Available online at www.sciencedirect.com
ScienceDirect
European Journal of Operational Research 189 (2008) 459–475
EUROPEAN JOURNAL OF OPERATIONAL RESEARCH
www.elsevier.com/locate/ejor

O.R. Applications

Models and software for improving the profitability of pharmaceutical research

Jiun-Yu Yu *, John Gittins

Department of Statistics, University of Oxford, 1 South Parks Road, Oxford OX1 3TG, UK

Received 19 July 2006; accepted 15 May 2007
Available online 26 May 2007

Abstract

The pharmaceutical industry is highly competitive, and the discovery and development of new drugs is extremely expensive and time consuming. This paper is a contribution to the task of improving the effectiveness of pre-clinical research. Our model investigates for any given project the number of lead series which should if necessary be optimised in the search for a development compound which is sufficiently promising to proceed to clinical trials. The numbers of scientists which should be allocated to each research stage are also investigated. Two widely-applied profitability criteria are considered. Computer software designed to implement the optimisation calculations is described and shown to produce reasonable results, leading to a potentially dramatic improvement in profitability.

Keywords: OR in research and development; Project management; Decision analysis; Applied probability; Economics

1. Introduction

Pharmaceutical companies require great patience and enormous capital. It typically takes 12–15 years to successfully complete the research and development (R&D) process of a new drug, with probability of success less than 20%, while the combined cost of R&D and market introduction for a significant product today exceeds £700 million (Chen, 2004). For these reasons, bringing research projects to an early successful conclusion gives an important competitive advantage.

There is a substantial literature, some of it specific to the pharmaceutical industry, on criteria for project selection and resource allocation in R&D. These range from simple check-lists to sophisticated pharmacoeconomic analysis. The journals *R&D Management* and *Pharmacoeconomics* are good general sources, see for example the review papers by Miller (2005) and Poh et al. (2001). The earlier literature is reviewed by Bergman and Gittins (1985).

* Corresponding author. Tel.: +44 1865 282853; fax: +44 1865 272595.
E-mail addresses: yu@stats.ox.ac.uk (J.-Y. Yu), gittins@stats.ox.ac.uk (J. Gittins).

0377-2217/$ - see front matter
doi:10.1016/j.ejor.2007.05.023

The model discussed in this paper is a stochastic economic model. There are three important themes with a bearing on models of this type, as follows:

- The methodology of decision analysis. This has been around since the 1960s. Key ingredients are personal probabilities, utility functions, sequential decisions expressed as a decision tree, and solution by a dynamic programming algorithm. McNamee and Celona (1990) have written a useful handbook, and Lindley (1991) gives a good introduction to the main ideas.
- *Real options*. Black and Scholes (1973) provided a methodology for valuing financial options. Others, notably Dixit and Pindyck (1994), have pointed out that a similar analysis is possible for options to invest in specific projects.
- *Pharmacoeconomics*. This is the science of relating the costs and benefits, both to individuals and to society, of therapeutic regimes, including drugs. Analysis along these lines is becoming routine in the planning of clinical trials. The journal *Pharmacoeconomics* started in 1983.

The insight from financial options theory that the ability to postpone, and possibly eventually not take up, an investment opportunity can strongly influence its value has been important, see for example Burman and Senn (2003), Chen (2004) and Perlitz et al. (1999). However, the match between financial and real options is far from exact, and current economic approaches to pharmaceutical project planning tend to owe more to decision analysis than to real options theory. The papers by Stonebraker (2002), Ding and Eliashberg (2002) and Loch and Bode-Greuel (2001) are good examples.

All these papers focus at least as much on development as on pre-clinical research, and so far as the authors are aware we have modelled the pre-clinical stages of research, in discussion with people working in the industry, in a much more detailed fashion than is to be found elsewhere. This is borne out by the comment in Miller (2005) that there is currently very little pharmacoeconomic planning in the early stages of research. Islei et al. (1991) have written an important paper describing a planning system for those early stages. However, it does not include an economic model.

Section 2 describes what happens in pre-clinical pharmaceutical research. Section 3 describes our model and the *OPRRA* (*Optimal Pharmaceutical Research Resource Allocation*) software. Section 4 sets out the details of some of the optimality calculations, with further details in an appendix. Section 5 discusses some numerical examples which show that large increases in profitability may well be possible. Brief concluding comments including plans for further work are given in Section 6.

2. The setting

Until the mid 1990s most pharmaceutical research projects proceeded in the following sequence. Bioscientists first work out an hypothesis for the way in which a chemical intervention in the body's processes might achieve the desired result. Then bioscientists and chemists devise tests using animal tissue or live animals in order to screen compounds for relevant activity. Afterwards, chemists synthesise compounds designed in the hope of finding relevant activity. These are then subject to a series of screening tests. Compounds which were not synthesised for this specific purpose may also be screened. The main change in recent years has been that the initial screen has almost always been a high throughput robotic screen on tens of thousands of library compounds.

When a compound with a sufficiently high level of activity has been found, other compounds with similar chemical structures are synthesised and tested. The original active compound is termed a *lead compound*, and the string of similar compounds is a *lead series*. The testing of these compounds is known as *optimising the lead*. From those compounds which achieve promising results on the screening tests, which include tests for toxicity, a small number are selected, usually one at a time, for tests in man. The clinical trials are often referred to as the *development* phase of a project, and consequently, a compound that goes on to clinical trials is called a *development compound*. At most 20% of development compounds emerge from clinical trials as marketable drugs, so typically more compounds are screened while a compound is undergoing clinical trials, in order that one or more *backup compounds* may in turn be selected from them for development. In summary,