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STABILITY ASPECTS OF PACKAGING

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13.1 Introduction

The apparently obvious statement that a product cannot exist and have an adequate shelf life without a pack, needs to be emphasized since this can only be effectively achieved by a successful marriage between the two. However, all packs are a compromise between such factors as cost, presentation, protection, identification of and information on the product, convenience and compliance. Attempts in the past to deal with the product and pack in isolation have exposed numerous risks with this approach and as a result it is now generally accepted that a joint product-pack development involving both formulator and pack developer is essential. Packaging expertise should be involved at any time when a drug entity, product or its exipients are used in preformulation, formulation, animal feeds, safety studies, clinical trial supplies, bulk or intermediate storage, through to the pack in which the formulated product is to be ultimately sold.

13.2 Fundamental Requirements for Packaging

It is essential that sufficient data is accumulated at all the stages of product development, to establish, in the widest sense, that all packs are

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suitable for their functions. Investigations involved in reaching these conclusions can be divided into background or feasibility/challenge studies leading to the formal stability testing program of three batches, etc. Since inadequate attention to packaging detail can totally invalidate even the most technical and scientific stability program it is important to make packaging support work meaningful. A number of these supporting activities are identified hereafter. Although these points are particularly essential for projects involving new drug developments many may equally apply where any subsequent alterations are made to the product and/or pack. The level of testing required for the latter may simply be the change of emphasis applied to each factor, as there must obviously be a balance between the adequacy of the data and the expenditure which can be afforded to justify the change proposed. Possible approaches to existing product-pack changes will therefore be discussed later. It is therefore essential:

13.2.1 That the formulator/packaging areas have carried out adequate feasibility support work to establish the functional and esthetic aspects of the pack, both primary and secondary. The primary pack may be defined as the pack which is in immediate contact with the product and the secondary pack as the ancillary materials required for presentation, warehousing and distribution purposes. Feasibility work may involve information gathering on the pack and its components, etc., basic research into materials, packs and processes, and compatibility studies, accelerated or otherwise on product and pack.

13.2.2 That the materials used for the primary (and secondary pack if such components may be migratory) are non-toxic and non-irritant and that this information can be adequately supported by the study of:

a) The constituents in the materials

b) Toxicological data on the constituents with

c) The availability of adequate analytical methods to detect migration.

Note: constituents in terms of plastics would include:

Residues (from polymerization process)

Additives (those ingredients which are added to enhance or modify certain properites)

Processing aids (those ingredients which are added or used to assist in a fabrication or conversion process, e.g., mould release agents, lubricants, etc.).

13.2.3 That sufficient in depth extractive and compatibility investigations have been carried out to establish likely levels of extractives with conventional stimulants and the actual product(s).

Note: Although NF(National Formulary, now part of U.S.P.) and WHO(World Health Organization) extractive proceduries only give limited information and are ususally only mandatory for opthalmic products and injectables, this type of test may be useful for company assessment of various types of plastics. Compatibility tests at the feasibility stage may involve so called accelerated conditions. It should be recorded that higher temperatures may in some way either destroy or make the pack less effective with a result that the product is no longer fully protected by the pack. Thus, unless these higher temperature conditions are to be found in practice, some accelerated tests may not provide realistic extrapolations.

13.2.4 That provisional specifications have been created for all packaging components and are subsequently used to clear all materials through a quality control plus type operation prior to use in any tests irrespective of whether these are feasibility or formal stability studies. Procedures should include material identification (e.g., by infra-red or ultra-violet spectroscopy or differential scanning colorimetry), physical assessment including dimensions and functional tests, and be of greater technical depth than the quality control procedures used for subsequent regular incoming production materials-

13.2.5 Repeat 4 with a provisional product specification and in particular have records of how drug entity was produced and the formulation processed into a product. Note any subsequent changes may not solely require monitoring but possibly lead to further stability work to support the product stability profile.

13.2.6 That accurate details are kept (product-pack assembly specification) and recorded on how the product-pack was assembled. This detail should include reference to environmental conditions, machine speeds and settings, heatseal

strength, cap torque, fill volumes and where and by whom the operation was performed, etc.

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

13.2.8 To ensure that packaging evaluation work where possible includes a 'control' pack and involve recognized test procedures which provide good comparative type data (e.g., tests to show moisture loss or moisture gain, changes in closure torque and heat seal strength on storage, etc.). Test procedures should involve adequate analytical and instrumental support. Remember, even in a scientific society, the use of observation by the experienced worker to detect visual and organoleptic changes, is still invaluable.

This work should cover not only the primary pack but the secondary packing (effects of storage, stacking, vibration, etc.). Remember no test method is finite and each test should be constantly reviewed and updated. Also, equipment has to be checked, monitored and validated.

13.2.9 To ensure that in use testing, patient acceptability and possible mis-use aspects are adequately covered and interpreted since most formal shelf life testing does not involve any 'use' of product and pack. It is possible that the product/pack may have a restricted shelf life once the pack is opened and is in use. Therefore, it may be occasionally necessary to have two shelf life periods.

i.e., i) For the unopened pack, e.g., 3 years plus

ii) For the opened pack, e.g., "use within 4 weeks" or "the contents should be discarded after one month", etc.

It is anticipated that greater emphasis will be placed upon "in-use" shelf life in the future, and indeed during 1983 a number of F.D.A. officials have indicated a support for this trend.

In use life can involve physical, chemical and microbiological stability - i.e., does the product remain microbiologically effective over the period and conditions in use as well as physical and chemical aspects.

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

i) To test in the same materials using a similar design of pack.

ii) To test in the correct design, using packs produced for a single impression prototype tool.

iii) To test in similar materials using the nearest size which may, in fact, be significantly different design.

Which route is adopted varies between countries and companies. If tooling is required for both a bottle and a closure, then the situation is further complicated by higher tooling costs. Also, if a pack either acts as, or incorporates, a delivery system, then tooling may become even more complex and costly, particularly if the numbers of components involved are increased. However, as the pack becomes more complex there is a greater need to complete stability work on the pack to be ultimately used.

13.2.11 That the data generated from any programme whether formal or otherwise may have to be used to satisfy:

a) The company

b) Regulatory Authorities

Consider the philosophy that if the data does not convince the company (yourself and colleagues) how can it be confidently used to satisfy Regulatory Authorities.

13.2.12 Finally all companies should work towards a total data philosophy, whereby all data, literally from inception of drug to ultimate discontinuation

of product, should be used to justify not only stability, but safety, efficacy and integrity to preserve both the position of the company and the ultimate patient/user. Some examples of where problems have occurred with reference to the above, are given below.

13.3 Examples of Problems in Packaging

13.3.1 Examples of inadequate monitoring between the pack tested and the pack adopted.

13.3.1.1 Stability samples using low density polythene bottles were identified by magic marker inks. After the stability test the sales pack used a self adhesive label. A migratory ingredient from the adhesive passed through the plastic into the product causing degradation of a preservative system.

13.3.1.2 A device (separate to a pack) which used a rubber bulb was stored under a range of conditions and observed for deterioration (visually and performance). None was detected. It was subsequently packed in a dark coloured carton and still no problems occurred. It was then packed in a printed white carton with a polypropylene film overwrap. The white carton changed slowly to a yellow-orange colour as a volatile organic copper ingredient from the rubber bulb was retained by the polypropylene film. This was lost through the previously non overwrapped carton without detection, partly due to the printed dark colours.

13.3.1.3 A low density polyethylene bottle, identified by a self-adhesive label, was used for stability test. When the bottle for sale was printed by the silkscreen process in two colours, one colour became detached during in use flexing, due to the effect of a slowly volatile ingredient in the product, on that colour.

13.3.2 Example of where lower temperatures gave an accelerated effect.

13.3.2.1 Zinc and castor oil cream was tested in a polystyrene jar using a four start lug finish to simplify removal of the closure (This simple closure was selected in order to assist the user, the mother, when applying this remedy for diaper rash to the baby. Holding a baby does not allow for the ready opening of complex closures!). Samples were stored at $4^{o}C$, $20^{o}C$, $30^{o}C$ and $37^{o}C$.

Jars cracked at the four stress points created by the four lug closure, first at 4°C then at the higher temperatures in ascending order of temperatures (i.e., 6 weeks, 3 months, 7 months, 10 months). The subsequent use of an impact modified polystyrene with the return to a conventional continuous screw thread and screw cap ultimately provided a satisfactory pack.

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

13.3.3.1 A strip pack using an aluminum foil/low density polyethylene laminate was used for a tablet containing volatile oil constituents. Delamination between foil and film subsequently occurred as the volatile constituents passed through the polyethylene and softened the adhesive bond. An extrusion coated laminate provided a satisfactory answer.

13.3.4. Example of insufficient investigation prior to formal stability.

13.3.4.1 A neutral unbuffered aqueous solution was stored in a polyethylene bottle. On storage the pH value dropped from 4.3 - 4.5 but reverted to pH 6.5 when the solution was heated. The change was identified as carbon dioxide permeation with the formulation of carbonic acid.

Possible solution: - change of plastic, an overwrap or possibly a buffered formulation.

13.3.4.2 An injection product stored in a cartridge tube using a natural rubber component containing wax showed a significant pH shift and product degradation due to oxygen permeation. The use of a butyl rubber, with a siliconising treatment prior to assembly, overcame both problems.

13.3.5 Examples of adequate investigations prior to formal stability.

13.3.5.1 It was required that a veterinary iron injection be packed in a collapsible (for withdrawal of multiple doses) low density polyethylene, LDPE, flask. The product was susceptible to oxygen permeation and pH shift. The preservative system, phenol was readily lost through LDPE which is also permeable to oxygen. The flask, when packed in a paper/foil/polyethlene sachet provided a three year plus shelf life.

13.3.5.2 It was desirous that a new multi-dose preserved nasal product be packed in a squeeze spray bottle that allowed world wide production and

packing. This involved consideration of the conventional LDPE nasal spray bottle which was permeable to the preferred preservative system. The bottle was packed in a polyvinylcholoride, PVC, blister with foil peelable lid as an 'overwrap'. This system allowed the use of the LDPE pack and readily achieved a three year product shelf life. An "use within 28 days" statement was placed on the pack, to cover the usage period, after removal from the blister pack. The blister pack is also pilfer indicating.

13.3.6 Example of ineffective monitoring of environment.

An effervescent tablet packed in a foil strip pack subsequently "ballooned" due to release of CO_2 within the pockets. A searching investigation showed that the dehumidification of the room where the trial had been packed had not functioned properly and that reaction had resulted from the introduction of moisture to the product because of the high relative humidity in the packaging room.

13.3.7 Lack of process monitoring.

A sterile product prepared for stability testing using a hand plugging, capping operation because of the non-availability of automatic capping equipment. The team doing the plugging and capping used rubber gloves lubricated with a sterile glove powder based on starch. Examination of the product prior to placing under test revealed a 'haze' in some samples which was subsequently identified as grains of starch that had become detached from the gloves.

Although the above clearly identifies some of the risk areas associated with packaging and the need for Good Laboratory Practise, GLP, and Good Manufacturing Practise, GMP, including adequate records of all activities, this type of thinking may well have to be extended outside the true development area. For example, many companies tend to assume that bought in materials are adequately packed and are stable for frequently an indefinite period. This type of attitude does require to be questioned and if an ingredient is to be stored for prolonged periods some allowance for re-analysis is always advisable, particularly as some products and packs may never have been subjected to any formal assessment.

Most companies have systems involving retention samples of ingredients, intermediates, completed formulations, etc., which are sometimes based on the belief that all retention packs are perfect. The author has on a number of occasions discovered totally unsuitable packs being used, i.e., small polyethylene bags, polystyrene tubes and PVC bottles or glass with an unsuitable closuring system. Even such packaging systems therefore need monitoring if reference to and analysis of retention samples is to be meaningful should complaints arise.

One further aspect, is the handling of materials in house. It has been noted that ingredients may occasionally be transferred and stored in polyethylene bags or formulations or intermediates in a process stored for unexpectedly long periods, in containers which have not been shown (or proven) suitable. Instances have also been known where changes to equipment (e.g., the introduction of plasticized PVC tubing or the use of non-approved filters) have introduced migratory ingredients or particulate matter into the product.

The above indicates that the ultimate shelf life of any product may depend on how and in what containers and materials, the ingredients and the intermediates are stored, prior to and during processing, including bulk storage of the product, unitl the time when it is packed into the pack for sale.

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

13.4 Changes in Product and Pack (after initial launch).

13.4.1 General Considerations.

The means of proving product or pack equivalency when either the product or pack is altered or modified, is often discussed, for example, when the pack is changed in terms of size, materials, shape, closure, etc. Of these, a change in pack size using the same container materials and closure size, should be

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

a) A high density polyethylene, HDPE, is lowly permeable to both moisture and gases - hence exchange via the container walls may be more relevant than

the closure - dependent on container wall thickness and eveness of distribution.

b) Closure may react differently on plastic, i.e., change of torque, backing off, under variable conditions of temperature and humidity (humidity less significant). The thread form may not be ideal for a metal closure (e.g., buttress thread form is preferred for a plastic to plastic closure fit and is more likely to be used on an available stock container). Additional tests are necessary to confirm suitability of metal to plastic fit and effectiveness of the closuring systems. Cycling stress storage tests may be useful here.

c) Dimensional assesment of drawings essential - particularly bottle to closure tolerances.

d) Detail of plastic and constituents. Incompatibility is unlikely, unless volatile constituents are present, but some form of accelerated test is probably essential if there has been no previous experience with the material. Check odour and taste plus possible degradation.

e) Moisture ingress tests - use glass as a control to establish combined closure and container permeation differences.

f) Light penetration may be greater with plastic (compared with amber glass). Additional checks advised.

Likely Conclusions

The decision is largely dependant on the stability of the formulation and whether any degradation, physical/bioavailability changes related to moisture, oxygen, light, carbon dioxide, etc., could occur. Long term stability data on pack appears essential and could be part of procedure prior to agreed release (i.e., check via the above 1-6 tests then do three to six months of a formal stability test prior to release).

13.4.2 Change from an amber glass bottle to a foil strip pack.

An aluminum foil strip (i.e., paper/foil/polyethylene or foil/polyethylene) should in theory give as good or superior protection against moisture ingress as a glass bottle if an effective closuring system is used and machine pro-

blems are absent (i.e., good heat sealing, no excessive extension of pockets by size or location of item in the packet, etc.). There will, however, be a new contact material with the product, namely the heat sealing ply. Product headspace (air) may differ from a glass pack. The factors to consider include:

a) General machine efficiency - delivery and location of product in pocket, extension of pocket area. Strain on seal area, etc.

b) Does heat sealing operation raise any product problems with heat retained by pack and transferred to product.

c) What is material in contact with product (heat-seal material) - query compatibility against material specification including any constituents in plastic.

d) What are sear requirements, etc.:

Elimination or avoidance of capillary channels in seal margins.

Peel strength of seal (i.e., related to temperature, swell and pressure)

Vacuum testing requirements

Moisture ingress/egress (weight change on product or desicant tablets).

Does heatseal pattern avoid perforation of pack?

Likely Conclusion

Not simple to prove total equivalence - some stability testing advisable prior to acceptance.

13.4.3 Current pack high density polyethylene. Changes proposed to a polypropylene copolymer (cost saving, slight weight saving). No change to closure envisaged.

Permeation values of HDPE:(polypropylene),PP, are similar in terms of moisture. PP shows a higher permeability to oxygen and carbon dioxide. The factors to consider include:

a) Check bottle weight dimensions/against specification paying particular attention to wall thickness as this will influence permeation.

b) Investigate constituents of PP, establish grade of homopolymer/copolymer, identify grade, supplier, etc., obtain data sheets.

c) Check closure efficiency against current pack as control. Torques may differ especially under variable conditions of temperature and time of removal after application.

d) Check permeation by desicant or other relevant tests.

Likely Conclusions

Stability work prior to release probably not essential - but longer term stability back up necessary. Release very much dependant on the thoroughness of the above tests.

13.4.4 A 5 ml opthalmic pack in low density polyethylene is currently ethylene oxide treated and aseptically filled and assembled. The bottle and plug are made from two different grades of LDPE and the cap from polypropylene. A recommendation is made to change the sterilization process to gamma irradiation.

The factors to consider include:

a) Compare non-irradiated components (separately) with gamma irradiated components for:

a. Dimensional change/appearance

b. Changes in physical properties (flexibility)

c. Extractives.

b) Check extractive results on new process

a. Chemically

b. Toxicity

c. Irritancy (Draize test)

Advise gamma irradiated components are smelt in bulk as first sign of degradation products may be detected this way.

c) If satisfied with 1) and 2) proceed to a formal stability program - consider release after three or six months data has been accrued.

Likely Conclusion

There is a fair chance that the above exercise will not pass stages 1) and 2). Certain grades of LDPE when gamma irradiated will release acids and sometimes lachrymatory substances. Some grades of PP may discolour and hence fail on appearance.

13.4.5 A product (aseptically produced and filled) in an multi-dose injection vial (20 ml) uses a natural rubber stopper through which the volatile preservative system is lost. As a result a three year shelf life (predicted and assumed previously) cannot be achieved. An alternative rubber stopper is advised. The supplier recommends a chlorbutyl synthetic rubber stopper.

Actions advised:

a) Check new stopper for fragmentation, resealing (following multiple penetration) and force for needle to penetrate - note synthetic stoppers are generally inferior in these properties hence questions as to whether new material is satisfactory.

b) Check extractives before and after autoclaving of stoppers - chemically and toxicity.

c) Check preservative absorption and moisture loss via stopper (synthetic stopper should be significantly superior with regards to both).

d) Check if washing and sterilization process (i.e., autoclaving of stoppers) generates any particulate matter.

e) Consider stability test parameters including analytical methodology (if product has been marketed for a number of years methodology may be out of date and not specific).

f) Make up necessary batches for stability and place on test.

Likely Conclusions

Formal stability type tests essential before clearance can be given. Release most likely after a six-month or longer period even if certain accelerated conditions are used (i.e., no room for error on an injectable product).

Note: The number of batches required for formal stability data to support changes does vary between regulatory authorities. In certain cases there does appear to be good reasons to support a one or two batches approach rather than the more conventional three batches.

The remainder of this chapter covers the more general background of packaging and the hazards which the product and pack may have to face.

13.5 Package Function and Selection

First for a definition of packaging, which can be describes as the ECONOMICAL means of providing:

PROTECTION

PRESENTATION

INFORMATION/IDENTITY

CONVENIENCE/CONTAINMENT/COMPLIANCE

for full life of the PRODUCT during:

STORAGE

CARRIAGE

USE and

DISPLAY

until such time as the PRODUCT has been used, or administered or simply disposed of. In whatever way the above definition is met the pack inevitably finishes up as a COMPROMISE.

Since no compromise can ever be considered perfection, any pack chosen has to be recognized as a human judgement reached by human devised evaluations (tests), where some risk of failure (even if by misuse by the ultimate user), however small, is invariably present.

In this context for example any pack which involves multiple opening and reclosuring always evokes the question, "how often is the pack effectively reclosed during use"? Since the answer must at least be "not always", this may create a case for a unit dose pack which involves individual protection right up to the time of use, albeit in some instances at a higher cost per dose. Although there has also been a tendency towards introducing microbial limits for many types of product, any support for these limits may be difficult to substantiate, if gross contamination can occur during a product in use period. Thus, although it may be relatively easy to justify the absence of certain pathogens, it is more difficult to accept, for example, an argument for sterile nasal preparation especially as we do not continuously breathe "sterile air" and the product is used to treat a highly contaminated zone (i.e., the nasal passages).

The PROTECTIVE aspects of the pack will vary from product to product with differing emphasis on:

CHEMICAL (including compatibility)

CLIMATIC

PHYSICAL or MECHANICAL

BIOLOGICAL

} PROTECTION

With pharmaceutical products the protective aspects of the pack may be both critical and diverse. It is therefore essential to clearly identify a whole range of hazards against which some products may require PROTECTION especially as their obvious nature can easily be overlooked on the basis that 'familiarity breeds contempt'. The author therefore advises even the most knowledgeable to use some form of check list and therefore the headings below may provide a useful reminder. It is also important to remember that hazards tend to work in combination rather than in isolation.

13.6 Hazards Which May Affect Packs

13.6.1 PHYSICAL OR MECHANICAL HAZARDS

SHOCK - impact, drops, deceleration

COMPRESSION - pressure applied by stacking during storage or during transit.

pressure applied during product line operations, particularly capping, plugging, etc.

VIBRATION - effects of a range of amplitudes and frequencies from bumps (low frequency, high amplitude) to high resonance (high frequency, low amplitude).

ABRASION - usually the effect of vibration but listed separately so that it is not overlooked. May create electrostatic effects.

PUNCTURE - penetration from handling operations or contact with sharp objects.

13.6.2 CLIMATIC HAZARDS which may lead to deterioration or contamination. Climatic hazards cover the effects from atmospheric gases, pressure differentials, light rays, airborn contamination (solid), temperature variations, moisture/ relative humidity, etc.

Although all require some further explanation only a few examples will be given below:

Atmospheric Gases

These include oxygen, nitrogen, and carbon dioxide. Of these, oxygen is likely to have the most severe effect mainly due to oxidative action or ability to support microbial activity. Carbon dioxide particularly in the case of unbuffered products, may cause a pH shift to 4.3 - 4.5 (carbonic acid) or occasionally lead to chemical reaction. Although nigrogen is inert there

have been instances where nitrogen flushed containers have suffered from internal pressure increases where the material (e.g., plastic) is permeable to other gases. All plastics are to some degree permeable to gases usually in a ration of 1:4:20 for nitrogen, oxygen and carbon dioxide, where the latter is the most permeable. Airborne odours, either inorganic (e.g., SO_2, H_2S) or organic (solvents, perfumes) etc., may cause organoleptic changes associated with taste (taint) or smell (odours). Once these are identified by panels, analytical limits may subsequently be established.

Temperature Variations

World wide variations are usually greater than most people realize. They cover both temperatures below freezing point (although obvious for arctic and antarctic conditions, low temperatures may also occur for periods of days with non-insulated vehicles or warehouses during vacations, holidays, etc.), and natural or artifically high temperatures. As many climatic charts and data sheets only record in the shade conditions, temperatures of well above 50°C (122°F) can be readily found, i.e., storage area in a low building with a metal corrugated roof, outdoor storage, direct exposure to sunlight, indoor storage directly behind windows with southern exposure, stock stored under overhead hot air heaters, goods carried in the trunk of a black car in hot climates, exposure in shop windows under and close to bright illumination - just to mention a few. In extremes, products may be exposed for short, or ocassionally longer, periods of temperatures of 70-80°C (i.e., 158°F - 176°F). However, it should be strongly emphasized that many packaging materials are readily affected by temperatures of 45°C and above and therefore the use of temperatures above this for prolonged periods does not necessarily give a true or predictable accelerated effect. (E.g., a metal closure on a glass bottle could become so 'tight' that the bottle seal is improved - hence moisture loss via the closure could be reduced and thereby incorrectly predict a longer shelf life, if moisture loss was a shelf life determining feature). Likely domestic conditions should also be noted. For instance a deep freeze is -15°C to 22°C (deep freeze conditions vary between countries), a refrigerator 4°C ± 4°C and conditions in bathrooms, kitchens, etc., may

frequently exceed the extremes (in both temperature and humidity) of most external climatic conditions. Storage of medicines well out of the reach of the children may therefore lead to exposure to hotter conditions (based on hot air rising) if these are on shelves or cabinets near to ceilings.

Finally, one's attention should be drawn to storage conditions which are advised on the pack as frequently such recommendations cannot be met in the pharmaceutical company's own premises let alone in other warehouses, stores shop, hospitals and the patient's home.

Temperature variations may also give rise to condensation or even shower effects both within and outside a pack when high temperature, high humidity conditions are reduced to lower temperatures.

Fluctuations in temperature will also lead to dimensional changes and pressure changes which may cause a pack to breathe or alternatively leak and seal to a variable degree. Stability storage at one selected condition, may therefore not represent what will occur under normal conditions, where fluctuations in temperature, humidity, pressure, etc., may give rise to different results. This type of problem can partially be compensated by either 'normal' storage tests or challenging the packed product under cycling conditions, e.g., 15°C 50% RH, 37°C 90% RH over 12 hour cycles. A pack/product which withstands these conditions is then unlikely to fail in practice. However, if the pack fails the latter test (other than identifying and investigating the failure further) it does not necessarily mean that the pack will inevitably fail under normal, less severe conditions.

Pressure differentials

Pressure changes may occur around and within packs due to the packaging conditions/operation, changes in temperature, or barometric pressure, which may be accentuated by moving from one altitude to another.

For example, a product packed at 50°C, sealed and then cooled to 20°C, will be under negative pressure (creation of a partial vacuum), depending on the formulation. Conversely a product packed at 5°C (material brought in from an unheated warehouse) and then moved into a warmer (25°C) area, is likely to be under positive pressure.

Temperature will cause different pressure changes according to both the vapour pressures (liquids, gases and some solids) and the product's thermal coefficient of expansion. Products containing significant quantities of alcohols, (e.g., after shave), require more ullage or container headspace to allow for the greater expansion under warmer conditions. Temperatures of product, at time of fill, can be important in such instances.

Pressure differentials will also occur to products filled at one altitude and then moved to another, either on the ground or in the air. For example, 0 to 8000 feet involves a pressure differential of -3.8 psi. Since this is also the average atmospheric condition to which pressurized aircraft are adjusted (not sea level) it is possible that any flexible pack (laminate or plastic bottle, etc.) may partially collapse* during air transportation. Although warnings of this are given by International Air Transportation Association, IATA, and most airlines carrying cargoes, some pharmaceutical companies do not appear to have this information. These IATA warnings cover both possible leakage effects on plastic packs and indicate how aircraft (and occasionally the goods which they carry) can be subjected to temperatures well below zero (in the air) and up to 55°C (130°F) on the ground in tropical areas. With non-pressurized aircraft (these do still exist) then pressure differentials of approaching -8psi may occur even though they fly at lower altitudes, (up to 22000 feet). From the above indications it is advisable to consider such points as:

1. How goods are likely to be transported (will they withstand air transportation or can air transportation be avoided - note small plastic (LDPE) dropper and spray packs are particularly prone to seepage when transported by air).
2. What ullage is required in the pack particularly with products having a high coefficient of expansion.
3. Do filling conditions (temperature) have to be controlled.
4. Do packaging operations have to be controlled, e.g., some more flexible containers may flex or partially collapse during plugging or capping thereby introducing a partial vacuum. Note: (This would be less likely to occur when the same pack was laboratory hand filled, capped, etc., at an initial testing stage than when mechanical plugging and capping is employed. It is therefore important to ensure that pressure differentials do not become a problem.)

* If leakage occurs

Humidity, moisture, liquid contamination

Moisture (including both the liquid and vapour states) may give rise to a number of deterioration effects:

Chemical reaction - effervesence, hydrolysis

Physical change - softening, hardening, expansion, and contraction, change in dissolution, disintegration, solubility, etc., brittleness, haze or turbidity.

Encourage or initiate microbial growth

Attract or act as a carrier to organoleptic changes

Encourage particulate contamination, e.g., low humidity increases electrostatic charges on plastics.

When relative humidity RH, is mentioned, there is always a tendency to think of high humidities which usually present the greater hazard. However, change may be brought about by either fluctuations in RH, or low RH which may bring about drying out (dehydration) or encourage more rapid moisture loss from a product either be permeation or physical loss. Moisture change for aqueous based products, either as loss or gain, whereby a drug entity is concentrated or diluted, may in some instances become a stability limiting feature.

The most quoted hydrolysis reaction is probably the breakdown of acetylsalicylic acid into acetic acid and salicylic acid. Other chemical actions can occur and these should be readily identified by early preformulation challenge studies where the drugs, excipients, and proposed formulations, are subjected to either liquid water or water vapor. Non-identification of any reaction under liquid conditions does not however rule out changes under the broader influence of atmospheric moisture in the presence of air, temperature fluctuations, etc.

The corrosive nature of moisture on metals should also be borne in mind, particularly when coupled with abrasive actions.

The more physical affects of moisture exchange are probably less predictable. The hardness, and possibly the disintegration and dissolution of a tablet may reduce or increase with either loss or gain of moisture. Moisture released from a product during storage at higher temperature may re-enter the product by a different process under cooler conditions. For example,

moisture may be lost slowly by desorption and diffusion into the head space but produce an adsorption effect on re-entry, whereby the surface of the product is altered. The product may also be changed by both the amount of water available and the rate at which it is taken up (or lost) from the product.

Moisture may, in certain circumstances, act as a plasticizer, e.g., gelatin capsules (both hard and soft) become considerably more flexible as the moisture content increases. Conversely moisture loss will produce a more rigid, less flexible and possibly brittle gelatin shell. The effects of surface adsorption may again alter the solubility of various materials.

Light including Photolysis

The effects of light are sometimes more difficult to quantify as direct exposure to actual conditions, shop window, open (outdoor) storage, etc., is very much dependent on the weather conditions prevailing at that time. For example, six months exposure in Singapore would be much dependent on whether this covered the dry or rainy season or a combination of both.

Artifical conditions Xenon*, fluorescent tubes, carbon arcs*, etc., may again involve variables, particularly the distance from the light source, the wave length intensities, the temperature of the test (*these invariably involve higher temperatures generated by the light source), together with possible influence from oxygen, ozone, moisture, etc. It should also be noted that certain packs may absorb the infra red wave length and therefore incur an additional heating effect (example amber glass which provides good protection for the ultra-violet wave length will absorb more infra-red than a clear glass container).

Although protection from light is essential with some products it should be noted that a carton and fiberboard combination, as found with many distribution packs, will afford virtually 100% protection from light until the pack is removed from the carton for final usage. Cartoning (and the packaging insert) or the overwrapping of a primary pack in less light penetrating material will also improve the shelf life of light sensitive products.

Other Atmospheric Contamination - Solid particulates

Airborne contamination of a microbial nature is covered under biological hazards. However, any solid particulates that can be conveyed via an air stream may sometimes represent an additional hazard, which depends on size, shape, hardness, solubility, etc., and whether they are a chemical or physical liability. Included under these categories, the most frequently listed materials are, dirt, dust, hair, powder, crystals, grit, fiber (natural or synthetic), etc. Such materials may lead to obvious particulate contamination, encourage or increase the microbial risks, cause abrasion of closures and decorated surfaces, etc., or simply downgrade the product/pack by an unsightly appearance. The abrasive nature of certain particulates is also likely to accelerate the corrosion of metallic surfaces.

Aging

"Aging" is used as a general term frequently when the cause either cannot be clearly identified or where a combination of causes may be involved. For example, a change in disintegration or dissolution time may fall into such a category, particularly where this changes according to the storage period of of the product. Until recently, with the advent of improved synthetic rubber components, natural rubber materials could limit the shelf life of a product by an aging phenomena. In this context aging was accelerated by the combined effect of oxygen, light, higher temperature, whereby the elastic properties were lost and the rubber ultimately became tacky, crazed, etc., to a point that it could split when stretched.

13.6.3 CHEMICAL HAZARDS

Since chemical interaction, if inherent to the formulation, cannot usually be reduced or avoided by pack selection (unless it is associated with exchange between the product pack and external atmosphere) tests to eliminate any risk of interaction or incompatibility between product and pack are essential. Compatibility basically covers any exchange which will occur (i.e., includes any exchange both between product and pack and pack and product), and may be associated with interaction or contamination covering migration, absorption, extraction, whereby ingredients may be lost or gained. Such exchange may

be identificable as organoleptic changes, increase in toxicity/irritancy aspects, loss or gain of microbiol effectiveness, precipitation, haze, turbidity, colour change, pH shift, etc. Again other external influences may catalize, induce, or even nullify chemical changes.

Chemical interaction, contamination, can also arise from impurities in ingredients (1), accidental ingredients arising from the production process (2), abrasion (3), etc. e.g.,

(1) Oxidation process could be accelerated by the presence of copper.

(2) Contamination arising from the extraction of plasticizers in PVC pipe lines.

(3) A bulk product with a clarity of solution test was packed in an LDPE bag within a metal drum. The clarity test was failed due to a presence of a haze after a travel test. This was traced to the slip additive in the LDPE which functions by being present at the surface of the film. The latter became detached from the product/film interface by physical vibration and friction between the product and the slip additive. Other examples of exchange between product and pack are given below:

a) Adsorption of chemical entities onto component surfaces which are frequently related to the surface areas involved - losses of ethylenediamine tetra acetate, EDTA, and certain preservatives have been known to occur by surface adsorption. Losses have also varied between different suppliers of bottles and different plastic grades.

b) Absorption and surface evaporation. The more volatile preservatives, e.g., chlorbutol, phenol, 2-phenlethanol, show fairly rapid loss through low density polythene. If an external overwrap, which is not permeable to the preservative is used, the loss can be restricted to relatively low level, i.e., less than 10%. This also indicates that the actual solubility of the preservatives in the plastic are relatively low.

c) Other surface active ingredients which may be found in plastic materials and suffer loss into product by solution, surface abrasion,

etc., include anti-static additives, slip additives, anti-slip additives, mould release agents, antiblock agents, lubricants, etc.

d) Detachment of glass spicules, may occur when alkaline solutions of citrates, tartrates, chlorides, salicylates are stored in soda glass containers. Spicules may occur when treated glass is autoclaved, in the presence of similar alkaline salts. Multiple autoclaving (e.g., container reuse), will also increase the surface erosion risk.

e) Organoleptic changes - permeation of volatile or odourless substances through plastic materials (note converse to loss of perfume through plastic containers) may also occur.

13.6.4 BIOLOGICAL HAZARDS

These cover animal, human and microbiological aspects. Although the handling and storage of all drug substances, irrespective of whether of animal, vegetable or synthetic origin has now reached a more hygienic level than previously, contamination by animals (particularly rodents) and insects, may still occasionally occur, particularly with substances of vegetable origin. Such contamination may arise from the cocoa moth, the drug room beetle (*Stegobium panaceum*) leather beetle (*Dermestis maculatus*) and smaller insects such as termites.

With microbiological contamination from bacteria, moulds, fungae, yeasts, whilst it is not intended to deal with these in detail, it is important to recognize how microbiological effects can be minimized by depriving them of those factors which are fundamental to their survival.

Bacteria for example, need free liquid water, food (a source of nitrogen), oxygen (unless anerobic of facultative) and are readily affected by temperature. Most rapid growth usually occurs between $20^{o}C$ - $40^{o}C$. Moulds although requiring similar conditions to bacteria need high RH to survive and generally grow best around a temperature of $25^{o}C$. Few species of mould can grow at RH's below 70%.

The need for sterile products may impose reservations on the packaging materials depending on whether sterility is achieved by a terminal or aseptic process. For each process, i.e., dry sterilization at 150-160°C (vaires between pharmacopoeial standards), moist heat (autoclaving) 115-121°C or even lower temperatures provided sterility is proved, ethylene oxide sterilization, gamma irradiation and accelerated electrons, needs careful evaluation to check any change in both product and pack.

A word of warning is also advised on plastics and sterilizing processes. Literature, on for example, ethylene oxide retention, and the effects of gamma irradiation and accelerated electrons tends to lag behind practical experience. As a result the level, of ethylene oxide retention reported in many earlier papers may have used analytical methods and procedures of extractive which do not reflect the total residues likely to be present. Similarly, the widely reported suitability of certain types of plastic to irradiation does vary according to the grade(s) selected and the constituents present in the plastic. It is therefore advisable to thoroughly check all materials, as belief, that a literature search may yield the information to support the use of certain materials, may sometimes be misleading.

13.6.5 PROTECTION - SUMMARY

The above should clearly establish that the important protective function of the pharmaceutical pack can be both variable and complex. Although each protective aspect when taken in isolation may be relatively simple, the total interaction between a number of factors has always to be considered. Perhaps the best way of indicating this is by a few further examples:

1. A sterile product incorporated a preservative system to cover withdrawal of a multi dose product. The product passed the USP XX microbial challenge test when first made and packed. After six months it was noted the level of ethylenediamine tetra acetate (EDTA) had significantly reduced (chelation with heavy metals + surface adsorption onto the plastic). A repeat microbial challenge test failed. It was 'believed' that this was due to slight preservative loss plus loss of EDTA which tends to enhance the preservative efficacy.

(i.e., a chemical + physical effect had created a drop in preservative efficacy).

2. A powder formulation product designed to give an accurate dose when dissolved in water was packed in a sachet. Immediate analysis indicated no problems. Subsequent analysis after 3 months showed a drop in the active drug by approximately 5%. This was traced to preferential adhesion of the drug (not the excipient) to the inner plastic layer of the sachet. The situation was corrected by an overage whereby the full dose could then be delivered at the solution stage.

   Sachet vibration tests could have established the above at a much earlier stage.

3. A liquid was placed on stability test in the belief that a stable product had been produced. One member of staff illegally decided to try the product, and partially used one bottle. Returning to the bottle some four weeks later the person found that the product had 'gelled' solid.

An investigation revealed that a gel was produced by absorption of oxygen and that this occurred more quickly at higher temperatures.

All full bottles showed virtually no change except very slight thickening - attributed to drying out at air/solution interface. An investigation showed that all batches had been immediately filled when produced - right from development stage. Any residual material was then discarded.

Further work clearly established that the product stood a high chance of gelling in a partially used bottle - dependent on the rate of use. The product was then reformulated.

The PRESENTATION aspects of a pack which cover both ESTHETIC and FUNCTIONAL requirements will also vary according to whether the product is an

ETHICAL

SEMI-ETHICAL

OVER THE COUNTER (OTC), PROPRIETARY

required for:

HOME TRADE

GENERAL or SPECIFIC EXPORT MARKETS

and whether SALE/USE is

via RETAIL

HOSPITALS/NURSING HOMES

HEALTH CENTRES, etc.

The 'elegance' of a pack frequently contributes to the user's or patient's confidence in the product.

INFORMATION and IDENTITY requirements of a pack may occasionally conflict with the general esthetics in that legalities may literally occupy most of the available space. The type of information which may be required may include some or all of the following:

Product form (tablets, capsules)

Product name - possibly trade name and compendial name if different

Quantity

Strength

Directions on how to be taken/used

How to be stored

Precautionary warnings

Product license number

Name and address of supplier

Batch number

Expiry date

Route of administration

Universal* product code, etc. (*renamed Uniform product code)

Since the primary objective of most pharmaceutical packs, is to convey confidence to the patient by enhancing the product-pack relationship, this has to be met by the correct balance between general presentaion and the information/identification. It is important that the latter is concise, clear and unambiguous.

CONVENIENCE and CONTAINMENT are both important packaging factors. For example the last 30 years has been a significant increase in packaging forms which assist in the administration of the product (a range of squeeze bottles for liquid applications - ear, eye, nasal drops - sprays, disposable syringes, aerosols, metered dose pump systems), etc., just to mention a few. CONTAINMENT is now accepted without question as few appreciate that some drugs of the past could at one time be literally handed over a drug counter unwrapped. However many in accepting this now familiar role of the pack do not realize the importance of the successful 'marriage' between product and pack. This chapter has therefore been set out to amplify and emphasize the functions of the pack in the shelf life of a product.

Finally, it is necessary to state that packaging development has recently had to consider two newer aspects - patient compliance and the pack's relationship to such environmental issues as pollution, disposal and conservation of energy and the world's natural resources. It is obvious that a pack can either assist or deter patient compliance and therefore greater emphasis may be placed on this by investigational research on this issue. As regards to the second environmental aspect, this also will need more consideration in the future, particularly as some patients will see this as an additional emotional issue if the anti-packaging lobby concerns continue to be publicized, without the advantages which packaging contributes to today's society, being equally explained to the public in general.

To conclude a company has to generate data to

a. Satisfy itself

b. Satisfy regulatory authorities

The first aspect should be the more important as

i) If a company cannot satisfy itself how can it be expected to produce authorative statements which will satisfy b.

ii) Too much emphasis on (b) may lead to risks being taken or incorrect assumptions being made. (This is easily done when pressure is applied).

Data should be considered as all the information which is collected from project conception to final withdrawal of product from the market (cradle to

grave approach). Monitoring of all stages is therefore essential both at the initial development stage and during subsequent ongoing production and sale. These will therefore include:

1. Full knowledge of the drug entity or active substances (from initial research phase) related to identity, purity, process residues, degradation routes, (when challenged by light, oxygen, moisture/water, acid, alkali, oxygen, carbon dioxide, temperatures, etc.), plus inter-related safety and toxicological (toxicity/irritancy) studies.
2. Initial scale up and a recheck of 1) leading to a provisional specification for drug entity.
3. Preformulation studies including interaction, challenge (similar to 1), dissolution studies, release, bioavailability, etc.
4. Clinical trial supplies.
   Full Q.C. and supporting stability studies to satisfy product/pack use.
5. Formulation studies - feasibility, part of or an extension to clinical supplies leading to final formulation(s). Accelerated stability and longer term stability tests on pharmaceutical development batches and scale up batches, leading to product specification.
6. Packaging studies - feasibility
   usually carried out in conjunction with 5. Provisional pack specifications.
7. Formal stability.
   Three production scale batches - final pack where possible.
8. Initial production batches for first scale supplies - additional stability work, using limited storage condition.
9. Ongoing production.
   Batches representative of production placed on confirmation stability tests at regular intervals.
10. Warehousing inspections, drug store inspection and end user checks.

11. Monitoring all complaints - product and pack, adverse reactions, etc.

At all stages attention should be paid to both GLP and GMP.

Having surveyed the broad functions of the pack, emphasis should be placed on the role of the packaging specification and the method of pack assembly. Attention to these two factors are of high importance to both the development and an ongoing production situation.

13.7 The Packaging Specification

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

Standard title, Bottle, cap, laminate, etc.

Specification reference number

date written Replace previous specification

ref no - date

General description

Materials of construction - types, grade, etc.

Construction - process by which constructed

Size/weight/capacity - with tolerances

Drawing ref, date, details of dimensions and tolerance

Decoration, detail of print, method of decoration

Performance tests

How to be delivered and identified

Signatures of approval: Supplier/purchaser.

It is therefore advised that prior to the commencement of taste, materials should be clearly identified, quantified, measured and checked for performance, etc. In this way the components used for any test circumstances, irrespective of whether they are investigational, feasibility, formal stability, travel test, etc., can be used more confidently and better

comparison can ultimately be achieved between a series of tests. If materials, product and pack, cannot be properly quantified, then obviously test results may become or verge on being meaningless.

13.8 Pack Assembly Detail

This follows similar importance in the philosophy of knowing what you are testing. The establishment of full records of both, how a pack was assembled and the tests performed to show that the pack was satisfactory, are likely to cover the following details, most of which can be related to GLP or GMP.

Batches references and batch numbers of the components and product used. Any previous history of components and product.

Date assembled where assembled

How assembled Responsibility for assembly

Quanitity of material/components issued and used/recovered. Equipment used for assembly operations (assembly speed/output). Product/pack specification, i.e., target figures associated with fill (volume, weight, number), cap torque, heatseal strength, etc.

Figures achieved

Problems encountered during assembly.

Results of any special functional tests applied to finished pack.

Environmental details where relevant

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

This type of situation can readily occur when production is asked to do a production operation on a relatively small scale. As a result the exercise may be treated as an inconvenient 'special' which is done by a make-shift team with little attention to detail. There are also circumstances where

the opposite may occur, i.e., expertise from several areas descends onto the production line whereby the production operators are put under strain and the ultimate activities in no way represent a typical production process. Both extremes may not only invalidate the ultimate tests, but create political unrest between the various parties involved, stemming from "we were not told", "lack of interest" or "interference", etc.

Although emphasis has been placed on specifications and the examination of all test materials prior to the initiation of any tests the more formal quality assurance, quality control, QA/QC, approach in a continuing production situation also needs mention. Records acquired from such ongoing examinations may yield valuable data on changes to incoming materials, process modifications, changes in pack assembly procedures, which in turn may result in a modification to the product shelf life. It is therefore important that QC records are constantly monitored so that any trends can be recognized as even in today's climate, technologists can be overcome by the simple pass or fail syndrome rather than using data to sense change. For instance one company introduced an apparently impressive supplier or vendor rating system which ultimately graphed each supplier on a points system every few months. Suppliers at the top of the table were naturally considered good and those at the bottom bad, with constant efforts being made to upgrade the latter through more rigorous and critical approach to defectives. However a quick assessment by an outside consultant immediately indicated that some of the top suppliers had items of good design and those at the lower end of the scale, poor or difficult designs. The table therefore gave a general design rating in addition to being a vendor rating system. Technical discussions which concentrated on the design, upgraded the ratings of some of the poor suppliers.

As occasionally suppliers introduce minor or even major modifications which to them improves the process or the item being produced, it is important to insist that any change is notified to the user company. A phrase to cover this is normally incorporated on the specification. Once a company has been notified of an impending change, judgement has then to be made on whether any further tests are required to prove whether the change has any significance.

13.9 Conclusion

Formal stability work is only of relevance if it is backed by an effective team which studies the project and the product/pack in total. Within this team there must be a high level of packaging expertise and a thorough co-ordination system between formulator, analysts, statisticians and packaging technologists. Even when a shelf life has been initially established, this must be supported not only by ongoing stability from the sampling production batches but also a monitoring system which ensures that the product and pack continues to meet those requirements essential to providing efficacy, safety, integrity, uniformity, etc., and confidence to the ultimate user. Only by this approach can the success of a product and the industry as a whole be assured.

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

There must also be an overall co-ordinator who is responsible for ensuring that all data provides a consistent and logical assessment of the product. It is therefore important that such a person is able to question information related to MATERIALS, MACHINERY, DOCUMENTATION, INCLUDING TEST PROCEDURES, ENVIRONMENT, SUPPLY SERVICES and PEOPLE as there is always a chance that those nearest to specialist activites "cannot see the wood for the trees".

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