal tubes is doubtful with the advent of laminated tubes. Rigid aluminium containers, other than aerosol containers, showed a rapid drop in usage some 8–10 years ago, when costs, compared with glass and plastic, became unfavourable. The conversion of bauxite to aluminium involves high energy levels. This means that aluminium is top of the recovery list in terms of the widely used packaging materials with a value of £600 to £700 per tonne when recycled (cf. glass £45–55 per tonne).

Composite containers involving laminations to board with metal or plastic ends are surviving to a degree, but use will undoubtedly be limited to a few mainly OTC types of product and possibly a growing healthcare/healthfood market. Lined carton systems incorporating foil compete with composites for similar markets.

The basic materials cited above being on the decline, the reverse can be expected for the remaining basic materials, i.e. plastic, paper and board, and films, foils and laminates.

Paper and board are likely to increase due to an expanding label market (greater quantities of smaller pack sizes) and their associated need for cartons (to give sufficient label area) for OPD products. The latter point is a contentious issue and the debate on where the community pharmacist should place the label will continue. However, if a bar code is essential (and possible) with smaller pack sizes, a carton may be the only way to combine an adequate surface area and a means of collating a patient leaflet.

Films, foils and laminates, including coextrusions and metallisation

Although OPD is not synonymous with the use of blisters and strip packs, and products will be found in small glass and plastic containers, the unit type of pack offers possible advantages, especially when the item and quantity, occupies a relatively small volume. Films and combinations of films, foils and paper as laminations, together with metallised substrates, coatings and coextrudates, etc., will all be part of an overall growth. This growth will not be related solely to thermoformed and cold formed blisters, but also to strips, sachets, overwraps, etc. and growth of shrink and stretch materials in the form of secondary packaging for warehousing and transportation. Again this may conflict with some environmental factors where composite or compound materials are difficult to recycle or reuse.

Metallisation (coatings of aluminium/oxide), which is more effective as a barrier when two materials are metallised and then laminated with the two metallised surfaces in contact, is likely to provide a better barrier than most plastic combinations (even Aclar—PVC). However, for an excellent barrier, foil of 0.025 mm and above will continue to be a popular choice as, provided the heat sealing is effective, a hermetic pack can be achieved. Lower gauges of foil down to 0.006 mm when part of a lamination incorporating a plastic ply or plastic plies also provide a high degree of protection against moisture, oxygen, carbon dioxide, etc. Although such a construction inevitably contains small pinholes, permeation through these is extremely low provided the foil layer is not stretched and/or perforated during machine handling and sealing.

Coextrusion, e.g. a process incorporating two or more plies of a plastic, will undoubtedly find more use in flexible pharmaceutical packs. Coextrudates can also be moulded into rigid containers, bottles, tubes, tubs, etc. subject to the quantities justifying the costs.

It is with some regret that in discussing plastics, one has to again admit that the glass—metal era is now in decline. In fact it can be positively stated that in the introduction of any new product, plastic now receives first consideration. Glass is frequently still used as a control in any test procedure, perhaps as a mark of respect for a material which has served the pharmaceutical industry with honour.

The history of plastics dates back to the mid nineteenth century when celluloid and Bakelite were discovered. Bakelite (phenol formaldehyde) and urea formaldehyde, both thermosetting plastics, found wide use in the pharmaceutical industry in the form of screw closures and are still used today. Although recognised as plastics, the thermosets play only a minor role as a packaging material and it was not until around 1953 onwards, when the first thermoplastics were used as low density polythene squeezee packs, that the real plastic revolution began. In 1996 five, in fact the most economical five, were the ones most widely used. These include the:

- polyethylenes (PE)—LDPE, MDPE, HOPE, LLDPE, ULDPE, VLDPE
- polypropylenes (PP)—homopolymers and copolymers of polypropylene
- polystyrenes (PS)—crystal and to some extent impact modified polystyrene

- polyvinylchlorides—unplasticised PVC and plasticised PVC
- polyesters—PETP and PETG.

These materials cover a wide range of properties, e.g. a range of densities 0.9–1.45, are clear to very hazy, hard, brittle to flexible, some virtually unbreakable; from highly permeable to ones of low permeability (with reference to moisture, gases, solvents, etc.), relatively inert to only fair inertness, etc., and all cost in the region of £700–800 per metric tonne (except PET at around £1,100 per tonne).

Changes in packaging processes

In the past 25 years there have many progressive changes in packaging processes, and several significant improvements are detailed below.

Form fill seal processes for liquids and semi-liquids

The Bottlepack system (Rommelag, Germany) and a similar process by Automatic Liquid Packaging (USA)—blow fill seal—continue to be successfully used for pharmaceutical products. These processes are now found throughout the world and container manufacturing details are covered in previous chapters.

In use they usually operate in a clean area but also with a laminar flow type hood over the moulding-filling stations. With these precautions the unit can produce sterile non-preserved products. Output largely depends on the pack size, but with a 10×2 ml stick the Rommelag 3012, 305 and 4010 M machines have outputs of approx. 4,000, 8,000 and 20,000 singles per hour. The machines also offer the advantages of very low paniculate levels. ALP has a 301 and a 303–624 with six parisons coming from a single extruder giving 24 moulds. Special machines can also insert sterile components, e.g. rubber stoppers. Machines can handle PE, PP, PVC, PET, etc.

Container cleanliness

Many years ago it was common practice to store glass containers in crates out in the open. Washing was an essential prerequisite prior to use, but today producing containers and components clean in terms of both bioburden and particulates and then keeping them clean by effective handling is rapidly becoming the norm. This is now common practice in both the glass and plastic industries and, with a few exceptions (sterile and aseptic packaging operations), washing is now rarely used. (Note that rubber stoppers are normally washed (and siliconised) at the supply source.)

Faster strip and blister packaging

Filling via slat counters into bulk packs brought speed capabilities in excess of 20,000 items (tablets and capsules) per minute, thus making small OPD type products both comparatively slow and relatively costly.

Unit dose packaging in the early years suffered from speed limitations where a maximum of 250 items per row per minute represented the best that could be achieved, i.e. the faster 4 and 8 row strip packers achieved 1,000 and 2,000 per minute (maximum) and blister packs of 8 and 12 rows, 2,000 and 3,000 per minute (maximum). Today wider webs (more rows) and higher feed speeds per row have brought about outputs of up to 7,200 in strip packs (Siebler) and over 6,000 on blister pack machines.

In addition to catering for conventional thermoformed blisters using a plastic tray and a foil-based lid, most blister machine manufacturers now offer facilities to increase moisture protection, by use of either a tropicalised blister (by an additional foil over cover) or a cold formed, foil-based tray. Considerable competition is expected between these and similar options, where a high level of climatic protection is required. The other options include blisters in sachets and overwraps to cartons. Output speeds, climatic protections achieved, overall cost and patient/marketing preference, will influence the final pack choice.

Machine efficiency has also been improved by faster change-over times (15–30 min) and trim waste has been significantly reduced.

To improve child-resistance (see BS 7236), opaque or dark tinted packs and between-pocket perforations can be employed.

Faster lines, pregauging on-line or pregauged components and tighter specifications

Years ago the pharmaceutical industry was handicapped on output speeds, cost and security by the short runs, maximum line flexibility syndrome. This has gradually changed, particularly where companies have become international or streamlining of inventories has provided larger quantities for a few companies. Small runs, however, still frequently apply to generics.

As a result of this and generally expanding sales, many companies now have dedicated lines which have moved away from 60 packs per minute to 200 to 300 packs, with better flexibility (e.g. on-line changes). High speeds have inevitably required better material control, and tighter specifications. New techniques have been introduced to negate faulty containers, components and materials either interrupting production line flow or resulting in a substandard or faulty pack emerging from the production line. These new techniques frequently involve video technology with such processes as imaging, where individual components can be matched against a standard in dimensions and the identification of imperfections. SPC is now widely applied to achieve quality improvements.

Line segregation, dedicated machines and areas, cubiclisation, cleaner areas and clean air classifications

The need for cleanliness and the trend towards producing materials clean was identified above. The onus is then on the pharmaceutical manufacturer to maintain this cleanliness throughout the packaging process. There is also a need for improvements in product security with ideally a nil risk of admixtures, incorrect labelling, etc. All these aims can be optimised by clear segregation of operations, dedicated areas, the use of cubicles, operating under positive air pressure using filtered air, with properly clothed and trained operators, etc. These factors, which are all embraced by GMP, need to be supplemented by validation procedures and total accountability, reconciliation of materials delivered to and taken away from the production area. These latter security activities may be further improved by prior label scanning/reading with a possible repeat operation on a production line using such processes as ‘imaging’. However, sophisticated equipment of this nature not only is expensive but requires more frequent validation. End of line inspections are therefore receiving increased attention, as are ‘isolation’ units for sterile/aseptic packs.

Packs and devices

In introducing product trends which could influence the pack, drug targeting was identified as an important factor. In this targeting activity, packs can be identified with an administration role or packs may be tailored to more readily fit an actual device (see Appendix 17.1).

Examples of this include metered dose pump systems, which to some extent are replacing the well-established nasal squeezee pack.

Powder inhalation devices are currently proving very popular, in spite of the fact that patients generally prefer metered dose aerosols. However, this preference is counterbalanced by the fact that compliance is much more difficult to achieve with aerosols. There is also a third category where the pack and the device are totally independent, e.g. a unit dose of nebuliser solution which is subsequently transferred to a pressurised or an ultrasonic nebuliser unit for delivery to the patient.

Other special considerations

There are occasions when demands or considerations related to a pack conflict. This applies to some of the general observations listed below, and in certain instances an acceptable compromise may be difficult to achieve.

Tamper-evidence

The 1982 Extra Strength Tylenol incidents have had worldwide repercussions. Demands for a totally tamper-proof pack are difficult to achieve, certainly economically. Even so it is reasonable for a patient or user to expect that none of the product has been removed, substituted, diluted, contaminated, etc. Tamper-evidence is therefore both advisable and justifiable for pharmaceutical products provided the recipients do not expect it to safeguard them against the ingenious adulterator out to do mischief against ‘life and limb’. However, the pharmaceutical company should not be liable provided reasonable steps have been taken to safeguard the patient under normal conditions. Freak conditions, as created by the maniac, are virtually impossible to safeguard against and prevent. The use of the word ‘tamper-proof’ is therefore not advised, but ‘tamper-evident’ and ‘tamper-resistant’ are accepted expressions.

Child-resistance

Child-resistance as such must receive everyone’s support. However, child-resistance can frustrate the elderly, infirm, poor of sight, aged, arthritic, to a point where the product is transferred to an alternative (unsuitable!) pack, or the closure is never adequately replaced. There is therefore a need to recognise these problems in a growing elderly community and to find an acceptable solution. Effective answers to this, have to date, been complex and expensive.

It should be noted that the guidelines issued by the (UK) Pharmaceutical Society and the Association of British Pharmaceutical Industries (ABPI) on OPD indicate that packs should be both tamper-evident and child-resistant.

Security coding

There are many ways in which packed products can be security coded: edge slits, coloured edges, printed edges, punched hole codes, bar codes, colour bar codes, ink jet codes, laser codes, just to mention a few. Most manufacturers operate to some coding system which frequently adds to the total 'wording' complexities. Although bar codes plus scanning or imaging appears the simplest long-term answer, on-costs will play a significant part in any ultimate decision or solution.

Labelling—self-adhesive labels

Although 10 years ago the US pharmaceutical industry predominantly used heat seal labels, the UK was rapidly moving to the more expensive self-adhesive labelling systems. Since Europe is now predominantly using self-adhesive, there appears to be an international trend even though it is a more expensive label process. It has the advantage, with the correct choice of materials, that it will adhere to most substrates.

Lower microbial limits and lower particulates

The need for higher standards of cleanliness and hygiene has already been mentioned. Since the safety factors for aseptic processes and terminal sterilisation processes rely on a low initial bioburden, attempts will continue to minimise contamination. Packaging manufacturers of materials, components and containers will therefore slowly adopt GMP procedures currently found as part of the 'Orange Guide' in order to lower both bioburden and particulates. Cleanliness and improved hygiene are an order of the day, in terms of facilities, procedures and training.

Sterilisation methods

Although sterilisation methods may initially appear to be well documented, there is a need to review how each may change both the physical and chemical properties of packaging materials, containers and components.

This entails residues related to ethylene oxide sterilisation, and physical and chemical changes when gamma irradiation or accelerated electrons are employed, particularly when plastics are involved. It should be noted that plastics include lacquers, enamels, certain adhesives, etc. Surface analysis is emerging as a critical evaluation for any 'treatment' process. The need to establish the purity/impurity of packaging materials will also become necessary for most sterile products.

The need for cartoning, leaflets and packaging inserts

The USA, which is not OPD-oriented, has during the past 10–15 years moved away from the use of cartons, and leaflets have been attached to the primary pack by banding or adhesives. Although these means of attaching leaflets are available in the UK and the rest of Europe, the greater use of blister and strip pack and reluctance to change tradition should retain the carton for at least the next 5–10 years. If the move to OPD is accelerated, then a substantial growth in the use of cartons and patient (information) leaflets can be predicted. This will mean extra business for specialised printing industries, which have the security/GMP aspects of pharmaceuticals well covered.

Batch and expiry dating

Batch coding is not new, but expiry dating is essential for virtually all forms of pharmaceutical packs. However, when and where this is printed will be an interesting topic, with ink jet printing and possibly laser printing being some of the main contenders for an on-line production operation. Laser printing, which burns off colour/printing/decoration, should be coupled to vacuum extraction for safety reasons. The legibility/clarity of debossing and embossing codes is constantly being criticised.

In-house printing

It has already been mentioned that many pharmaceutical companies serve an international industry, thereby contributing to the balance of import/export payments. Since exports frequently demand different print layouts, and one or more languages in the text, there have always been problems associated with small print runs. In-house printing is expected to increase either as a separate printing operation away from the production line or as an on-production line process. Although several printing

processes can be employed, hot die stamping and thermal printing, which gives good quality print, quick drying and reasonable freedom from rub and smudging, is currently leading the field. Letterpress, direct and offset, and flexographic printing are also employed. The advent of DAR (digital artwork and reproduction) is making a major contribution to faster origination.

Bar coding

Bar coding, coupled to scanning and the use of computerised data/record keeping, can serve several purposes from security aspects, stock keeping and accountancy to data retrieval (i.e. product information etc). With products which are sold via various outlets (community pharmacies etc.), the EAN or ANA code is an obvious choice. This is, however, frequently used in addition to the PIP code which was introduced by the National Pharmaceutical Association (NPA) some 20 years ago. The EAN code suffers certain weaknesses if it is to form part of a security code, and this problem may be resolved by better reading equipment or the introduction of a more user friendly code system. Coding therefore remains a highly debatable topic, with little chance of standardisation immediately in sight.

Computer dispensing and costing

The OPD guidelines have requested the use of the EAN code for stock control (hospitals and retail) and as a simplification for the UK Pricing Bureau where a peelable code is transferred to the prescription (form FP 10) for pricing and reimbursement to the dispensing pharmacist. The fact that other European countries have used a similar system (e.g. the Vignette, France) which was introduced many years ago does not necessarily mean that it is ideal for tomorrow's technology. Rapidly expanding computer technology could therefore bridge the gap and benefit the doctor and community pharmacist, by use of electronic transfer systems.

Original pack dispensing (OPD) (now termed 'patient packs')

In any attempt to discuss future trends there must be at least a few comments on this subject. Guidelines have been agreed between the Pharmaceutical Society and the ABPI, but the most contentious issue still derives from the 7 versus 10 common denominator for solid dosage forms. Argument has been put forward for the preference of multiples of 7 (7 day week), 4 week (28 day/month etc.) whereas other parts of Europe are based on 10s. Since multiples of 10 appear more prevalent in Europe, why do we have such an insistence that UK OPD can only relate to a unit of 7? Having a pack size suitable to take a label measuring 70×35 mm also causes problems, particularly as tablet/capsule sizes get smaller and fewer doses are needed per day with delayed and sustained release products. Of course there are ways of achieving an area of 70× 35 mm, i.e. use blisters or strips in cartons or prohibit the use of container sizes below, say, a 40 or 50 ml capacity. Australia achieved this through a minimum pack size of 35 ml. This could, on some occasions, find seven tablets of small dimensions occupying only, say, 5–10% of the container volume. This raises questions as to whether it be filled with cotton wool, and whether the high space to volume changes product stability aspects, etc.

Although there are other, less contentious issues, the proposed changes inevitably introduce on-costs to the pharmaceutical industry, the wholesaler (initial costs have been given) and possibly the community pharmacist.

Controlled dosage systems (also called monitored dosage systems)

Controlled dosage systems are basically aimed at use by the elderly, infirm, or partly infirm, poor of sight, arthritic, as an aid to improving medication compliance. Doses or dosages of medication are enclosed in individual sealed compartments on a card, or in multiple blister packs, usually with a medication identity code (heart tablets, water tablets, etc.) together with clearly written instructions as to when each medication should be taken (day 1, 2, 3, etc. plus times, e.g. morning, afternoon, evening). These systems, of which there are now many, are already operating in the USA, Canada, Australia, Holland, and other places. However, they somewhat cut across OPD philosphies, particularly if a country is 100% OPD, since the quantities prescribed have to be transferred from bulk to the system which is then labelled or printed with the directions, solid medication codes, patient's name, etc.

The recent successes with these systems indicate that they should increase in use, subject to costs being acceptable.

Conclusions

It is evident that no pack is perfect or ideal (some are undoubtedly better than others), hence all packs are a compromise involving consideration of many factors—some of which are conflicting. The number of factors which need this consideration constantly increases.

Packaging has now come of age and packaging expertise, combined with packaging technology, should receive the highest respect. This is essential if the most effective compromise is to be reached between those involved with such decisions, e.g. marketing, medical, production, regulatory. For this purpose a packaging co-ordinator who provides an overview is becoming increasingly essential.

GMP is not simply the 'Orange Guide' and the interpretation of it, but ongoing improvements in pharmaceutical quality. This means more control over the total packaging function and a greater use of computerised data, records and information.

The packaging technologist must remain aware of the environmental issues, not because pharmaceuticals are a large user compared with food, beverages, household items, etc. but because it is known to be a caring and responsible industry—hence it could be prone to attack. This risk is increased by the fact that many companies use 'care' titles, e.g. healthcare, skin care.

Pharmaceutical packaging is very intense and the clearance of the primary pack (the packaging components in contact with the product) involves in-depth knowledge of product and packaging materials, including highly sophisticated testing procedures. Changes to the primary pack are therefore expensive. As the industry often over-packs in terms of the secondary packaging which covers warehousing and distribution, this is one area where cost savings can be achieved, without re-submission of data. Materials, space utilisation and handling methods, when studied together with computerised records, should therefore warrant investigation as this has until recently been a neglected area in the packaging chain.

Thus if we repeat the initial definition of packaging—'Packaging is the means of economically providing protection, presentation, information, identification, convenience, containment, and compliance for a product during storage, distribution, display and use'—the complexities of what this simple statement entails will now be better appreciated. In the hands of an expert, everything looks simple. Packaging is now an advanced technology where training is achieved through experience as there are few books on the topic, and even where there are they rapidly become, at least in part, out of date.

The writer would like to stress that making predictions is becoming increasingly difficult, because of general consumer pressures (i.e. a more aware and critical general public) and the environmental/ecological issues.

The USA and Japan are using more and more coextrusions and what might be termed composite materials, consisting of layers of various materials. Such materials are increasingly being criticised by the environmentalists in Europe as they are difficult to reuse or recycle (except as the scrap for the conversion process). Several years ago one would have predicted an enormous future for these composite materials, but whether they will have a future is now becoming a serious question.

There is a call for the use of single effective materials. Predictions were made for plastic coated glass and silica (glass!) coated plastics. Does this mean that the future for glass and/or plastic will change? If plastic coated glass becomes widely used, does this mean that special equipment is required to eliminate the plastic from the cullet or are expensive 'scrubbers' to be added to all glass furnaces so that the plastic can be 'burnt off' without the emission of suspect gases into the atmosphere? Does this also mean that the material used in the sophisticated versus Third World countries will become significantly different, i.e. could one predominantly use glass while the others predominantly use plastic?

Consumer pressure (other than environmental issues) are highlighting needs for higher quality, convenience in use, restriction in so-called overpackaging, the need for special packs (which are easy to open and reclose) for an increasing elderly population, etc. The last of these may conflict with child-resistance, tamper-resistance, tamperevidence, etc. and provide even greater conflict if coupled with environmental concerns. What is the future?

Ten years ago or so the USA led the world in the removal of 'cartons', with labelling systems combining leaflets or shrink/stretch sleeving in which a leaflet could be retained. It was predicted that the rest of the world would follow the USA. Today there is a move back to cartons for a number of reasons: improved stacking, space reduction, all-around recognition, better presentation coupled to good graphics, and as a means of retaining/collating a packaging insert/leaflet.

Trends therefore tend to follow cycles, emotive issues and consumer demands, which may be logical or totally illogical.

Packaging, which was earlier company-oriented, is gradually moving through national and international trends. These trends are divided according to what can be afforded in the developed and developing worlds. At one extreme packaging can be costly, complex, and sophisticated, while at the other the key phrase is minimum cost.

The effectiveness of the treatment is now being judged by the total cost of a disease/symptom and its treatment. This involves not just the cost of the packed medication but the cost of the GP, improved (specialist) diagnosis, reduced hospitalisation, etc. A pack involving an improved mode of delivery at a higher cost may therefore be the most effective form of treatment. This is found under the broad heading of 'disease management'.

While some trends come and go, others, related to GMP/CGMP, security and integrity, intensify. This also applies to legal issues which extend as law, directives and guidelines (FDA, ICH, EU, etc.). Counterfeiting or 'pass-offs' are one of the current concerns, and no doubt this trend will result in increased technology and improved practices.

ICH guidelines which define climate conditions for formal stability tests give a greater challenge to the pack and make the assumption that prior to formal stability the pack has been thoroughly challenged. Both these put a greater responsibility on the packaging technologist in terms of the test used and the conclusions reached. Packs must therefore be better challenged using both the ICH and other conditions. The latter should include those aspects which are not effectively covered by the ICH guidelines, as packaging people were only 'indirectly' consulted when the guidelines were devised. Some of this information can be learnt from directives, and guidelines related to devices (see Appendix 17.1).

Appendix 17.1: Packaging and medical devices

In some companies packaging and medical-pharmaceutical devices share areas of development and evaluation. For example, most devices are made in plastics using injection moulded components, which have factors common to closures and certain types of container. However, directives on medical devices tend to be ahead of those on packaging, hence packaging technologists should be conversant with the directives, if only to consider whether they can or cannot be applied to packaging. The device related directives are as follows:

- Medical device directive (MDD) 93/42/EC
- Active implantable medical device directive (AIMD) 90/385/EC
- In vitro diagnostics directive (IVD).

The MDD covers four classes of device:

- Class: I Low risk devices
- Class: IIa Selected medium risk devices
- Class: IIb Selected medium risk devices
- Class: III High risk devices.

Typical Class I devices include powder delivery systems to the lungs such as the Spinhaler, Rotahaler, Diskhaler, spacers which are used in conjunction with a drug and are part of a drug submission. Typical Class IIa devices include power operated nebuliser systems which are usually sold separate to the drug.

The amount of detail for approval of the device increases from Class I to Class III. In the UK submission of data and subsequent approval is through the Medical Device Agency (MDA). Devices have to be independently assessed by MDA Notified Bodies, which on approval can issue the authorised CE mark; this allows unrestrained distribution across Europe.