FROM THE ANALYST'S COUCH

Clinical forecasting in drug development

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The cost of developing an innovative drug remains the subject of ongoing debate, with some estimates now exceeding the widely quoted figure of US$802 million[1]. Whatever the true cost, however, it is clear that late-stage clinical failures account for a large proportion of the expenses. This can be as a result of both the large out-of-pocket investments in Phase III clinical trials and because unsuccessful trials tie up capital resources during their conduct, and potentially also for the time spent during any attempted recovery following regulatory rejection. So, there is an interest in strategies that could halt, as early as possible, the development of drugs that eventually fail. Even a small improvement could have a considerable impact; it has been estimated that terminating just 5% of Phase III failures in Phase I could reduce out-of-pocket clinical costs by 5.5–7.1%[2].

Obviously, clinical factors — drug efficacy and safety — have a major effect on attrition rates and the associated costs[1,3]. However, clinical forecasting to predict late-phase safety and efficacy based on earlier-phase clinical data with sufficient accuracy to facilitate early termination of eventual failures without stifling would-be successful drugs is a major challenge. Furthermore, although various market-forecasting approaches — which generally aim to assess the financial effect of future market share, competition and profitability — are established[4], the working assumption of these approaches is that the drug in question will receive regulatory approval. Indeed, it has been noted that early-stage market-research efforts have almost always failed to predict blockbusters[5], and so accurate clinical forecasts would also empower assumptions related to drug success that underlie market forecasts.

With these issues in mind, here, we briefly discuss evidence related to the ability of clinical forecasting strategies to significantly reduce failure rates without impeding innovation, and highlight issues that need to be addressed to allow the widespread implementation of such strategies.

Forecasting strategies

Pharmacokinetic/pharmacodynamic (PK/PD) and trial simulation models help investigators improve later-phase trial designs in terms of trial length, sample size, selection of target populations and optimization of dosing regimens[6–10]. For example, Hunt and colleagues[6] demonstrated the value of a specific PK/PD forecasting model, and De Ridder used Phase II data from a single drug to develop a dose–response model that approximated the actual Phase III dose–response curves[10]. PK/PD modelling and trial simulation usage will probably increase as adaptive trial methodologies gain wider acceptance[11].

However, the comparison of a drug in development with a broader range of drugs is beyond the aim and scope of conventional models. As an initial step to tackling this challenge, we considered clinical forecasting from the perspective of modelling populations of drugs rather than populations of patients in a given development programme. Our goal was to use knowledge of prior successful and failed new chemical entities (NCEs) stratified by therapeutic class (for example, antineoplastic and cardiovascular) to inform a predictive model for NCEs in development in a particular class (BOX 1). The resultant Bayesian network model predicted the probability of Phase III success and New Drug Application (NDA) approval for an independent validation set of antineoplastic NCEs with 78% accuracy[12]. In this case, application of the model was shown to reduce the mean capitalized expenditures by US$283 million per successful new drug compared with the pharmaceutical industry's reported success rates[12].

Widespread implementation of predictive models with this degree of accuracy could have a significant positive effect not only on the pharmaceutical and biotechnology industries and their investors, but also on public health and health care delivery. Patients enrolled in Phase III studies would be more likely to be administered effective, safer drugs. Companies could reduce drug development costs, and pass on some of these savings to the consumer while remaining competitive, and investors could place more confidence in market forecasting models.

Challenges for forecasting models

The task of building our independent validation data-set highlighted a major impediment to widespread clinical forecasting: the lack of data sharing in the pharmaceutical industry and between industry and the public, particularly with respect to terminated or failed drugs. Current models cannot address non-adherence to eligibility criteria by specific clinical trial centres, idiosyncratic adverse events, or any other variables unrelated to safety or efficacy. However, with access to high-quality data on past failures, these seemingly 'unpredictable' factors could be modelled informatively. If certain changes can be effected (TABLE 1), predominantly with respect to data sharing, the power of clinical forecasting approaches could grow exponentially.

It is understandable that incentives exist for a given company to keep clinical trial data proprietary, but clinical forecasting approaches could increasingly demonstrate the broad benefits of exploiting this gold-mine of information. Indeed, the Pharmaceutical Research and Manufacturers of America (PhRMA) have launched a publicly accessible database of clinical trial results, and their supporting position paper[13] indicates a willingness to share information. Other efforts to improve the transparency of clinical research have resulted in the creation of clinical trial databases such as ClinicalTrials.gov, which is currently a mechanism for connecting potential study subjects with relevant trials that are actively recruiting (trial results are not as yet available).

However, although it seems there is growing acknowledgment by industry of the importance of releasing late-stage trial data, the public release of early-stage trial data, which is perceived as being potentially harmful to competitive firms, is much more controversial[14]. Less controversial is the role that Bayesian methods could have in the post-marketing surveillance system recently proposed by the Institute of Medicine[15]. Indeed, it has been shown that Bayesian analysis would have identified the cerivastatin–rhabdomyolysis association within 6 months of approval had this method been available[16], and Bayesian methods are a part of the WHO ▶

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► Program for International Drug Monitoring[17]. The adoption of clinical forecasting technologies could improve the appeal of legislated data-sharing efforts to industry by allowing better predictions, thereby improving the efficiency of drug development, and benefiting all of the stakeholders in clinical research.

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Competing interests statement
The authors declare competing financial interests: see web version for details.

Box 1 | **Application of a Bayesian model for clinical forecasting**

We have developed a Bayesian network model that calculates the probability of Phase III success and New Drug Application (NDA) approval for a drug, given pre-Phase III safety and efficacy data[12]. The model operates on summary statistics (for example, mean, variance or frequency distributions) and does not require access to raw, elemental data, which can be difficult to obtain. Publicly available data — including therapeutic indices, *in vitro* and *in vivo* efficacy data, early clinical efficacy data, true versus surrogate biomarkers or endpoints and drug-invention source (either in-licensed or developed in-house) — for ~500 new chemical entities (NCEs) stratified by therapeutic class were used to develop the model.

The model was validated on an independent data-set consisting of successful and failed drugs for one class (antineoplastics), and found to perform with 78% accuracy (80% sensitivity and 76% specificity)[12]. Entering hypothetical models with a range of sensitivity and specificity values into the same Monte Carlo simulation framework used to assess the Bayesian network model showed that model sensitivity and specificity values of only 60% or better demonstrate a potential financial benefit over the recent reported performance of the pharmaceutical industry (see figure).
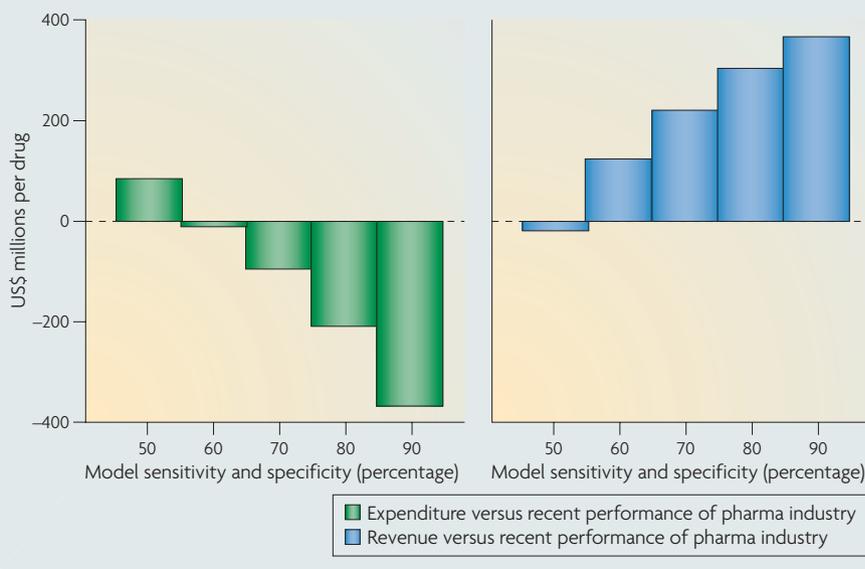

■ Expenditure versus recent performance of pharma industry
■ Revenue versus recent performance of pharma industry

Table 1 | **Clinical forecasting: recommendations and potential effect**

Recommendations	Potential effect
Development of industry standards for data annotation and storage	Firms capitalize on future collaborations
Regulatory changes that encourage data sharing of summary statistics on failed compounds	Reduce patient exposure to unsafe and/or ineffective drugs
	Reduce industry-wide failure rates
Regulatory support for the development of models that assimilate data on failing compounds	Reduce development costs
	Reduce prescription drug costs
Dissemination of Phase I and Phase II data from ongoing trials only on completion of Phase II trials	Increase transparency
	Protect proprietary industry data during earlier development phases
Investor valuation methods that integrate the probability of clinical success for early-stage compounds	Empower market-forecasting methods
	Improve investor confidence
	Improve cash flow
	More robust development pipelines