Research and Reviews: Drug Delivery

Time and Cost Requirements for Creating a New Chemical Entity and Project Failure Causes

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Opinion Article

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DESCRIPTION

Drug development is risky and time-consuming, and it requires substantial investments in terms of capital (~$500 million), human resources, research skill, and technological expertise. Costs are high, even in the initial phases. Determining whether or not a small molecule can be developed currently requires about 6 months and $500 000. Long-term animal testing requires approximately $3-7 million, and a detailed breakdown of these costs has been published. The development of new drugs requires nearly $1 billion and 12 years to bring the average NCE to commercialization. $200 million might be attributed to compound failure. Recently, an NCE targeting the peroxisome proliferator activated receptor γ family ragaglitazar (NN622), a dual acting insulin sensitizer, was found to be positive in the carcinogenic bioassay study (urinary bladder tumors were observed in mice and rats), and the drug had to be dropped during phase III trials, after many millions of dollars had been spent on its development.

The costs of fundamental clinical testing for an NCE are even higher (in millions of dollars): 15.2 for phase I, 15.7 for phase II, and 27.0 for phase III. Compounds that are abandoned during the testing process (some as late as phase III) represent an enormous loss, amounting on the average to roughly $200 million. Since the mid-1960s, the process of drug approval has been modified to significantly improve the safety and the efficacy of new drugs for

use in general practice. However, one of the consequences of these changes has been an increase in the time and costs associated with placing a new drug on the market. It has been shown those small improvements in clinical trial outcomes and decision making translate into hundreds of millions of dollars of development cost-saving and a faster time to market.

The mean interval of time between synthesis of a compound and approval of the NDA was 7.9 years in 1960: by 1990, it had risen to 12.8 years. Estimates for 2004 dropped to between 3.2 and 8.5 years, but intervals of 10-20 years are not uncommon. The increasing time requirements are the result of the growing complexity of clinical tests, the demand for increasingly rigid testing protocols, administrative aspects of testing, and the indispensable inclusion in the study of particular population subgroups, such as the elderly.6 The duration of clinical testing ranges from 53 to 86 months for NCEs belonging to major drug categories: anti-infective agents: 74 months; antineoplastic drugs: 116 months; cardiovascular drugs: 103 months; endocrine agents: 115 months; and immunological drugs: 100 months. A 25% reduction in the time needed for the clinical phases of drug development would decrease the capitalized cost of NCE development by 16%.5

Approximately one out of every 12 leads completes the process and becomes an NDA59 (1:500025). Between 1983 and 2001, the overall final clinical success rate for all investigational drugs was 21.5%. The main causes of project failure in the advanced phases of NCE development are pharmacokinetic issues (3927-40%8) and animal toxicity (11%8). Late evaluation of safety and efficacy, low therapeutic indexes (the ratio of the maximum tolerated dose to the therapeutic dose per kilogram based on repeated treatment in two animal species), and the time, size, and costs of clinical studies are other major reasons for compound attrition. The latter variables can be reduced by the use of reliable and specific biomarkers that can be used as early predictors of efficacy and long-term toxicity. Minor improvements in clinical trial outcomes and decision making have been shown to translate into major savings in terms of cost (hundreds of millions of dollars) and time to market.

The increasing number of potential hits generated each year has not resulted in a corresponding increase in the number of NCEs that reach the clinical trial stage, and this is due in part to inadequacies in the investigation of the candidate drug's pharmacokinetic properties. The advisability of requiring early pharmacokinetic studies in humans has recently been underlined by some authors.

In any case, due to the high cost and specificity of the drug development process, most manufacturers adopt a step-by-step approach, with well-defined points for evaluating the results obtained and deciding whether or not to proceed. A balance must be struck between investments and the length of intermediate periods between testing phases, and a continuous evaluation of the project time is needed to make decisions and ensure a reasonable possibility of success as early as the lead stage of the NCE.