1
Introduction

This book and the nebulous area of science it belongs to are based on the evaluation and concept of assuring quality and good practice. This knowledge is routinely employed in the safe and hygienic manufacture of pharmaceuticals (medicines), cosmeceuticals (cosmetic-pharmaceuticals), and nutraceuticals, (nutritional-pharmaceuticals). However, the subject area is diverse and might also routinely apply to those aspects of pharmaceutical manufacture that are intimately associated with production, such as process control testing. Equally the subject matter might be relevant to disparate industries and environments such as the hospital histo-pathology lab, clinical biochemistry lab, cosmetics and semi-conductor industries, or paints, pigment and dye product industries, to name but a few. The basic elements of routine production of a non-exhaustive list of pharmaceutical products are shown in Figure 1.1. Three elements are key: the raw material (RM), process, and human intervention. The way in which these components interact or rather *are made to interact* for a range of products such as solid dosage (tablets) and dispersions, for example vaccines, defines their compliance, safety and ultimate suitability.

The full picture of drug formulation is complex, by necessity, and dictates the efficacy of the drug product in addition to its universality of use, application, regulatory status and need for careful administration. This is not the complete picture of drug product because successful medicines can only be made by using a complementary mix of paradigm models of 'quality' practice and scientific advancements [Sharp (2002)]. These quality models are essential and have evolved, having been borne out of a key craft and essential skills in the distant past, and are now defined by technological progress and know-how (Figure 1.2). The vast array of medicines and their appropriate engineering for purpose also comes from both empiric discovery and a rational design of medicines.

Quality Systems and Controls for Pharmaceuticals D K Sarker

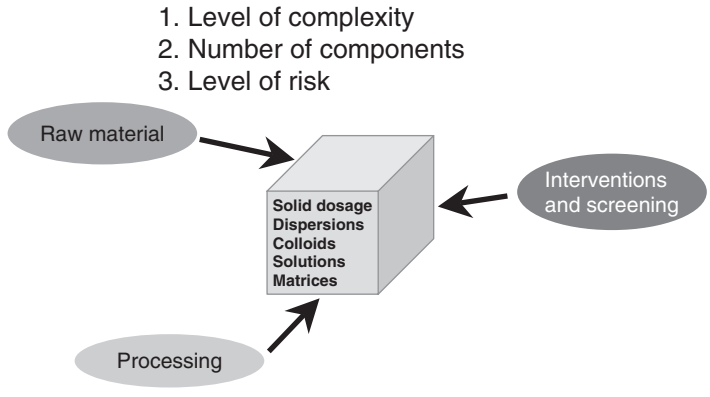

Figure 1.1 Pharmaceutical products overview

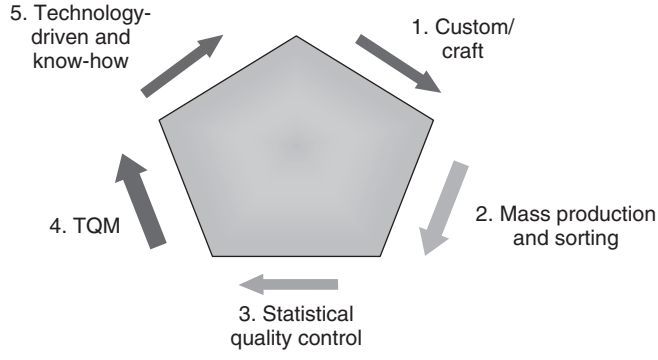

Figure 1.2 Paradigms of industrial quality practice

1.1 The process of finding new lead medicines

Recent drug development history begins with opium discovery in 1806. It was a most significant, ground-breaking discovery that gave rise to morphine and its subsequent associated compounds used ubiquitously since Victorian times for pain relief; other examples from the same era include quinine from Cinchona tree bark, revealed at the turn of the nineteenth century [Schacter (2006); Rang (2006)]. Serendipitous discovery features to a significant extent alongside empirical and purposeful experimental design in discovery; for example analgesics such as aspirin from willow; theobroma oil from cocoa butter, used for body temperature melting waxes; and cardiotonics, for example digitalis. The classic, often quoted example of chance discovery is that of the mycotoxin penicillin (*P. notatum*) in 1928 by Fleming, used for groundbreaking therapy from the 1940s, and a whole genre of new engineered medicines, drug discovery culture and biotechnology.

A number of serendipitous discoveries have included disclosures identified from *favourable* side-effects:

- Mogodon (nitrazepam) – routine use: hypnotic and sedative; second use: anti-emetic
- Tamoxifen – routine use: anti-rheumatic; second use: anti-oestrogenic (breast neoplasm)
- Aspirin – routine use: analgesic; second use: anti-coagulant
- Pyridoxine – routine use: enzyme cofactor; second use: serotonin inhibitor (depression disorders)
- Alginate – routine use: red seaweed/polysaccharide, excipient in tabletting; second use: acid reflux retardant
- Minoxidil – routine use: cardio-therapeutic; second use: hair growth (re-growth).

A number of fortunate discoveries have also included scientific findings by *chance*:

- Antibiotics such as myxins (*Sorangium* spp.); cephalosporins (*Cephalosporium* spp.)
- Toxins e.g. melittin (polypeptide) – in honey bee venom, used as anti-rheumatic; curare – Chondrodendron bark, used as muscle relaxant
- Codeine, from the giant poppy (diamorphine/morphine) – used for pain relief and as a sedative
- Quinine, from cinchona bark – used as an anti-malarial
- Salicylates, from willow bark – used as an analgesic
- Digitalis, from foxglove plant – used as a cardiotonic
- Cannabinols – from hemp bush – used as an analgesic or hypnotic drug
- Atropine – from deadly nightshade plant (belladonna) – used as an anti-cholinergenic.

Clinical and pre-clinical testing and file submission for a lead compound to candidate takes about 10 years. Revolutionary cytotoxics such as Taxol® (paclitaxel) from yew trees, cis- and trans-platinates/oxyplatinates (colon cancer), are examples of inorganic therapeutics valued for treatment of cancers and are other novel and innovative classes. Drugs now used for alternative therapy (to the original filing) as a result of side-effects include e.g. Minoxidil, now used as a

hair restorative, and thalidomide, which keeps on finding new applications, other than the original use as a sedative. One of the most controversial and criticised of contemporary cosmetic drugs in use is 'botox', botulin and its derivatives, a powerful neurotoxin, which now relies on routine 'biotech' fabrication. Newer aspects of medicinal delivery include stealth preparations and prodrug moieties to avoid first pass degradation and permit active delivery; typical examples include PEGylated liposomes and peptides, such as insulin. This is also a strategy widely used to avoid the blood brain barrier (BBB) and target tumours [Tian *et al.* (2005); Wang *et al.* (2005); Thomas and Campbell (2004)]. This paints rather a glorious picture of unflawed and successful progression of lead compound to drug and drug product. In 2005 there were about 75 new potential biopharmaceutical candidate drugs. Many will fail due to the rigorous burden of testing placed on them. Even successful drugs are not without their drawbacks, for example three products or combinations used in cancer treatment by inhibition of tyrosine kinase. These very successful products include Trastuzumab-Herceptin™ (Genetech) used with the cytotoxin adriamycin for breast cancer metastasis, Gleevec™ (Novartis) for chronic myelogenous leukaemia, and Sutinib Malate-Sutent™ (Pfizer) for metastatic renal and gastric carcinoma; however each silver lining has a potential black cloud as they are reported [Mann (2006)] to have significant administration side effects including possibilities for heart damage, heart failure and heart ventricular dysfunction, respectively.

1.2 A drug discovery framework

Pharmaceutical innovation is really big business, for example in the USA in 2005 it involved half a million people and the spending of $30 billion on research and development, and this related to more than $200 billion sales in North America. It has been estimated that in the US the top ten strategic targets for illnesses in 2004 were cancer (32 per cent), diabetes (9 per cent), arthritis (7 per cent), infections (6 per cent), HIV (4 per cent) and cardiovascular ailments (4 per cent), respectively. The business is healthy and investment is growing based on global sales, growing from $590 billion in 2003 to an astonishing $900 billion in 2008 (prediction based on current growth patterns). The biopharmaceutical market alone was $50 million in 2005 accounting for some 25 per cent of all drug candidates. Of these sales it is estimated that over-the-counter (OTC) will account for 11 per cent, generic medicines for 7 per cent, biopharmaceuticals also 7 per cent and ethical medicines have the greatest share at 75 per cent. In 2003 the top ten pharmaceutical companies accounted for 46 per cent of global sales and of the sale 50 per cent were in North America. In recent years the costs have forced investment down in absolute terms but in relative terms there is something like a two-fold increase in investment each five years [Tambuyzer (2002); Carpe Diem Publishers (2004); Mudhar (2006)]. Current drug discovery (Figure 1.3) also makes use of

Step	Activities	Significance
(a) Start point – disclosure	Target compound identified	
(b)	Strategic compound identified by organisation	
(c)	Pre-clinical screening tests e.g. in animal	A 'lead' molecule of pharmaceutical value leads to (d)
(d) Permission of human tests for IND	List value, threats, deficiencies, urgency (short referential tests)	
(e) True clinical trials (SDU)	Phase I, phase II, phase III (long, extensive and detailed)	Success here: organisations are looking to phase IV and V testing
(f)	Make filing of NDA	
(g)	Authority review process e.g. direction from EMEA, FDA*	
(h)	Approval of NCE (long, arduous)	
(i)	Phase IV and industrial commercialisation steps#	
(j) Finish point – product	Launch, commercial review	This is not the end of the line for the product
(k) Post-approval activities	Phase V	Periodic review based on clinical (e.g. GP) data

Key:
NCE – new chemical entity; new lead compound
IND – investigational new drug
NDA – new drug application
SDU – establishment of safety-dosage-use comes from clinical trials.
– many steps here and the economic and practical considerations mean some candidate molecules are lost.
* – further down the development cycle list means a greater degree of investment by the organisation and also the risk of failure or at least the consequences of failure are multiplied. Different bodies within the organisation may review the drug based on its chemical nature e.g. biologic, human or veterinary pharmaceutical class.

Figure 1.3 Process flow showing the fundamentals of making new medicines: there are 11 key steps, although many more sub-steps

chance discovery and not just rational experimental design and, consequently, many scientists in the field are still using the notion of miracle cures from natural sources as a basis of new drug products. This is and will continue to be part of the culture of drug discovery. However, increasing use of rational experimentation, bioinformatic profiling and high throughput screening (HTS) for analysis or pharmacologic/pharmacokinetic testing and early stage candidate screening is finding an ever more prominent position (Figure 1.4). This stands to reason, after all why put all your 'eggs in one basket' and hope for a miracle discovery.

Clinical trials and the integrity of clinicians and analytical biochemistry, pharmacology and chemometric aspects of clinical testing are crucial. All tests require an environment of good clinical practice (GCP) and this is explained more

Phase I	Where small-scale studies* reveal working dose and safety (immunity compromising drugs not tested in 'healthy' patients). Primary goal is evidence gathering for drug activity.
Phase II	At this point a more significant large group of models are evaluated in different types of trials (with statistical relevance e.g. double-blinded, random, placebo, etc.) to prove the molecule is efficacious and safe. Cost can be high as testing is performed in diverse testing centres (c. $50 million).
Phase III	Measurements undertaken in a heavily scrutinised and controlled environment over diverse sites (to prevent bias) with an extensive number of volunteers; the candidate molecule is tested in terms of SDU and toxicology and in replicate evaluations. Their overarching aim is to demonstrate utility in particular groups and provide a basis for marketing and supplementary file validation information (c. $120 million, [Schacter (2006); Rang (2006)])

* Small scale does not mean limited but rather of a survey type, rather than proof-of-efficacy.

Figure 1.4 What is the true picture of processes involved in clinical trialing?

in terms of generic components in the section on current good manufacturing practice (cGMP), in Section 5.

Less than a quarter of drugs at phase I entry will progress to reach NDA status. The development system is fraught with problems of burdensome cost (clinical trial cost up to $10 000 per patient) and the extent of randomised uncontrolled study. This means the cost of producing a new medicine can run to about $1 billion and the process can appear to be painfully slow, taking in many cases more than a decade to gather regulatory support and subsequent approval for use of a new drug. The regulators find themselves in an unenviable position of needing to prove the new drug will be 'sufficiently' risk free. Yet, based on a number of ongoing and past difficulties, find an increased public scrutiny and pressure to release new and exciting drugs quickly and not stifle creative innovative therapy.

Phase III trial data forms the main argument in favour of progression of the drug to pre-launch phase IV viability studies. Suitable information must be generated prior to clinical studies on a near optimum form of presentation and suitability of production of the intended candidate molecule for best results. This presupposes the organisation operates within an ongoing cGMP and cGLP quality system, which operates from the point of discovery. This production development goes on in the background and can take approximately 10 years with each of the other overlapping steps in the process and each of the clinical trial portions and filing or approval taking between one year and two years. It is not uncommon for 70 per cent of the time for intellectual property rights for a new substance to be consumed by development and approval. In most cases patent lifetime is of the order of twenty years but this varies on a case-by-case basis and with the country of filing.

The backbone of drug development is based around clinical acceptability of the investigational drug application (IND) compound. The trials move progressively to more rigorous and in-depth particularities of the candidate molecule when

in human models. This is often also considered to be the most contentious part of the development cycle as there needs to be 'real proof of principle.' This consequently leads to some notion of an equilibrium of competing forces between input and provision of 'full information' or fact by developer and the regulator. Both parties have a vested interest in their successful participation and more often than not these interests are mutually compatible. After successful review of data by expert regulators the candidate molecule moves from IND class to one of a new drug application (NDA) class.

Development of new medicines should consider:

- Development of drugs and their societal value
- Profiling of drugs with respect to the potential market/customer
- Profiling of drug products with respect to the potential market/customer
- Specific design for a targeted application.

Alternatively new, improved or better drugs may be developed by planning and rational design. In this case key considerations should be:

- Use of disease prevention (retardation) strategies and models
- Use of chemical libraries or alternatively by new drug synthesis (empiric discovery)
- Use of pharmacological site targeting based on e.g. drug chemical structure
- Use of drug selection or screening (*in vivo*/*in vitro*) and bioassay (empiric discovery)
- Evaluation for favourable side-effects (not a main form of discovery) and chance by taking drugs from natural sources (e.g. plant extracts)
- Looking for more efficient yields and synthesis cost. High cost is more likely to reduce or limit the potential use of the drug
- Use of drug and product profiling (requirements of a drug such as target product profile)
- Use of the clinical trial and appropriate toxicological surveillance
- Use of placebos in product validation and random/blind/sequential trials aligned against the validity of clinical data [Tambuyzer (2002); Benoliel (1999)]
- High throughput screening and evaluation based on drug absorption, metabolism, distribution and elimination
- Consideration of bulk manufacture and process stability.

Some specific design considerations, which reduce the likelihood of new drug molecule acceptance, are:

- Risk of chemical or bio-mutagenesis
- Drug–excipient interactions
- Drugs involving poisoning of receptors e.g. stereospecific fouling and inhibition
- Drug delivered by a non-receptor pathway
- The time course of drug action
- Non-conventional modes of delivery that might require widespread novel clinical trials data to support their use
- The need for effective administration and its drug delivery ratio (delivered dose/absorbed dose)
- The risk of DDS toxicity and allergy.