3
REGULATORY ASPECTS OF PHARMACEUTICAL PACKAGING

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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	

Area of interest	*Technologist*	*Regulator*
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 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

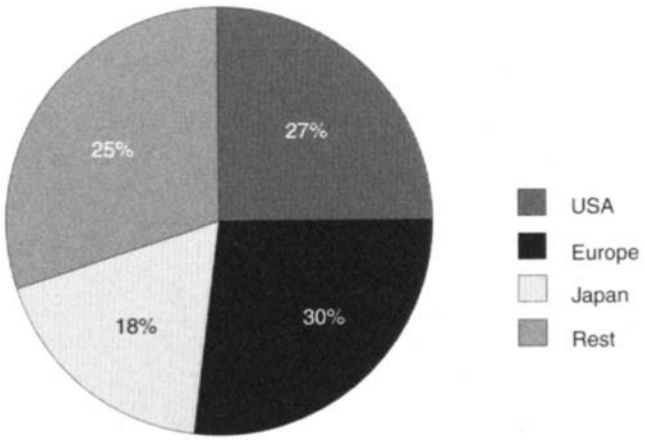

Figure 3.1 The world pharmaceutical market

Figure 3.2 The worldwide regulatory split

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 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 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,

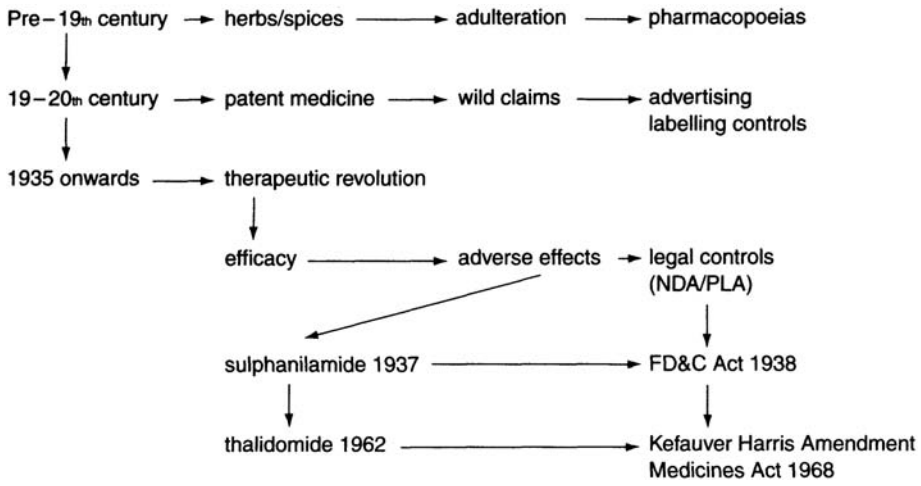

Figure 3.3 Outline of pharmaceutical history

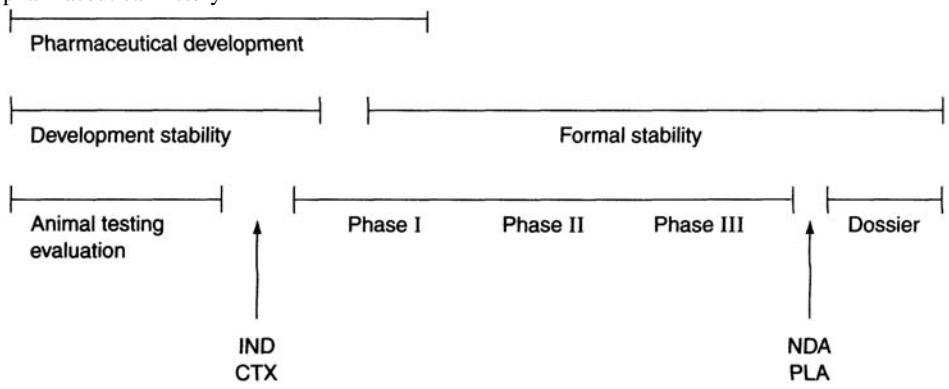

Figure 3.4 The development process

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.

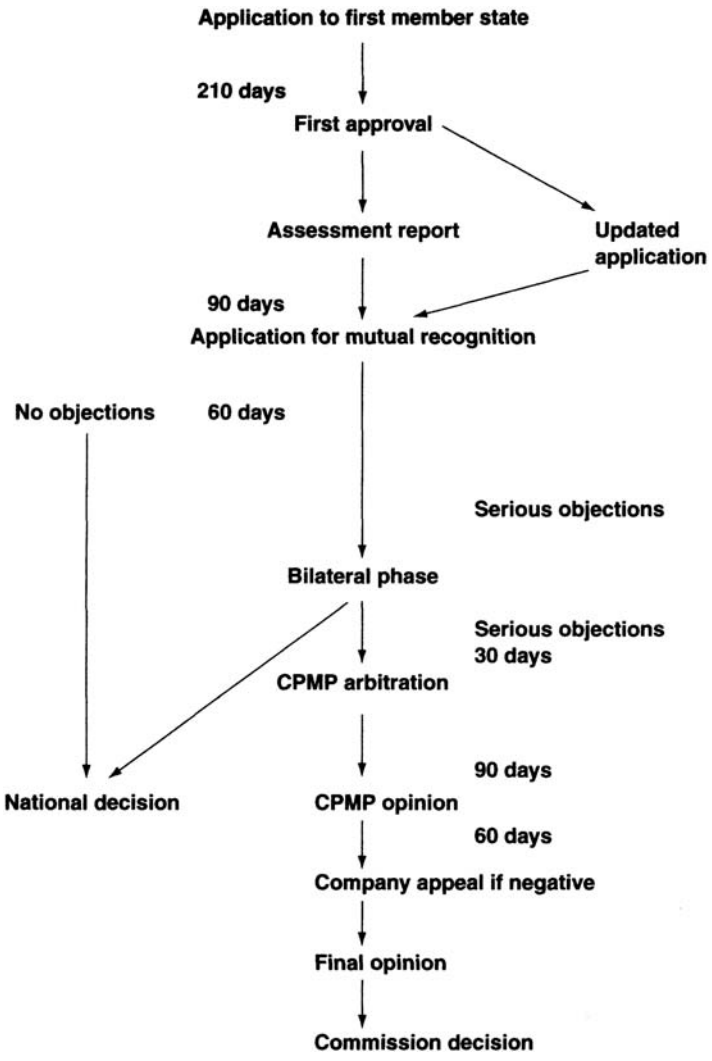

Figure 3.5 The mutual recognition process

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	

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.

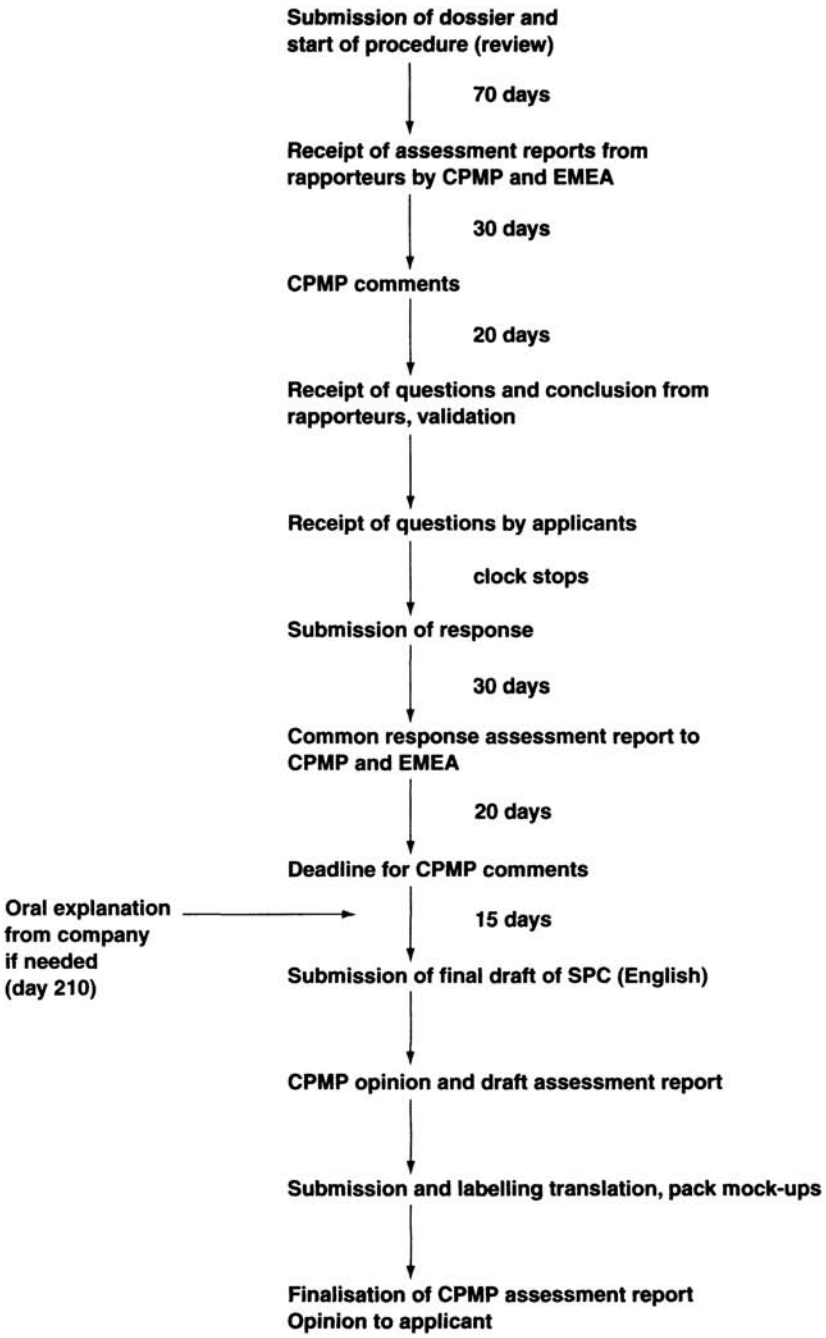

Figure 3.6 Outline of the centralised procedure

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

Dart	Nebuliser	Vaginal sponge applicator
Dredging applicator	Needle applicator	Vial
Dredging container	Nozzle	

- *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 foodapproved 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

Semni-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
-
-
-

part in the assessment of the application. Three expert reports are provided, covering chemistry and pharmacy, toxicopharmacology 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	

5 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 Pharrmaceutical 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.

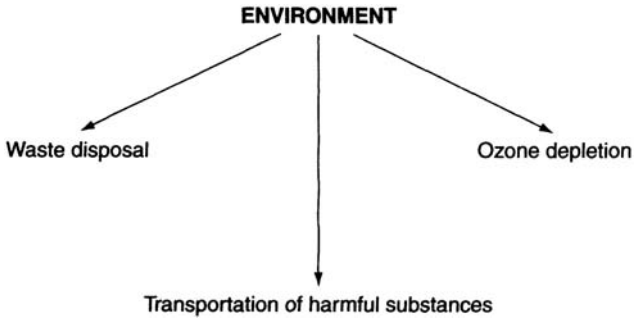

Figure 3.7 Environmental concerns

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.

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, childresistant 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.