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FOR THE PHARMACEUTICAL INDUSTRY

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ALGERIA

Technical report: Opportunities for plastic materials in the Algerian pharmaceutical industry*.

Prepared for the Government of the Democratic and People's Republic of Algeria by the United Nations Industrial Development Organization

Based on the work of Mr D.A. Dean, expert in the production of pharmaceuticals packaging materials-plastic

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I. SUMMARY

1. It can be positively stated that plastics and plastic technology will be available in the next 5-10 years to a point where there is the capability of packaging the majority of pharmaceutical products in plastics. Occasionally this will involve the combination of plastics with other materials, e.g. foil.

2. The majority of the plastics which will be used either on their own or in combination can be identified today. The main groups include the polyethylenes, polypropylenes, polyvinyl chlorides and polystyrene for which manufacture is ongoing or proposed in Algeria. There are also plans for polyester, the fastest growing plastic.

3. The current technology on plastics and knowledge of processing (conversion), design, decoration and testing procedures for product suitability are to a large degree lacking in Algeria at present. This applies not only to pharmaceutical packaging in plastics, but packaging in general.

4. Acquisition of adequate technology which is defined in the report should, with the purchase of conversion equipment, allow the plastic industry to rapidly develop and expand initially using imported polymers followed by Algerian-produced plastics of an adequate specification. Period 1988 onwards.

5. Following 4. a phased programme associated with pharmaceutical, foods, toiletries, cosmetics can be programmed and actioned. Recommendations for the packaging of pharmaceuticals over the 1990-2000 period have been detailed together with initial quantity predictions.

Production could be associated with an industry (producing in the same pharmaceutical factory) or producing in special factories.

6. It must be stressed the whole development programme not only depends on technical input in terms of quality and quantity but financial support to

meet the growing demands for factories with high quality equipment and adequate quality control procedures. Recommendations must be constantly reviewed in a time of fast changing technology.

7. Although plastics can be divided into thermoplastic and thermosetting polymers the vast majority of plastics for packaging fall into the thermoplastic group. Thermosetting plastics currently have few applications except for some closures. They have therefore to be excluded from the report although factories to produce phenol, urea and melamine formaldehyde currently exist in Algeria.

An Over Rider

Although background knowledge on the chemical and physical properties of a plastic before it is used for packaging is a pre-requisite, specialistic information which coordinates plastic and packaging technology is equally important. Having expertise in one without the other will re-expose the problems and the learning curve which have been experienced by other countries in their efforts to progress plastics and packaging. If this combined knowledge can be obtained, this will enable Algeria to cover in 10 years where other nations took 20 years to identify and solve problems in order to progress to where they are today.

A too scientific approach which relies heavily on laboratory tests and experiences can also be restrictive to progress as the results achieved by a production operation followed by distribution, sales etc. may give entirely different results.

Thus to achieve success in plastic packaging all activities from the polymerisation of the plastic - right through to the final use of the product - must be identified and studied. This rather pragmatic approach is absolutely essential if the technologies of plastic and packaging are to be fully commercialised.

II. AN INTRODUCTION TO PHARMACEUTICAL PACKAGING WITH PARTICULAR REFERENCE TO PLASTICS

A primary function of the pharmaceutical industry is to cure or alleviate suffering or disease. As many products are likely to generate some secondary or side effects, it is important that the balance is clearly in favour of the effectiveness of the drug and that any secondary effects are kept to a minimum in terms of both the product and its immediate pack. The pharmaceutical industry therefore devotes considerable time, effort and money to ensure that the pack more than adequately meets its primary function of economically providing, presentation (and user confidence), information/identification, protection against ingress and egress plus compatibility between the product and the pack, and user convenience (to assist compliance), until such time as the product has been totally used or administered. As this definition of a pharmaceutical pack has to cover storage transportation, possible display plus a final use period it is normally required that a shelf life of 2-5 years is essential and that this is supported by in depth testing. The Pharmaceutical Industry therefore requires in most instances a level of safety which is superior to that required of a foodstuff. This is of obvious relevance when one considers that medicaments are usually taken when a person is exhibiting symptoms of illness, hence any additional side effects are not only undesirable, but against the general interest of public health.

Although glass and metal have traditionally been used over a long period for pharmaceutical products, it should not be assumed that they are inert or that they are ideal materials, since all types finish up as a technical-commercial compromise. Glass for instance is heavy, particularly hazardous when it breaks and alkaline glass can readily alter the pH of non buffered aqueous solutions. The drastic increase in the use of plastic has frequently been associated with use convenience features (such as squeezability, collapse to restrict the ingress of air, bioburdens, etc.), a more psychologically acceptable image, the greater ability to produce packs and devices in functional and complicated shapes (not achievable with other materials), involving less weight and frequently with lower volumes, and last but not least, at economically acceptable prices.

New concepts (transdermal devices, implants, IUDs and delivery systems) which would have been impractical with other materials have further assisted the progress of plastics and the pharmaceutical industry.

Thus when it comes to new pharmaceutical products, plastics stand an extremely high chance of being used in spite of certain reservations on permeability; none are totally inert and the fact that special technological knowledge has to be acquired in order to ensure their success.

It therefore follows that during the past 35 years there has been a gradual but significant movement away from the use of the more conventionally established materials, e.g. glass, metal, paper and board, to a point where plastic is not only the preferred choice but is in many instances the more economic approach. As pharmaceutical products also show a substantial growth in the quantities needed and sold, plastics now hold a strong position as the prime packaging material.

Whereas plastics did initially have certain negative features which at one time tended to be restrictive to some usages, these have today been either largely overcome or put into their correct perspective. As a result of this, coupled with rapidly advancing plastics technology, it could be predicted that 99% of pharmaceutical products could be packed in plastics by the next 5-10 years. Whilst this does not immediately mean that conventional materials are obsolete, it does indicate that plastics must be considered every time an opportunity arises (i.e. change of equipment, unfavourable price rises with other materials, etc.).

Having made the above positive statement indicating the long term capability of plastics, the objectives of this report are seen as:

a) to identify those plastics (particularly of internal availability) and packaging processes which can be used for selected product groups.

b) to identify selective areas where packaging in plastic offers technical advantages and could replace materials and processes which currently largely rely on imports (glass, metal, etc.).

It is noted that the social-economic acceptability for each of the above has to be fully investigated. In several examples it is recognised that if a high speed line has or is about to be introduced for, say, the packaging of glass ampoules and glass vials, it would not be economic to change this to plastic until a reasonable usage of the machinery had been achieved (cost versus depreciation). Thus, although a change to plastic can be recommended, the final decision must be related to local conditions.

III. INTRODUCTION TO THE USE OF PLASTIC PACKAGING MATERIALS FOR CONSUMER GOODS (OTHER THAN PHARMACEUTICALS)

Since high attention to detail is required for pharmaceutical packaging in terms of safety (no side effects, no increase in toxicity or irritancy, excellent compatibility with the product giving no or only limited product degradation), it follows that food packaging shares much in common with pharmaceuticals. This also applies to a slightly less extent to toiletries, cosmetics, veterinary products, etc. As the food group is usually 8-12 times the volume of pharmaceuticals, it usually follows that pharmaceuticals use plastics acceptable for food use rather than the converse. The combined uses of the product groups mentioned above demand very large quantities of plastics. These quantities can further be extended by hardware, household, horticultural and agricultural products, chemicals, car care products, etc.

The proportions of plastic used by the above groups can be obtained, as a guide line, from current European analyses.

IV. THE NEED FOR A TECHNOLOGICAL BACKGROUND REFERENCE THE PHYSICAL AND CHEMICAL PROPERTIES OF PLASTICS

Plastics consist of groups of material which widely differ in the way they are produced, their chemical and physical properties, how they are subsequently compounded and converted into suitable forms of packaging.

Pharmaceutical packaging needs to have a detailed definition (specification) for each plastic proposed, as safety, effectiveness (of the product), uniformity, integrity, reproducability must be controlled if a satisfactory product with a clear shelf life profile is to be maintained.

This can only be achieved with an adequate specification, coupled with adequate initial stability tests followed by ongoing checks on quality (quality control).

Although the properties of a specific plastic (polymer), can be broadly defined under physical and chemical parameters, the ultimate suitability of the plastic used depends to a significant degree on the polymerisation process, the compounding stage (what other ingredients are added), the final converting process and the product formulation.

Syrups, for example, should generally be satisfactory in high density polyethylene but the ultimate proving of this statement depends on the preservatives and flavourings employed, as either of these may absorb or adsorb to some degree into or onto the plastic. The final question must therefore relate to whether these apparently or possible minor adverse effects are acceptable. In this example acceptance tends to be a judgement as well as a scientific opinion.

It can therefore be concluded that technological expertise in plastics needs to be supported by commercial judgement and that continuing contact with other international expertise is recommended to achieve this. A too academic approach may suggest that glass is always preferable with regards to

compatibility particularly if the severe disadvantages of glass (weight, fragility), are ignored.

Technology must also include expertise in design, mould making, printing and decorating. Lack of attention to details in any of these areas can otherwise lead to a pack which either will not be aesthetically acceptable or will not adequately provide protection of the product.

A summary table (Annex I) provides a broad indication of the general properties of the more widely used plastics.

A paper "Packaging and Plastics" is also attached (Annex II).

V. THE AVAILABILITY OF PLASTICS WORLD WIDE AND IN ALGERIA

Currently a large proportion of the plastics used are imported. Whilst this means that any plastics can be selected and the grades available are infinite, the long term standardisation on internally produced material and grades must obviously be recommended.

World wide the most economical thermoplastics are those which are most used and most readily available. At this moment in time these are:

a) The polyethylenes (PE)

Low density (LDPE)
Medium density (MDPE)
High density (HDPE) and more recently
Linear low density (LLDPE)

b) The vinyls (polyvinylchloride) (PVC)

Unplasticised polyvinylchloride (UPVC)
Plasticised polyvinylchloride

c) The polystyrenes (PS)

General purpose or crystal polystyrene (GPPS or PS);
acrylonitrile butadiene styrene (ABS), styrene acrylonitrile (SAN), may come under this heading but are significantly more expensive.

d) The polypropylenes (PP)

Polypropylene homopolymer
Polypropylene copolymer (usually with ethylene)

e) Polyesters (PET)

(Available as PETP and PETG (Kodak))

Note: Polyester is significantly higher in cost than the others.

All of the above find major usages for many types of mouldings including bottles and closures, films and in combinations (laminations and coextrusions) where they may be additionally associated with foil and/or paper and other more expensive plastics. Of the latter polyvinylidene chloride (PVdC) is particularly useful (excellent moisture/oxygen, compatibility, barrier and a good heat sealant). Others include polycarbonate (PC), polyamide (PA - nylon), ethylene vinyl alcohol (EVAL*, EVOH), ionomer (Surlyn*) * trade names, etc.

Study of the plastics available or likely to be availale in Algeria reveals.

1. Low density polythene - available in a limited number of grades

2. Polyvinyl chloride - available in a limited number of grades

3. High density polythene - programmed for 1986-90

4. Polystyrene
5. Polypropylene
6. Linear low density polyethylene

) under constant review - production intended within the next 10 years

7. Polyester - under a further review since this is now the world's fastest growing plastic.

The above provides an excellent basis for the growth of plastics for a wide range of outlets. To penetrate the largest markets (food) and to be suitable for the smaller pharmaceutical market, requires further study so that specific grade requirements can be identified with the maximum degree of standardisation.

Grade limitations and adequate quality standards may initially be restrictive to growth. However, initial purchase of materials from overseas coupled to expansion in compounding, converting facilities should build up expertise to a point where internally produced plastics can gradually be phased in.

As detailed previously, this requires additional training in plastics' technology (polymerisation, compounding and conversion) packaging technology as well as adequate control (quality control) facilities for all these activities.

Since plastic compounding and conversion processes (into packaging materials) are relatively easy and economical* to instal (compared with glass) this will further encourage the rapid growth of the plastics market. It should therefore be possible to expand at a greater growth rate than that seen in the USA, Europe, etc. provided the technological training is maintained.

* Note - a single extrusion bottle blowing machine can be installed in an area of 8 by 10 metres at a cost of £120.000** plus support building and have an output of 25,000 bottles per day based on a 24 hour day. Compare a glass manufacturing area 100 x 200 metres output 200,000 units per 24 hour day but an investment cost of £35 - 40 million - and in a fixed location without reference to the substantial weight/volume differences which are in favour of plastic.

** Includes ancillary services like pressure and cooling as well as electricity.

Although outputs can be quoted from any type of machine the final cost of a single item (bottle) will vary significantly depending on the machine chosen in the first instance and the number of cavities in the mould.

The example below covers an injection moulded screw cap.

Machine	Number of cavities	Tooling cost	Output per hour	Machine cost	Unit cost
A	2	£ 1,500	1,200	£ 3,000	X
B	4	£ 2,700	2,200	£ 5,500	.7 X
C	8	£ 5,500	4,500	£20,000	.5 X
D	16	£ 9,000	8,000	£35,000	.4 X
E_1	32	£17,000	15,000	£60,000	.3 X
E_2	32	£25,000+	20,000	£60,000	.25 X

+ with hot runners and fully automatic removal.

It can be seen that higher investment either generates a lower cost item or permits more rapid recovery of the investment cost. However, these figures will only be achieved if the most acceptable (for the process) grade of material is chosen. Use of substandard or incorrect material could drastically change the economics expressed above.

VI. A REVIEW OF THE ALGERIAN PHARMACEUTICAL INDUSTRIES - OPPORTUNITIES IN PLASTIC PACKAGING

The introduction indicated that the majority of pharmaceutical products could, with the growing plastics technology, be packed in plastics within the next 5-10 years. Since much of this technology is already available, certain product groups can be identified where plastics are either already used or could be recommended. These are now reviewed and the plastic options identified. From these options, positive recommendations, subject to approval by some testing scheme, can be made.

These options are discussed below:

1. Tablets and capsules (solid dosage forms)

Although the major worldwide trend is towards multiple unit dose packaging (blisters or strips), packaging in bulk (for dispensing into smaller quantities) or multidose original pack (OPD - Original Pack Dispensing), all remain options. Each of these are viable in plastics. Each option must be economically and socially evaluated for an ultimate decision. Certain generalisations are considered,

i) Blister (and strip packs)

Blister and strip packaging machines can pack at between 2000-6000 (blisters) and 800-2400 items (strips) per minute. Blisters are subsequently packed into cartons, bags or sachets and strips in cartons, or catch covers. Depending on the output speeds, blisters tend to be more economical when 50 or less items are packed and when compared against a multidose container.

Although the blister can be made from a number of materials, PVC or PVdC coated PVC remain the preferred options. As PVC and PVdC coated PVC are still permeable to moisture a small number of moisture sensitive products may be unsuitaole in a blister pack unless suitably

overwrapped. This overwrap may be a sachet or a carton film overwrapped with a material like PVdC coated polypropylene. Alternatively, a cold formed foil blister or a paper/foil/polyethylene strip pack could be employed. Both of these are capable of providing better protection than a glass bottle. (Possible problems associated with opening and reclosing).

(ii) Bulk or Multidose (original pack)

Polypropylene or high density polyethylene containers of adequate wall sections are recommended. Closures (in plastic) may be tamper evident and/or child resistant.

Recommendations

i) Blister packaging with PVC or PVdC coated PVC and foil soft 18 - 20 micron + heat seal coating plus suitable overwrap.

Foil blister or foil strip pack for highly moisture sensitive products.

or

ii) If multidose packaging required containers of polypropylene or high density polyethylene. (Note this form of packaging may eliminate the need for a carton by using shrink wrapping in trays.) Trend in UK for generics.

2. Large volume parenterals e.g. intravenous solutions

A substantial part of this market is now in plastic instead of glass. However, the type of plastic used and the design of the container remains a contraversial subject since a compromise has to be reached between pack weight, clarity, collapsibility, the way used (with or without additives), risks of particulates and extractives and the process of sterilisation employed.

Containers are therefore divided between those which are preformed and then filled as a separate operation and those made as a form, fill, seal operation.

Preformed containers may be made of plasticised PVC (good collapsibility, possible high evaporation losses, high clarity, needs specific autoclaving procedures, relatively costly to produce, somewhat difficult to keep clean, some extractives but risk considered low).

Polypropylene (collapses with difficulty, low evaporation loss, poor clarity unless orientated, costs fair, easier to keep clean, low on extractives, less autoclave problems but special procedures needed to prevent distortion).

Polyethylene (LD, MD, HDPE)

Containers become more rigid and less clear LDPE⟶HDPE. Lower permeability, ease of autoclaving also follows LD⟶HD.

Discussion

PVC has greatest design options in terms of 'ports' or possible opening areas. All of the above need special areas for manufacture (as containers), special packaging and the minimum of handling so that particulate contamination risks can be minimised. All these precautions add to the cost of the preformed unit.

Form Fill Seal

One company, Rommelag (Germany and Switzerland), produces specialised equipment called Bottelpack which is widely used for LVPs on a world-wide basis. The machine, which is presterilised by high pressure steam melts a plastic granule, moulds it into containers (cooled in a mould), which are then filled and sealed (with or without a rubber stopper) under Hepa filtered air using a double (0.2 micron) filtration of the product. The unit produces, usually in LDPE, a sterile, low particulate product. However, Regulatory Authorities still require a final steam autoclave

operation so that sterility can be ensured.

Discussion

Of the packs detailed above PVC (plasticised) is generally preferred by hospital staff although the Rommelag system is widely accepted as it is generally the lowest in particulates and can be more economical than glass, especially in terms of rejects.

Although Rommelag equipment is expensive, the costs related to the handling of preformed containers usually justify the purchase of this equipment. As with all sterile products which are produced aseptically, a clean area for installation is required. Plastic LVP packs require the use of a balanced or over pressure autoclave, when steam autoclaved.

Recommendations

Rommelag Bottel pack equipment is the process of choice using LDPE.

Although the preformed container (PVC) may have advantages the precautionary handling procedures are difficult to maintain and the system is never free from extractives or particulate contamination. Mr. Muerc (Ciba Geigy) also supports the Bottelpack system. The Bottelpack system is particularly economic if extended (double shifts) or 24 hour shifts are worked. Ideas on layouts particularly for the production of bulk solutions will be provided by Rommelag depending on the outputs required. Machines will give 1 to 5 M units per year depending on hours worked and the type of machine (301 or 305).

3. Ointments and toothpastes

At present the metal aluminium tube (lacquered internally if necessary) offers some positive advantage, i.e. ease of closure, collapsibility in use, non-permeability, etc. which is difficult to achieve with plastic. Polypropylene plastic tubes (coated internally or externally) could provide adequate protection provided the lack of collapsibility is accepted.

Specialised equipment is necessary for the sealing of such tubes fast and economically.

The preferred alternative, now widely used for TOOTHPASTE, is a laminated tube which includes combinations of plastic and foil. This gives a reasonable degree of collapsibility and good product protection. This concept requires special laminating, injection moulding equipment (for the nozzle) and make up equipment. In some designs (tapered tubes), it is possible to nest* the tubes, thereby saving storage space on incoming materials.

* i.e. like a telescope.

Recommendations

Currently remain with aluminium but maintain an awareness of the long-term possibilities in lacquered or coated plastic (PP) or laminated tubes as both are capable of economically replacing metal.

This applies both to toothpastes and pharmaceutical ointments.

4. Double-ended glass ampoules for special oral products

DE glass ampoules have remained economical due to the low cost of the materials and the high speed vacuum filling operation. Althouth they have remained well accepted by users, the cut finger risk during opening and breakage in production and transit are negative features. Two alternatives are a plastic bottle of 100 ml, i.e. 20 x 5 ml (using HDPE or PP) if acceptable by the consumer or a plastic 5 ml ampoule. Longer term use of coextruded 100 ml bottle is a further option should additional protection be required against oxygen permeation and vitamin degradation. (EVAL layers are now widely used as an oxygen barrier layer or a coating of PVdC).

Plastic ampoules can be produced as sticks and filled at relatively high speeds++ or Rommalag bottle pack could be considered. A flow pack of polypropylene - PVdC containing say 2 sticks of 10 ampoules would control oxygen ingress.

++ Cioni Italy offers speeds up to 24,000 units per hour.

Recommendations

100 ml plastic bottles is an option but needs investigation for marketing acceptance.

Plastic ampoules should be regularly reviewed as a long-term option using LDPE (or PP) with an additionally protective overwrap. If DE glass ampoules are retained replace board tray with PS tray (as at Medea).

5. Powders - internal and external

Subject to testing both HDPE and PP are suitable candidate materials either as plastic containers or as composites (in combination with paper/foil or metal). Costs for these alternatives and availability need checking. Injection moulded polypropylene containers with sprinkler inserts are widely used for external powders and polypropylene containers with tamper evident (peel off rings) for oral powders. Coextruded packs are an additional possibility.

6. Effervescent tablets

Options are a strip pack using paper/foil/polythene or an injection moulded (1 to 1.5 mm wall section) HDPE or PP tube. The latter may use a closure (plug) incorporating a desiccant.

Both the HDPE or PP tube may be externally coated to further reduce moisture permeation.

Recommendations

Plastic tube technically preferred (should have lowest cost) but strip pack with foil provides best protection. Strip pack has an advantage that it can be sold in different sizes and user can detach tablets for carrying around for daily or emergency use.

7. Injection vials and ampoules

Glass injection vials and ampoules usually require neutral (type I glass) which is expensive and very special moulding operations from tubular glass in order to retain the dimensional tolerances necessary for high speed handling.

Although glass is likely to remain the preferred option for the next 5 years moulded plastic vials in HDPE and PP are gradually becoming more accepted. Water for injection is already available on a small scale in plastics but is expected to expand rapidly. These ampoules may be preformed as sticks then filled or produced by a form, fill, seal process.

Recommendations

Plastics will slowly replace glass with significant inroads being made in the next 5-10 years. It is advised that the economics and advantages of plastic are constantly reviewed.

8. Suppositories

The availability of relatively specialised equipment tends to restrict the choice between foil/sealant and PVC/sealant.

Choice depends on appearance, protection, and output speeds, etc. with Sarong equipment leading the field.

The foil pack is preferred in terms of protection whilst the PVC blister

usually provides for a better looking product.

Recommendations

Choice to remain as at present. PVC blister or foil/heat seal.

9. Liquid products including syrups

Most liquid products including syrups are capable of being packed in either HDPE or PP bottles; HDPE is marginally the better in terms of "protection". The exclusion of light if not achieved through the use of a carton may be obtained by suitable pigmentation, fillers or if acceptable U.V. absorbers.

Recommendations

Liquid products, subject to adequate clearance testing should be capable of being packed in plastic containers, HDPE or PP. HDPE is marginally preferred.

10. Sacheting of oral liquids

A bulk pack using an HDPE plastic bottle, if socially acceptable, is more economic than a sachet. It also saves space.

Recommendations

Use a bulk pack as per liquids; alternative - consider other sachet materials using different combination of plastics. Long-term metallized plastics may be a suitable option for a sachet.

Conclusion

Any introduction of the above recommendations needs a phasing in programme involving fabrication and conversion equipment with suitable

production facilities, testing, quality control, trained staff, etc.

This could be achieved by:

a) the use of imported plastic polymers followed by the

b) phased in supply of Algerian produced polymers.

In 20 years it could be expected that both the use of imported polymers and a major replacement of both metal (other than aluminium foil) and glass would have been achieved.

Procedures for 'clearing' the use of plastic for a specific purpose does, as initially identified, require specialised knowledge of

The polymerisation process	)	involving residues
The compounding process	)	processing aids
The conversion process	)	and additives

and

The design of the container or packaging form in order to achieve the right specification for the groups of product concerned and the correct packaging equipment.

Advice on the above can be given. For initial reading articles: "The pharmaceutical clearance of a plastic pack/device* by D.A. Dean (Annex III)

and

"Stability Aspects of Packaging" by D.A. Dean
(Drug Development and Industrial Pharmacy 10 (849) 1463 - 1495 (1984)

are recommended for reading as GUIDELINES.

Although these articles represent what should and is done in the USA and Europe, they should NOT be taken as what should be done in ALGERIA. The totality should be achieved by slow evolution.

In the above conclusions, the preferred materials have been selected. This suggests that the use of polystyrene (highly permeable to moisture and gases), polyvinylchloride as bottles (fairly permeable to water based products) and polyester bottles (orientated or non-orientated) might be excluded. This does not mean that pharmaceutical usages are precluded for these materials.

Wide usage of HDPE, PP and to a lesser extent for LDPE are also seen for closures of the containers defined.

VII. SUMMARY OF RECOMMENDATIONS FOR PLASTIC IN PHARMACEUTICAL PACKAGING

1. Solid dosage forms (tablets, capsules, dragees, etc.)

Options

a) Multiple unit dose packs - Blister or strips
b) Multiple dose packs - an original pack for a prescribed course of treatment.

Recommendations

a) Multiple unit dose packs

i) Blister of PVC or PVdC coated PVC with an overwrap to improve overall protection, particularly against moisture where necessary.

ii) Cold formed foil blisters or strip packs of paper/foil/LDPE for the most moisture sensitive products.

Note: THE ABOVE REQUIRES THE IMPORTATION OF FOIL.

b) Multiple dose packs

Bottles or wide diameter tubes made of HDPE or PP (possibly with a protective coating) or longer term coextrudates (yet to be defined in detail).

Note: THE USE OF SMALL BOTTLES COULD AVOID ANY IMPORTATION OF FOIL.

2. Large volume parenterals

Options

a) Preformed containers - bags in PVC, LDPE, PP or laminations - problems - cleanliness, cost.
b) Form fill seal.

Recommendations

Rommelag Bottelpack system - pack starts with a plastic granule (less storage space, less handling problems), high integrity (microbiological), low particulates. Fairly costly, high technology but overall produces pack economically (low rejects) with high consistent quality. Note needs balanced pressure autoclave and special label adhesives.

3. Ointments, creams and pastes

Options

Metal tubes, lacquered plastic tubes, laminate tubes.

Recommendations

Stay with metal initially, further investigate lacquered PP tubes and laminated tubes. Latter have replaced metal for toothpaste to a large degree in USA and Europe.

Plastic replacement achievable by 1990.

4. Double ended glass ampoules

Note board trays could be replaced by PS trays on machine replacement.

Options

a) A bulk pack, equivalent 100 ml in plastic

b) Plastic ampoules

Recommendation

Consider marketing acceptance of 100 ml HDPE or PP plastic pack. If not acceptable maintain longer term review on plastic ampoules. Viable with an additionally protective overwrap.

5. Powders, internal and external

Options

Plastic containers with or without sprinkler.

Recommendations

HDPE or PP containers possibly with protective over lacquer. Review composites including coextrudates long term.

6. Effervescent tablets

Options

a) Plastic tubes (multidose)
b) Foil strip packs (multidose unit dose)

Recommendations

Check PP or HDPE tubes possibly over lacquered; if excellent protection against moisture essential, use paper/foil/PE or foil/PE strip pack.

7. Injection vials and ampoules (small volume parenterals)

Options

a) Stay with glass

b) Move to plastics

Recommendations

Stay with glass next 5-7 years, constantly review progress of plastics; introduce plastics if acceptable 1993-2000.

8. Suppositories

Options

a) Foil - heatseal

b) Plastic - heatseal

Recommendations

Remain as at present but review materials and equipment as the latter is more likely of deciding future trends. Plastic pack provides more aesthetic appearance.

9. Liquid products including syrups

Options

a) Multiple dose - bottles in plastic

b) Unit doses in multiples (sticks)

Recommendations

Use multiple dose plastic containers standardised on site, with HDPE or PP or long term coextrudates.

Review acceptability of stick* unit dose (less economical pack) but may be of interest for certain dosage forms - note the converse of DE and sachet recommendations.

10. Sacheting of oral liquids

a) Multiple dose pack - bottle equivalent

b) Consider sachet in alternative material or alternative forms (sticks)

* small containers joined together in a row.

Recommendations

a) Bottle in HDPE or PP or long term coextrudate if acceptable to patients.

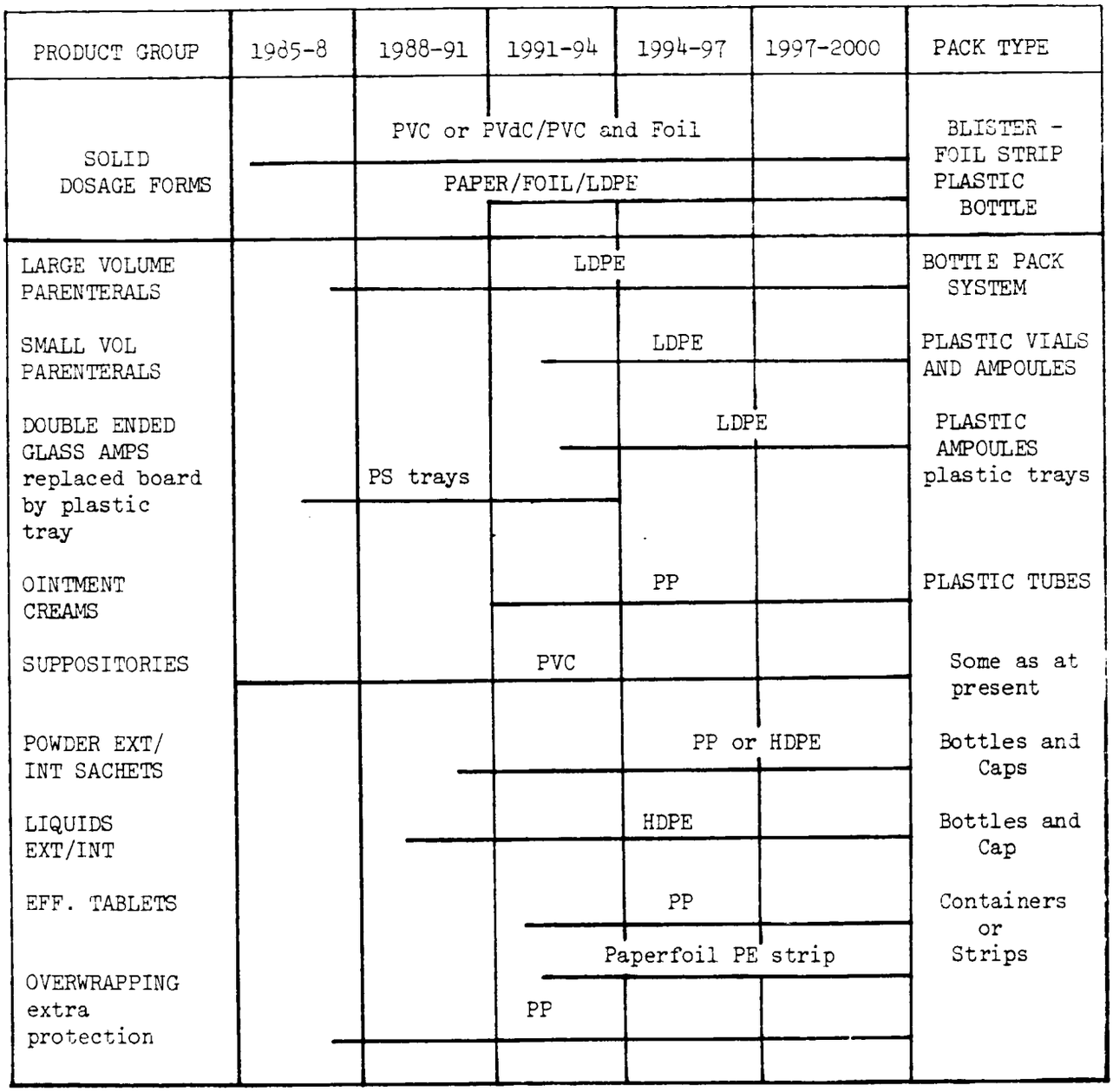
b) Consider more economic sachet combinations, e.g. thinner foil, metalised plastic lamination or coextrudates. Sticks* are a further option.

* small containers joined together in a row.

Conclusions

The use of plastics with a supporting plastic industry will long term significantly reduce imports. There will be a continuing need for the importation of aluminium foil where foil is used in combination with plastic.

PHASING IN OF PLASTICS



VIII. PHARMACEUTICAL PRODUCTS, PLASTIC PACKAGING, SHELF LIFE AND SOME OTHER IMPORTANT FEATURES

It can be said that all plastics are to some degree permeable to oxygen, carbon dioxide, moisture and do not exclude all light unless heavily pigmented or contain UV absorbers or are further packed in a carton. Plastic may also adsorb and absorb ingredients from a product and ingredient in the plastic may either be lost to the atmosphere or migrate into the product. Most of these apparently adverse effects can be controlled by the choice of plastic or plastics, attention to the thickness used, knowledge of the product and plastic (knowing what may migrate) and understanding that a packed product is likely to have several shelf lifes in its packaging to product use/pack disposal cycle.

For example a PVC blister pack is permeable to moisture (8 x greater than an equivalent wall thickness in HDPE). A blister pack put in a storage area at $30^{\circ}C$ 75% RH may therefore show unacceptable deterioration of the product after one month. A blister using 60-80 gm^2 PVdC + PVC will show the same deterioration after 4 months. If both of these are placed in a carton which is overwrapped with say PVdC coated polypropylene and well sealed, this shelf life may increase to 3-4 months and 12-16 months for PVC and PVdC/PVC respectively.

However, a packed-product is likely to spend a considerable part of its life either as an isolated bulk outer or as a full pallet load in a warehouse. In both these situations the shelf life is further extended by the fact that moisture can only penetrate slowly into (or out of) the pack.

A pallet additionally protected by a shroud or stretch wrap will further extend the shelf life provided it is stored in a well controlled warehouse and is not left in the sun/stored in the open for any length of time. It is therefore possible to finish up with a series of shelf life stages, as shown below for a moisture sensitive product.

PVC blisters		PVdC/PVC blisters
+	Shroud or stretch wrapped pallet	+
2 years		3 years
12 months	Isolated outer	2 years
3 months	Overwrapped Individual Carton (unopened)	12 months
4 weeks	Exposed blister pack (not opened)	16 weeks

Study of the above (and any differences) will enable a decision, on whether the pack is satisfactory, to be made. The final question must be whether the pack is used in 4-16 weeks once it is isolated as a blister.

The critical question "what is unacceptable deterioration" will vary from product to product. It may be a scientific judgement based on actual degradation of the product with a lower limit or a subjective judgement based on changes in colour, texture, appearance, flavour, taste, etc. In certain instances a product shelf life will become more acceptable if an overage is put in (e.g. 30% more Vitamin than that declared on the pack) to allow for some degradation during manufacture and storage. In the case of

multivitamin products, as well as an overage, manufacture under nitrogen, storage of bulk under nitrogen and gas flushing (of the final pack) may all be an essential part of obtaining a satisfactory product-pack shelf life.

Other Important Factors

Most plastic suffer from electrostatic effects which increase under hot dry conditions and increased handling. Static can be reduced by incorporating anti-static additives in the plastic (subject to approval for use in product contact), by processing under an humidified atmosphere and attention to cleanliness of handling conditions and clean packaging materials. Once dirty, plastics become very difficult to clean, hence producing and keeping clean is very important.

Distortion - as plastic components and packs are often made from non-rigid materials, sometimes of thin wall section, it is usually easy to damage packs in handling, on the production line (particularly during capping), by incorrect or inadequate secondary packaging, incorrect stacking especially on poor or inadequate pallets and during transportation. Special attention is therefore required to all of these activities.

For example, the outer of say 1 dozen for a glass bottle has to protect the container against impact damage.

With glass bottles being strong in compression, high stacking is unlikely to be a problem as the glass will take the weight if demanded (i.e. not the outer case). The opposite applies with many plastic containers (e.g. those made from LDPE in particular) where the breakage risk is low but the compression strength is poor. The outer case must then either be designed to take stacking pressures or the stacking heights must be restricted both in the warehouse and in transit.

Storage out of doors or in direct sunlight must especially be avoided as all plastic become more mobile (distort, flow or collapse more easily) as temperatures rise.

Knowledge of environmental stress cracking or mechanical stress cracking is also essential. In the former case (which mainly applies to LDPE) a plastic under strain in contact with a stress cracking agent (wetting agents, detergents, volatile oils) may show cracking. Strain may be created in the moulding operation (in built) or subsequently occur from capping, plugging or stacking. Cracking can be avoided by the design of good moulds, good moulding conditions or the correct choice of LDPE in terms of density and melt flow index (MFI). Polyethylenes of low MFI are generally more stress crack resistant.

IX. PLASTIC TONNAGE PREDICTIONS FOR THE ALGERIAN PHARMACEUTICAL INDUSTRY, 1990 AND 2000

Although there is insufficient data to give accurate predictions, some initial estimates have been made against the product predictions available.

Those estimations need to be updated as better information becomes available. The fact that there are several options for the type of plastic which may be used, finite estimations are difficult.

Whilst certain products are already moving into plastics (e.g. the use of blisters) others will be phased in more slowly. This results in relatively low figures for 1990 and much higher figures for 2000.

	YEAR	
	1990	2000
	TONS	TONS
PVC rigid (blisters)	500	3800
(Foil for lidding, + laminations)	80	560
HDPE (containers + closures)	100	1500
LDPE++ (LVPs, closures, flexible bottles, laminations, shrink wraps, etc.)	800	3800
PS (mainly thermoformings + few mouldings)	225	400*
PP (containers, closures, overwrapping)	250	1800
PVdC (coating)	50	400

* PS is the most permeable of the material listed above - hence use for primary packaging is limited long term.

++ LDPE also covers introduction of LLDPE as these materials will have shared usages.

Other usages

The predictions on pharmaceuticals are possible as the specialised product groups can be identified against certain plastics.

Extrapolation of the pharmaceutical data is for this same reason not possible as the proportion of each plastic used will change according to what the product demands.

As a general rule a factor of 15 to 20 times the above will give a general indication for other consumer items as the use in pharmaceuticals is usually 5% or less (food, household, toiletries, cosmetics, etc.).

Uses for other plastics will also be found and these are likely to include:

Polyester (Pet) - drinks general and laminations
Ionomer, Polycarbonate, ethylene vinyl alcohol, nylon - mainly laminations

plus a range of plastics which are either currently under investigation or have at this movement relatively low usage.

The use of PVC bottles for cosmetics, toiletry and household products will extend more rapidly if extrusion stretch blow machinery is introduced.

The use of polythene and PVC is also likely to be extended by stretch and shrink sleeving to be used for labelling/decoration.

X. THE PRODUCTION OF CONTAINERS FROM PLASTICS OR PLASTICS IN COMBINATION WITH OTHER MATERIALS

The word 'Container' covers any material or materials which when 'converted' can hold a product. Such containers may be preformed then later transported to a place where they are filled with a product and closed, or where a material only becomes a container by a form fill seal process, i.e. the container is formed from a reel fed material for example at the time when the product material is added and then 'sealed'.

Containers may be for single dose (blisters, strips, sachets) or multiple doses. The latter includes both the unit of use (by the user) and bulk containers with volumes upwards to thousands of litres.

Although containers once defined in size can be defined by numbers, form fill seal materials are more readily expressed by tonnage.

Plastics can be used for the PRIMARY container - that which holds the product and for both secondary materials (overwrapping, transit protection of the primary pack), and ancillary components (pouring aids, spoons, measures, administration devices).

The type of moulded item required will vary according to the moulding process employed.

Primary Packaging

Preformed containers

These can be made by:

Injection blow moulding
Injection stretch blow moulding
Extrusion blow moulding
Extrusion stretch blow moulding
Thermoforming by vacuum, pressure, mechanically or combinations of these.

Other processes available include:

Scrapless forming process (SFP)
Solid phase pressure forming (SPPF)
Reaction injection moulding (RIM)
Rotary cast moulding
Slush moulding, etc.

These may have specific applications, some of which will be more relevant to foods than pharmaceuticals.

Output from any machine depends on the size of container, the number of cavities per mould, the material used, the cycle time, etc., hence any one machine can give a wide range of outputs.

Ancillary components, measures, devices

Largely injection moulded - occasionally thermoforming methods can be used.

Form, fill, seal - sheet or reel fed processes
(including overwrapping, laminations, coextrudates)

Extrusion (as a sheet) via a slit or die
Extrusion (as a lay flat tube)
Extrusion plus orientation in one to two directions
Extrusion coating
Roller coating (coating and adhesives)
Calendering
Coextrusion
Dry and wet coating/waxing/adhesives or combinations of the above
Casting

All these machines vary substantially in cost - the faster the machine plus the greater width of the material equates with the highest investment

cost - whereby a lower packaging material cost can be achieved. Small macnine, lower investment cost equates with a higher material cost.

Form Fill Seal bottles

Bottles can also be made by a form fill seal process. This means plastic granules replace the larger storage space required by preformed bottles. The Rommelag bottlepack system is typical of this type of process but a few others do exist, e.g. 3D system, Schupbach.

Bulk containers

Bulk containers can be made from many of the above processes. The machinery and tooling is large and costly, e.g. Machine £500,000, one tool - £120,000.

Bulk containers are an important part of many industries - and find use in chemical, pharmaceutical, agricultural, etc. type products.

They have, however, been excluded from the calculations which follow since a greater study is essential if realistic predictions are to be achieved.

Very large containers can be made by relatively labour intensive slush type moulding procedures (e.g. 50,000, 100,000 litres, etc.).

Package decoration

The printing of plastic materials frequently requires pretreatment of the plastic surface (oxidative treatment by flaming or corona discharge) and/or the use of special inks. Although labelling is a further alternative the surface to which the label is applied may either require pretreatment, the use of special adhesives, or the use of self adhesive or heat sensitive labels. In some circumstances where the surface of the plastic has been treated and correct inks used, migratory ingredients in the product or the

plastic may lead to print deterioration (bleed, flaking or fade, etc.).

The printing processes vary according to the subtrate form, i.e.:

bottle round surface
bottle tapered or flat surface

and whether the material is presented for printing as flat sheets or as reels. The printing options for these are listed below:

Bottle	Reel	Flat sheet
Silk screen	(letter press)	Silk screen
Hot die stamping	(lithography)	Hot die stamping
Dry offset	Flexography	Flexographic
In mould printing (transfer)	Gravure	Gravure
Letraset		
Therimace		
Cliché or tampon printing		
Ink jet and laser printing		

Costs significantly vary according to the number of colours printed and the colours printed per pass. In the case of flexographic and gravure printing the cost of the machine increases according to the reel width. A 6 to 8 colour gravure machine can cost well in excess of £1 million.

XI. CAPITAL INVESTMENT REQUIRED TO MEET THE INCREASING DEMANDS FOR PLASTIC PACKING

A. Mouldings

Since plastic packaging for pharmaceuticals needs clean, relatively hygienic facilities coupled to good quality control, in many instances new or segregated premises are essential. Such facilities will equally be suitable for the production of packaging components for food, toiletries, cosmetics, etc.

The calculations attempt to cover the requirements for 1990 and 2000. In all cases the estimates cover both containers and closures, separately.

None of these estimates should be considered finite as capital cost and the final cost per item not only depends on the size (capabilities) of the machine but in the case of injection, and injection blow and extrusion blow moulding the numbers of cavity in the mould tooling. It is assumed that most equipment will be worked 24 hours a day either 5 days a week or up to 300 days per year.

The working area per machine and support areas* are included.

Injection moulding - closures

	UNITS	AREA	OUTPUT	MACHINE COST
1990	2 machines	20 x 40 m	15 - 30 m	£180,000 with support equipment
		+	+	
2000	5 machines	10 x 25 m	75 - 250 m	£150,000
		additional tooling costs		£100,000

Injection moulding - tubes

	UNITS	AREA	OUTPUT	MACHINE COSTS
1990	1 machine	10 x 20 m	15 m	£160,000
		+	+	
2000	3 machines	10 x 40 m	60 m	£160,000
		(different no.s per tool)		
		(additional tooling tool costs)		£80,000

Bottle moulding

Extrusion blow moulding

	UNITS	AREA	OUTPUT	COST
1990	2 machines	20 x 50 m	10 - 12 m	£350,000
		Additional tooling		£50,000
	+			
2000	10 machines	120 x 100	75 - 100 m	£1,500,000
		Additional tooling		£160,000

Injection blow moulding vials

1990		NIL		
2000	4	65 x 50 m	120 m	£650,000
		Additional tooling		£120,000

Injection blow moulding ampoules

	UNITS	AREA	OUTPUT	MACHINE COSTS
1990		NIL		
2000	4	65 x 50 m	150 m	£700,000
		additional tooling		£120,000

B. Reel and sheet fed materials

Calendering for PVC/PS reels

1990	1	50 x 25 m	1000 tons	£800,000
	+		+	
2000	2	100 x 40 m	4000 tons	£1,250,000
		additional tooling		£125,000

All numbers are approximations

If the above were in the same facility (area) staffing, estimated as technical staffing and management, would be 110 to 130 persons. However it would be advised that these activities are spread over 4 - 6 specialised factories - fire risks and to assist distribution.

C. Form Fill Seal

Lamination/Extrusion/Printing

	UNITS	AREA	OUTPUT	MACHINE COSTS
1990	LAMINATION 2	40 x 60	4 - 5000 tons	£2 - 3 million
	PRINTING 2			

High quality of equipment will enable thinner gauge materials to be handled.

2000	2 LAMINATION			
	2 COEXTRUSION	80 x 100	10,000 -	£3 - 4 million
	3 PRINTING		15,000 tons	(see later for details)

Staffing 1990 60 - 70
2000 120 - 145
} 3 shifts covering 24 hours per day

Rommelag Bottel Pack equipment for LVPs

	UNITS			
1990	1	20 x 20	3 - 4.5 m	800,000 + (Autoclaves £350,000
	Extended shifts			
2000	4	60 x 50	12 - 16 m	1,600,000 + (Autoclaves £600,000)

It should be noted that machine areas have not been costed into the above: areas have been given as a guide line. Estimates include ancillary equipment, compressors, vacuum, cooling water, etc.

It should be observed that centralised chilled water for a number of machines will improve the overall economics. As all of the above consists of fairly sophisticated equipment high quality services are demanded, e.g. good voltage control of electricity. If a large number of machines operate in one factory, consideration should be given to an emergency generator should the natural grid supply fail or excessively fluctuate.

No machinery has been provided for rubber components as this is an extremely specialised industry. Importation is therefore still recommended.

D. Machinery for overwrapping

Preferred material - polypropylene coated with PVdC.

The above material has wide use applications and is made on an extruder followed by a coating process.

If new equipment is required.

Extruder

	Unit	Area	Output	Cost
1990	1	20 x 25	1000 tons	£800,000
	Coater	Area	Output	Cost
1990	2	20 x 25	1000 tons	£500,000

2000 As above but multiplied by 20 using equipment currently being developed - hence not priced.

E. Machinery for printing

Machines	Colours per pass	Plate costs	Machine cost
SILKSCREEN	1 - 3	£40 - 60	£1 - 30,000
HOT DIE STAMPING	1 - 2	£50 - 150	£1000 - 10,000
	cost is in reels camping the ink		
DRY OFFSET	1 - 2	£100 - 150	£10 - 25,000
LETTERPRESS	2 - 4	£150 - 350	£15 - 35,000
THERIMAGE	1 - 4 (could be 6)	£1000 - 4000	£18 - 60,000
	needs special sets of rolls @ £4000 per set		
CLICHE or TAMPON	1 - 4	£250 - 2400	£1500 - 30,000
FLEXOGRAPHIC	1 - 6	£300 - 3000	£10,000 - 700,000
GRAVURE	1 - 8	£500 - 7000	£450,000 - 2,000,000

Fuller detail on decoration requirement can only be defined when further information is available.

Reel fed printing processes need additional cutting and reeling equipment so that the jumbo reels can be reduced to the actual diameter and reel width to be run on the packaging machine. Costs for these need adding to the above figures.

For all of the above calculations NO allowance has been made for the warehousing of the manufactured packaging materials. The size of any warehouse will not only depend how the items are packed but the length of time which is held prior to despatch. It is assumed that virtually all packaging items (bulk) will be protected from dirt and dust by polythene or a similar material as an additional wrap (bags, shrunk wraps). This usage reflects in the volume of LDPE required in 1990-2000.

XII. ECONOMICAL FACTORS

As with many other commodities plastic polymers can be purchased over a wide range of prices, particularly as price reduces as the tonnage increases.

Most prices are based on natural (non-coloured, with limited or no additives, etc.) which for the economic four, polyethylene, polypropylene, polystyrene and polyvinylchloride means a non-tariff, non-import duty price of around £625-725 per tonne in EEC countries.

Once materials are compounded, pigmented, etc. prices rise because of the compounding operation and the costs of the additives.

As most converting processes produce some degree of scrap, this is usually reworked, frequently on a less critical moulding process as regrind. Regrind may only cost 10% to 20% of the original polymer price. Good quality regrind occurs on the converting equipment. It is not normally acceptable or practical to recycle used packaging materials due to possible contamination and uncertainties of the source, type, grade, etc. unless the end use is a non-critical item.

To obtain a full economical evaluation the supply of a common component delivered to point of sale should be considered, e.g.

a) European material source, delivered as a finished item into Algeria.

b) Same European plastic delivered to a moulder in Algeria where it is compounded and converted to the same item.

c) Same or similar polymer of Algerian original passing through the same compounding - conversion cycle.

To obtain totally meaningful comparison the exercise should identify

Cost of all ingredients used
Cost of all energy activities
Cost of warehousing and transportation (c.i.f.)
Losses at any stage
Costs of other direct and indirect overheads
Cost of all labour activities
Losses in the process - destination/use of scrap material
Return on investment/profitability
Any import duties or tariffs
Output versus time.

Capital expenditure (equipment, buildings, etc.) - depreciation

and be carried out on similar equipment with the same number of mould cavities. Unfortunately with the time available together with a lack of international contacts it has not been possible to carry out such a comparison. It must however be stressed that it would provide valuable data for this current exercise.

XIII. DIRECT APPLICATIONS OF PLASTICS TO PHARMACEUTICALS (other than packaging and ancillary packaging components)

Plastics are finding increasing applications in formulations and administration aids. The former include delayed, controlled and sustained release preparations, special administration aids covering transdermal patches, interuterine devices, implants, and special devices which assist the delivery of the drug by being part of a pack (an adaptor on an aerosol) or a device which is used separately.

There is a distinct upward trend with all the forms identified above. Each use calls for a precisely defined plastic with proven safety in terms of both toxicity and irritancy related to extraction or direct contact.

The development of these devices will probably take place after 1990 as even greater specialisation is required compared with plastic packaging. As the trends could substantially change in the next five years, it is extremely difficult to advise on both material and conversion process/facilities required. Certain applications do require plastic outside of the most economical ones and call for the use of acrylics, nylons, polyurethanes, polyformaldehydes, and a variety specialised low usage, high cost materials.

XIV. VISITS

1. Mr. Mezian - Conseiller de Ministre (Ministere de l'Energie et de l'Industrie Petrochimique) Production of LDPE and PVC identified. Plans for HDPE (1986). PP, PS, indicated over the next 5-10 years

July 14th

2. Entreprise Nationale des plastiques et Caoutchoucs ENPC TPIM B.P. 10. DRAA-SMAR, MEDEA
Contact Ahmel BOUMAHDI July 16th

ENPC have facilities for injection moulding (most plastics) the extrusion - calendering of PS sheet, extrusion of rigid PVC sheet, extrusion of lay flat tubing for PP and LDPE or LDPE/LLDPE mixtures, the compounding of rigid PVCs, printing by gravure or flexography on film, paper or foil, and the lamination of paper, foil and film combinations using adhesives. The equipment employed does not allow the use of thin foil or give good caliper control on the extruded materials, e.g. PVC. The unit has a fairly large capacity with a small quality control lab. It could be suitable for producing plastics for pharmaceuticals with improvements in equipment and the segregation of such processes from the remainder of the factory operations.

3. Saidal and new pharmaceutical plant at Medea

Although the factory site is not ideally situated it should finish up with good quality buildings suitable for pharmaceutical manufacture. The equipment chosen is generally excellent and should be capable of high speed outputs once cleaned and commissioned.

It is perhaps unfortunate that the machinery arrived before the site and buildings were completed as the dirt and dust covering the machines will undoubtedly lead to longer running in and commissioning times. The specifications provided by the machinery manufacturers are indeed good and

will need well-trained staff and engineers to ensure material quality meets the demands of the very sophisticated machinery. It is estimated that the time for total operation, covering the fully effective running of the machinery on a production basis may take up to two years to achieve. Whilst the layout and equipment is capable of high performance this will only be achieved once staff become highly trained. It could therefore be said that the whole scheme was somewhat over-ambitious and that the phased completion of certain areas (manufacture plus the packaging area) could have ensured an earlier, consistent output with less problems at the commissioning stage. It is possible that some equipment will fail to reach effective performance and thereby down grade a line which was initially capable of high performance.

A similar situation will be found in the printing, leaflet, carton production plant where again high quality equipment was found. Poor performance of one machine, inadequate air conditioning (control), inadequately trained staff, etc. would again leave output below that anticipated - hence production packaging equipment could be awaiting supplies. Printing equipment for example must have relatively long runs to be economic and can therefore only produce one design at one time. It can therefore be predicted that a number of short falls in production will occur as machines will be either held up for adjustment or corrections or be awaiting supplies from earlier stages in the total manufacture, packaging, supply cycle. Even the presence of highly qualified staff (engineers and fitters) in excess cannot necessarily adjust in such situations.

Visit PCA El Harrach July 20th

The El Harrach site is not a purpose built complex but a series of buildings converted into a number of production facilities and a set of development laboratories. Since the production of the site far outstrips the storage facilities a large proportion of the stock is stored in the open, frequently under direct sunlight. The production and packaging can be divided into product types, i.e. syrups, powders, ointments, suppositories, tablets and surgical spirits. The syrup area covers production on the 1st floor and packaging on the ground floor with one full line (approx. 60 per minute) and a smaller line. The former includes an unscrambling table, a

cleaning unit, volumetric filling, PPRO aluminium capping, cartonner with leaflet insertion and vignette with final hand packaging into outers of 42. Both lines only run on glass bottles up to 180 ml in capacity. The ointment manufacture and packaging is also on the 1st floor with two lines for small and large tubes 15-100 gm. Cartons, leaflet, and vignettes are used; all tubes are of lacquered aluminium with a latex end seal. A triple fold seal is used to close the tube.

The suppository area (ground floor) contains an impressive Sarong machine which uses an opaque and clear heat seal coated PVC. Two Dot Bonapace machines use PVC (clear/clear) preformed reels (made on the Sarong) for gelatin suppositories.

Tablet uses Kilian machines (direct compression) followed by blister packaging on either a hand fed Noack or a Farmac (4 x 5) 8 across. The latter is coordinated with a cartonner which takes 20, 40 or 60 tablets followed by vignette, etc. Output is up to 1800 tablets per minute PVC or PVdC coated PVC is used with a soft foil. A range of surgical spirits (litre in glass with wadless cap) are packed in a further area.

Powders are manufactured and packed in a final separate area using a Hassia sacheting machine.

Laboratory for Research and Development. M.B. Mansouri.

The laboratories cover formulation analytical, toxicology and a library. The formulation area is well equipped for conventional tablets on a small scale. Stability is done at 4°C, 25°C, 37°C for [illegible], 3, 4, 6, 9, 12, 18, 24 and 36 months. Products are chosen from ministry list based on impact on health, economics, technology available and therapeutic index. The analytical area is well served with most physical instrumentation including one Waters HPLC unit. The pack chosen for stability is related to the original pack of the product originator/patentee. The toxicological laboratory uses mice and rats for small test programmes.

Materials for production are [illegible] on tender via a Saidal central control zone. Finished products are [illegible]ributed through three regional

bases at Algiers, Constantine and Oran.

Visit to a local 'Super' market

The store was visited in order to obtain a general appreciation of packaging materials and pack types. However it was difficult in many cases to identify whether packages were imported or produced and packed in Algeria.

The following materials were found:

Metals - cans and collapsible tubes
glass - bottles and jars
plastic - PVC, LDPE and HDPE as bottles
paper and board - cartons, outers and labels
laminates - paper/foil
wraps - polyethylene and possibly regenerated cellulose

Observations on plastic containers at store

A high percentage of plastic containers showed leakage, mainly due to poor closures. A few containers were split, whilst many were distorted due to physical damage or panelling. In some plastics the product had permeated through the container and in many cases either the printed decoration was being lost, the label on partly adhered or totally absent. In one instance the printing had reached a liquid state and was trickling down the container walls. In some instances the plastic caps had cracked and the tops of the caps had risen like trap doors, exposing the product (probably caused by a phenomena known as environmental stress cracking). Other closures were poorly fitting or very loose on the containers (this may be due to poor initial cap tightening, poor storage or transportation, or the use of an incorrect cap to bottle design whereby the cap rapidly loosens under the prevailing climatic conditions). If the latter is the case improved cap designs could be recommended.

Plastic container designs were in general poor, thereby increasing risks of damage and of poor appearance. All the containers checked were extrusion blow moulded.

Visits to other local shops showed higher standards with some glass and plastic cosmetic and toiletries packaging. However it was not established whether these were of local origin. Poor labelling standards and damaged decoration was also observed in some of these packs. Small toys also showed a lack of appreciation of good plastic moulding standards, i.e. flash and distortion.

Summary

The standard of packaging technology and that of plastic generally is low. Transfer of technology is required for materials, closuring and moulding, printing and decoration. This transfer is essential if an expansion into plastics for pharmaceuticals is to be practical.

Visit to PCA, Pharmal

The flow through system on this site is more conventional where formulation - packaging to warehouse (finished product) covers one direct line. However, the same warehouse is used for raw materials.

The manufacturing, packaging and warehouse facilities were visited.

All glass, plastic, closures, blister, strip materials are imported. Cartons, labels and outers are produced internally+ by SONIC and run well on the equipment found with speeds up to 60 packs per minute. Certain operations were in a large hall with open lines whereas others were cubicalised.

Lines were seen doing the following operations

1. Hand packing in cartons of foil packed suppositories.
2. Hand filling of an external suspension (180 ml glass, PPRO Al cap) plus carton, leaflet, vignette and outer.
3. King counter packing of capsules and tablets into glass vials with LDPE plugs.

+ in Algeria

4. Packaging into LDPE bags (then to go into glass) for hospitals (tablets)
5. Fully automatic syrup line 60 pm, vacuum fill, PPRO al cap, carton, leaflet, vignette packed in outers of 25.
6. Aspirin tablet packaging paper/PE to foil PE on an Uhlmann strip packer, 4 across. Approx. 240 singles per minute.
7. One Wolkogen blister pack - defunct.
8. Hand line - French plastic bottle, plug and cap - nasal spray.
9. Automatic powder filling and plastic bore seal closure, glass bottle. Paediatric pack for making Ampicillin Syrup. Speed probably just over 60 per minute.
10. Bottle (glass) with cap/dropper assembly.

In the production area Kilian tableting and Zanazzi capsule filling was noted.

Warehousing had a good racking system and excellent access to items.

Visit to Biotic, July 21st

Although the buildings are old the equipment can still perform operations effectively. Lines were seen for double ended ampoules (SFAM), 500 ml IV solutions plus inspection area, syrups and a relatively modern King line for packing tablets into glass vials with LDPE stoppers. The warehouses were spacious but needed racking to improve stock control. Suppository lines used two Wolkogen machines with aluminium foil heat seal materials.

The facilities are restrictive to output but could be seen as adequate until such time as equipment needs replacing. New premises and new lines would then be advised with modern flow systems to improve GMP. This will be particularly relevant when the present autoclaves need replacement - autoclaves with an opening for in and out could then be installed.

Observations and recommendations related to Biotic, El Harrach and Pharmal

The premises at El Harrach are unlikely to be economical for improved

production facilities mainly because an efficient flow system from raw materials, through manufacture, packaging and final warehousing would be difficult to introduce. This is particularly essential if plastic are to be introduced as the complexities of handling could cause many problems. The premises at Pharmal which already have a reasonable flow system can be further improved by defining the straight through zones for specific products. At the moment the ampicillin powder operation cuts across this and it is recommended that it is removed to Medea. Production between all sites needs standardisation on products to be produced.

Further growth will require either expansion or new factory sites. The latter is positively recommended as these can be built on a modular plan which allows early manufacture of products followed by expansion to meet future demands. New premises tend to encourage a step forwards in the updating of people's attitudes towards new standards and technologies. It is also recommended that these new factories produce specific product groups rather than mixtures as this approach offers many advantages. Not least is the increase in professional attitude by the staff who clearly recognise that they are experts in a specific field. This with new premises, new equipment and advances in quality control and professional technology assists in the upgrading of operations to the standards which will be needed both for today and tomorrow.

Visit to ENIP, July 21st

Production of LDPE and PVC was confirmed at 50,000 tons and 36,000 tons for 1985 with the possibility of increasing PVC by an extension of the current process.

Future plans involve:

HDPE start plant erection 1986 - production 1990-1 planned for 75,000 tons.

A further stage depends on the steam cracking operation. This will

lead to production in the 1990-2000 year period of

LLDPE - 100,000 tons (partly a replacement and partly an extension to LDPE)
PP - 50,000 tons
PVC - 80,000 tons (to be confirmed)
PS - yet to be defined
PET - 50,000 tons fabrics
10,000 tons other usages including plastics for packaging.

Algeria currently imports quantities of all plastics - detail of these together with a breakdown of the uses of materials of internal and external manufacture was promised.

A request was made for a price indication for each material.

Chemical ingredients for plastics

Quantities of talc, kaolin, kieselgehr, and calcium carbonate are produced in Algeria as fillers.

Capacity of 8000 tons DOP (dioctyl phthalate) for plasticized PVC is planned.

All other materials are imported and are likely to remain so.

Fully converted plastics, e.g. films, carry a 60% importation tariff. Tariffs on raw materials (polymers) are lower and details will be provided.

Conclusion

Although the proposed production schedules on plastics will meet a proportion of the demands, the limitation of grades available will always call for some imports. The basic materials being produced cover those plastics which will have the most wide use over the next 10 years. ENIP

were interested in the possible specialist usages of PVdC (Polyvinylidene chloride) for a good barrier coating and will keep this under review.

XV. ABBREVIATIONS

EVAL*	Ethylene vinyl alcohol
EVOH	Ethylene vinyl alcohol
GPPS	General purpose polystyrene
HDPE	High density polyethylenes
IUD	Inter Uterine device
LDPE	Low density polyethylene
LLDPE	Linear low density polyethylene
LVP	Large volume parenteral, e.g. intravenous solutions
MDPE	Medium density polyethylene
PC	Polycarbonate
PE	Polyethylene
PET	Polyethylene terephthalate
PET	Polyester
PP	Polypropylene
PS	Polystyrene
PVC	Polyvinylchloride
PVdC	Polyvinylidene chloride
SVP	Small volume parenteral, e.g. vials, ampoules
UPVC	Unplasticized polyvinyl chloride

* Trade Mark

XVI. REFERENCES

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ANNEX I

Properties of Thermoplastics

The attached tables on the properties of plastic are offered as general guide line information. Plastics used for films, sheets, containers and solid mouldings may be required to offer specified properties which may in some instances be at variance to general trends. The presence of residues, additives and processing aids can also change both the physical and chemical properties of a material in either a positive and negative way. For example, the addition of a UV absorber or carbon black can substantially improve the resistance of a plastic to the effects of light. The presence of an impact modifier may not only change physical properties but change the chemical resistance and increase the permeation to moisture, gases, etc.

The letters and figures quoted in the table are intended to provide general comparisons, none are absolute. In the scale A - E, A offers the best performance. With figures for costs, permeation to moisture, gases, etc., the lower numbers offer the lowest cost, best performance.

Temperatures covering the softening point (e.g. Vicat), heat distortion temperature, melting point of plastics also tend to be confusing. The temperatures quoted in the tables are related melting points, which largely depend on the crystalline or amorphous nature of the material involved. Orientated materials generally offer improved properties both in terms of clarity, strength and permeation to moisture and gases.

For general purposes a ratio of 1.4.20 can be used to calculate the permeability of a material to Nitrogen : Oxygen : Carbon dioxide.

Chemical Name	Physical Characteristics										General Resistance						
	Density	Melting Point °C	Clarity	Tensile	Impact Strength	Low temp performance	Dimensional Stability	Typical Shrinkage per Inch	Cost	Oil	Water	Oxygen	Acid	Alkali	Organic Solvent	Sunlight
Acrylic	1.17 - 1.20	90 - 105	A	B	D	B	B	0.008	1.7	A-B	10	4				
Acrylic High Impact (HI)			A	C	C-D	B	B	0.010	1.75	A-B	12	5	B-C	A-B	D	A
Cellulose Acetate (CA)	1.28 - 1.32	230	A	C	B	B	D	0.009	1.9	B	750	80	C-D	C-D	D	B
Cellulose Acetate Butyrate (CAB)	1.15 - 1.22	140*	A	C	B	B	C-D		2.6	B			C-D	C-D	D	B
Cellulose Acetate Proprionate (CAP)	1.18 - 1.24	140	A	D	B	B	C-D		2.6	B			C-D	C-D	D	B
Acrylonitrile	1.15		A	B	B	A				A	35	0.2	A-B		B-C	
Ethylene - Vinyl acetate copolymer (EVA)	.92 - .95	75	B	E	B	A-B	B		1.5	C	40	600	B	A	B	B
Fluoroplastics polytetra fluoroethylene (PTFE)	2.10 - 2.15	320	B	D	B-C	A	A		6.0	A	0.4	1	A	A	A	A
Polymonochlor trifluoro ethylene (PCTFE)	1.68 - 1.70	245	A	C	B-C	A	A		20	A	0.01	1	A	A	A	A
Ionomer	0.93 - 0.96	90	A	D	A	B	B-C		1.4	B	10	200	C-D	A-B	B	D
<u>Polyamides</u>																
Nylon 6	1.12 - 1.4	265	D	A	B	B	B-C		2.4	A	25	1	B-C	A		B-C
6.6	1.13 - 1.15	210 - 220	D	A	C	B	B		2.5	A	45	5	B-C	A		B-C
Nylon 11	1.03 - 1.06	195	B-C	B	C	B	A		6.0	A	12	15	C-D	A-B	B-C	B
Nylon 12	1.01 - 1.02	180	D	B	C	B	B		4.0	A	15	25	C-D	A-B	B-C	B
<u>Polyacetals</u>																
Acetal Homopolymer (POM)	1.42	180	D	B	C	B	A-B	0.022	1.8	B			C-D	C-D	A-B	B-C
Acetal Copolymer	1.42	175	D	B	C	B-C	A-B		1.8	B			C-D	D	B	B-C
Polybutylene terephthalate (PBT)	1.31	225	B-C	A	A	A	B	0.015 - 0.030	2.5	A			B-C	B-C	A-B	A

Chemical Name	Physical Characteristics									General Resistance						
	Density	Melting Point °C	Clarity	Tensile	Impact Strength	Low temp performance	Dimensional stability	Typical shrinkage per inch	Cost	Oil	Water	Oxygen	Acid	Alkali	Organic Solvent	Sunlight
Poly Carbonate (PC)	1.2	150	A	B-C	A	A	B	0.007	2.5	C	15	150	A-B	C-D	A-B	B
Thermo Plastic Polyesters																
Polyethylene Terephthalate (PET)	1.3 - 1.38	230-270	B-C	C	B-C	B	B		2.0	A	10	2	C-D	C-D	D	A
Polyolefins																
Polyethylene (LDPE)	.910 - .925	110-130	A-B	E	B	B	A	0.015	1	D	4	200	A-B	A-B	B	B
Polyethylene (MDPE)	.926 - .940	120-135	B	E	B	B	A	0.025	1.1	B-D	3	40	A-B	A-B	B	B
Polyethylene (HDPE)	.941 - .965	120-140	B-C	D	B	B	A	0.045	1.2	B	2	25	A-B	A-B	B	B
Polypropylenes																
Polypropylene Homopolymer PP	0.90- 0.91	175	B-C	D	B	C-D	A	0.017	1	B	2.5	60	A-B	A	B	B
Polypropylene Copolymer PP	0.89- 0.90	160-175	B-C	D	B	B	A		1.1	B	3.0	80	A-B	A	B	B
Styrenes																
Polystyrene (PS)	1.05	90-100	A	C	D	D	A	0.005	1	C	80	250	A-B	A	B-C	A-B
Polystyrene High Impact (HIPS)	1.00- 1.10	85- 95	C-D	D	B-C	C-D	A-B	0.005	1.4	C-D	100	350	A-B	A	B-C	A-B
Acrylonitrile Butadiene Styrene (ABS)	1.00- 1.10	90-120	C-D	C	B	D	A-B	0.006	1.6	B	50	150	B-C	B-C	B	C
Acrylonitrile Butadiene Styrene High Impact (ABS HI)	0.99- 1.1	85-110	C-D	D	A-B	C-D	A-B		1.8	B	60	180	B-C	B-C	C	C
Styrene Acrylonitrile (SAN)	1.075-1.1	115	D	B	C-D		A	0.004	1.5	B	60		B-C	A-B	D	C
Polysulphone	1.37	230	A	A	A				8.0	.	20		A	A	A-B	B
Polyvinyl alcohol										A	soluble in water				A-B	C
Poly Vinyl Chloride (PVC)	1.35- 1.45	80-100	A	C	B-C	B	A	0.008	1.2	A-B	18	1	A-B	A	B	B
PVC Plasticized	1.20- 1.40	75- 95	A	E	A-B	B	A		1	B	80	100	A-B	A	B-C	B
Poly vinylidene Chloride (PVdC)	1.60- 1.70	190-210	A	B	C-D		A		5.5	B	0.1	0.5	A-B	A-B	A-B	B

ANNEX II

PACKAGING AND PLASTICS

by

D.A. Dean

Packaging may be defined as the economical means of providing protection, presentation, identification/information, convenience and containment of a PRODUCT during storage, carriage, display and use until such time as the product is removed or used. Fulfilling these functions in the broadest sense will inevitably produce a compromise as emphasis on each of these factors will vary according to the product being packed. The type of packaging material used will also affect this compromise and a subject such as plastics in packaging may be influenced by any of the following:

1. The type of product and the characteristics of the product which can benefit from the use of plastic.

2. The basic characteristics of plastic which can be exploited to the general benefit of packaging.

3. The plastic materials which are most economical to use. This normally includes polystyrene, polyethylene, polypropylene and polyvinylchloride but costs vary from country to country.

4. The negative features of plastic, some of which may now be historical, but must at least be acknowledged and borne in mind if the more overwhelming positive features are to be optimised.

5. The conversion process associated with containers, components, films and laminations by which the use of plastic can be extended. These may be related to trends in design, processing and decoration methods.

6. The possible cost advantages of plastics when compared with other alternative materials such as glass, metal or paper-based materials.

7. The pack characteristics. A technological study of the types of pack and packaging systems available.

8. The environmental issues which may relate to reuse, recycling, the general conservation of energy and problems arising from disposal and possible pollution.

9. Consumer habits and product trends.

The steady growth of plastic packaging not only depends on a balance of all the above points, but on on-going awareness how each may change with time. However, most of these factors interact one with the other, hence many of the various examples of plastic in packaging which follow cannot be necessarily

isolated as typical of one group. Virtually all products now benefit from the use of plastics and examples can be taken from food, pharmaceutical, chemical, agricultural, household, hardware, toiletry and cosmetic, etc. products.

Plastics are found in primary packaging (those items which immediately enclose the product), secondary packaging (those items which add to the presentation and assist in the protection of the pack during warehousing and distribution) and any ancillary items which add to the convenience or the administration of the product. Indirect uses of plastics should also be included, e.g. hot melt adhesives, self-adhesive and heat seal labels, shrink and stretch labels, certain adhesives used in laminations, all of which are plastic based. However, before expanding on the broad usage of plastic and specific trends it would be advisable to identify some of the longer standing negative features, as occasionally these may be restrictive to the use of plastic. Because of their historical nature, some may be overlooked. These are listed as follows:

Permeability - all plastics are to some degree permeable to gases and moisture - hence poorer barrier materials may be unsuitable for even lowly moisture or gas sensitive materials.

Limited light exclusion - plastics, unless thick and highly pigmented (carbon black is the most effective) tend to provide only limited screening to light. The addition of U.V. absorbers may be used as an alternative to pigmentation.

Environmental stress cracking - normally applies to certain grades of low density polyethylene which under stress (in-built or applied) and in contact with certain groups of chemical substances (wetting agents, detergents, some essential oils) known as stress cracking agents, may give rise to stress cracking.

Electrostatic attraction - usually of dirt, dust and fibres which in turn may increase the risk of microbiological contamination. Pick up varies according to the nature of the plastic and can be normally reduced by anti-static additives, earthing, ionic discharge or avoiding handling under dry conditions.

Panelling or cavition - whereby a plastic container may partially collapse or indent. It may occur for a number of reasons, i.e.:

1. Hot fill leading to a partial vacuum after closuring.

2. "Compression" during capping which leads to a partial vacuum (note this may occur momentarily and only be confirmed by a high speed camera).

3. Adsorption of gases from container headspace - usually related to oxygen.

4. Atmosphere and air space changes, e.g. under conditions of steam auto-claving (sometimes called dimpling).

5. Adsorption and absorption at the inner container wall - leading to swelling or expansion of the wall thus causing distortion.

Poor impact resistance

The earlier belief that plastics are unbreakable only broadly applies to selected materials. Plastics such as polystyrene and PVC will crack on impact (say 1 metre drop) unless either modified in some way or produced by a process which improves impact strength (e.g. orientation).

Clarity or transparency

Only a few plastics have high clarity (like glass). Many tend to be translucent and therefore may not display the product to advantage. Orientation may be useful in improving clarity.

Key of the print - Pretreatments

Some plastics are difficult to print unless the surface is 'oxidised' or pretreated to improve the key. This treatment can be achieved by:

(i) Flaming
(ii) High voltage corona discharge
(iii) Chemical agent, e.g. hydrogen peroxide
or
(iv) The use of a coating.

Compression and distortion

As a light-weight material many plastic based materials may become distorted by top pressure as found under conditions of stacking. It may therefore be necessary to increase the compression strength of the outer packaging. Designing a primary pack with strengthening features (rings/ ribs) also overcome such problems.

Adsorption, absorption and migration

A two-way exchange can occur between a plastic material and a product, i.e. a constituent from the product can be lost onto, into or through a plastic or a constituent from the plastic can be removed into the product by extraction, migration or even contract abrasion. This may be relevant to foods, toiletries and cosmetics and in particular pharmaceuticals. In the latter case loss of part or all a preservative system may render a product microbiologically ineffective. Migration of constituents from a plastic into a product must be checked for safety (toxicity/irritancy), changes to flavour or odour, or product changes due to chemical interaction. Some plastics (e.g. LDPE) are particularly permeable to organic odours, hence product flavourings, perfumes may be lost and external contact with odourous substances may pass through to the product.

Odour - Flavour changes

Odour and flavour changes can occur due to the permeation of external

substances, loss or changes in product constituents, and natural odours associated with plastics and their constituents. LDPE for example has a typical wax - like aroma which may become recognisable as an off flavour or taint. Although plastic like odour or flavours were at one time considered unacceptable, this situation is slowly changing to one of limited acceptability.

Low Density (compared with glass which has a density of 2.25 - 2.5).

This may lead to problems on production lines which are not properly designed to handle plastics, i.e. instability, mushrooming, etc. The majority of plastics (if not reinforced) have a density below 1.5.

Poor design

Weakness in plastics related to breakage, distortion, indentation, panelling, etc. may all be related to poor design which in turn may give rise to uneven wall distribution. Angular, square sections will inevitably cause design weaknesses and hence well radiused shapes, radiused angles plus special strengthening features may need consideration. Design features may have to vary according to the conversion process chosen.

Examples of how some of these adverse effects can be overcome include:

1. A hygroscopic pharmaceutical in moisture permeable PVC blister was additionally packed in foil sachet overwrap which provided a five year shelf life until such time as product was removed. The PVC provides adequate protection even against a high RH, during the then short in use period.

2. A veterinary product was packed in a collapsible multidose LDPE flask which allowed pack to collapse as doses were withdrawn via special syringe.

   Again the addition of a foil sachet was essential, as this prevented loss of preservative, moisture and the ingress of oxygen which could cause product deterioration.

3. A pharmaceutical product which was packed in a squeeze (LPDE) bottle suffered loss of a volatile preservative system. A blister overwrap with peelable backing retained the preservative system, reduced moisture loss and acted as a tamper evident feature.

The writer considers it essential that problem areas in plastic packaging are clearly identified, as a problem recognised is usually half way to having a problem solved. The above therefore provides a check-list of what could occur. It is equally important to have a check-list on the advantages of plastic since many of these features are so 'obvious' that they can also be overlooked.

Positive features of plastic

Light weight

The fact that the majority of plastic lie within a density of 0.8 - 2.0 (glass 2.25 - 2.5) and may be moulded in relatively thin sections can significantly reduce distribution costs for the delivery of raw materials, supply of packaging 'material' and the distribution of the packed item. Ref.: The Role of Plastics in the Export and Packaging of Pharmaceuticals by D.A. Dean, published in Plastics and Rubber, Materials and Applications, February 1977.

Lower volume

A plastic container will occupy less volume than the equivalent glass bottle (a glass bottle and a PVC bottle of the same external dimensions will hold approximately 75 ml and 100 ml liquid respectively. The advantage may be less with metal but this largely depends on the process used to produce the metal container.

Lower volumes can significantly reduce the space required to store and distribute both the empty and filled container. This can be even more improved where plastic materials are delivered as reels (form, fill, se operations, i.e. blister packaging) or as granules for manufacture into containers immediately prior to a production line operation (selected examples - Rommelag Bottlepack equipment that forms, fills and seals a liquid into a container on one machine).

Flexibility

Many plastics (thermoplastics) exhibit degrees of flexibility which can br exploited, i.e. squeezing to aid product expulsion, to reduce or adsorb impact or shock, collapsibility (to avoid air being drawn in during use, e.g. bag in box for paint, plasticised PVC bags for blood or IV solutions). Many other areas can be quoted where flexibility adds to the presentation, e.g. overwraps or bags for vegetables, clothing, confectionery, etc., many of which have become so accepted that they virtually go un-noticed. Plastic liners for drums are another useful example.

Water resistance associated with low water permeability

Since most plastics are water repellent plastics can be used for external storage (sacks of fertiliser) or as a protective overwrap to pallets (shrink, stretch or prestretched wraps). Such systems will also increase the stacking strength of fibreboard (protected from moisture extremes from the atmosphere) and further restrict moisture loss or gain between the product and the outside atmosphere. Internal plastic coatings or loose linings in fibreboard, metal containers, etc also enables wet goods, such as frozen fish, to be handled more economically and without risk of interaction with the external material.

Low toxicity/Irritancy risks

Although much has been written on the migratory nature of certain constituents in plastics (e.g. plasticisers from PVC and DEHP in particular) there are few reported cases where migratory constituents have caused difficulties. For example, the vinyl chloride monomer (VCM) saga whilst clearly establishing the dangers of high monomer concentrations at the polymer plant, risks from any packaging usage have remained extremely low. Today Europe and the USA work at a VCM limit of less than 1 ppm for any packaging usage. Many constituents in plastic tend to be non-migratory unless a specific solvent is the contact material. Constituents such as antistatic additives, lubricants and slip additives, etc., which are only effective if they are present at the surface of the plastic although removable by abrasion as well as extraction are normally only present at low levels. Provided plastic formulations are chosen with recognised food grade approved constituents, risks associated with toxicity/irritancy are usually minimal. Special clearance procedures are obviously advised for plastics containing blood or I.V. solutions since these products are administered directly into the blood stream. Extra test procedures are also advised for eye and injectable preparations. Pigments likely to be toxic, based on for example lead, cadmium, arsenic, etc., are now avoided for foods, pharmaceuticals, cosmetics, toiletries and toys. Moulding processes may dictate the presence of certain processing aids.

Versatile moulding and design capabilities

The fact that plastics can be fabricated and moulded by a wide range of processes (injection, reaction injection moulding (RIM), injection blow and stretch blow, extrusion blow and stretch blow, rotational moulding, thermo-forming, cold forming, etc.) gives flexibility in both design, output and quality capabilities. It is also frequently possible to make shapes and configurations in one piece whereas a similar design in metal could involve several fabrication processes plus an additional assembly stage.

Versatility in decoration

Decorative appeal can be added to plastic by various means, i.e. labelling by paper, plastic and shrink or stretch labels; printing by offset lithography, dry offset letter-press, hot die stamping, (silk) screen, therimage and letraset, cliché or tampon, gravure, flexography, jet and laser printing and such in-mould operations as embossing, debossing and transfer printing. Each process may have some limitations - for example gravure, flexography, offset litho and silk screen can be used on film or sheet based materials printed in the flat or from a reel. The fact that the cliché or tampon process can actually print in three dimensions has seen a substantial expansion to this process.

Pretreatment or applying a surface wash or lacquer-type coating prior to printing has also given rise to fewer problems from poor ink key. Protective coatings may also be used after printing, to improve resistance to abrasion, increase product resistance and reduce moisture/gas permeation. (More recent examples include PVdC coated PET bottles).

Improved moisture vapour and gas barrier properties

As indicated earlier all plastics are to some degree permeable to moisture and gases (note permeability of gases is usually of the ratio 1:4:20 for nitrogen:oxygen:carbon dioxide (i.e. carbon dioxide shows the highest permeability). Improved control of wall thickness and the more selective use of materials and processes has meant that more products can be packed in plastic provided the turnover/shelf life is acceptable to the product. It should be noted that a good moisture barrier material may not necessarily be a good gas barrier material. Moisture barrier properties for some plastics are given rough comparative figures below.

Aclar*	(polymonochlorotrifluoroethylene) (PCTFE) $ 20,000 per tonne (trade name Allied Chemical Company)	0.01
PVdC	(polyvinylidene chloride) copolymer $2,500 per tonne	0.1
HDPE	(high density polyethylene) $ 900 - $ 1,250 per tonne	1.0
PP	(polypropylene - homopolymer and copolymer) $ 900 - $ 1,250 per tonne	1.2 - 1.5
LDPE	(low density polyethylene) $ 900 - $ 1,250 per tonne	3.0
PVC	(polyvinyl chloride unplasticised) $ 900 - $ 1,250 per tonne	8.0
PET	(polyester) $ 1,500 - $ 1,800 per tonne	8.0
PS	(polystyrene) $ 900 - $ 1,250 per tonne	60.0

Prices quoted as per Europe early 1984.

Aclar, PVdC, PVC and HDPE have good oxygen barrier properties whilst LDPE, PP and PS are considerably inferior. Aclar (Allied Chemical Co.) although the most inert and impermeable plastic is also the most expensive. Other than a coating for pharmaceutical blister packs it has few commercially viable packaging applications. The total economics recommending the use of any one plastic are dependent on many additional factors, i.e. density, moulding cycle, (temperature/cooling), moulding process, design, capital expenditure, etc., as no decision should be taken on polymer price alone. Barrier properties can usually be improved by coatings, co-extrusions etc. but at an additional cost.

Versatility in appearance - colour, clarity, opacity, texture, etc. Plastics can be produced which are clear, completely opaque, have metal finishes (metallised), opalescent, marbled etc. with a whole range of textures from high gloss, matt, artificial leather, etc. Light penetration can be restricted by pigmentation (carbon black being the most effective), dyes and the use of UV absorbers. Metallisation may be used for decorative effect or to reduce permeability to moisture. Metallisation can be a relatively variable process hence the barrier properties achieved have to be critically evaluated. A metallised PET, coated with LDPE to give additional scuff and flexing resistance can offer barrier properties approaching that of 9 um foil. Scuff and flexing resistance can be poor if a protective layer is not included. Metallised materials are finding success in bag-in-the-box applications (e.g. paints), and in sachets and flow wraps. Opaque materials are available in a wide range of colours. White opaque may be obtained by the use of fillers such as chalk or talc, whiteners (titanium dioxide 1 - 3% level) and modified by optical brighteners (e.g. ultramarine.

Colouring can be carried out by precompounding, dry colouring, liquid and solid master batching and concentrates or high let-down master batching. Fillers, depending on their affinity for moisture can either increase or reduce moisture permeation. This also applies to other constituents, for example, plasticisation of PVC can cause a significant increase in moisture permeation.

Versatility in material modification to assist certain properties

Examples:

Stackability and stability (will not slide so readily) can be improved with plastic sacks if an anti-slip additive is incorporated into the material. Reel fed form fill seal operations can be improved if friction and drag (possibly leading to stretch) is reduced by the addition of a slip additive. Circumstances could however be envisaged where the above two features are in conflict with each other.

The incorporation of lubricants into the polymer can assist a moulding operation and lead to less rejects or generally improve the overall quality of the item being moulded.

Reuse of clean scrap, i.e. regrind

Scrap from moulding processes (e.g. tops and tails from extrusion blown bottles, sprue and runners from injection mouldings), if handled cleanly can be recycled provided it is permitted and has not been subjected to excessive (e.g. overheating) conditions. Regrind up to a defined level, e.g. 20% is frequently allowed. The moulder should however obtain permission for the 'user' and have it written into any specification.

Product resistance

Although plastics cannot be described as inert and lack the high level of compatibility enjoyed by glass, plastics exist which can be used for a majority of products (for example plastic petrol tanks are currently becoming a distinct trend).

Few problems exist with many aqueous-based products provided they are not strongly acid or alkaline. Greater selection has to be exercised with organic-type solvents, volatile oils and synthetics generally. Vegetable oils, for example, which are widely sold in PVC would not be suitable for storage in LDPE where both oxidation and penetration of the oil through the container could occur.

Easily altered or modified so that specific properties can be more readily exploited

This can be achieved by both physical and chemical means (see earlier). Physically, plastics can have their molecular structure orientated in a machine and/or cross direction by a process of stretching at a temperature below the material melting point. Orientation in films provides a shrink wrap material unless the film is held and heated to 'set' the in-built 'stretch'. Newer process such as injection stretch blow and extrusion stretch blow involve a stage where the parison is cooled and stretched (orientated) prior to the final blowing operation. Orientated materials show improvements in both physical and chemical properties, i.e. improved clarity, impact (drop) resistance and lower moisture and gas permeability. The highest success (USA and Europe) is found in PET (polyester) stretch blown bottles in the 1 - 2 litre size for carbonated drinks and coated PET bottles for beer. PVC and PP are also being stretched moulded. Bottle shapes for some designs, currently have some restrictions with the base which may either have to be 'petalled' or rounded. In the latter case a base cup has to be added to give stability. (As seen on larger 1 - 2 litre containers). With this interest in PETP for stretch mouldings, interest is increasing in the use of this material (or PETG by KODAK) for conventionally, moulded bottles. Stretch blown PVC bottles are usually cheaper and more resistant to drop (impact) than a conventionally blown impact modified grade. The addition of an impact modifier to PVC (normally up to 15% of MBS)* is a further example of how the properties of a plastic can be changed. Straight PVC is likely to shatter if dropped when full with product at a 1 metre drop height. The addition of the modifier overcomes this problem. Impact modified PVC (with vinyl acetate*) will also thermoform faster, at lower temperatures, and give better distribution than an unmodified material, and is used for blister or bubble packs.

However, the addition of modifiers will increase permeability to moisture. Stretch moulded PVC bottles can achieve good drop resistance without the additional costs associated with the use of a modifier. Although additives are the group of substances used to modify a plastic, it

* Note: MBS is used in bottles whilst vinyl acetate is usually used in PVC films used for thermoforming. MBS = methyl methacrylate butadiene styrene.

should be recorded that plastics, in terms of total constituents may also contain residues and processing aids. Since terminology in the industry tends to be rather loose it may be necessary to ask questions on additives, residues and processing aids from the polymer supplier, compound/master batch supplier and convertor, if the detail on the total constituents is to be obtained.

The more commonly found constituents which may be in plastics include:

monomer residues
catalyst
accelerators
solvents
anti-oxidants
emulsifiers
mould release agents, lubricants
fillers
colourants - pigment and dyes
stabilisers (for PVC)
plasticisers - modifiers
extenders
slip additives
antislip additives
antistatic agents
whiteners and opacifiers
UV absorbers
flame retardants
antiblock agents
release agents

Reference to many of the above are found throughout the text.

Undue publicity and emphasis on plasticisers has frequently led to misuse of this word, particularly as many less informed people see plasticisers as being migratory, possibly toxic and found in most plastics. It must be stressed that relatively few plastics contain plasticisers. (The main ones which are plasticised include PVC and the cellulose group (acetate, butyrate, propionate, etc.)). However, the question 'does the plastic contain plasticisers?' should frequently be re-addressed to the word 'additives' (processing aids and residues).

Most plastics can be 'welded' by one means or another

More important with engineering applications but welding may occasionally be used in a packaging context. Methods of welding include hot gas, hot plate, high (or radio) frequency, adhesives, 'spin' and friction, and ultrasonic.

Coextrusion and lamination

For film and sheet material the properties of two or more plastics can be combined by multiple extrusion or lamination. These materials, depending

on their thickness, can be used for sachets, strips, blisters, tubes, solid phase pressure forming (SPPF), scrapless forming process (SFP), conventional thermoforming or directly coextruded and blown into a container. Co-extrusion though excluding the use of paper and foil does enable the best properties of several plastics to be combined.

Positive Features - Summary

The above list, although not complete, clearly establishes both the flexibility and versatility of plastics and the processes associated with them. Many of these plus features can be combined to the general benefit of plastic packaging. Since packaging is inevitably a compromise of many factors, the earlier listed negative factors can either be overcome by selecting the plastic (e.g. a LDPE with a low melt flow index will normally eliminate a stress cracking risk), by preventative measures (e.g. using additional protective packaging to reduce risks associated with permeation of moisture, oxygen, etc.), process controls or by simply accepting that the positive features outweigh any disadvantages. A number of examples of specific package or pack component usages are identified below to emphasise the effective utilisation of plastic.

New closure systems

1. Wadless closures

A range of wadless closures are now widely used on metal, plastic and glass containers for solid and liquid products. The materials used include LDPE, HDPE and PP. The seal part of the closure can be achieved by a plug, an internal skirting, sealing rings or a curled-over feature (this is sometimes referred to as a 'crabs claw').

2. Pilfer resistant closures

Again, a similar range of plastics are used. Designs include lock-on bead with tear-off skirt, rachet bottles with interlocking tear-off skirt, or heat shaped under lock with screw-off perforated tear caps (e.g. Obrist closure) or caps with perforated extensions which lock on bottle with lugs, etc. Heat shrinkable (PVC) seals provide another means achieving a pilfer resistant system. (Note increasing world wide interest since the Tylenol affair in the USA in September 1982).

3. Child-resistant packs and closures

Virtually all reclosable child-resistant packs are based on plastic, with squeeze, press down, line-up features being widely utilised to achieve release. In the case of blisters and strips child-resistance is achieved by hidden access features, in between unit perforations or by the strength of the material used. Opaque or deep tinted materials are essential to make the contents less attractive to children. Peelable and heat sealable packs such as blister, strips, sachets are inherently tamper evident.

4. Overwrapping, collation, pallet stabilisation

Shrink, stretch, prestretch stretch wraps are being increasingly used to stabilise pallets, overwrap packs and items (either for purpose of collation or to reduce general spillage, or simply to make the product self-identifiable (recognition) or to encourage the more responsible handling of semi-fragile goods.

5. Closures - General

An increasing proportion of plastic closures are moving from thermosets (UF and PF)* to thermoplastics (PS, PP, HDPE). Whereas years ago a wide range of waddings and facings were used these are gradually reducing in number. Composition cork is largely being replaced by pulpboard, expanded polyethylene and flowed-in compounds. The most widely used facings include PVdC, polyester, vinyls (reducing) and polyethylene (reducing).

Sprinkler top closures (widely used for powders and at one time all in metal) have gradually been replaced by plastic.

Dispensing fitments for toiletries, pouring aids for medicines and difficult to control products, and general dropper systems for food colourants, sweetening liquids, etc., are further extending the use of plastics. Plastic toggle caps are an extension of dispensing aids in that the caps contain spouts or tubes for controlling the flow of a product from a squeezable plastic container.

Container trends

To overcome the poor size impression of single walled plastic jars when compared with the thick walled glass jars then available, double shell plastic jars became the vogue in the late 50's, early 60's. A recent ruling in the UK which argued against the deceptive nature of double walled jars, has made the single walled, smaller jar virtually acceptable overnight. Single walled jars are now widely available in HDPE, PP, PS although the latter material may be suspect for creams where moisture losses can be problematical.

The plastic can - 1/4 litre bottles in polyester (PET), PP and PVC with a wide neck have recently been introduced as a further competitor to the metal can and glass bottle beverage containers. Coextruded materials which can be thermoformed, e.g. PETP/PVdC/PE are also competing in this field.

Plastic drums

Increasingly stringent safety regulations for the carriage of dangerous goods and chemical substances generally are encouraging the use of fairly thick walled plastic drums with high molecular weight, high density poly-

* (urea formaldehyde and phenol formaldehyde)

ethylene being the preferred material. Drums of this nature have good impact resistance (including drop strength), good stacking strength, good chemical resistance and although some degree of chemical absorption may occur this is usually extremely small. However, if drums are reused it is always advisable to refill with the same material.

Films, foils and laminates

The use of plastic films and coatings is showing continuous growth with a predictable expansion in the future due to the more recent success of retortable trays and pouches. As a laminant ply plastic can play a variety of roles, covering heat sealing and cold sealing, protective plies giving climatic and biological protection and as a decorative ply to aid presentation. Collapsible tubes made from laminates are now showing a fairly rapid growth. An injection moulded neck is bonded to a tubular body lamination.

The more widely used heat sealing plies include LDPE, LLDPE, ethylene vinyl acetate (EVA), polymers modified with EVA, PVdC, Surlyn (Iomomer, DuPont) and a range of heat seal coatings. Surlyn in spite of its higher cost has seen considerable success in Europe and USA as it shows advantages on lower weight, lower caliper of ply, lower sealing temperatures, a wider in the seal (both powders and liquids), all of which lead to fewer rejects and higher output speeds.

For clarity, polyester, cellulose acetate (poor in dimensional stability), certain gauges and grades of polypropylene are widely used and for a protective over lacquer (against rub and permeation) PVdC provides a useful coating base. Coextrusions can give higher barrier properties by the selection of the correct material provided relatively long runs are involved. Coextrusion materials can be used to make bottles, thermoforming etc. Typical coextruded combinations include:

PS/PE, PS/PP, PS/PE/PS (medium barrier materials), and

LLDPE/EVAL/LLDPE)
HIPS/PS/PVdC/PS)
HIPS/PS/PVdC/PE)
PS/Eval/PE) which give relatively high barrier properties
PP/PVdC/PP)
PP/Eval/PP)
PETP/PVdC/PE)

(EVAL or EVOH = ethylene vinyl alcohol)

Note 'tie' layers are frequently used between materials hence some of the above are actually made of more layers than those initially indicated, i.e. PP tie layer EVal tie layer PP is used for blow mouldings to make ketchup bottles in the USA.

Films

Polypropylene film is still finding increasing usage as a laminant ply, as an overwrap material replacing cellulose film, and as a form fill seal material for bags, sachets, etc. The brittle nature of PP at lower temperature is overcome by copolymerisation, usually with ethylene. This addition improves its sealability. Coated PP using either a PVdC or PE coating also gives a good heat sealing and protective lamination. LLDPE linear low density polyethene, which is a combination of ethylene with either butene-1, octene-1, is a relatively new family of polymers which according to all accounts will largely replace LDPE as a film material in the near future. LLDPE also shows certain advantages over LDPE for other applications involving injection and extrusion moulding. Although the initial cost of LLDPE may be slightly higher than LDPE, the fact that it can be made in thinner gauges with good impact, tensile and tear resistance make it economically viable for stretch wraps, bin liners, bags, etc. Large usage is already being seen in the USA, Canada, Japan and Europe. However, competition is being met by combinations of LDPE with MDPE or HPDE, vinyl acetate/PE copolymers and other combinations: bubble film (film containing bubbles of air) is being increasingly used for product protection. Polyester, nylon and polypropylene strapping has widely replaced metal strapping. Plastic sacks, woven or unwoven, are offering a significant competition to paper sacks.

Form fill seal - Reel fed

Reel fed materials passing through a series of stages whereby the material is formed into a container which is subsequently filled and sealed are on the increase. As well as the better known thermoforming processes (vacuum, pressure forming with and without plug assistance), forming at lower temperatures (to give orientation) and cold forming are now finding specific applications. Both the food and pharmaceutical industries are using a cold forming process for such materials as nylon/foil/PE, polypropylene/foil/PVC and nylon/foil/PVC. These materials enable a fairly thick gauge (4o um) of foil to be stretched without perforation provided the form is well radiused and not too deep and angular. The formings give virtually 100% protection against moisture and gases and can be used for a retortable tray pack with the correct material combination. From a pharmaceutical point of view cold formed blisters are not only competitive with foil strip packs but occupy less space, are easier to handle and provide a similar high level of moisture protection. Conventional pharmaceutical blister and strip packs for solid dosage forms vary considerably in their usage throughout the world, i.e. less than 5% in the USA, approximately 20% in the UK and approximately 80% in Germany. Whilst the latter mainly use blister packs of the pushthrough type, the USA relies on peelable liddings. These conventional blisters use UPVC, and combinations of UPVC/PVdC, PVdC/PVE/PE, PVC/Aclar as the thermoforming ply, with paper and foil covered with heat seal layer for the peelable or push-through lidding. However, none give a high level of moisture protection, hence the need for a foil bearing material (strips or cold formed blisters) if moisture sensitive products need to be packed in a unit dose form.

Expanded plastics

The density of plastics can be further reduced by producing a cellular structure to give an expanded material. Expanded polystyrene is most used, usually to mechanically protect such delicate items as camera, TVs, videos, either as set formed pieces or as small pieces as a filling. Material can also be formed directly around an item when in its final pack. Expanded polystyrene sheets (sometimes laminated to polyethylene) are also used as protective covering. Plastishield (trade name) coated glass is an excellent example of a marriage between glass and plastic which enables a light-weight glass bottle to withstand impacts on the production line and in transportation. PVC coatings (plastisols), shrink and stretch labels also add to the protection of glass containers. Expanded materials can also be used to give insulation for products which require specific storage conditions (e.g. vaccines). Expanded polyethylene is now being widely used as a cap wadding, replacing naturally based composition cork.

Other coatings

Cold sealing

A material based on a plastic coating which can be sealed by pressure offers faster throughput for a form fill seal process than one involving heat. Cold sealing materials have therefore been developed and are in use for confectionery sticks and bars (i.e. flow wraps).

Labels

Two label types are based on plastic coatings (a) self adhesive labels and (b) heat seal labels. Both types are extending in use, frequently at the expense of plain paper labels which are applied by the addition of an adhesive (dextrin, starch, PVA, etc.). Coated labels present advantages in cleanliness, less machine down time, improved tack and setting time and their ready application to a range of substrates. Both heat sealing and self-adhesive labels are available in cut singles and reel fed form. Since the latter indicates a degree of security, reel fed labels now with an additional identity code have become widely used for pharmaceuticals and products where security is essential. In the USA heat seal labels are predominant whereas in Europe self-adhesive labels are preferentially used. Application speeds up to 600 labels per minute are now practical with both.

Environmental issue

The above examples emphasise the extensive usages of plastics in packaging. However, no paper would be complete without reference to certain environmental issues, which may occasionally take on an emotional aspect. Although many plastics are derived from petroleum, it should be noted that the main use of petroleum products are related to transportation and the production of energy whereas conversion to plastics still remains a relatively small percentage. Plastics do suffer criticism when compared with other materials in both energy required to convert them into a packaging application and difficulties associated with reuse and recycling. The

attached Table 1, ex Metal Box Company, indicates typical energy comparisons.

Reuse of plastic packaging other than for the larger containers as mentioned previously is not usually recommended, except where circumstances have clearly established that reuse (plastic milk bottles in polycarbonate) is practical. Recycling again is difficult as once a plastic has been used for a product, some degree of contamination may have occurred. There is also a significant difference to the recycling of glass as cullet where the material is reheated to around 1200°C, thus driving off virtually all likely contaminants (other than certain metals) as carbon, hydrogen, etc. Plastic scrap from the converting processes is suitable for recycling provided it is not contaminated by oil, dirt, dust during the conversion process. Whether a plastic is recycled as regrind from the conversion scrap largely depends on the final usage - it may not be permitted or restricted where food and pharmaceuticals type products are involved. Recycling is also difficult for a mixture of products involving various plastic packs since individual plastics cannot usually be segregated. Usages for recycled materials therefore tend to look for opportunities where an admixture of plastics can be found, i.e. pallets, corrugated sheets for roofing, cavity wall insulation, etc. 'Flotation' methods can provide limited segregation of plastics.

Conclusion

The introduction indicated a number of ways plastic and packaging could be considered. These have only been covered on a very broad basis in this paper. Each of the many aspects touched upon could be expanded into a topic which, when discussed in detail, could form a conference in its own right.

It is perhaps reasonable to conclude that every packaging function is a compromise of many factors - whether the compromise reached is the best can only be judged by the functional and aesthetic success which in turn relates to both the initial sell-in and the follow-up sales. The roles of plastics in packaging is already a success story and will continue to increasingly dominate the packaging scene. The environmental issues are being closely studied and will ultimately be solved by common sense and logic.

Two final points. First, the above paper places emphasis on the plastics which are already successful and economic. Although expansion tends to develop along such a path, usages for higher priced materials, like polyester (current prices in Europe $1400 - 1600 per tonne), can occur, with a result that the larger volume applications can further reduce the price of the basic material. Many plastics which have not been mentioned have and will have packaging applications, particularly where certain specialised properties are required. Their exclusion from this paper does not mean they have been forgotten, but that time and space has not permitted their inclusion. Secondly, any future developments in the extension to plastic packaging will largely depend on consumer trends and their purchasing power. Europe, the USA, etc. have seen two virtually opposing trends, the need to have smaller portion packs to meet the demands of a growing elderly population and the need for larger pack sizes to meet the demands of the less frequent shopper, i.e. shopping done once a month instead of once a week.

An acute awareness of such trends is essential to predict any packaging development with constant reference to the definition of packaging given in the introduction. Other recent general trends which will benefit plastics include aseptic and controlled atmosphere packaging for a variety of foodstuffs.

Table 1: Energy used in container production (Toe*/Tonne)

	Tinplate	Aluminium	Plastics	Board	Glass
Conversion to containers	0.1	0.2	0.4	0.05	0.1
Heating and lighting	0.04	0.08	0.16	0.07	0.04
Transport of containers	0.02	0.02	0.06	0.02	0.02
Raw material production	1.0	6.0	2.3	1.45	0.3
TOTAL	1.2	6.3	2.9	1.6	0.5

* Toe = Tonne of oil equivalent

By kind permission of the Metal Box Co.

I am indebted to Fisons plc - Pharmaceutical Division for their support in the production of this paper. The opinions expressed are my own and do not necessarily constitute an indication of Company policy.

ANNEX III

The Pharmaceutical Clearance of a Plastic Pack/Device

D.A. Dean

"GMP is both a philosophy and an acquired attitude of mind aimed at protecting both the producing company and the patient".

"GMP applies to both product-pack development and subsequent production".

A primary function of the pharmaceutical industry is to cure or alleviate suffering or disease. As many products are likely to generate some secondary or side effects, 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 time, effort and money 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, and convenience, until such time as the product is used or administered. As this definition of a pharmaceutical pack is normally required to maintain a shelf life of 3-5 years, in depth testing is an essential requirement. The pharmaceutical industry therefore requires in most instances a level of safety which is superior to that of a foodstuff. This is of particular relevance when one considers that drugs are only normally taken 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 over a long period for pharmaceutical products, it should not be assumed that they are inert or that they are the ideal packaging materials, either technically or commercially. Glass for instance is particularly hazardous when it breaks and glass of the alkaline type can readily alter the pH of non-buffered aqueous solutions. The considerable increase in the use of plastic has frequently 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, and last but not least, at competitive and economically acceptable prices. New concepts, which would not be practical in glass and metal, have also assisted both the progress of plastics and the pharmaceutical industry. Thus when it comes to new pharmaceutical

products, plastics 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 rarely as inert as other 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 the author would stress that in many instances this might be considered unfair, plastic can at least be used as an example of how a material can be thoroughly 'cleared' in the widest pharmaceutical context.

Aspects which may need consideration can be identified from the following:

Functional and aesthetic design
Process of manufacture
Selection of plastic type - general physical and chemical properties
Selection of plastic grade - detailed physical and chemical properties, plus knowledge of ingredients
- toxicity and irritancy aspects
Compatibility requirements - with product involving
Feasibility stages
Formal stability stages
Performance requirements during

use
warehousing
distribution and
display including
closure efficiency
durability of identification/decoration/print
development versus production pack

plus possible special tests such as environmental stress cracking resistance; surface changes, e.g. crazing; panelling/cavitation etc.

Although certain of the above have been listed separately, in actual 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 ingredients found in the plastic. It is therefore intended to discuss some of the above factors on a broad basis and then consider the 'safety' clearance of a particular plastic in greater depth.

Design - can be considered a relationship between size, shape, colour, including opacity or transparency, the type of closure and the functional and aesthetic requirements of the pack.

Functional aspects must be considered in the broadest context, i.e.

(i) Efficiency and ease of production for supplying company - for instance will production involve wastage due to deficiencies in the design or even problems with handling/transportation.

(ii) How can container be effectively unscrambled and cleaned if necessary.

(iii) Minimum of production line problems during filling, closuring, labelling,

cartonning, etc.

(iv) Satisfactory in situations involving stacking and transportation.

(v) Suitable for all aspects of patient usage.

(vi) Effective in terms of opening and reclosing where applicable.

(vii) Meets such newer aspects related to acceptance in terms of the packaging code practice, i.e.

- disposal, conservation of energy, recycling and reuse.

- not be deceptive, etc.

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 in that it aids the administration of the product.

Depending on whether a design requires rigidity or flexibility, this will relate to the type of material and distribution of the wall thickness. Good radii and the avoidance of square or angular designs are essential if a good wall distribution is to be achieved. Poor wall distribution, particularly where thin sections are involved, may also reduce the product shelf life by increasing the effects of permeation and migration. Whereas gas permeation is directly related to thickness, water or water vapour permeation does not halve or double according to whether the thickness is doubled or halved. Since some product ingredients will diffuse through a plastic by solution in the plastic followed by volatilisation from the external surface the effect of wall section thickness will be largely related to the solubility coefficient.

Design wall distribution will also relate to the physical strength of the container and its ability to withstand drops and possibly breakage, if brittle, top pressure during long term stacking, which may lead to distortion or spilling, function and handling during use, and production filling, capping, etc. In the latter instance the top pressure applied during a capping operation may be quite significant with considerable distortion to the container. This may occasionally have to be overcome by alternative closuring methods or supporting the container during capping by holding the body or by holding the neck.

The effectiveness of the closure will depend on the design of the bottle neck and closure which in turn must relate to the material from which the closure and container are made. Where a flexible material is used, a buttress thread is to be recommended. However, if the material is substantially harder, e.g. HDPE, PP or PVC a conventional type 60°C thread as detailed in BSI 1918 (R3/2 and R4 finishes) can be employed.

The aesthetics of a container are of equal importance to both ethical and OTC packaging although this requirement may differ between the two. Ethicals must generally be elegant, simple with clear and concise wording

which tones in well with the presentation in order that a mutual level of confidence can be created between the product and pack. Although this may equally apply to some proprietary products these tend to require greater eye appeal to attract a purchasers' attention, particularly if they are to be self-selected.

Process of manufacture

Pharmaceutical containers can be produced by a number of moulding processes, each of which being influenced by the design and the material to be employed. These processes 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.

Preformed containers can be manufactured by:

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

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

Without going into indepth detail the broad advantages and disadvantages of these processes are as follows:

Injection moulding

Ideally suited to most types of component, i.e. caps, aerosol valve components, plugs, etc. and full aperture (wide mouthed) containers such as tubes, tubs, vials, etc. With the simplest shapes (e.g. tubes or tubs) undercuts must be avoided and containers must taper from opening to base to allow easy removal from the mould, if a two piece simple mould is to be employed. More complex mouldings using split moulds, travelling inserts, core pins* can be used for more intricate designs but tooling up costs are considerably higher. A simple single impression mould can cost £750, six impression £2500, 16 impression £7000, 32 impression £12000 etc. The cost per item will reduce significantly as the number of impressions or moulds increase so it is a case of balancing between the quantity required, how long the savings with the lower cost will take to equate with higher tooling costs, and what can be afforded in terms of capital expenditure.

* retracting

Injection blow moulding

In this process a container is moulded in two stages. The first stage involves an injection moulded parison during which process the neck is formed, with an initial body shape. This is then transferred to a cooled finishing mould where the parison is blown to the final shape. The design of the parison is critical to wall distribution in the final container. Since the neck section is injection moulded in the parison stage better control can be achieved on this part of the moulding than with other processes.

Extrusion blow moulding

This consists of extruding a round or oval tube (the parison) downwards which when of the correct length is clamped into a finishing mould. This process welds the tube at the base (pinch off) with a double pinch off at the neck and which leaves an open tube into which a blowing pin extends. Air is then blown into the tube so that it is extended to the full size of the cooled mould. The pinch off (wastage) known as tops and tails are subsequently removed either automatically or by hand. The extruded tube may be blown either neck downwards or neck upwards depending on the type of equipment involved. Machines may extrude a number of tubes at a time with a similar number of finishing moulds, have tubes furnishing two sets of usually reciprocating moulds, or have a simple extrudate which is picked up by a number of rotating moulds on a carousel.

Thermoforming consists of softening an area of relatively thin plastic (150-400 micron) by heat and then drawing it in to or onto a mould by vacuum, pressure or mechanically or a combination of these. The process will produce a preformed container such as a tub, or pot or a series of formings (for a form fill seal process) from a continuous reel. A typical application of the latter is found on blister packaging equipment.

Cold forming is somewhat similar to the above in that a material is forced into a mould by pressure or between matching male/female moulds (or a combination of these) without the use of heat. Certain plastics and combinations of plastic and foil can be cold formed to give either preformed containers or blister like packs.

In both thermoforming and cold forming the starting material can either be sheets or a continuous reel.

Stretch and blow is a new process, which is currently being used for soft drinks, in the form of polyester 1 and 2 litre bottles, may ultimately become a process for pharmaceutical containers. Although the container is again made in two stages the second stage consists of blowing the parison at a temperature below its softening point. In this way the material is orientated thus giving a clearer, stronger pack which offers lower permeability than an unorientated material. The speed of production related to all of the above processes depends on the number of articles produced in a given moulding cycle. This cycle involves heating the plastic to correct

temperature, transferring it through the moulding operation(s) and then a cooling phase, after which it is removed from the mould. The selection of incorrect moulding conditions will affect both the production rate and the quality of the mouldings.

Decoration and printing is usually an extension of the process of manufacture although in mould debossing or embossing or the use of in mould transfers may be employed.

Decoration and printing may use one of a number of processes:

Paper or laminated labels
Shrinkable sleeves
Dry offset letterpress
Silkscreen
Hot die stamping
Transfer processes - therimage, letraset, dinacal, etc.
Cliché print, i.e. tampoprint - tampon transfer
Card sleeves

It should be noted that migrating substances may occasionally arise from the printing process, i.e. inks or solvents. Flexographic and gravure printing are used solely for plastic films.

Materials and their properties

A basic knowledge of the chemistry of plastic, the polymerisation processes by which they are made, and their physical and chemical characteristics or properties is essential. Although plastics can initially be divided into two groups, thermosets and thermoplastics, their relative usage now firmly falls in favour of the thermoplastics. Since most believe that thermosets tend to be restricted to closures where there is no contact between the product and the closure, the fact that certain internal coatings (lacquers) are thermoset based is frequently forgotten. Thermosets such as urea formaldehyde, phenol formaldehyde 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 or overcure therefore reflects in sub-standard material. As with the thermoplastic materials residues will inevitably remain and these, in spite of the cap liner, may occasionally migrate into a product. These residues may be phenol, formaldehyde and ammonia. The latter is particularly likely with phenol formaldehyde caps where the formaldehyde may be fixed by using hexamine + phenol in the condensation polymerisation reaction. Thus during the 'cure' both water and ammonia are released - some of which being retained by the moulding.

Thermoset lacquers are found in use in adhesive systems (including laminations) and as coatings for metal tins and tubes (i.e. epoxy resin and urethane chemicals).

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, four basic types stand out as more economically viable than the others. These are

polyethylene LD, MD and HD
polystyrene GP and various impact grades
polypropylene monomer and copolymers
polyvinylchloride - plasticized and unplasticized

The cost of these start in the region of £650 per tonne (for 5 tonne lots) and rise to around £800 depending on the type and grade.

Price increases occur according to whether a material is natural, white opaque or coloured.

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 this may be quite acceptable for many non-critical usages, further parameters must be considered when the plastic is to be used for injection and eye type products and possibly this will extend to other products. This is because each plastic may contain different ingredients.

Of the economical plastics mentioned above polystyrene certainly of the general purpose (GP) type is becoming less popular, as it is one of the most brittle plastics, unless it is impact modified. GP styrene is also highly permeable (compared with most other plastics) to moisture and gases. It also has poor solvent resistance and in contact with isopropylmyristate (which is used in many pharmaceutical formulations) crazing followed by embrittlement and total disintegration occurs.

Impact modified or toughened styrene (which normally incorporates a small proportion of synthetic rubber) is generally less transparent (GP, PS has excellent clarity and transparency), more flexible but again poor 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 and gas transmission is required. These materials have generally good resistance to chemicals, particularly many organic type products including 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. Densities of LDPE to HDPE range from 0.912 - 0.965, with MDPE within the middle range of 0.925 to 0.940. Rigidity, crystallinity (a property related to moisture and gas transmission) chemical and particularly oil resistance all increase from LD to HD. Low density polyethylenes may be prone to environmental stress cracking, a phenomenon associated with either an internal or externally applied strain in the presence of a stress cracking agent, unless a material of low melt flow index ie less than 1.5 is used.

Polypropylene usually has similar properties to HDPE with a much lower density .905 - .910. Its clarity and transparency may be improved by orientation.

Polyvinylchloride is rigid and transparent although it lacks the sparkle of polystyrene and is less brittle. Drop strength is further improved by the use of an impact modifier such as vinyl acetate. PVC is moderately permeable to moisture but has excellent resistance to oil and oxygen permeation. Plasticized PVC has high flexibility and it is particularly useful when a collapsible pack is required. It is a poor barrier to moisture and only a moderate barrier to gases.

Of the four economical plastics PVC (both plasticized and unplasticized) tends to be worst for the total ingredients/additives present. LDPE is generally likely to contain the least with PS, HDPE, PP being slightly worse. How these ingredients can be identified, quantified and 'cleared' is discussed in greater detail later.

Other thermoplastics

The use of other plastics tends to be related to specialised needs and whether their advantages justify the additional cost. Costs may range from £800 per tonne (ABS) through £3500 per tonne (Nylon II) to Aclar (polymonochlortrifluorethylene (PCTFE) ar around £13,000 per tonne. Aclar is however the nearest approach to an inert/impermeable plastic. It is approximately ten times less permeable than Saran (PVdC - polyvinylidene chloride) which is widely used as a film coating. However foil even when thin (.007 mm) remains the best barrier material.

Amongst the plastics which have limited but specialised usage may be included:

The cellulosics - cellulose acetate, cellulose butyrate, cellulose acetate butyrate, cellulose propionate, this group is one of the few which contain plasticizers.

Polycarbonate
Styrene acrylo nitrile (SAN)
Acrylonitrile butadiene styrene (ABS)
Polyester - polyethylene terephthalate or terylene
Polyvinylidene chloride (PVdC) a copolymer
Polyamide - nylons 6, 66, 610, 11 and 12
XT polymer, poly 4 methylpentene
Phenoxy
Polypropylene oxide (PPO)
Acrylonitriles i.e. Barex, Lopac (trade names)
Acetal copolymers and homopolymers (polyformaldehyde)
Ionomer resins, e.g. Surlyn (trade name)
Polysulphones
Polytetrafluorethylene (PTFE)
Polymethyl methacrylate

Plastic grades

Once a plastic type has been broadly selected the final grade can be decided. Grades are generally based on density, melt flow index, the fabrication process for which they have been made, usage i.e. food, consumer durables, car accessories, etc. and the additional ingredients which they may contain.

These ingredients may include:

Anti-static additives, UV absorbers, anti-slip additives, slip additives, colourants (pigments and dyes), opacifiers, fillers, extenders, plasticizers, stabilizers, impact modifiers, anti-oxidants, lubricants, etc. which may be added at the compounding stage.

However, other ingredients may be present from the polymerisation and/or the converting process.

The polymerisation process may involve two basic groups:

Residues - i.e. ingredients remaining from the polymerisation process. Residues may include monomer(s), emulsifying agents, solvents, accelerators, catalysts, etc.

Processing aids - additional substances to aid or prevent something. Processing aids may include anti-oxidants.

The converting or moulding process may also include the use of processing aids. These may consist of lubricants, mould release agents, etc.

It should be clearly stressed that asking the question "What additives are included?" is frequently unlikely to provide information related to the polymerisation or converting process since additives tend to be added at the compounding stage. An additive is normally used to modify a plastic in order to give it a specific property.

Toxicity and Irritancy - Safety aspects

Although in an ideal situation no extractive from or loss into a plastic should be permitted, in most practical circumstances some compromise must be reached between both of these possibilities. One is thus required to identify not only the level of migration from or to the product but whether any risks have been incurred in terms of the products effectiveness or toxicity/irritancy. In respect to the latter, data is generally more readily available on toxicity aspects than irritancy. Thus before one decides on the type of clearance procedures which can be employed, the vital question is whether one is justified in choosing a pack involving a plastic. It is therefore proposed to explore this background in order that the safety stages in 'clearing' a plastic for a pharmaceutical usage can be identified.

Stage One

Material background

In order to investigate any potential risks associated with plastics, information is required on both the plastic and its ingredients and the analytical means by which they can be identified and quantified.

In an ideal situation there should be a discussion in which the pharmaceutical industry meets with the 'suppliers' identified above.

Finally, if this information is forthcoming, it should be noted that certain aspects may have to be incorporated into the packaging material specification, e.g. "No lubricants to be used". This may be relevant if magnesium and zinc stearate or similar lubricants are incompatible with either the drug substance or certain excipients.

If the above information cannot be obtained, then some formal guarantee that the polymer and the included ingredients meet some level of Food Clearance (FDA, German, French, EEC, etc.) must be sought. This type of information is normally accepted as the minimum information required before a plastic is considered further, in the development stage of a pharmaceutical product.

Stage Two - Extractive tests

The next testing phase is normally an extractives procedure either to a company in house standard or an externally recognised standard (i.e. USP/NF extractives tests USA, WHO 26th report, etc.) covering chemical extractives and toxicity/irritancy, using pharmaceutical simulants under selected conditions of time and temperature. These tests can generally be classified under three categories.

(i) National regulations and compendial standards and guide lines.

(ii) Standards issued by Standards Institutions.

(iii) International Guide lines proposed by the World Health Organisation (WHO).

A survey carried out by Jack Cooper under the auspices of WHO resulted in the publication of Plastics Containers for Pharmaceutical Testing and Control in 1974. This then covered all the available data on categories i) and ii) above and as a result iii), Technical Report Series 614 (WHO Export Committee on Specifications for Pharmaceutical Preparations) 26th Report was published in 1977 (available through HM Stationery Office or booksellers). The main proposals relate to IV and ophthalmic products (see Appendix I). The interpretation of these tests will depend on the product and the product usage.

Stage Three - Formal product/pack compatibility and shelf life testing

The third stage covers feasibility testing (initial testing to establish the general suitability of the product/pack combination including accelerated

testing) which then leads to a formal stability programme. The latter usually lasts up to 5 years, where the drug and pack is regularly analysed for changes, degradation, migration, etc. and may over the period of test involve further toxicity/irritancy tests to check that no significant changes occur in the product or pack when it is stored under a range of climatic conditions.

As mentioned earlier the word ingredients has deliberately been selected, as additives can be wrongly interpreted as those ingredients added at a compounding stage and thereby exclude chemical entities involved in the polymerisation stage or processing aids which can be used at this or the conversion stage. However, there is still a certain reluctance for manufacturers, compounders and converters to declare ingredients to the pharmaceutical industry although there is a reasonable willingness to provide this information to official regulatory or government departments. This situation has and is improving but obviously where ingredients are not identified, greater difficulties are experienced in pronouncing clearance. Whether such information is freely given or not, it does seem relevant to pose three sets of questions, i.e.

1) Of the polymer manufacture for each identifiable grade

   i. What ingredients (catalysts, accelerators, antioxidants, emulsifying agents, etc.) are used in the polymerisation process and what level of residues (particularly monomers) can be expected?

   ii. What toxicity/irritancy data is available on these?

   iii. What levels of extractive for these residues can be expected from various solvents or simulants.

   iv. Details of analytical methods and accuracy/reproducibility of the method.

2) Of the compounder (who may also be the polymer manufacturer)

   i. What ingredients are added, at what level and for what reason? i.e. colourants, dyes, opacifiers, anti-static agents, U.V. absorbers, anti-slip additive, slip additive, stabilizer, modifier, plasticizer, etc.

   ii. What toxicity/irritancy data is available on these ingredients and from whom (this may reside with supplying companies)?

   iii. What levels of extractives can be expected when these ingredients are in contact with various solvents, simulants, etc.?

   iv. Analytical methods and accuracy/reproducibility of the method.

3) Of the converter, i.e. laminate, film, bottle moulding manufacturer

   i. What processing aids are used by either direct addition to the granules or onto moulds (particularly relevant to lubricants, and

possibly anti-static agents).

ii. As 2) above if 'compounding' occurs, e.g. colourants added immediately prior to the moulding operation.

iii. What toxicity/irritancy data is available on these?

iv. What levels of extractives can be expected when these ingredients are in contact with various solvents, simulants?

v. Analytical method and accuracy/reproducibility of the method.

The work related to the above may be done entirely by the pharmaceutical company concerned, or be partially or fully contracted out. Whichever course is followed all the test procedures must be properly documented and follow the guide lines established by GMP (Good Manufacturing Practice) and GLP (Good Laboratory Practice). As a result the data so obtained should be adequate to satisfy:

i) The Pharmaceutical Company ITSELF

ii) World wide 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 or supporting documents.

This with supplementary clinical data should establish that the product is both safe and effective.

Although the above stages to clear a plastic have been identified, i.e.

i) Information on the pack or device ingredients

ii) Extractive tests

iii) Short and long term stability tests between product and packaging/ device components

there are additional activities whereby information is built up in order to establish the 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.

For instance, information is 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 and the means by which the product may deteriorate, degrade etc. are clearly established before it is placed into contact with a pack/ device.

At this stage accelerated tests in a 'control' pack such as a sealed neutral glass ampoule may also provide useful data on the likely 'stability' of the drug entity by itself and the same in a formulated form. This

information coupled with the challenge studies mentioned above provide a background which assists in the selection of the final primary pack in terms of both functional design and the material to be employed. Each product-pack must be considered on its merits, as it is only the last stage (stability), which ultimately proves that both are achieving their objectives. In reaching this conclusion consideration must also be given to the type of product, the dosage and frequency of use, and where and how it is used and whether it is professionally or self-administered.

Ingress, egress, migration of product and plastic components must also be related to the product-pack volume ratio. For instance in terms of extractives parenteral preparations such as IV solutions represent the highest risk as any 'extractive' immediately passes directly into the general blood circulation, e.g. a 0.1% extractive from 2 x 500 ml of IV solution represents 1 gm of foreign substance circulating in the body.

Hence the extracted ingredient must either be proved as 'safe' and not to produce adverse reactions or the level of extractive of such an ingredient must be extremely low. On the other hand a nasal product delivering 0.1 ml of solution four times a day for a 30 day period with the same extractive level (0.1%) only represents the introduction of 0.012 gm onto a mucous surface from which absorption into the blood stream may or may not occur, and therefore be less critical.

Any comparison between foodstuffs and pharmaceuticals based on simulated extractive tests is inevitably difficult, not only because the site and mode of absorption may vary, but because the difference in the pre-storage period, the frequency of use, and the volume/weight taken. With foodstuffs, the contact period between product and pack is usually shorter, but the quantity taken and frequency of use greater, e.g. daily intake of margarine. Thus the proposed EEC extractive procedure may provide useful additional information for the pharmaceutical industry as part of the stage one involving the screening of the material. However, it must be recognised that the simulants used in the EEC tests may bear little relationship to the final pharmaceutical form. The tests are more relevant to toxicity aspects rather than irritancy. Thus the EEC test is unlikely to drastically alter the total clearance programme and as such should be carefully monitored and reviewed in terms of foodstuff before any extension is considered to other areas (pharmaceuticals, toiletries, etc.).

An additional fact to consider is that the pharmaceutical usage of any plastic tends to be relatively small when compared with other industries, food, car, household wares, etc. and tends to become even more fragmented when these small quantities are divided into the grades of material used by each company.

This situation poses considerable problems to both the pharmaceutical industry and the polymer manufacturer or the converter, when any quest for information is made, as invariably the in depth data required is out of proportion (compared with the other industries mentioned) 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.

In addition, there is also the problem of obtaining sufficient in depth knowledge of the plastics without exposing the alleged secrecy of the processes involved. However, this general lack of information does create problems between the product and pack, where on one side considerable analytical resources is put into product identity, purity and impurity (the latter now being of the greatest relevance) whereas on the other hand the ingredients 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 (a little knowledge is initially a dangerous thing) can only long term improve the relationships of suppliers and users. This must also be a two way process where the pharmaceutical industry must provide more information to the supplier (converter or polymer 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 not forget that the information in total must satisfy both the

i) Pharmaceutical company itself
ii) The regulatory authorities.

I believe that the pharmaceutical company itself is the more important of the two as if it is not convinced itself, how can it be expected to convince others?

Additional comments

Such phrases as familiarity breeds contempt and change evokes new thinking, have historically gone hand in hand. For example, the advent of the horseless carriage soon brought forward legislation restricting their speed (a man with a red flag had to walk in front) whereas horse-drawn vehicles had virtually gone unrestricted. This type of thinking can still prevail today, and in fact does to some extent, when one considers the difference in attitude towards glass and plastic.

Glass is generally considered inert and safe as it has been used for 5000 years and proved by time whereas plastics being modern are under a constant surveillance. This attitude is partially based on the fact that inorganics (glass) are old hat, whereas organics are modern and more sophisticated. Although one would not deny that these generalisations are incorrect 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 type of tests which are now being applied to plastics.

Another current example of 'attitudes' appertains to 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 are not always exposed to an extractives type procedure.

We must therefore recognise that there is a danger for test procedures to grow to a point where they are either meaningless or unnecessary. This does not infer that every enthusiastic investigator is dishonest or 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 the 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 compacent. Thus the 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 more indepth knowledge on the plastic, modifications in the currently recognised extractive procedures, it seems extremely unlikely that the last approval stage (formal stability or shelf life tests) can ever be eliminated.

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

1) Type of product
   Contact phase
   Contact area - during storage, transit and in use

2) Storage conditions (where stored) at all stages of its shelf life, e.g. refrigerated conditions may be far less encouraging to extraction.

3) Shelf life and length of time product is likely to be in contact with product.

4) Mode of administration and the risks of absorption of extracted ingredient via that route.

5) Dosage level, frequency of use and application, i.e. treatment period - continuous, intermittent or temporary.

6) Misuse by patient or children

Finally, the possibility of product migration into the pack (e.g. loss of preservatives), coupled with permeation of oxygen, carbon dioxide and moisture must not only be considered as part of the broader issue of product/pack compatibility but also factors which could cause changes in the migratory nature of ingredients in the plastic.

Oxygen may cause slow oxidation of a plastic resulting in a slight change in the 'ingredients' extracted after long term 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. Nitrogen, oxygen, carbon dioxide permeation is generally of the ratio 1:4:20.

General performance requirements

i.e. performance related to both functional and aesthetic aspects. Since the functional aspects may vary according to how a pack or device is used, some general headings will be considered first.

Closure efficiency

Giving consideration to leakage, seepage losses via closures, effectiveness during use, i.e. opening and reclosure, any problems associated with stacking (top pressure); how controlled, i.e. torque range, and the effect of time and temperature; tolerances, agreement with drawings etc. Tests to differentiate loss via the closure versus the main body of the container are frequently necessary.

Decoration permanency

Print and colour may suffer from discolouration (fading or darkening), surface rub or abrasion, print or label lifting due to poor adhesion or key, and product resistance. Various types of tests are available to check these but some tend to vary between companies.

Discolouration may be checked by direct exposure to sunlight, storage in a north or south facing window, artificially accelerated conditions, e.g. Xenon test. With the latter 'fade' must be compared with changes based on the British Wool Scale. In such tests it is also advisable to check the temperature as occasionally discolouration is increased by the combined effect of temperature and light. Light may also cause changes to the plastic material itself.

Surface rub may be checked by various methods. If paper or board surfaces are involved tests may be made according to BS 3110.

Print key may be checked by the Scotch tape test where a strip is applied to the surface to be tested. This is then removed in a standard way and observed to whether any print is lifted.

Product resistance consists of applying the product to the print or decoration at a given temperature for a selected time, at the end of which the product is cleaned off in a rubbing motion to see if any is removed.

Environmental stress cracking

Environmental stress cracking is less prevalent today and more readily understood. As indicated earlier stress cracking is a phenomena related to internal (in built stress arising from the moulding operation) or externally applied stress, which in conjunction with a stress cracking agent will lead to a low density polythene cracking. Most detergents or wetting agents act as stress cracking agents. The normal test is the Hedley test where the container is filled with the product, the closure applied as normal and subjected to storage at 60°C for 48 hours. If no cracking occurs the test

is passed. If the storage is then extended to 7 days the point of cracking (if it occurs) can be used to indicate a weakness or the weakest point(s) in the moulding.

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

Warehousing and distribution

Warehousing and distribution involves a number of physical hazards, i.e. impacts, compression and vibration. Individually or a combination of these may distort the container, loosen or tighten the closure, and cause deterioration to decoration. Thus any of these aspects may have to be tested by simulated laboratory tests or actual warehousing/travel tests. The packaging technologist must therefore assess these possibilities and ensure that damage does not occur during storage and distribution.

It should be noted that climatic conditions (particularly temperature and humidity) may adversely affect the pack. High RH for instance will severely reduce the stacking strength of fibreboard outer packaging, which may partially collapse and result in stacking pressures being transferred to the pack.

Use - and misuse by the patient

Usage tests which identify how a consumer uses and misuses a pack or device are a critical part of any product-pack, device assessment.

User type tests may also have to be supported by microbial challenge tests, identification of any microbial contamination and chemical analysis to establisn that the product still remains within specification during the period of usage.

It should be noted that opening and closing allows the atmosphere to 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 the pack size must be limited. In these circumstances 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.

Sterilization

Sterilization processes which may have adverse effects on various plastics need careful checking. Basically three processes may be employed.

1) Steam sterilization - autoclaving at 121°C for 15 minutes or 115°C for 30 minutes
i.e. terminal sterilization

2) Gamma irradiation and accelerated electrons
3) Ethylene oxide

) associated normally with aseptic processing

Each process raises a number of questions since all may give rise to some adverse effects which may be directly or indirectly associated 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 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 as well as the material of construction. A dimpled pack normally results from a negative pressure situation and is particularly likely to occur in packs which have thinner sections.

Gamma irradiation of 2.5 mega rad and accelerated electrons may create similar changes to the product/pack. These processes are normally used as part of an aseptic process to sterilize the pack components since many products tend to degrade if this process is used as a terminal means of achieving sterilization.

Lists of types of plastic and specific grades which will withstand these processes are readily available from suppliers. This in no way clears a plastic for gamma irradiation until a company has satisfied itself that no change occurs. 2.5 mega rad treatment invariably causes some cross linking of the plastic molecules which gives rise to a small change in physical properties, i.e. elongation at break, reduced flexibility and increased rigidity. Occasionally, chemical changes may be related to either the polymer or the ingredients within the polymer. Certain grades of LDPE when irradiated will show a low level of release of acidic and/or lachrymatory substances. The latter may only be detectable when the containers are handled in bulk. Carrying out extractive type procedures before and after irradiation may be an initially useful way to detect whether any change has occurred.

Ethylene Oxide treatment

The sterilization of a plastic by 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 may be carried under vacuum or by simple storage in an area with a good air circulation for periods of up to 1 month (7-14 days are more normal). Since ethylene oxide will degrade to ethylene glycol and epichlorhydrin (when chloride ions are present) and both these exhibit some degree 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 the external atmosphere. Figures therefore have to be set for both the plastic and the product. Target figures in the product are now reducing to the region of less than 50 ppm or 25 ppm. In the USA new device/pack enactments are quoting figures

below for devices/packs sterilized by ethylene oxide:

Ophthalmics	Ethylene oxide	10 ppm	Injectables	10 ppm
	Ethylene chlorhydrin	20 ppm		10 ppm
	Ethylene glucol	60 ppm		20 ppm

Tyndallisation - coupled with Preservative Retention

Since heating at around 100°C with a bacteriocide has not entirely disappeared this may be still used in certain circumstances. However, quite a few chemical preservatives systems are readily adsorbed or absorbed into plastic and hence losses could be expected where such substances as phenol, chlorbutol, benzyl alcohol, chloroxylene, 2 phenyl ethanol, etc. are used. Presoaking the containers in a double strength solution of the preservative can reduce losses (note the solution can then over concentrate) or if a product in plastic is autoclaved, having a solution of the preservative also present in the autoclave. With the latter the preservative atmosphere in the autoclave reduces the permeation gradient and the preservative is reasonably retained in the product.

However, neither presoaking nor sterilizing in an atmosphere of the preservative will prevent further losses during the shelf life of the product. Although this may be reduced by careful selection of the plastic (HDPE, PP and UPVC provide reasonable to good retention) low and medium density polyethylene are particularly prone to both adsorption, absorption and desorption if the preservative is volatile. Retention can still be achieved in these circumstances by over-wrapping the pack with a good barrier material. Examples of what has been used include blister packs, sachets and flow packs of a suitable material. In these circumstances a foil laminate is a particularly impermeable barrier. The solubility of preservatives in LDPE and the surrounding atmosphere, for an equilibrium with such overwraps are relatively low and the retention of 90% plus of the preservative can usually be achieved.

Panelling and cavitation

Occasionally packs may partially collapse or indent. This phenomena known as panelling or cavitation may occur in flexible type packs for a number of reasons:

i) Hot fill plus partial vacuum.

ii) Pack partially collapsing during capping plus effective closuring whereby a degree of vacuum is retained.

iii) Adsorption of gases usually oxygen from the headspace.

iv) Adsorption and absorption whereby the inner surface swells, thus giving rise to a distortion effect.

Normally these possible effects can only be checked by long term storage.

Impact resistance

Plastic packs which may crack when exposed to impact may be controlled by a drop test procedure whereby a certain percentage must not break when dropped from a selected height ontc a standard surface. The pack is dropped in a certain way so it falls (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, e.g. Japan Eye Drop Containers have a test which indicates that a certain level of light transmission must be achieved in order that levels of particulate contamination can be checked.

Light exclusion

This is the opposite to light transmission in that the majority of the light must be filtered out (particularly UV). This test may define the wall thickness (i.e. 2 mm in the case of glass). Exclusion of light may be achieved by selection of certain colours, fillers for opaqueness or the addition of U.V. absorbers.

Electrostatic

Most plastics are prone to electrostatic unless special precautions are taken to reduce it. Static is increased by dry conditions or excessive friction between the packaging materials and the surrounding materials (e.g. conveyor belts, handling and winding machinery, etc.). Static can be reduced by i) moisturising, i.e. using higher conditions of RH, ii) earthing or deionising the surrounding atmosphere, iii) washing with the correct detergent, anionic or cationic, iv) adding an anti-static agent to the plastic. Items iii) and iv) 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.

Pretreatment (printing and labelling)

Certain plastics need a pretreatment stage prior to printing whereby the surface of the film is oxidised to improve the 'key'. This treatment can be achieved by i) Flaming
ii) High voltage corona discharge
iii) Chemical treatment (this may also be similar to surface sterilization as used for some food packaging processes).

Containers are normally pretreated by i) flaming and films by ii) corona. Whether a material has been pretreated can be checked by wetting the surface and either 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 film is oxidised.

Surface treatment also enhances the effectiveness of some ingredients which operate at the surface of the container, e.g. anti-static additives, slip and anti-slip additives, etc.

Development versus production pack

Before any pack reaches a production-marketing situation differences between the pack tested and the pack to be marketed must be both identified and cleared. It is virtually inevitable that there are some differences. One of the most likely lies in the decoration or printing of the pack. If it is subsequently decided to label a pack by either a label + adhesive (probably a PVA), thermoplastic or a heat seal label these must be thoroughly checked since all contain ingredients (in the adhesive system) which may possibly migrate through the plastic. Migration from self-adhesive labels has been reported whereby formulation ingredients, 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 (cellophane or polypropylene) 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 item suffered from discolouration which would not have otherwise occurred.

* i.e. not overwrapped

Conclusion

Thus the ultimate task of the pack is to provide confidence in the product in terms of convenience, presentation, protection from the environment whilst 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. With the advent of product liability investigations will not relax but rather intensify.

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

As the cost of clearing any product-pack combination is inevitably high, it is extremely important to adequately define the product, the pack, and the processes involved in these original clearance schedules, i.e. finish with:

i) a product specification including process of manufacture,

ii) a pack specification covering the pack and its component parts,

iii) a specified means of bringing the product and pack together, i.e. the packaging process.

The future control of the product and pack then revolves around these specifications. In the case of a plastic pack or plastic components, it may be necessary not only to tightly define certain critical factors in the specification, but purchase under a certificate of warranty as exhaustive quality control procedures (particularly biological tests) which might be necessary to detect change, would involve a prohibitive cost. Regular Q.C. checks are likely to include Melt Flow Index, density and an I.R. identity. The latter is particularly useful means of providing plastic identification.

As an additional insurance, a selected number of production batches are placed on an 'existing' product stability test annually. This monitoring system ensures that the stability profile (and shelf life) of the product does not change with the passage of time. 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.

It can therefore be concluded that packs and devices supplied by the Pharmaceutical Industry which utilises plastics normally pass through a thorough and rigorous test procedure, but even so such procedures will be improved upon with progress. If possible loopholes in the present systems are to be identified, then more attention will be required on the internal storage containers which are usually found in factory production areas and the bulk containers used to supply the industry with drugs and other excipients, as these receive far less attention than the pack destined for the 'patient'.

It can therefore be concluded that work related to the clearance of the pack, the establishment of total integrity and GMP cannot, repeat cannot, be isolated into apparent water-tight compartments such as product development, pack development, production, marketing, quality control, as all must operate as an effective team with a high degree of communication and coordination. A packaging coordinator with an ability to give an overview is therefore essential to success but to date this has only been recognised by a few companies.

Finally let it be stressed this paper has been written to give both a degree of alertness and understanding. It in no way sets out to say that any approach is the ultimate. Test procedures must also be constantly reviewed and updated. If a company (or its representative for a certain function) says we have done it this way for the last 20, 10 or 5 years or have always used this test for a similar length of time, it is quite likely that they are <u>not</u> up to date and are currently not being fully effective. Virtually all stages identified in this paper must be treated as long term information gathering. Extractive tests fall into this category; they provide the best information available at this stage and therefore must not be treated as the ultimate. To date there are no records of people dying from plastics but rather the processes by which they are synthesised (ref. VCM)*. However the industry must remain responsible particularly in terms of product/pack liability and at the same time remain commercially viable.

* Vinyl chloride monomer in UPVC

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 - with frequently the wisdom of Solomon. The glib saying "common sense will ultimately prevail" can be extremely difficult to achieve. Tests to clear a pack initially must not be confused with tests to clear bulk deliveries, i.e. an in house Q.C. situation.

Appendix 1

World Health Organisation - proposed international requirements for plastic containers for pharmaceutical preparations

General	-	Guide lines on selection of Plastics
		Code of practice
Infusions and Injections		Physicochemical 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		Physicochemical on aqueous extracts
		Non-volatile residue, buffering capacity, reducing substances.
		Biological test on aqueous extract
		Eye irritation in rabbits on repeated instillation (Draize test).

Appendix II

Suggested programme for the evaluation of a plastic container for a multidose injection product

1. Establish suitable grade of plastic. Identify that plastic and ingredients meet food grade standards. Discuss residues, additives, and processing aids which may be present with relevant parties.

   Note - additive content should be low and certain heavy metals (Cd, Pb etc.) should be absent.

2. Apply Physico-Chemical (on plastic or extract) and Biological Tests (on extract)

   a) Metallic additives - B.P. BP 1980 Appendix XIX A200-202
   USP XXI Containers (661) P1237-1238

   b) Non volatile residues, residue on ignition and buffering on purified water injection extract - USP XXI P1237-38

   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 XXI Containers (661) 1235-37

   f) Intracutaneous test on rabbit
   Sodium chloride injection extract - see USP XXI P1235-37

   g) Eye irritation in rabbits - repeated instillation (Draize test) reference possible irritancy effects. USP XXI P 1238

3. Actual injection 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.

   b) Formal long term stability tests

      i) usually carried out on 3 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, 37°C for full period and possibly 45°C for 12 months. Conditions to be humidity controlled.

      v) To check product and pack at related intervals for chemical change. Purity/degradation/loss of active ingredients and primary constituents (e.g. preservatives). Preferably by analytically specific methods.

Recheck microbiological effectiveness (USP XXI challenge test or BP 80 challenge test)

Check plastic for chemical change, absorption of ingredients (by extraction if necessary).

vi) Physical change

vii) At selected intervals and conditions (e.g. 25°C and 37°C after 12 months and 24 months) etc. for possible changes in toxicity i.e. acute LD50 should be no greater than initial sample - alternatively BP 1980 toxicity test B on A201 should be employed. This would also be advised for rechecks on possible irritancy (Draize Test).

viii) 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.

4. Write up specifications for plastic, pack and pack components. Agree with suppliers.

Appendix III

Examples of National Standards for plastic containers for pharmaceuticals - USA and UK

USA

FDA	- General guideline 1984.
FDA, NDA	(New Drug Application) - Composition and method of manufacture of plastic.
USP (and NF)	Chemical tests on Extractives
USP XXI)	Containers (661) P1235-38
)	
)	Biological tests for parenterals and ophthalmics

Reference should be made to CFR. (Acceptance of plastics and gradients for Foodstuffs).

UK

BP 1980	General Guidelines - Specific tests for large volume parenterals
DHSS (1973)	ref. 008 and 020. Specifications for blood bags and I.V. solution. - with specific reference to PVC.
BS 1679 pt IV 1969	Plastic containers for tablets and ointments. (currently under revision)

Appendix IV

Examples of National Standards for plastic containers for Pharmaceuticals - EUROPE

i) EAST GERMANY — Implants and containers
Biological tests for oily, aqueous, Alcoholic products
Physicochemical tests

ii) FRANCE (Pharmacopée Francaise Xth Ed. 1962)

General statement of interaction.
Parenterals - Biological and Physico chemical tests
Ophthalmic preparations - Transparency and neutrality.

iii) JAPAN (Pharmacopoiea 10th Ed. 1982)

500 ml (or larger) aqueous infusion containers only apply
Physicochemical and water permeability tests
Biological tests

Note: Japan Pharmaceutical Affairs Bureau Notification covers Ophthalmics.

iv) ITALY (Ministry of Health circular no. 84 28/12/77)

Comprehensive list of permitted plastics (1973).
Migration tests into simulants - 50 ppm or 8 mg/dm^2

v) NORDIC PHARMACOPOIEA - Transfusion tubing
containers for blood, aqueous solutions, infusions, injections, irrigation solutions
Biological (Pyrogenicity, acute toxicity, haemolytic) and physico chemical tests.

vi) NATIONAL SWEDISH PHARMACEUTICAL LABORATORY — Submission on standard form. Composition and properties of plastic and constituents.

vii) SWITZERLAND (Pharmacopoeia Helvetica VIth Ed. 1971)

Must meet food requirements
Parenterals and Ophthalmics - Colourless, translucent, chemical tests, permeability to water and micro-organisms.

Note - The European Pharmacopoeia (2nd Edition) 1982 has now replaced many of the national ones.

Appendix V

References

1) J. Cooper, Plastic Containers for Pharmaceuticals, Testing and Control. WHO, Geneva 1974.

2) WHO Expert Committee on Specifications for Pharmaceutical Preparations (26th Report). Technical Report Series 614, Geneva 1977.

3) British Pharmacopoeia 1984.

4) United States Pharmacopoeia XXI - 1985 incorporating the NF.

5) Pharmacopoeia Helvetica VI. 1971.

6) Pharmacopée Francais X 1982.

7) Japanese Pharmacopoeia 10th 1982 (P762-770).

8) Nordic Pharmacopoeia 1970.

9) National Swedish Pharmaceutical Laboratory.

10) Deutscher Normenauschuss (German Norm). DIN 13098, 13099, 58368.

11) The International Pharmacopoeia Vol. I and II, 3rd Edition WHO 1981.

12) CRF (USA) Code of Federal Regulations.

13) Japan Pharmaceutical Affairs Bureau Notification 958. Testing methods for plastic containers.

14) European Pharmacopoeia 1980, Second Edition.

15) Pharmaca Fennica (Finland) 1984.

Appendix VI

Outline specification for a plastic component

Standard name/title

Specification reference/computer number/code ..... dated

Replace specification reference ..... dated

General description.

Construction/design detail

Material of construction - type - grade

Size/Capacity

Drawing ref. No. dated

Decoration

Special tests/performance which article must meet

*Acceptable quality levels (AQL's) defined as critical, major and minor defects.

Mode of packaging for delivery and how items are identified.

Authorisation - user - supplier

Supplier(s)

Appendix VII

The Pharmaceutical Industry, Plastics and the EEC

A European committee (under the EEC) is currently considering the introduction of monographs on plastic for certain pharmaceutical packaging applications as part of the European Pharmacopoeia. These have initially been based on the French Pharmacopoeia which identified certain plastics, and the ingredients which could be associated with them, which could be 'permitted'. Although the majority of the European committee initially supported this view it is becoming increasingly evident that a 'permitted' list is both 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 a means of circumnavigating the original intentions. The UK BP commission has always stood out against approach taken, maintaining 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 ingredients which can be declared as "food grade" should be used for pharmaceutical products, the "global migration" approach, currently being adopted in Europe, has come in for considerable 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, it is difficult to control.

In defense of this approach, it must be noted that dependence on "FDA" approved materials is not as foolproof, as many earlier considered, since many substances included are based on a concensus of opinion by a committee (years ago) rather than detailed toxicological evidence. However, records of deaths from plastics (note this does not include the polymerisation or compounding process) are virtually unrecorded and reports of adverse effects are also relatively rare. The latter tend to be related to toxicological and pharmacological work on ingredients where mutagenicity, carcinogenicity etc. has been shown whereby such ingredients become excluded from use even though the risk of these being extracted may be nil. In general quite a few of the recorded adverse effects tend to be related to the plastics used internal to the body (implants) or similar surgical applications (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. In the UK this is not helped by the fact that most pharmaceutical companies have not had access to the European proposals which have been dealt with through the BP Commission with a selected number of advisers.

Appendix VIII

The Plastics Industry and GMP

The extensive testing carried out by the Pharmaceutical Industry, to clear a plastic and identify the ingredients from which it is made are of no avail if the polymerisation, the compounding and fabrication processes are not controlled by some code of practice. The orange guide on Good Manufacturing Practice (GMP) which provides guide lines for the pharmaceutical industry could equally be applied to the plastics industry. Some of the more basic aspects would relate to:

i) Clear batch identification of all materials.

ii) Control on materials issued so that incoming and outgoing materials can be accounted for and documented.

iii) Identification of what batch is used in what process so that all 'ingredients' can be traced back to an original 'supply' batch.

iv) Clear flow paths from raw to finished materials with 'hold' and quarantine areas where necessary.

v) All materials and finished goods to be identified by name, batch number, date etc. and to pass through a 'hold' or quarantine area (whilst under inspection) to a clearly defined storage area when 'passed' or 'restricted' or a separate area if 'failed' or held pending further negotiations.

vi) The QC operation identified above in v) would also be covered by a coloured label code which indicates the various stages, e.g. (white) booking in, (yellow) quarantine, (blue) sampled, (green) pass, (red) failed and (white with red lettering) for restricted.

vii) Associated with the above all materials require a specification by which they can be ordered and controlled.

viii) Documentation associated with all of the above must be simple and logical so that all materials can be traced from receipt to final issue or despatch.

ix) Materials used in any process must also undergo checking operations to ensure that i) materials cannot be incorrectly labelled, ii) an incorrect material cannot be issued, iii) the quantity issued is of the correct proportion.

x) Additionally retention samples should be kept for specific items and any change (process or materials) should be carefully monitored - e.g. it cannot necessarily be assumed that a material of the same

name or description is identical when it is received from different sources.

xi) Material segregation to be organised and controlled to prevent admixtures. This is particularly important if regrind is permitted.

xii) Item segregation to be organised and controlled to prevent admixtures of items from adjacent machines.

xiii) Machines to operate under acceptably clean conditions so that air borne contamination is minimised (particulate contamination).

xiv) Items emerging from machine to be exposed for a minimum of time, i.e. direct feed into suitable (clean) PE bags, etc. Particular attention to be paid to electrostatic which may encourage particulate pick up.

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 provided the supplier and user have discussed and agreed what is required and what can be achieved.