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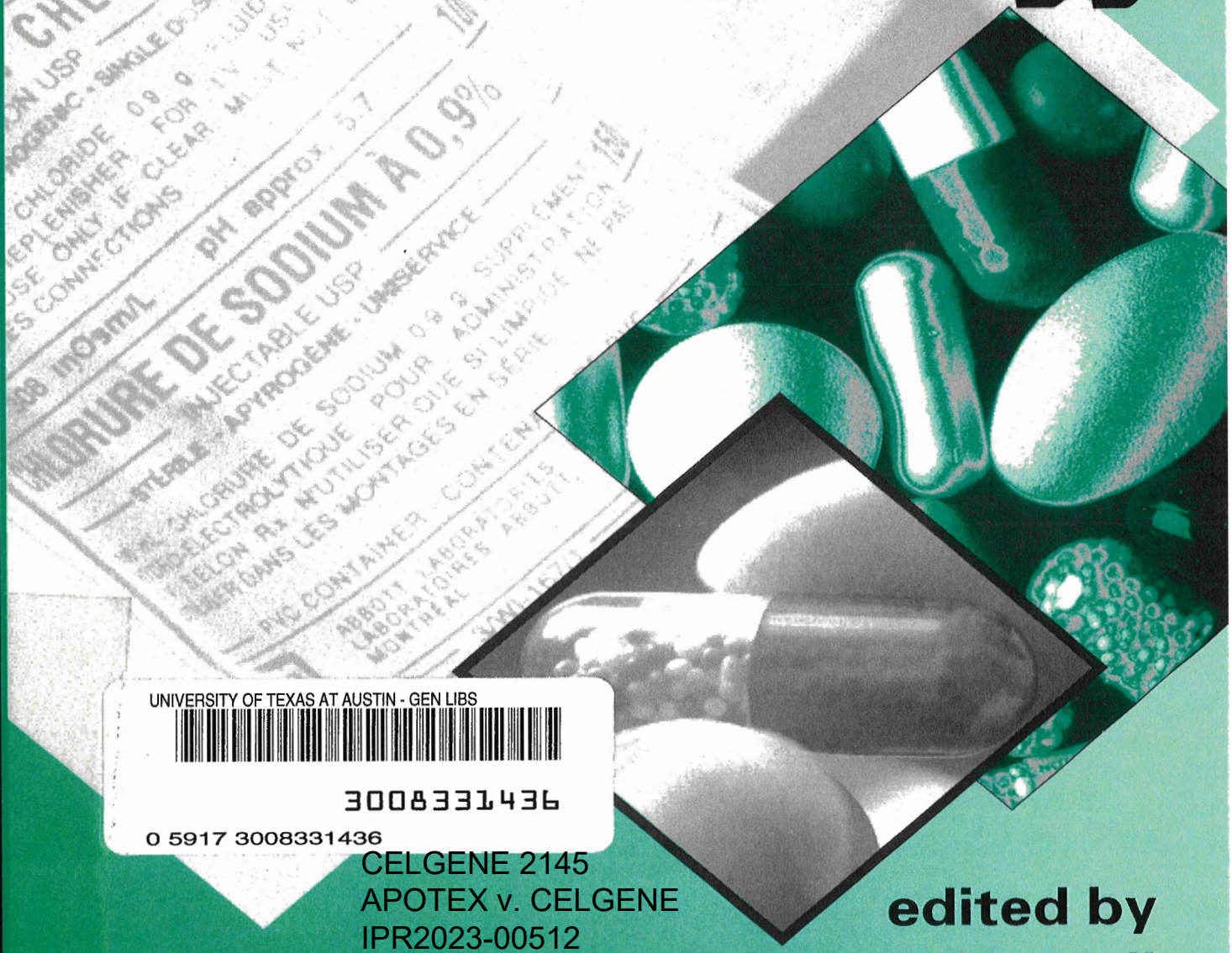

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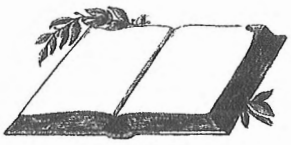

Let us first understand the facts and then we may seek the cause.

-Aristotle

PHARMACEUTICAL PACKAGING TECHNOLOGY

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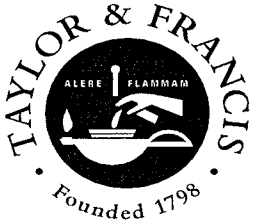

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3

REGULATORY ASPECTS OF PHARMACEUTICAL PACKAGING

J. Glasby

Introduction

The pharmaceutical industry is one of the most highly regulated industries in the world, the aerospace industry perhaps being the only one more highly regulated. Control is imposed on:

1 how the product is developed (toxicology testing is controlled through good laboratory practice (GLP); clinical testing is controlled by good clinical practice (GCP))
2 how the product is manufactured (through good manufacturing practice (GMP))
3 how the product is sold (through controls imposed through the Product Licence Application (PLA))
4 how the product is labelled (in Europe through the Labelling Directive and summary of product characteristics (SPC))
5 how the product is advertised (in Europe through the Advertising Directive)
6 how the product is disposed of (in Europe by the Packaging Waste Directive).

Thus, from the origination of the first idea to the final sale of the product, the legal system plays a key role in shaping and controlling the product. In this chapter we are particularly interested in how regulatory demands affect packaging.

Definition of the pack

The packaging technologist defines the pack as 'a device for carrying and protecting the product from producer to user', thus it is involved in containment, convenience, compliance, and confidence. The regulator, however, is interested in only some of these aspects (Table 3.1). In particular, the regulator sees the pack as having the following characteristics:

1 containing the product
   - protection of the product
   - protection of the consumer
   - dosage control
2 carrying the label
   - legal control of the product
   - informing the recipient

Table 3.1 Respective areas of interest of pack definition technologist and regulator

Area of interest	*Technologist*	*Regulator*
Economics	X	
Protection	X	X
Identification	X	X
Containment	X	X
Convenience	X	
Market appeal	X	
Presentation	X	
Disposal	X	X
Compliance	X	X
Primary pack	X	X
Secondary pack	X	
Tertiary pack	X	

3 contaminating the environment

- packaging waste
- ozone depletion

4 protecting the consumer

- child-resistant closures
- tamper-evidence.

The pack as a container of the product

At one time the container excited little interest since, it being invariably made of glass, there was little potential interaction with the product. The glass bottle was regarded as little more than an inert receptacle. Since there were also severe limitations on the form of the glass bottle there was little scope for ingenuity, thus packaging development tended to be considered as a separate topic tagged onto the end of the development programme, i.e. almost as an afterthought. Now the situation is different, and product development is totally integrated with packaging development. Of course, the packaging technologist had been saying for years that packaging development cannot be separated from product development, insisting that it was not possible to separate the pack and product. Why then has the attitude of industry and the regulators changed? There are several factors, as detailed below.

Increasing sophistication of the pack

Glass, being so inert, does not present a very interesting problem to the packaging technologist. Once plastics are involved, however, the situation changes and there is much more scope for interactions between product and packaging. Packs can also be designed to be more closely tailored to the needs of the patient. Like all advantages, however, there are associated disadvantages to the use of plastics, for example the extraction of materials from the plastics into the product. Once the possibility of contamination arises, regulatory authorities become much more interested in the selection, composition and performance of the package.

Increasing sophistication of the product

New chemical entities are so few and far between these days, and are so expensive to develop that companies regularly look at their ageing products with a view to revamping them by means of new presentations. One way to do this is to repackage the product in a more sophisticated way. Once there is more complexity, there is greater potential for problems to occur between the pack and product.

Incorporating a device into the pack

Control of dosage and administration has always been interesting both to pharmacists and to regulators, but it can be a major problem with pharmaceutical products. The pack can play a key part in controlling the dosage, for example in the use of a pressurised aerosol for dispensing powders or solutions. Once the pack and product administration system are integrated in this way the development cannot be separated and neither can they be separated in regulatory terms. A drug is thus affected by its packaging, both in practice and in the eye of the regulatory authority. For example, in the USA a parenteral drug product, even if it is an old drug such as sodium chloride, when produced in a plastic container does not fall within the category of 'generally recognised as safe' (GRAS). It is regarded as a new drug (Federal Food, Drug and Cosmetic Act S201(P)).

Cost of development

It is not only the development of new chemical entities that is becoming more and more time-consuming and, thus, expensive (Table 3.2). The cost of development of any product is now so high that a company must look to worldwide distribution in order to recoup the development costs. Ideally the same product should be used worldwide. However, while the pharmaceutical development department will be trying to develop a single formulation, the packaging development department's aim must also be to try and develop one single pack for worldwide use. This trend, however, will be countered by marketing departments trying to obtain precisely the right presentation for each market, insisting that markets differ in their needs.

Just as market needs differ, local regulatory agencies also have different requirements. While it may be possible to convince marketing departments at least to reduce the number of variants required, what about all the different regulatory agencies, of

Table 3.2 Time to develop new drug

Activity	*Time (years)*
Research	2
Toxicology	3
Development	3
Clinical	4
Registration	?
Total	12+

which there are over 150 in the world? How can they be satisfied by the same product and data?

In regulatory terms the situation is not quite as bad as it might appear. If we look at the world market (Figure 3.1), the EU represents approximately 30% of the market, the US approximately 27% and Japan approximately 18%. In total this represents 75% of the total market. Therefore, in commercial terms if one can satisfy these countries then a large step has been made towards meeting the commercial goal.

This situation has been improved through the International Conference on Harmonisation (ICH) between these three areas, since agreement has been reached on stability testing, impurities of active materials and others. As this expands, the multiplicity of data requirements will be significantly reduced. However, although there is some harmonisation between the three major regulatory areas in terms of the data required, it is likely that in regulatory terms the world will continue to be split into three different types of regulatory system: EU, USA and Japanese. Other countries will tend to follow one of these approaches with local modifications.

Regulatory authorities – background

The EU, although under criticism in many areas, has been fairly successful in the pharmaceutical area, with the following achievements:

- centralised system in place
- decentralised system in place
- harmonisation of format
- expanding acceptance of format outside EU
- harmonisation of standards (PH EUR).

A standard format of product licence application has been adopted, making the preparation of regulatory documents much simpler. The format and data requirements of

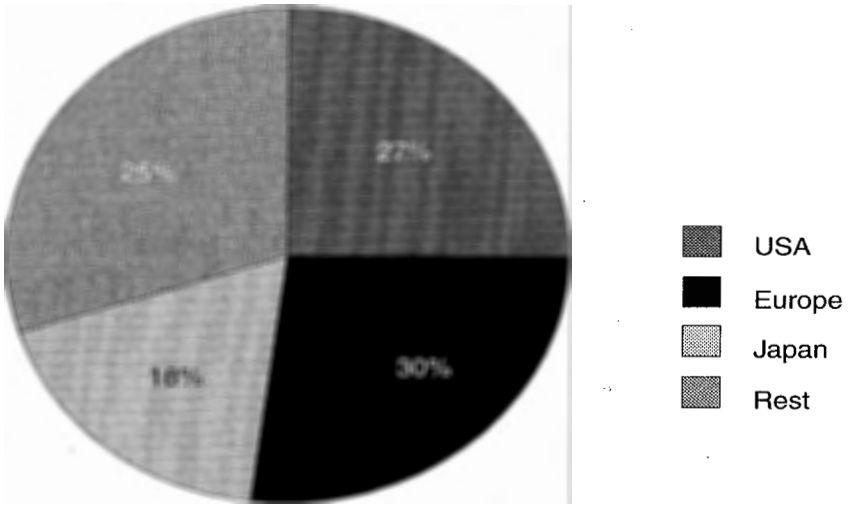


Figure 3.1 The world pharmaceutical market

the EU are being adopted by several countries outside the union, so reducing the number of types of application necessary.

The Food and Drug Administration (FDA) is finally recognising the competence of certain overseas agencies and the skill of scientists, and accepting more data that has been generated overseas (Figure 3.2). Even Japan is becoming more international, with several initiatives suggesting, in theory at least, that data from overseas should be acceptable within Japan.

In order to understand the approach of regulatory authorities, it is necessary to understand their attitudes and for this it is necessary to look back into history.

The history of pharmaceutical products is, in fact, rather short (Figure 3.3). Before the nineteenth century there were few really effective drugs apart from a few herbal remedies such as digitalis from foxglove. In general, only herbs and spices were used in treating disease. Since they had variable and unproven efficacy, the main perceived problem was that herbs and spices were expensive. Certain unscrupulous dealers tended to dilute the material in order to maximise profit, and this led to the introduction of the first control of drugs. First local pharmacopoeias and then country-wide pharmacopoeias were introduced which defined the specific composition and quality to be applied to drugs.

In the nineteenth and early twentieth century, with the increased urbanisation and industrialisation of the UK, the majority of medicines were the so-called patent medicines which contained few active ingredients but had extensive claims for their curative actions. Thus, the controls that had to be applied were on the advertising and claims for the product. It was only after 1935 that the 'therapeutic revolution' brought products which actually had some proven and consistent efficacy. Unfortunately, along with the efficacy came side-effects and problems, since for every pharmacological activity which is beneficial there will inevitably also be side-effects. If we look back at the introduction of controls on medicines, it is generally a problem or disaster which leads to introduction of the specific control.

In the USA, the death of a large number of children from a sulphanilamide preparation led to the Food, Drug and Cosmetic Act (1938). For the first time, proof of safety was required before any product was introduced to the market. It was not until the 1962 thalidomide tragedy that proof of efficacy was required in the USA through an amendment to the FD&C Act, the Kefauver Amendment, and this led to the

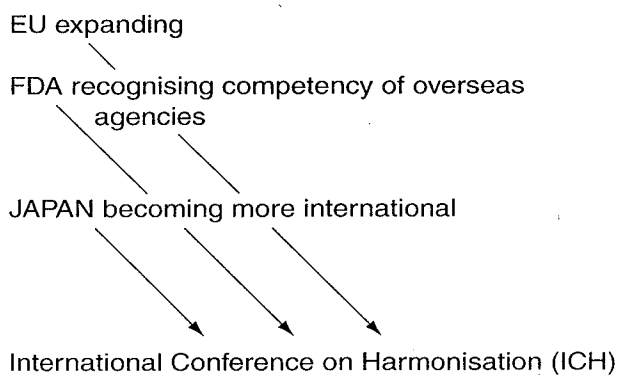


Figure 3.2 The worldwide regulatory split

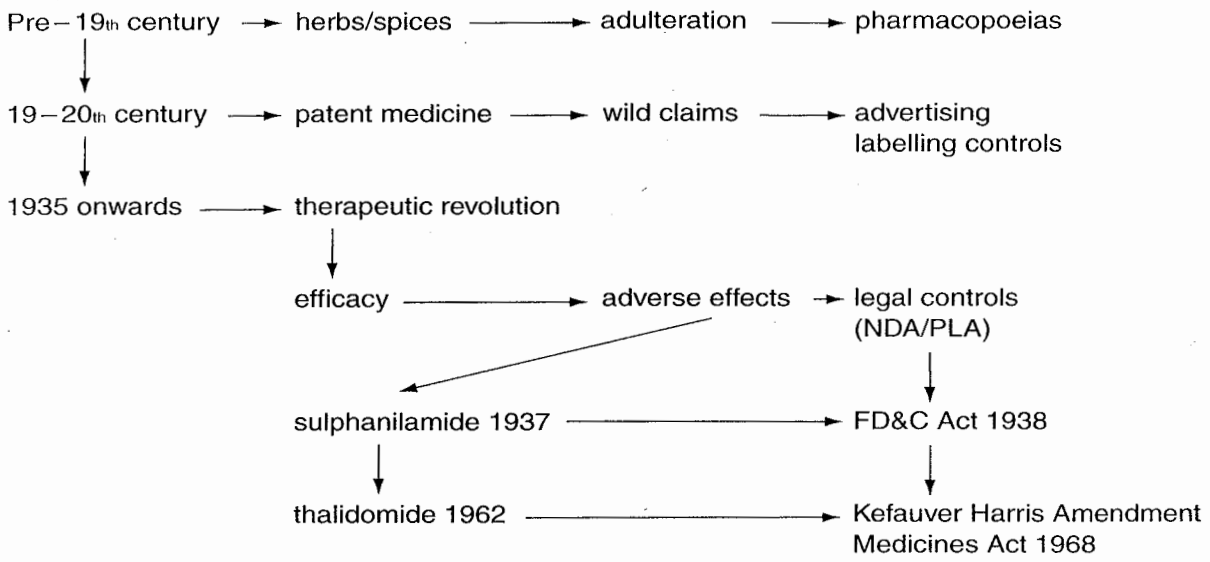


Figure 3.3 Outline of pharmaceutical history

introduction of other regulatory controls worldwide including the Medicines Act 1968 in the UK. Such problems, together with other factors such as political pressure, public pressure, consumerism and bureaucracy, have created the regulatory agency attitudes we see today.

Despite the differences in regulatory agencies, the actual registration approach is very similar (Figure 3.4). The process starts with the research area producing compounds for evaluation, followed by toxicology testing, first in animals and then the first introduction into human volunteers to determine safety and tolerance. This is followed by small clinical efficacy studies and finally the Phase III full efficacy studies involving large numbers of patients. In parallel to these clinical programmes the product development progresses with finalisation of the formulation and pack, and stability testing. Once sufficient clinical and pharmaceutical data are available, the product licence application can be prepared and submitted to the authorities. For review, it is generally

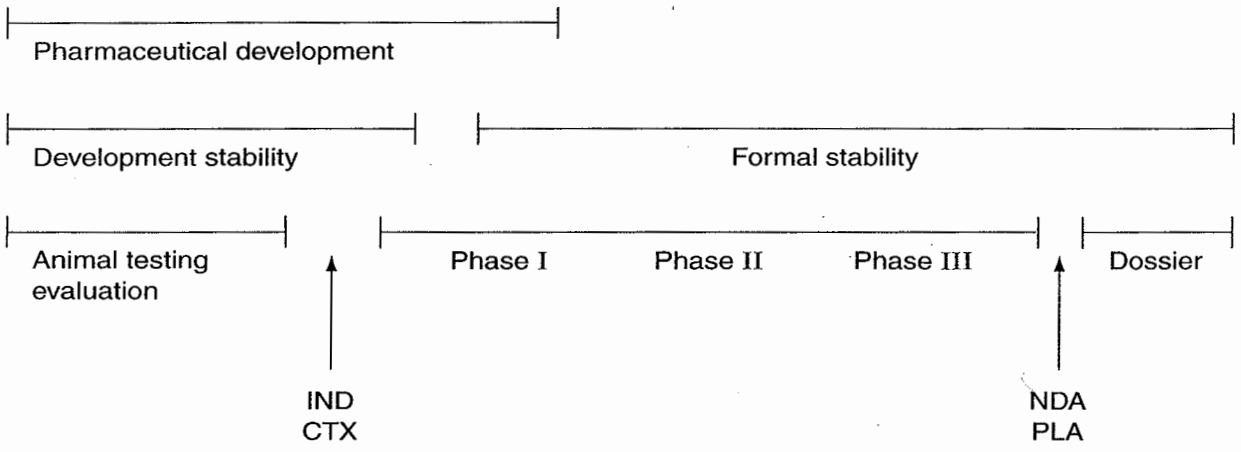


Figure 3.4 The development process

split into the three different sections, chemistry and pharmacy, pre-clinical studies and clinical data, so that these separate parts can be examined by specialist reviewers. It is almost certain that reviewers will have questions during their review which have to be circulated back to the company while the application is put on hold, pending suitable replies. This circuit may be followed several times and, in part, explains why the review cycle can be so long and variable. Finally, once all the questions have been resolved and the precise labelling agreed, a licence is issued and the product can be launched.

European Union processes for drug evaluation

Within the EU there are currently three processes by which a drug can be approved for marketing (Table 3.3). These are individual local applications to specific countries, the decentralised system, (mutual recognition route), and the centralised system.

Local applications

For products intended for a single country a local application can be made. Since 1 January 1998 any subsequent application to a second country must be made through the decentralised system.

Decentralised system (mutual recognition)

The decentralised system is, in effect, a system of mutual recognition. An application is first made in a single country and when approved the application, translated in certain aspects, along with the assessment report prepared by the regulatory agency, is sent to the other countries. Each country then has a limited time to accept the application and assessment report or to provide reasoned objections. If the objections cannot be resolved by bilateral discussion then the application is referred to the CPMP for a binding recommendation (Figure 3.5). Alternatively, the country or countries with objections can be withdrawn from the procedure. Although not without its problems, the system is working and products are receiving approvals in many European countries by this route. At present however, individual countries tend to be carrying out a full review of the applications despite the availability of the original approval and assessment report, and have not yet fully embraced the idea of mutual recognition.

Centralised system

It was recognised that certain products, such as biotechnology products, were taking a considerable period to become registered in Europe because of their complexity and

Table 3.3 EU processes

Local applications	*After 1998 for one country only*
Decentralised applications	Mutual recognition Majority of applications
Centralised applications	Innovative products and biotechnology Single licence for all EU

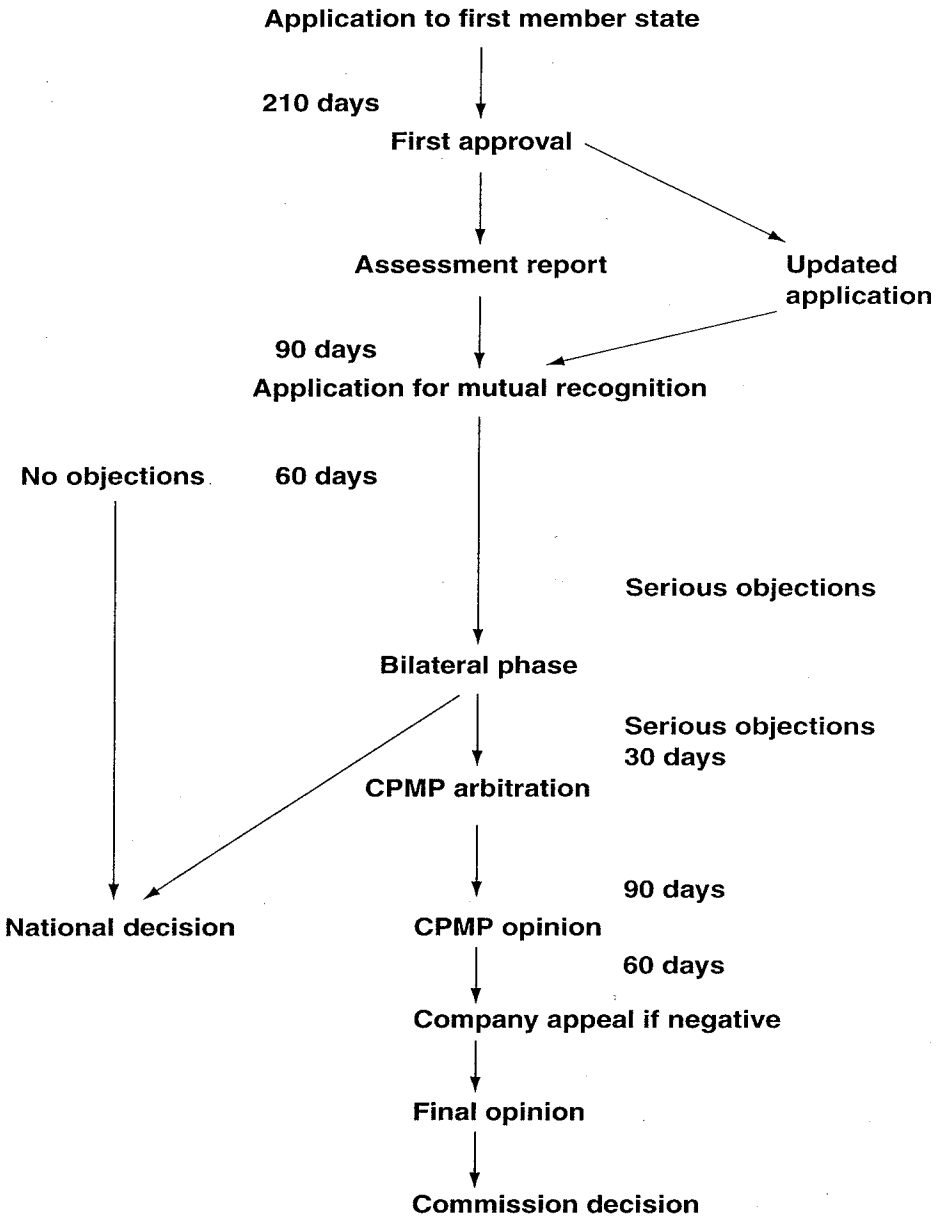


Figure 3.5 The mutual recognition process

the absence of skills to evaluate them in certain countries. A central scheme was therefore set up where by a single evaluation of the application is made and a recommendation for approval issued by the CPMP followed by issue of a single licence issued by the London-based European Medicines Evaluation Agency (EMEA) for all the EU (Figure 3.6). Since 1 January 1995 this centralised procedure has been mandatory for all products of biotechnology and optional for projects which are very innovative such as new chemical entities or new presentations of drugs. CPMP appoints one or two of its members to act as rapporteur to co-ordinate the assessment using the facilities of the various regulatory agencies within Europe. Once the evaluation reports are available the CPMP makes an opinion within 210 days of receipt of the application and a single licence is then granted, valid throughout the Union.

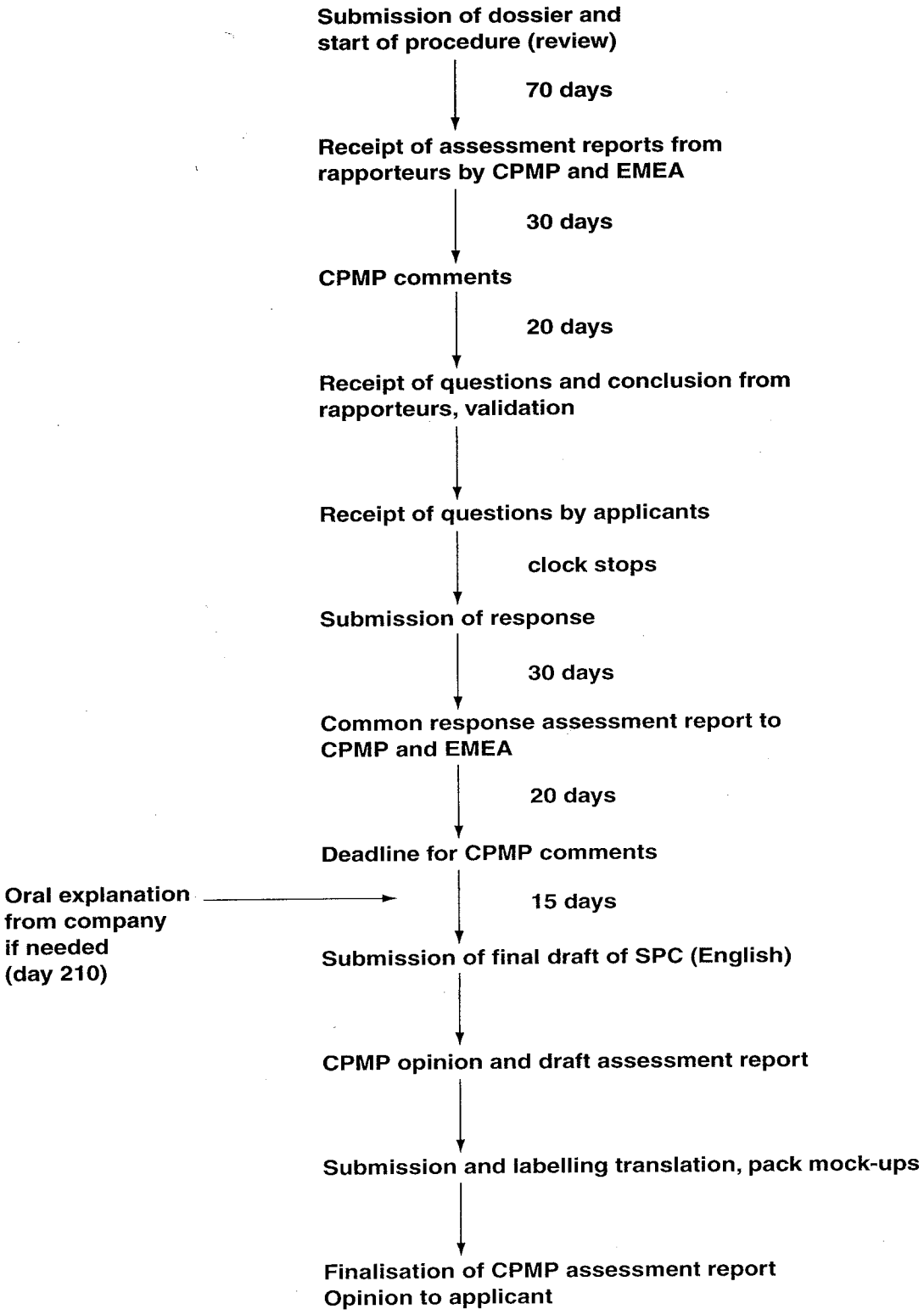


Figure 3.6 Outline of the centralised procedure

Product licence applications – data requirements on the package

A few years ago there was almost no legislation concerning packaging. The 1968 Medicines Act in the UK, for example, makes almost no mention of the subject. However, for the reasons discussed earlier, certain specific EU guidelines applying to packaging have now been published. These are:

- CPMP List of Allowed Terms (III/3593/91) (new list issued in February 1998)
- Notice to Applicants (Updated 1998)
- Plastic Container Guidelines (III/9090)
- Plastics in Contact with Food Directive (90/128).

These, along with the requirements of the European Pharmacopoeia, provide guidance for the data requirements for packaging and its format for presentation in the product licence application.

CPMP list of allowed terms

Descriptive terms for pharmaceutical forms, routes of administration, and packaging and delivery systems allowed to be used in a Product Licence Application are now prescribed by EU Regulations (Table 3.4). It is hard to understand the value of this legislation except in terms of the legal nature of the Product Licence Application. It must be remembered that a product licence is more a legal than a truly technical document. As with all legal documents, it is necessary to ensure the definitions are consistent wherever the application is made. It is not clear, however, how much attention is being given by regulatory agencies to this list, although experience has suggested that they do insist on using the appropriate terms in at least the application form part of the submission, since this becomes the legal body of the licence. The official terms should also be used in the labelling, particularly the summary of product characteristics.

Notice to applicants

The main pharmaceutical Directives 65/65 and 75/318 do not actually spell out in detail what is required in a Product Licence Application. These key directives require that applications be made, and define only in outline the data requirements. It is therefore necessary to expand the guidance and this is done in the Notice to Applicants (1986) and its subsequent amendments. The Notice to Applicants prepared by the European Commission has no legal standing, but gives additional advice over and above that given in the various EU Directives. The notice actually forms volume 2 of 9 volumes of the Rules Governing Medicinal Products in the European Union, and has two parts:

- 2A deals with the legal procedures for marketing authorisation
- 2B deals with the presentation and content of the application dossier.

In these documents the Marketing Authorisation Application is defined in the following sections.

Table 3.4 Standard terms for marketing authorisation applications, Notes for Guidance III 3593/91 EN final (updated February 1998)

Covers standard terms for:
- pharmaceutical dosage forms
- route of administration
- container
- closure
- administration device.

Containers
Ampoules
Applicator
Automatic injection device
Bag
Balling gun
Barrel
Blister
Bottle
Box
Brush
Brush applicator
Cannula
Cap
Cartridge
Child-resistant closure
Cup
Dabbing applicator
Dart
Dredging applicator
Dredging container
Drench gun
Dropper applicator
Gas cylinder
High pressure transdermal delivery device
Implanter
Inobo injection device
Injection needle
Injection syringe
Internal graduated calibration chamber
Intramammary syringe
Jar
Measuring spoon
Metering pump
Metering valve
Mouth piece
Nasal applicator
Nebuliser
Needle applicator
Nozzle
Oral syringe
Pipette
Pour-on container
Pre-filled syringe
Pressurised container
Sachet
Scarifier
Screwcap
Single dose container
Spatula
Spot-on applicator
Spray container
Spray pump
Spray valve
Stab vaccinator
Stopper
Strip tablet container
Tube
Vaginal sponge applicator
Vial

- *Section I*: application form, administrative details, labelling and expert reports (chemistry and pharmacy, toxico-pharmacological, and clinical).
- *Section II*: chemistry and pharmacy data.
- *Section III*: toxicology data.
- *Section IV*: clinical data.

For most of our purposes, the data on packaging is included only in the chemistry and pharmacy section and in the pharmaceutical expert report, although if a new plastic or polymer material is used, toxicology data may be required along with comment in the toxicology expert report.

With Section II, data is required on the packaging in four areas:

- *Section IIA2*: composition – immediate package
- *Section IIA4*: development pharmaceutics
- *Section IIC3*: control of starting materials
- *Section IIF2*: stability testing.

The Notice to Applicants remained the only guidelines available until 1990, when the draft Plastic Container Guidelines III/9090 was published which expanded the requirements in these four areas (Table 3.5).

Table 3.5 CPMP Guideline III/9090 EN final, plastic primary packaging materials

Take account of:
- Directive 90/128/EEC – plastic materials intended to come into contact with foodstuffs
- European Pharmacopoeia
- Notice to applicants
- Volume IV of Rules Governing Medicinal Products in European Community. Parts covering packaging:
  - IIA2 immediate packaging
  - IIA4 development pharmaceutics
  - IIC3 packaging materials
  - IIF2 stability.

MAA application section IIA2 – container

This requires only a brief description of the nature of the container and of the components, with a qualitative composition and details of the method of closure and opening (Table 3.6).

MAA application section IIA4 – development pharmaceutics

The development pharmaceutics area is often neglected, but is proving to be a key area in submissions. In this section the applicant must justify the choice of the formulation and of the packaging. Thus, the selection of the resin must be discussed and data provided on the interaction or compatibility between product and pack. If there is processing involved, such as sterilisation, then the influence of the process on the product and container must be studied and reported (Table 3.6).

MAA application section IIC3 – control of starting materials

The container is regarded as one of the starting materials for the product along with the other ingredients of the formulation. For this reason the specification, testing regimen and details of any tests carried out must be provided for both the plastic resin material and the container (Table 3.7).

Resin

The name of the resin material, the name and address of the manufacturer, the chemical name, the complete formulation, characteristics and quantity of all ingredients and the function are required where the material is to be used in a container which will be exposed very intimately to the product, such as a large volume parenteral solution or eye drop. The identity, using IR absorption along with a reference spectrum must be provided. Additives, particularly those likely to migrate, including antioxidants, plasticisers, catalysts, initiators and materials such as phthalates, adipates and organic tin in PVC or any dyes used in the resin must also be identified.

Tests on plastics should include physical, mechanical, dimensional, purity in terms of monomer and additives, buffer potential, reducing substances and UV absorption.

If the material is not listed in the European Pharmacopoeia then its status as a food-approved plastic must be described with reference to the EU Directive. If these data are

Table 3.6 CPMP Guidelines III 9090

IIA2 Immediate packaging
Description container including:
- nature of material (qualitative)
- description of closure
- method of opening
- information on container
- Description of tamper-evidence and child-resistant closure.

IIA4 Development pharmaceutics
Justification of choice of containers in terms of:
- stability of active ingredient and product
- method of administration
- sterilisation procedures.

Choice of plastic including information on:
- tightness of closure
- protection of contents against external factors
- container–contents interaction
- influence of manufacturing process.

Table 3.7 CPMP Guideline III 9090, IIC3 – packaging materials

Specification and routine tests
- Container construction, list components
- Nature of polymers used
- Specification of material:
  - identification
  - visual inspection
  - dimensional test
  - physical test
  - microbial tests.

Scientific data collected during development
Plastic:
- name/grade
- manufacturer (parenteral and ophthalmic)
- chemical name
- monomers used
- qualitative composition of interaction
- description and solubility in solvents
- identification material
- identification additives
- Tests (general and mechanical).

Container:
- Name converter (ophthalmic and parenteral)
- Reproducible process
- No changes in composition without verification

not available then toxicology data may be required, along with an assessment by a toxicologist. Where there is less contact, such as the case for a solid dosage form, it may be possible to reduce the amount of data supplied, particularly if the plastic is of pharmacopoeial grade.

Container

The container must be described in terms of the plastics used and the name of the manufacturer, along with an evaluation of its suitability and risk of toxicity through extractives. Consistency of the container quality is a key aspect and data must be provided on containers tested in conditions similar to those to be used, including sterilisation if this is part of the process.

Once the resin and the container have been fixed there should be no changes in materials or manufacturing process. If a change is made then further testing and approval of a product licence variation by the regulatory authority will be necessary. This means that pharmaceutical companies look to resin and container suppliers to maintain supplies for many years without making changes to processing or composition.

MAA application section IIF2 – stability

The final section of III/9090 covers the stability data required (Table 3.8). It does not provide a comprehensive coverage of the subject but relies on the existing general stability guidelines, adding extra points which specifically cover the package.

The guideline makes the key point that the choice of test conditions is influenced by the compatibility and protectability of the resin and the product type involved. In setting up stability tests, both normal and stress conditions are required. Normal conditions look at interaction between pack and product, migration of components and protection of the product under normal temperatures and humidities. Stress testing is carried out using higher temperatures, light, high humidities and increased surface ratio to highlight the migration and interaction potential of the components.

Table 3.8 CPMP Guideline III 9090, IIF2 – stability

Choice of plastic based on protective effect and compatibility
Compatibility study part of product stability test
Solid forms:
- migration risk low
- no interaction study needed

Semi-solid:
- migration of additives or dyes
- study with actual formulation

Liquid:
- migration risk for formulation
- O&P – active and preservative
- studied under simulated use conditions

General
- Study at least one batch of finished product
- Normal and accelerated conditions
- Extraction tests with solvents (as foods) only predictive
- Migration studies should include technological characteristics, leaching antioxidants, monomers and oligomers, plasticisers, mineral compounds
- Sorption of formulation components to be studied

Study methods should include technological characteristics, the leaching of antioxidants, plasticisers, minerals (calcium and barium), and absorption of the active component of the product into the plastic.

For solid products the risk of migration is low and therefore interaction studies are not required over and above the normal stability test results. For semi-solid products it is necessary to look particularly at the migration of additives, vapour permeation and the effects of the product on the physical parameters of the pack. For liquid products the migration potential for the specific formulation is required, and the determination of active ingredient content under simulated use, along with extractives data is required for parenteral and ophthalmic products. Moisture permeation is important, particularly for solid products packaged in blister packs.

In the past it has been difficult to satisfy in a single test programme the requirements for the EU, the USA and Japan. However, following the 1992 International Conference on Harmonisation, tripartite stability recommendations have been produced which have considerably simplified the situation (Table 3.9), laying down storage conditions and means of evaluating results.

Expert reports

The major difference between an EU dossier and that for other regulatory authorities, such as FDA, is the requirement for expert reports. These documents play an important

Table 3.9 ICH tripartite stability guidelines – final product

Test frequency
- 3 months for first year
- 6 months for second year
- 12 months thereafter
- continue to test to shelf life

Packaging
- final marketed pack plus unprotected product (useful)

Evaluation
- systematic approach (protocol)
- matrixing possible
- variability affects protocol
- shelf life is suggested as 95% confidence of the mean reaching the specification limit
- can combine batch results to determine shelf life if variability low
- if variability high, use minimum values
- if little degradation, no need for stats
- mass balance

Extrapolation
- limited extrapolation can be done – must be justified (e.g. linear and mechanics)

Labelling
- as national requirements, e.g. store below 25 °C in UK (cannot use room temperature)

Storage conditions
- 25 °C ± 2 °C/60 ± 5% RH
- 40 °C ± 2 °C/75 ± 5% RH
- if 40 °C fails, test at 30 °C ± 2 °C/60 ± 5% RH

part in the assessment of the application. Three expert reports are provided, covering chemistry and pharmacy, toxico-pharmacology and clinical aspects of the product. Only the chemistry and pharmacy expert report will cover packaging aspects, unless a new packaging material is involved. The expert report must provide a balanced evaluation of the data and therefore may be critical of the data presented. Many companies find this difficult to accept, but regulatory authorities expect criticism and thus even a critical expert report need not prejudice the review of an application. If done properly the expert report can, in fact, assist the company since it allows some flexibility. It can, for example:

- justify a temperature other than 25°C having been used for room temperature storage
- provide a shelf-life prediction at 25°C based on overall data from various temperatures
- justify fewer than three batches having been used in the stability tests
- justify the use of non-production batches
- explain different stability profiles between batches
- provide a materials balance if decomposition appears
- justify the statistical methods or explain the absence of a statistical method.

Thus, the guidelines need not be followed absolutely providing the expert can justify the alternative approach taken.

USA procedure for drug evaluation

The New Drug Application (NDA) is the formal request that the FDA review and approve a drug for marketing in the USA. FDA has the responsibility to determine that the drug is safe and effective, the proposed labelling is appropriate, and the methods used in the manufacturing are adequate to control the drug's identity, strength, quality and purity. Thus, all new drugs must be subject to an approved NDA before they can legally be marketed or transported across state lines. The NDA was introduced in 1938, and required only proof of safety for the product until 1962, when the need to prove efficacy was introduced. A 1985 rewrite of the NDA procedure modified the content of application, the format and the review procedures to make them more effective and logical to review. The NDA currently contains the following sections:

1 application form
2 index
3 summary
4 chemistry and manufacturing controls
5 non-clinical pharmacology/toxicology
6 human pharmacokinetics/bioavailability
7 microbiology (for anti-infectives)
8 clinical
9 statistics
10 case report forms and tabulation section
11 samples and labelling.

The content of the various sections is identified in very detailed guidelines which contain much more guidance than the more outline type of guideline issued by the EU. In terms of packaging the data requirement is covered in the 'Guideline for submitting documentation for the manufacture of and controls for drug products' and, more specifically, in a guideline reserved for packaging, the 'Guideline for submitting documentation for packaging for human drugs and biologics (February 1987)' (Table 3.10).

FDA packaging guideline

An applicant may rely upon the guideline in preparing the application or, alternatively, can follow a different approach, although if the latter is chosen, FDA encourages the sponsor to discuss the matter in advance with it in order that an unacceptable approach is not taken. The role of the drug packaging in maintaining the standards of identity, strength, quality and purity of the drug for its intended shelf life is stated in the guideline and reference is made to the pharmacopoeia for guidance on the type of packaging to be used and the test and procedures to be applied.

Much more detailed information on the package is required by the FDA than is generally required in the EU, but the data may be submitted in the form of a drug master file, which allows container or resin manufacturers to supply the FDA directly with detailed confidential data.

The guideline defines the types of container to be used, dividing into parenteral (glass or plastic) or non-parenteral containers (glass, plastic and metal), along with pressurised containers and bulk containers for active ingredients and drug products. The information that must be submitted for each of these categories is defined.

Closure types are also listed, including tamper-resistant and child-resistant caps. Liners are also given prominence, along with inner seals and elastomers when used as closures. Aerosols are given specific coverage since they affect both the rate and the amount of drug delivered.

The suitability of packaging components is discussed in terms of their physical, chemical and biological characteristics, specification and tests to be applied, stability and compatibility considerations and the involvement of adhesives and inks. In selecting a package it is recognised that ingredients added to the resin such as plasticisers, lubricants, mould release agents, pigments, stabilisers, antioxidants and binding or anti-static agents may be leached from the plastic. Certain ingredients of the drug

Table 3.10 FDA Guideline for submitting documentation for packaging for human drugs and biology

1	Purpose • Package must maintain standards, identity, strength, quality and purity of drug for shelf life • Full information needed • USP provides guidance
2	Type of containers/closures
3	Suitability for intended use
4	IND needs
5	NDA needs
6	Submission of packaging information and data (format)

preparation may bind to plastics or be absorbed by them. It is also possible for a component of the drug to migrate through the walls of the container and for oxygen, carbon dioxide and other gases to permeate through the plastic into the drug system.

Clear reference is made to the USP/NF for definition of the specifications and tests required for the package. Such tests can involve extractive testing, IR or UV spectra, thermal analysis, melt viscosity, molecular weight, molecular weight distribution, polymer linearity, degree of crystallinity, permeability, stiffness, softening temperature, ash and heavy metal content. It also may be necessary to carry out biological testing where appropriate, using the specific USP/NF tests.

As in the EU, the basic details of stability testing requirements are not given, since reference can be made to the general guidelines on stability testing. Instead, the packaging parameters that must be added to them are described. Special note is made that formal stability studies should be carried out in product packaged in the container/closure system in which the drug is to be marketed. Tests should be performed to check the absorption of toxic impurities from the container/closure system so that appropriate tests can be defined to control the problem. Leaching studies should be carried out in accordance with the USP procedure and, where appropriate, checks should be made that contamination with micro-organisms will not occur through the container or closure.

Attention is given by FDA to the fact that cements and lacquers used as label adhesives are often dissolved in organic solvents which may allow migration of adhesive components into the contents of the packaging. Appropriate testing should, therefore, be performed to determine whether this occurs (also being considered by the EU). In addition, testing should be conducted on the effectiveness of the adhesive under appropriate challenge conditions of temperature and humidity.

Format of NDA application

Information necessary for the various types of packaging is detailed in the guideline and should be submitted in the following order:

1 name of manufacturer
2 description of packaging components and processes
3 sampling plan
4 acceptance specification
5 test methodology.

Although the NDA requires a summary, this should be strictly factual and should not contain the evaluation and opinion found in the European style expert report. In the USA it is the FDA that draws the conclusions based on the factual data and summary provided by the applicant.

Packaging for clinical trials in the USA

Before any clinical study can be carried out in the USA, an exemption from the need to hold an NDA must be obtained from the FDA. The detail required on the packaging provided in the Investigational New Drug Application (IND) depends on whether the

study is in an early phase (Phase I) of testing or in the late phase (Phase III). It is recognised that at the early phases, an outline of the packaging used and an indication of the appropriate stability studies which have been initiated may well suffice, but at Phase III the information supplied should be directed towards fulfilling the requirements of the full NDA.

Comparison of EU and FDA data requirements for PLA or NDA

In general the data required for packaging, as in other parts of PLAs, is basically the same. The differences lie in the format of the application and the depth of information provided. This is mirrored by the type of guidelines issued by the respective organisations. FDA guidelines are very detailed, providing reviewers and applicants with the detailed basic requirements for the application. In addition, the FDA requires and encourages companies to consult it at various stages during the development programme, since the period between IND submission and final NDA approval is seen as a continuous process. The FDA sees this advisory role as an important part of its work, and as development progresses additional data is generally filed to the IND with the aim of increasing the data held within the IND such that, by Phase III clinical testing, the amount available is almost that required for the NDA, and has already been FDA reviewed.

In Europe the two phases are kept separate, although some guidance is given during the clinical testing procedure as to future requirements for the PLA. The guidelines are less detailed and the applicant is encouraged to formulate its development plans and to justify them through the vehicle of the expert report without the considerable interaction that goes on between company and FDA.

Pharmacopoeias

The main guidance on package requirements can be found in pharmacopoeias (Table 3.11). Of the three key pharmacopoeias of the world (USP/NF, Ph Eur and Japanese Pharmacopoeia), it is the European Pharmacopoeia that is the main reference source in the EU, being set up by the Convention of Elaboration of European Pharmacopoeia of the Council of Europe. Once a monograph is accepted, EU members are charged to make the monographs official standards in their own countries. However, this does not

Table 3.11 Pharmacopoeias and their contents

Pharmacopoeias	*Contents of pharmacopoeias*
Key publications	Mainly active ingredients
↓	+
USP	Tests for reagents/other materials
↓	↓
Ph Eur	including
↓	↓
WHO	Glass
↓	↓
	Plastic

If material is in pharmacopoeia it must meet the standard

mean that compliance with a pharmacopoeial monograph automatically makes the substance acceptable to the regulatory authority, since there is always the option for the regulatory authority to require additional testing over and above that in the monograph. Nor does it mean that all the tests in the pharmacopoeia necessarily have to be carried out. Alternative methods can be used, providing that comparative data are provided to show equivalence. If there is a dispute, however, the pharmacopoeial method becomes the reference standard.

In terms of packaging, the European Pharmacopoeia provides a list of plastics that are permitted for use in pharmaceutical containers. These are:

- PVC for containers for human blood, blood components and aqueous solutions for IV infusion
- PVC for components used in blood transfusion
- polyolefines
- polyethylene (low density) for parenteral and ophthalmic preparations
- polyethylene (high density) for parenteral preparations
- polypropylene for parenteral preparations
- ethylene–vinyl acetate copolymer for total parenteral nutrition products
- silicone oil as lubricant
- silicone elastomer for closures and tubing.

For each, appropriate specifications are given, along with the test methods and permitted additive levels.

Although the main packaging material covered is plastic, it must not be forgotten that glass is still often used. Type I, Type II, Type III and Type IV grades of glass are described in the pharmacopoeia. In this chapter, however, we will concentrate on plastics.

The section on plastic containers states that the plastic material can consist of one or more polymers along with certain additives, but must not contain any substances that can be extracted by the contents in such a way, or in such quantities, to alter the efficacy or stability of the product, or increase its toxicity.

The monograph states that the nature and amount of additive used will depend on the type of polymer, the process used to convert it into a container and the intended purpose of the container. Approved additives include antioxidants, stabilisers, plasticisers, lubricants, colour and impact modifiers. Anti-static and mould release agents can be used only for containers for oral and external preparations. Specific permitted additives are given in the specification for the material within the pharmacopoeial monograph.

In selecting the appropriate polymer material the key aspects are that the drug is not absorbed, that it does not migrate through the material and that the plastic does not yield any material in a quantity sufficient to affect the stability or the toxicity of the product. Tests of compatibility should include physical changes, permeation, pH change, effect of light and chemicals or biological testing as appropriate for the type of product involved.

The method of manufacture must ensure reproducibility between batches and the conditions should be chosen to preclude the possibility of contamination with other plastic materials or their constituents. Containers made should be similar in every

respect to the type sample. For the testing on the type sample to remain valid, there must be no change in the composition of the material or in the manufacturing process, particularly with regard to temperature to which the plastic material is exposed during conversion or subsequent procedures such as sterilisation. Scrap materials should not be used. Recycling excess material of a well-defined nature and proportion may be permitted if the appropriate validation is carried out.

Plastic material in contact with food (90/128 and amendments)

If a material is not listed in the pharmacopoeia then reference must be made to a further Directive dealing with plastic materials in contact with food. Materials authorised for use in contact with food are generally acceptable for contact with pharmaceuticals (Table 3.12), but if this approach is taken it will also be necessary to provide a list of countries where the plastic has been approved for pharmaceuticals. If these two aspects can be covered, then toxicology data should not be required in the application. The Plastic Material in Contact with Food Directive lists, in an annexe, the monomers and starting materials which can be used for food purposes after January 1997. A second annexe lists the monomers which can be used, but which may be deleted if data were not supplied to enable the Scientific Committee to evaluate the product before 1 January 1996 (since then amendments have been inserted updating Annexe 1 as the data have been provided). Finally, specific migration limits are given for each material listed.

There is no doubt that the regulatory authorities are now requiring much more information on plastics and plastic containers than was required previously. At the same time reviewers are beginning to become more knowledgeable in the area of resins and containers. However, they are not yet packaging experts and, as such, some of the regulatory requirements may not be strictly logical when reviewed by an expert in the area. However, the requirements stem from guidelines which are suggestions rather than

Table 3.12 Plastic materials and articles intended to come into contact with foodstuffs – Directive 90/128 and amendment Directives

Framework Directive 89/109
Legal basis (framework Directive for future Directive)

Food contact materials must be inert and have no transfer constituents
Scientific Committee for Food (SCF) will set criteria

↓

Plastic materials in contact with food directive 90/128

- Defines plastics
- Sets overall migration limits 10 mg/dm^2 or 60 mg/kg food where container capacity > 500 ml or for caps
- Sets standard test conditions amended or extended in Directives 82/7118, 85/5728 and 93/8
- Specifies overall migration limit (amended in Directives 92/39, 93/9).
- Lists permitted monomers and starting materials

↓

Annexe IIa – sufficient data to evaluate
Annexe IIB – insufficient data (to be deleted January 1997 if data not provided)

mandatory requirements and, therefore, in the EU at least it is possible to argue for an alternative approach using the vehicle of the expert report, provided the case is well documented and reasoned. In the USA the same result can be obtained by discussions with the FDA. If a good case is made, backed up by sound data, then experience would indicate that authorities are still prepared to review specific cases according to specific data available. (Care must be taken not to over-interpret European flexibility, since mutual recognition reviews could introduce fifteen different viewpoints.)

The pack as carrier of the labelling

Just as the container cannot be separated from the product in regulatory or technical terms, the container, label and leaflet are also intimately connected, and in pharmaceuticals the term 'labelling' generally includes both the labels and any leaflet included with the product.

The term 'label' can mean the label on the immediate container, the carton label, the outer label or the label on the case or pallet. Each label has a different function. A leaflet, enclosed within the carton, can be a patient leaflet or a professional user leaflet, or in some cases a summary of product characteristics (SPC).

The function of labelling

The function of the label and leaflet is to inform the patient, to inform the pharmacist/wholesaler/manufacturer, to control the product in terms of its distribution and medical aspects, and to reduce the risk of product liability claims.

For a prescription medicine the patient wants to know about the treatment being given, to supplement that given to him or her by the doctor or the pharmacist and possibly to counteract information provided by the media, friends and family.

The pharmacist, in making up the product to the doctor's order, needs to identify the product and detect any gross prescribing error in order to advise the patient where required. The wholesaler needs to identify packs and outers readily and quickly and thus needs access to the name, strength, pack size, storage and handling conditions, expiry data and batch details.

The doctor who has prescribed the medicine does not generally handle it personally. He or she does, however, require reliable information on the name, presentation and strength, indications, contra-indications, dosage instructions, precautions, interactions, side-effects and pack sizes which must be absolutely consistent with the details on the immediate label, carton label and any package leaflets enclosed. Since he or she does not handle the product, some other mechanism must be found to provide him or her with this information separately from the product. This is probably the SPC or summary of major product characteristics (SmPC, see below) data sheet.

Thus, the patient has the label on the primary container and package insert, the wholesaler has the carton and pallet labels, and the pharmacist has the immediate container label, the carton label, package insert and possibly the SPC. The doctor looks at the SPC or equivalent document, probably in a compilation of such documents, such as the data sheet compendium in the UK.

All this information must be accurate and consistent both scientifically and legally.

The SmPC

The key document from which all other text is derived, is the summary of product characteristics (SPC), sometimes referred to as the summary of major product characteristics (SmPC) to differentiate it, as abbreviated, from the supplementary protection certificate which is concerned with patent protection.

The purpose of the SmPC is to set out the agreed position of the product between the regulatory authority and the company. It thus controls all the labelling and advertising of the product. Any changes to the SmPC must be approved by the regulatory authority before they are introduced (Table 3.13). The SmPC also provides a vital document in the harmonisation of products within the EU. The centralised procedure results in one licence and one SmPC and is, therefore, relatively straightforward, but the decentralised procedure involves gaining approval in one country and then seeking mutual recognition in other member states, based on that first approval. In this case, it is recognised that complete harmonisation of the SmPC throughout Europe would be very difficult and discussion continues, particularly for generic products.

The information to be provided in the SmPC is clearly defined in the CPMP Notes for Guidance document (III/9163/90) (Table 3.14) which defines the sequence of data and then gives some explanation as to what is required under each heading. In addition to III/9163/90, the key EU legislation for labels and leaflets is as follows.

- Directive EC 65/65 provides the particulars required for labels in outline.
- Directive 75/319 provides the particulars for leaflets in outline.
- Directive 89/341 makes a leaflet compulsory if all the details required are not displayed on the label.
- Directive 92/27 consolidates and provides greater detail on the requirements for labels and leaflets.
- Directive 92/73 makes similar provisions for homeopathic drugs.

European Directives do not actually make local law, they merely place an obligation on countries within the EU to introduce specific legislation to fulfil the requirements of the directive. For example, the requirements of Directive 92/27 have been achieved in the UK through Statutory Instruments (1992) 3273 and (1992) 3274.

Table 3.13 SmPC

Role and summary given in 65/65 article 4(A)

Purpose:
To set out agreed position of product
- between competent authority and company to provide common basis of communication
- between competent authority and all member states

Controls the product:
- All labelling, advertising must be consistent
- Any changes must be approved by regulatory authority
- Must be presented to doctor by representative
- Must be supplied with any samples

Table 3.14 CPMP Notes for Guidance III/9163/90; SmPC – content and sequence

1	Name of the medicinal product
2	Qualitative and quantitative composition
3	Pharmaceutical form
4	Clinical particulars
	4.1 Therapeutic indications
	4.2 Posology and method of administration
	4.3 Contra-indications
	4.4 Special warnings and special precautions for use
	4.5 Interaction with other medicaments and other forms of interaction
	4.6 Pregnancy and lactation
	4.7 Effects on ability to drive and use machines
	4.8 Undesirable effects
	4.9 Overdose
5	Pharmacological properties
	5.1 Pharmacodynamic properties
	5.2 Pharmacokinetic properties
	5.3 Pre-clinical safety data
6	Pharmaceutical particulars
	6.1 List of excipients
	6.2 Incompatibilities
	6.3 Shelf life
	6.4 Special precautions for storage
	6.5 Nature and contents of container
	6.6 Instructions for use/handling
	6.7 Name or style and permanent address or registered place of business of the holder of the marketing authorisation
7	Marketing authorisation number
8	Date of approval revision

Label and leaflet directive 92/27

Directive 92/27 starts with a definition of name of product, common name and strength of product, immediate packaging, outer packaging, labelling and manufacturer. It then defines the particulars which must occur on the outer packaging (Table 3.15). When the immediate packaging takes the form of a blister pack which is placed in an outer package that complies with the provisions above, then the blister pack (Table 3.16) can show reduced particulars, but must show at least the name of the product, the name of the holder of the authorisation, the expiry date and batch number. Some other immediate packaging may be so small that it is impossible to display all the requirements. In this case it is possible to reduce the number, but all packs must display at least the following: name of the product, method of administration, expiry date, batch number and contents by weight, volume or unit. There is no specific definition of 'small' in terms of the pack, although 10 ml is generally regarded as a good guide for the limit.

The presentation of the particulars on the label should be easily legible and clearly comprehensible, indelible, and must appear in the official language of the member state. Other items which may be required locally, such as price, reimbursement conditions and legal status, can also appear.

Table 3.15 Labelling and packaging Directive 92/27/EEC

Immediate packaging must contain:

- product name
- active ingredients
- pharmaceutical form and contents
- list of excipients
  (all for ophthalmic or parenteral)
  (any with recognisable effect)
- method and route of administration
- special warnings
- expiry date
- special precautions
- name and address of authorisation holder
- authorisation number
- manufacturing batch number
- instructions for use for self-medication product

Table 3.16 Directive 92/27, exemptions from full labelling

Blister packs:

- product name
- authorisation holder's name
- expiry date
- batch number

Small units:

- product name
- strength (if necessary)
- route of administration
- expiry date
- batch number
- contents

Leaflets

All products must contain a patient leaflet unless all the information can be conveyed on the outer packaging label. The content of the leaflet and order of presentation are defined in Directive 92/27 and must be as follows.

1 Identification of product.
2 Name of product, statement of active ingredients, pharmaceutical form, pharmaco-therapeutic group, name and address of authorisation holder.
3 Therapeutic indications.
4 Information needed for taking the product.
5 Contra-indications, precautions for use, interactions, special warnings, including use in pregnancy, elderly, effect on ability to drive vehicles and details of any excipients which may be important for the safe and effective use of the product.
6 Instructions for use.
7 Dosage, method and route of administration, frequency of administration, duration of treatment where limited, action to be taken in the case of an overdose or lack of dosing and risk of withdrawal effects where possible.
8 Undesirable effects.
9 Effects that can occur under normal use of the product and action to be taken.
10 Expiry date.
11 Warning against use of the product after the date, appropriate storage precautions and warning against visible signs of deterioration.
12 Date on which package leaflet was last revised.

The leaflet must be written in clear, understandable terms, be legible and be in the official language of the member state. Inclusion of symbols or pictures is permitted if in compliance with the SmPC. Since this is a user leaflet the language must be understandable to the lay person.

At the time the Directive was issued there were a number of tasks that the Commission had not yet undertaken and items that were to be introduced:

1 special warnings
2 special needs for self-medication products
3 legibility of text
4 identification and authentication of medicinal products
5 list of excipients which must appear on the labelling.

The above information relates to a package insert designed for the patient, but in some cases further information is required for use by the doctor, dentist or nurse in supplying or administering the product. To cover this need a professional user leaflet may be included provided it is within the scope of the SmPC, but even if the product is administered by a professional a patient insert must also be provided.

The package as a contaminator of the environment

Packaging waste

Just as public and political pressures have increased the amount of information required by regulatory authorities on packaging as a result of concern for the safety of drugs, the same changing attitudes have made the environment of greater concern. Hence there has been considerable pressure to reduce contamination of the environment through waste products (Figure 3.7). Of particular concern is the amount of packaging used today and how it is disposed of. Of course the amount of pharmaceutical packaging waste is small compared with the total amount (probably less than 1%), so that any reduction will have little impact on the environment. The industry, however, must comply with any regulations made, and experience has shown that it will not be regarded as a special case.

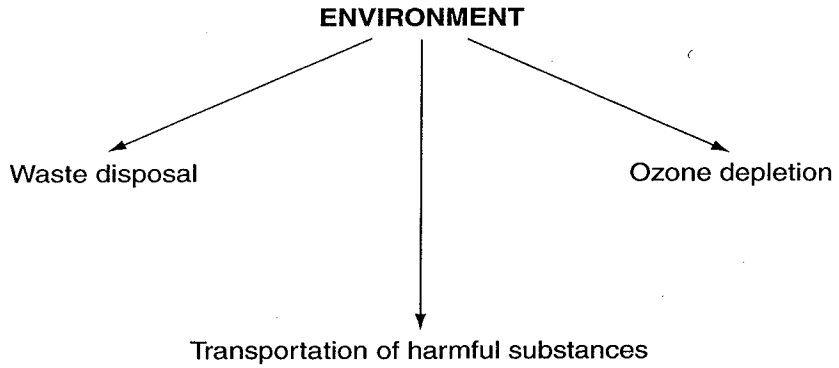


Figure 3.7 Environmental concerns

This increase in concern has led to the EEC Packaging Waste Directive 94/62 (Table 3.17) which requires:

- reduction in the quantities of waste
- reduction in harmfulness of waste
- promotion of reuse of packaging
- recycling and recovery of packaging waste
- reduction of the total packaging to be disposed of.

Since the first Directive there have been several amendments increasing the scope and reducing the time scale for achievement of targets of recycling and reuse. Targets of 50–60% waste recovery in 5 years and 25–45% recycling with a minimum of 15% for each material have been set, and tightening of the targets can be anticipated at any time (Table 3.17). Return, collection and recovery systems for packaging must be set up and there must be a marking system on the pack to allow the nature of the plastic to be identified.

All new packaging introduced must now meet the Directive, and to avoid differences between countries the elements of standardisation are outlined. With recycling there is likely to be an increased concentration of heavy metals, and this aspect is also covered.

Table 3.17 Directive 94/62, packaging and packaging waste

Objective
To harmonise national measures for management of packaging and packaging waste by
- prevention of production of waste
- promotion of reuse and recycling
- reduction of disposal

Scope
All types of packaging

Definitions
Packaging, levels of packaging, waste

Reuse
Postpones creation of waste

Recovery/recycling (5 years from implementation)
- 50–65% recovery
- 25–45% recycled
- minimum 15% each material recycled
- return, collection and recovery systems

Marking and identification systems
To identify material used

Heavy metal content
- 600 ppm by 30 June 1998
- 250 ppm by 30 June 1999
- 100 ppm by 30 June 2001

To ensure that progress is properly monitored, a database on packaging use is prescribed and the information that should be supplied to users defined.

At first there was hope that pharmaceutical products would be exempt from the Directive, and considerable pressure was applied. However, most representations were unsuccessful. It is not easy for the industry to meet these requirements and, at the same time, meet the requirements of GMP which, for example, restricts the amount of recycling of plastics that can occur and generally prevents the use of scrap material.

The industry may have to produce new materials for packaging since several of the current ones, such as PVC and foil laminates, have limited scope for recovery or recycling. The packaging development department must take account of these factors since the waste Directive must be a key factor in choosing packaging for new products.

Ozone layer depletion

Pressurised aerosols play a major part in modern pharmaceuticals and in many ways are a perfect pack in efficiently protecting the product and dispensing an accurate dosage of the contents when required. They are, therefore, clinically effective and convenient to use. Unfortunately, the propellants originally used (generally a mixture of chlorofluorocarbons (CFCs)) were shown to be depleting the ozone layer. As a result, an international agreement was reached in 1987 that CFC production and consumption should be curbed. This agreement, the Montreal Protocol, was signed by 27 nations and originally called for a 50% reduction in CFC consumption by 1999. In the EU the proposals were incorporated into Regulation 594/91 which required that there be no production of CFCs by 30 June 1997. Controls have also been introduced on exportation and importation of CFCs from the EU, and the original Directive has been expanded to cover such substances as methylbromide, hydrobromofluorocarbons and hydrofluorocarbons.

To overcome the non-availability of CFCs for use in metered dose aerosols, alternative propellants have been developed and are being introduced progressively. The process is complex, requiring first long-term toxicology studies in two animal species on the propellants themselves, followed by pharmaceutical work using the propellant and product to determine compatibility and stability of product and propellant in combination. Normally a new propellant can only be approved by regulatory authorities as part of a marketing authorisation for a product, but in this case applications were made in the EU to cover the propellants alone so that the safety issues could be cleared prior to review of individual applications for specific products. The first stage has been achieved for two alternative materials, and products containing them are now reaching the market.

Classification, packaging and labelling of hazardous materials

In discussing the environment a further Directive should be considered which specifically excludes medicines, but still may impact the pharmaceutical industry since companies package and transport hazardous intermediate materials between production sites (Table 3.18). Such intermediate materials are often toxic, inflammable, oxidising or irritant and, therefore, are caught by Directive 67/548. Because of the increased pres-

Table 3.18 Directive 67/548 (and amendment), classification, packaging and labelling of dangerous substances

Excludes:	Medicines
Includes:	Explosive, oxidising, inflammable, toxic, irritant substances
Classifies:	Very toxic, toxic, harmful
Testing:	Obligation to investigate properties
Safety data sheet:	Needed to protect operations
Notification:	Technical dossier needed, detail depends on quantities produced
Packaging:	Must avoid loss of contents
	Materials of construction not attacked
	Strong and solid to meet normal stresses and strains
Labelling must include:	Name of substance
	Origin (name and address of manufacturer)
	Danger symbol
	Special risks
	Precautions

sure on costs and profit margins there is an increased trend today for the centralisation of production worldwide, which means that more and more intermediates must be transported.

The original Directive covered:

1 inclusion and exclusion of materials
2 selection of packaging which avoids loss of content, is not attacked by the product, and is strong and solid enough to meet the nominal stresses and strains of handling
3 labelling, including the use of specific danger symbols
4 notification of the competent authority of new materials by use of a technical dossier.

Since 1967 there have been many amendments to the original Directive. For example, Directive 88/379 shows how the physico-chemical properties of the compound must be determined to evaluate the health hazard. Directive 67/548 reiterates the requirements for packs requiring the pack shape not to attract children. For certain substances, child-resistant or tactile warnings are required and the labelling is covered in great detail, including the dimensions and colours to be used. Directive 91/115 requires that a data sheet be produced which covers identity, composition, hazard identification, first aid, fire fighting, accidental release measures, exposure control, personal protection, physical and chemical properties, stability, disposal, transport, regulatory and other information. Directive 72/32 (amendment 7) pulls together many of the earlier amendments covering testing, classification and notification, describing the technical dossier that must be submitted, covering unfavourable effects, classification, data sheet and notification requirements. The amount of data that must be supplied increases as the production/supply quantities increase, from smaller amounts of data if the quantities are less than 1 ton per annum, increasing at over 1 ton, over 100 tons and over 10,000 tons. After submission of the dossier the material can be placed on the market after 60 days if no response is received.

Polymers (Directive 92/105)

Directive 92/105 provides special notification needs for polymers. The Directive states that the notification should contain the information necessary to evaluate the foreseeable risk to man and the environment. It is possible to avoid preparation of several dossiers and to group polymers and produce representative tests covering the whole group. A reduced package of data is possible for high molecular weight materials if they meet certain criteria. In an annexe to the Directive, homopolymer, copolymer, polymer (RTP) and family polymers are defined, and the standard test package required is defined, the amount of data varying according to the annual production level.

Protecting the public

Child-resistant closures

As well as protecting the product, the package can also protect the public through the use of child-resistant closures (CRCs) or tamper-evident packs.

There has been criticism that child-resistant closures are difficult to remove by the elderly. This is true for many of the devices, but on the other hand there is no doubt that CRCs have been effective in preventing poisoning in children. For example, the number of analgesic poisonings in children in the UK reduced from 626 in 1974 to 181 in 1977 after introduction of the requirement for use of CRCs.

Although there are no EU requirements for child-resistant closures for medicines, there are directives (91/442 and 90/35) which require containers for products that are toxic or corrosive to be made child-resistant. For pharmaceutical products individual countries have introduced requirements; for example, the Pharmaceutical Society of Great Britain requires in its code of practice that all solid and liquid preparations be dispensed in reclosable child-resistant containers, unless:

1 the medicine is in an original pack such as to make this inadvisable
2 a specific request is made that it not be so dispensed
3 no suitable child-resistant container exists for a particular liquid preparation.

Tamper-evidence

Tamper-evident and tamper-resistant packs were few and far between until the Tylenol incident in the USA, when such packaging became the rule for OTC products almost overnight. WHO, in its guideline on the assessment of medicinal products for use in self-medication, recommends that such packages are highly desirable.

Child-resistant, tamper-evident and tamper-resistant closures are dealt with in detail in Chapter 11, and therefore will not be dealt with further here.

Summary

In this chapter, I have tried to cover the registration requirements for packaging, along with other regulatory constraints imposed on the pack. There is no doubt that the

regulatory climate is getting more restrictive for pharmaceutical products and it is likely that packaging for pharmaceuticals will have more and more constraints placed upon it

In terms of the regulatory attitude, it must be remembered that the product licence is a legal document and that regulators are bureaucrats. Regulatory agencies were set up generally following disasters and as such they are very cautious and open to both political and public pressure. In approaching data requirements, therefore, it is necessary to look at the guidelines, but also to try to think not only as a packaging technologist but also as a regulator. Data needs are increasing and the regulators, although not yet packaging experts, are increasing their expertise, so increasing demands for the volume of information.

The data needs on packaging required in a product licence are becoming more clearly defined and more consistent worldwide with such initiatives as ICH. However, as the needs become clearer, they become more restrictive. Industry, thus, has the choice between having some open general guidelines which do not provide a great deal of help, but are not over-restrictive as we find for the EU, and much more detailed guidlines similar to those of the FDA which are clearer and more helpful, but become more restrictive.

5

PAPER- AND BOARD-BASED PACKAGING MATERIALS AND THEIR USE IN PACK SECURITY SYSTEMS

I. H. Hall

Introduction and history

In this chapter, packaging materials based on 'cellulose' or natural fibres will be discussed. They provide a major contribution to the packaging of pharmaceuticals, the size and nature of which can readily be overlooked since the number of applications is far more diverse and more paper and board is used than glass, metal or plastics.

The history of paper-making in particular is long, and the earliest recorded British mention is in the thirteenth century. It has always used forms of cellulose fibre, but began to use wood pulp in the mid-nineteenth century, which has continued gradually to replace the older materials, so that 98%+ of the papers and boards made today are from the wood pulp route.

Boards (in the case of pharmaceuticals, lined folding box boards) were introduced in the mid-nineteenth century, as hand-made constructions to help protect and transport products. Only at the end of the nineteenth century were machines invented to produce what we would now know as cartons.

Corrugated boards are a fairly recent introduction, starting in the early 1870s and becoming widely commercially available in the late 1890s. From then on there has been a continuous development, both where corrugated board is used and in the technical production processes of developing better, stronger and more hazard-resistant boards.

Papers and boards are used in the following pharmaceutical packaging applications (the list may not be comprehensive):

- labels and leaflets
- wrapping materials
- bags and sacks
- collapsible and rigid cartons and boxes
- shipping and transit outers, both corrugated and solid
- gummed tape
- fitments for cases
- composite tubes and drums
- moulded pulpboard containers
- paper liners, linings and laminations.

Being based on 'natural' fibres, i.e. cellulose, potentially from a wide range of sources, paper and board are seen as renewable resources as distinct from petroleum- and metal-based resources. However, in some circumstances the energy required for conversion of the natural fibres into packaging materials may be more than that required for non-renewable sources in a competitive form. This is part of the debate on environmental/ecological factors which is exercising the minds of the packaging profession, and will be discussed as we go through the chapter in relation to the use of recycled material in paper and board.

There is a major problem with 'natural' products. They are not as consistent as synthetic products, therefore anything made from a natural material cannot be guaranteed to be exactly the same all the time, i.e. they usually need wider tolerances than, for example, glass, metal or plastics. Its easy to see why. Living organisms grow with a large number of factors influencing that growth: availability of nutrients, light conditions, damage to seedlings by animals, local environment, difference in age of each tree, etc.

Sources of cellulose fibre

Although trees are the major source of wood pulp, other cellulosic fibres such as cotton, flax, bamboo, esparto, jute, hemp, straws, bagass (from sugar cane), grass, rags and sisal have been used in the manufacture of papers and some of them for boards. The quality of the fibre varies according to the source, with certain hardwoods being excluded on the grounds of cost or undesirable constituents. Softwoods such as spruce, fir, pine and eucalyptus are usually commercially preferred, as they are grown in colder climates where they are arguably the best use for the land. In the past 20 to 30 years the 'farming' of softwood forests has developed into an environmentally friendly industry, under the term 'silviculture'.

The basis of all paper and board is 'pulp', which is in fact refined cellulose $(C_6H_{10}O_5)_n$, where n is between 800 and 1500. The crude extracted cellulose is made up of three parts, as follows.

1 Holocellulose – this is 70–80% of the wood. It is the whole water-insoluble carbohydrate fraction comprising:

   - alpha-cellulose, which is insoluble in strong caustic soda
   - hemi-cellulose, which is soluble in dilute caustic soda
   - beta-cellulose, which is reprecipitated by dilute acid
   - gamma-cellulose, which is the remainder of the cellulose fraction.

   There is in fact no single compound holocellulose, since the structures and crystallinity of the cellulose fibres vary with the source of the wood. This is part of the reason for the variation in properties of pulps.

2 Lignin – this varies between 17% and 30% of the bulk and is an amorphous phenylpropane polymer which is found intimately associated with the holocellulose. It is not a fibrous material and therefore is of no value in the pulping process.

3 Extractives, which form between 3% and 8% of the bulk, are mainly other carbohydrates, soluble mineral salts, resins, fats and tannins which may be washed out with water.

The individual fibres of cellulose are very strong and of varying lengths, e.g. esparto grass 1.5 mm, coniferous wood 3.5 mm and broadleaf wood 1.2 mm, and those that are preferentially used for paper and board are between about 1 and 4 mm in length.

The manufacturing process

To manufacture paper or board there are two basic processes: pulping, then machine conversion into paper or board.

Pulping

The treatment of the fibres (pulp) is the major influence on the properties and costs of the paper or board produced. The objective in pulping is to 'tease' out undamaged fibres from the mass of the wood, so that these fibres can be reworked into the smooth paper/board required.

There are three major processes which reduce raw material, i.e. any of the cellulose-containing materials mentioned above, to 'pulp':

1 mechanical pulping
2 chemical pulping
3 semi-chemical or combination pulping.

For practical purposes only wood pulp will be considered. The wood pulp is supplied from the two most popular sources which are the managed softwood forests, mentioned above, and 'recycled' fibres, which will be covered later.

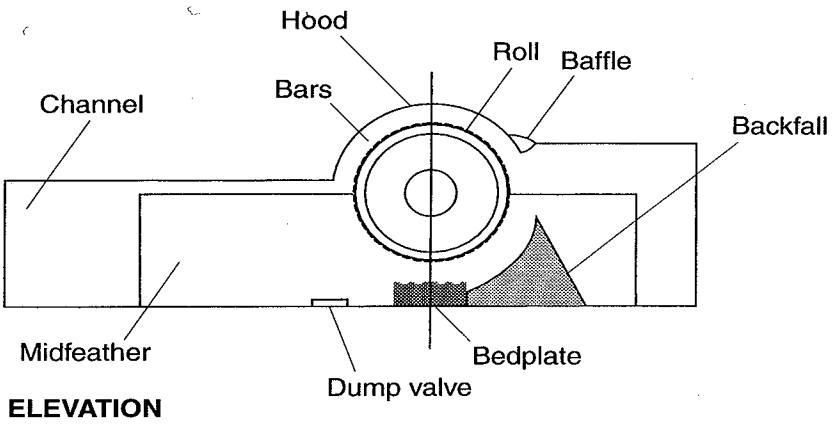
Most label papers are chemical pulp, with additives, only. Most box boards are layers of mechanical or semi-chemical pulps with chemical pulps on the face and sometimes the back facings. Corrugated will probably, today, be nearly all recycled material, whereas unbleached semi-chem would have been used in the past for the corrugated medium. Any Kraft facing paper will probably still be 80–90% virgin Kraft pulp in make-up.

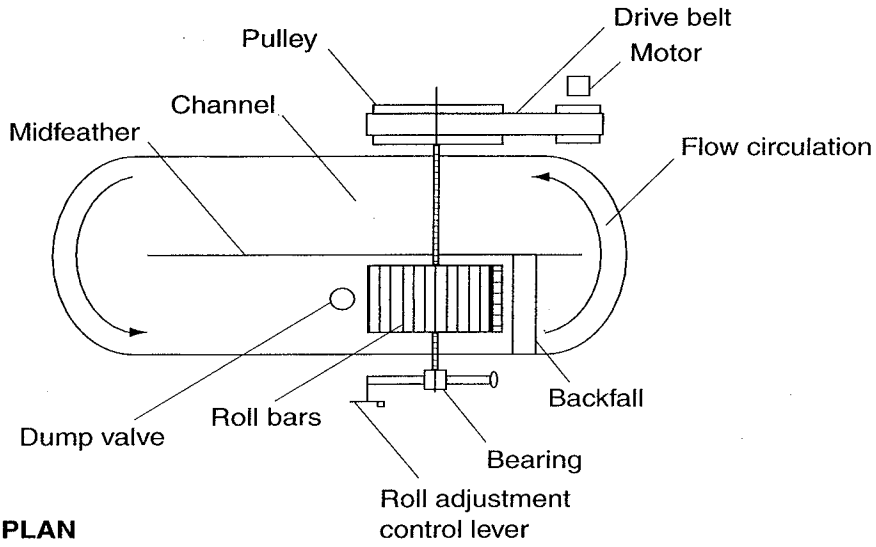
Bleaching

If this is required it is achieved by using either hydrogen peroxide or chlorine (or a hypochlorite) dissolved in water to remove the coloured residues that are in the cellulose fibres. It is usual to bleach only the chemical pulp made from the sulphite or soda processes, as these are grades probably used for white paper and the white plies of board.

Beating and refining

Beating is the batch process where the pulp suspension is recycled through a specially designed vessel which shortens the fibres and softens (plasticises) them (Figure 5.1). Refining is a continuous process whereby the pulp suspension is pumped between a static outer housing and a tapering rotor (Figure 5.2). Figure 5.3 shows the properties of paper/board influenced by beating.





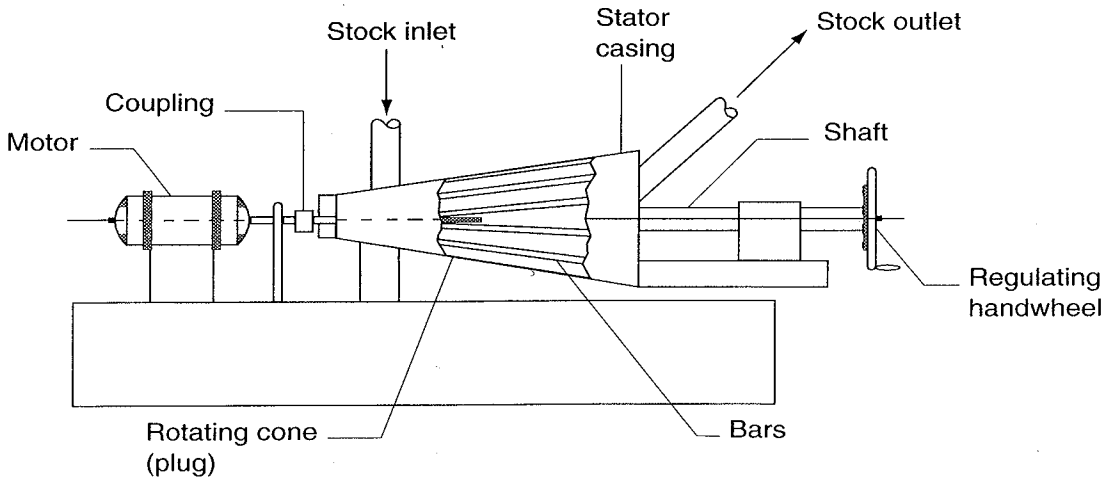


Figure 5.1 Beating

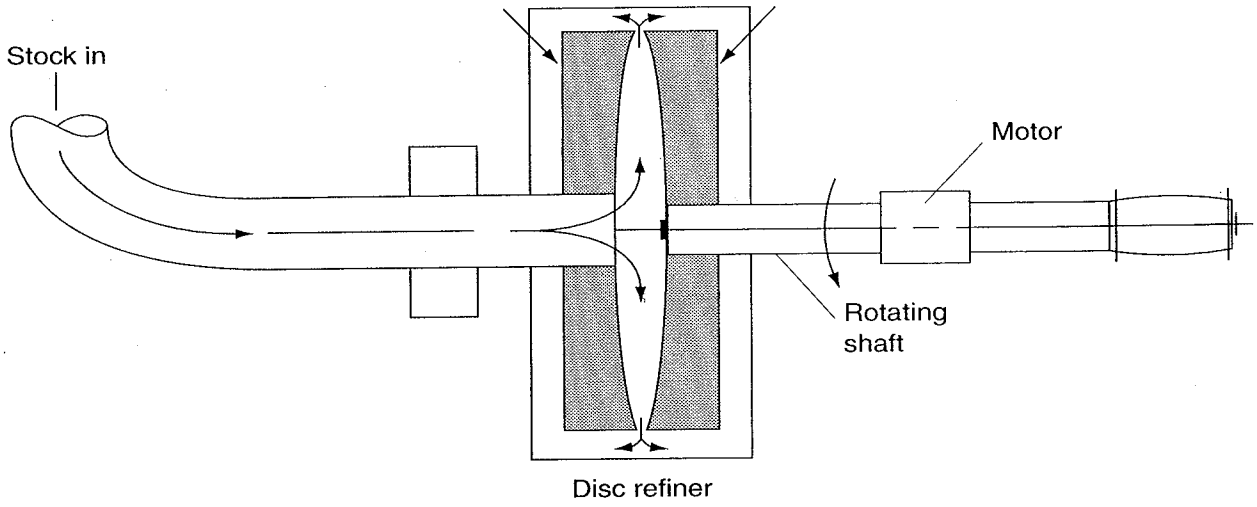


Figure 5.2 Refining

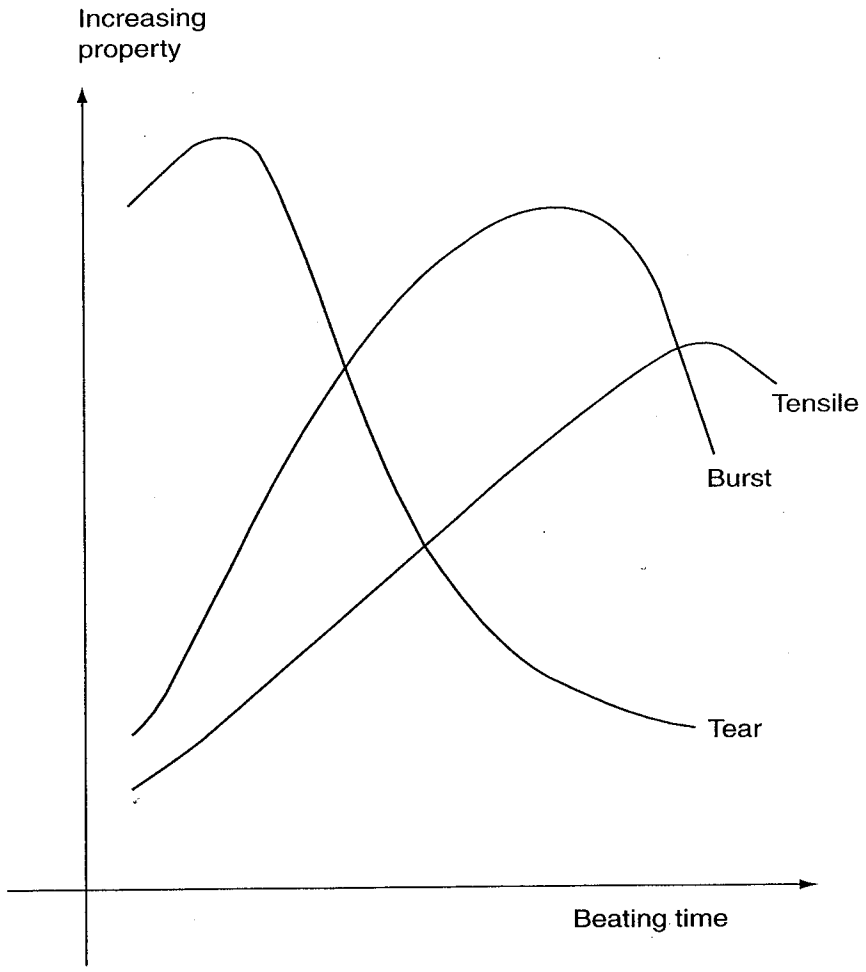


Figure 5.3 Effect of beating on strength

Mixer stage

Here the pulps are stirred vigorously in a hydropulper with copious amounts of water and the additives are added to make the final mixture.

Additives

These are added to the beaten or refined pulp to produce the final form of the paper. Typical additives are loadings and fillers (to improve opacity/brightness), colouring materials, sizing agents which reduce the penetration of water and inks, binding agents to increase strength, gums, antifoam agents, wet strength resins and optical brightening agents (OBAs). It is at this stage that the pH of the paper can be adjusted to make it 'acid free'.

Machine conversion into paper

Fourdrinier system

This is the most popular system still used today, even though the basic system was invented in the early nineteenth century (Figure 5.4). The machine starts at the 'wet end' (1–4) and finishes at the 'dry end' (5–9), thus:

1 a stuff chest
2 a breast box or head box
3 a slice
4 Fourdrinier wire with vacuum boxes
5 presses
6 driers
7 machine glaze drier
8 calender stacks
9 reeling.

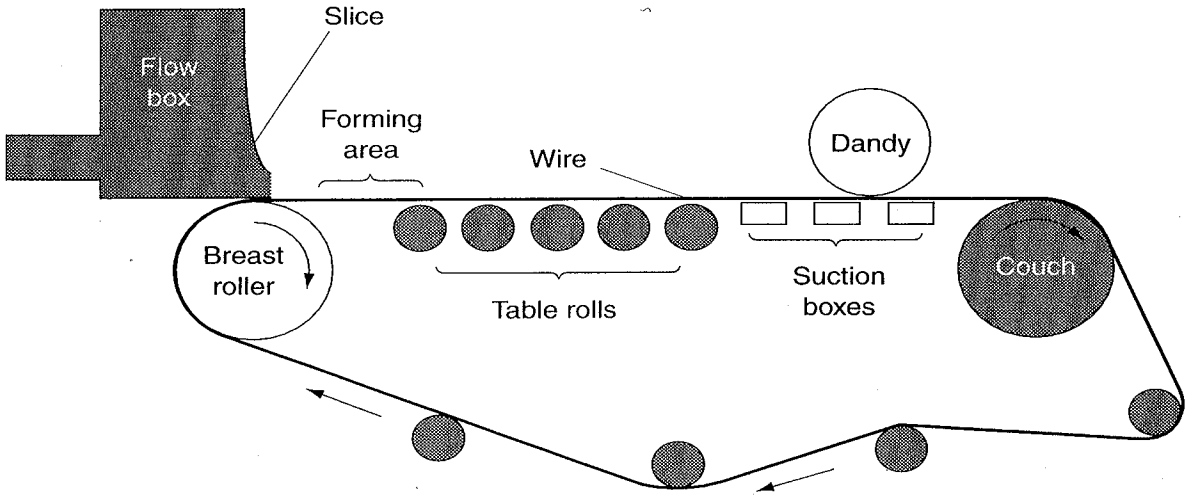


Figure 5.4 A Fourdrinier system

Pulp, including all the additives needed for a particular paper, in suspension is pumped into the stuff chest then let down into the 'head box' which sits over a continuously fast moving fine 'wire' (nowadays usually nylon) mesh, i.e. the Fourdrinier wire.

The suspension (99% water) is fed onto the wire mesh through the variable 'slice' in the bottom of the head box. (The aperture of the slice and the speed of the wire mesh control some of the physical properties of the paper, i.e. caliper.) The water from the suspension drains away and then is pulled through the wire by a vacuum, leaving a mass of solids on the wire. The movement of the wire induces the fibres to align themselves preferentially in the machine direction (MD), producing the 'grain' of machine-made papers, although a cross-directional oscillation is built into the machine to try to minimise the orientation of the fibres.

Towards the end of the wire the water content is below 85%. The material leaving the 'wire' is called the 'felt'. This 'felt' is pressed through speed-synchronised cold rollers (the presses) to reduce the water content to 65–70%. This is followed by the drying section, which is a series of steam-heated cylinders over which the felt winds its way with alternate sides being dried.

Sizing or coating is carried out about two-thirds of the way through the drying section. A machine-glazed (MG) finish is applied towards the end of the drying section, by a very large diameter steam-heated highly polished roller.

The paper is then taken up the calender stacks which are stacks of rollers that press onto the alternate sides of the paper. Only the bottom roller of the calender stack is driven; all the other rollers burnish the paper by slippage.

The paper has by now been dried down to 3–4% water content. It is then conditioned to 7–10% water so that the paper is no longer brittle, prior to reeling. The reels are stored on end on skillets under covered conditions, until needed for reel slitting and/or sheeting.

Papers in use in the pharmaceutical industry vary from about 40 g/m^2 substance up to about 175 g/m^2.

Finishing processes

These consist of additional treatments which are carried out on the material after the paper-making process. Surface sizing may, for example, be performed by applying a solution of gelatin, together with other chemicals, to the paper. This improves water resistance and printing properties, and is called 'tub-sizing'. Coating suspensions, e.g. containing china clay, may also be applied to the surface by spraying, air knife or rotating brush methods.

Other surface treatments

These processes include coatings (Figure 5.5), impregnations and laminations which are mainly aimed at reducing moisture, gas, permeation, etc. or for creating a heat-sealing capability. Typical examples include both dry and wet waxing processes.

Paper may also be solvent or aqueous coated, e.g. PVdC, emulsions, varnishes, lacquers, or laminated to plastics by adhesion or direct extrusion or to foils by adhesion, all to form laminates. These laminates containing paper are dealt with in Chapter 9.

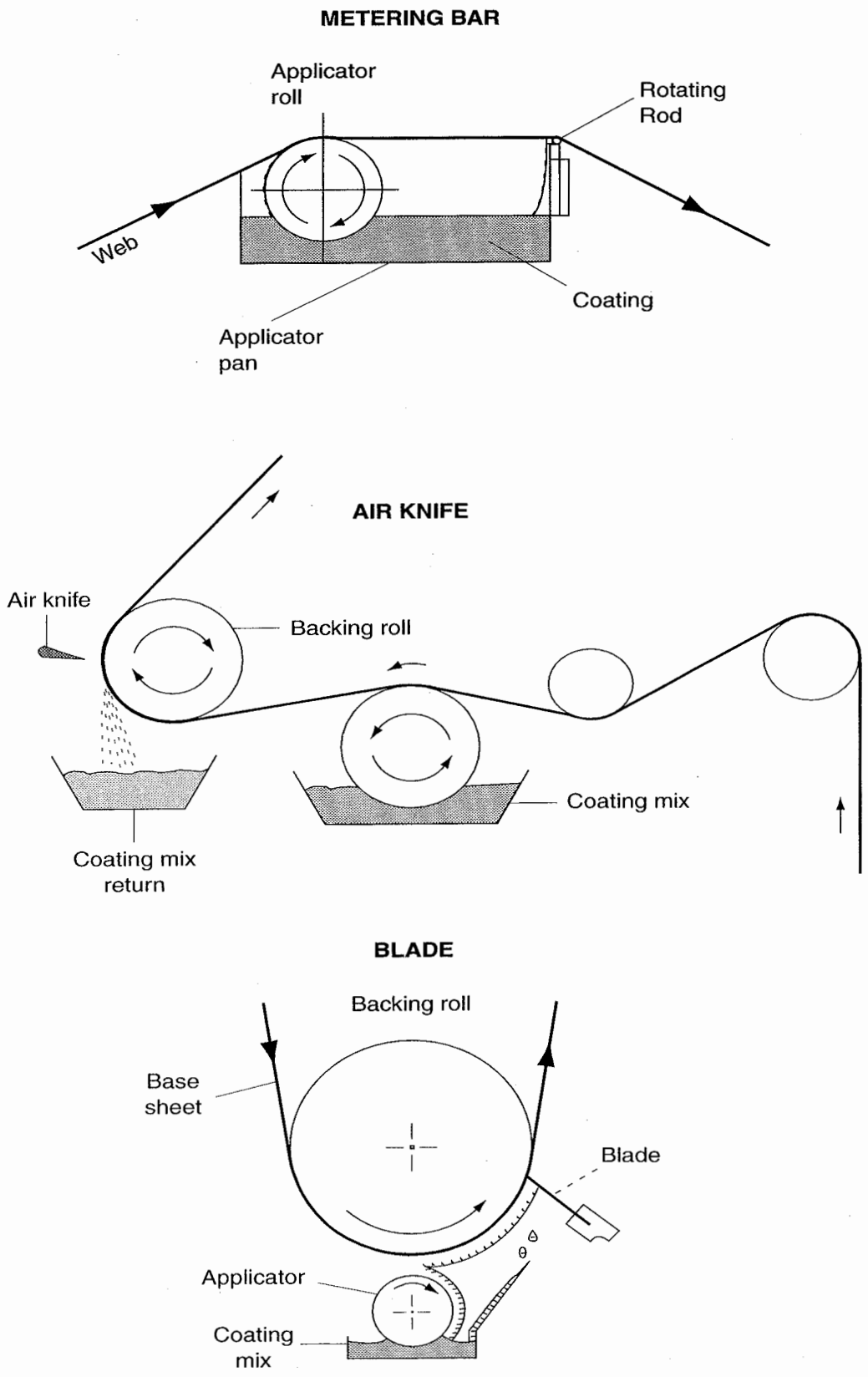


Figure 5.5 Coating methods

All surface treatments are used either to enhance the 'printability' of the paper or to modify and 'improve' the characteristics of the paper.

The more common types of paper used in pharmaceutical packaging are as follows.

1 'Kraft' paper used as an outer facing for corrugated board, solid board, spirally wound kegs and fibreboard drums.
2 Uncoated paper, usually from high-grade chemical pulp source, used in thin calipers for small labels and leaflets. One-side coated and MG papers are used for the heavier weighted labelling material. Two-side coated lightweight papers are used for leaflets. Glassine paper is super-calendered greaseproof paper. Greaseproof paper relies on the closing-up of the pores between the fibres achieved by beating the fibres for a very long time.
3 White wood-free paper for laminates is usually one-side coated paper that has been super-calendered to make the outside (coated) surface less permeable.
4 So-called test liners in two grades are made entirely from recycled material. Used for internal liners in corrugated board production and as both liners for corrugated fitments.
5 Vegetable parchment paper is made by a process of treating the absorbent paper with sulphuric acid, which enhances the wet strength of the paper. This is the most water-resistant paper of all. It is usually used for 'dressing' packs. It has good resistance to fats and greases.

Machine conversion into board

In many ways this is very similar to the making of paper, except that the multi-ply production systems are more suitable than the basic single wire Fourdrinier system. Board covers rigid and folding boxboards, solid and corrugated fibreboard, fibre drums and components of composite containers.

One of the different types of machine used at present for making board is the vat or cylinder machine. The machine starts at the 'wet end' (1–4) and finishes at the 'dry end' (5–9) just like the Fourdrinier machine:

1 pulp preparation
2 make-up tanks with different pulps
3 vats with a constant level of pulp
4 vacuum applied cylinders in vats
5 presses
6 dryers
7 machine glaze drier
8 calender stacks
9 reeling

Figure 5.6 shows a vat system.

Twin wire machines are Fourdrinier-type processes which are drained between the two forming fabrics or wires in a horizontal plane. There are also multiwire Fourdrinier types of machine in operation today. Figure 5.7 shows a twin wire system.

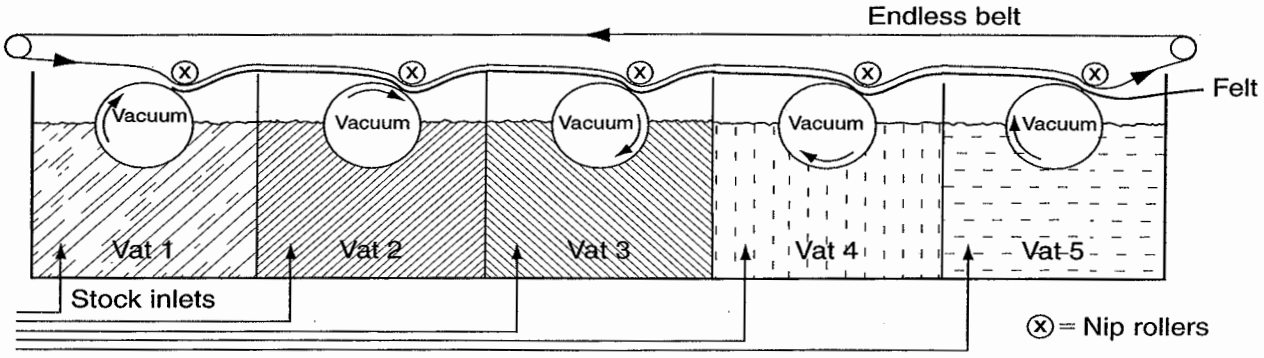


Figure 5.6 A vat system

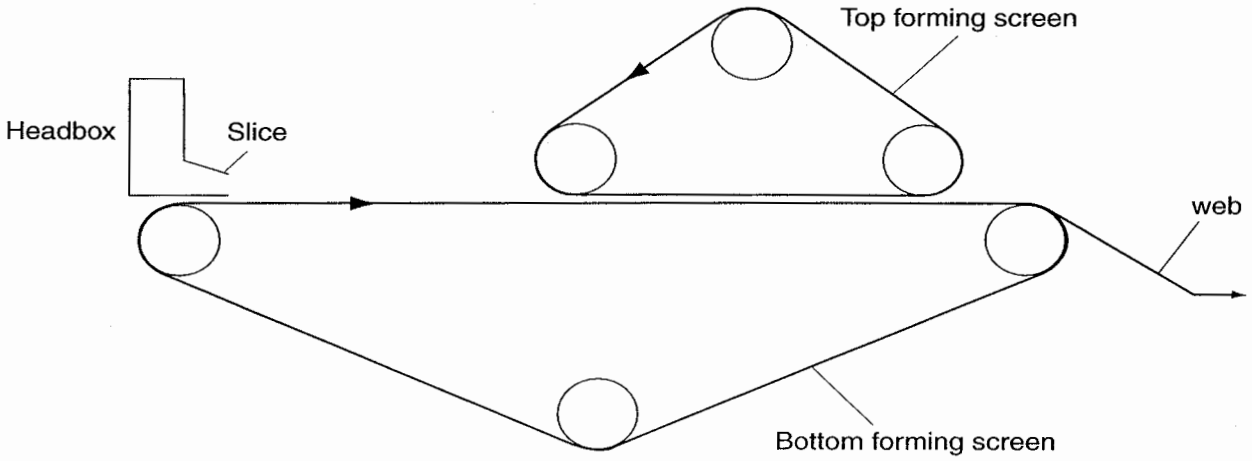


Figure 5.7 A twin wire system

Vertiform machines are twin wire machines arranged vertically. Figure 5.8 shows a vertiform system.

The inverform process is that in which the slurry is forced between two wires. Figure 5.9 shows an inverform system.

Common types of board in use

Millboard

This can be made on a single cylinder or vat machine, where a moist web of thick paper is built up in plies and then milled between heavy rollers.

Chipboards

These use post-industrial waste (PIW) and some post-consumer waste (PCW) in their middle plies. They can be faced with better quality facing materials and may or may not have a quality backing used for low-grade small boxes and cartons.

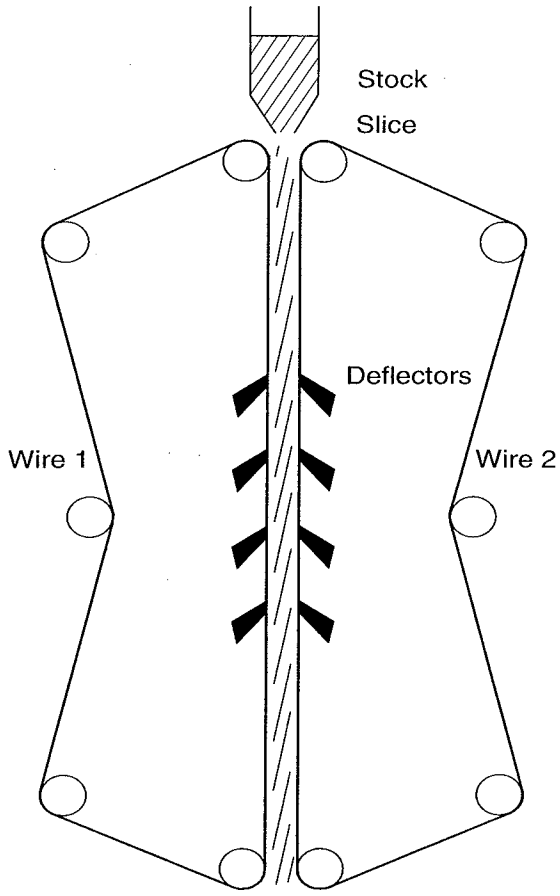


Figure 5.8 A vertiform system

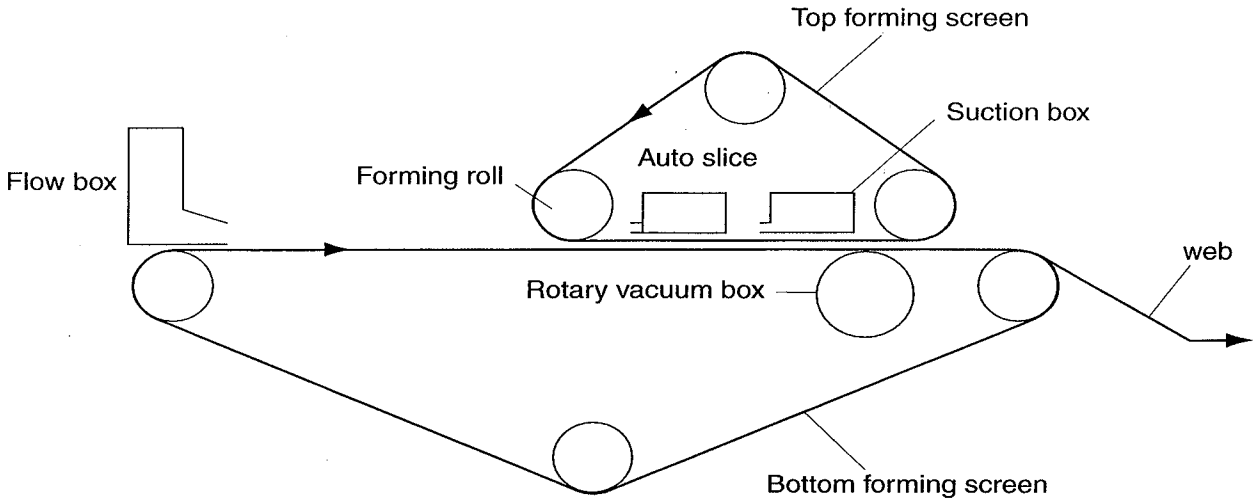


Figure 5.9 An inverform system

Box boards and coated box boards

VIRGIN PULP USED

Figure 5.10 shows a white lined folding boxboard in section. High-grade mechanical pulp is usually used for the centre plies of the board, with high-grade bleached sulphite pulp in front and behind the core plies. On the face 'printing' side of the sulphite pulp there is a base coating and finally a clay/size coating (up to 20–25 g/m^2).

'RECYCLED' BOARD

Figure 5.11 shows a typical high-quality recycled board structure. Typical 400 μm grade plies from printside inwards consist of: 28 g/m^2 clay coating; topliner 47 g/m^2 bleached virgin sulphite pulp; under-liner 69 g/m^2 unprinted recycled newspaper pulp; main body up to six plies of general recycled pulp adding up to 134 g/m^2 of mostly PIW waste; back-liner 22 g/m^2 bleached virgin sulphite pulp. This means that the average percentage of recycled fibre is about 75% by fibre weight and 68% of total board weight, including coatings. Most recycling mills will claim to be to be well inside *any* current or proposed limits on any part of effluent control.

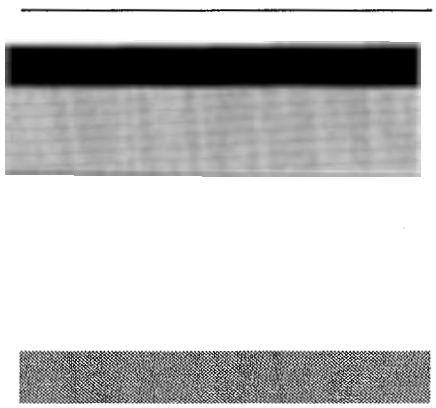


Figure 5.10 A white lined folding boxboard in section

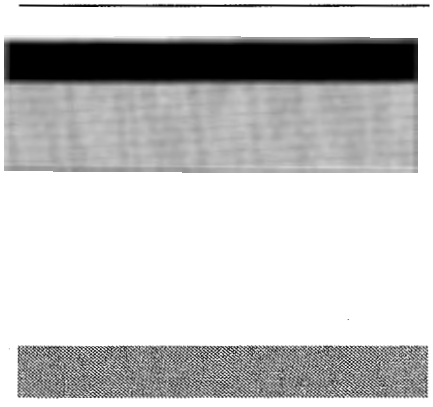


Figure 5.11 A typical high-quality recycled board structure

It is also claimed that the bacterial count in the finished recycled board (which is obviously variable) compares with virgin board. For polybichlorinated phenols (PBCs) the claim is <l ppm against a limit of 2 ppm specified for the contact of greasy foodstuffs. See Table 5.1 for contamination levels.

Strawboards (lined or unlined)

Used for some rigid boxes, e.g. solid board enema boxes where the slight odour and high chlorine content are of little importance. Fibre is provided by straw and is made on a conventional board machine. Lining is achieved by pasting paper, of the desired type, to one or both sides on a continuous process machine. It is quite rigid, but has limited use in pharmaceuticals because of the slight odour.

Paper and board merchandising

Usually the larger paper and board mills do not sell their final 'jumbo' reels direct to printers or converters. They sell them to merchants who store the reels of the many specifications of paper and board available (in controlled conditions) and market the papers and boards to the printers and converters. These jumbo reels can vary from 1 to 4 m wide and be up to 2 km long.

All paper merchants market the papers and boards to users; many convert the paper or board into a form in which it can be used directly. The latter type of merchant has substantial quantities of machinery to slit the jumbo reels down for reel-fed printing equipment or slit, sheet and pack for sheet-fed equipment. The slit reels are usually delivered on end to the printer, but the sheets could be anything from packed on special skillets to wrapped in Kraft paper parcels.

Labels and labelling

The following discussion covers the requirements for labelling with paper onto various types of packaging material used in this industry. Specific reference is made to the four main types of paper labels, i.e. plain with adhesive added, pregummed, heat sensitive and pressure sensitive.

Printing can be basically divided between information which is 'fixed' and information which is 'variable'. Variable information is usually that which is added either immediately prior to the production line process or as part of the production line process (see below).

Table 5.1 Contamination data (mean values) based on samples taken and tested by the University of Graz (Austria) in 1992

Heavy metal	*Virgin fibre (ppm)*	*Recycled (ppm)*
Cadmium	0.3	0.2
Arsenic	5.45	4.2
Lead	7.6	10.6
Mercury	0.15	0.14
Chromium	0.8	4.1

Label systems are also found in combination with leaflets, of which the Denny Bros FIX-A-FORM system is an example (PEEL 'N' RESEAL from Harlands, INSEAL from Instance, MULTIPEEL and DOUBLE-DRI are others).

A dictionary definition of a label is 'a slip of paper, cardboard, metal, etc. for attaching to an object and bearing its name, destination, description, etc.'. A label may therefore be made of any material and may be attached to its parent item or pack by any means, e.g. tying, stapling, nailing, adhesion. Decoration or wording may be achieved by any printing process (depending on the material), i.e. embossing, debossing, letterpress, flexographic, offset litho, gravure, screen, dry offset, etc.

Labels are, if anything, increasing in importance as carriers of more and more information about the product, e.g.:

- product identity
- corporate image and sales appeal
- pack contents and ingredients (in ever more detail)
- legal and moral warnings
- bar codes (of both the retail and security variety)
- security (increasingly a problem in manufacture, retail, distribution and transportation)
- identity and address of manufacturer (and marketing company)
- instructions/warnings for use
- information on handling, disposal, destination, hazardous goods, etc.
- promotional information.

This list is not exclusive, but is a guide to the pieces of information which one part or another of the packaging chain could be required to affix to a product, not forgetting the warehousing and transportation systems. The amount of information is more likely to increase than to decrease, due to consumer demand for more and more relevant information on what they buy:

- more awareness of health and safety issues
- better inventory control needed, therefore more bar coding to carry more easily automatically retrievable information
- more environmental pressure
- more legislation by the UK and the EU
- more security, either as devices or preventive.

Will it be necessary to design packs where the information will dominate the design parameters? This is already a reality in some limited areas of packaging, e.g. leaflets on small parenteral antibiotic packs! More importance is now placed on eye appeal with the creation of consumer preference for the product, particularly in the case of OTC medicines. However, less ornate and more functional forms of labelling must not be ignored, i.e. identifying features for parcels, cases, crates, etc. and as seals to show when a product has been tampered with.

Labels may be used in addition to the main pack decoration (special offers, price tags, etc.) and, as in the case of certain materials, for instance glass, are the most

economical means of applying printed detail. (Ceramic printing has limited applications to reusable glass containers.)

As this chapter is concerned only with paper label material, the foils, foil laminates and plastics are not considered.

Label fundamentals

When working with labels and the designs thereof, the prime responsibility of the packaging specialist is to look after the technical side, i.e. paper, adhesive, carriers, etc. However, in order to perform that function correctly the fundamentals of decoration need to be understood. (This chapter does not deal specifically with the printing processes: see Chapter 16.)

1 A good design – prominent brand image.
2 Well printed, full use of colour: note that a single printing on a coloured surface gives a two coloured label at the cost of one printing. The method of printing is important as the best overall effect is what matters, allied with the best price. For example, do not use gravure printing on short run labels for outer cases.
3 Best paper for the purpose, i.e. white, tinted, coloured, coated, substance (most label papers between 60 and 110 g/m^2), etc.
4 Features that may be critical for machine application:

- direction of grain
- dimensional tolerances – frequently dependent on the method of paper cutting (punching or guillotining)
- paper substance/caliper
- absorbency (Cobb test) – water absorbency
- porosity – vacuum pick-up is used on many labelling machines
- method of storage and handling, i.e. top and bottom card stiffeners, wrap around banded (not rubber bands), restrict number per bundle (say 500s) for block cut labels
- shape – artistic value, radiused or square corners
- size of area (and tolerances) to which label is being applied.

5 Surface finish (also critical to (4) above):

- varnished (roller coated, plate varnished – varnish type (water varnish, spirit varnish), coating weight)
- high melt varnish – critical for heat sealing areas or export markets
- nitrocellulose or PVdC coating systems
- laminated to other materials – PVC, PP, cellulose acetate, etc.

Note that any external coating (varnishes etc., solid print, bands of print) can have a direct effect on the 'curl' of the paper, which is liable to occur when the paper is wetted or dried. This is because inks and varnishes 'stiffen' the paper in both the machine direction and the cross direction. Coatings may vary from matt to high gloss.

6 Print requirements:

- colour standards – target plus light/dark tolerances (e.g. Pantone)
- rub resistance, fade resistance, odour level (see Chapter 16)

- product resistance
- ink thickness.

7 Suitable adhesive (mechanical or specific) – dependent on the surface to which the label is being applied. Note the importance of tack, setting time, polarity (polar or non-polar) of materials.
8 Cut or roll form (i.e. singles or rolls).

The fact that paper has fibres oriented mainly in one direction, i.e. 'grain' or 'machine direction' and 'cross direction', plus the fact that it consists of hygroscopic vegetable fibres, frequently has a strong influence on the labelling process. The application of an aqueous based adhesive to a paper label causes a swelling of the fibres. This change in dimension is greater in the cross-grain direction, hence the paper curls around or parallel to the machine direction. This 'curl' is away from the wetted area and may be accentuated if the outer surface is covered by a less moisture sensitive covering: varnish, printing ink, etc. Any labelling process which involves the application of water must recognise 'curl' as a distinct problem which can be reduced to a minimum by consideration of a number of factors, i.e. label shape, size, grain direction, adhesive (solid to water content, tack), method of application, speed of application, etc.

Label 'curl' also occurs when paper is heated and moisture is 'lost'. In addition to the relationship grain direction has with moisture (this applies to both loss and gain), two other factors associated with it are as follows.

1 Tear strength – this is lower along the grain; note difference on edge appearance when paper is torn in both directions (at right angles to each other). Tear along the cross-grain direction shows a more fibrous (feathered) edge.
2 Rigidity or stiffness – paper bends more easily in the cross direction. Another test for grain: cut two strips of paper 0.5 inches × 6 inches at right angles from the same sheet. The length which shows the greatest bend has grain parallel to the 0.5 inch measurement.

Grain can also be detected by a Mullen burst test (and tensile strength) – see 'Paper and board testing' below.

Types of paper labels

As indicated above there are basically four types of paper labels, as follows.

1 Plain paper – applied after the addition of an adhesive.
2 Pregummed paper – where the label is applied after wetting with water. The paper is pre-coated with dextrine or gum arabic using single to treble coatings.
3 Heat sensitive labels – applied after the activation of a thermoplastic coating by the use of heat. Two types of thermoplastic resin exist:

- instant type – activation is a factor of heat, pressure, time; sets immediately the source of heat is removed
- delayed action type – activation by heat, pressure, time but once activated, adhesive remains tacky.

4 Pressure sensitive or self-adhesive – applied by the application of pressure. Paper is pre-coated with a permanently tacky adhesive which is attached to a separate backing paper (which has an easy release coating on it).

In addition to the above, there are shrink-and-stretch plastic sleeving and pressure sensitive plastic labels. These two are not dealt with here, but they are making considerable headway in pharmaceutical labelling at the present time.

The above labelling methods are listed in ascending order of cost; using for example a label printed in two colours, size 90 × 63 mm, prices quoted in Table 5.2 are per 1,000 labels delivered, based on orders of 100,000 and 10,000 using 1991 prices.

Plain paper labels plus suitable adhesive

The thin film of adhesive applied costs only a few pence per 1,000 labels, plus labour costs. Plain paper is most widely used for glass, but can be applied to metal, particularly in the form of a complete wrap around label. Application can be by hand, semi-automatic or fully automatic methods. Speeds of 1,000 or more per minute can be achieved. Pharmaceutical labelling usually ranges from 10 to 300 per minute.

Hand application

This routine is not covered in detail here, but application speeds can reach as high as 400–600 units per operator hour.

Semi-automatic labelling

In this operation the machine selects, glues and applies the label but the item to which it is applied is placed into position by hand. Labels may be picked up by vacuum or the adhesive. Higher tack is necessary than that used for hand labelling. Speeds range from 25 to 60 per minute, i.e. 3,600 per hour maximum.

Fully automatic labelling

The item is positioned and labelled automatically. This requires even more critical limits in terms of setting-up, material and adhesive tolerances. Change over time or adjustments also take longer. Speeds can range from 3,500 to 60,000 per hour.

Table 5.2 Costs of labelling methods (1991 prices)

Type of label	*Order-size*		*Approximate ratio (plain paper = 1)*
	100,000	*10,000*	
Plain paper	£6.00	£13.00	1
Pregummed paper	£8.00	£18.50	1.3
Thermoplastic coated	£9.00	£20.00	1.5
Self-adhesive	£12.50	£26.00	2.0

Adhesives

The type of adhesive used depends on the surface of the item to be labelled. The adhesive must provide an adequate bond between the label and container. Labelling of paper-based materials (unless specially treated) and glass usually presents little difficulty. Tinplate, although slightly more difficult, can involve problems of corrosion unless special corrosion inhibitors are incorporated into the adhesive. Labelling to plastic surfaces requires the use of specialised adhesives which may be based on latex or synthetic resins, e.g. polyvinyl acetate (PVA). In certain instances pre-treatment of the plastic (in common with printing) with flaming or corona discharge can aid adhesion.

Dextrine is the most widely used adhesive involving different levels of solid content. For instance, a low solid content is used for hand labelling since low tack (after initial placement it may be slid into position) and a long setting time are necessary. On mechanical labelling, particularly where the label is picked up by the adhesive, a high tack plus quick set is important. In addition, the adhesive must be non-threading and non-foaming. The addition of borax increases tack and setting speeds.

Problems of curl

Although this has already been mentioned, it is always a factor to consider when any label is applied by a wetting adhesive. Both printing inks and coatings tend to reduce the moisture absorbency of a paper and thereby increase any curl (which is always parallel to the grain direction). If the amount of water used in an adhesive can be kept to a minimum, curl will be reduced. Using a thin film of adhesive is also effective. When labelling a round container there is a choice between a complete wrap around (probably leaving a varnish-free area on the under lap) and using, say, three-quarter wrap with a gap. It should be recorded that many containers (particularly injection moulded plastic) have a natural taper which may cause problems of alignment.

It is normal to have the grain direction parallel to the base of the label, but there are occasions where this does not apply, i.e. some labels on circular containers.

Pregummed labels

Paper is pre-coated with dextrine or gum arabic. As only water is required to activate the adhesive, the labels are clean to apply and a complete labelling operation can be carried out by one operator. They are ideally suited to small runs or intermittent production, such as parcel labels. They provide good adhesion to paper, board, glass, but as the range of adhesive types is very limited, they lack flexibility in terms of adhering to a wide range of surfaces.

Pregummed labels are difficult to apply if large, due to problems of creasing. They also have a high tack and therefore cannot be adjusted readily once on the item to which they are being applied.

Heat sensitive or thermoplastic adhesive-based labels activated by heat

As indicated above, two types are in use: instant tack and delayed tack. Both are based on synthetic resins; the former has to have heat and pressure applied to affect the transfer but sets immediately the source heat is removed. The latter is usually

activated to tacky state after which it can be affixed to any item without a heat source. However, most frequently the heating operation plus pressure of application are applied simultaneously. The tacky state remains for some time after the source of heat is removed.

As heat sensitive labels do not rely on conventional gums or water as a wetting agent they will adhere to a wider range of materials including metals, plastics, and varnished, coated and printed surfaces. However there is one criterion that is very important in storage of thermoplastic materials either as flat sheet prior to printing or as labels after printing. All heated areas (pipes, radiators, overhead heaters) must be avoided; also high stacking pressures, both of which can cause partial activation and/or blocking. Care also has to be taken in the selection of printing inks and varnishes, as certain volatile constituents of these decorative materials will also cause activation and blocking.

As the delayed action resin takes up a permanent set very slowly, the grain direction (shrinkage after heating) will cause curl to occur. In certain circumstances this can be greater than the adhesive forces so the label may lift, particularly if the radius to which it is applied is tight. For this reason labels should be produced with the grain parallel to the axis of curvature of the container to which they are applied.

During activation, temperatures above 100°C are used, causing drying-out of the paper and shrinkage. Labels return to normal after exposure to the atmosphere, but on larger sizes (say 100 cm^2) there is a tendency towards creasing and blistering. Activation by steam can partially overcome these problems provided the outer (printed) surface is not waterproof.

Instant tack labels

There are a few well-known makes on the British market. They may be applied by hand (hot plate), semi-automatically or automatically. Machinery is similar in price to conventional gluing/labelling machines but those with more sophisticated heating systems can be more expensive. The machines involve far less cleaning time and generally get less 'gummed up'.

Instant tack labels find special usage on seals, pleated overwraps, various header labels (cellulose films must be heat sealable variety). They are not used for bottle or can labelling.

Delayed action labels

These are more versatile than the instant tack type, particularly in their application to bottles, tinplate, plastics, coated or laminated surfaces. Speeds of around 600 per minute can be achieved.

Both instant tack and delayed action labels are more costly than the conventional paper – adhesive labelling. Selected advantages may offset the cost increase, i.e.:

1 virtually no cleaning down, no wastage of adhesive
2 shorter setting-up time
3 adhesion to a wider range of surfaces
4 less affected by powder contamination or varying ambient atmospheric conditions (humidity and temperature)
5 provide a high standard of cleanliness – no labour for wiping down.

Thermoplastic adhesive labels generally find a special usage and are now meeting increasing competition from self-adhesive or pressure sensitive labels.

Pressure sensitive labels (created by RS Avery 1935)

It is preferable to call these pressure sensitive labels, rather than self-adhesive, as both the pre-gummed and heat sensitive labels can be thought of as self-adhesive.

They consist of a suitable label paper coated on the reverse side with a permanently tacky adhesive which is in contact with a backing paper that protects it prior to use. The backing paper is coated with a special release coating which permits the label to be removed easily. Labels may be provided in reel or sheet form; both can have the label 'laid on', i.e. the non-printed area has been cut and removed. Sheet label forms also exist as split top type – both printed and non-printed area is present but printed area is 'split' away so that it can be removed. Split back type has the backing paper split or cut so that it can be removed. (Applies to larger sizes.)

Numerous papers, usually of the single face coated types, are now available with a wide range of pressure sensitive adhesives. These adhesives may be:

- *temporary* – can be easily removed from the item onto which it has been placed
- semi-permanent – difficult to remove
- permanent – virtually impossible to remove without a fibre tear.

Pressure sensitive labels are removed from the backing paper and then applied by pressure. Ideally they should be removed by turning the backing paper over a right angle so that the label comes off straight. If some labels are peeled off (backwards) a curl is induced, which in the less permanent form may result in a peel back or lifting from the item to which it is applied. Figure 5.12 shows the structure of a pressure sensitive label.

Self-adhesive labels normally have the following type of structure (layers):

- facing material (90 μm)
- key coating adhesive (12 μm)
- silicone release backing (50 μm)

giving a total thickness of 150 μm (0.006 inches).

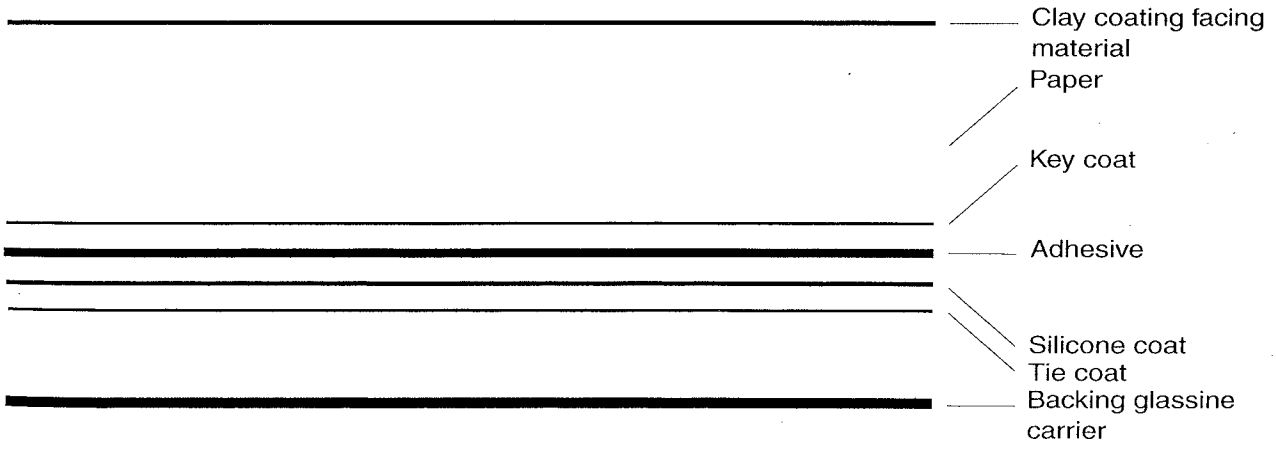


Figure 5.12 Structure of a pressure sensitive label

The silicone release usually has a coating weight of approx. 0.5 g/m^2. Die cut accuracy is usually ± 5 μm.

Self-adhesive labels can be applied to most materials: wood, plastic, metal, glass, paper and board. As the adhesives are resin-based (plasticised thermoplastics), migration problems can occur when they are applied to certain plastics (PVC, LDPE, etc.). Adhesive systems for pressure sensitive labels include latex and acrylic bases and adhesives which may be applied as a hot melt, or via a solvent, emulsion or dispersion base. Water-based adhesives are currently increasing in use.

Until recently the printing processes have tended to be limited, i.e. flexographic, rotary letterpress (four colours), with gravure (occasionally). The labels are produced in accurate register on the backing paper – on reel-fed machines, printing, punching and removal of trim are carried out as a continuous operation (platens are also used.)

Labelling can be carried out by hand, semi-automatically or fully automatically. In all instances accurate positioning is essential as the label cannot be slid into position. Machine speeds of 800 per minute are attainable. The cost of pressure sensitive labels is higher (than that of all other forms).

Reel-fed labels offer one huge advantage in security – they dramatically reduce the risk of admixture, which is particularly important in the case of pharmaceuticals.

Applying labels to tight radii still may give butterflying (edge lift) with certain label types and styles. Improvements can be achieved either by an adhesive change or using a paper of a lower substance weight (i.e. replace 90 g/m^2 with 65 g/m^2), or by reducing the stiffness of the printed face by reducing the amount of ink used, ceasing to use a varnish or using a lighter coat weight paper.

Modern adhesives for self-adhesive labels include acrylic, polyethylene combinations. There is a distinct move away from solvent-based adhesives (for ecological reasons) to water-based dispersion/emulsion systems.

Adhesion can be normally checked by a press-down test, followed by removal after 3 s, 6 h, 24 h. Bond normally improves with time due to the cold flow of the adhesive. Long-term adhesion may use a test involving 7 days at 70 °C, which gives an indication of any change over 12 months. Be certain that 70 °C is well below the degradation temperature of the adhesive, otherwise the results are spurious.

Leaflets

Leaflets have loomed large in the minds of packaging people in the industry in the past few years, primarily with the implementation (from 2 January 1994) of the relevant parts of the European Community Directive 92/27/EC, which brings together requirements for labelling and package leaflets into one directive by repealing parts of Directives 65/65/EEC and 75/319/EEC. In addition, the obligatory nature of Article 3 of Directive 89/341/EEC on packaging leaflets (unless *all* the required information is on the pack or label) is confirmed and reinforced.

Paper leaflets can be found broadly as one of four types, as follows.

1 *Cut sheet.* Usually printed both sides, delivered as blocks of cut sheet and folded on the cartoning machine. The restrictions on block cut papers are also relevant, i.e. they should be backed and fronted with band bound card.

2 *Reel-fed.* Like reel-fed labels, but with no backing paper. They are both guillotined and folded on the cartoning machine. Claimed to be more secure than all other types of leaflet.
3 *Pre-folded.* Are delivered as bundles (these need to be 'broad banded', *not* with elastic bands round them) or contained in plastic cartridges and fed via a hopper system direct to the cartoning machine,
4 *Combined label/leaflet.* Delivered as a thick pressure sensitive label (either reel-fed or block cut), containing a fold-out portion which is the leaflet itself. Applied as one would apply a pressure sensitive label. These have now been around for a number of years. As far as can be ascertained, at least six patents have been taken out in this field. Recently there has been more use of multi-ply construction of these types of label, often using dissimilar materials with rather specialist adhesive systems. Probably the best known are Fix-a-Form from Denny, Peel 'n' Reseal booklet labels, Multipeel, a peel off promotional leaflet or sticker, Dri-peel, Incore and the Double-Dri system. Leaflets use high-opacity (80% + EEL) lightweight (40–70 g/m^2) coated or uncoated papers.

In order to maximise the smooth production of these thin (lightweight) papers, the following facts about paper should be borne in mind when designing the leaflet.

1 *Grain direction.* The grain of paper has been mentioned several times already, but with lightweight papers it becomes once again a critical feature, as the papers are both thinner and weaker than label paper or board.
2 *Stiffness.* Paper is nearly twice as stiff in the machine direction as it is in the cross direction. The degree of stiffness is related to the caliper (substance), so that the thinner the paper, the lower is the stiffness, to the extent that the stiffness factor is proportional to the cube of thickness. Arising from this is a basic recommendation that the thinner the paper the more advantageous it is to print in the machine direction because of its greater stiffness.

The other parameter of lightweight paper to be considered is the porosity of the chosen paper. This is because many cartoning machines use a vacuum type of pick-up for the leaflet no matter in what form it may be presented to the cartoning machine. Even so-called reel-fed leaflets have to be cut, picked and moved through folding plates up to the insertion point into the carton. For this reason both specification of paper porosity to air and pick tests (to keep down the amount of lint or dust) are sensible.

The other point to take into account is the 'conditioning' of the lightweight papers prior to printing and folding. This just means that the paper should be kept, as far as practical, in optimum storage conditions.

All leaflets, though folded tightly for insertion, have inherent problems of ink 'show through', particularly with ink colour solid blocks, e.g. photos or pictures. Security bar code reading can be a severe problem on the thinner papers. The amount of copy required on all types of leaflets has increased dramatically over the past ten years, so much so that packs have had to be devised to accommodate very large leaflets (A3); this has created its own cartoning machine design problems.

Folding or collapsible cartons

These difficult to handle, temperamental objects in white lined folding boxboard are popular in the industry because they are good at their job, which is to contain, protect and distinguish the product from *all* others in an economical manner. They are sometimes known as 'secondary' packaging.

Ethical products should either have a print free area or a printed area which does not contain vital or legally required information which would be covered or obliterated when the pharmacist's label giving information for the patient is applied. The standard size for this label is 70 mm × 40 mm, or 70 mm × 35 mm.

Choice of design

When choosing a carton design the following points should be noted and fully discussed with a printer used to dealing with pharmaceutical products and with the necessary levels of hygiene control, QC, and inspection.

1 *Style* – This could be from a catalogue of carton designs, e.g. that of the European Carton Makers Association (ECMA). This includes the method of flap retention in its style parameters, e.g. lock slit, friction fit, claw lock, crash lock, envelope lock. Are dust flaps required? Is reverse tuck or aeroplane tuck wanted? Figure 5.13 shows a typical reverse tuck twin lock slit carton.

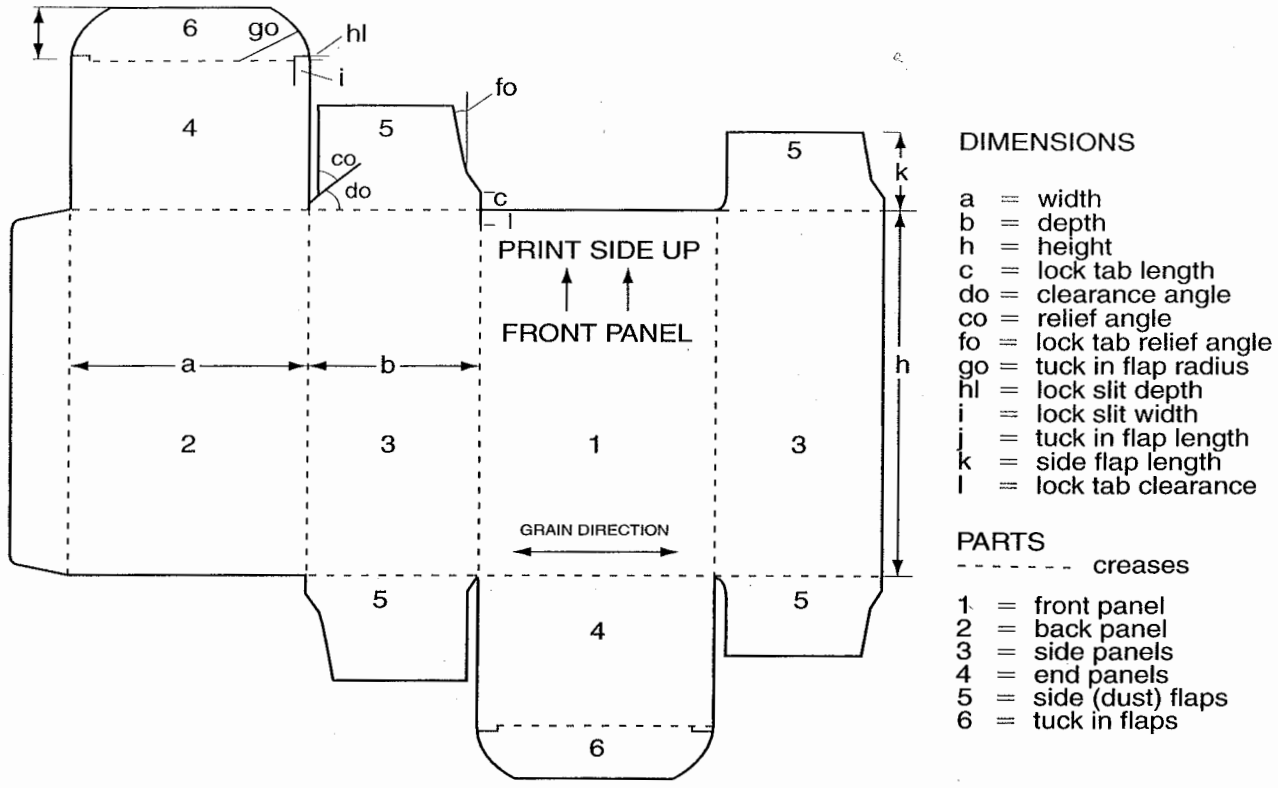


Figure 5.13 ECMA 2120 style carton with twin lock slit flaps

2 *Type of board* – This has been discussed above. Each of the types of board mentioned comes in various calipers ranging from about 200 μm up to around 700 μm. This will depend to a large extent on what is going to be put into the carton, allied with the size. Board surface facing materials need to be decided, as these will affect the type of printing chosen and may affect the creasing and subsequent carton erection.
3 *Layout* – It is usual to have the top opening flap opening away from the opener, with the 'glue flap' around the back of the carton, placed so that it interferes as little as possible with the overprinting operation.
4 *Size* – This has been mentioned above. Only make the carton big enough to contain the contents and allow enough clearance for machine operation.
5 *Graphics* – Understand what graphics are needed and the limitations of each of the printing processes you are likely to use. One colour is easier and cheaper to print than four colour process.
6 *Quantity to be produced* – If only running a few hundred cartons of one particular type, then choose the process with the cheapest plates and shortest make ready: that will be the cheapest, e.g. one colour flexographic or letterpress printing. At the other end of the scale, if you wish to produce four colour process printing with screens and tones and produce them by the tens of millions then either offset litho or gravure printing is the choice.
7 *Method of printing* – Usually using offset litho, flexography, letterpress or gravure. May include hot die, stamping, foil blocking, embossing, debossing.

Origination

1 *Plates* – Need to be made from the artwork, one per colour specifically designed for the machine on which it is going to be used.
2 *Cutting and creasing formes* – These are the cutting (sharp) and creasing (blunt) knives fitted into a sheet of thick plywood so as to cut the flat printed sheet of board and press in the creases needed to form up the carton. Each sheet of plywood that carries the knives is called a forme. The knives are surrounded by strips of foam rubber, to prevent them from tearing the board. Opposite to this sheet is a 'negative' sheet of plywood called the 'counter'. On this there is a mandrel of hard material for the sharp knives to cut against.
3 *Cost of origination* – This entails looking to the best way of minimising the costs of artwork, plates, printing processes, sheet, sizes, formes and counters, etc.

Make ready

This is 'simply' the preparation of the printing machine to make it ready for production, including the selection of the board sheet size and which way the grain of the board in the finished carton will run. The figures, drawings of cartons and artwork should all indicate in which direction the grain is to run.

Printing

May be printed on flat sheet or from reels. May use either a four colour process system (cyan, magenta, yellow and black), or a multi-colour system. As indicated above,

almost any printing process can be (and is) used. The most common methods of printing today are all sheet fed, mainly using letterpress and offset litho.

Cutting and creasing

The basic purpose is to stamp in the crease lines, at the same time cutting out the outline of the carton. The prime reason for creasing the carton blank is to define the shape of the carton panels and allow it to fold without distortion. This is achieved by using sharp cutting and blunt creasing 'rules' (either flat bed or rotary). The sheets of preprinted board are fed into what looks like an ordinary small printing press, located over the counter and the forme comes down with some force, cutting and creasing that single sheet.

Stripping

This is the removal of unrequired waste surrounding the printed cut and creased flat carton blanks on the sheet. It is still quite often a hand-based operation.

Pre-folding and gluing

Cartons are usually supplied in a collapsed state, with a glued side seam and two of the folds already made. Folding/gluing is done at high speed and it is necessary for the adhesives used to have a high tack, since freshly folded creases are quite resilient. At this stage, crease quality is very important, since unduly stiff creases will resist gluing.

Following gluing the carton is usually compressed to a flat state where it already exhibits some degree of 'crease set'. To minimise this it is frequently advisable to open the carton through 90° to 180° momentarily to literally break the crease, reduce possible crease set and generally assist final erection. This process is termed pre-folding. (Tests that it is sensible to know about and use during a carton design sequence are covered below.)

Packaging and identification

The cartons should be loosely bundled together, stacked on their edges into strong corrugated box. It is detrimental to stack them 'flat' as the weight of cartons above will inhibit the pre-break (or natural springiness of the carton), making automatic handling an impossibility. The looseness is for similar reasons to prevent having problems with cartons. The case should be securely sealed and identified in the manner prescribed by the specification, with at least the security code (item code, part number), customer, batch/lot, a QC pass stamp/mark and a description.

Carton erection and filling

The action of mechanically erecting, inserting primary pack, insertion of leaflet, then the closing of the carton is another world in which technical expertise may be required. The criteria on which the form of carton filling will be decided include, quantity per batch/lot/order, size and weight of the goods to be cartoned, cartonboard caliper,

design of closure flaps, and what else, apart from the primary container, has to be inserted.

Hand cartoning

Basically any carton style, with any form of goods, of any caliper board, with any of the closure flap designs (lock slit, friction fit, claw lock, crash lock, envelope lock), with any number of leaflets or measures or droppers etc. can be used in hand cartoning.

Semi-automatic

This is usually a machine where the carton is erected, the bottom closed and the top opening presented to the operator who drops in the goods and any accessories. It would be expected for this type of machine to have an overprinting unit of some type built into the cartoning machine.

Quantity per batch/lot/order needs to be greater than the time needed to change the machine from one size of pack to another, which could be from 30 min to 3 h. Works at a speed of 40–60 items per minute with two to four operators. The size and weight of the goods to be cartoned have some relevance, as large heavy objects (2 l Winchesters of liquid) will need to run more slowly than, say, 5 ml bottles.

The cartonboard caliper, particularly the consistency, is more critical than for hand cartoning as it affects the 'pre-break' of the carton and once a machine is set to open pre-break there is little tolerance for variation. The faster and more sophisticated machines need tight tolerances.

The following designs of closure flaps, lock slit, friction fit, claw lock, envelope lock and glued flaps can be made to work on an appropriate semi-automatic machine. One would recommend for simplicity that attention be paid when using claw locks and envelope locks, ensuring that they are really necessary before introducing them, as they are not the easiest carton closures to handle.

Note that cartons can have different locks on each end, e.g. lock slit at the bottom and friction fit at the top, or (more usually) envelope lock base seal with friction, lock slit, claw or glued flaps at the top.

Automatic

There are two basic types of machine – intermittent motion and continuous motion. The intermittent is the smaller, slower and cheaper, usually with a blade opening action for the carton pre-break, so that it is likely to accept a lower quality of carton than the really high-speed machines. The continuous motion machines tend to be much larger, faster and more expensive and, being much faster with vacuum pick-up of the carton for a 'knock' pre-break, are much more sensitive to the quality of the carton presented.

Automatic cartoning should only be used when the quantity per batch/lot/order is large enough to keep the machine running for more time than it is down on change-over.

The size and weight of the goods to be cartoned is something of a limiting factor, as our 2 l Winchester would probably not be candidate, but a 300 ml bottle certainly would be run automatically. Speeds range from 60 to 350 per minute, with machine prices rising to match the speed. The design of closure flaps is probably practically

limited to lock slit, friction fit and glued flaps. This again is in the interests of speed. What else, apart from the goods, has to be inserted may create a problem. Leaflets can be inserted, as can probably one other accessory, but for more than this specialist machines have to be designed to do the job.

Rigid boxes

These are still occasionally used e.g. rigid nested fibreboard boxes for ampoules, but nowadays any paper-board near parenteral products is viewed critically, due to the fibre load from the board itself contaminating the local atmosphere.

Rigid boxes need similar stages to folding cartons see 'Choice of design', 'Origination' and 'Make Ready' above. Printing, if necessary (but usually labelled with a pregummed label, which might act as a tamper-evident seal as well), is usually applied as a pre-printed liner after the rigid box has been formed. Hence the further stages are:

1 selection of board, board size and cutting to size on a cutter/scorer machine, e.g. one of the chipboards
2 corner cutting – removing the corners so that the box can be erected
3 corner staying – adding gummed paper to each corner to make the erected box rigid
4 quad staying – an alternative to (3)
5 paper slotting – printed or plain covering
6 QC to specification
7 packaging and identification.

Rigid boxes are normally hand packed.

Overprinting

This is sometimes known as 'batch coding' as well as the more popular term, overprinting. This has become a necessary evil in the modern world. All overprinting (this may include off-line methods as well) is used to add variable data as late in the production cycle as possible, i.e. batch/lot numbers, manufacture and expiry dates, price blocks for the Middle East in particular and registration numbers for many other places. If these problems are approached by the method of using fixed copy for a large area of the world allied with a fairly sophisticated overprinting system, one can save the cost of the system in inventory savings alone.

The overprinting of 'variable' information as late as possible in the label application and carton closing processes gives the production company a high degree of flexibility to allow for unforecasted emergency information to be added. This copy is normally added to the printed label or carton either just prior to the packaging operation or during the operation itself. As with all printed copy, the print must be indelible, legible and not fade during the shelf life of the product under normal usage conditions. It is usual to overprint in black and occasionally red. *Note* that red is traditionally used for warnings or poison markings, so check carefully before using.

Overprinting is usually carried out with one or other of the following printing

processes: hot foil stamping, flexographic, letterpress, tampon, thermal printing, and stamp debossing.

Some of the information required may be in the form of bar codes. This has stimulated the European Pressure Sensitive Manufacturers Association (EPMSA) in line with the Article Numbering Association (ANA) EAN guidelines, to produce a standard for bar code overprinting on pressure sensitive labels. EAN bar codes can now be successfully printed onto labels using flexographics, or thermal transfer printing.

Contact printing techniques

Contact printing is the more traditional type of printing in the industry.

1 *Letterpress* – the traditional slugs of type in either lead/antimony alloy or hardened steel letters. Usually locked up (set) in a chase (holder), or using a 'baselock' type of system where the type has a foot which slips into a holder and can be locked by a spring clip, being inked each pass and 'kissing' the substrate to deposit the ink. Can be used on most substrates, but is best on paper and board which is not too shiny. Cast coated papers and boards give problems.
2 *Debossing* – the same as letterpress except that no ink is involved and the characters are pressed quite hard into the substrate. Used occasionally for paper, but more normally for blister and strip packs. This method is likely to generate complaints, due to the difficulty of reading it clearly.
3 *Hot foil* – again similar to letterpress, but the ink is carried as a solid on a PET carrier and is stuck to the substrate by the type face using a combination of heat, pressure and time. This means that it is probably not as quick as letterpress or debossing. This system can now be operated by a clip-in rotary flickwheel typeholder, which means that information can be changed very quickly.
4 *Thermal transfer* printing is the selective heating (computer-controlled) and cooling of small elements in a print-head which can be used to impress a one-use thermal ribbon onto the substrate surface. Resolutions of up to 12 dots per mm can be achieved.
5 *Flexographic* – here the characters are formed on a flexible 'plate' of rubber or plastic. The characters pick up ink (probably thinner than letterpress ink) and transfer it to the surface of the label or carton. Can be made to run quite quickly. There is today a cheap rubber-type 'baselock' system on offer, primarily designed for the Third World.
6 *Offset litho* – this technique has occasionally been used in the past by using a special paper plate that can be photocopied and uses the properties of oil and water separation. Usually used only for fairly large labels.
7 *Impact dot matrix* – where a block of 'needles', usually nine but sometimes more, are electronically selected to strike forward onto a typewriter type of ribbon, thereby placing the ink from the ribbon onto the substrate.

Non-contact printing techniques

These are more modern types such as ink jet (solvent-based and hot plastic based) and laser.

Ink jet

These printers come in two types:

1 Drop-on-demand printers have an array of nozzles which fire a drop of ink when commanded by their computer control. Can use either a solvent-based ink or a solid base which is melted and ejected by the print-head.
2 Continuous flow works by using piezo electric crystal to generate an ultrasonic beam to disturb the flow of ink by producing uniform sized droplets. These are then electrostatically charged under computer control. The charged droplets are deflected to a catching mechanism and the neutral ones pass onto the substrate forming the image.

Toner-based laser

A computer-controlled laser beam forms an image on a charged photosensitive drum. A carbon toner is applied and adheres to the charged areas, developing the image which is then transferred to the substrate and fixed with heat and pressure. Text, graphics and bar codes can all be produced this way.

Ion deposition printers are used in similar circumstances, but their method of operation is different. A latent image is formed on a dielectric cylinder which is directly imaged by a projection of ions. Development is by a toner adhering to the charged areas and simultaneously transferred and fixed to the substrate under pressure.

It is predicted that on short-run label production/overprinting there will be increases in use of non-impact printing, especially thermal, thermal transfer and laser technologies. Ink jet coding design with small characters is also expanding into pharmaceuticals.

On-line or off-line printing?

In all overprinting operations the economics of the situation must be addressed, e.g. on-line or off-line.

On-line overprinting has the advantage of being directly under the control of the person in charge of the operation, but has the disadvantage that if there is a problem with the overprinting operation the production line halts. Off-line overprinting has the advantages of not directly holding up production if it has problems, and having staff that are usually better trained and specialist in printing. The disadvantages are that generally extra overprinted components have to be supplied to compensate for potential packaging line problems, and the overprinting operation can sometimes become a bottleneck.

A capability for in-house design in overprinting and printing in production is discussed referring to EPiSYS or the MAP80 systems of in-house label design and printing (as often currently used in clinical trials packaging).

Reel-to-reel laser printers are seen as part of the answer to low-volume orders needing variable information, along with the success of the EPiSYS technology. These laser printers will probably have an expanded use in the not too distant future to encompass primary pack labels, when the development of better and more light-fast colour printing is achieved. More recently both Indigo and Xeikon have introduced 'digital' in-house printing systems.

Solid and corrugated boards for casing

Too little attention is usually paid to this important area of packaging. If the transit packaging is poorly designed then the product will not reach the market in usable condition. This automatically puts up costs and leads to intense customer dissatisfaction. There are several types and structures of boards for casing.

Solid fibreboard

This is two to six layers of recycled paperboard which is treated with an adhesive between the layers and press-laminated together. The outside layer can be of 'Kraft' paper to improve the strength and help better resist water and water vapour. It has good crush-resistant and anti-puncture properties.

It is usually specified as just the thickness of the board, 0.95 to 2.9 mm (340 to 700 g/m^2 with 60 to 125 g/m^2 of Kraft). It may be printed by flexography or letterpress or ink jet.

Corrugated fibreboard

Popularly known as just 'corrugated', this is the most popular form of outer protection used in the industry today. It comprises one or more sheets of fluted (corrugated) paper secured by an adhesive to two or more liners. The paper used for the 'corrugations' is made up of recycled paper, e.g. semi-chem chipboard or 'strawboard', 25–75% straw with various quantities of waste-based pulp added. As the corrugated layer is impregnated with a stiffening agent (usually starch or synthetic vinyls) during the corrugating process, the relative strengths of the three types of recycled paper are not too different. Usually printed by flexography or ink jet, which can weaken the board.

Note that pre-printed sheets may also be employed using offset or gravure printing techniques. With a pre-printed outer liner, care has to be taken in the print design and layout so that when a case is made the print corresponds to the case shape, i.e. is kept in register on the cutters. Figure 5.14 shows a corrugator. There are various types of corrugated fibreboard:

1 single wall, i.e. one sheet of fluted paper between two liners (Figure 5.15 shows single wall corrugated)
2 double wall, i.e. two sheets of corrugated paper between three liners (Figure 5.16 shows double wall corrugated)
3 triple wall, sometimes known as Triwall (trade name), i.e. three sheets of fluted paper between four liners (Figure 5.17 shows triple wall corrugated).

Flutings are described as A, B, C, E and micro flutes. This describes the depth of the fluting (see Table 5.3).

Abbreviations commonly used for describing the structure of boards are:

- K, Kraft liner
- BK, bleached Kraft liner
- T, test liner

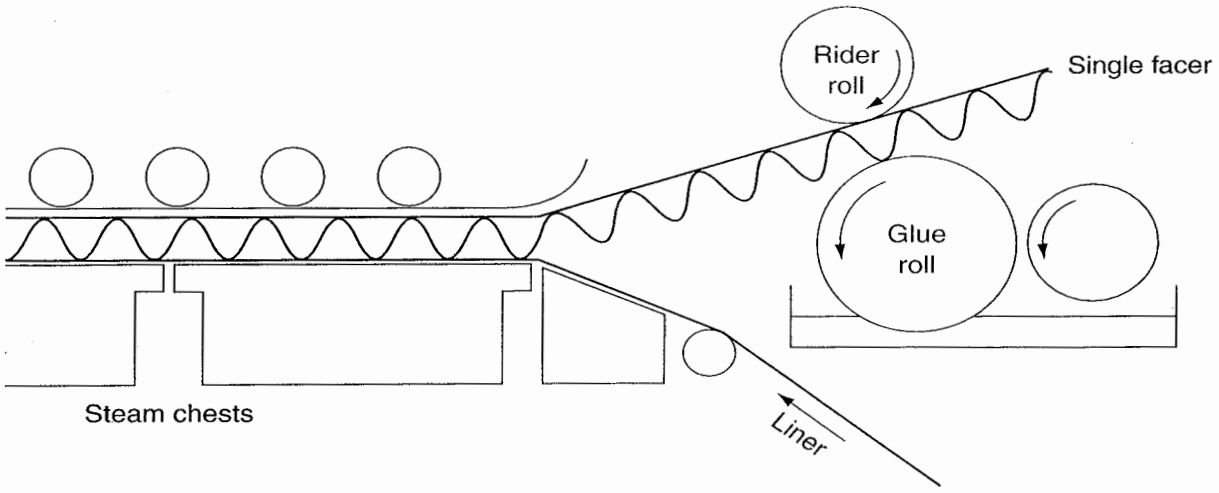


Figure 5.14 A corrugator

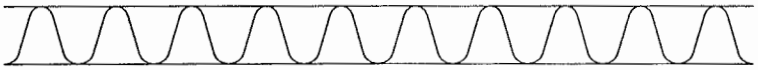


Figure 5.15 Single wall corrugated fibreboard

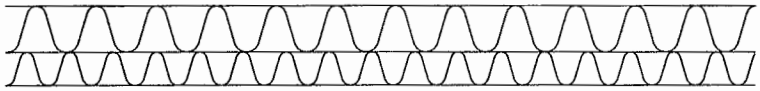


Figure 5.16 Double wall corrugated fibreboard

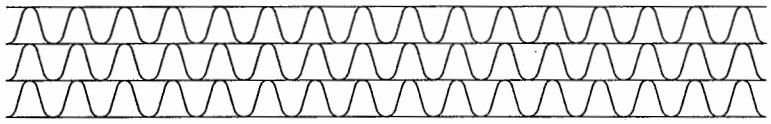


Figure 5.17 Triple wall corrugated fibreboard

Table 5.3 Flutings in corrugated fibreboard

Flute form	*Approx. height of corrugations (mm)*	*Approx. corrugations/m*	*Case wall corrugations*
A flute	4.5–4.7	105–125	Triple
B flute	2.1–2.9	150–185	Single and double
C flute	3.5–3.7	120–145	Single, double and triple
E flute	1.1–1.4	290–320	Single
F flute	1.0–1.2	340–390	Single
Micro flute	0.9–1.0	400–440	Single

- C, chipboard liner
- MK, mottled Kraft liner
- WTK, white-topped Kraft liner
- SC, semi-chemically prepared board.

The grammage (substance) of the corrugated fluting would normally be expected to be 112 g/m^2, but 125, 150 and 175 g/m^2 can be found in use. The liners should be of approximately equal grammage so that the corrugated board is balanced; anything from 115 g/m^2 right up to 400 g/m^2 has been used. It is usual to use Kraft liner, with its better water resistance and smoother surface, as the outside liner. To print (usually flexographically) the corrugated board, the smoother the liner, the better the quality of printing that results.

'Test' liner (pulped waste-based paper) is usually used both as the inner liner and for fitments. The centre liner(s) in double or triple walled containers could be semi-chem, chipboard or test liner according to the properties required.

There is no single industry-wide way of describing a corrugated case wall, but below are examples of those recommended in BS 1133 section 7.5.

- 150K/C/150T – single wall case with C flute 112 g/m^2 with an outer liner of 150 g/m^2 Kraft paper and an inner liner of 150 g/m^2 test paper.
- 150K/B/150SC/C/150T – double wall case with B flute outside C flute, both with substance of 112 g/m^2, with 150 g/m^2 Kraft outer liner, 150 g/m^2 semi-chem middle liner and 150 g/m^2 test inner liner. Note that this system assumes a 112 g/m^2 corrugated layer, so that if a 150 g/m^2 corrugated layer is really needed then this must be specified to the supplier.

Use of corrugated boards in distribution

Manufacture of corrugated and solid-board cases

The flat sheets of board (solid or corrugated) are fed into machines which produce the cases. These may consist of:

1 a slotter creaser
2 a printer slotter
3 folder/gluer (or stitcher or stapler)
4 rotary or flat bed die cutters (including waste stripping).

Any decoration is usually done flexographically and currently uses solvent-based inks to improve drying. Delivery is usually of made-up cases in the flat, stacked onto pallets and either stretchwrapped or banded.

Collation and casing of packs

In packaging, a carton may or may not be chosen as the prime container. If it is not chosen then a number of containers may be held together in a tray, or containers on their own, both held together with some form of film wrap, e.g. shrinkwrap. Product in

a carton must be arranged so that the longest side of the carton is vertical, as this is the way to use the maximum strength of the carton.

Structure of cases and design parameters

Cases should be designed to the FEFCO, sometimes called the International Fibreboard Case Code (IFFC), system. This is an international system which has codified the various designs of cases into a simple book of basic designs. Figure 5.18 shows FEFCO case designs.

At this point it is sensible to include fitments, either solid or corrugated, into the equation. Fitments are also described in the FEFCO book, and are used to provide added strength and protection to the casing system by:

1 thickening the walls of the case
2 thickening the top and base of the case
3 being added as nests to prevent collisions between products in the case
4 preventing movement of the product
5 increasing the puncture resistance of the case.

Fitments are usually made of entirely waste-based materials.

In order to optimise the strength/cost balance an understanding of the way cases behave under load is vital. In helping to determine this optimisation, tests and estimates of the various parameters surrounding cases must be considered. Probably one of the most useful tests performed is the edge crush test.

Edge crush test (ECT)

This is defined in ASTM 2808 and BS6036 and TAPPI 811 and is a useful way of estimating the way a particular board will react under standard conditions. From the ECT, box compression ratios (BCRs) can be calculated for any case, thus:

$$\text{BCR} = 17.7 \times \text{ECT}1.06 \times d0.85 \times (L + B)0.31$$

where ECT is in kN/m, d is the board thickness (mm), L is the length of the case (mm) and B is the breadth of the case (mm).

When one is designing a case, a useful piece of knowledge is that in general each 1 g substance of fluting is as strong as 2 g substance of liner. Cases may be held together at the 'manufacturer's join' by:

- stitching the join together – abbreviation 'S'
- gluing the joint together – abbreviation 'G'
- taping the joint together – abbreviation 'T'.

Factors affecting design

Determine whether the product is going to be single, double or higher stacked on pallets, as this will create the need to increase the strength of the board accordingly.

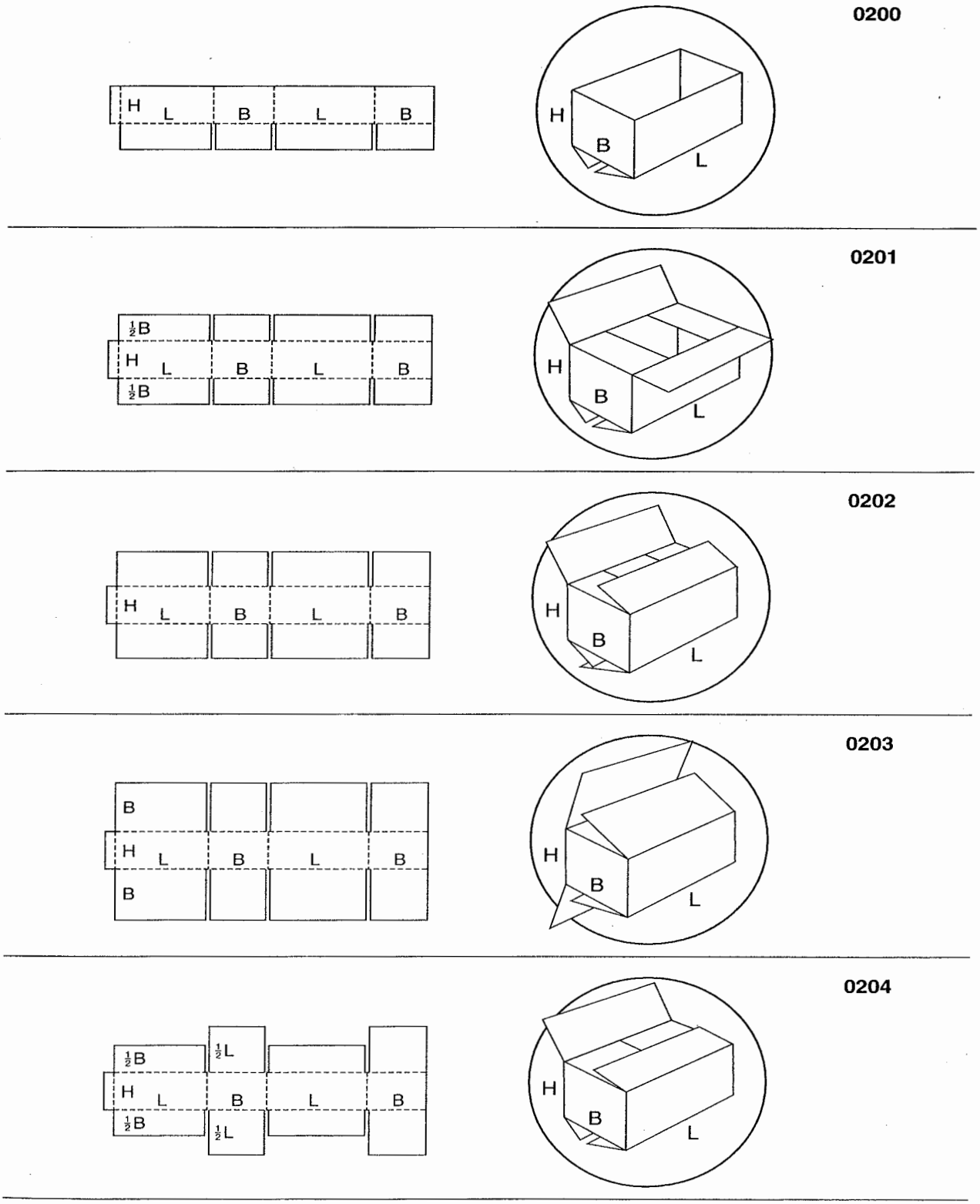


Figure 5.18 FEFCO case designs

Note the design of pallet being used, as the gaps between the deck boards may be too wide for the case size, letting case edges 'dive' down between the boards. Note also the pallet 'footprint' in any option used for multi-stacking pallets. Ensure that cases are stacked with their vertical walls directly above each other as this is the best way to carry load from above. Know the weight of the product to be carried per case. There are weight limits in various parts of the world. The author's personal experience suggests about 12 kg as the maximum case weight.

Closing of cases

This is carried out by one of five methods.

1 Gluing, either hot melt or cold adhesive. This would only be used on cases where the inner flaps of the case protected the product, e.g. FEFCO 0204 design.
2 Large staples can be used, but they puncture the liners of the outside corrugation and can let in water to the corrugations; nevertheless they form a secure closure and are widely used.
3 Water-based adhesive tape, where the adhesive is activated by wetting and this soaks into the outer liner of the case forming a strong closure, provided the relative humidity remains reasonably low. Not recommended for tropical markets where the high humidity makes paper taping a security risk.
4 Pressure sensitive adhesive tape, probably the most used today. At least 50 mm down leg of tape is needed to form a positive bond with the surface of the liner and there needs to be a substantial overlap of tape over the join of the outer flaps. For this reason 50 mm or 2 inch tape is the most popular. Clear tape pressure sensitive adhesives are susceptible to UV light degradation. It therefore makes sense to incorporate UV blocking agent either into the plastic material or into the adhesive itself.
5 Interlocking flaps may be used, but they are not considered to be a secure form of case closing.
6 Specific hot melts are used for very hot and very cold climates.

Environmental issues

All vegetative materials undergo respiration and transpiration, thereby making a major contribution to the atmospheric balance in which we live. Since trees are a major land-based part of this balance, forest destruction is a concern. There is also a linkage to global warming.

In addition to the management of the forest, great strides have been taken to salvage *all* waste wood, bark, chippings, sawdust and waste pulp so that it can be turned into fuel for the upkeep of the paper mill itself. Rain forest hardwoods make very weak, poor paper or board and are not used. The use of chlorine-based products for the bleaching process has virtually died out in Scandinavia, but remains in some other parts of the world.

Some questions are posed in the next few paragraphs. There are probably no right answers, but many opinions and certainly many more questions.

The impact of the use of paper and board has to be seen in the context of what we would do without it. One could print directly onto containers all the information dis-

cussed above for labels and leaflets. One might suspect that massive warehouses would need to be built in order to contain all the printed variables on the prime containers, and this would be a doubtful benefit to the environment.

The prime containers in warehousing and distribution could be protected with plastic boxes or in wooden crates, which could be made returnable and therefore reusable. This would entail the problem of retrieving the containers, cleaning (thereby creating effluent), re-marking them and putting them into the cycle.

The trite answer is to do a life cycle analysis for each material used, theoretically from 'the cradle to the grave'. That is all very well, but where is the cradle and where is the grave? It has been suggested that with materials tied into the 'carbon cycle' there is no cradle and there is no grave. What has to be done is to make the best analysis possible taking account of as many factors as are known!

Paper- and board-based containers

Fibreboard kegs and drums

Fibreboard kegs can be used for solid bulk drug, bulk tablet, or bulk excipient containment and transport. These are made up of multiple plies of test or Kraft liner board, convolutedly wound on a mandrel and bonded with sodium silicate adhesive between the plies. There may be an LDPE or other inside liner and the exterior may also be varnished. The base could be of either metal or plain thick board, the latter waterproofed by dipping into paraffin wax.

There may also be a galvanised mild steel base chimb bonding a board base to the wall. The lid may be of the slip-over type, in which case there is no need to protect the top of the keg, or of the push-in type, where a top mild steel chimb is added to the wall of the keg to carry the lid. This latter type of lid, made of either metal or plastic, will usually have some more sophisticated closure, e.g. lever lock.

Paper and composite open mouth sacks

These may be used for bulk excipients where there is no risk to or from the environment, e.g. chalk. They comprise two to six plies of sack Kraft types of paper, with possibly LDPE coated or metallised paper or one ply of LDPE in the case of composite sacks. The sacks may or may not have a gusset. They will all be either stitched or glued at the base and usually stitched to close the open mouth.

Composite containers

These can be used as tubes for protection or for small powder drums of 100–200 g. They are made by spirally or convolutedly winding the various plies in turn around a mandrel (similar to kegs), bound together with suitable adhesives. The materials are basically grades of paper or light board but may contain PE, aluminium and fine calendered coated decorated paper as an outside layer.

They are usually closed with metal (tinplate) or plastic bases, with closures of similar materials which may also contain dosing devices.

Paper liners, linings and laminations containing paper

Papers of various grades are used as liners inside bags made of another material. Glassine has been used as linings for the inside of plastic, metal or fibreboard kegs, where there has been a suspected problem with the compatibility of the drug and bulk container.

Paper is used extensively in laminations where it is bonded, usually by heat and/or adhesive, to other films, notably plastics and aluminium, e.g. LDPE/adhesive/aluminium/adhesive/calendered paper. This type of lamination can be used for form fill and seal work, e.g. sachet packs of deliquescent powders.

Cellulose films

The coated film is usually used as an overwrap, has been used for strip packaging when metallised, but has lost popularity in recent years with the better barrier and stronger olefin-based films becoming more available, cheaper and with 'tailored' properties. Cellulose acetate (CA), cellulose nitrate (CN), cellulose acetate propionate (CAP) and cellulose acetate butyrate (CAB) may all be found in use. The poor tear resistance, once the tear has started, does not help their case. Also, the most popular method of using cellulose films is deadfold wrapping holding down the envelope corners by heat dabbing which bonds the coating. This method has proved not to be tamper-evident.

Paper and board testing

All uses are related to the function requirements which are necessarily linked to the material properties and characteristics. Details of material tests for paper, board, cartons and corrugated are given in Appendices 5.1–5.4.

Pharmaceutical product and pack security

To cover this subject fully product issues are reviewed independently and in the context of their contribution to overall security made by 'paper'-based materials and printing.

Paper and board as security features may seem a little far from reality to the uninitiated, but seals, tapes, labels and cartons can all be utilised as devices to ensure the security of your product. The security issues will be dealt with in two ways: first the really criminal issues, i.e. tampering and counterfeiting in particular; second the security of ensuring that the correct copy gets onto the correct paper material, onto the correct substrate containing the correct pharmaceutical product.

The security environment in pharmaceuticals

There is massive fraud or illegal activity in the sale of all goods worldwide. Figures quoted in 1993 indicate that up to 5% of world trade or $80 bn per annum is involved, and this is rising each time fresh estimates are released. Pharmaceuticals are not exempt from these problems ($200 m per annum estimated), despite having theoretically tighter systems of manufacture, storage and distribution due to governmental licensing of products, storage, and distribution, thereby authorising sale by wholesalers

and dispensing by pharmacists. Here it must be pointed out that this refers largely to Europe, the USA and Japan. Procedures may not be as tight in developing countries, despite government controls and licences.

The illegal, fraudulent and unauthorised practices can be placed into eight broad categories:

1 product copying
2 product substitution
3 'pass off' or counterfeit packaging to support (1), (2) and (7)
4 adulteration or tampering
5 'shrinkage'
6 illegal parallel trading
7 'poaching' of territories by agents
8 invention of 'new' products.

Some of the examples which follow will fall into more than one category, e.g. how does one substitute something in a pack without tampering with it? Two further points should be considered that will affect the way in which companies react:

- producer liability legislation
- the legal need to track hazardous materials comprehensively

Product copying

This category of illegal activity attempts to copy the physical appearance of the pharmaceutical formulation without going to the massive expense of setting up all the legally necessary control systems, thereby producing something similar but cheaper and probably of much lower quality. The copy could be in either original packaging or 'pass off' packaging. Copies that have been seen have either contained impure amounts of drug substance or no active ingredient whatsoever.

The dangers of these copies are:

- impure active ingredient – uncontrolled effects on patient
- no active ingredient – no therapeutic effect for the patient and overall loss of confidence by patients and the medical profession
- impure or incorrect excipient substances – as above (note that deaths have been recorded where, in the Third World, 'glycol' was added to a product to extend the volume).

Product substitution

The substitution of one product by another, 'dressed up' to look like a more expensive product, e.g.

1 the labelling of a low-cost antibiotic as a much more modern and potent antibiotic
2 refilling or recycling vials using even non-sterile products
3 one company's counterfeit product in a second company's reused packaging.

The great danger inherent in this type of activity is that the substitute is probably cheaper, older and a lot less potent than the original, consequently the patient may not react in the way the health professional intended. The result here may not be fatal, but at the minimum a loss of confidence in the original product by the health professionals.

'Pass off' or conterfeit packaging

The term 'pass off' is the correct one in English law, since 'counterfeiting' is theoretically used only for offences concerned with currencies. However, 'counterfeiting'is the term usually used.

In the past few years some remarkable copies of packaging materials have temporarily fooled packaging experts. At the other end of the scale there have been many poor copies that would cause one to wonder how anyone could be so easily fooled.

Any of the examples quoted in 'Product copying' and 'Product substitution' above can be taken, plus out-of-date material or factory rejects 'obtained' and recycled with fresh packaging and different manufacture and expiry dates.

The danger in date-expired materials is that pharmaceutical products are given very strictly controlled shelf lives. Past the end of the shelf life there is *no* guarantee that the degeneration products produced will not be harmful to a patient. If the 'obtained' materials were factory rejects, then they had been considered by the factory QC system as not within the specification necessary for administration to patients.

Adulteration or tampering

Adulteration is the deliberate contamination of a product for extortion or for some other malicious intent, e.g. personal revenge. The two best known examples in the pharmaceutical industry are the 'Tylenol' affair in 1982 and the 'Sudafed' affair in 1991, both in the USA.

In both of these cases OTC pharmaceutical preparations, analgesics contained in capsules, were contaminated with a cyanide salt and deaths resulted. In the author's opinion, making packs fully tamper-evident is one of the hurdles that the industry has to tackle. Many companies have decided to add additional tamper-evidence, but it can be argued that there is still a long way to go. Experience to date suggests that adulteration appears to be more prevalent in the more sophisticated markets whereas tampering, in its widest sense, is worldwide.

Shrinkage

This describes the loss of goods through pilferage in production, storage, distribution or even disappearance from hospital and pharmacy stores. This is more prevalent than might be thought. Even lorry-loads of goods have been known to disappear.

The only real answer, at present, is the rigorous 'policing' of all parts of the manufacturing, storage and distribution areas. The pharmaceutical industry tries very hard to reconcile all input materials, be they drug substances, excipients, drug delivery systems or packaging materials. Some companies and countries claim that their control systems are so good that 'it cannot happen here'. Despite very rigorous systems and

controls, materials still 'disappear', especially if there is money to be made! Human ingenuity knows no bounds.

Illegal parallel trading

All parallel trading of pharmaceuticals inside the European Union is legal, provided that the following three conditions are fulfilled:

1 the product is registered and approved in the receiving market
2 the manufacturer is fully licensed to manufacture the drug in the country of origin
3 the importer in the country of sale is registered and licensed to handle pharmaceuticals.

The reasoning behind parallel trading is that of the 'free market' and that the best (i.e. lowest) prices can be obtained for any particular pharmaceutical presentation. Having worked in the industry for 36 years, there is one point the author has learnt – Ministries of Health actually control all the prices.

Over the past several years parallel trading has increased into the high-priced countries (e.g. Holland, Germany) from countries where the prices are lower (e.g. Greece, Belgium and Spain). Included in this trading have been products that are pass offs.

There is also the problem of illegal imports from both within the EU and non-EU areas. Illegal imports from within the EU usually do not comply with the three conditions above. In the UK the levels of control exercised by the DoH inspectorate have recently been revised, to try to combat illegal parallel imports.

Poaching of territories by agents

This is what might be termed a contractual offence between a manufacturer, an agent (who is contracted for specific markets) and the regulatory authorities in those markets. In many ways it is similar (if not identical) to the illegal parallel trading mentioned previously.

Inventing 'new' products

Human ingenuity in making money is nowhere more evident than where illegal operators have 'invented' a new product for the company, e.g. a well-known dermatological product name from an international company was used for a soap in certain markets and allegedly sold quite well.

There are two dangers here. First, the patient is paying good money for a product that has little or no therapeutic effect, and in certain cases might be exactly the wrong thing for the consumer's complaint. Second, the reputation of the company involved can suffer.

Two major factors which influence the reactions of pharmaceutical companies to the eight problems discussed above will now be considered.

Producer liability

There is a growing need for companies to be able to trace and authenticate their products so that claims arising from customer complaints and product performance liabilities, in particular, are proved. The probable nightmare scenario to a pharmaceutical company is where deaths are reported in the international media and attributed to its product – and it cannot 'prove' conclusively that the product was not its own but a 'pass off'. To the best of the author's knowledge this has not happened yet.

Most pharmaceutical companies are taking responsible counter-measures to avoid this dramatic situation.

Tracking of hazardous materials

There is a legal obligation to be capable of tracing hazardous goods, i.e. those classified under the UN hazardous goods scheme. It may not be appreciated that a number of pharmaceutical products are UN certified. Pharmaceutical companies can trace any 'batch or lot' of product up to the time it leaves their immediate control. There are techniques of 'trace back' used to investigate product complaints. Each company tries to reconcile 100% all materials, e.g. raw materials, drug substances, excipients and packaging materials, during all stages of progress through the company. It also holds records of the sources of all those materials, and today most of these sources are regularly audited.

Parameters needed for the design of a pharmaceutical security package

In this section only the solutions that encompass the use of cellulose-based materials in their make-up will be covered.

Project objectives

First, project objectives must be clear through an analysis of the problem(s) appertaining to the product(s). Do not proceed blindly into a strategy which does not suit the situation. The final objective will be to prevent, or at least minimise, product copying, substitution, etc. at a realistic cost. There are only two options:

1 do nothing and hope that the problem is solved by the forces of law and order
2 protect the product with the most cost-effective systems to minimise the problem. The totally criminal-resistant pack may never be achieved, but building in a number of layers of protection increases the chances of the criminal making a detectable error, or giving up the attempt and going to try it out on someone else's pack.

As stated earlier, one should carefully analyse the problem before deciding which of the above eight problem categories one intends to protect against.

1 Is more than one protective system needed?

2 Are the correct reasons for introduction being considered?
3 Is protection against more than one type of activity being considered?

Some of the issues – the vulnerability of packs and the concerns of the industry – are discussed below.

The issues involved in the initial evaluation of what, if any, actions should be taken are probably the most demanding. They must not be taken in isolation but supported by the company management. An approach to consider is the effects of an illegal action and the follow-up company action, e.g. is the incident fully understood? Have the reasons for the illegal incident really been analysed? Has the company the expertise to examine the problem and think the way the criminal thought?

Probably the hardest decision that has to be made is the need for public announcement. Is it worth taking the risk of losing public and professional confidence in the product, or is it better to rely on their understanding that what is happening is not the fault of the company and that the company is making considerable efforts to rectify the situation?

Which systems are considered to protect the goods? This will largely rest on what illegal activities have happened to the goods, the markets involved, and the type of packaging. Is an overt or covert feature to be used to protect the goods? Whatever overt measures are taken, an eye must be kept on public education because without it, vast numbers of inspectors might have to be employed to achieve the same level of inspection and coverage.

Have all the avenues of supply with reference to security considerations been examined, for example, security of printed materials supplies and suppliers and the movement of security packaging (and indeed ordinary genuine packaging) materials between the supplier and the final assembly workplace?

Vulnerability of the packaging system could include the following.

1 Product 'look alikes' can be easy to produce using conventional printing processes. The average label and carton used in pharmaceuticals are quite easy to reproduce well enough to fool both the pharmacist and the patient, even though they may not mislead the expert.
2 There is a very long period between drug patent and market approval, during which information and graphics can leak from a company. It is not unknown for the illegal route of pharmaceutical supply to outstrip the legal route into certain markets.
3 There are different prices in different markets, with more likelihood of illegal parallel trading and the introduction of 'pass offs'.
4 The multiple supply chains used by pharmaceutical companies can be bewildering, sometimes leading to the genuine product landing up in a market for which it is not intended.
5 No tamper-evident systems are employed on packs. This omission is gross negligence on the part of the company, since a degree of tamper-evidence can be provided very easily and cheaply, e.g. tamper-evident fragile paper labels. Anti-counterfeiting systems should, as has already been said, only be used after long, detailed and very careful consideration of the problems.

The concerns of the pharmaceutical manufacturer could include the following.

1 That patient safety is of paramount importance. The biggest risk is to the patient and all else should be a secondary consideration. The pharmaceutical company exists to supply safe, secure, therapeutic treatments to its customers. Any break or interference in the chain can only result in the final consumer, the patient, receiving inferior product with results ranging from loss of money for a placebo product look alike to serious health complications if a parenteral product is compromised.
2 Either of the above could cause a loss of confidence to the health professionals and the public, with the most serious effect on the economics of a company. Loss of confidence by anybody means loss of prescriptions, therefore loss of business. This could feasibly occur even though the product itself was OK, if the mass media were given a story of a drug being substituted. This does not have to be true, and the company can probably prove to the authorities that the product is not affected, but the medical professionals and the general public will be difficult to convince that the product is safe if anti-tampering and anti-counterfeiting measures have not been taken.
3 The product liability laws are such that if the company cannot prove that the goods that were bought/prescribed/taken by a patient are not its own, then the company is liable. How much easier to prove that the goods were not the company's if there are security features which are not to be encountered on an illegal pack.
4 There is a great fear of going public when one of these types of problem arises in the industry. When faced with this problem certain companies have introduced packaging measures, gone public and advertised the overt counter-measures to the health professionals. The net result was a rise in sales for 8–10 months after the event.
5 The fear of loss of revenue is always present in these cases. Facing up to the security problem and being proactive might in the short term cost money, but in the long term will protect the company revenue – look on it as insurance!

Key features

1 It is suggested that a 'horses for courses' approach be adopted, i.e. look at each problem individually and decide on the best answer. With cellulose-based materials the following might be considered: specialist inks (UV, photochromic, thermochromic), holograms, special prints, clever multicolour designs, watermarks, chemically marked paper and board, etc. Any of them could be appropriate, depending on the circumstances of the problem.
2 This is why clearly defining the problems and what is to be achieved is critical, so that any counter-measure designer is in a better position to defend the product. If the company doesn't have an expert in this field, there are consultants who will help identify problems.
3 What is wanted: authentication or deterrent, or both? This decision will change the way to approach the design.
4 This goes back to covert or overt features, depending on the answer to (3) above.

5 Assess whether there should be a single feature on one product pack or continuous throughout the product range, even though it may only be one or two product presentations that are being targeted.

The produced anti-criminal device must then have the following characteristics.

- Very difficult to counterfeit. While this may be obvious, some pharmaceutical products are like currency in some parts of the features world. Hence consider if currency without anti-criminal features built in would be accepted. The answer will be *no*!
- A device which needs no specific marketing monitoring i.e. self-policing after public education.
- An obvious deterrent to put off the criminal.
- The ability to maintain public confidence, through a form of label/seal with a distinctive secure print on it, advertised wherever advertising is allowed in order to get the public to check the goods on receipt.
- Relatively easy to introduce, for speed is of the essence. If the company is seen to be taking steps to protect its customers, then those customers will probably react favourably.

Which deterrent?

1 It is important to treat security as security features and not to be drawn into treating them as promotional. There may be a promotional angle that the marketing department can employ, but security of the system is paramount.
2 Simple design can be easily reproduced particularly with the advent of the colour photocopier. Review the design and include features that change when photocopied.
3 All markets will need consideration for both literate and illiterate patients, i.e. a company logo may not be a good idea as it might mean little to the end user.
4 Ensure that a secure supplier is chosen for the designs that are being considered. Although obvious it is often missed.
5 The format must be carefully chosen as it must fit in or onto production lines efficiently and securely. All staff must understand what is happening and how important is the (particularly) overt device. It may not be necessary to tell them about covert devices, as the less said about them outside the security circle the better.

Other considerations

1 The issue of public education will only apply to overt devices. Educate the health professionals first and rely on them and legitimate publicity to ensure that if the security device is not on the pack then questions are raised immediately. Speed is important, as the trail of the criminal will go cold very quickly.
2 The total security throughout all the supply, manufacture, and distribution chain

has been mentioned before. It has been known for a counterfeit supply of goods to be sold in original packaging material. If the counterfeiter can counterfeit goods he can do the same with individual company's purchase orders. Build in checks throughout the system, particularly the habit of making personal contact with people in the supply chain to check that orders received are genuine.

3 There are other controls, e.g. governments, patents, discarded production equipment. Ensure that the government being dealt with doesn't 'leak' any security secrets. Use patents whenever possible to protect packs. Ensure that on disposal of production or packaging equipment there are no tools, change parts or packaging materials belonging to the company that go with the old machines. It has been known for the criminals to get hold of them and reproduce counterfeit packs.

4 It is essential that a series of controlled changes of security feature be devised to keep ahead of the criminal. Change small features of the design, keeping accurate records of when and what was changed. This means that the company can take account of the latest in technology and keep the criminal guessing as to what might be done next.

Deterrent design and use

The type of deterrent

Is it to be label, a specially designed sealed carton or perhaps watermarked paper or board, chemically marked paper or board security inks, holograms etc.? In a large proportion of the potential methods of protection you will need to ensure that the device, print, etc. actually 'permanently adheres' to the substrate.

The substrates

The substrates could be any of the following:

1 cartonboard – what surface is to be used (cast coated, clay coated, uncoated)?
2 label materials – what paper surface (cast coated, clay coated, uncoated)?
3 cellulose films – with or without surface coatings?

The primary pack could also be glass, metal or plastic needing a security label, carton or overwrap.

The adhesion system

It is vitally important that the adhesion between the security system and the final substrate cannot be breached by any means without leaving conclusive 'easy to see' evidence. It is no use using a hot melt adhesive, which can be reheated and allows either a label to be removed and a 'pass off' put on or a sealed carton to be opened. More harm than good may be done with such a system.

Tests must be performed so that one can be satisfied that the above criterion is fulfilled all the time, throughout the distribution and storage chain, worldwide if necessary.

Additional items to be considered when designing security systems

1 The surface exposed to the public: This must be robust enough to withstand the scuffing and vibration of a normal pack in transit and use by the medical service. If overt it must have a bright clear image to attract the public.
2 Production systems of transferring the system to the final pack: Again this may seem obvious, but check carefully the feasibility of the laydown of final design onto the final pack. Also make sure that there is equipment to do the job economically and accurately. The design must have a high degree of accuracy and design procedures which cover the entire system of design production, including all aspects of producing and applying the design to the final pack.

The evaluation for end use must be thorough and realistic, e.g. fragile papers for seals might not apply well on machines and fracture in transit, yet be easy to open. The post-addition of additional security system packaging processes, e.g. overwrapping with securely marked or designed cellophane incorporating a tear band, can also be practical.

Costs

1 There are project and evaluation costs (non-recoverable).
2 Possible research costs into an adhesive, carriers and substrates to be considered.
3 The implementation and education costs to introduce a total security system (setting up and training everyone from designer to supplier and company staff).
4 The cost of educating health professionals and the public if the system is to be monitored effectively.
5 Audits of supply distribution system are needed to check system integrity.
6 Costs of additional material needed for the job.
7 Additional capital needed for machines.
8 Possibly additional staff to monitor and work in key areas.

What the project must achieve is total security of production, public education (particularly health professionals), security of supply chain, effective monitoring and keeping features updated.

Security in the packaging operations

The second form of security to be addressed is the one of ensuring that the printed word, as laid down by the competent authority, is securely translated onto label, leaflet or carton by whatever means, and affixed/placed on or around the correct drug container.

Although simple in principle, the industry gets it wrong time after time. Both the FDA and the MCA state that the single most common cause of a product recall is a mistake in 'labelling' or identification, commonly known as a 'mix-up'. A breach of internal security has been devised to prevent such a mix-up happening. Detailed below

are some recommendations on the best way to approach the problem when handling labels, leaflets and cartons.

There must be an integrated approach to the problem. Putting a bar code reader on a packaging line doesn't address the problem: it is an important addition to the system, but not the whole answer. Some additional points that might assist in the discrimination of one piece of printed material from another are as follows.

1 Distinction in colour layout and shape, especially when manual inspections are the norm.
2 Critical information should be in one colour, to minimise problems should one plate in the printing process cease to function.
3 Use ISO 9000 registered suppliers especially those used to dealing with pharmaceutical printing. Codes of practice are issued by the Pharmaceutical Quality Group of the Institute of Quality Assurance and linked to ISO 9002, specifically aimed at printing suppliers to the industry.
4 In-house systems, e.g. warehousing, should be set up in such a way as to minimise the risk of mix-ups, e.g. using discrete lidded storage bins.
5 All machines, packaging areas, printed material transport systems, etc. should be specifically designed to facilitate clearance of all the 'current' set of printed material.
6 Formally document all the checks that are carried out, ensure that the person checking has been trained and knows what to look for, knows what to do when a mix-up occurs and knows that the success of the system depends on their ability. Note: The results of checks must be recorded.
7 Increase the number of security safe positive accepting electronic/mechanical machines. Be careful in choice of systems and never forget that an integrated system that cannot be bypassed ensures the best security for your company.

The next few paragraphs work through the procedures for designing, approving, printing, supplying and using a label (but the same principles apply to all printed materials).

First, the copy must be written by a competent person, fulfilling copy guidelines laid down by the various regulatory authorities. This approved copy is then laid down as artwork which meet the demands of the pharmacy label/leaflet regulations, regulatory authority, company corporate identity and the container label design (size) which is best suited to the container and application system.

Note that the adhesive performance requires validation on the substrate being used, beyond the shelf life of the product and in the extremes of storage and use conditions predicted for the markets that are to be supplied with that particular label/adhesive/container application. A label that does not remain on its container is a security risk! The problem of adhesion failure occurs in cartons with the 'glue flap' being a vulnerable point, due to inefficient gluing on the folder/gluer, or the wrong adhesive being used.

When the artwork is completed it must be authorised for use by the originator, regulatory affairs, marketing, quality assurance and packaging to ensure that all the parameters are in accordance with requirements. The completed colour separated artwork should be sent, by the purchasing department, along with the remainder of the label specification, to an audited authorised printer.

The printer should be used to dealing with pharmaceuticals and have been audited to ISO 9002. This will ensure that all the correct procedures for line checking, physical separation, printing plate separation, line, make-ready, records, absence of gang printing etc. are in place and followed. Some companies call this GMP at suppliers. Colour proofs of each colour to be used should be returned for checking prior to the actual print run.

The artwork must include a unique part number (or item code) as the basis of identification, security and reference, which will change for every change to the printed component (however small). This identification is the key to all security traceability. This code may be represented by either alpha-numeric human readable characters or an associated bar code. This requires the capability for automatically reading either the bar code or the part number using suitable equipment on the printer's press and on packaging lines. The printed part number and/or the bar code should be unique and verified on the printed component artwork, in as many colours as the reading system is capable of reading to ensure that all the printing is there on the label.

If the printer is equipped to read either type of code then ensure that all labels are read, not just one line of codes on an unslit label reel, for example. This last reading should take place as the final act of inspection just prior to the labels being securely wrapped and sealed into their transit packaging ready for dispatch.

There are options to sample and test each delivery of labels or, through confidence in the printer, accept a 'certificate of conformance' and only randomly sample occasional deliveries. Labels, once delivered and accepted, should be stored in individual, segregated and secure closed bins, one bin per part number. They should be issued on a 'first in first out' (FIFO) system.

When quantities of the label are requisitioned against the packaging documentation, (based on the packaging specification) they should first be visually identified, counted and code checked (preferably by machine reading) and then signed off by the authorised store issuer. The materials are then securely held away from the packaging line area, awaiting use.

If the overprinting of LOT, BATCH, or EXP, etc. is to be carried out away from the packaging line then a similar separate loop of the checking procedure must be written and used.

When the order is ready to be packaged on a production line it must be preceded by a formal line clearance procedure and the material then carefully visually checked for accuracy of part numbers and accuracy of quantity.

The printed packaging material should be kept away from the packaging line machinery while the bar code reader or vision system code is set from an independent source of information, e.g. the pack specification or the works order document. The printed packaging material itself must not be used to set the checking equipment as this is a known GMP risk. With the advent of computer integrated lines it is possible to download the bar codes or number directly to the reading system, leaving the packaging line personnel the task of only aligning the reading heads.

The system of code reading must be challenged at regular intervals by feeding slightly wrong codes to it and confirming that they are not accepted. It is advisable for automatic systems on packaging lines to be 'positive accept'. This means that the line/machine will reject everything unless a positive accept signal is received from the sensor, which then 'opens' to 'pass' the package.

The parts of the packaging line between stations (open conveyer) should be covered so that the goods once passed through the automatic checks cannot, as far as is practical, be handled by operators again. This is because it has been reported that up to 70% of product mix-ups and adulteration in the whole British industry are caused with the supply company deliberately bypassing systems.

A mix-up leading to a recall means at least a loss of reputation through adverse publicity in pharmaceutical journals, loss of revenue, cost of collecting the recall and stock replacement and loss of confidence in the company.

Bar coding

This is an essential form of printing nowadays, usually in two forms for two totally different reasons as detailed below.

Non-security bar codes

These codes are used every day in the UK on the supermarket checkouts, and an extended version of them is used to control movements of goods in warehouses. They are being applied in the pharmaceutical industry, both on OTCs and, less obviously, on POM classified medicines. The OTCs are sometimes sold by the large supermarket chains, and therefore have been brought under the same rules and regulations as all other fast-moving consumer goods.

EAN (UPC) codes

These codes are 'market' codes designed to be used at point of sale, so that the inventory can be kept up to date to the minute. They are made up of thirteen numeric characters all with a meaning. Note that there are some eight character codes, discussed below.

The first two EAN codes denote the country of issue of the number, e.g. UK for the number 50. The last or thirteenth number is a 'check character' calculated to modulo 10, which completes the code, confirming that the code is genuine and has conformed to the number structure. The remaining ten are split into two groups of five. The first five is the number assigned by the Article Numbering Association (ANA) to the purchaser of the sequence of numbers, e.g. 50 99999 00001?. The 99999 is specific to company 'X' and no other company or supplier can use it without permission of the owner. The next group of five is the number that the owner assigns to the specific product name and size, e.g. in 50 99999 00001? the 00001 could describe a bottle of 50 Cureall tablets, 100 mg.

So the code tells us that it is UK issued, the code is owned by company 'X', the product is a bottle of 50 Cureall tablets, 100 mg.

To return to the last character, i.e. the check character, at modulo 10 it would work out as 9 so the full code reads 50 99999 00001 9, and thirteen meaningful characters.

Difficulties in printing these codes in a readable form resulted in a complicated series of specifications written by the ANA. These specifications have been somewhat modified in the light of improved readers, but if codes are to be read efficiently, follow the ANA guidelines.

To optimise the contrasts between the bars and spaces, it is preferable to print black onto a white surface. Print gain is a term used by printers to quantify the amount by which the printed bar is bigger than the plate used. Different printing processes and machines have different gains, so leave control to the professional printer to obtain the code films to the correct gain.

A normal 100% magnification EAN 13 code is exactly 37.29 mm long and 26.26 mm high. These dimensions include the quiet zones around the bars themselves. The magnification has been reduced successfully to 80%, and the height can be reduced or 'truncated' 16 mm overall.

There is an EAN 8 code. These are certain numbers in the code sequence in which the zeros can be ignored, giving only eight digits, thereby reducing the code width to 26.73 mm overall. The same rules on reduction and truncation apply.

Warehousing codes, e.g. EAN 128 or traded unit outer codes

This is a system of extending the basic EAN code to 'add on' data to the basic code, e.g. bar coded batch code and/or expiry date. In order to achieve this, 'addition identifiers' (AIs) are used to delineate where the additional part of the code begins and ends. This code is much larger than the primary EAN code, e.g. 123 mm long by a minimum of 27 mm high. As it would usually be printed onto cases or trays or tray or case labels, there is more space in which to accommodate the code. Figure 5.19 shows an EAN 128 code.

Interleaf two of five (ITF) codes

An alternative to the EAN 128 is an ITF code. This is a bar symbology which allows numeric characters only (i.e. 0–9 inclusive) to be portrayed as a series of thick and thin bars and spaces. Using our EAN number we have to add a zero to the front of it, making it a fourteen numeric code. The overall size of this code is 159.828 mm across (remember this is totally inclusive of all the margins) and 48.1 mm high. Figure 5.20 shows an ITF codes. Again, supplementary information can be added to this code.

Figure 5.19 An EAN bar code (not to size)

Figure 5.20 An ITF bar code (not to size)

Other codes

Interleaf 3 of 9 or code 39 has been used, particularly in some European markets, as a means of helping to control the reimbursement of drug costs, by electronic reading means, to the patient. It is similar in structure to ITF, but allows the full alphanumeric range of characters to be used.

The Health Industry Business Communications Council (HIBCC) code was originally developed in the USA to establish its own codification structure for the full range of health sectors, but has come to be used mainly within the US hospital system. In the UK, HIBCC is also called the Health Industry Bar Code Convention by the Article Numbering Association (ANA), and also the Health Industry Business Code Council. In the Netherlands it is known as the Health Industry Bar Code (HIBC). The code is composed of five elements:

1 1st character '+' denotes HIBCC
2 2nd to 5th characters denote the manufacturer or proprietor of the product at international level – 'E' as the second character denotes Europe
3 6th to 18th characters (variable in number) identify the product (could contain an EAN code)
4 19th character denotes the level of packaging, e.g. unit of sale, pallet, case
5 check character in a maximum of the 20th position calculated at modulo 43.

The code can be represented in any of the following standard bar formats: code 39, code 16K, code 49, and code 128.

Other codes coming onto the market are answering the problem of more and more information being required by the warehousing, wholesale and retail pharmaceuticals trade. It may soon be possible by using an individual bar code to be able to trace at least every batch of product right down the chain to individual patients.

Security codes

These are usually called 'Pharmacodes'. This is a misnomer, as the term 'Pharmacode' belongs as a trade mark to one company only. They are in the form of thick and thin bars of dark print on a light background. The thick and thin bars are of specified dimensions and give the effective signal of '1' and '0' respectively when moved past a scanning head. The 1s and 0s are then compared with a pre-loaded code and the result passes or fails.

The pre-loaded code can be entered in one of two ways. It can be loaded as a number, e.g. 112. This is then set by the decoder as 110001, i.e. to read thick, thick, thin, thin, thin, thick. The other method is to set the code directly by pressing usually the thick bars on one side of a decoder and the thin on the other side. Whichever method is used, the information for the code reader must be obtained from a controlled source, e.g. pack specification or works order.

The purpose of the code is to provide an affordable easy machine-readable form of the item code (part number) and prevent mix-ups at any point in the system. The mechanism by which this is achieved is by the code moving past a combined light source and sensor. The reflected light generates a peak voltage over a short time for a

thin bar and about times three for a thick bar. In order to prevent mis-rejects the contrast between the background and the bars must be as great as possible. The background should always be white, but there are many problems with white: shine, uncoated paper, print show-through, etc. This means that the ground voltage (that voltage from which the spike is measured) might *not* be zero volts. Figure 5.21 shows high ground voltage.

Ground voltages up to as high as 0.9 V have been experienced. The reason for this is that the light source is constant (over a short period, even though it might decay in value over months). If it is calibrated to zero volts on the whitest source available, e.g. standard white tile, calcium carbonate block, any white darker or less reflective will not register zero volts but a positive value as the conditions controlling the detector must remain the same for the duration of the testing period, i.e. the production run. Again if the contrast between the bars and the background is poor, there is a greater chance of a misread.

There are a number of competing systems on the market, all doing approximately the same job and being successful provided all the systems governing the running of these bar codes are themselves secure.

The advent of vision verification systems is now competing with bar codes in the security field. These systems read the preprinted part number and either compare it with a pre-loaded independently obtained code or the whole system can be fully computerised and the reader told what component to expect and read as it passes.

Conclusions

This chapter has covered one of the oldest yet most useful of pharmaceutical packaging materials which has survived the onslaught of plastics and, being biodegradable, has considerably contributed to the store of natural materials that can be used for product protection. The chapter has also included sections on security, since papers (in

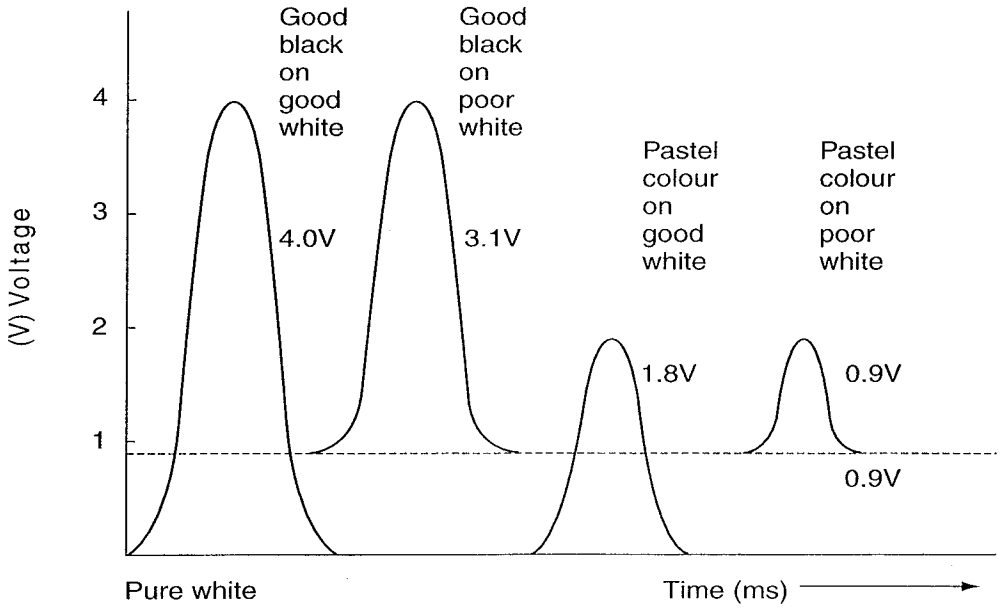


Figure 5.21 High ground voltage

particular) are frequently involved to assist security, a key example being the printing of bar codes – both for security and for efficient stock control and movement tracing.

The objective of the chapter is to provide a reasonably detailed amount of information on this very important and varied group of packaging materials, widely used in the pharmaceutical industry.

The best known applications of paper and board are labels, leaflets, folding boxboard cartons and corrugated cases. Without these, packaging or products would be more expensive and difficult. Please also note some of the 'rarer' or more hidden uses of cellulose, e.g. cellulose film, layers in laminates.

The major problem discussed in this chapter is not in the technologies of cellulose materials but in the question of security. Companies can be made less competitive by non-adherence to security rules. The two major areas are mix-ups in the production, delivery and use of labels, leaflets and cartons and the more modern phenomenon of passing off counterfeit drugs.

The future is bright for cellulosic materials, due to the more detailed requirements needed for information – particularly the expanded EU leaflet requirements.

On the environmental front, the success of Scandinavia (in particular) in managing its forests in an eco-friendly manner and cutting pollution of the environment during the manufacture of paper and board has countered many of the environmental objections to the paper- and board-making industries. Trees, grasses, etc. are renewable and as such preferable, where they are an economic alternative to petroleum-based materials.

In short, paper board and other cellulosic materials have a major future in this industry.

Appendix 5.1: Testing of paper and board

It is fundamental to a good understanding of paper and board that the testing regimes that can be used and the specific tests and the reasons for using those tests are appreciated.

The reason for testing is to gain information, thereby ascertaining the acceptability of the test piece in comparison with a specification. That specification should be drawn up so that if all results pass, the material is fit for the purpose that it is intended to fulfil. All tests must be relevant to the use of the material, and must be understood by all the parties involved. This need has led to a series of standard tests: British BSI, ASTM, etc.

Testing conditions have also to be defined, as paper and board are very susceptible to humidity and temperature changes. It is therefore essential that the test pieces for paper and board are in fact 'conditioned' so that the tests can be carried out under 'standard' conditions, thereby giving fair comparisons. Those conditions usually quoted are:

- temperature – 23 °C ± 1 °C (BS 3431 and ISO 187)
- relative humidity – 50% ± 2% (BS 3431 and ISO 187).

Note that there is one major exception to this rule – moisture content of the material. How to test is simple. Just follow carefully and accurately the standard test methods. Note also that test pieces should be cut accurately for tests where dimensions are criti-

cal. If one is using specific test instruments it must be ensured that the instrument is properly set and calibrated (if necessary) prior to the commencement of a test.

The reporting of results should include at least the following data:

1 The test method used, e.g. Grammage BS 3432:1980 (always specify the date of the method, as the BS and all the other standards are routinely updated)
2 the instrument used (its reference no.)
3 the test conditions
4 the size of the test piece, where relevant
5 the number of replicate tests per sample
6 the units used – this is very important, as a number of different units are used in reporting (both the SI and Imperial systems are in use together)
7 any other facts relevant to the test piece, e.g. discoloration of a white test piece on moisture content testing.

Appendix 5.2: General tests for paper and board

1 Sample conditioning of paper and board: BS EN 20187; 1993, ISO/R187 1990. This is the way to condition any test piece prior to testing by the appropriate BS method.
2 Pre-test procedures for paper and board. BS 3430:1986 (91) ISO 186 (1985) sets out the methods of obtaining a representative sample of the paper or board for testing in order to ensure that an average can be taken and compared with the original specification.
3 Moisture content of paper and board is measured according to BS 343:1986 (91) ISO 287 (1985). All papers and boards can be covered, i.e. all calipers of paper, chipboard, pasteboard, folding boxboard, solid and corrugated fibreboards provided there are no substances that will escape at the temperature specified for the test.
4 Folding endurance: ISO 5626:1993 describes four methods, i.e. Köhler Molin, Lhomary, MIT and Schopper. These various instruments fold the test piece back and forth through a specified angle until rupture occurs. Applies to all forms of paper and board, but there may be different instruments for different boards.
5 Density of paper and board: BS 4370:1973–1991. These are methods of test for rigid cellular materials. There are fourteen different test methods for aspects of the physical properties – dimensions, apparent density, compression strength, dimensional stability, cross-breaking strength, shear strength, shear modulus, thermal conditioning, water vapour transmission, tensile strength, friability and coefficient of linear thermal expansion.
6 Methods for determining air permeability: BS 6538:1985 (95) ISO 5636 (1984). Permeability is the mean airflow through unit area under unit pressure difference in unit time, under specified conditions, expressed in $\mu m\ Pa^{-1}\ s^{-1}$. Beware as there are several types of instruments that can be used and the results may be quoted as, for example Bendtsen. Note that this is only a valid test in what is termed the 'medium air permeance range'. This is important when you are using lightweight uncoated papers on machines that have a vacuum pick-up system.

7 Methods of test for the assessment of odour for packaging materials used for foodstuffs: BS 3755:1964 (71) This particular test has been deleted from the latest lists of the BSI.

8 Grammage or substance: BS 3432:1980 (90) ISO 536. The weight of material per unit area of the sample, usually confined to papers and boards, excluding the manufactured corrugated sheet but including the component parts of the corrugated sheet. Units are usually g/m^2.

9 Paper caliper BS EN 20534 1993 ISO 534 1988. Single sheet thickness between one surface and the other. Measure over a specified area and under a specific static load by means of a high precision dead-weight micrometer.

10 Tensile strength, both wet and dry: BS 4415:1992 ISO 1924 (1992). The maximum tensile force per unit width that a paper or board will withstand before breaking. The stretch at break is the measured elongation at the moment of rupture of a test piece, when tested under specific conditions.

11 Tear strength either across or along the grain: BS EN 21974 1994 ISO 1974, 1990. The mean force required to continue the tearing of an initial cut in a single sheet of paper and four torn together through a fixed distance using a pendulum to apply the tearing force. The work done in tearing the test piece is measured by the loss of potential energy of the pendulum. This obviously can be done either across or along the grain. The scale is calibrated to indicate the average force.

12 Burst strength, both wet and dry: BS 3137:1972 (95) ISO 2758, 2754, 3689. The maximum uniformly distributed pressure, applied at right angles to the surface, that a test piece of paper and board will stand under the conditions of the test. The test piece is placed into contact with a circular diaphragm, the test piece being clamped around the periphery, but free in the centre to bulge with the diaphragm. Hydraulic pressure is applied to the diaphragm, bulging it until the test piece bursts. This denotes the general strength of the test piece.

13 Puncture resistance: BS 4812:1972 (93) ISO 3036. A triangular pyramid puncture head is attached to a pendulum. It is released to swing onto a test piece. The energy required to force the puncture head right through the piece, i.e. to make the initial puncture and to tear and bend open the test piece, is measured.

14 Stiffness of thick papers and boards: BS 3748:1992 ISO 2493 1992. This is the degree of resistance offered by a paper or board when it is bent under specified conditions.

15 Ply bond of boards: TAPPI 403. This test ensures that the various plies of a multiply board have bonded together enough to ensure that they will perform satisfactorily in service. This test applies not to boards that use an adhesive as the bonding agent, e.g. pasteboard, but to those in which the plies are joined by heat and pressure only.

16 Creasability of boards: BS 4818:1993 described the method of determining the creasing quality of cartonboard within the range of 300–1000 μm. This is important to the packaging line, since if the creases are not correct and do not assist the carton erection, the cartoning machine will not function correctly.

17 Cobb test: BS EN 20535 1991 ISO 535 1991 for water absorbency. This measures the mass of water absorbed by 1 m^2 of the test piece in a specified time under a head of 1 cm of water. It is determined by weighing before and after exposure to the water, and usually quoted in g/m^2.

18 Rub resistance: BS 3110:1959 (94). This is the resistance of a printed test piece to withstand rubbing against either another similar printed test piece or against a plain test specimen. The objective is to see that the ink/print has cured and will not scuff or smear in service.

19 Pick test: BS 6225:1982 (95) ISO 3782, 3783; also called the IGT test (Instituut Voor-Grafische Technical TNO Amsterdam). It is a small printing unit which allows one to print a small strip of paper under controlled conditions. A specified amount of a special oil is added to the printing system and printed onto the test piece. The surface is then examined for signs of disruption (otherwise known as 'pick' in the trade). Results are correlated from a time calibration table. It is essential that the paper surface does not pick when printed, as pick means that some of the deposited ink may be lost from the surface, and in extreme cases the paper surface may start 'dusting'. This means that the sizes and binding agents are not working and the fines of the fillers and opacifiers are loose on the paper surface.

20 pH, chloride or sulphate by BS 2924:1992 Parts 1–4, ISO 6588, 6587, 9898, 9197 or DEF STD 81–1. These factors are tested on a aqueous extract of the test piece. The acidity or alkalinity (pH) can help the life of the paper or board, as the natural pulp is slightly acidic and goes dusty and powdery in 50–70 years. Most papers today are neutral. Sulphates should be >20 mg/kg of sample and chlorides can vary with the cleaning processes of the pulp. The conductivity of the test piece can be also be determined in the aqueous extracts.

21 Roughness/smoothness: BS 4420:1990 (95) ISO 8791 (Bendtsen) or BS 6563:1985 (90) (Parker Printsurf). This is a measure of the extent to which a paper or board surface deviates from a plane and involves the depth, width and number of departures from that plane. This is very important for the 'printability' of the paper.

22 Brightness to BS 4432:1980 Parts 1–4 (95) ISO 2469, 2470, 2471. This is the reflectance factor measured at the effective wavelength of 457 nm with a reflectometer having specified BS characteristics. Note again that this might be quoted with a manufacturers name behind it, e.g. Technibrit.

23 Opacity to BS 4432:1980 Parts 1 and 2 (95) ISO 3688. This is the ratio, expressed as a percentage, of the luminous reflectance factor of a single sheet of the paper with a black backing to the intrinsic luminous reflectance factor of a layer, or pad, of the same paper which is thick enough to be opaque.

24 Dennison wax test. This is an older test that was largely replaced by the IGT test, but is still used by some older paper and board mills. It consists of a series of specialised waxes, which are heated to a specified temperature, placed on the paper surface, left to cool, then removed. The wax formula 'picks' dust and debris from the surface, and the wax formula number that shows the picking indicates the degree of ink viscosity (or stickiness) that the particular paper will tolerate without risk to the print.

25 Wet burst strength: BS 2922 (PT1):1985 (95) ISO 3689. This is used for determining the wet bursting strength of any paper or board following immersion in water.

26 Wet tensile strength: BS 2922 (PT2):1984 (95) ISO 3781. This is a method of determining the wet tensile strength of any paper or board after immersion in water.

27 Ash in paper and board: BS 3631 : 1984 (94) ISO 2144. This is a method of determining the ash content (i.e. the inorganic matter left after controlled combustion) in paper and board. The method is suitable for most loading materials and coating pigments.

28 Detection and estimation of nitrogenous agents in paper: BS 4497:1969 (93). This standard describes the problems involved with the nitrogenous treating agents for paper and gives qualitative and quantitative methods for use with certain agents used in paper treatment. It applies only to substances that have a strong affinity for acid dyes.

29 Ink absorbency: BS 4574:1970 (91). This gives recommendations for the determination of the ink absorbency of paper and board by K & N ink. Applies to both paper and boards to be printed by the litho gravure or letterpress process.

Appendix 5.3: Specific tests for cartons

1 Compression to BS 4826 (PT3):1986 ISO 2234. This standard lists three methods which can be used to assess the strength of the erected package, thereby estimating the degree of protection that it confers on the contents. This is particularly useful for products with no inherent strength in one plane or another, e.g. strip packs.

2 Carton opening force. The method that is often used is to hold the flat carton, as delivered, by its creases between thumb and first finger and press. The carton should spring open into the 'square' position without a need for unreasonable force. If the carton does not spring open, or buckles in on itself, then it is reasonable to assume that those particular cartons will cause problems on any cartoning machine. This can be measured by instrumentation.

3 Coefficient of friction: BS 2782 (PT2):1983 method 824A or ASTM D1894. Both the static and kinetic coefficients of friction are determined by sliding the specimen over itself under specific test conditions. As discussed earlier, the finish of board can differ dramatically. Compare a corrugated case with a test liner and with a Kraft liner, or a cast coated or varnished carton with an uncoated carton. Where machines are involved there could be problems with different coefficients of friction, since friction is used as part of the control on carton and corrugated case erecting machines.

4 Crease stiffness: BS 6965:1988 (94). Also called the crease recovery test. This involves testing a carton board piece and folding it through 90°. It will then try to recover its former position when the bending force is removed. The increase or decrease in the inherent board stiffness after folding is measured. As with all tests involving forces, the test should be performed both along and across the grain.

5 Joint shear strength: BS 5350 Part C5 1990. This is a method of testing the glued lap seam on the side of a carton for strength of the adhesive, using a tensile testing machine. This quantity is important in ensuring that the correct adhesive for the cartonboard finish has been used, and in the right quantity. Another problem that frequently occurs is skewed lap seams. This means that the carton is out of true, and will not erect on a machine.

Appendix 5.4: Specific tests for corrugated

1 Flat crush resistance test for corrugated board: BS EN23035:1994 ISO 3055 1982. This only applies to single wall and single faced corrugated. Test pieces are placed perpendicular to the paper surface between two platens, which move together until the fluting collapses. Measure the maximum force obtained.

2 Edge crush test for corrugated board: BS 6063:1992 ISO 4097. A rectangular test piece of corrugated FBB is placed between the platens of a crush tester with the fluting perpendicular to the platens. Compress until failure, measuring the maximum force. Useful in assessing stacking strength

3 Ring crush test (corrugated): TAPPI T818 1987. A compressive force is exerted on a specimen, held in a ring form in a special jig and placed between two platens of a compression machine. The upper platen approaches the lower platen at a uniform speed, until the specimen collapses. This correlates with the edgewise compression strength of the paperboard or fluted medium.

4 Flat crush of corrugating medium (Concora test): BS EN:ISO 7263 1995. Paper is fluted by passing between heated rollers and then formed as a single faced corrugated board using a pressure sensitive tape as the liner. A crushing force, perpendicular to plane of the paper, is applied and measured at the point in time the paper crushes.

5 The specific apparatus and detailed procedures for the measurement of corrugated board caliper are contained in BS 4817:1972 (93) ISO 3034. This obviously differs from the other methods already described in that the corrugations could be crushed when using calipers or any other form of measuring equipment.

9

FILMS, FOILS AND LAMINATIONS (COMBINATION MATERIALS)

D. A. Dean

This chapter covers single layer, multi-layer and combination materials found as films, foils, laminations, coextrusions, coatings, etc.

Single ply materials

Although a proportion of 'flexibles' are multi-layer materials, a number of flexible packaging materials are found as single plies. Single ply materials are found in the form of paper, and those plastics which either do not require an additional coating to achieve a heat seal or can be employed as a direct wrap. Examples of these include various grades of polyethylene and plasticised PVC, which have to be high-frequency welded. A few foils may be used uncoated. (Note that most foils are varnished, lacquered or wash coated to improve scuff resistance or to assist print key.) Other single (monolayer) plastics may also be found as wraps which are restrained by a secondary feature (such as a tie or tape) or rely on special properties, e.g. cling films, for their retention around a product. Cling films, skin wraps, etc. involve such materials as thin gauges of plasticised PVC, Surlyn ionomer, modified grades of low-density polyethylene and Saran (PVdC) copolymers. Thus the use of single ply materials should not be ignored, particularly as these are frequently seen as being more environmentally friendly (i.e. multilayer materials are always more difficult to recover or recycle). Of the single ply materials listed above, paper needs special mention since it was one of the earliest wrapping materials and still has significant use worldwide.

Polyethylene, as LDPE, LLDPE or a mixture or blend involving combinations of LDPE, MDPE, HDPE, EVA, etc., finds a wide usage in bags, sacks, sachets, overwraps, shrink wraps, stretch wraps, etc. Most deep freeze packs, for example, use LDPE or an LDPE mixture which is produced from a reel on a form fill seal type machine. However, as many of these packs are up to 100% printed, even ink of 2–5 μm could be considered as a separate layer which modifies some of the physical and chemical properties. As all polyolefins need a surface (oxidative) treatment to ensure a good print key, this or any other surface treatment process may further modify the film properties.

Another use of single ply plastics is found in window cartons (cellulose acetate, polyester, regenerated cellulose, OPP, PS, etc.) and in plastic cartons (PVC). The use of thermoformings as bubble and blister packs for toiletries, pharmaceuticals, etc. and

trays, soaps, etc. frequently falls in a grey area as to whether they are forms of flexible or rigid packaging. Frequently the final category is decided by the lidding material.

As mentioned earlier, foil can be found as a single layer material and applied as an overwrap using the dead fold characteristics of soft foil. Thin foil can be partly strengthened by embossing, but due to its extensibility it tends to demand an additional support ply.

Since it is sometimes difficult to identify whether a material is a single ply or a multiple ply, most students should examine a range of thinner materials to try to establish any constructional differences. However, many apparent single ply materials, e.g. biscuit, confectionery and chocolate (bar) wraps are actually multi-ply materials: these frequently use a type of OPP (oriented polypropylene – especially the pearlised variety) where a special (coextruded) outer and inner heat seal ply has been added. MAP and CAP food materials are likely to have an 'anti-mist' coating.

Finally, the use of recycled paper/board requires mention since continuous recycling leads to shortening of the fibres and a steady reduction in physical properties.

Although only a few single layer materials may appear to be used for pharmaceuticals, the largest use is likely to be found in shrink and stretch wrapping. As these may confer some barrier properties as well as acting as a means of collation and tamper-evidence, they are expanded on below.

Shrink wrapping

If molecular orientation is introduced into a plastic, by extension under certain conditions, it will undergo deorientation or shrinkage, back to roughly its original dimensions, if subsequently reheated to the temperature above that at which it was earlier oriented. This property is normally achieved in a film by either the stenter process or the extrusion lay flat tubular process. The stenter process, which usually involves extrusion-casting, has one advantage in that the oriented film can be heat set (somewhat similar to annealing), thereby giving an improved degree of dimensional stability (reduces deorientation when heated). It is, therefore, more widely used for heat sealable wrapping films which are not used via a shrinking process. In both cases the orientation operation occurs at a temperature just below or above the softening point of the material in question. The most common shrink materials are low density polythene, polypropylene, polyvinyl chloride or ethylene vinyl acetate copolymers.

As the name implies, shrink wrapping utilises an oriented plastic which, when placed around an object, can be heated to a temperature where it returns, or tries to return, to its original dimensions – thereby forming a tight shrink wrap. Shrink wraps may be employed to wrap individual products, cartons, groups of cartons, packs in trays, etc. They can thereby be used to add to individual protection, act as a tamper-evident feature, improve certain barrier properties, act as a waterproof covering, or as a means of collating and protecting a number of items.

The shrink wrap material may be applied in two basic ways.

1 As a *full overwrap* – to provide a total wrap – where all of the item or items are enclosed by a film, i.e. an all-round wrap.
2 As a *sleeve overwrap* – a sleeve wrap where the ends of the longer direction are open and therefore exposed.

The shrink wrapping process involves several functions:

1 placing the film around the item(s) to be shrink wrapped
2 sealing the film
3 passing the unit through a heated (shrink) tunnel, arranged to give uniform heating, and avoiding hot and cold contact areas.

To create a total wrap, an L sealer or a fold-heat seal is usually required, while in the case of a sleeve wrap, a single longitudinal seal is used. The method of sealing is usually via a heated wire which may be used in conjunction with an impulse and pressure system or an impulse and radiant heat system.

While orientation gives a broad improvement in physical and chemical properties of plastics, i.e. improvements in clarity, tensile strength, inertness and reduced permeation to gases (oxygen, carbon dioxide), moisture, etc., these properties are lost once deorientation occurs.

Shrink films

Low-density polyethylene

Oriented LDPE is the most widely used of the shrink wrap materials. It has good strength, toughness and tear resistance. It also has good low-temperature resistance, hence is suitable for parts of the world with well below zero conditions. LDPE is a reasonable moisture barrier but is a relatively poor oxygen and carbon dioxide barrier.

Special grades of plastic need to be selected for satisfactory shrink films which need to cover a wide range of shrink ratios (machine versus cross direction). In the case of lay flat tubing, the ratio is achieved by bubble blow-up, rate of draw-off and other factors. Grade factors which are of special significance include density and melt flow index. Higher density materials have poorer puncture, impact and seal strength but have a higher shrink strength and lower percentage shrink. The melt flow index also relates to shrink strength, i.e. a lower MFI gives a higher shrink strength.

The incorporation of vinyl acetate into LDPE provides a softer material which shrinks at a lower temperature. Shrink temperature is around 108–115°C for LDPE.

Oriented polypropylene

This material offers high clarity, very good tensile strength and has high shrink energy. This means it should not be used on flimsy materials (e.g. light weight cartons) as this can give rise to distortion. OPP requires a higher temperature for orientation, hence needs more heat to give controlled shrinkage. However, PP has a much narrower deorientation range than LDPE and can prove more difficult to heat seal effectively. The shrink temperature is high, around 130–140°C.

Polyvinyl chloride

Both unplasticised and plasticised PVC shrink films are available. Plasticised material feels softer to touch, is less brittle, has a lower softening point and shrinkage.

Unplasticised PVC has good surface gloss and clarity, but tends to be brittle, of poor impact strength and rather easy to tear once initiated. Shrink temperature is around 90–100°C.

Multi-layer materials

Multi-layer materials are used for special reasons, e.g. where an already shrink wrapped material has to undergo a further (secondary) shrink wrapping operation. This means that a different material is essential to prevent sticking, e.g. coextruded LDPE/EVA/PP where the PP inner layer will not stick to LDPE. Usage of multi-layer materials is limited.

Shrink wrap applications

Pallet shrink wrapping

This can be achieved using a preformed shroud (or hood), two single webs or a pre-cut tubular form from a lay flat reel. In each case the perimeter should only exceed pallet size by around 7–12%. LDPE is the most widely used material, of 75 to 200 μm gauge.

Transit wrapping

This may involve the collation of packages of similar or variable shapes. The most popular form uses either a direct shrink wrap (e.g. multi-packs) or a shallow tray which is usually made from corrugated board or solid board. Thermoformed plastic trays with a formed base (and/or a lid/cover) are also widely employed (e.g. bottles and aerosols). These systems offer restriction to pilferage and due to the see-through nature of the film may avoid the need for external labels. (Internal labels may be necessary if stock is controlled via a bar code.) Although LDPE has the major use, PVC may occasionally be used for its higher clarity. Gauges of 25 to 100 μm are usually employed.

Display wrapping

Shrink wraps may be used on a number of materials (products) and packed items (e.g. cartons) to maintain cleanliness, to prevent or restrict pilferage or access to the product, to provide good surface gloss, etc. PP and PVC are used for their excellent clarity and sparkle. PP, however, has a narrower deorientation range and higher temperature than LDPE and PVC, hence may be more difficult to control. LDPE is available in high-clarity grades and has a 'soft feel' (similar to plasticised PVC). Gauges of 25–40 μm are widely used.

In the above applications, either a sleeve wrap or a total wrap may be employed. The total overwrap has the advantage of excluding dirt and dust; it can also be a significant barrier to moisture. In the case of the total wrap, holes are initially required to allow any air to escape.

Reel materials

Reels may be unwound and used in different ways. L sealers usually use a single reel of a centre folded film.

In other systems two reels are used and these are welded together by a transverse sealing jaw. This is presented as a curtain to a moving product, so it is then enveloped by the curtain.

Shrink terminology

- Percentage free shrink – ratio measured in both the transverse (cross) and machine directions of the shrunk film versus its original dimensions.
- Shrink ratio – ratio of machine direction to cross direction shrinkage.
- Shrink energy – energy built into the film by orientation which is subsequently released during shrinkage.
- Retained shrink – shrink retained when film is tightly wrapped around an article (after shrinkage has occurred).
- Shrink strength – various oriented materials have different shrink energies, hence forces applied to the enveloped item vary.
- Film slip – this is the reciprocal of the coefficient of friction.

$$\text{Film yield} = \frac{\text{area of film } (m^2)}{\text{weight of film (g or kg)}}$$

Stretch wrapping

Stretch wrap films are elastic in nature, hence possess a memory. The film must have high elasticity, and once in position must not relax and lose tension (i.e. become loose).

Film materials

Linear low density polyethylene (LLDPE) is the predominant stretch wrap material, but films based on LDPE combinations, EVA and plasticised PVC are also found. Stretch materials can be produced by various processes, i.e. from lay flat tubing, casting, etc. The latter process gives orientation in the machine direction which assists stretch in the wrap around direction. Cling properties required for grip may be achieved by incorporating a cling additive or coextrusion to the outer surface(s) of a more tacky material, e.g. EVA.

Use of stretch films

Stretch-materials are usually applied in one of two ways. In the first of these, the material is extended by tightly wrapping it around an item or group of items in such a way that stretching occurs between the item and the unwound reel, i.e. it is extended at the point of application.

This process usually relies on the item or load rotating (e.g. a pallet) while the film reel is held vertically so that it can operate with a spiral motion. With simple hand

wrapping, the operator walks around the item, applying layers which overlap in a spiral motion. Since these processes can only be applied to the sides of a pallet, a top sheet inserter may be employed to cover the top. This is then held in position by a stretch layer. The level of stretch achieved depends on the material employed, the uniformity of the load and the process employed. If a material is over-stretched i.e. the natural yield point is exceeded, the film becomes less puncture resistant and may break. Limits of stretch by these processes are around 50–60%.

Cling films usually can be categorised under stretch films.

In the second method, material is mechanically pre-stretched before application, using materials that can be stretched over 100%. This is partly because a pre-stretching process has a better control over the stretching operation, which occurs between two rollers placed near the reel of film. Since these two rollers are fitted with variable gears, the degree of stretch can be both controlled and altered. The width of the reel is maintained during this stretching process, which alters the properties of the film and increases the yield (lowers material used, hence reduces material cost). Improved methods of stretching are now available and can stretch the material three fold, i.e. up to 300%, by using motorised units.

Applications of stretch wrapping

Pallet stretch wrapping

This is the most popular use of stretch wrapping, hence it is frequently compared with shrink wrapping in terms of advantages and disadvantages. All the methods previously outlined are employed with LLDPE being the predominantly used material, in conjunction with a pre-stretching operation. Gauges of 15 to 50 μm are usually employed.

Stretch bundling

Stretch bundling can apply to single products or packs, or groups of somewhat irregular loads. The film is normally stretched around the 'product' to give a tight wrap with up to 25% stretch. The material finishes with an adhesive or heat seal. Modified LDPE, VLDPE or EVA are normally used.

Other applications for shrink and stretch materials

Skin packaging

Skin packaging employs material properties which are similar to stretch wrapping in that the film employed may stretch in the process. However, heat and vacuum are usually employed, hence stretch may also approach an orientation operation. In terms of material, Surlyn ionomer and Saran may be used as well as the more conventional materials.

Shrink sleeving

Shrink sleeving made from lay flat tubing or welded tubing is widely used as a tamper-evident overwrap to enclose either a whole container or neck and closure. Materials

include PVC, polypropylene and polyester. Shrink sleeving can improve container barrier properties or light exclusion.

Cling film

Cling films are usually elastic-type materials which will undergo stretch. The originally used cling films were based on plasticised PVC and PVdC (Saran) films. More recently, LLDPE and LDPE, particularly as mixtures with other plastics, are being widely employed.

Shrink versus stretch wrapping

Each of these has advantages and disadvantages which are given in Table 9.1. Further comparisons could be made against fibreboard outers which offer advantages in stacking strength and cushioning properties. This is often more important during transportation as in many warehouses stock is racked and not stacked two or more high. Both shrink and stretch wrapping offer significant cost savings over fibreboard if circumstances permit their use.

Table 9.1 Shrink versus stretch wrapping

Shrink	*Stretch*
Equipment more expensive, involves sealing, wrapping plus heat shrink tunnel.	Lower cost, frequently smaller.
More energy: orientation plus heat energy to shrink.	Less total energy stretching, no heat.
May not be suitable for heat sensitive items.	Can even be used under cold (refrigeration) conditions.
May distort under transit conditions.	Retains load more tightly.
Shrink in shrink wrap (two or more) may stick together.	Virtually no film-to-film sticking.
Shrink film will take up uneven contours more readily.	Will create areas of higher tension due to irregular products.
Needs different film widths for a range of sizes.	Needs fewer reel widths for a range of sizes.
Can be printed using distortion printing where shrinkage is uniform and well controlled.	Easier to print as stretch is mainly in one direction.
Can provide better weather protection etc., particularly if a total wrap.	Less protective, may not be totally waterproof.
Adds to general protection (climatic).	Lower climatic protection.
Uses (generally) more film (heavier gauges).	Uses less film.

Combination materials covering flexible and rigid applications (or multilayer materials)

The above heading has been selected to include all variants which may be now used for both flexible and rigid applications. Whereas previously these may have been introduced under 'flexibles', 'film, foils and laminates', etc., the use of new technology such as coextrusions, metallisation and different coating techniques has produced some confusion as to what terminology should be employed, so the word 'multi-layer' may be more appropriate.

General properties

Basically these combinations employ a range of materials to achieve certain specific functions, i.e. to offer:

1 support to other plies
2 barrier properties
3 heat sealing or sealability, including cold sealing
4 ease of decoration or printing
5 reflectivity when desirable
6 a means of bonding two or more materials together
7 ease of opening
8 security in the form of child-resistance, tamper-resistance or tamper-evidence
9 improved machine ability or improved machine performance
10 cushioning
11 acceptable cost
12 minimal use of resources (renewable or non-renewable)
13 suitability for disposal.

Certain materials, depending on caliper, grammage, grade, etc., may serve several functions. It is therefore only possible to indicate the primary function of some materials.

Base web materials

Base web materials may consist of or include:

1 paper
2 regenerated cellulose
3 plastic film
4 aluminium foil
5 coatings
   - protective
   - heat seal or cold seal
   - surface appearance or texture (may also be protective)
   - metallisation
   - adhesive or tie
   - waxes – surface or wax impregnation
6 plastic coextrusion and extrusion.

General construction – specifying

It should be noted that combination materials are specified (from the outside inwards) by weight (g/m^2), gauge or caliper. Most are made as a 'reel'-fed operation and into 'sheets' if required.

Printing processes

Printing may occur before, during or after 'combination' and then the material is covered by a clear coating or a clear film. Although virtually any printing process could be employed, flexography and gravure are the main contenders for reel fed materials. More recently offset lithography has increased in use.

The base web materials and the role they may play are now covered in greater detail.

Paper

Paper may be made from mechanical or chemical pulp. The latter is preferred due to its purity, white colour (if bleached), strength, slow ageing, etc. Paper is usually below 300 μm in thickness; above this caliper the material falls into a 'board' or 'carton' category.

The advantages of a paper ply are as follows.

1 Basically of a non-toxic origin (be aware of 'dioxin') – starting with relatively pure cellulose fibres and water.
2 Relative low cost with ready availability. (Wood is preferred origin, but other sources are used.)
3 Available in a wide range of types, substances, finishes, etc., depending on fibre length and the method of finishing. Typical papers include:

- opaque glassine
- vegetable parchment
- MG sulphate
- tissue
- MG bleached Kraft
- super-calendered (SC) bleached Kraft
- coated papers
- glazed imitation parchment (GIP).

4 Various additives can be incorporated at the beating, refining or finishing stage, i.e. the paper can be modified to suit specific uses (improve opacity, printability, etc.).
5 Can be printed by a wide range of processes, especially prior to lamination.
6 Can readily be coated by emulsion, lacquer, solvent, or extrusion-based processes, etc.
7 Can be laminated to other materials with a low-cost aqueous adhesive due to its absorbent (porous) nature.
8 Has good rigidity and strength – hence makes a good supportive material.
9 Porosity can be adjusted to allow diffusion of gases, steam, etc. for sterilisation while maintaining a barrier to bacteria and moulds.

10 Opacity can be varied according to the fillers used. It can also be coloured or tinted.
11 Paper shows a degree of compression, hence acts as a slight 'cushion'.
12 Paper can readily be torn or cut open.

The main disadvantages of paper are as follows.

1 Paper is moisture sensitive and contains on average 7% moisture under 'normal' storage conditions. Changes in moisture may induce temporary 'curl' or distortion, or 'boil-off' when heated.
2 Paper has no moisture-resistant properties (unless specially treated), hence no barrier properties against moisture, gases, etc.
3 Has no heat seal or cold seal properties, hence special coatings or films are required for effective sealing.
4 Has poor transparency and gloss when compared with certain coatings and plastic films.
5 The porous nature of paper with air entrapped between the fibres acts as an insulator. This makes heat transfer more difficult, particularly on high-speed heat sealing equipment.
6 Paper is usually thicker than plastic films, hence gives less coverage for the same weight.
7 'Grain' in machine or cross direction confers various property changes.

Summary

Paper is widely used in laminations to give support and add strength; it is readily printed, easily opened, biodegradable, etc., all at a relatively economic cost. It is usually used within the range of 10 to 90 g/m^2. For further detail see Chapter 5.

Regenerated cellulose film (RCF) (Cellophane, Rayophane, Diophane, etc.)

The process of manufacture is detailed in Chapter 7. Natural RCF, apart from natural clarity, is similar to paper in its general properties, although it is a continuous film and not fibrous in nature, e.g. it is moisture sensitive and not heat sealable. Moisture permeability can be improved by coatings which can also confer heat sealability. These coatings, which may be applied to one or both sides, are usually based on nitrocellulose or Saran (PVdC).

These materials are covered by various earlier used codings:

- DMS – one side coated with nitrocellulose lacquer
- MSAT – two sides coated with nitrocellulose
- MXXT/S – solvent coating of PVdC, both sides
- MXXT/A – aqueous dispersion coating of PVdC, both sides
- MXDT – single side coated PVdC.

The coding definitions include:

- M, moisture vapour coating
- S, heat sealing
- D, one side coated
- X, PVdC coated
- F, extra flexible
- Q or P, high moisture permeability but heat sealable
- H, tropical
- QF, quick freeze
- PT or P, plain, transparent, colourless, non-moisture-proof
- C, coloured.

However coated, the base film remains moisture sensitive and gains or loses moisture via the raw (cut) edges. This means that the material shows a degree of dimensional instability and reels of material if stored under incorrect conditions will expand (dumb-bell reels) or contract at the edges. Most regenerated cellulose materials contain humectants and plasticisers aimed at resisting changes in moisture levels. Reels should, however, be stored flat and under controlled climatic conditions to avoid reel distortion affecting machine performance.

Summary

Although regenerated cellulose plants still exist, worldwide usage has significantly reduced due to the better dimensional stability properties of various polypropylene-based films. However, regenerated cellulose still finds usage for certain special applications, e.g. overwraps.

Cellulose derivatives are also found in other forms, as detailed below.

Cellulose acetate (e.g. Clarifoil)

Like regenerated cellulose this is a clear sparkling film with a high gas and moisture permeability (i.e. the film breathes), but has poor chemical resistance and is difficult to heat seal. Like RCF it has poor dimensional stability and has been used for window cartons and an external glossy film for laminations.

Films and coatings based on plastics

Films are continuous, thin, clear, coloured or opaque materials derived from organic polymers. Most polymers are synthesised whereas the 'cellulose'-based films mentioned previously are mainly of natural origin.

Films are usually less than 250 μm thick with most lying between 12 and 50 μm. Films can be produced from a number of processes:

- extrusion – from a slit die (flat die extrusion) or lay flat tubing (cylindrical die)
- extrusion plus calendering
- regeneration casting – as regenerated cellulose
- solvent casting
- calendering
- coextrusion – involving two or more materials.

Most of these processes are described in Chapter 7 and only exceptions are covered here, e.g. solvent casting involves a polymer dissolved in a solvent. The solvent is subsequently evaporated from the cast film by heat, thereby leaving a film. Cellulose acetate film is made by such a process.

Calendering is basically a rolling or roller process (like an old-fashioned mangle) where a plastic is heated and then rolled with heated and then chilled rollers. The caliper is controlled by the gap between the cylinders.

All manufacturing processes may be combined with other operations such as slitting, surface treatment (usually corona discharge), printing. Differing properties may be created in the plastic according to the conversion process.

Orientation

One special additional process is called orientation, where a plastic film is stretched at a temperature below its crystalline melting point in the machine or cross direction or both. The latter is called biaxial orientation. These orientation processes increase molecular alignment thereby improving strength in the direction of stretch, improving clarity, reducing permeation to moisture and gases and usually improving chemical resistance. When subsequently heated above the temperature of orientation, most oriented films will revert to their original dimension.

Oriented films are usually coated with a heat sealant which seals at a temperature below the orientation temperature, otherwise the film will shrink in the heat seal zone, crystallise and possibly become distorted (cockle) and brittle. Oriented films can be 'heat set' by special treatments.

General properties of films

Appearance

Films vary in transparency (haze); most are transparent with a glossy surface. Reverse side printing usually improves appearance and eliminates rub – but beware of process solvents affecting product. Films may also be tinted or pigmented (opaque).

Strength and flexibility

Most films are flexible and fairly strong. Some resist tear but usually tear easily once a tear point is initiated (slit, V-shaped notch, etc.). Most plastic films remain reasonably consistent for several years under reasonable storage conditions. Films generally age more rapidly when exposed and not in reels.

Heat seal

Most films can be sealed by some means – direct heat, hot air, ultrasonic, HF or RF, etc. Some need special heat seal coatings.

Protective properties

Generally all plastic films are water-repellent (water-resistant). Various degrees of barrier are offered against water vapour permeation, gases (organic and inorganic), oils, solvents, aromatics, preservatives, etc. All films, if free of pinholes, provide a barrier to moulds, bacteria, etc., i.e. are a hygiene barrier.

Permeation is usually measured as:

- gas: $cm^3/m^2/24$ h, at 25°C
- moisture – $g/m^2/24$ h, 90% RH 38°C (tropical) per 0.025 mm thickness
  – $g/m^2/24$ h, 75% RH 25°C (temperate).

The USA tests use 100 in^2 instead of m^2. The 'total' barrier depends on a number of factors such as caliper, area, gradient on either side of barrier, temperature and any damage due to creasing, printing, etc., including diffusion/solubility factors associated with permeant and film.

Films show different resistance to oil, solvents, perfumes, preservatives, acids, alkalis and other organic and inorganic substances.

Other special features

Other special features include shrink films, stretch films and cling films. These features are, however, unlikely to be used in combination materials although oriented plastics are used in cold formed blister packs.

Special individual films and their uses

All plastics are to some degree permeable to moisture, vapour and gases, but are considerably superior to untreated or uncoated paper. The following material factors may require consideration in the selection of a plastic film, but it should be noted that only some of the factors listed below are subsequently considered under the general review on each plastic:

- weight per unit area (g/m^2) and/or caliper
- yield and cost (depends on caliper/density)
- transparency – light transmission; haze
- tensile strength and tear resistance
- ageing characteristics – under light, oxygen, temperature, light and low-temperature performance, softening point/melting point
- water vapour permeability
- gas permeability – note that permeation of N_2, O_2, CO_2 is usually of a 1:4:20 ratio
- odour permeability (organic and inorganic)
- resistance to water, solvents, oils and fats, etc.
- ease of printing (choice of process/ink/need for pretreatment)
- ease of heat sealing (temperature range, dwell time, pressure)
- freedom from static or level of static
- odour and taste characteristics (food grade acceptance)

- adsorption/absorption of preservatives
- non-inflammable
- presence of additives, processing, aids, etc.
- slip characteristics/coefficient of friction (critical for form fill seal machines)
- toxicity (risks for food grade acceptance
- irritancy
- blocking – tendency for two layers of laminate to stick together
- dimensional stability – important with print registration
- stress crack resistance
- extractives
- melt flow index (MFI)
- converting characteristics – each process may modify the basic polymer in a small way e.g. sealability, by heat, high frequency, ultrasonic or impulse sealing; so they also need consideration.

The polyolefins

These include the

- polyethylenes (PE), density 0.90–0.96
- polypropylenes (PP), density 0.90–0.91.

Polyethylenes (polythenes) include materials designated as low, medium, high, and linear low: PE (LD, MD, HD, LL, VL, UL).

Low density (0.915–0.925) offers a reasonable barrier to moisture but is a poor gas barrier and odour barrier, is permeable to oil, perfumes, etc. and tends to absorb or adsorb certain preservatives. Some grades, particularly with a high MFI, are prone to environmental stress cracking (ESC) when under a stress (in-built or applied) and in contact with a stress cracking agent (e.g. detergents, wetting agents). LDPE may be modified by the addition of EVA which increases its flexibility (it is already a very flexible material), widens and lowers its heat sealing range and optimises heat sealing speed. (LLDPE is steadily increasing in use and can generally be used where LDPE is referred to.)

As density increases (MD 0.925–0.935, HD 0.935–0.965), the material increases in rigidity, improves in barrier and chemical properties, becomes more difficult to heat seal (higher temperature), reduces in transparency and increases in haze. HDPE is approximately a threefold better moisture barrier than LDPE of equivalent thickness. Polythene surfaces need pretreatment prior to printing or adhesive lamination.

Uses for the films include:

- heat seal inner ply in laminations, sacks, shrink and stretch wrapping, etc.
- LDPE is frequently used as a lamination ply to bond two materials together
- HDPE is employed in boil-in-the-bag applications.
- All have applications as bags.

LLDPE is actually a copolymer of ethylene, with butene, octene or hexene. It is finding increasing use due to economies of polymerisation and film strength. It provides the

strongest heat seal of the PEs, has more extensibility and a capability of being down-gauged. Other ethylene polymers include the following.

Ionomer (Surlyn) is a methacrylic acid and ethylene modified molecule with a metal ion (sodium, zinc, magnesium). Easy sealing, soft, strong, grease-resistant clear film, and seals well in contact with contaminants. Puncture-resistant, with a high hot tack. Approximately double the price of LDPE, but can be used in thinner gauges. Can be used in the inner ply of laminates, at approx. $\frac{2}{3}$ gauge of LDPE and as a skin pack over sharp or pointed objects.

Other ethylene copolymers

EMA, ethyl methyl acrylate, is a random copolymer consisting of a polyethylene main chain with methyl acrylate side branches. One main application is the film used for surgical gloves. It is more flexible than LDPE, less crystalline and much softer with a rubbery elasticity. It also has low softening and heat seal temperatures, good strength but poor optical properties. It can accept high pigment and additive loadings and is therefore widely used as a carrier for masterbatches.

Cast polypropylene (PP) is extensible, moisture-resistant, clear and seals at temperatures above those used in steam sterilisation. Oriented PP is strong and can be used in thin gauges. Unless coated or coextruded the film cannot be heat sealed without distortion. OPP is very clear, but can also make an opalescent film. Has a similar degree of inertness to HDPE.

Unless PVdC coated or metallised, OPP is a poor gas barrier and needs pretreatment prior to printing.

Oriented PP is used for overwrapping cartons, generally as a replacement for regenerated cellulose. Cast PP is used as the seal layer for packs designed to withstand autoclaving. Special grades of PP are now available for blister packing. Woven PP with across and diagonal plies are used for sacks and bags. Trade names: Propophane, Propofilm.

Polyvinyl chloride (PVC, density 1.35–1.40)

Clear, good gas barrier, does not heat seal. Found in the following forms.

- Plasticised PVC – rarely used except as bags (IV solutions, blood) or as pillow packs. Sealed with special adhesives, or by HF/RF welding. Plasticised film is highly moisture permeable.
- UPVC (unplasticized PVC) – may contain a low level of modifier (vinyl acetate). Has a low permeability to oxygen but is moderately permeable to moisture. The material is fairly rigid and is not heat sealable.

PVC is used in overwrap film, shrink film, shrink sleeving, thermoforming for all types of blister and bubble packs. Plasticised PVC IV bags are usually PP/Nylon overwrapped to reduce moisture loss.

Polyvinylidene chloride (Saran, PVdC, density 1.65–1.70)

PVdC is a soft cling type film but very strong. Difficult to handle. An excellent barrier to moisture, gases, grease and odours generally. Has a fairly narrow heat sealing range unless modified. May discolour slightly and embrittle slightly with age.

PVdC has limited use as a film but may be used as a central core in some co-extrusions. Often used as a coating material, e.g. on other films as a good barrier and heat seal.

Polystyrene (PS, density 1.05)

Relatively highly permeable to moisture, and fairly permeable to gases. Used for thermoforming (non-barrier usage) and as a shrinkable film on a limited basis. Relatively brittle material unless impact-modified when clarity reduces.

Used mainly in blister-type packs (and as bubbles on cards for display) and OPS for some labels.

Fluorochloroethylenes

Chlorinated and particularly fluorinated derivatives of ethylene usually offer high inertness and good barrier properties. One film, Aclar (trade name) based on polymonochlorotrifluoroethylene (PCTFE), is the most moisture-impermeable commercial film currently known. For a similar thickness it is approximately ten times less permeable than PVdC. Derivatives generally have high melting and softening points. Found both as homopolymers and copolymers. For detail see Chapter 13.

Polytetrafluorethylene (PTFE, trade name Teflon)

PTFE is a very hard, chemically inert, low-friction material. It is mainly used to coat machine parts (to reduce friction) and heat sealing jaws to aid clean release. It is not used as a lamination film but has been used as a coating on closures (densities up to 2.2).

Polyvinylidene fluoride (PVdF)

More inert than PVdC; may find some application, but is more expensive.

Polyvinyl fluoride (PVF)

Has high weather resistance, but again, high costs restrict packaging applications.

Polyester (polyethylene terephthalate, PET; density around 1.38)

Usually found as a cast film. It can readily be oriented and heat set. It can be produced in thin gauges (down to 12 μm) as it is an extremely strong and tough material. Polyester is also clear and glossy.

It is heat seal resistant unless produced as a coextrusion or coated. A good barrier to most gases and volatiles, but only fair to moisture. It is easily metallised. Found as PETP and PETG (Kodak), Pet G contains an additional glycol molecule.

Often used as an outer ply to laminates and makes a good abuse-resistant layer. Use of metallised polyester is increasing as single and double metallised layers. Difficult to tear – needs a tear propagation point.

Thicker grades can be thermoformed (medical and pharmaceutical applications) and

subsequently sterilised by steam autoclaving, gamma irradiation, etc. Non-oriented PET has a high melting point, around 250°C.

Polyamide (Nylons, density around 1.1)

Although various grades are available, Nylon 6 is mainly used for films (also 6 : 6 and 11). Generally flexible and tough at low and high temperatures. Only fair in resistance to grease and oils, with low gas permeability and a poor moisture barrier (due to absorption of water). Can be heat sealed in spite of high temperature and steam autoclaved. It can also be thermoformed. Usually slightly hazy although oriented nylon is clear. Usual gauges 25, 50 μm with orientation producing films down to 12 μm.

Combined with polythene to give various thermoformed packs for cheese, bacon, etc. Also used as an outer ply for boil-in-bag applications and as an outer ply in some cold formed blisters.

Polyvinyl alcohol (density 1.25)

PVOH is a water soluble film, with good gas, odour and grease barrier. Used as a water soluble sachet, but usually needs protection from moisture.

Polycarbonate (PC)

Another tough, clear film. Withstands steam sterilisation. Rather expensive. Only fair moisture resistance but good scuff resistance. Used in some laminations.

Polyacrylonitrile (PAN, trade name – Barex)

Good gas barrier. Only fair moisture barrier. Clear but not as clear as some other films, i.e. polystyrene, polycarbonate, polyester.

Polyurethane (PU)

Strong and rubbery. Frequently used as an adhesive or tie layer. Widely used as foams.

Ethylene vinyl alcohol (EVOH, trade name – Eval)

Good gas and odour barrier. Good moisture value when dry, but as moisture is absorbed, moisture barrier properties reduce. Relatively expensive. Usually used as a central ply in coextrusion processes. Replacing foil layer in some laminated tubes. Good barrier to certain flavours: peppermint, spearmint, etc.

Spun bonded materials (Tyvek)

Very tough with paper-like appearance. Used in medical packaging as a steam sterilisable porous material, (excludes bioburden). Based on HDPE. Has high strength.

Pliofilm – rubber hydrochloride

Was an excellent sealing medium but had few other properties to recommend it. Still available on a limited basis. Deteriorates rather rapidly with age.

Coatings

Coatings are an alternative means of adding properties which are not present in the base material: improved barrier, heat or cold sealing, improved appearance, adhesion, etc.

Types of coating processes

- Water-based – usually as a dispersion or emulsion coating, e.g. PVdC, cold seals.
- Solvent-based – followed by evaporation, e.g. heat seal lacquers, high-gloss lacquers, primers and key-coats.
- Vapour – e.g. vacuum metallisation.
- Molten materials – are applied hot then allowed to set, e.g. waxes, hot melts, plus extrusions or coextrusions and such new coating processes as plasma enhancement, sputtering, vacuum deposition, etc. (see below).

The application of coatings

Other than the newer coating methods mentioned above, many coating methods apply a liquid-based material to a solid web. These coatings may be applied either as a continuous (overall coating) or by a pattern system which may involve a 'printing plate' principle. Coating processes may apply excess, followed by controlled removal of the excess (e.g. by a 'doctor' blade system) or by a controlled (premetered) amount being applied directly (Figure 9.1)

Deposition can also be obtained by electrostatic spray or electrodeposition.

Typical examples of coatings are as follows:

1 Nitrocellulose, which was one of the earliest coatings used, as per MS regenerated cellulose film.
2 Saran or PVdC (usually a copolymer of vinyl chloride and vinylidene chloride). Applied by either solvent or aqueous dispersion coatings, with high coating weights (up to 180 g/m^2) requiring a number of coatings. Dispersion coating generally tends to have better moisture barriers.

PVdC may be used as an internal barrier-sealing ply or an external layer for protection and gloss.

Lacquers and waxes

1 Widely used as an external coating to provide a protective coating to the print, and to provide a product-resistant finish. UV cured lacquers, varnishes and inks can offer a very high gloss.
2 Microcrystalline waxes may be used for barrier properties or as a heat seal. They

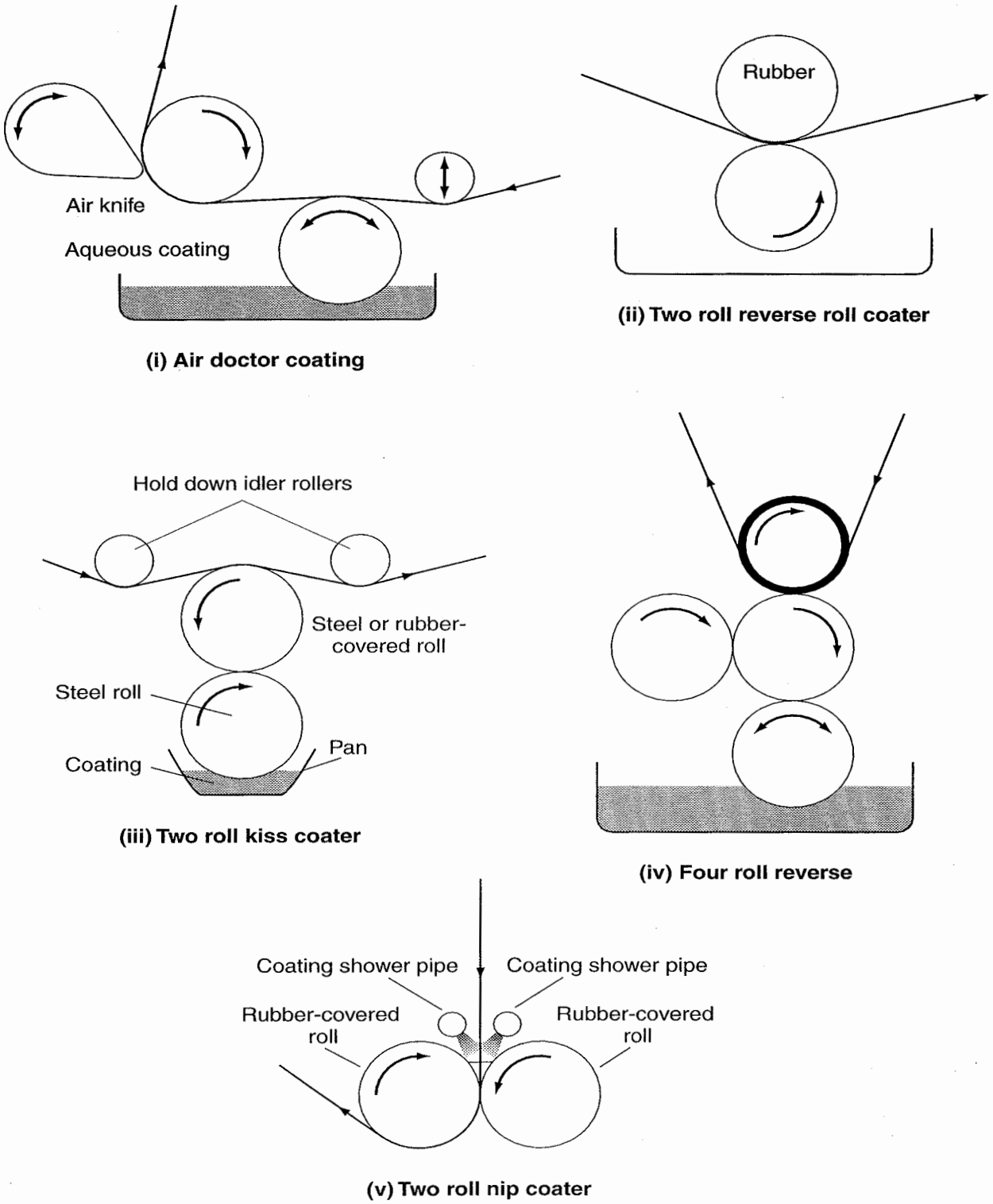
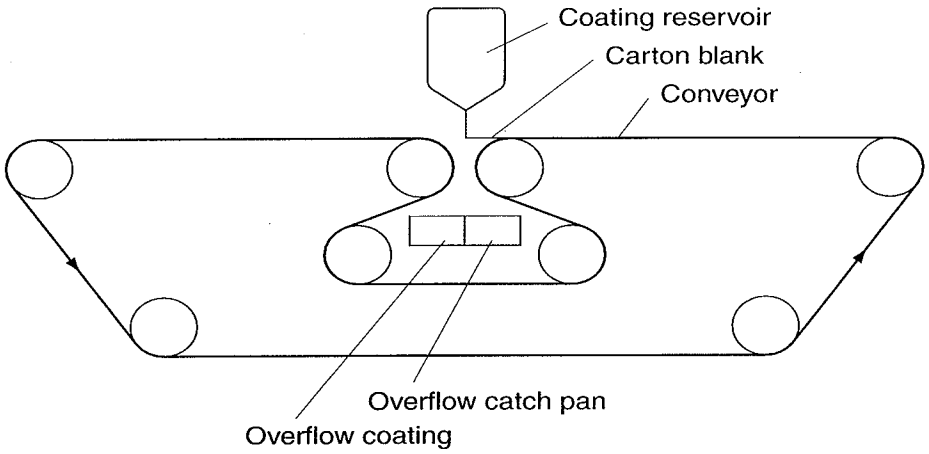
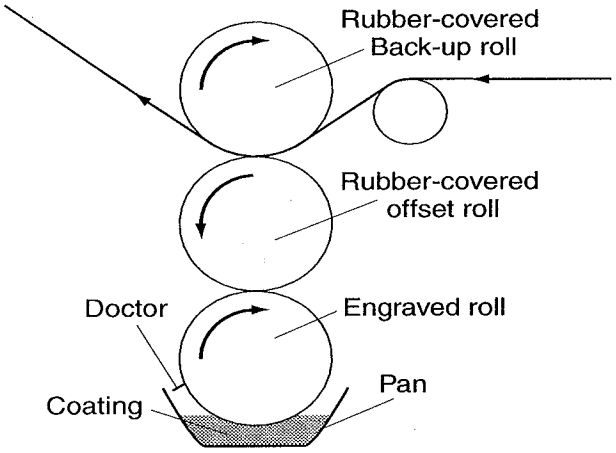


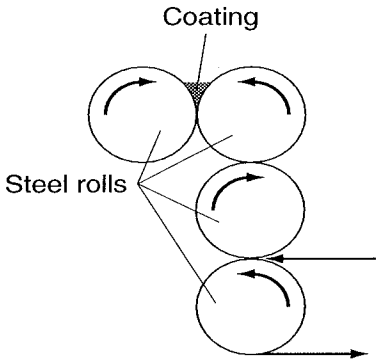
Figure 9.1 Liquid coating processes: (i) excess application technique; (ii–viii) predetermined (measured) systems; (ix) for higher viscosity materials



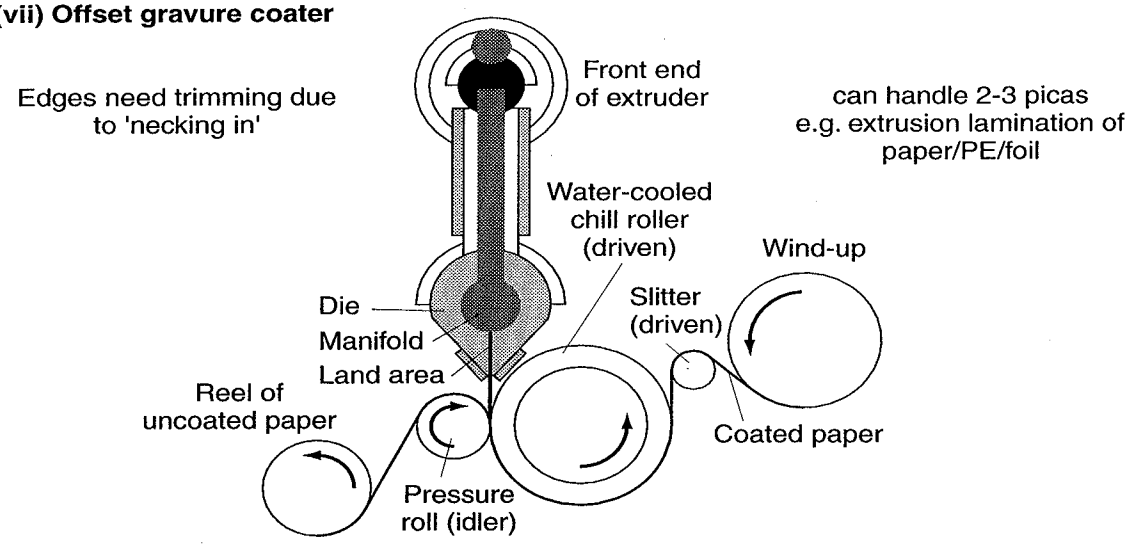
(vi) Curtain coater



(vii) Offset gravure coater



(viii) Four roll calender coater



(ix) Extrusion coating paper

may be used as either a surface layer or as a total impregnation (paper). Known as wet and dry waxing respectively.

3 Hot melts and adhesives. May be used in a lamination process, but are usually considered as coatings. Hot melts may confer some protective properties, even when used for adhesion purposes, as they are based on plastics, i.e. are 100% solids.

Extrusion coatings

Extrusion is a process where plastic film is delivered hot onto a substrate ply. A more economical way of attaching a ply of plastic and widely used for LDPE. Is less practical with certain other plastics due to risk of degradation (PVC) or the high temperatures employed. Direct extrusion and coextrusion enables use of thinner gauges of materials typically down to 12 μm.

Coextrusion coatings usually employ materials of similar viscosity, softening or melting points, whereby two or more layers can be joined together internally or externally by extrusion dies.

Vacuumised treatment, e.g. metallisation

Used to deposit a coating of aluminium onto the surface of films. Gives foil type appearance, reflecting light and heat and reducing moisture and gas permeation. Covering of particles is not continuous and can be demonstrated by holding up to light when the degree of visibility enables items to be identified through the film. Using two metallised webs laminated with metallised area to metallised area contact gives much superior protection. Lamination to a flexible substrate reduces cracking of the metal layer which can happen when the material is creased or flexed, i.e. by the addition of an LDPE or LLDPE layer to give PET/metallised/LDPE.

Foil – aluminium

Aluminium is the most abundant metal on the earth's surface, but it is one of the most costly constituents in a laminate.

Foil is obtained from metal of 99% purity and above. The gauges range from 0.006 mm to 0.040 mm. The foil is annealed to give a soft foil with a 'dead fold' property. Hard tempered (non-annealed) foil occasionally finds special applications, i.e. push-through lidding for blister packs. Lubricants are removed from hard foil by either solvent washing or controlled heating. For any nominal gauge +8% variation is normally allowed.

Foil offers the following properties:

- attractive metallic appearance
- brightness and reflectivity (light and heat)
- no light transmission; total barrier
- odourless, tasteless, non-toxic
- hygienic (process of manufacture eliminates any microbiological contamination; it will not support growth of bacteria or mould)

- excellent barrier to moisture and gases – even pinholed varieties offer better protection than plastics and papers (particularly when laminated to a plastic ply).
- can be printed and embossed.

The disadvantages of foil are that:

- it is not heat sealable
- in thin gauges it is extensible, hence needs a support layer
- under unfavourable conditions foil may corrode, either in contact with 'chemicals' or due to bimetallic corrosion (e.g. in contact with a ferrous metal)
- surface oxidation causes loss of lustre
- perforates or pinholes relatively easily with thin grades, when creased, folded or excessively flexed.

Where thin foils are used in laminations the bright or dull side needs to be nominated. Matt usually gives the best adhesion. This may also be improved by the use of a key or primer coating, also called wash coatings, weight 0.5 to 2.0 g/m^2.

Pinholes and moisture permeation

Foil of 0.038 mm is guaranteed pinhole-free; 0.017 mm can be considered commercially free for most purposes. Lower gauges gradually increase in the likely number of pinholes, e.g. 0.009 mm foil may contain 100–700 pinholes per m^2 and 0.012 mm foil 30–150 per m^2. If these are laminated to plastics then the permeability relates to the area of pinholes and type of plastic when equated against the total area of foil. Hence the permeation figures remain low unless the perforations are increased or enlarged during the lamination and subsequent machining operations on the packaging equipment. For this reason pick-up on finished packs is more relevant than direct permeation figures on the basic packaging material. Gas permeation is usually greater than moisture, hence could be more critical.

Foil strength

Soft aluminium foil has a fairly low tensile and tear strength, so it is essential that very thin gauges are supported by paper or film. In general, foil of 0.025 mm and below has to be supported. For example, 0.025 mm foil laminated to 30 g/m^2 LDPE is a widely used strip packaging laminate. In theory, 0.015 mm foil laminated to 30 g/m^2 LDPE would be a more economical proposition. However, at this caliper any undue stretch would be likely to perforate and tear the foil. Hence it is possible to reduce the foil caliper only if support is increased, i.e. by the addition of a paper ply. Thus if cost savings are to be made the final laminate would probably be either

- 37 g/m^2 GIP/0.012 mm foil/30 g/m^2 PE, or
- 44 g/m^2 GIP/0.008 mm foil/23 g/m^2 PE.

Foils used on the external ply are invariably given a light coat of lacquer to reduce scuff and improve slip. However, if paper is a middle ply any excess moisture may literally

'boil off' during the heat sealing operation. Paper as an external ply is therefore generally preferred.

Foils of 0.006 mm and 0.007 mm are now offered and may be incorporated into a variety of laminations. Special thicker foils of 0.040 mm (40 μm) and above (up to 60 μm) are used for some cold forming operations.

Summary

Flexible packaging foil is usually coated with heat sealing material or laminated to other plies that include a heat sealable layer. Lacquered, sometimes embossed, foil is used to lid containers, e.g. blister packs. Foil is used in a wide variety of laminates. However, it cannot be used in any coextrusions, hence alternative barrier materials have to be used.

Laminations and lamination processes

Laminates are combinations of various plies created to obtain the properties which are not provided by one material alone. They use the minimum of materials (thin gauges and low grammage), and are cost-effective. However, they conflict with certain environmental issues, as recycling and/or reuse is either impossible or difficult.

Two widely used laminations are paper/foil/polythene and paper/foil/Surlyn. In these constructions the paper provides strength, brilliance and printability, the foil provides an excellent barrier to moisture, oxygen, light, odour and flavour (loss or gain), and the polythene or Surlyn gives heat sealability. These are widely used for strip and sachet packaging.

Lamination processes

Lamination may be achieved by adhesives, extrusion and coextrusion (Figures 9.2 and 9.3).

The more traditional method to make laminates uses separate plies combined with adhesives, which can be divided into groups – molten, water-based and solvent-based. Wax and polythene extrusion are the main molten laminants. Water-based glues are often used to combine paper and foil. Solvent-based adhesives include the polyurethanes, but recent developments use water dispersions and molten curing systems to replace the solvent systems. Cross-linking reactions develop high heat and product resistance in all these adhesives.

Extrusion consists of extruding a film from a slit die where the hot film may be nipped in contact with a second material and then cooled to give a bond between the two (or three) materials. Extruded LDPE is widely used both as a film in its own right and as a ply which combines plies on either side of it. Circular die extrusion can also be employed without the 'nip' stage in slit die laminating, i.e. it involves true coextrusion.

Coextrusion produces a multi-ply material directly from the individual resins. The method is limited to thermoplastic materials such as polythene, polypropylene and nylons. Thin layers of extruded bonding resins are necessary to combine many of the resins. Coextrudates have to be surface printed and the outer film cannot be reverse printed as it is often used with more conventional laminates with a film outer ply.

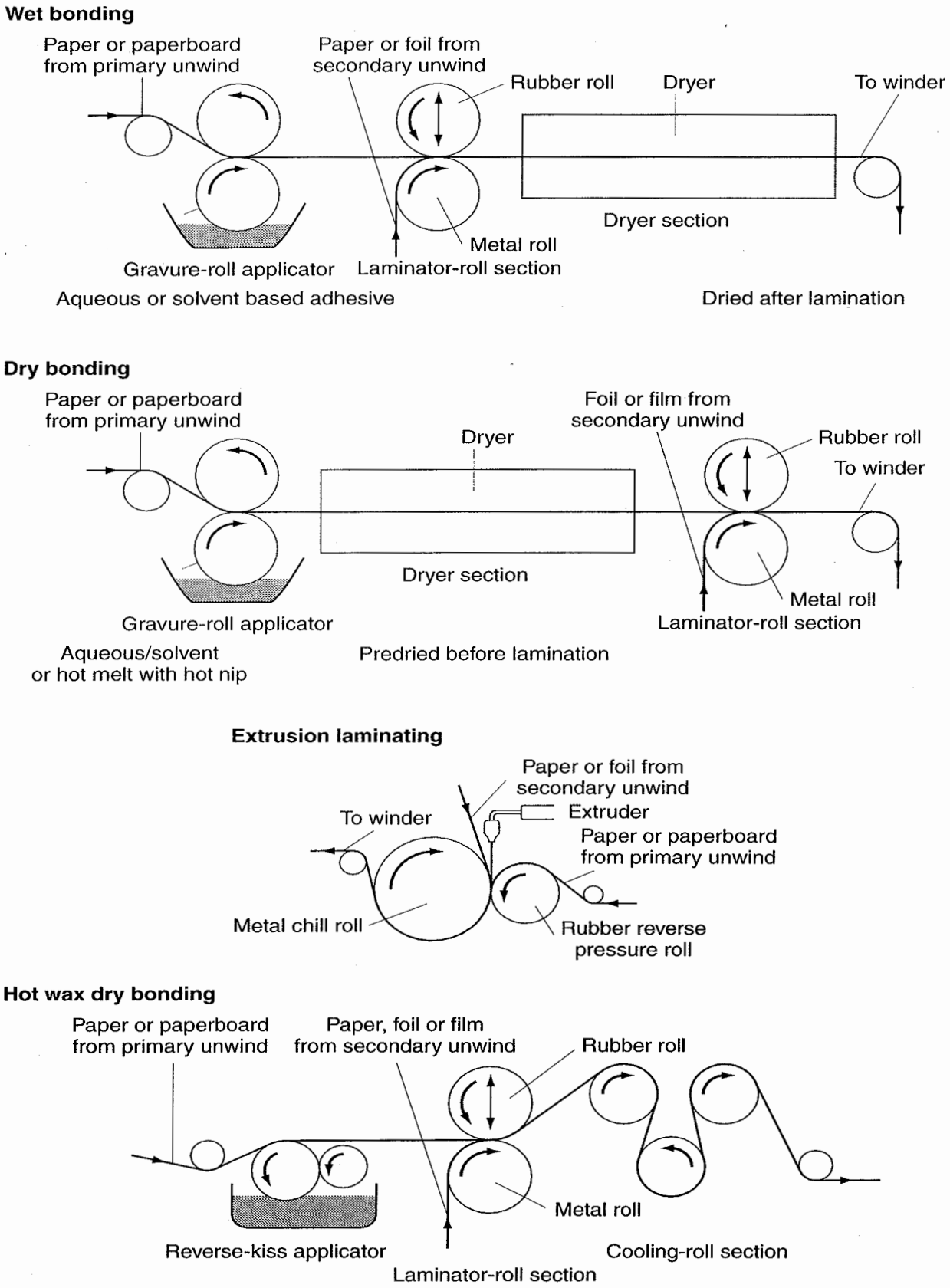


Figure 9.2 Lamination: wet and dry bonding

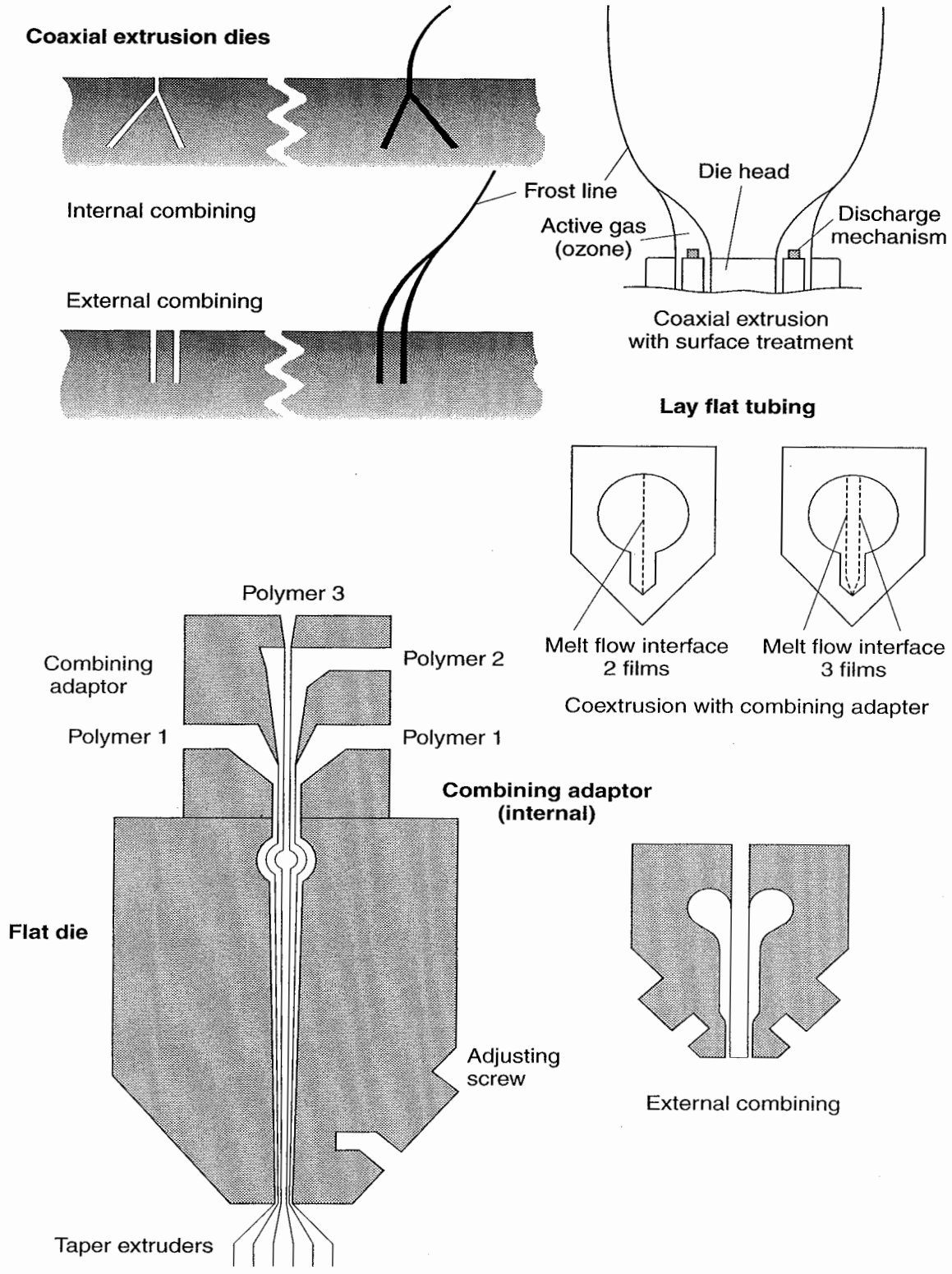


Figure 9.3 Extrusion and coextrusion processes

Adhesives – traditional

Various types of adhesive may be employed, i.e.

1 aqueous – with paper-based materials or where moisture can be lost from or through one web
2 solvent – loss of a volatile carrier by heating and special ducting
3 hot melts – advantage of virtually instantaneous set once heat is removed
4 hot wax – similar to hot melt except that wax remains pliable for a longer period.

(1) and (2) are termed 'wet' bonding while (3) and (4) are known as dry bonding processes. However, the second type (solvent) can also be used as a dry bond, where the solvent adhesive is applied to the substrate, excess solvent is evaporated off and then the second ply is bonded to the tacky adhesive via a nip roller.

Adhesive coatings may be applied by several means, i.e.

- excess of coating is added to the web and the surplus is removed by means of a rigid knife, flexible blade, or air jet knife, i.e. 'doctor' systems
- a controlled amount is applied to the web by means of rollers (roller coating), brushes, a calender, or by curtain coating.

A coating may be achieved by passing the ply between a coating roller and a back-up roll (usually rubber) or by kiss coating whereby the tensioned web makes contact with a coating roller. With certain more difficult materials a nip roll system (hot or cold) may be employed. In this instance the area between web and roller is flooded with the coating medium. Gravure cylinders may also be used for coating.

In general, hot melts offer production advantages in cleanliness of operation and the elimination of solvent extraction problems. Hot melts can also be modified to contribute to the barrier properties of the laminate. Control of heat and cost are the main disadvantageous factors.

More modern systems include polyurethane and acrylic-based adhesives and two-part curing adhesives are gaining popularity.

Examples of the various laminations used include:

1	OUTER PLY PAPER (strength, appearance)	CENTRE PLY FOIL (barrier)	INNER PLY POLYTHENE OR SURLYN (heat seal)
2	OUTER LAYER COPOLYMER (heat seal)	CORE POLYPROPYLENE (strength/barrier)	INNER LAYER COPOLYMER (heat seal)

Laminate 2 has the advantage that it will seal to either the external or internal layer to itself, i.e. an overlap seal can be achieved.

Coextrusion is the latest process by which a series of plies can be joined together in the hot state. This may involve direct adhesion between plies or the use of extruded 'tie' or 'adhesive' layers. These bonding layers are frequently only a few micrometres thick and involve relatively low grammage levels. However, coextrusion is only cost-effective as a long-run process since set-up times can be lengthy.

Table 9.2 Provides a comparison between laminates and coextrudates

Laminates	*Coextrudates*
Versatile, include thermoplastic, paper and foil.	Limited to thermoplastic materials of similar viscosity. Exclude paper, foil, metallisation.
Sandwich print and coating can be used for good appearance and protection.	Surface print and coating only can be used.
Various adhesives can be employed. Cross-linking adhesives are often used, giving good heat and product resistance. Older adhesive systems are more prone to delamination.	Thermoplastic adhesives have to be used with limited product resistance. Some layer combinations do not require adhesives or tie layers.
More rigid.	Less rigid (especially cast).
Extra cost is necessary to pre-make individual layers before laminating. These layers also have a certain minimum thickness (limitations related to producing and handling this material).	Most cost-effective, especially for long runs. Thinner layers of more expensive materials can often be used. Setting-up operation needs greater expertise and may be lengthy, with various levels of wastage.

Decoration and printing

Materials may be surface printed, reverse side printed (if transparent) or sandwich printed (between two plies – either surface or reverse side). Two basic printing processes are usually employed:

Flexography and gravure (offset lithography may eventually come on stream).

Flexographic and gravure or photogravure printing

Flexography was a relief process on a rubber or composition type stereo mounted on a printing cylinder. Originally suffered from squash-out but better control on registration means that good half tone printing can now be achieved.

Gravure printing employs an intaglio process whereby the print area lies below the surface of the plate in small cells. The tone or colour depth may rely on the depth of etch (i.e. amount of ink which lies in the cells) and/or the number of cells per linear inch. All gravure is basically half tone (solid line gravure plates are used in some tampon or cliché processes).

Gravure printing plates are expensive, £750–1,000 per cylinder (per colour), so four colour printing will involve an outlay an of £3,000–4,000. Make ready is also fairly lengthy, hence long runs are necessary to offset the high cost of the setting-up. Gravure gives very high-quality reproduction. Lower cost plate making processes have recently become available via the use of laser technology.

Both flexographic and gravure are reel-fed (web-fed) printing processes. Both can use solvent type inking systems which are suitable for non-absorbent materials such as films and foils. Drying processes usually employ heated drying tunnels where the solvent is removed (and reclaimed). Special UV inks and UV curing systems, IR drying systems, etc. are also available.

With the flexographic process, water-based inks can be used on paper (original aniline dye process) where adsorption forms part of the drying process.

The choice of printing process depends on the design, the number of colours, the quality, the printing surface, the length of run, etc.

Heat sealing – peelable, semi-permanent, permanent

Basically any heat sealing operation depends on the correct combination of temperature, dwell time, pressure and removal of heat, with pressure being the least critical (note that if pressure is excessive, sealant can be squeezed out of the seal zone).

However, for an effective seal consideration must also be given to the following.

- Sealing jaw pattern (line, cross-hatch, etc.) may involve two matching patterns or one side smooth.
- Area or width of seal zone (if too narrow, the seal may not be totally effective).
- Condition of machine, evenness of seal pattern, alignment of jaws.
- Type of temperature control and operational range (thermostat control is better than simmerstats, ±7.5°C possibly drifting to ±15°C with time). Electronic control is most accurate, say ±2.5°C.
- Product contamination – can interfere with sealing.
- Material to specification, e.g. no excessive caliper variation.
- How seal is achieved – platen or tangential contact (i.e. roller process where only a point of contact is made as distinct from a platen process where an area is sealed by a flat contact).
- If made from a reel process (which is usual), how resulting pack is removed from web by guillotining or punching. Hence accuracy and tolerance of cut are important so that an adequate heat seal margin is maintained.
- Number of joins in reel (should be flagged).

As a general rule 5 mm margins are recommended, but with push-through blister packs 3–4 mm is fairly normal.

Failures in heat seal can occur because of creases in the seal area giving rise to capillary leakage. Such capillaries are more likely to cause microbiological contamination than product losses. Under fluctuating temperatures the pack may breathe.

Seal defects may be detected by vacuum, pressure, pack deflection or gas sniffing.

In the case of multi-ply packs some plies (particularly the foil) can be perforated but, as other plies may be continuous, leakage will not be detected by a vacuum test. However, this perforation may be sufficient to affect product life. This type of leakage may have to be detected by visual means (microscope) or by careful separation of the plies by suitable solvents. The other alternative is to subject the pack to a cycling climatic test, i.e. 15°C 50% RH and 37°C 90% RH with 12 h cycles.

In some instances the heat seal ply of a lamination has to be peelable. These should be checked for peel strength over the shelf life of the product as in some instances the peel strength may reduce and so jeopardise the seal or increase it to a point where a permanent non peelable seal is obtained. The use of pattern lacquers also assists peelability.

Sealing can also be achieved by impulse, ultrasonic and RF/HF (radio or high frequency) methods and by cold sealing (pressure sensitive) type materials. See Chapter 11 for fuller details.

Lamination selection

Any laminate may consist of a number of plies selected from paper, cellulose, films, foil, coatings, tie layers, metallisation, etc. From previous pages the permutation possibilities are enormous. However this choice is restricted by:

- quantity/commercial availability
- technical requirements
- cost of base materials
- cost of lamination processes
- cost of printing cylinder and process (origination)
- the amount of laminate required (quantity)
- the yield (and from which choice the cost per area of laminate is derived).

One of the more complex laminates used consisted of clear LDPE/LDPE white/paper/LDPE/LDPE copolymer/30–50 μm, EVOH or Al foil/LDPE copolymer/LDPE clear. As another example, many laminated tubes now consist of five layers e.g. two plies LDPE/40 μm foil/two plies LDPE.

By listing some of the more widely used flexible (lamination) materials it will be seen that certain materials are rarely used in laminations except for very specific and very specialised cases. For the purpose of this list, 'paper' will cover any variety.

- paper/PVdC and PVdC/paper/PVdC
- paper/LDPE and paper/Surlyn
- regenerated cellulose/LDPE
- foil/LDPE and foil/Surlyn
- foil/heat seal lacquer
- paper/foil/LDPE and paper/foil/Surlyn
- polyester/foil/polyethylene or Surlyn
- Nylon/polypropylene.

Note: Reference to specific gauges has been deliberately avoided, as final choice may depend on the many factors mentioned earlier. Surlyn is slightly more expensive than LDPE but gives a better seal if seal area is likely to be contaminated with the product. It also seals at a lower temperature, allowing increased output speeds.

Examples of pharmaceutical applications

Strip packaging

1 82 g/m^2 (25 μm) Al foil/30 g/m^2 LDPE or 25 g/m^2 LDPE. Gives excellent moisture, gas and light protection. External foil image.
2 30 g/m^2 glassine/ink/poly/67 g/m^2 Al foil (20 μm) 25 g/m^2 LDPE. Good protection – more subdued metallic image.

Sachet packaging

1 59 g/m^2 paper/14 g/m^2 PVdC – here PVdC provides protection and heat seal.
2 37 g/m^2 paper/glue*/24 g/m^2 Al foil (8 μm)/25 g/m^2 LDPE. Provides a good barrier and LDPE as heat seal medium.
3 24 g/m^2 foil/glue*/44 g/m^2 paper/37 g/m^2 LDPE. Similar to (2) but with foil external. See Appendix 9.1 for a typical QC specification for a Laminate material.

Blister packaging

Tray:

1 UPVC, 100–300 μm
2 PVdC coated (30–100 g/m^2), PVC or PET or PP (150–300 micron).

Lidding:

1 hard foil (18–20 μm), heat seal lacquer (3–15 g/m^2)
2 soft foil (25 μm), heat seal lacquer (6–12 g/m^2).

Food and confectionery packaging

The latest feature in food packaging is the retortable pouch as a replacement for an open topped can. At the moment economics are improving as the cost of steel and tinplate rises. However, filling speeds for pouches are considerably lower and additional strength outers (for stacking) add to the cost.

Retortable pouches can be made from combinations of foil, polyester, nylon, polypropylene, HD polythene, provided the laminant (or the process of lamination) employed will withstand the autoclaving conditions of temperature and moisture. Due to the flat shape of the pouch and high surface area, sterilisation times can usually be reduced compared with cans.

An important factor in both pharmaceutical and food packaging is that materials employed have FDA clearance with reference to any hazards. This may be checked by reference to the supplier and by obtaining full details of the formulation of each film employed.

The above are included as the pharmaceutical industry often follows the food industry when new materials are involved. This is sometimes economically sound where quantities are not sufficiently high to support the development of a specific material for the pharmaceutical industry, e.g. a retortable material in the food industry could be applied to a non-retortable use.

Other points

Laminates can be fabricated in a vast number of combinations and therefore the choice of the correct technical material may appear to be extremely complex. However, if the

* 12 g/m^2 LDPE is an alternative, extrusion laminated.

choice is restricted to what is adequate rather than perfect for a given purpose, it is possible to introduce a reasonable degree of standardisation and therefore obtain further economic advantages from larger demands.

An additional factor must also be considered. How do laminates compare with other competitive materials (such as glass, metal and plastic containers) in terms of disposal, pollution, reuse and conservation of the earth's natural resources? There is no doubt that combinations of plastic, cellulose, foil, etc. do present a disposal problem and although two of these can be incinerated, the economics of recovering the foil is relatively poor. The overall economics of using laminates can be compared with other materials by quantifying the packaging costs and disposal/reuse costs. This approach does not include any 'convenience' value associated with each type of pack.

However, since most are reel-fed materials involving form fill seal activities, the space required for the storage of incoming materials is significantly less than for preformed containers which store air. There is also a significant saving in weight and space in many circumstances.

Life cycle analysis is expected to help in the long term the environmental aspects associated with the future of packaging. Life cycle assessment can also be applied. However, each involves factors which are difficult to accurately quantify.

Virtually all forms of flexible packaging find some use in either pharmaceutical or medical products. Pack forms include:

- conventional strip and blister packs
- cold formed foil blisters
- specially selected strip and blister packs with additional child resistance
- sachets and pouches (single and compartmental)
- sterilisable sachet and pouch systems
- a wide variety of overwraps.

Although the majority of the above will use conventional types and combinations of material, some will use specific or specialised forms which are solely related to pharmaceutical or medical products. Strip and blisters tend to fall into this latter category and are covered in Chapter 13.

Products and instruments requiring sterility need special mention, as both the materials and the processes offer a number of combinations. In total these can cover all the previously mentioned methods for obtaining a sterile pack, i.e. terminal sterilisation by steam autoclaving, or gamma irradiation, or the aseptic approach using dry heat, moist heat, gamma irradiation, accelerated electron or gaseous treatment, plus newer on-line aseptic processes. The last of these, which are currently being developed as a total in-line system for the food industry, are normally reel-fed. The material is sterilised by UV or chemically by hydrogen peroxide or any similar sterilising chemical process, provided it is non-toxic with a low level 'residue'. In the USA hydrogen peroxide has been approved for the sterilisation of food materials with a residue limit of 1 ppm. This or a similar system is likely to find pharmaceutical applications.

Although certain products can be terminally sterilised by moist heat, gamma irradiation or accelerated electrons, these tend to apply to relatively few pharmaceutical applications where flexibles are involved (the last two are more widely used for medical instruments in pouches or sachets).

Moist heat is only a practical process where the product contains sufficient moisture and the seals are robust enough to withstand the temperature and pressure of the process. Stresses on the pack can be reduced by autoclaving under water and/or by using a balanced/overpressure autoclave. The latter is normally programmed to provide an external pressure during the cooling cycle in order to balance the internal pressure within the pack and thereby prevent the seals of the pack from rupturing. Paper plies (unless treated to repel water/steam) are usually excluded from pharmaceutical packs which are sterilised by steam. However, special paper plies with low porosity to prevent penetration by bacteria are available which are steam sterilisable, provided some degree of 'wrinkling' is acceptable.

Plastic 'papers' such as Tyvek, a porous spun bonded HDPE, are particularly suitable as an alternative to a sterilisable paper. Where non-porous plastics are involved sterilisation can be achieved by gamma irradiation, accelerated electrons, or gaseous treatment. Gamma irradiation can cause critical changes to some plastics, e.g. a less flexible material, discoloration or the release of gaseous substances. The last of these may give rise to organoleptic changes or increased risks with toxicity or irritancy, with a possibly greater emphasis on irritancy or allergenic type substances. Gamma irradiation can also change the structure of adhesives and alter the bond strength. It has been used to improve the peelability of some semi-permanent bonds.

Although ethylene oxide readily penetrates most plastics, attention has subsequently to be paid to any degassing phase and the level of residues associated with ethylene oxide, ethylene glycol and epichlorhydrin.

To conclude, it is likely these pharmaceutical applications for new combinations of flexible materials will follow those of the food industry, although occasionally there will be concepts which are specifically developed for pharmaceutical products. The purchasing power of the industry (compared with foods) will frequently restrict progress.

Increased growth in the materials currently used (listed below) is therefore more likely than a surge in the use of raw materials.

1 Foil:

- soft aluminium foil, 0.006–0.038 mm (as a ply in combination with other material)
- hard aluminium foil, 0.015–0.025 mm (as a ply in combination with other material)
- special foils for cold forming, 0.040–0.060 mm.

2 Paper: tissues, Kraft, bleached Kraft, glassine, glazed imitation parchment (GIP).

3 Plastic plies:

- LDPE, MDPE, HDPE, LLDPE (and combinations of these)
- Surlyn ionomer
- nylon and oriented nylon
- polypropylene (PP and OPP)
- Aclar
- Saran (PVdC)
- ethylene vinyl acetate
- polyester

- cellulose acetate
- regenerated cellulose
- polycarbonate
- ethylene vinyl alcohol
- polyvinyl chloride.

4 Coatings:

- metallisation
- polyvinylidene chloride
- nitrocellulose
- various heat seal coatings, washes, lacquers and varnishes
- solvent coatings
- silicon oxide and carbon coatings.

Conclusions

It is clear from the preceding text that polymers and coatings can provide a wide range of properties. Since most heat sealed (or cold sealed) flexibles are tamper-evident, this is obviously a positive feature which can encourage further unit dose type packaging. UK investigations have also established that, provided the materials are opaque or dark tinted and reasonably substantial (i.e. not flimsy), most strip and blister type packs offer reasonable child-resistance. This is generally as good as reclosable child-resistant packs where there is always a risk that the closure is not properly reapplied and any removal usually exposes a child to a greater quantity of a product.

It can therefore be concluded that there are many good reasons why the use of flexibles for pharmaceutical products should enjoy continuing success.

Other alternative coating processes

These alternative processes include metallising with metals other than aluminium, e.g. Camvac offers a coating of aluminium oxide on a material called Camclear. More recent additions include silicon oxide, (SiO_x) coatings, carbon like coatings, etc. Such coatings and volatile polymer coatings can be applied by a range of relatively new techniques found under the following headings: vapour, vacuum or electron beam deposition, sputtering and plasma enhancement, etc. (Figure 9.4). Coatings may involve gases, fine particles or a liquid which is usually deposited on the exposed material to be coated when it is passed over a chilled cylinder in a vacuum chamber. The thickness or weight of material deposited varies from very thin (measured in Angstrom) to that measured in microns.

Metallisation

This consists of fine particles of aluminium or other metals. Gain in barrier properties is often 20× or 40× but this reduces to 4×/5× if the material subsequently becomes severely creased and the surface is broken. Virtually any material can be metallised, e.g. PET, LDPE, PP, paper. They have a highly reflective surface but can be seen through against a bright light. Metallised materials can be laminated by wet or dry laminating systems, directly coated, etc.

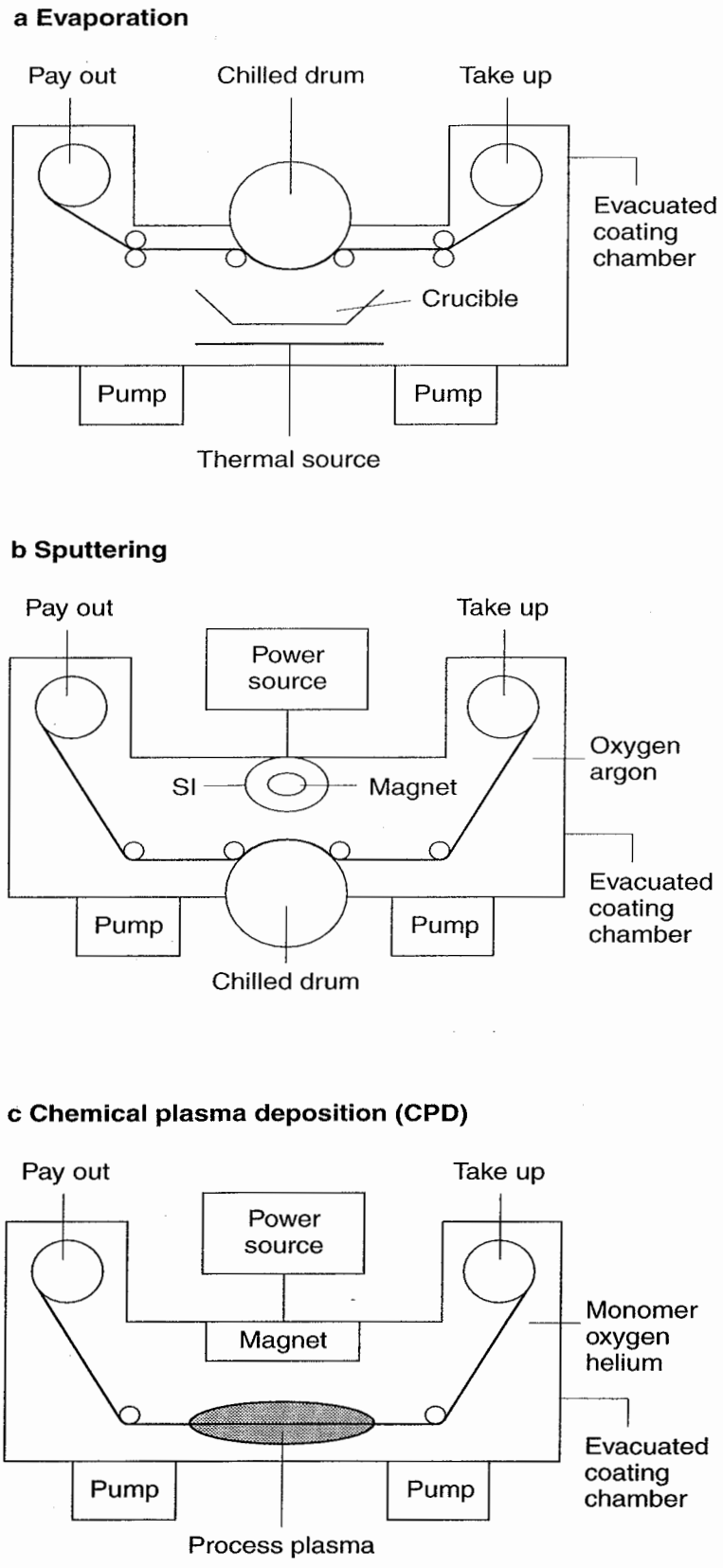


Figure 9.4 Alternative coating processes. In (A), the crucible contains material to be evaporated (aluminium, SiO/SiO_2, etc). Evaporation is by resistive heater or electron beam gun

Silicon oxide (SiO_x) coated materials (thickness 1500–3000 Å)

These are produced by several conversion processes (evaporation, sputtering, chemical plasma deposition). Evaporation is the same method as that used to create metallisation using aluminium. A material is heated in a crucible by either a resistive heat or an electron beam gun (hence the name electron beam deposition), whereby the material evaporates and subsequently condenses on a chilled film in a vacuum chamber. In the case of SiO_x coatings, the aluminium used in metallisation is replaced by SiO/SiO_2.

Sputtering (coating thickness 400–500 Å)

This process relies on an electromagnetic powered source which, together with an ionised gas mixture of argon and oxygen, causes the argon to bombard a silicon source whereby silicon atoms are created and subsequently attach themselves to a chilled substrate. The level of SiO_x created is controlled by adjusting the oxygen content. This process is the least economical (high energy required).

Chemical plasma deposition (CPD) (coating thickness 300 Å)

Although this can use a chilled drum, it is not essential, as the process involves a relatively low heat loading. The process again uses a vacuum chamber provided with a helium–oxygen mixture and a silicon-based monomer such as tetramethyldisiloxane or hexamethyldisiloxane. An applied power creates a plasma which activates the oxidation of the silicon gas, creating reactive chemical molecules which form the SiO_x coating on the film surface.

In general the CPD method, as used by Airco Coating Technology, gives the lowest deposit, a clearer film (others may have a yellow tinge), a better bond (chemical rather than mechanical), a more extensible material (stretches further before the surface ruptures), and this is achieved at a relatively low power input and a reasonable output speed.

SiO_x can be applied to films such as PET, PP, nylon and PE. O_x usually lies between 1 and 2 (but excludes 2, i.e. SiO_2). Improvements in barrier properties are up to 120× for oxygen and 45× for moisture, but severe creasing can cause a reduction. It has been shown that CPD coated SiO_x films will withstand autoclaving (moist heat) of 121°C, or perhaps above.

Diamond-like carbon (DLC) (coating thickness in micrometres)

This is the newest coating process to emerge and has been applied to PET and PP films. The coating shows high hardness, transparency and impermeability, reducing moisture permeation by 40–60× and oxygen by up to 100×. In the process of manufacture acetylene is ionised in a vacuum chamber, releasing carbon onto a film.

Fluorination

Fluoride treatment of HDPE conveys improved resistance to solvent-type organics. Use for certain pharmaceutical products is under test, with manufacture of single and multilayer material including coatings.

Appendix 9.1: Packing material specification

STANDARD NAME: LAMINATE PRINTED ABC			DATE:	CODE REF:
SUPERSEDES SPECIFICATION:		CODE:	DATED:	NEW DESIGN:
REASON FOR REVISION:				
GENERAL DESCRIPTION:	Paper/Foil/Polyethylene laminate, sachet front, printed ABC			
MATERIAL DESCRIPTION:	37g/m^2paper/12.5g. m^2LDPE/0.012mm soft aluminium foil/25g/m^2LLDPE. Paper to be spirit varnished.			
CONSTRUCTION:	Four ply laminate, foil extrusion coated with LLDPE. Paper to foil extrusion laminated with LDPE on bright side of foil. Reel to meet no 3 on standard unwind chart of National Flexible Packaging Association.			
SIZE/CAPACITY:	Reel width 100mm to be within ± 1mm of nominal width, core diameter 76mm. Maximum reel diameter 400mm			
DRAWING NUMBER:	Reference/date			
DECORATION/ PRINTING:	Printed as per artwork... .. Varnished except for batch no area, incorporating APE registration mark, to be within ± 0.5mm of nominal distance. Text correct to proof previously approved ref... ... ... Colour to be within agreed colour tolerances and matching Pantone colour references.			
SPECIAL TESTS:	See cross references to master manual for printed laminates, i.e. heat sealing, adhesion strength, varnish test, rub resistance, fade resistance of print.			
ACCEPTABLE QUALITY LEVELS:	Critical 0% Major 0.65% ALSO SEE NOTES ON REVERSE Minor 4.0%			

MODE OF PACKED FOR DELIVERY AND IDENTIFICATION

Rolls to be individually wrapped, fitted with core plugs to prevent core damage and palletised. Alternatively, they may be packed in strong boxes fitted with core rods. The rolls to be sufficiently well packed to prevent movement and impact damage. Rolls to be wound sufficiently tight to prevent telescoping. All packs to be correctly identified externally and within core.

AUTHORISATION:	
SUPPLIER:	DATE:
RECEIVING COMPANY:	DATE:

SUPPLIER

Notes

1. Where PHARMACEUTICAL COMPANY X HAS APPROVED BUYING SAMPLES FOR GOODS, any orders for goods of the same description subsequently placed by the Company shall unless otherwise indicated, be deemed to be placed on the basis of such buying samples as well as on the description and/or specification, and in all such cases the goods shall conform both to such buying samples and the description and/or specification.

2. The supplier shall effect no physical or chemical change to the product or its method of manufacture without the prior agreements in writing of the Company.

3. The Company reserves the right to revise or amend the specification after formal notification to the supplier.

4. The right is reserved to reject individual reels at the time of their use, should a fault appear within the confines of the reel.

5. Sampling, inspection and classification of defectives is conducted strictly in accordance to ..... (The AQL's for this are shown overleaf).

6. Visual defect classifications

CRITICAL

a) Admixtures
b) Print defects which result in non compliance with Statutory Regulations

MAJOR

a) Print defects which result in the illegibility of the text
b) Defects which are likely to materially affect the usability of the laminate when used on automatic packaging machinery
c) Defects which are likely to result in the product not meeting the required standard

MINOR

a) Print defects which do not affect legibility of the text but are a departure from normal commercial standards
b) Colour variation outside of the established tolerances
c) Defects which are not likely to materially affect the usability but are a departure from normal commercial standards

AUTHORISATION:	
SUPPLIER:	DATE:
RECEIVING COMPANY:	DATE:
SUPPLIER	

13

BLISTER, STRIP AND SACHET PACKAGING

D. A. Dean

Introduction

Although strip packs date from the late 1920s (starting with the single Aspro strip in waxed paper) and blister packs from the early 1960s, both are now well established forms of pharmaceutical 'unit dose' packaging. As unit dose packs offer individual protection until the dose therein is removed, personal dosage, tamper-evidence, child safety, no cross-contamination risks, no opening and reclosing problems, etc., their popularity has limited the growth of typical multipacks. Against these advantages, blisters and strips generally occupy larger volumes than their multipack equivalents. However, this increased pack external area, particularly when cartoned, may enhance the product display image and offer more label space.

Elderly patient compliance has been raised as a point for criticism. This has usually been a result of the question 'do you have difficulty in opening blister or strip type packs?' where 'have you tried opening them this way?' might have been more helpful.

Blister packs originally consisted of a thermoformed plastic tray with a lidding material made from plastic, paper, foil or a combination of these, with the product being removed either by pushing through the lid or via a peelable lidding. Today this definition has been extended by cold forming of plastic/foil combinations and the so-called tropical lidding over the blister.

Similarly, strip packs consists of one or two plies, made from regenerated cellulose, paper, plastics, foil or any combination of these, whereby an item is inserted into a pocket area against a recess in a heated platen or roller. However, some systems now involve the use of preformed pockets thereby making it increasingly difficult to differentiate between blister and strip packaging (Figures 13.1 and 13.2).

Blister packs

Blister machines utilise the fact that a plastic film can be softened by heat and then formed in a mould by:

1 mechanical forming between male and female moulds
2 vacuum or negative pressure – which draws the softened film over or into a mould
3 pressure – in which compressed air forces the film over or into a mould
4 combinations of the above.

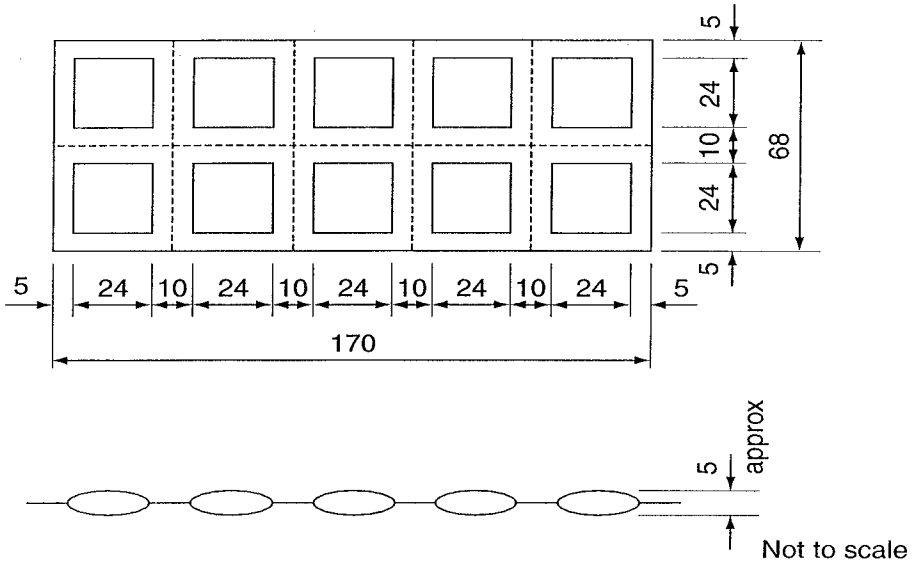


Figure 13.1 Strip pack (based on tablet 13 × 6 mm)

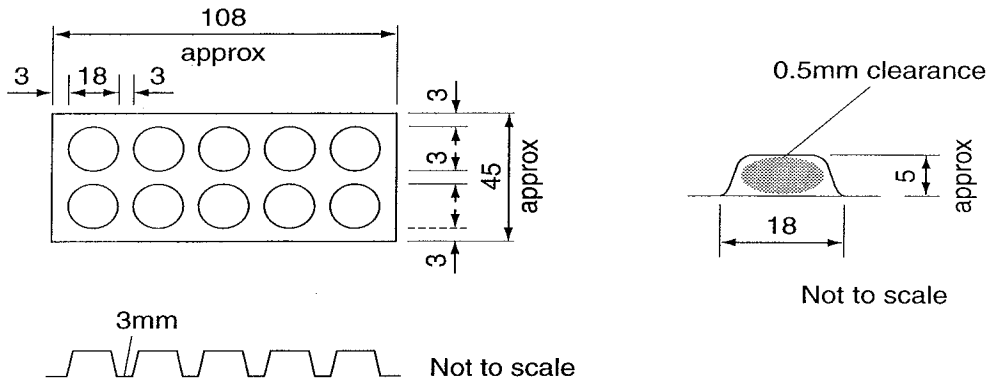


Figure 13.2 Blister pack (based on tablet 13 × 6 mm)

The trays thereby formed are subsequently filled, lidded and cut out into specific tray sizes and configurations.

The distribution of the wall thickness achieved by the moulding operation depends on the process: whether the material is formed into or over a mould, film thickness, depth of draw, softening temperature, type of plastic, etc. For an identical blister shape, pressure plus plug assistance generally gives the most uniform blister. Pressure forming usually gives a thicker top section and vacuum is thicker near the base of the web, thinning towards the top. In-built strain within the blister can be observed by viewing under polarised light (provided it is a clear or natural material).

Basic equipment principles

Fully automatic machines are based on either continuous or intermittent movement of the web through the unit, or a combination of the two. Until recently this motion depended on whether certain processes were carried out on platens or cylinders. It is now possible to use platens which have a reciprocating action whereby continuous motion can be maintained. The basic machine operations performed on a machine are:

1 heating + thermoforming or cold forming
2 filling
3 heat sealing of the lidding material
4 punching-out or guillotining the tray from the web.

Additional operations may be printing of the lidding web, registration reading units, batch marking, product check/rejection on not fully filled trays, perforating or scoring between blisters, code reading and disposal of trim (wind-up or shredding). Machines may also incorporate anticurl devices, stacking of the trays, cartoning, etc. (Figure 13.3).

Thermoforming

Heating of the reel-fed base (tray) web is usually achieved by either infrared heaters or contact heaters. Heat may be applied at the forming stage or at a preheat station with or without further heating. The preheat station may be either a cylinder or platens; in certain instances the platens may be differentially heated (top and bottom).

The moulds into which the plastic is formed can be cooled by air, water or chilled water.

The web may be held by grippers, rollers, etc. as it is passed through the machine. Platen machines usually impart less tension to the web but generally operate at lower speeds, i.e. 8–12 m/min whereas 12–16 m/min can be achieved by continuous motion or by reciprocating motion machine with platens.

In general only the simpler materials can be thermoformed on cylinders using vacuum (e.g. PVC, polystyrene, PVdC coated PVC). Platens using pressure forming, particularly with plug assistance, not only offer more uniform blisters but can utilise the more complex materials, e.g. Aclar/PVC, polypropylene, coextrusions (Figure 13.4).

Feeding and filling

The type of feeding mechanism largely depends on the product being fed, i.e. suppositories, ampoules, tablets, capsules, etc., size and the number of tracks across the web. Uncoated tablets and capsules are normally fed from a vibratory bowl via channels or tubes by gravity. Vacuum extraction is frequently applied to the bowl, tubes, etc. to minimise powder and tablet chips which may finish up in the seal or tray. Conventional flat-shaped uncoated tablets usually present no problems, but sugar-coated or bevelled tablets with little side edge thickness may cause difficulties due to dovetailing or shingling. In such cases a rotary table feed may be used. A flood and sweep fill may be employed for sugar-coated tablets when speeds in excess of 300 per track are possible.

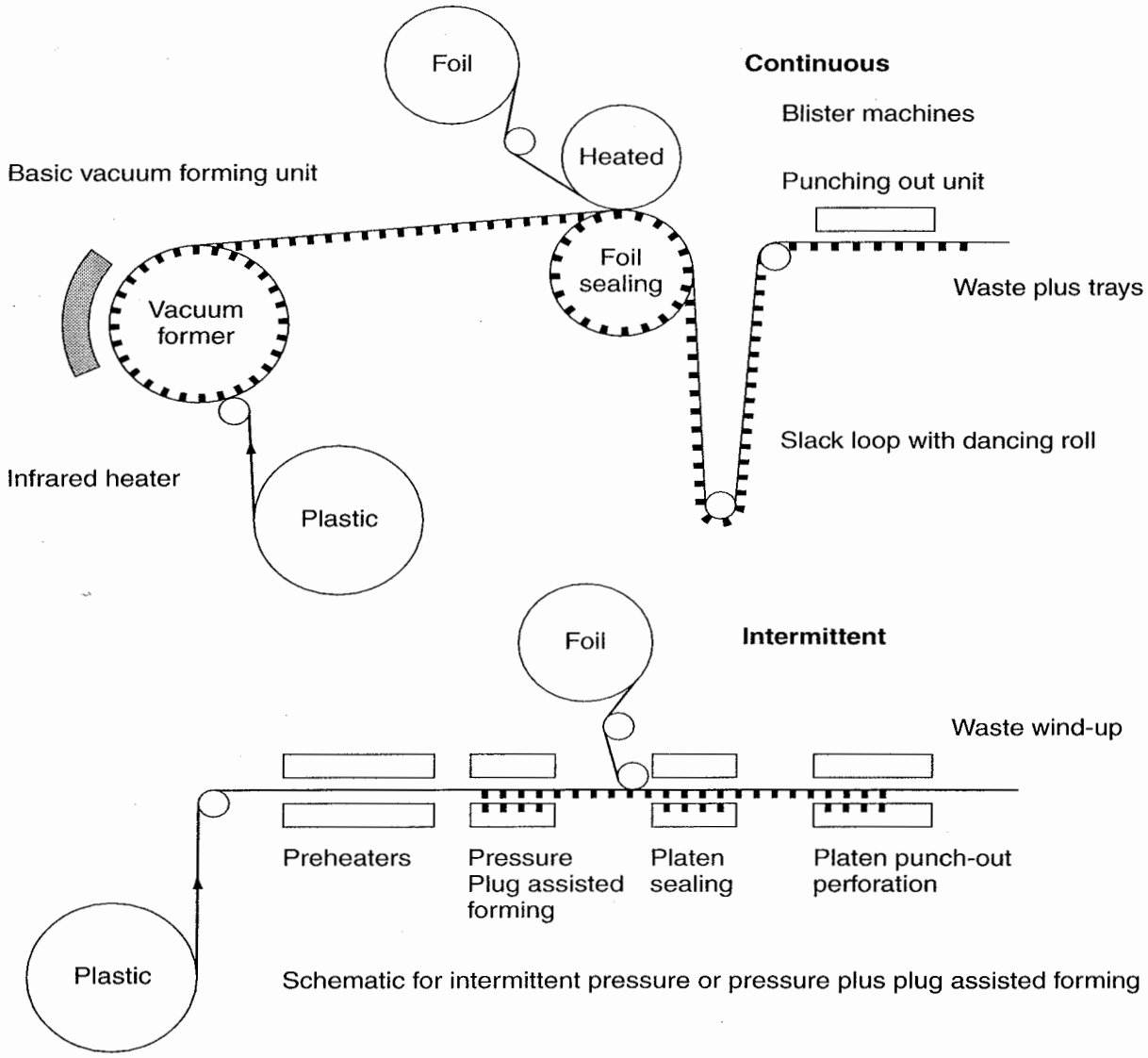


Figure 13.3 Blister machines

However, on most machines a fill speed of 250 items per minute per track is considered good. These speeds are related to the physical restrictions of feeding an item by gravity. Reciprocating tube fillers and chevron roller fillers are used on some machines where the close proximity of the tracks would cause restrictions to the filling speeds.

Lidding and heat sealing

As with the thermoforming process, heat sealing may be based on platens or cylinders or occasionally a combination of the two. Irrespective of the process the pocket must be sufficient to allow a clearance between the product and the lidding (normally around 0.5 mm), otherwise the product may adhere to the lid on heat sealing. The platen requires two uniformly flat surfaces with the base platen-shaped to accept the blisters. On certain machines one platen applies the heat via thermostatically or

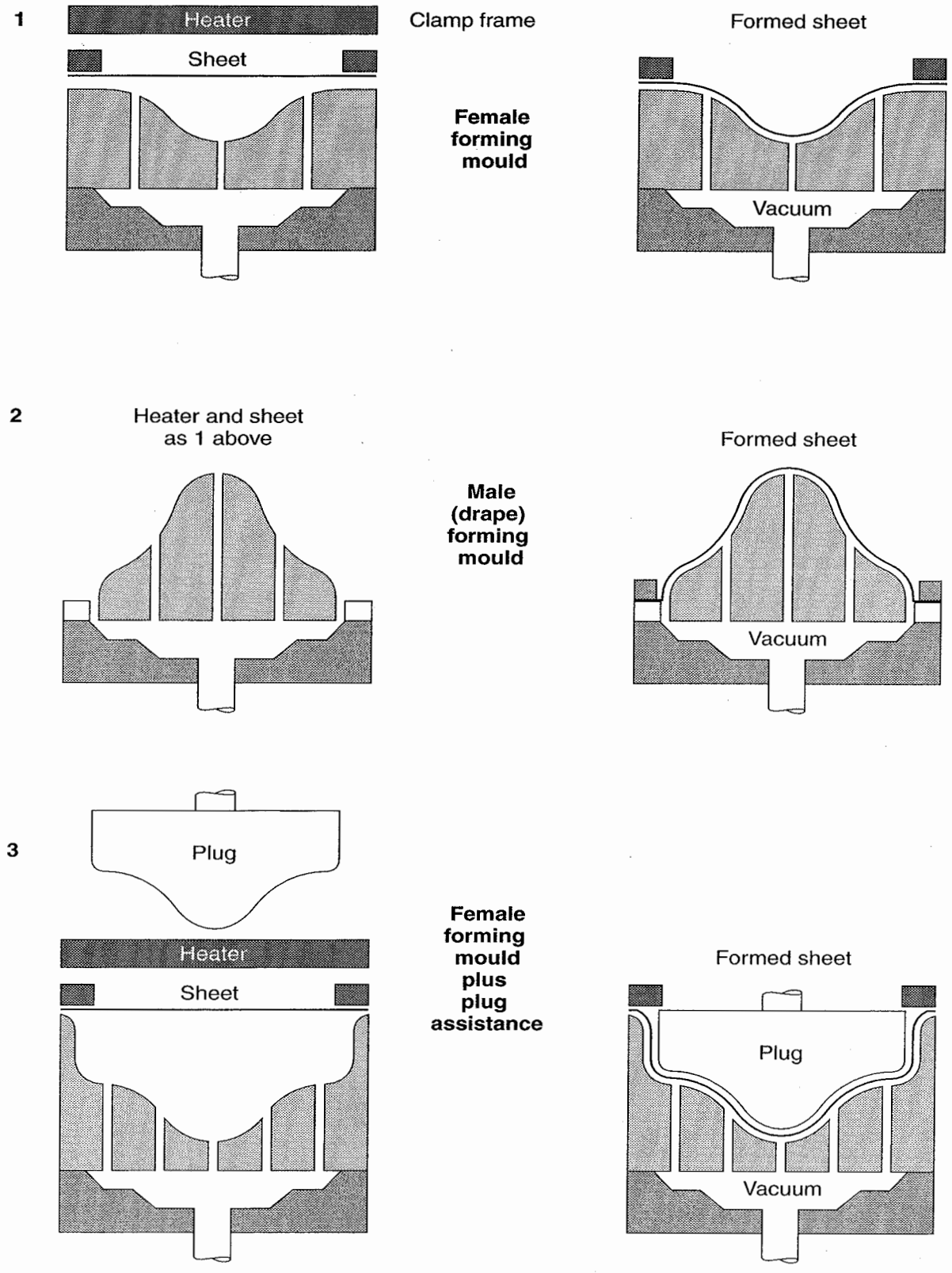


Figure 13.4 Thermoforming operations by vacuum

electronically controlled heaters and the other is cooled by air or water to facilitate rapid and effective sealing with minimum of web distortion. The platen process usually operates at a lower temperature and longer dwell time than cylinders, but can suffer from transferring more heat via the web to the product. On other platen machines the web passes through preheaters.

As stated earlier, uniformity of seal depends on the perfect matching of two platens which under well-controlled conditions undoubtedly gives a better seal. The pattern of seal may be line, pyramid or cross-hatch, but the last of these is invariably preferred. In the case of the cylinder type, the seal is achieved at the circumferential contact between two rollers, one of which is heated. As the process dwell time is very short, a higher temperature generally has to be employed.

It should be noted that the seal pattern is only on the heated platen or sealing roller, with the cooling platen or cylinder being smooth or flat (i.e. there is no impression or pattern on the plastic side of the web).

The effectiveness of either type of seal is checked by the uniformity of the seal impression, by vacuum tests or material deflection under vacuum/pressure.

Curl of trays (particularly relevant with hard foil)

The heat sealing operation can impart a degree of 'curl' into the tray, thereby creating problems for automatic enveloping or cartoning. The amount of curl depends partially on the type of machine employed, the type of web and design of the tray and what happens to the web when it leaves the sealing station. Theory suggests that the different coefficients of expansion for foil and film are partly the cause, plus film shrinkage due to molecular reorientation. Curl can be reduced or overcome by incorporating thermoformed ribs in the tray, or by reversing the web curvature by passing over a tension roller or through radiused guides. In the last of these the radius of the bend back has to be ascertained by trial and error experiments. Curl is less of a problem with soft foil as it stretches more readily. Between-pocket perforations or cuts can also reduce curl.

Removal from web (after perforating, where carried out)

Removal of the sealed trays from the web by punching-out or die cutting enables shaped trays without sharp corners to be produced. Guillotining, if used, invariably produces sharp corners which if not carefully handled may penetrate pockets of trays. Punching-out (unless a reciprocating or rotary unit is employed) is usually carried out as an intermittent action with platens. In the case of continuous motion machines the web is usually converted to intermittent by a 'slack loop' prior to either punching-out or guillotining. However, continuous motion can be retained by rotary die cutting, which is inevitably more costly in terms of dies and equipment. Wastage can be minimised in platen punching by staggering the action, i.e. 2 then 1 in a 3 tray across the web configuration. Reciprocating cutting forms can also maintain a continuous motion, hence increase output speeds.

Product inspection and between-pocket perforation

Product inspection prior to lidding suffered problems when the web jerked or slowed down/accelerated whereby items could be thrown out of the previously filled pockets. Although this aspect has now been eliminated from most machines, the after-lidding option had further problems when clear materials were replaced with dark tinted or opaque or foil/foil blisters to improve either child-resistance or moisture, light, oxygen protection. Thus depending on the machine or/and web materials, the original before and after lidding options remain. Prior to lidding inspection now offers mechanical/electrical sensing or an imaging technique, while after lidding tends towards either infrared or X-ray methods.

Perforation or similar options offer a means by which pockets can be readily separated and/or the prevention of any opening method from exposing more than one product. In the US-type peelable packs, perforation or something similar is usually essential to control the peel. Perforation may be achieved by true perforation (a series of bridges and cut-through zones), a part cut through by sharp blades or knives, or the use of a form of laser technology. Such operations usually require a larger between-pocket distance (3 to 4 mm increases to 5 to 7 mm), adding to the overall size of the blister. The operation is normally carried out either prior to the punching out or within the punching, guillotine stage. It must be performed on well-cooled trays, as warm or flexible materials are less easy to penetrate and can blunt the knives more easily.

Machine summary

Although individual machines may be built for specific functions, standard machines generally offer fixed platen or cylinder sizes. The factors which may have to be considered in the choice of a machine are:

1 area available per stroke on machine (width and length)
2 size and configuration of trays
3 area of wastage or minimum wastage
4 size of product and physical–chemical characteristics
5 type of material used for lid and tray
6 type of feed, number of feed tracks
7 output required or strokes per minute
8 critical nature of blister wall distribution and seal effectiveness
9 type of blister (push-through, peelable)
10 number and frequency of change-overs
11 type of forming available or necessary, e.g. vacuum, pressure, mechanical plug assistance, and combinations of these
12 type of heating available – radiant, conducted, preheat, etc.
13 type of web transfer, i.e. continuous, intermittent, or a combination of these
14 type of removal from web, punch or guillotine, etc.
15 need for perforations, scores or slits between pockets
16 whether machine is integral with a cartoning unit or can be coupled to one.

On some machines printing of the lidding by gravure or flexography can be added. Batch marking can be achieved by printing, embossing or debossing. Various types of product detection systems are available.

Invariably any machine is a compromise between a number of the more important factors.

Tray and blister design

As indicated earlier, total efficiency will relate to the minimal wastage and the maximum throughput. Both imply that the layout of the trays allows the use of a full web and this therefore means that the theoretically ideal blister shape may rarely be possible. Blisters should avoid square or near right-angled corners or bases as this may make release from the mould difficult and lead to thinning in those areas. Similarly, undercuts should either be avoided or be well radiused. Generally blisters should have an adequate clearance with the product and have an adequate radius at both the top (dome) and where the blister emerges into the tray flange. As vacuum forming gives less uniform wall distribution, this can be partially compensated by changing the angle of the draw from say 6° to 12°–20°, but this may add to cost if the tray size is increased to a point where output/tray per area is reduced.

Similarly, the draw angle is less critical with pressure and pressure plus plug assisted forming, where a draw angle of 3°–6° is usual.

Satisfactory seals can be achieved with a separation of 2–3 mm between blisters but there may be some danger of exposing the adjacent pocket when a product is pushed out. Thus 3–4 mm is more general for both between blisters and margin seals. With in-between pocket perforations or scores this distance becomes 5–7 mm. In the case of peelable blisters it is necessary to extend the peelable edge by at least 5 mm. Alternatively, a cut-away part of the blister tray either internal to the design or on an edge seal may be employed, to enable a good grip for the peel feature. Whether the edge seal remains uniform depends on such features as accuracy of registration, method by which web is held and drawn through the machine, method of tray removal from the web. If the tolerances of these is excessive then wider in-between blister and edges will be necessary. If a tray of the push-through type without perforations provides minimum wastage and maximum machine output, then any change to a larger tray (perforations, or perforations plus peel, etc.) will lead to fewer trays per stroke, more wastage and lower output. In the cost examples it has been assumed that the same output/wastage can be maintained with larger trays. This is based on the availability of machines with the best area per stroke. In practice this may not be possible.

Work in Germany by Professor Gadecke has shown that blister trays with properly designed perforations will meet the US protocol for child-resistant non-reclosable packs. In these tests children tended to be satisfied by tearing along the perforations rather than penetrating into the pack. Opaque or dark tinted plastics are essential to render the item contained therein less attractive. The advent of original pack dispensing (OPD) and the fact that the UK has not followed the European norm (European packs are based on 10s, 20s, 30s, etc., and UK on 7s, 14s, 28s, etc.) has led to various attempts to use common tooling for both. This has frequently meant that certain sizes have pockets blanked off, e.g. a 14 pack can be produced by incorporating a 'blank' in a 15 pack.

Protection and use

In order to obtain a full pack evaluation it is necessary to consider a number of requirements. For instance:

1 ingress from the atmosphere which may result in product deterioration, e.g. oxygen, moisture, carbon dioxide, microbiological hazards
2 migration of product ingredients from within the product to the outside atmosphere
3 migration from the pack into the product or reaction between the product and pack, e.g. discolouration, softening of the heatseal
4 mechanical damage to pack or product: note that on-edge stacking of blisters usually offers the best strength.
5 a convenient means for removing the product without exposing other units
6 the pack must satisfactorily retain the product for the declared 'shelf life'.

The above has to be established by laboratory testing prior to a formal stability programme. As with all pack selections, detailed knowledge of the product, the packaging materials and the process to be employed is an essential requirement. Blister packs are unlikely to give sufficient protection to products severely affected by moisture, oxygen, carbon dioxide, as all known plastic materials are to some degree permeable to these factors.

In such instances additional protection can be achieved by foil sachets, foil lined cartons or overwraps. If the last of these is used it is then necessary to establish that the 'shelf life' of a tray following its removal from its additional wrap is satisfactory for the 'in use' period.

Protection against moisture

The usual practice of making up a few blisters and placing them on test in a cabinet at 25°C 75% RH, 40°C 75% RH, etc., may produce very misleading results. In actual practice blisters may be enclosed in a carton (possibly overwrapped), placed x cartons per outer (overwrapped), y outers per pallet or with the pallet being shrink wrapped. All of these activities reduce the flow of moist air around the pack, and provide a possible series of moisture barriers. It therefore may not be surprising to find in 24–48 months' storage of a pallet that there is no actual moisture change in the product. Overwrapping of individual cartons or the outer can significantly increase the shelf life of the product. The predicted shelf life from a cabinet test may therefore carry an unnecessary safety factor or even indicate that a blister pack would not be suitable, when under actual conditions it could be acceptable.

Having established a pack/product by an adequate testing sequence, it is necessary to emerge with:

1 a fully and correctly specified product
2 fully and correctly specified packaging materials and finished pack
3 a recognised and defined means of bringing (1) and (2) together, i.e. SOPs.

The successful operation involves not only those who originated the pack and the product, but production and quality control. The latter will be involved in the inspection of incoming materials and the finished packed product.

Child-resistance, tamper-evidence/resistance and OPD (original pack dispensing, now called patient packs in the UK)

Blister and strips by their design are inherently both tamper-evident and tamper-resistant. In 1987 the PAGB, with the support of the ABPI, produced *Design Guidelines for Strip and Blister Packs*, which basically eliminates any 'flimsy' blister or strip packs that might be questionably child-resistant. The above design guidelines led to the issue of BS 7236 1989, *Non Reclosable Packaging for Solid Dose Units of Medicinal Products*. For further details see Chapter 11. An ISO standard based on ISO/EN 28317 has now been approved for reclosables but the standard for non-reclosables is still under debate. German standards for 'type approval' are based on DIN 55559 (more detail is given in Chapter 11).

OPD or patient packs

Although some people considered OPD as synonymous with blister and strip packs, any type of pack can be used. However, the advent of OPD will see a significant swing to blister and strip packs for a number of reasons, including the following.

1 Products are becoming more potent, hence tablets/capsules are smaller.
2 Sustained, delayed and controlled release products are reducing the 3 to 4 times a day dosage regime to 1 and 2, hence quantities and packs will become smaller.
3 Small packs are difficult to label and to accommodate the 70 × 40 mm or 70 × 35 mm community pharmacist's label.
4 Cartoned blister and strip packs give adequate label space and provide a means of collating a patient leaflet (i.e. flat rectangular cartons).
5 Cartoned blister and strip packs also provide adequate space for a bar code and a removable bar code if required for pricing bureau costings.

It should be noted that the volume resulting from the use of blister and strips will be more significant in the warehousing activities of the pharmaceutical supplier and the wholesaler. It will probably be less critical than the community pharmacist envisages, since lower stock levels of OPDs are likely to be kept compared with a bulk pack of 500, 1,000, etc., and the dispensing containers which have to be kept for their use. An actual reduction in space could occur as cartons stack better than bottles, particularly if the bottles are not contained in cartons.

Blister materials – trays and lids

The majority of the packs used in Europe are of the push-through variety. In these instances hard foil of 0.015 mm and above is used. This is adequate as the permeability of the plastic tray tends to be far higher than the foil.

Opaque or tinted materials are necessary if the pack is to meet the UK child-resistant requirements. Opaque films (usually incorporating titanium dioxide) tend to be slightly

more permeable than clear materials. Permeation increases with the filler or modifier content of the plastic.

Note that impact modified grades of PVC usually soften at a lower temperature hence may improve machine throughput. Vinyl acetate is widely used as an impact modifier. Impact modified grades generally show higher moisture vapour figures than UPVC.

Lidding materials can also use soft (annealed) foil (0.025 mm) or laminations of soft foil and other substances (tissue paper, glassine, etc.). Soft and embossed soft foil extends in the push-through stage, hence may give added child safety provided it does not damage the item concerned.

Environmental concern with reference to PVC and the fact that burning (possibly as a distinction from controlled incineration) may generate obnoxious acid fumes has created pressure on the pharmaceutical industry to move away from PVC. The alternative materials which have been considered include PET (polyester) and PP (polypropylene). Both require higher softening temperatures than PVC and good heat control, which can be more readily achieved with modern equipment with an effective preheat system. However, this only applies to certain selected and special material grades. Although these materials can be coated with PVdC to improve the moisture barrier, there are pressures to ban PVdC as it also contains a chloride component. Suffice it to say that the replacement of PVdC and its associated barrier/heat seal features may not be easy to achieve. Current opinion is that PVC will not be replaced.

Currently specific grades of PP are being preferred to PET and most machine manufacturers are offering modified machines which will handle these materials. For cold forming, multilayer materials are now being offered with two thinner layers of soft foil which are separated by a plastic ply.

Blister materials (tray – plastics)

In the following list, 1 = moisture barrier provided by PVC; 2–10 = times improvement in WVP.

1 PVC or UPVC (1). Homopolymer – may be opaque or tinted.

2 PVC (0.7). Impact modified (usually with vinyl acetate), up to 50% higher permeability. Can be opaque or tinted. Note that impact modified grades show white in fold area when bent over.

3 PVdC coated PVC (3–5). Usually 36–100 g/m^2 PVdC on various calipers of PVC.

4 PVdC coated PP (3–5).

5 Aclar*/PVC (10–15).

- Copolymers (Aclar 22A/PVC, Aclar 33C/PVC, Aclar 88A/PVC)
- Homopolymers (Aclar R_x 160/PVC, Aclar R_x 160/PETG, Aclar UltR_x2000, 3000 SupR_x900).

6 Polystyrene PS (0.2). Rather more brittle than PVC – improved by the addition of modifiers (increases opacity).

* Aclar is the trade name of polymonochlorotrifluoroethylene supplied by Allied Signal. (Generally, UltR_x3000 offers the best moisture barrier.)

7 Polypropylene – copolymer (3–5). Good resistance to WVP but poorer gas barrier. Not easy to control when thermoforming due to higher temperature involved, but improving with specialist grades.
8 Polypropylene – talc filled (1–1.5). Better thermoforming, but WVP only slightly better than PVC. Chalk filled PP is also available.
9 PVdC–PE–PVC, sometimes called triplex.
10

PVC	PE	PVdC	PE	PVC
100	30	180	30	100 μm

11 PET (polyester) selected grades (usually as a copolymer), e.g. PETG.

Blister lidding materials (push-through)

Foil hard 0.018–0.020 mm plus 6–8 g/m^2 wax, 4–12 g/m^2 vinyl type lacquer or PVdC coating of 10 g/m^2 and above. Lowest foil gauge in use is 15 μm. Note that special HS lacquers can be formulated to adhere to PVdC, Aclar, PP, etc.

Hard foil tends to be more expensive than soft foil if the former has to be subjected to the removal of lubricants by solvents before it can be washed, lacquered and/or printed. However, low-temperature heating (below the annealing temperature) has also been used to remove the oil-based lubricants.

Foil soft 0.025 mm and above plus wax, vinyl type, PVdC or HS coatings for heat seal – note that greater stretch risk with soft foil necessitates a thicker gauge. When soft foil is laminated with 35 g/m^2 glassine, improved child-resistance is achieved. Note that most foils have a primer coat applied on either side prior to coating, printing or laminating, etc.

Peelable

Paper-foil–heat seal lacquer of various combinations. Also cold seals.

Note that heat sealable lacquers have to be 'compatible' with the tray material. If PVC/PVdC is formed with the PVdC on the inside of the blister, a PVdC type compatible lacquer is necessary for the lidding material. All lacquers should be checked for peel strength both initially and at each shelf-life period (1, 3, 6 months, etc.) as ageing effects have been detected, e.g. push-through becoming peelable and peelable becoming permanent (Figures 13.5 and 13.6).

Cold forming (or mechanically formed blisters)

Laminations of plastic and foil, usually of 40 μm + foil, can be physically formed on modified blister packing equipment by a cold mechanical forming operation which is carried out between male and female dies. These laminations of plastic and foil enabled foil to flow without flex cracks during forming although limitations in draw angles and forming depth still remained. This limitation has been improved (but not totally overcome) by using a modified aluminium alloy, the selection of the lamination, the forming design and the best machine factors. The forming material currently consists of such combinations as a biaxially oriented plastic laminated to 40 to 60 μm, aluminium foil and an internal (third) layer of plastic (PE, PVC). Cold forming is also being achieved with multilayer materials containing two layers of soft foil separated by a polymer layer.

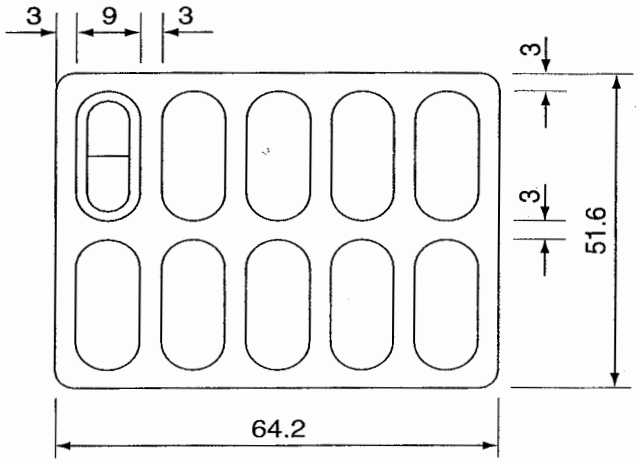


Figure 13.5 Conventional push-through pack

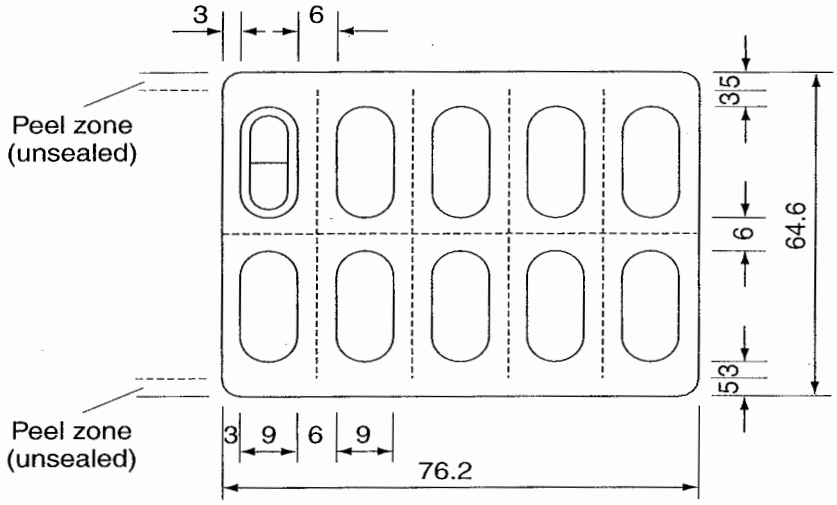


Figure 13.6 Same as Figure 13.5 but with peelable pocket perforations

Cold forming processes have been developed using a number of basic ideas, as follows.

1 Clamping the material and carrying out a true punch action where the non-held area is extended (stretch forming).
2 Taking a foil which has been embossed or finely creased; can be extended by air or mechanical pressure without showing flex cracks.
3 Taking a reel of material with regular cross-direction slits (as used on Servac suppository machine). A male/female mechanical forming operation is carried out between each slit. This mechanical operation forms the foil and the slit area moves (opens), thereby preventing any high degree of stress (uses 12.5 μm OPP/40 μm foil/HSL).
4 Latest innovations include a double forming operation which reduces the tray size to 20% (Advanced Forming Technology (AFT) process). These tend to use Teflon stretching dies.

Stretch or cold forming

Although foil is an excellent barrier material, gauges of 40 μm and less were difficult to form without fracture. This was partly due to the fact that metallic materials have a crystalline structure and commercially pure grades of aluminium foil had a grain size of around 40 μm (foil of 40 μm was likely to be a mono-grain layer). By the production of special foils of smaller grain size, new 40 to 60 μm foils consisting of multiple layers can more readily stretch without any fracture risk. Laminating this foil to biaxially oriented polypropylenes, polyamides and polyester films further added to the stretch forming possibilities.

It was also shown that the better the laminating bond between the foil and the plastic, the better is the forming operation. To date a typical forming ratio is approximately 1 : 2.5 (i.e. a cavity diameter of 20 mm would have a depth of 8 mm), using polyamide/aluminium 40 μm /polyamide/PVC film.

In the development of the above technological progress, two selected techniques have been employed:

1 the MAD unit developed by Bosch (a machine to measure multiaxial elongation)
2 Hoogoven screen – a specially printed screen from which stresses and deformation during forming can be quantified (also useful for plastic films).

Summary

Cold or stretch forming is growing as a commercial operation. The factors which influence the stretch forming operation include:

1 the gauge and type of foil used
2 the fineness of the crystalline structure of the foil
3 the design of the formed area including angle of draw and the depth of draw (width to depth currently does not exceed a ratio of 2 : 5)
4 the structure of the supporting or carrier lamination including the uniformity of the oriented plastic
5 positive lamination between foil and outer ply
6 the forming speed and the friction properties of the laminate
7 the quality of the die, especially the surface finish.

However, further improvements should not be overlooked. New laminations and configurations have recently become available to improve further the child-resistance features of both blisters and strips. In the USA these are typically peelable configurations.

Tropicalised lidding

While cold forming remains relatively expensive, alternative ways of obtaining excellent moisture protection will be sought. Putting a foil lid over the tray section and sealing it to the blister margins, known as the 'tropicalised' blister, is now available from several suppliers. This type of lidding may be achieved by a preforming operation, thereby allowing a seal with relatively narrow margins or by direct lidding (no stretch)

with a more gradual 'draw' and wider margins. Both methods increase the pack size and add to costs.

Costs

Costs are related to material prices, output speeds, wastage, machine depreciation, downtimes, etc. (see below). Depending on the choice of material, blister packs of the push-through variety can be as economical as glass bottles in quantities up to around ninety items per pack. At quantities below twenty-five items, there are positive cost advantages in most cases. Both these comments must be accepted as rather general statements – the actual break-even point has to be calculated for each set of circumstances. The above indications assume that both a glass bottle and the blisters have to be packed into cartons, with a CRC fitted to the bottle pack.

Greater emphasis has been put on blister packaging systems in recent European developments. Most machines can be coupled with a leaflet/cartoning system. In many instances the cartoning operation is an integral part of the blister machine. Labour costs can change relatively rapidly, particularly at times of rapid technical development, allied to salary inflation, so it would be misleading to include details in this chapter. However, in general, labour costs on bottling/blister lines of a similar size will largely be comparable.

Continuing competition is expected between cold form and tropicalised blisters, which compared with straight PVC blisters, offer area ratios of 60×48 (PVC), 70×58 (tropicalised) to 112×66 (cold form) with cost ratios of approximately 100 : 170 : 285.

Summary

Blister packaging equipment can extend from a fairly basic piece of machinery which covers a form fill seal, and removal from the web operation to a highly sophisticated unit covering a far more complex range of operations. Invariably complexity must be associated with higher prices, more highly trained operatives, less flexibility, etc. Plastic blister materials cannot offer full climatic protection, hence additional protection may have to be achieved by some form of overwrapping system.

A broad summary can be made of machines, materials, outputs, costs, etc. in comparison with glass and plastic bottles, metal cans, and strip packs as shown by the general costings. As the requirement for a unit dose or multiple unit dose increases, both blister and strip packs are ensured of a significant increase. Blisters may gain in space and cost saving but lose out in climatic protection, unless cold formed foil, a foil tropicalised blister, or an overwrapping system is used.

New machines, cold forming, a plastic/foil blister/pocket, which use areas of materials between those of blisters and strips are also likely to increase. Whether these are actually strips or blisters will depend on the forming process used.

In summary, any individual type of dosage form offers obvious advantages in product hygiene, personalisation and protection if the correct materials are selected. It also enables the patient to carry a daily dose readily.

Finally, in small quantities of items (say fewer than seventy-five) blister packs are likely to be both economical and competitive with other packs, showing in addition a weight saving with a volume increase.

Normally the lidding is printed (for transparent trays both sides can be printed) but not the tray. On-line or in-house printing of lidding materials is increasing.

Note that semi-automatic blister packaging employing large preformed trays which are filled by hand then lidded from reel or sheet, followed by punching-out or guillotining, can offer speeds of around 1,200 items per minute with two or three operators. Under such conditions prices can be reasonably competitive with more sophisticated automatic equipment, particularly if runs are relatively short and a variety of tray and product sizes are involved. This can be particularly useful for clinical trial supplies.

Controlled or monitored dosage systems for the elderly

Various blister tray systems using large blisters which will take several products are now being offered for elderly, infirm, arthritic patients, etc. These trays normally hold twenty-eight to forty-two blisters, which are filled with the patient's medication and then lidded. The nature of the medication can be marked in various ways, i.e. water tablets, heart capsules, etc., with clear indication when each is to be taken, e.g. morning, mid-day, bedtime. In some systems these times are colour coded.

Examples of these include:

- Manrex Controlled Dosage Medication Systems
- Nomad by SurgiChem
- PCI (Pharmacy Consultants Incorporated)
- Webster Systems (now taken over by the Boots Company)

and may be found in the USA, Canada, the UK, Holland and Australia.

It is forecast that these systems will increase in popularity, particularly as the elderly population is showing a steady increase, often residing in special homes.

The pharmacist normally purchases the blisters in reels, and has a special sealing machine for the lidding operation. The pockets can usually be individually labelled (on the lidding) using a computer-based system involving self-adhesive labels.

Since the monitored dosage systems conflict somewhat with the OPD concept (a pharmacist does not like transferring products from blisters and strips) there may still be a need for a bulk pack, particularly if the use of these dosage systems continues to expand.

Blisters – liquids and semi-liquids

Although conventional horizontal formed blisters can be used with semi-viscous to viscous products (or even smaller quantities of liquid), it is necessary to turn them to a vertical position if a higher fill volume per pack is to be achieved. Filling single or double sided formed blisters in the vertical position can be carried out in cut individuals, cut sticks or an intermittently or continuously reel-fed system. Initial attempts to utilise a double sided formed blister led to low operational speeds. The introduction of laminate or coated webs whereby the sides of each web can be heat sealed led to significant increases in output. For example, the Lamps san Prospero, Unifill machines (Elopak) can produce packs with liquid volume fills between 1 and 90 ml with output speeds of up to 20,000 an hour, Dott. Bonopace also offers machines, a development of

its suppository packs, where preformed blisters are delivered in reels. In theory machines of these types should be capable of aseptic production and hence in the long term could compete with other machines which operate on aseptic systems.

In the food industry such equipment would use either a presterilised web exposed by a removable peelable layer, or UV or hydrogen peroxide as an on-line surface sterilising agent. Currently none of these would be acceptable for a pharmaceutical operation, although use for sterile oral liquids might bear consideration.

Strip packs

Strip packs present an alternative form of pack for a unit dosage. Strips can be produced from single or multi-ply materials, provided the two inner plies can be sealed by heat or pressure (e.g. cold 'self-adhesive' seal). Materials can range from relatively permeable plies to those which incorporate a foil ply of sufficient thickness (and effectiveness of seal) that an individual hermetic seal is produced for each dosage. To date strip packs are usually produced at lower speeds and also occupy greater volume than blisters. The break-even cost with glass containers largely depends on the material used, output speed, and item size.

Strip packaging process

Basically a strip pack can be formed by introducing an item which extends a pocket area during insertion or by a preforming operation prior to filling (see Figures 13.7 and 13.8). As the latter method gives less strain (or more controlled forming) to the pocket area and reduces the material needed by 20–35%, it is suggested that this type of strip pack may increase. Either one or both sides of the plies may be mechanically formed, but this process can only be applied to materials which will 'stretch' without tearing.

Strip packaging machines are far simpler and smaller than blister packaging units, usually simply consisting of a feed system, product insertion plus heat sealing, and a guillotining operation to size.

Feed is usually via a vibratory bowl with feeding tracks (usually up to a maximum of sixteen). Alternatives are a rotating table plus drop or sweep. Most machines employ a

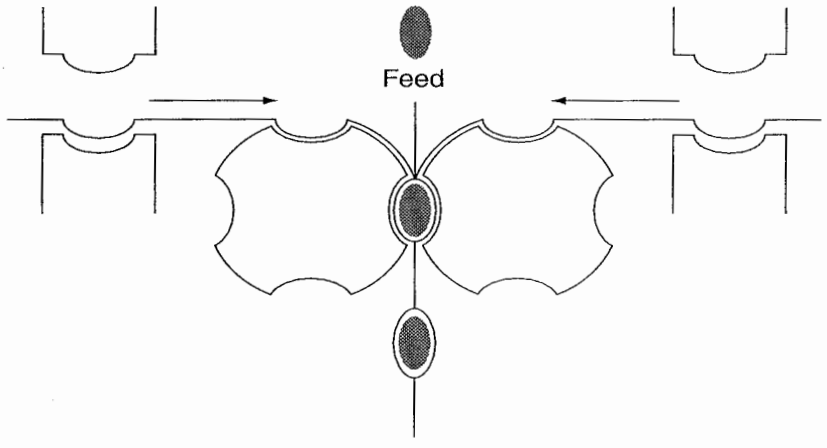


Figure 13.7 Strip pack preformed pocket

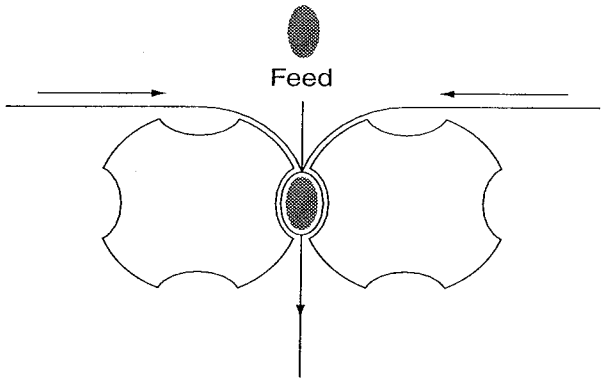


Figure 13.8 Strip packs in item formed pockets

vertical feed (gravity drop) but occasionally the web is run horizontally with a platen-type sweep. The pocket area is created by recesses either in a platen or more usually in a heat sealing cylinder, where a circumferential point seal is made between two intermeshing cylinders.

As with blister packs, the maximum speed depends on the size of the item and gravity. A maximum speed of 250–300 per track is likely with a 325 mg (five grain) type of aspirin product. Removal of powder, chips, etc. is achieved by vacuum extraction.

Cutting of the emerging web is invariably done by either a scissors or guillotine motion or rotary die cutting. Additional stages which can be incorporated into the machine include printing, perforating, batch coding, magic eye registration, etc. As distinct from blisters, perforation does not usually add to the seal width, as pocket seals are nominally 5 mm or more. Most machines use two separate webs but occasionally a single centrally folded web may be employed. Strip packaging is closely allied to sachet packing and in certain cases it is difficult to differentiate between the two. Two different plies can also be used (top and bottom) provided the sealants are compatible.

Machine speeds

A few eight-track machines exist (maximum output around 2,000 items per minute); four, two and single tracks are more usual with outputs of 1,000, 500 and 250 respectively. As a result of this speed limitation, few machines are coupled to a cartoning unit.

More recently sixteen- and thirty-two-track machines have achieved output of 4,000 and 8,000 items per minute. These are similarly priced to blister units and have an integral cartoning option.

Strip designs

Strip designs are very basic, as the emerging units are invariably rectangular or square strips. The pocket portion can, however, be round, oval or square. The pocket area is critical to the diameter, shape and thickness of the product. If the pocket is too 'tight', tearing, perforation of the pocket periphery or wrinkling of the seal area may occur (Figure 13.9). The seal width may be as low as 4 mm, but usually 5 mm and above is employed. If the seal area is likely to wrinkle or crease then wider seals may be

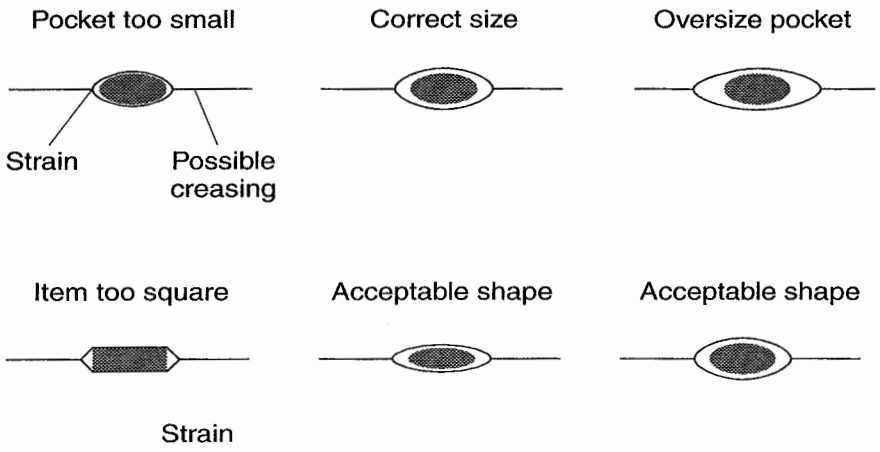


Figure 13.9 Strip packs in item formed pockets

necessary. It should also be recalled that the cylindrical-type sealing process does not usually have a distinct cooling cycle – hence any pull on the seal ply will tend to weaken the seal when the sealant is still pliable. This is particularly relevant with foil, where it may be necessary to have air cooling cylinders if a small seal margin is used. Warm materials are frequently more difficult to cut than cold materials. This may introduce a need for extra cooling or moving the cutting operation further away from the heat sealing area, as a 'soft seal' may string or prevent a clean cut. Use of cold seals (self-adhesive materials) is extending, particularly as such materials can be sealed at higher speeds than conventional heat seals.

Machine sizes and heat control

Most strip machines consist of two cylinders driven from a large one-sided control box. This inevitably creates possible heat control difficulties, particularly as the cylinders get either wider or of greater diameter (i.e. the drives act as a heat sink, whereas the ends furthest away from the drives are exposed to air). Based on this, the greatest heat is likely to be retained somewhere between the two ends of the cylinder, possibly causing overheating, metal expansion, leading to pressure increases, etc.). Latest machines therefore incorporate two-ended supports (or drives), thus allowing wider diameter and longer cylinders to be used.

Materials

Full details and examples of typical materials are given in earlier chapters, so they are not covered here.

Materials employing foil inevitably provide the best, indeed excellent, protection provided an effective seal is achieved and the foil is not unduly stretched to form perforations during the handling.

Vacuumised metal coatings are gradually improving. Tests indicate that these substantially increase the protection offered by plastic materials but do not equate with a ply of foil. Two plastic plies, each with a vacuumised foil, when laminated in direct

contact with one another, can give excellent barrier properties. The barrier properties achieved by metallisation may reduce somewhat once the material becomes creased. Protection from some of these creasing effects can be improved by the incorporation of a more flexible ply (e.g. LDPE), i.e. PET metallised/LDPE. PET is very resistant to tear, hence needs a tear initiation feature. It also confers child-resistance.

Costings

Good protection means the incorporation of a foil ply, but such packs are usually greater in cost than either a blister or blister with an overwrap. This is due to the cost of the material, the greater area involved and the likely lower production rate.

Cheaper plies such as regenerated cellulose film provide the lowest cost form of unit pack coupled with restricted protection, but this can be improved by an overwrap. PVdC coated PP is the preferred substitute material today.

Volumes

The volume occupied by strip packs is invariably high. Some reduction can be achieved by preforming the pockets. Cartoning with the more flimsy materials may create difficulties. For single strips, envelope or catch covers are a useful alternative to cartons. They also make cartoning a much easier operation. Particularly useful for clinical trial supplies (Figure 13.10).

Identification

Strip plies are usually printed by gravure or flexographic processes either on or off the strip pack machine. Registration is usually carried out on one ply. Repetitive printing is frequently employed, i.e. three repeats to two pocket areas, so that one full print will appear on each unit.

Conclusions

Strip packs incorporating a suitable foil ply offer excellent protection and are superior to all reclosable packs (there are no risks associated with opening and reclosure) and conventional blister packs. In general strips are produced at lower speeds than blisters, occupy a greater volume, and are more expensive. Cellulose or OPP films (single ply)

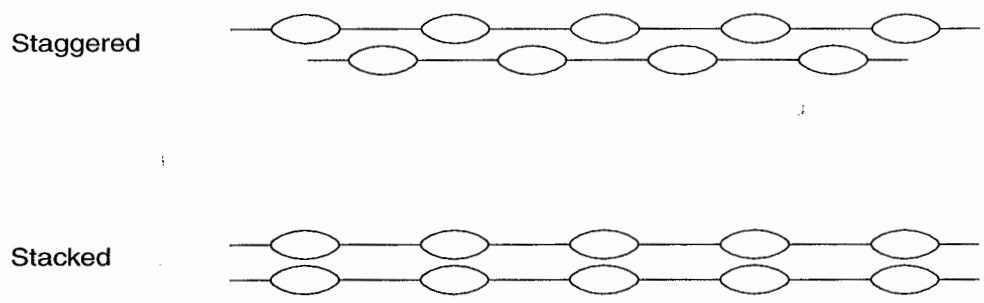


Figure 13.10 Staggered and stacked configurations

are likely to break even with bottles of 100 items, and a foil ply with 20–25 items. However, certain sophisticated machines handling 1 inch effervescent tablets offer high speeds of over 7,000 items per minute, hence are faster than most blister machines.

Strip packaging machines are generally more flexible than blister packers; change-over times are shorter and much lower in cost (except for the very widest machines). They are, therefore, more ideal for short runs. The largest machines with integral cartoning are similar in price to the fastest and largest blister units.

Machines can readily be coupled with catch covers (Wrapade and Siebler machines) and due to their smaller size have versatility in movement between packaging lines.

One of the most widely used materials with excellent moisture protection is paper, 40–45 g, extrusion coated LDPE, 12 g/m^2, 7–9 μm soft aluminium foil, 25 g/m^2 LDPE. The presence of two layers of plastic more than amply fills in any pinholes in the foil layer. The same laminate is also widely used for sachets and is technically preferred to a similar laminate with the foil on the outside.

Package integrity

The need to check pack integrity has increased in importance, both to guarantee product shelf life and to ensure that the product has not become 'contaminated' from some external source. Contamination may be related to organoleptic, physical, chemical or biological change, e.g. increase of bioburden, loss of sterility, which may be related to closure effectiveness.

Improving pack integrity can be related to on machine control (i.e. the quality assurance approach) or quality control (regular checks are made on the packs produced). Until recently the historical way of checking the integrity of blisters, strips, sachets, etc. involved the use of destructive-type testing, e.g. vacuum tests under water, burst tests. The more recent introduction of non-destructive tests should therefore not only improve output, but enable better on-line statistical evaluation to be carried out, thereby giving a better feedback on machine performance. This also means that where seal integrity is lost or is suspect more effective corrective actions can be undertaken, including improvements in on-line controls (i.e. more emphasis on quality assurance). Non-destructive testing equipment is usually based on a dry pressure vacuum procedure followed by detection of pack distortion (deflection) or non-distortion (non-deflection), i.e. packs with effective seals become concave then convex as positive pressure changes to negative pressure, while leaking packs either do not change or show less or limited distortion, depending on the scale of the leakage.

Vacuum tests

Vacuum tests under water vary from company to company. BS 7236 1989, Non-Reclosable Packaging for Solid Dose Units of Medicinal Products, gives the following seal integrity test.

> Immerse the test package in a container containing coloured water (15–25 °C) and place the container in the vacuum chamber. Apply the appropriate vacuum of 33 kPa (250 mm of mercury) for strip packages or 24 kPa (180 mm of mercury) for blister packages, for 30 s. Restore atmospheric pressure and

remove the container from the vacuum chamber. Remove the test package from the container and blot off the excess water. Examine the package for ingress of water into the pockets.

Pinholes and foil (aluminium)

Pinholes normally refer to the minute holes which may be present in the foil after conversion. Foil of 0.017 mm caliper and above is generally recognised as commercially pinhole-free. 0.025 mm foil can normally be 'guaranteed' pinhole-free. Foil below 0.017 mm gradually shows an increasing number of pinholes. However, the WVP of foil of 0.006 mm is lower than any nominal gauge of plastic when used in a heat sealing lamination. When foil is laminated or coated the initial pinholes tend to be 'filled in', thus reducing any permeation risk still further. Permeation is then related to the plastic which covers the pinholes.

In the case of blister packs permeability via the foil side is extremely low, hence permeability relates mainly to the plastic of the tray and the wall distribution. With strip packs permeation may occur through edge seals, or more likely capillaries created by creases in the edge seal, as well as actual foil perforations. In general pinholes and perforations cannot be detected by vacuum dye tests as the plastic plies normally remain intact. Capillary leakage can be detected by this method – it may be assisted by adding a wetting agent to the solution.

Although the effect of pinholes may be minimal, the shelf life of the product can be reduced where the pack is exposed to high humidities for prolonged periods. Pinholes are likely to be irrelevant for short shelf life or rapid turnover products, where a certain degree of risk can be taken. See Chapter 10 for more details.

Sachets

Sachets achieved success when the first effective heat sealants were marketed. Their use, initially as a replacement for powders in folded paper, was extended into granules, moisture sensitive solid products and liquids (particularly shampoos).

Sachets can be fabricated from a single web with a centre fold, using a three or four sided seal or two webs using a four sided seal. The reels may be fed horizontally or vertically and be sealed by a series of heated platens or rollers (cylinders) or a combination of the two. In certain ways they are an enlarged version of a strip pack. The sachet seal can also be made peelable by a non-seal part on the web which may involve a pattern lacquer rather than a full heat seal coating. Difficult to tear plies, like PET, can also be used provided a cut or V-notch is added to initiate the tear.

Small sachets usually start with narrow seal margins of around 5 mm, but become wider as the weight of the contents increases. Like strip packs, an over-tight fill should be avoided, as this can lead to perforation on the inner side of the heat seal and capillary channels, resulting from seal creases. Although seal patterns can follow strip packs, line seals, either all parallel or across at the top and down at the sides, tend to predominate. A cross seal at the top tends to give a more secure seal whereas parallel downward lines make for an easier tear open feature. Although sachets can be received preformed for filling, reel-fed processes based on a form fill seal principle are

preferred. Speeds of between sixty and ninety sachets per track can usually be achieved.

Sachets also have the advantage that they can be used for liquid and semi-liquid packaging. Flow wraps are a further extension of a sachet-type pack. Both have been widely used as a protective overwrap to extend the shelf life of blisters.

Recent developments in blister and strip packaging

Although this question could be answered in terms of material, machinery and their performance, where each may be influenced by the properties of the product, costs, change-over time, output, etc., there are broader issues today, i.e. what standards should be used for child-resistance, how does one improve moisture protection, etc.

Although cold formed materials started with 40 μm foil and utilised a relatively shallow well-radiused draw, perforation problems with the foil have arisen. As a result, 45–50 μm foil has been substituted with gauges available up to 60 μm.

Most machines, which are now based on pressure forming with plug assistance, can be adapted to cold forming. There has been a tendency for a machine to occupy less length by operating over two levels or by doubling back on itself. Although maximum speeds of over 6,000 items per minute are still relatively rare for conventional blisters, higher speeds are predicted.

Aclar copolymer based materials using 22A, 33C, 88A have more recently been challenged by the homopolymer R_x series with lower costs coupled to good moisture barrier properties. However, there are many alternative overwrapping systems which may be used to improve moisture barrier. In this context the Japanese have recently introduced silicon oxide coated PET overwraps. Use for thermoforming, a multilayer material, a coated material, or the lowest cost material with some form of overwrap remains an emotive issue as to which is most environmentally friendly. Multilayer materials are likely to be the most difficult to recycle, but recovery of energy may be possible by effective incineration. One newer material for cold forming uses two thinner layers of soft foil separated by a polymer layer, while another has involved a double forming process (AFT).

Machinery and machine improvements

Machine improvements include use of larger reels (frequently now without joins), various forms of preheat with variable temperature ranges either side of web, preference for pressure forming with plug assistance, improved cooling of moulds, possible preheat for foil sealing section, automatic splice facility, Geneva driven notched drum for accurate forward progress and accurate registration, on-line printing, e.g. flexo, accurate perforation or cutting, minimising of curl, improved GMP, faster changeovers, integrated cartoning, microprocessor–computer controls and fault diagnosis, etc. Removal of the blisters from the web with the minimum of wastage is now the rule rather than the exception. Machines have also become more compact, with a trend towards more versatile units. Modular machines and Servo technology driven systems are also being offered.

Deblistering units (on and off the machine) are more readily available.

Tamper-evidence, tamper-resistance and child-resistance

Emphasis on the above continues to grow, with the result that some companies do not know the current state of the art. Companies therefore continue to present attractive looking products to children in clear materials and design blisters where the products interact when the blister is bent into an arc, with the risk of the items literally 'popping out'. Fuller information on the subject can be found in Chapter 11. It is of interest to note that since the introduction of child-resistant packaging, commencing in the mid-1970s in the UK, there has been a significant reduction in the reported cases of child poisoning instances. This has involved those reclosable CRCs which have passed a test using children and non-reclosable packs which have not passed any test but have shown a significant growth in use over that same period. Although this implies that either many blisters, strips, sachets, etc. are inherently child-safe or children are less interested in a pack where the product is not visible or shows less rattle (compared with tablets in a container), there is still a need to improve the more 'flimsy' forms of pack. In addition, many child-resistant packs still present opening problems to the ever-increasing elderly population who rely on regular medication in order to survive. This can result in either inadequate replacement of the closure or the transfer to open containers, thereby exposing both the product and children at risk. The industry has still to address these concerns fully.

Costs

A summary of typical comparative costings based on glass, metal, strips and blisters is given in Table 13.1. Earlier published tables also gave comparisons in terms of volume and weight, related to both incoming materials and finished packs. It should be noted that costings can significantly vary according to individual circumstances.

It must be stressed that Table 13.1 gives examples based on specific circumstances where many of the factors can change between different companies, hence each organisation must do its own costing exercise for its own particular operation.

Table 13.1 Comparative costings (costs cover materials, labour, carton, outer pack, etc.)

Item	*Pack*	*Cost ratio*
Bottle glass	10s	1.15
Bottle glass	100s	1.9
Bottle plastic	10s	1.00*
Bottle plastic	100s	1.75
PVC push-through blister	10s	0.40
PVC push-through blister	100s	1.95
PVC blister, peelable, perforated	10s	0.55
PVC blister, peelable, perforated	100s	2.15
Can metal, aluminium	10s	1.70
Can metal, aluminium	100s	2.60
Strip (paper/foil/polyethylene)	10s	0.70
Strip (paper/foil/polyethylene)	100s	3.65

*Plastic pack taken as unity for ten items. Actual costs will vary according to the machine, output, labour, etc.

Semi-automatic blister packaging equipment

Other than being used to pack solid dose medication, blisters or bubble packs, as they are often known, may find further applications in pharmaceutical packaging. These may be as a protective overwrap against physical damage, to prevent ingress or egress, to aid display or to act as a tamper-evident/tamper-resistant feature (i.e. packs which are not involved with the solid dosage form).

Although the same principles apply to semi-automatic machines, sheets may be used instead of reels. The types of material and the process employed tend to be based on their economic and strength characteristics. Where a tray or container is not required for a direct form fill seal operation, the thermoformed item can be fabricated either in a female mould or over a male mould. The various combinations of vacuum, pressure and mechanical (plug assist) are indicated in drawings. With vacuum forming, and where a female die is used, the process is called straight vacuum forming. If a male die is used, the process is termed drape forming. In air pressure forming, greater pressures may be employed.

The majority of the individual type of blisters are made by vacuum forming either into or over (drape type) moulds, which are frequently made from metals such as aluminium. The choice between female and male moulds depends on a number of factors, as follows.

Female

Base (flange) is thickest, and uniform; top of mould is thinner. Formings can usually be put closer together therefore more mouldings per sheet. No webbing between moulds. Limitations in depth of draw. Good radiused corners required – not suitable for sharp corners. See Figure 13.11.

Male

Base (flange) is thin and non-uniform; top of mould is thickest. Capable of greater depth of draw for a given caliper. May tend to web if layout is not properly designed. Needs greater space between mouldings (rule of thumb 1.5 × draw height) therefore fewer mouldings per sheet. Capable of achieving relatively sharp corners. See Figure 13.11.

Plug assistance can be used, particularly where webbing is likely to occur, but this generally slows output. Air holes for venting vary between 0.50 mm and 1 mm for most small mouldings.

Mouldings can be 'ribbed' to improve strength or to enable a thinner material to be used, e.g. 300 μm reduced to 200 μm by ribbing. Improved wall distribution can also be achieved by extending the softened plastic sheet by vacuum or pressure prior to final forming (often known as balloon or bubble extension).

Materials

When clarity is required PVC, PS, PET, or cellulose acetate may be used. The last of these tends to cost more even though the moulding cycle is approximately 25% faster; this does not compensate for the higher material cost (+30%). Impact modified styrene or styrene is more widely used for coffret-type inserts which are invariably coloured or flock coated. Styrene offers a higher yield than PVC (note densities) and a faster forming time. PET is often the preferred material for surgical or medical device systems.

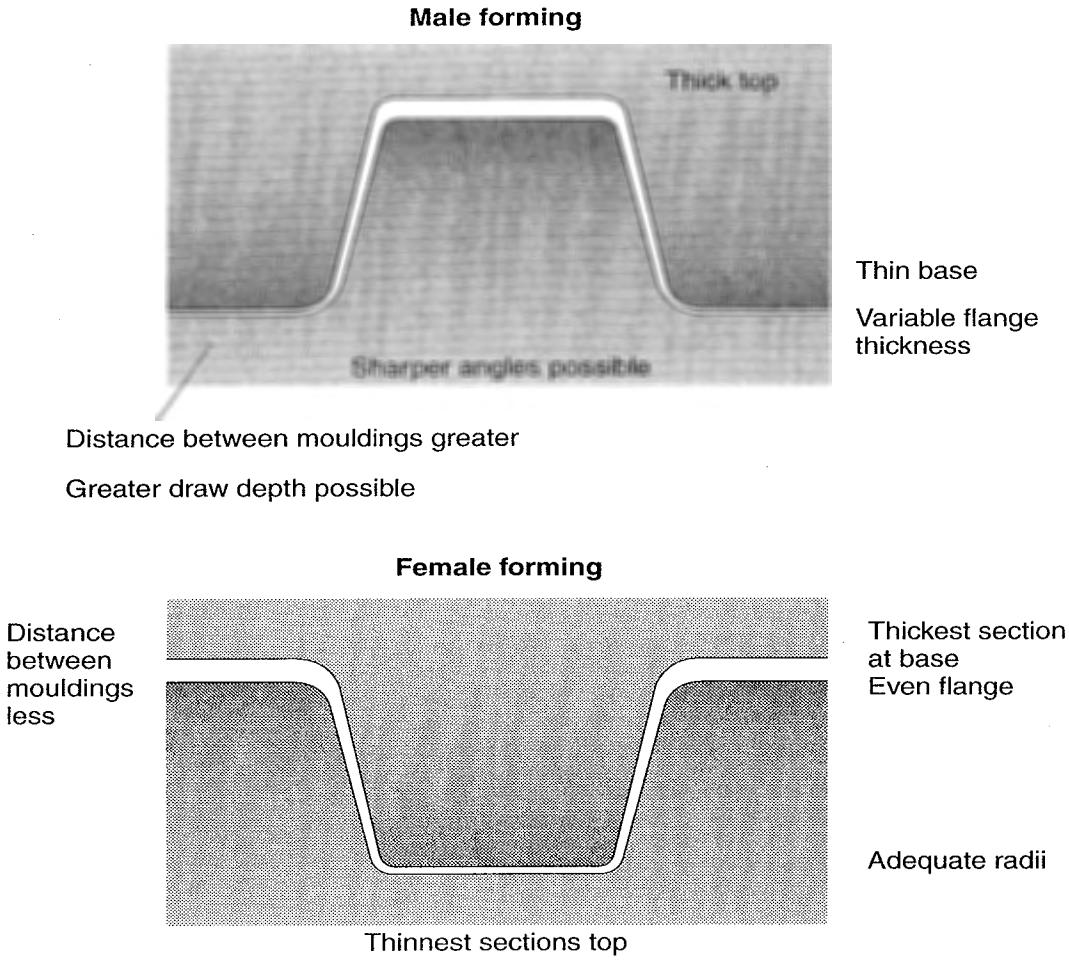


Figure 13.11 Male and female vacuum forming

Some relatively simple blister packaging equipment is produced on a rotary table principle whereby a blister can be formed, hand filled, lidded and the completed blister pack removed after four 90° movements. Others work on a reciprocating bed principle of forming and lidding. These are often used for optic lenses and opthalmic-type solutions for lens cleaning.

Some typical blister packs are shown in Figure 13.12. Various assembly and sealing methods can be used, e.g.:

- heat seal through lid (board, laminate or label)
- heat seal through plastic
- heat seal through plastic and lid
- blister locked between cards by adhesive or staples
- folded card – plus heat seal, adhesive or staples
- blister locked to card by label.

Blister packs offer good display advantage where clarity is essential. Punched hole systems provide for hanging cards.

Blister trays are particularly useful where several items are involved in the medication, i.e. lyophilised product plus water for injection.

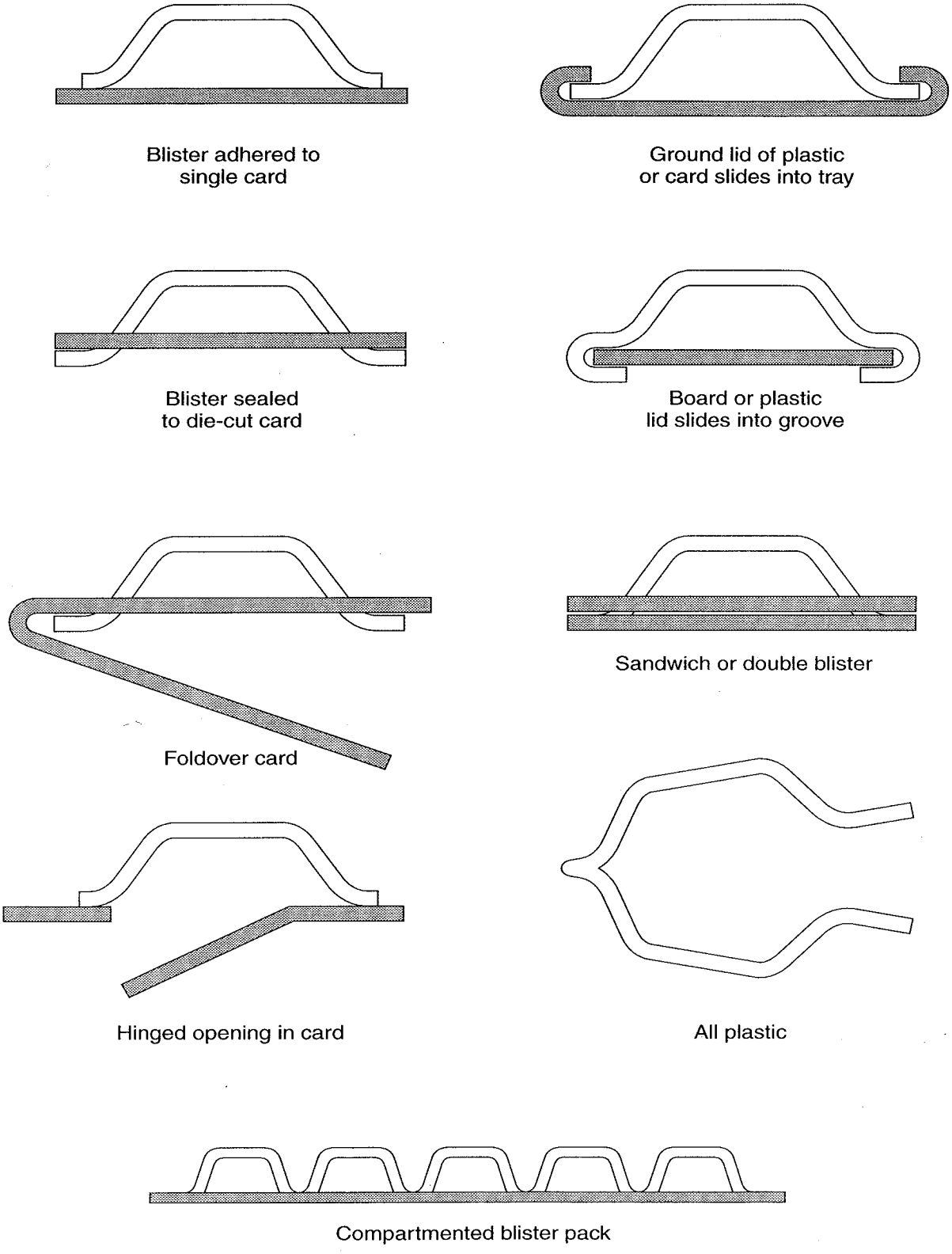


Figure 13.12 Thermoformed card pack constructions

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Current blisters, strips and sachets technologies have a strong historical foundation through the developments reported over the past 30 years, as can be seen from the following references.

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Awareness of the advances in technology are often correlated through national and international conferences and the subsequential technical papers.
In 1998-9 a series of Blister-pack 2 day conferences were run in Cologne, Germany and Newark, USA to review and update blister packaging. Presentations were made by people well recognised within the industry and a list of papers, purchasable fron The Packaging Group Inc (US), 70 Valley Forge Drive, East Brunswick, New Jersey 08816, USA. is given below:-

September 23rd - 24th 1998

1. A global view of Blister Packaging for Pharmaceuticals
   Stephanie Batz
   Kalle Pentaplast Gmbh, Germany
2. Why use Blisters?
   Dieter Janek ®
   Managing Director, Horn and Noack, Division of Romaco Gmbh, Germany
3. Alfoil Polymer High Barrier Films (PVDC)
   Monique Roulin, Manager Technical Sales
   Aerni Leuch AG(AEL) Switzerland
4. ACI-AR High Barrier Films
   Mike Phillips
   Allied Signal Speciality Films (UK)
5. Cold Formed Aluminium Foil and lidding concepts.
   DR Erwin Pasbrig ®
   Development Technical Application – Pharma
   Lawson Marden Singen Gmbh, Germany
6. Replacing PVC – the alternatives
   Dieter Laube
   PCI Allpack Gmbh Germany
7. Evaluation and Shelf life testing with reference to the ICH Guidelines
   Mervyn Frederick, Head of Packaging Development,
   NV Organon, Akso Nobel (Holland)
8. Heat Sealing – rotary v platen ®
   Dieter Janek, Magaging Director
   Horn and Noack, Division of Romaco
   Gmbh, Germany
9. Non destructive leak testing of blisters.
   Paul Sharpe Business Manager
   AI Qualitek (UK)
10. Preventing recalls – on line inspection and printing
    John Mackenzie, Sales Manager
    Romaco (UK) Ltd
11. Machinery – future trends in blister packaging
    Marielli Criscuolo, Marketing Research Manager
    IMA, Pharmaceurical Division. Italy
12. Machinery – flexibility of blister lines,
    Markus Mazger, Product Manager, Pharmaceuticals
    Robert Bosch, Gmbh Germany
13. Machinery – Thermoforming Machine and Lines -Latest
    Technology. Advanced Forming Technology (AFT)
    Dirk Briskorn, Managing Director

Klockner Hansell, Gmbh, Germany

14. Machinery – Jlister packs for Clinical Trial supplies –
Special equipment.
Matthew Vogelsanger, Managing Director,
Fleximation AG – Switzerland
15. Blister Packaging and Child Resistance – is there a future? Colin Scaife
CE Packaging Partnership
16. Strip – a substitute for blisters.
Paper by Siebler Verpackungstechnic
Presented by Dixie Dean (Consultant)
17. The role of the Contract Packer
Mr. G Russell, Sales & Marketing
PCI (Unipack) UK
18. Mobile Blister Machines, and deblistering – The neglected aspects!
A Ernest Parker, Managing Director
Sepa Products (Ireland) Ltd
19. Liquids and semi liquids in blisters ®
Werner Basler, Systems Manager
Unifil (International) Ltd
Krcuzlingen – Switzerland
20. The contract Packaging of Clinical Trial Supplies
Mike O'Donnell
Consultant acting on behalf of PCI – Unipack UK
21. Improving Barrier Properties by coating, coextrusion, lamination, metallisation and overwrapping
Dixie Dean (Consultant)
22. Future trends in Pharmaceutical Blister Packaging – an industry's point of view Mervyn Frederick –
Head of Pharmaceutical Development
NV. Organon, Akso Nobel (Holland)

A similar conference was run in the USA April 20th – 21st 1999. The speakers from the above event ® also presented the same papers. Different papers were produced by the following:

1) Evaluation and shelf-life testing – the influence of the ICH Guidelines
D A Dean (Consultant)
2) What's the Future for the Pharmaceutical
Blister Packager?
Dixie A Dean (Consultant)
3) Child Resitant Blister Packaging. US Regulations and Test Methods
Dr Suzanne Barone
Prof. Manager for Poison Prevention – US
Consumer Products Safety Commision
4) Aclar High Barrier Laminations – update and New Structure
Perry Fan General Manager
Rigid Films, Tech-Plex-Inc
5) Archieving longer term stability with PVC/PVDC
David Faghani, Marketing Sales Manager
Perlen Converting AG, US Region
6) Blisters and Clinical Trials: Recent developments
Mike O'Donnell – Consultant
7) Integrated Inspection on Packaging Lines
Geert Coudizer
CEO, Covan Vision Systems (Belgium)
8) Blisters and Contract Packaging – A Happy Marriage
Renard P Jackson, Exc V P Sales and Marketing
PCI USA
9) Blister Packaging – New Innovation in Child Resistance
Thomas Toren
Consulting Engineer, Australia

The Taylor & Francis Series in Pharmaceutical Sciences

Pharmaceutical packaging requires a greater knowledge of materials and a greater intensity of testing than most other packed products. To achieve an effective and successful pack requires a sound knowledge of pharmaceutical products and an understanding of regulatory requirements. For that reason this volume reviews the current status of product–pack relationships both as a multi-disciplinary activity and in the expanding role of the pack as a drug delivery system. Extensive coverage is given to the supplier chain, the means by which raw materials are converted into packaging materials, components etc. and then assembled into product packs. Testing and evaluation is therefore discussed from raw materials through to ongoing product sale, use and disposal. Particular emphasis is placed on traceability and the need to safeguard both the user and the producer in issues of product liability. All types of product and pack are considered, from those of low risk (e.g. solid dose forms) to those of greater risk (IV solutions, sterile products).

Packaging is a changing and important discipline, requiring constant review with a need for more and more knowledge. This book sets out to provide a firm foundation in pharmaceutical packaging technology for those in the industry.

Dixie Dean has spent the majority of his working life dealing with pharmaceutical packaging, commencing with quality control, followed by packaging research. More recently he headed packaging and device development at Fisons, until retiring. He has delivered over 6000 lectures on the subject.

Roy Evans was employed by Roussel Laboratories (Aventis) for 30 years, first as Packaging QC manager and finally QA manager. He is a founder member of the UK's Pharmaceutical Quality Group and is now an independent Pharmaceutical QA consultant.

Ian Hall has spent 31 years in pharmaceuticals, involved in packaging, production and security packaging design. He has been a Pharmaceutical Packaging and Security Consultant, and has been involved in lecturing and writing, as well as organising courses and conferences. He is also secretary of the Pharmaceutical Packaging Forum of the Institute of Packaging.

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