2 Target Discovery and Validation

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2.1 Introduction

The pharmaceutical industry as we know it is still relatively young and only started to emerge about 100 years ago, as advances in chemistry and biology made the discovery and synthesis of drugs possible. In the post-war years up to the late 1980s, the pharmaceutical industry grew at a spectacular rate and launched 44 new drugs in one year at its peak in 1994. The success was based on a deep understanding of physiology and pharmacology coupled to brilliant medicinal chemistry.
In the 1980s, the ability to rapidly clone and manipulate genes heralded the start of the molecular biology era that culminated in 2001 with the publication of the first draft of the human genome sequence. This had an impact on the pharmaceutical industry that underwent a dramatic revolution with the advent of the molecular pharmacology era. The speed of the change is highlighted by the fact that the first $\beta$-adrenergic drug was launched in 1965 and the cDNA for the $\beta_2$-adrenergic receptor was only cloned as recently as 1986 (Dixon et al. 1986). These advances in molecular biology coincided with breakthroughs in compound screening technology and chemical synthesis. Engineering and robotics solutions allowed hundreds of thousands of chemicals to be tested in biological assays every day, so-called high-throughput screening (HTS). Chemistry also changed to meet the growing demands for more compounds and more diversity to fuel these screening engines and strategies for combinatorial chemical synthesis evolved in this period. Thus, due to the introduction of high-throughput technologies in the 1980s, the drug discovery process was changed from a methodical, empirical science to a highly automated industry.

These dramatic changes to the drug discovery process were, and still are, widely expected to improve productivity in the industry. However, this has not yet materialised and there are some uncertainties about the future direction of the industry. In 2001, only 25 new drugs were launched, the lowest number for almost three decades. The industry is spending ever-increasing amounts of money on research and development, close to US $50 billion per year, and according to the Tufts University Centre for the Study of Drug Development (http://csdd.tufts.edu/), the cost of developing a new drug has also risen from $231 million in 1987 to $802 million by 2000. Investors expect major pharmaceutical companies to achieve 10% annual growth, and in order to achieve this, each of the major companies must launch, on average, four new chemical entities (NCEs) per year with average sales of $350 million. However, from 1996 to 2001 the industry launched on average less than one NCE per year per company and of all the drugs launched in 1996 only 25% had sales in excess of $350 million. Added to these pressures are the looming patent expirations for many of the world’s top selling drugs.