Microbiology and pharmaceuticals 2

2.1 Introduction

Pharmaceuticals represent a relatively small sector of manufacturing industry (and in hospitals, pharmacy units are a small part of the hospital function). Nonetheless, the pharmaceutical sector is highly innovative, closely regulated, and (in the private sector) very profitable. At some time or another, most people will use the products of the pharmaceutical industry. These range from life-saving drugs for the treatment of serious acute conditions, to drugs that can transform the life of patients with chronic, debilitating diseases, to proprietary medicines that can be bought over-the-counter (OTC; nonprescription) to relieve minor ailments. To add to this, a more recent development is the trend toward personalized medicines (for which an understanding of the human microbiome is essential). Drug expenditure varies globally, with high-income nations spending considerably more than low-income nations.

Pharmaceutical companies are chemical synthesis plants (manufacturing bulk ingredients), finished product facilities that process bulk ingredients or facilities that undertake both functions. In addition to this, there are hospital pharmacy units that produce smaller quantities of medicinal products, often on a named patient basis.

The pharmaceutical industry is global and covers everything from high technology companies, which have been founded to apply the very latest technology to the medical problems of today and tomorrow, to organizations that use relatively unsophisticated production methods to produce old, but needed, drugs at low cost. An example of the latter would be a tablet facility producing aspirin (acetylsalicylic acid).

This chapter introduces the key aspects of the industry, and later goes onto to show how microbiologists play a key role in the development of medicinal products and in ensuring that the products are safe and efficacious.

2.2 The basics of the pharmaceutical sector

The pharmaceutical sector can essentially be broken down into two main areas:

(a) proprietary;
(b) generics.

The sector can then be subdivided into two major distribution channels:

(a) prescription-only medicines;
(b) OTC medicines.

Proprietary (sometimes, without irony, called “ethical”) medicines, are primarily those medicines that, because of their potency, or their ability to induce adverse effects, must

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be taken under the supervision of a doctor and, therefore, are not available to the general public other than through a medical professional's prescription [1].

Generic products are a subgroup of prescription products. They are medicines produced by a variety of manufacturers after the original inventor's patent monopoly has expired. They are usually identical to the original product, except perhaps for minor differences, for example, in tablet color or shape, but are significantly cheaper, because the manufacturers do not bear the burdensome research and development (R&D) costs. An example here is ibuprofen.

OTC medicines are those medicines that, because of their record of safety, can be sold directly to the public and can be used without medical supervision. Aspirin is a good example of a very useful medicine that can be bought without prescription.

The pharmaceutical market is mainly dominated by the three major developed markets of the United States, Japan, and Europe (EU), although there has been substantial growth in China. Manufacturing hubs include India and Eastern Europe. The research-based, prescription pharmaceutical companies dominate the pharmaceutical industry in size, turnover, and number of employees. However, the industry is highly fragmented, and no single company is dominant. Nonetheless, mergers and acquisitions have taken place to an increasing extent amongst large companies as they seek to increase their market share, coverage of the worldwide market or gain access to new technology and therapeutic areas.

2.2.1 Pharmaceuticals

A pharmaceutical drug is a drug used in healthcare, selected on the basis of the intended action of the drug through pharmacology. Pharmaceutical medications aid the diagnosis, cure, treatment, or prevention of disease. Pharmaceuticals are classified either according to their origin or in terms of their treatment. Most pharmaceuticals are low molecular mass organic chemicals (produced by chemical synthesis); although some, such as aspirin, are isolated from biological sources. Others are of natural origin.

Variations include manufacture from biological sources, such as blood or hormones. These generally fall within the definition of "biologics" or biopharmaceuticals.

Biologics refers to pharmaceutical products derived from biotechnological processes, where cells, tissues, or biological molecules are used to manufacture the product. "Biotech" draws on a number of interdisciplinary processes including chemical engineering, bioprocess engineering, bioinformatics, and biorobotics. One key example of biotechnology is with the designing of microorganisms to produce antibiotics.

Biopharmaceuticals (alternatively biologic medical product) is a term ordinarily reserved for genetic engineering or hybridization technology. Examples of biopharmaceuticals include vaccines, blood or blood components, allergenics, somatic cells, gene therapies, tissues, recombinant therapeutic protein, and living cells. Many of these products are heat-liable sterile products; for this reason they are produced aseptically [2].

Pharmaceuticals are produced by pharmaceutical companies of varying sizes, compounding units, and within the hospital sector.

2.2.2 Product evolution

Research-based pharmaceutical companies produce new medicines that will be first marketed as prescription products. When first introduced into the market, a new product will be carefully monitored to determine if the assessments of its safety, made prior to authorizing its release on to the market, are borne out in wider usage. Such assessments are usually made at the national level (or intra-national level in the case of the European Union).

In addition, in order to recover the sizable development costs that are incurred in pharmaceutical R&D, research-based companies need the period of monopoly provided by the patent system. After some period on the market, the originator's patent will expire. This opens the way to other manufacturers to produce copies of successful products. Unlike the original medicine, which is usually sold on its brand name, these copies are usually sold, at a far lower cost, by their chemical or generic name.

It is also possible that, through widespread use, a drug may come to be recognized to be safe within broad limits. Although "safe" is never an absolute state as far as medicines are concerned, it is possible to achieve levels of safety that warrant the sale of approved formulations directly to the general public OTC without having first to obtain a prescription from a doctor. OTC products are strongly branded, and this gives them a proprietary life that can far exceed the patent life. These products also require authorization by the country regulatory bodies (e.g., in the United Kingdom, this would be the Medicines and Healthcare products Regulatory Agency; in the United States, this would be the Food and Drug Administration) and a number of further criteria, in addition to product safety, must be assessed.

2.2.3 Importance of R&D

Most industries conduct R&D at some level to improve existing products or services or to introduce new ones. As judged by R&D expenditure as a proportion of sales, the pharmaceutical industry is one of the high spending industrial sectors (exceeded, perhaps, only by computers and other electronic devices). R&D spending in major pharmaceutical companies typically lies in the range 15–20% of sales [3].

R&D is arguably the key driver in propelling forward the growth of the pharmaceutical industry, through the release of new products together with innovations to existing products. R&D is an ambiguous term. The meaning varies with the context in which it is used; for example, R&D for the insurance industry is entirely different to R&D for the aerospace industry. In the context of the pharmaceutical industry, *research* is the process that investigates disease mechanisms and substances that modulate the disease and which, if successful, will identify a substance that is considered to have the potential to become a drug. *Development* is what turns that substance into a marketed medicine that doctors can prescribe and that will be of benefit to patients.

2.2.4 Development

Drug development is the process of turning "an interesting compound" into a marketed product. It is partly concerned with proving the safety and efficacy of the chosen compound to get marketing approval from the regulatory authorities. It also includes

other activities that are essential for a marketed product, such as the manufacturing process, the shape and color of the tablet (if that is the chosen dosage form), and how the product will be packaged. Health and safety data, in addition to the safety data for the compounds as a drug, will be required to guide staff who will be working with the chosen compound. The "commercial profile" of the compound will become apparent during its development; it will need to have attractive indications and claims that will allow it to compete with other treatments for the target indications, including nondrug treatments if the new product is to be commercially successful.

Drug development is expensive. Each drug development project will be unique and its cost will depend on many factors, the main ones of which are:

- The cost of synthesis of the chemical, biological, or recombinant molecular entity that has been selected for development, especially when the manufacturing processes must comply with good manufacturing processes;
- The extent and nature of the toxicology program, for example, whether lifetime animal studies are needed to determine the drug's carcinogenic potential;
- The extent of the clinical program. Some drugs are approved with clinical data from a few hundred patients, but more usually several thousand will be involved in a clinical program;
- The complexity of the clinical endpoint in the studies needed for approval (and marketing). Trials with a new antibiotic in which the patient's return to health after a short course of treatment for an uncomplicated infection and the proven eradication of infecting organisms, for example, in a urine sample, is a simple and clear-cut clinical endpoint. This is to be contrasted with trials in patients who are very sick and have a number of concomitant medical conditions that require treatment at the same time as the indication under study. For example, patients with septic shock, or trials in patients that need to show that the drug being studied will increase a patient's life expectancy, as is sometimes the case with drugs intended to treat cancers or heart disease.

2.2.5 Cost

Prices of new pharmaceuticals are often relatively high, especially when the ingredient and manufacturing costs contribute only a small fraction of the retail price (sometimes less than 10%). The industry justifies its new drug prices on the grounds that they are needed to give an adequate return on the massive investment made in R&D over the (relatively) short period of patent-protected market exclusivity. Prices of new drugs are directly controlled by the state in a number of countries, which has the effect of creating a new regulatory step in the approval process to determine pricing.

2.2.6 Generic drug products

The pace of pharmaceutical innovation is relatively slow, and the long development periods mean that the period of market monopoly is sometimes only a few years. This means that generic copies of "state-of-the-art" therapies can sometimes appear within a few years after the first launch of a new medicine.

Related to generics is compounding. Pharmacy compounding is the process of preparing personalized medications for patients. Compounded medications are "made

from scratch," where individual ingredients are mixed together in the exact strength and dosage form required by the patient. This method allows the compounding pharmacist to work with the patient and the prescriber to customize a medication to meet the patient's specific needs.

2.2.7 Other sectors

Like any other major industry, the pharmaceutical industry has spawned a number of satellite sectors. This includes contract manufacturers, contract research organisations (CROs), companies specializing in formulation technology and biotechnology.

Contract manufacturers are companies that specialize in some aspect of pharmaceutical manufacturing technology and that other companies may contract to undertake some aspect of manufacture on their behalf. Firms in this category can range from fine chemical manufacturers, through formulation processors to specialist-packing companies. Contract companies can use conventional technology providing, for example, tableting capacity or sterile product facilities, or they can be developing new technology, as in the companies specializing in chiral synthesis.

Contract manufacturers may be contracted on a short-term basis to fulfil a one-off sales contract or on a long-term basis, providing, for example, manufacturing capacity in territories where it is desirable to manufacture within the country concerned. They also represent an alternative for research-based firms that may require new manufacturing facilities for a new product. A contract manufacturer can provide manufacturing capacity while the new product is being established in the market allowing the inventing company to delay making a capital investment until the future of the product is more secure and predictable.

CROs provide clinical services for drug development; they conduct clinical trials. A CRO may be contracted by a major company to conduct some specific studies as a part of an overall drug development program, or smaller companies may entrust them with a clinical development program in its entirety [4].

CROs have become commonplace for two reasons. First, the bigger companies are seeking to rationalize their operations and are outsourcing many of the activities that had been carried out within a company. While for big companies, clinical development is likely to remain a core function, it is no longer necessary to staff a clinical research department to a level that would be capable of dealing with unanticipated peaks of activity. Companies are now more prepared to use CROs to deal with these peaks. The second factor has been the appearance and growth of small pharmaceutical companies, particularly biotechnology companies, which may be based on a new technology and have one or two products in development. Such companies cannot afford to set up and staff a full-time clinical function, at least initially, and the CRO is an obvious choice [5].

Formulation technology companies are another part of the pharmaceutical sector. New technology allows drugs to be formulated so that their release characteristics can be modified for their intended use, for example, the introduction of an implantable device that will release a drug at a uniform rate over a period of months. Furthermore, the

life of old products can be extended by making them more convenient to administer; there are many examples of drugs that have been reformulated in "sustained release" formulations that make possible the once daily dosing of a drug that originally needed to be taken two or three times a day. Many of these developments have originated in small companies devoted to formulation technology rather than in the formulation development laboratories of the major companies.

Biotechnology has developed a wide range of technology relevant to the pharmaceutical industry. For some years, there was a widespread view that the proper place of biotechnology was in providing a better understanding of disease processes, which would enable conventional pharmaceutical research to invent better medicines. The launch of a number of very successful biotechnology products has shown that this sector of the pharmaceutical industry is of growing importance in its own right rather than just an enabling technology.

Biotechnology involves the use of microorganisms and biological processes, the most common example of which is fermentation. One application of fermentation is with the production of antibiotics, hormones, and enzymes, which are produced via the breakdown of an organic substance.

Fermenters are designed to contain an internal environment for the optima metabolization and efficient reproduction of microorganisms. They are also designed in a way to avoid contamination, beginning as aseptic spaces. With the operation of fermenters, there are a number of key operational aspects [6]:

(a) the supplied nutrients must meet the prerequisites for microbial growth;
(b) if the process is aerobic, then filtered air must be supplied;
(c) temperature must be regulated (via a thermostat);
(d) pH must be at an optimum level;
(e) mixing must be controlled; here bubble agitation is used to control nutrients and oxygen.

Such devices are either designed for batch culture (where microbial growth is halted, to allow for the removal of the required product) or continuous (where microbial growth is maintained at the exponential level and the product is continuously removed).

Thus, the biotechnology sector provides a vehicle for the rapid transfer of new technology from academia into a commercial environment. This serves not only biotechnology in the strict sense of the word but also related technologies such as computer-aided drug design, innovative approaches to formulation, and natural product screening.

2.3 Role of the microbiologist

Having outlined the basic patterns of the pharmaceutical sector, it is important to examine the oft overlooked contribution of the pharmaceutical microbiologist. Due to the diverse nature of pharmaceuticals and healthcare, the role will vary across the sector. Nevertheless, the microbiologist should play a key role within the organization. This is not least because microbial contamination in pharmaceutical products can have

significant consequences. It is not only important for compliance with standards but also reduces risk to the end user, and, consequently, to the manufacturer.

Microbiologists also play an important role in drug development. Understanding the principles of microbiology and human cell mechanisms allows pharmacists to discover antimicrobial drugs that would prevent an escalating number of communicable diseases. Pharmacists and microbiologists work synergistically to ensure that drug therapies target the opportunistic microorganisms without harming its human host. Another important role in pharmaceuticals is the use of microbes for the medically important studies. For example, in the development of Bacteriorhodopsin, a protein from the plasma membrane of *Halobacterium salinarum*.

Microorganisms are used to manufacture many types of biological drug products. Microorganisms produce a variety of secondary metabolites, some of which have been identified as having therapeutic value. A prime example is with antibiotics (low-molecular-weight metabolites that inhibit the growth of microorganisms), which can be sourced from microorganisms such as *Streptomyces*, *Cephalosporium*, *Aspergillus*, or *Pencillium*, or produced artificially. For example, species of the fungus *Penicillium* produces the antibiotic penicillin (an antibiotic with a 6-amninopenicillanic acid core ring structure; branded examples include phenethicillin, propicillin, and oxacillin). Other examples include tetracyclines such as streptomycin (from species of *Streptomyces*) and cephalosporins (from the fungus *Cephaloporium acremanium*) [7]. Further aspects of pharmaceutical microbiology include the R&D of anti-infective agents; the application of microorganisms to detect mutagenic and carcinogenic activity in prospective drugs; and the use of microorganisms in the manufacture of products such as insulin and human growth hormones.

Microbiology plays a significant role in medical devices, such as fluorescent fusion, which are used for fast and precise detection of pathogens in tissue samples. It is a technology for carrying out immunofluorescence studies that may be applied to find specific cells in complex biological systems [8].

There is also a part played by microbiologists in the cosmetics industry. This is because the contamination of cosmetics can result in them being converted into products hazardous for consumers. The water and nutrients present in cosmetics make them susceptible to microbial growth, although only a few cases of human injury due to contaminated cosmetics have been reported. More often, microorganisms are the cause of organoleptic alterations, such as offensive odours, and changes in viscosity and color.

Pharmaceutical microbiologists provide an essential contribution to risk assessment. This can be with assessing new systems and processes to determining where contamination risks may occur (linking with “Quality by Design” concepts). Risk assessment also applies to reviewing contamination events for their significance. With these two facets of risk management, proactive risk assessments should take up the greatest proportion of time. It follows that the more effectively this is done, then the less likely contamination situations are to occur. Tools for performing such assessments include risk analysis tools borrowed from other industries or professions including HACCP (hazard analysis critical control points) from the food industry, FMEA (failure modes and effects analysis), and FTA (fault tree analysis)

taken from engineering industries, such as, car production. These approaches share a number of things in common:

- constructing diagrams of work flows;
- pin-pointing areas of greatest risk;
- examining potential sources of contamination;
- deciding on the most appropriate sample methods;
- helping to establish alert and action levels;
- taking into account changes to the work process/seasonal activities.

In order to assess these aspects, it is important that the microbiologist builds up detailed knowledge of the production system and processes. Thus, the lead microbiologist will spend little time testing and accumulating data and more time formulating corrective and preventive actions and performing process reviews [9].

Risk assessment is also integral to drug development. Here the most important intent in risk determination is, of course, patient safety. Second intent is the risk to the product, to prevent batch rejection. Of these two, the patient's risk must always be the highest concern. Patients depend on products to be safe from contamination when they first use them and if they continue to use them.

A set of three parameters can be used to develop an understanding of the risks related to patient safety. These are:

- Route of administration—this concerns how the drug will be delivered to the patient: method, mechanism, or through which part of the human body will the drug impact the most;
- Patient health—this is the real time health of a patient receiving the drug and this is an aspect of age, culture, and pre-disposed conditions that could be environmentally imposed;
- Target dose intent—this concerns the target organ, region, or breadth of exposure to the human body for the pharmaceutical product.

Risk assessment concepts are discussed in more detail in Chapter 18.

It is not sufficient for the pharmaceutical microbiologist to have knowledge of microbiology. The microbiologist needs to have a wider knowledge of physics [10]. Without such an appreciation, the significance of results from a cleanroom, whether viable microorganisms or nonviable particles, cannot be fully understood. Physical tests, such as pressure differentials, clean-up times (recovery rate), and airflows frame the context of the microbiological result. Likewise, the microbiologist is required to have a greater understanding of chemistry, engineering, and engineering systems. For example, in assessing the results from a purified water system, some knowledge of flow rates, valve design, re-circulation, heating, and piping is required. To add to this, an understanding of the chemistry of disinfectants and antiseptics is necessary in order to select and monitor the most potent and effective compounds.

2.4 Conclusion

The purpose of this chapter was to provide an introduction to the pharmaceutical industry so that the importance of, and complexities involved with, drug development could be outlined. The cost and risks of introducing new drugs are high, and pharmaceutical

microbiologists are frequently required to play a part in this development process, including the establishment of test methods and the setting of test limits.

The role of the microbiologist also extends to mapping out contamination control strategies, undertaking risk review and assessing contamination control problems. It also extends to designing and executing an array of tests. In short, the microbiologist plays a critical role in the pharmaceutical development process.

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