2. THE EVOLUTION OF DRUG DISCOVERY AND ITS EFFECT ON PRECLINICAL DEVELOPMENT

The process of pharmaceutical innovation is complex and measures of research and development output are important in understanding trends in drug development (1). The recent history of pharmaceutical industry performance suggests that, despite the investment of billions of dollars in excellent human resources and state-of-the-art instrumentation, the development of new medicines is a risky business, one that has experienced many failures for each success. Several indices of success have been proposed including the number of NCE synthesized and the number of patents issued. However, time-to-market and the number of NCE approved in a given period of time may be the most practical measures of pharmaceutical success.

Between 1960 and 1980, development time of NCE from synthesis to market almost quadrupled and has remained relatively unchanged since 1980, with a present interval of 9–13 years (2). This has been accompanied by a corresponding decrease in the effective patent life, from nearly 13 years to 6.5 years (1). Typically, from the day of the discovery of new targets and new lead structures until the decision to proceed with full-scale development, 5–6 years have passed (3). It has been estimated that in order to discover such lead structures, an average of 50,000–100,000 NCE must be screened.

The failure of lead compounds in phase I and phase II clinical trials is a major source of scientific and economic difficulty. In Britain, over a 17-year period from 1964 to 1980, a total of 197 NCE were evaluated in man for the first time (1). However, 137 were withdrawn from development and 35 (18%) continued through development; the ratio of drugs innovated to those marketed was 5.6:1 (1). This is similar to the 5.6:1 ratio reported for the United States or 13.5:1 for Swiss companies (1). The major reasons for withdrawal included inappropriate pharmacokinetics in human subjects (39.4%) and a lack of clinical efficacy (29.3%). The incidence of unexpected toxicity or more subtle adverse effects was the third most common reason for termination (10%).

Every excess year of drug development is an unnecessary use of resources that could be applied elsewhere, the money being spent as well as the revenues being lost due to late marketing. Thus, time also becomes a most important factor in drug development (3). A rough calculation of daily revenues lost on a new medicine with average market potential suggests that each day of delay in getting NCE to market is approximately US$2M. The increasing cost of efficient drug development is associated with prolonged development time and increasing regulatory requirements. In 1987 expenses for the development of NCE averaged $US300M–$US400M. Currently, in the United States, the costs of drug research and development have increased to between $US800M and $US1B per approved medicine (4).