Introduction 1

Everyone is aware of the potential benefits of medicines and the patient takes them on trust expecting them to be fit for the purpose prescribed by the doctor or agrees with the claims of the manufacturer on the packaging or on advertisements. This book is a general introduction for all those involved in the engineering stages required for the manufacture of the active ingredient (primary manufacture) and its dosage forms (secondary manufacture).

All staff working in or for the pharmaceutical industry have a great responsibility to ensure that the patient's trust is justified. Medicines made wrongly can have a great potential for harm.

Most of the significant developments of medicines, as we know them, have occurred in the last 70 years.

From ancient times, by a process of trial and error, man has used plants and other substances to produce certain pharmacological effects. The best example is probably alcohol, which has been developed by every culture.

Alcohol has a number of well-known effects depending on the dosage used. In small amounts it causes flushing of the skin (vasodilatation), larger quantities produce a feeling of well being, and if the dose is further increased, loss of inhibition occurs leading to signs of aggression. Beyond aggression, somnolence occurs and indeed coma can supervene as the central nervous system becomes progressively depressed. This well-known continuum of effects illustrates very neatly the effect of increasing dosage over a period of time with a substance that is metabolized simply at a fairly constant rate. It further illustrates that where small quantities of a drug are useful, larger quantities are not necessarily better — in fact they are usually harmful.

Using the trial and error technique, the good or harmful properties of various other materials were also discovered, for example, coca leaves — cocaine, or poppy juice — opium, which contains morphine.

Today the pharmaceutical industry is faced with escalating research costs to develop new products. Once an active product has been discovered and proven

to be medically effective the manufacturer has to produce the active ingredient and process it into the most suitable dosage form.

Speed to market is essential so that the manufacturer can maximize profits whilst the product has patent protection. Companies are now concentrating products at specific sites to reduce the time-scale from discovery to use, to give economics of scale and longer campaign runs.

The manufacture of the active ingredient is known as primary production (see Chapter 5). Well-known examples of synthetic processes are shown in Figures 1.1 and 1.2 (see pages 3 and 4). The manufacturing process for methylprednisolone (a steroid) is complex (see Figure 1.1), but it is relatively simple for phenylbutazone (see Figure 1.2). The processing to the final dosage form such as tablet, capsule (see Figure 1.3 on page 4), or injection, is known as secondary production (see Chapter 6).

Bringing a mainstream drug to market can cost in excess of £200 million (300m US dollars). This involves research, development, manufacturing, distribution, marketing and sales. The time cycle from discovery to launch takes many years and will probably not be less than four years for a New Chemical Entity (NCE). Any reduction in this time-frame improves the company's profitability and generates income.

Many companies conduct the early studies on NCE's for safety, toxicity and blood levels using capsules. This is due to a very small amount of NCE being available and the ease of preparing the dosage form without loss of material. Only when larger quantities become available is a dosage form formulated as a tablet or other form. The product design process must take into account the demands of regulatory approval (manufacturing licences, validation), and variation in demand requiring flexibility of operation. The treatment of hay fever is a good example of a product only being in peak demand in spring and early summer.

All companies will attempt to formulate oral solid dosage forms, such as a tablet or capsule, as this is the most convenient form for the patient to take and the easiest product to manufacture. An estimated 80–85 percent of the world's medicines are produced in this form. Not all products are effective from the oral route and other dosage forms such as injections, inhalation products, transdermals or suppositories are required.

The discovery and isolation of a new drug substance and its development into a pharmaceutical dosage form is a costly and highly complex task involving many scientific disciplines. Figures 1.4 and 1.5 illustrate many of the steps involved.

Figure 1.5 illustrates the various departments and disciplines that need to co-operate once it has been decided that the product will be marketed. This

figure assumes that facilities are available for manufacturing the active ingredient (primary manufacture).

Failures by manufacturers led to the establishment of regulatory authorities initially in the USA, then in the UK and more recently in Europe.

In 1938 in America sulphonamide elixir was contaminated by diethylene glycol resulting in a large number of deaths. This led to the Food, Drug and

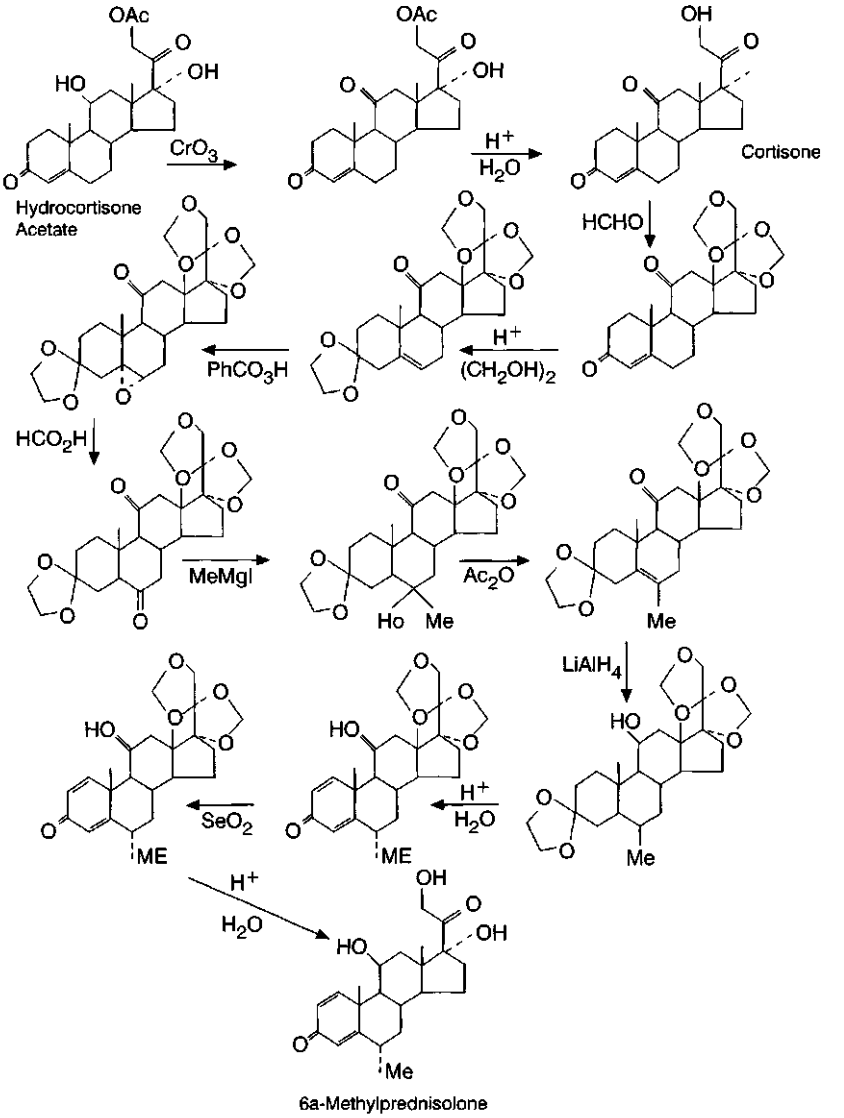

Figure 1.1 Synthetic route for 6a methylprednisolone

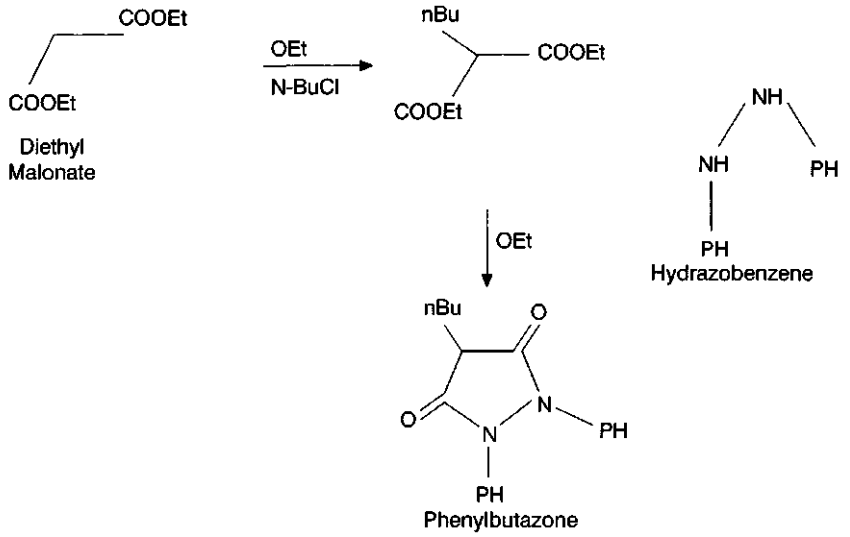

Figure 1.2 Synthetic route for phenylbutazone

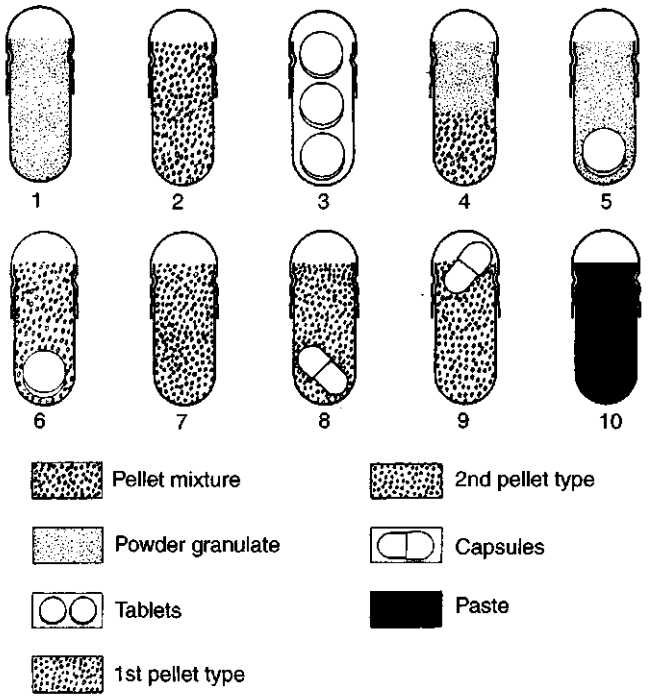

Figure 1.3 Various formulations filled into hard shell capsules

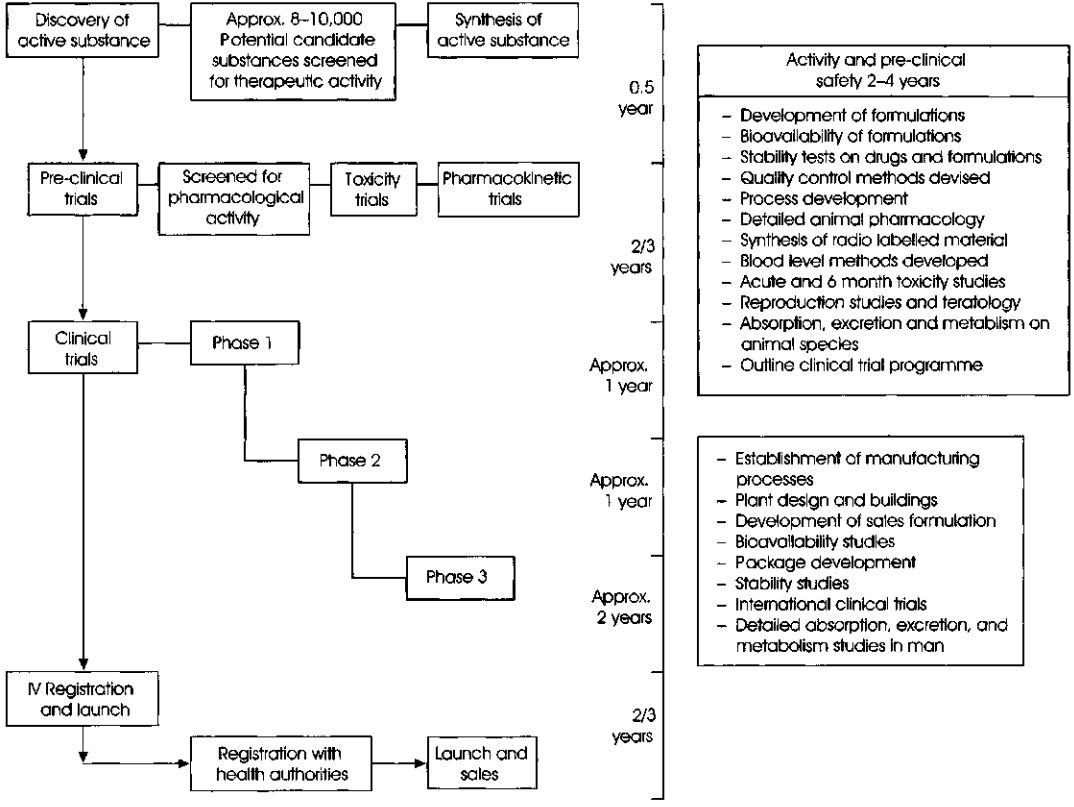

Figure 1.4 Stages in a new product launch (simplified)

Cosmetic Act coming into force in the USA, followed by the establishment of the Food and Drug Administration (FDA).

In 1962, there was the much publicized Thalidomide tragedy leading to the tightening up of the testing of drugs prior to marketing, and eventually to the Medicines Act 1968 in the UK. The Medicines Control Agency (MCA) was established to police the industry and there is now also the European Medicines Evaluation Agency (EMEA) and the National Institute for Chemical Excellence (NICE).

Such legislation (see Chapter 2) has had a considerable impact on the design, construction, operation and on-going maintenance of pharmaceutical production facilities.

The FDA, the MCA and European Regulatory Authorities have all issued codes of Good Manufacturing Practice, providing basic ground rules to ensure adequate patient protection from hazards associated with the poor design of manufacturing processes. Chapter 3 provides background knowledge on the regulatory framework and constraints on the manufacturer.

Validation has been introduced in recent years. This was defined by the FDA as the act of establishing documentary evidence to provide a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes. Chapter 4 provides details of the documentation required including concepts such as the User Requirement Specification (URS), Validation Master Plan (VMP), Design Qualification (DQ), Installation Qualification (IQ), Operational Qualification (OQ) and Performance Qualification (PQ).

It is important that the designer understands these requirements because it is far easier to collect validation documentation throughout the design process rather than to attempt to do so post-design, often known as retrospective validation.

Chapter 5 deals with primary production, or manufacture of the active ingredient. For many years designers considered this to be no different to the manufacture of any other chemical, but codes of good manufacturing practice and validation now apply. Reactions and other key unit operations are discussed with ideas for layouts to satisfy good manufacturing practice and other regulator requirements.

Chapter 6 is a comprehensive review of secondary production, turning the active ingredient into the dosage form.

Chapter 7 covering safety, health and environment explains how risks to these are managed in the pharmaceutical industry and how effective process design can eliminate or control them.

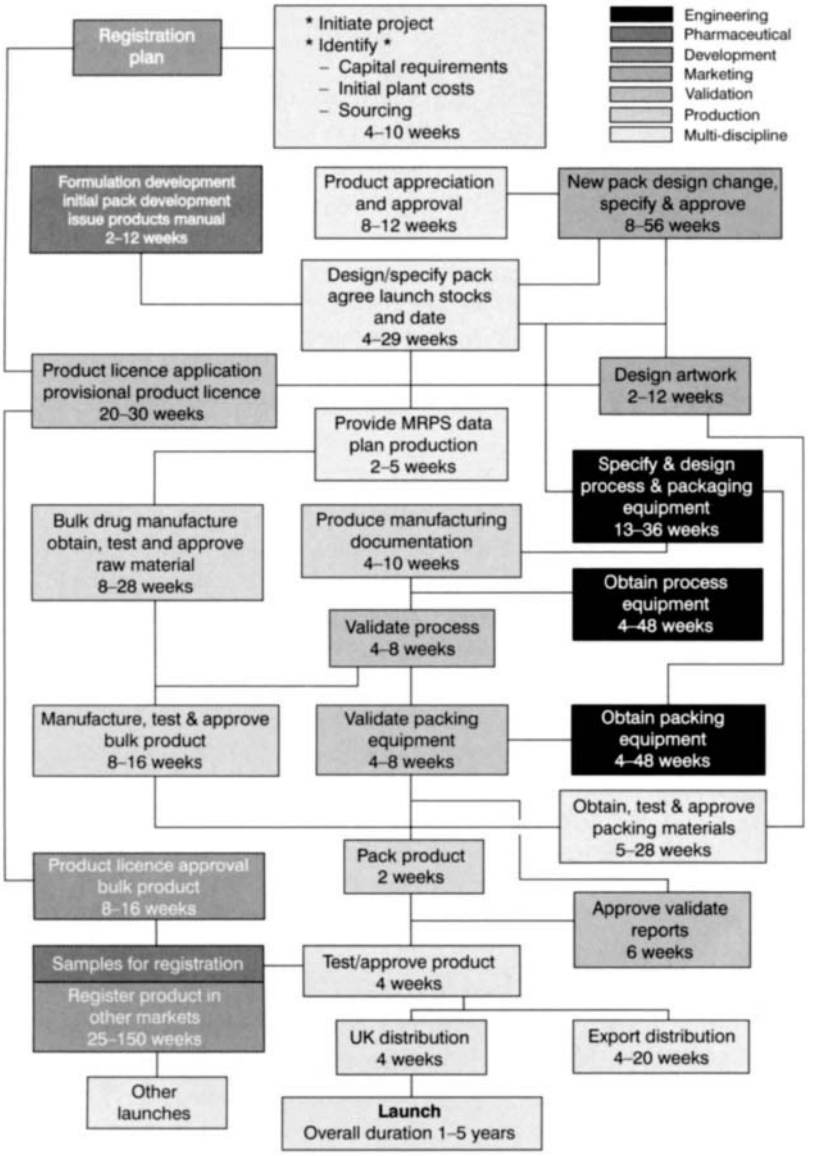

Figure 1.5 Implementation stages of the launch of a new product

The reader may ask why Chapter 8 has been included as process utilities and services are common throughout all industry. This chapter concentrates on aspects that are particularly relevant to the pharmaceutical industry. Regulatory authority inspectors, when inspecting plants, spend a lot of time looking at

water supplies, compressed air systems, air conditioning and cleaning systems which are all in the designer's control.

Much of the book is about the production of the active ingredient and dosage forms. However, Quality Assurance departments have an important part to play in ensuring medicines are of an appropriate quality. In fact, regulatory authorities demand that a Qualified Person (usually from the QA department) is legally responsible for the release for sale of the manufactured product. Chapter 9 focuses on the design of quality control laboratories which form an important part of the quality assurance process.

In a similar way, process development facilities and pilot plants are an integral part of the development of the manufacturing process for the active ingredient and its dosage form, particularly in the preparation of clinical trials. Chapter 10 gives ideas on the design, construction, commissioning and validation of these facilities.

Chapter 11 is a review of the special requirements of Bio-pharmaceutical products particularly for pilot-scale manufacture of these products.