



# Enhancing R&D in science-based industry: An optimal stopping model for drug discovery

Guozhen Zhao<sup>a,\*</sup>, Wen Chen<sup>b</sup>

<sup>a</sup> Rutgers, The State University of New Jersey, Ackerson Hall, Rm. 200F, 180 University Avenue, Newark, NJ 07102, United States

<sup>b</sup> McCombs School of Business, Department of Information, Risk, and Operations Management, The University of Texas at Austin, Austin, TX 78712, United States

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## Abstract

Drug discovery is a process of science work full of exploration and complexity. Drug researchers face the dilemma of either working ‘forever’ to create a perfect drug or delivering a workable drug within an acceptable deadline to both save lives and make a profit. Specifically, in the compound screening and optimization stage, drug researchers must decide whether or not to stop the research and deliver the result for clinical testing. This paper proposes a model of optimal stopping time to help drug researchers make such decisions. It examines the decision strategies drug researchers should take through maximizing their objective function. The numerical examples given here show that this model is widely applicable. The model offers potential merits in terms of its ability to clarify drug researchers’ decision-making practices and helping managers maneuver through the jungle of science work.

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## 1. Introduction

Organizational viability and competitive advantage depend on ongoing or sustained product innovation [1]. This issue is especially prominent in a science-based industry such as pharmaceuticals where the breakthroughs of R&D are often explorative. In order to obtain blockbuster drugs (i.e., the rare, exclusive and efficient drugs that are so profitable that they can finance the entire operation of the company [2]), pharmaceuticals often undertake robust R&D projects that require time to develop and entail a continuous flow of knowledge creation and discrimination. However, pharmaceuticals often have great difficulty with exploration in their R&D projects, spending increasingly on R&D to no avail. One reason for the limited mastery of exploratory product innovation is that, in contrast to

a linear process, drug innovation is rather chaotic [3], subject to uncertainty [4], trial-and-error, hard work, and serendipity. Thus, it is difficult for drug researchers to have clear insight into the fuzzy process of their explorations or estimate their future direction.

For a specific pharmaceutical R&D project, the scientific knowledge required to create new drugs is inevitably subject to a significant level of complexity, and the information necessary for managers and scientists to decide whether and where to stop the R&D project is limited by a high level of uncertainty. Due to such knowledge complexity, information uncertainty, and randomly evolving events in drug discovery, R&D managers often face serious difficulties in assessing whether their exploratory work is worth continuing [5]. Optimal stopping models could help them make such difficult decisions. Previous research on optimal stopping problems has mainly focused on the timing of economic investment decisions, and has introduced various methods ranging from scoring models and profitability indices to decision theory or analysis models [6]. A more recent paradigm holds R&D projects as part of a

\* Corresponding author. Tel.: +1 732 735 6510/973 353 1461; fax: +1 973 353 5691.

E-mail addresses: [guozhzhao@pegasus.rutgers.edu](mailto:guozhzhao@pegasus.rutgers.edu), [zhaogzh@alum.sem.tsinghua.edu.cn](mailto:zhaogzh@alum.sem.tsinghua.edu.cn) (G. Zhao), [w.chen@mail.utexas.edu](mailto:w.chen@mail.utexas.edu) (W. Chen).

pipeline and treats them as a real option-pricing models [7–9], and managers can either wait for more information or decide to stop the investment immediately. The existing research on pharmaceutical R&D projects mainly follows this fashion. However, management researchers pay less attention to the actual exploratory practices of pharmaceutical scientists. In other words, research in optimal stopping problem does not fully consider how the science work itself, rather than economic investment, can influence an R&D project. In pharmaceuticals, an R&D project has unique characteristics in terms of scientific discovery. It not only attempts to use existing science but also to advance scientific knowledge and capture the value of the knowledge it creates [10]. This indicates that science is at least as crucial a determinant as economic investment for any R&D decision-making. Moreover, the role of serendipity in scientific discovery, especially in the current pharmaceutical industry [11], suggests that money is not necessarily the best solution to R&D problems. How to take full advantage of science to provide quality drug candidates in a limited time frame becomes a key question for pharmaceutical R&D project managers.

The purpose of this paper is to introduce an optimal stopping model for pharmaceutical R&D projects by treating science as a key determinant in the project decision-making process. In science-based industry, R&D managers work with scientists to make stopping decisions based on the quality of the best scientific discoveries at hand and on the remaining time still allowed the R&D project. In fact, many R&D managers in pharmaceuticals are themselves scientists or have solid science backgrounds. A drug research project has multiple phases – from disease target identification, pre-clinical trials, to clinical trials and FDA approval. In pre-clinical trials, one crucial and specific stage is that of lead compound screening and optimization. This stage generally takes about five or six years in a twelve to fifteen year innovation cycle and consumes about one third of the total research costs [11]. This stage includes the combination of high throughput screening (HTS) of hundreds of thousands of molecular compounds and optimization of the lead compounds filtered from screening. It is an appropriate stage for our model building for various reasons.

First, this is the stage in which the majority of scientific knowledge is created and significant scientific breakthroughs are most likely to occur. Such knowledge creation and breakthroughs are the engine of research advancement from which lead compounds may turn into blockbuster drugs. Some renowned breakthrough cases include Alexander Flemings' use of pharmacology to isolate penicillin, and Kary Mullis's invention of polymerase chain reaction [11]. Second, this is the stage in which pharmaceuticals may invest the most for exploratory innovation, not only making full use of existing science and technology but also developing new science. Nearly all state-of-the-art chemical, biological, and computer technologies are used in this stage for the creation of new drugs. Third, this is the stage

in which the interests of different stakeholders conflict with one another. For instance, the priority of drug scientists is to have a thorough understanding of the secrets of the human body and develop a 100% perfect blockbuster that has no side effects. However, the time it can take to find the perfect drug is indeterminate. On the other hand, pharmaceutical companies facing economic pressures are primarily interested in make profits as large and as quickly as possible. This conflict of interest underscores the tradeoff between time and quality of science facing those involved in a drug research project. Thus, R&D managers have to make decisions about where and when to stop the exploration, accept the current best result, and deliver the lead compound for clinical trials on human subjects. Fourth, this stage faces more and more regulation. For instance, the Food and Drug Administration's (FDA) requirement to identify rare or unexpected side effects before a product launch poses higher scientific challenges in this stage of drug research [11]. Scientists must work more innovatively on lead compounds, a situation which increasingly emphasizes the influence of science on R&D project success. Fifth, this stage directly influences the cost of subsequent clinical trials and the drug's future profitability. A good quality drug candidate created in this stage will have significantly enhanced success rates in clinical tests, making its way to the market as smooth as possible.

Given the importance of the lead compound screening and optimization stage, the present study proposes a model of optimal stopping time based on the circumstances under which R&D managers should decide to stop screening and optimization, and deliver the best compounds to downstream clinical trials. Since time is crucial [12], the earlier the optimal stopping time is, the more the company and patients can benefit from the product.

The rest of this paper is organized as follows: Section 2 provides a brief review of relative research on pharmaceutical R&D project evaluations and optimal stopping times. Section 3 illustrates pharmaceuticals as a science-based industry and presents the argument that drug discovery is a knowledge creation but not necessarily a knowledge accumulation process. Section 4 gives the methodology, constructs the optimal stopping model, and derives its optimality conditions. Section 5 provides a detailed examination, through examples, of analytical and numerical methods, and, in addition to demonstrating the strength of our model in selecting the best compounds in a specific project, offers a brief illustration of how the model could contribute to the optimal design of a drug development portfolio. Section 6 summarizes and concludes the paper.

## 2. Literature review

The present study tries to optimize a specific stage of innovation in a pharmaceutical R&D project procedure by considering an optimal stopping model. The relevant literature focuses mainly on two aspects of study: evaluation of pharmaceutical R&D project procedures, and optimal

stopping models. To our knowledge, the research in pharmaceutical R&D project procedures is rather limited in management studies and mainly uses the Bayesian decision approach to information accumulation. The basic assumption of the Bayesian approach is that continued corrective action based on new information lies at the heart of successful R&D management [6]. For instance, Thach and Fisher [14] use Bayesian decision theory in the design of clinical trials and specify the trials' optimal sample size (i.e., the number of voluntary human subjects) in such a way that the trial minimizes the expected costs. Cressie and Biele [15] assume that a drug company can construct a realistic gain (or loss) function, and they discuss a sample-size-optimal Bayesian procedure for sequential clinical trials. Gittins [4] covers the entire stages of a pharmaceutical R&D project and develops a stochastic model to maximize the profitability of the project by optimally allocating different numbers of scientists to each stage. In general, the literature does not delve deeply into the pre-clinical stage at which our model aims. Also, a significant problem of pre-clinical lead compound screening and optimization is that the information gathered in one round of tests is rather independent from previous or subsequent rounds, making the prior probability and the posterior probability irrelevant.

The second school of R&D procedure research focuses on optimal stopping models. These models were first used to evaluate uncertain investment projects that take time to build and provide no payoff if development stops before reaching a well defined point of completion [16,17]. Chi and colleagues' [5] initial work releases the 'no payoff before completion' constraint; they develop optimal stopping models for re-engineering manufacturing systems by allowing a project's potential payoff to be partially realized at termination even if the attainment of its original objective fails. Cohen et al. [18] investigate the tradeoff between maximizing new product quality and minimizing time to market. They present a multi-stage model of new product development, using factors like profit margins, length of the window of opportunity, the firm's speed in product improvement, and competitor product performance to study time to market and product performance. Cohen et al.'s model is applicable in engineering industries where knowledge is accumulated in a path-dependent way, and the road map to the final product is clear. However, this model does not lend itself to science-based pharmaceutical R&D projects because the lead compound screening and optimization stage is not at all an incremental process; rather, this stage is full of chaos, surprises, sudden changes of research directions, improvisation, and chance.

Shepherd and Levesque [19] develop an optimal stopping model by considering a tradeoff between reducing decision accuracy vs. increasing search costs, and a higher probability that a competitor will take advantage of the same opportunity. They propose a heuristic algorithm that specifies three threshold lines, and managers can choose to stop or continue the search for information at each period.

Knowledge is assumed to increase over time, yet at a stochastically decreasing rate; the decision horizon may be randomly truncated at any time because a competitor moves first, and uncertainty regarding the expected profit of the business opportunity lessens through sequential information gathering. Most interestingly, the authors propose their model's potential use in biotechnology R&D projects. They demonstrate its usefulness for biotechnology companies in deciding whether to continue gathering information about a drug's attributes before seeking FDA approval, stop searching and abandon the project, or stop searching and submit the drug to the FDA. While Shepherd and Levesque's model proposes a possible optimal situation in biotechnology companies, they do not substantially consider the fuzziness involved in pharmaceutical R&D project. The model in our study is fundamentally different from theirs in several ways. First, we do not assume in our model that knowledge increases in the lead compound screening and optimization stage because researchers can only ever know a fraction of what there is potentially to know about the compound, the human body, and the interactions between the two. In fact, each round of compound screening and optimization is distinct, and previous rounds provide little 'experience effect' for later research. Thus, breakthroughs generated incrementally from previous experience are minimal, and knowledge in a specific project is generally not accumulative. Second, even if all pharmaceutical companies work on the same disease targets and compete with each other, a competitor's grasp of an opportunity does not necessarily result in loss for another company's drug development. In the pharmaceutical industry, a competitor's substantial advancement in a new drug's development always makes it easier for the other company to quickly generate similar drugs, as long as it handles the patent issues properly. In other words, instead of eliminating an opportunity, a competitor's achievement may create new opportunities for the company. Thus, in our model we do not consider competition among companies troublesome.

### 3. Pharmaceuticals as a science-based industry and the compound discovery stage

The pharmaceutical industry has been troubled by huge development expenditures, lengthy research timetables, and the tedious process of drug exploration. Discovering and developing a new medicine takes at least twelve years, and the average cost is now more than \$1 billion – higher than NASA's budget for sending a rocket to the moon [12]. Although the industry's collective investment in R&D from 1980 to 2006 mushroomed from \$2 billion to \$43 billion, the number of drugs approved by FDA in 1980 and in 2006 was roughly the same [12]. Besides the impact of lower R&D productivity on firms' costs and profitability, longer development times have also raised important public policy concerns [13]. As the industry remains the dominant provider of life-saving and life-prolonging

medicines, it is in the public's interest, as much as the companies' own, to make promising new drugs available to patients as quickly as possible [20]. Thus, enhancing the drug discovery process and optimizing decisions based on information gathered from drug researchers' work is essential if pharmaceuticals are to provide high quality drugs within reasonable time period.

Drug discovery is, in essence, a work of science, and case studies indicate that science unfolds in complex ways in pharmaceuticals [21]. The process of searching (including compound screening and compound optimization) for new active molecular entities that have never been marketed before is full of profound and persistent uncertainty rooted in human beings' generally limited knowledge of human biological systems and processes [10]. Thus, the search process is essentially an exploratory innovation with an extremely rugged landscape [22], which is reflected in the drug discovery process' high degree of unpredictability, despite extraordinary progress in genetics, molecular biology, and combinatorial chemistry. Whether a compound can be turned into a drug candidate can only be determined through a tedious course of trial-and-error and rounds of intuitive collective learning, and scientists still have great difficulty predicting how a particular new molecule will work in human bodies [10], making drug R&D very risky. This is fundamentally different from R&D in most engineering-based industries such as automotive design, semiconductors, computers, and aircraft in which products can only reach a level of complexity comparable to pharmaceuticals on some measures [23]. Furthermore, because so little is known about how the human body works, the causes of drug failure are just as uncertain: The molecule or target may be wrong, the dosage may be incorrect, the intended target may not have been hit, other targets may have been hit, and so on [24]. As a result, it is impossible for drug researchers to develop a so-called 'perfect' drug whose function in human body can be understood with 100% certainty. In fact, side effects often go undetected until after a drug has been on the market and millions of patients have used it [12].

The way in which complex scientific work unfolds in the lead compound screening and optimization stage indicates that knowledge about compounds is created but not necessarily accumulated. A brief description of the drug discovery process illustrates this idea. A typical drug discovery procedure begins with the identification of potential targets critical to the disease mechanisms; a target is often compared to a lock [11]. Once a target for attacking a disease has been identified and validated, the next step is to discover and develop the best molecule to attack it. The objective is to optimize the molecule, and time is of the essence [12]. The discovery of such a molecule is always compared in the field to finding a key for the lock (i.e., the target) and only that lock since a key that can also fit into other locks would generate unwanted side effects [11]. This process can be divided into two interdependent tasks: high throughput screenings and lead compound optimization. The screen-

ings involve searching through archival libraries of hundreds of thousands of chemical compounds with the purpose of identifying lead compounds - chemicals that roughly fit the target [13]. Lead compounds are like blanks with the potential to become appropriate keys for a lock [11].

When a lead compound is identified via high throughput screening, it will generally not meet all the criteria required to develop it into a drug candidate. For instance, it may display unacceptable side effects or be unable to be absorbed in the blood and delivered to the right target. Therefore, the lead compound optimization is set to test numerous variations of the original lead compound to find one or more that appears to have all the attributes needed for a successful new drug [13]. This task is like cutting a blank into a key [11]. Drug researchers maintain the basic molecular structure of the selected lead compound and add, exchange, or remove chemical groups around the basic structure. However, this is not as easy as cutting a three-dimension key blank; rather, drug researchers must attempt to simultaneously manage double-digit dimensions and synthesize them. For example, besides gauging therapeutic effectiveness and toxicity, they must also look for variants that are better absorbed, metabolized, distributed, and excreted [11].

This process is not linear; on the contrary, finding a promising compound involves many iterations of tinkering and testing [11] between screening and optimization. The reason for these iterations is due to the extraordinary complexity and unpredictability of the human body and scientists' incomplete knowledge of this complexity. For instance, scientists have found that the shape of a target receptor in human body can change dramatically when a drug is inserted into the receptor's 'binding pocket' [13]. Researchers may discover that the lead compound identified in one round of high throughput screening is totally useless because it causes unwanted changes in the target receptor; thus, they have to carry out another round of screening, shortly making the knowledge gained in the previous round obsolete. Of course, the lead compound identified in the former round of screening may be used for other targets, as in the case of Viagra, which scientists accidentally discovered while seeking a heart ailment drug. Even in this case, however, scientists' knowledge of the human body only transferred; it did not accumulate. Accordingly, science work in this stage unfolds itself in such a way that knowledge is created but not necessarily accumulated in terms of a specific R&D project.

In practice, knowledge creation without accumulation is reflected in the fact that the average American pharmaceutical company synthesizes approximately 6100 chemical compounds for each successful drug that makes it to market [25], and the compounds screened against a protein are always counted by the million [22]. Sometimes drug researchers do not even know what to optimize, and they try to make analogues to the lead compound and pick the best without really understanding the underlying mech-



anisms [26]. As a result, decisions about a specific drug discovery process must occur in the fog of limited knowledge and experience. Mistakes are common, not because of incompetence but because people involved are constantly dancing on the edge of knowledge [10].

The characteristics of science work in the screening and optimization stage raises special concerns. For instance, the quality of the drug candidates discovered in this stage is essential to the success of subsequent clinical trials. However, statistics have shown that the share of experimental drugs that fail in clinical trials has actually risen, hitting a record 93% in 2006 [12], which reflects questionable quality in the compound screening and optimization stage. The optimal stopping model in this study focuses particularly on this stage. The next section introduces our methodology, formulates the problem, and illustrates the optimal stopping model.

#### 4. Methodology

In this study, we formulate our optimal stopping model by focusing special attention on the compound high throughput screening and optimization stage of drug research. The methodology involves the following steps:

- Modeling the science work.
- Validating the quality effective factor.
- Formulating the model.
- Discussing the properties of acceptable minimum quality effective factor  $\rho^*$ .

##### 4.1. Science work

In this stage, science work is embedded in R&D managers' and scientists' goal to create the best quality molecular compound possible within a limited time period through several rounds of iteration between screening and optimization. In each round, hundreds of thousands of compounds drawn from chemical archives are first screened; then, from the most promising candidates, one is selected for molecular structure optimization. Several rounds of screening and optimization follow, and each round creates one lead compound. However, due to the complexity and fuzzy nature of the search process, we assume the essence of science work as follows:

- Each round is generally not related to other rounds.
- It is difficult for drug researchers to estimate the quality of a lead compound in the next round.
- The 'arrival time' of the lead compound generated in each round is random and independent. In the worst case, drug researchers may fail to meet the project's deadline without having discovered or created anything from millions of compounds.

These three points reflect the unpredictability and knowledge constraints inherent in drug researchers' work

in a science-based pharmaceutical industry. First, compound screening and optimization is a highly random task; researchers have to try different independent approaches and explore numerous irrelevant paths. Second, the knowledge created but not necessarily accumulated in drug research indicates that the compounds generated in each research round are highly unique. Therefore, it is unlikely that a compound's quality would increase incrementally, and estimation of quality based on former experiences is nearly impossible. Third, science work needs not only wide scope of knowledge but also intuitive inspiration, keen improvisation, and good luck. Thus, any new compound's arrival involves a certain degree of serendipity as much as hard work. More rigorous mathematical expressions of these characteristics appear in subsection 4.3.

##### 4.2. The quality effective factor

The quality of the lead compounds is essential for any drug research project. High throughput screening identifies some compounds that have desired effects, but these promising compounds must also pass different quality criteria, such as therapeutic efficacy, toxicity, solubility, absorption, metabolizing capacity, and so on. The objective of lead optimization is to re-structure the compound in such a way that all the attributes needed for a successful new drug should be created. Thus, these prerequisites are combined into a holistic focus on selecting those candidate compounds which simultaneously show both maximum biological activity and minimal pharmacokinetic problems. For example, a compound generated in one round may display the needed therapeutic efficacy very powerfully, but may not become soluble after ingestion or injection no matter how assiduously drug researchers work on it. In such a case, scientists may drop the compound because it cannot completely pass the quality requirement and begin searching for others. In this sense, scientists and R&D managers must set an overall quality threshold which represents a composite of all the required criteria; this threshold acts as a minimum standard for compound quality.

Although the minimum quality threshold is rather objective and mandatory, the ambiguity and complexity of knowledge leaves the maximum quality level of a new compound subject to interpretation [24]. Drug researchers use their latest scientific knowledge to understand and negotiate results generated in each round. Better knowledge about the lead compound is always possible but not guaranteed. For instance, scientists may ask themselves questions like, "Did we enhance the quality and reduce the ambiguity by adding more drug product properties into the development equation?" or "Is the new compound an up-scaled optimal synthesis for this round?" In this way, drug researchers use high throughput screening and optimization not only to answer whether the minimum standard is met but to search for clues which combine all the drug criteria to improve the overall compound quality. [22]. By doing so, scientists do not treat different quality

criteria independently; rather, they talk about the all-in-one paradigm, trying to synthesize their tests and assays among different disciplines all at once as early as possible [22,24]. This work style guarantees that an adequate metric could be developed to holistically measure the quality of the lead compound. This approach could allow for the quality requirements of different drug research disciplines to be integrated and modeled into a problem of risk by deriving some kind of drug quality indices from a joint probability distribution over the landscape of science work. On the one hand, this would enable scientists to make the best estimation about the efficacy of their lead and potential risks (side effects) by synthesizing different drug criteria; on the other hand, the minimum quality threshold would serve as a gatekeeper to prevent all poor quality compounds from entering the next stage of drug research.

Since the necessary drug criteria together form an integrated adequate quality metric, we introduce the idea of quality effective threshold and quality effective factor in our model. The quality effective threshold refers to the stipulated minimum quality standard a compound must meet in terms of therapeutic efficacy, toxicity, solubility, absorption, metabolizing capacity, and other criteria. The quality effective factor refers to the actual overall quality a lead compound has. Specifically, we stipulate that if the quality effective factor of a compound cannot pass the quality effective threshold, then the compound in a certain round fails and scientists must start another round of searching. R&D managers and drug researchers decide whether the lead compound screening and optimization stage should stop according to the best quality lead compound to date and the remaining time, then send the compound to clinical trials. The compounds generated in other rounds could either be used as backups or not.

#### 4.3. Model formulation

Suppose that each individual round of lead compound arrives according to a Poisson process with rate  $\lambda_1$ . Also assume each round  $i$  can generate one lead compound with a quality effective factor  $Y_i (0 < Y_i < 1)$ . Denote  $X_i = 1/Y_i - 1$ . Assume  $X_i$  is iid, which follows exponential distribution with mean  $1/\lambda_2$ . Then we have  $\text{Mean}(Y_i) = \frac{1}{1/\lambda_2 + 1}$  and  $\lambda_2 = \frac{1}{1/\text{Mean}(Y_i) - 1}$ .

Denote  $T_e$  as the maximum research time (i.e., the total time limit the R&D project allows for compound screening and optimization – say, five years or so). When the entire research project runs out of  $T_e$  unit time, this stage should end regardless of whether or not the current round is completed.

Let  $\rho$  be the quality effective threshold.  $\rho$  could be a figure (e.g., 0.9), and it could be regarded as the lowest benchmark of drug criteria, such as efficiency, toxicity, and so on. A higher quality level could be regarded as having less actual or potential side effects, better absorption and better metabolism, etc., which may require subtler and more complex science work. If the quality effective factor of one lead

compound is lower than the threshold, then this compound is a failure.

Denote  $N(t)$  as the number of individual lead compound arrivals during the first  $t$  unit time.

Denote  $T_n$  as the elapsed time between the  $(n-1)$ st and the  $n$ th lead compound. Denote  $S_n$  as the arrival time of the  $n$ th lead compound.  $S_n = \sum_{i=1}^n T_i$ .

According to Ross [27], we have the following results:

- $T_n, n = 1, 2, \dots$ , are i.i.d. exponential random variables with mean  $1/\lambda_1$ .
- $T_n$  and  $S_{n-1}, n = 1, 2, \dots$  are independent.
- The probability density function of  $S_n$  is given by  $f_{S_n}(t) = \lambda_1 e^{-\lambda_1 t} \frac{(\lambda_1 t)^{n-1}}{(n-1)!}$ .

Denote  $Z_n = \min\{X_i, i = 1, 2, \dots, n\}$ , and  $Y_n^{\max} = \max\{Y_i, i = 1, 2, \dots, n\}$ , ( $n = 1, 2, \dots$ ). Then  $Z_n = Y_n^{\max}$ .

Assuming the whole screening and optimization stage stops at time  $t$ , ( $t \leq T_e$ ), the drug researchers will pick up the lead compound which has the highest quality effective factor – that is, the lead compound having the minimum  $X_i$ . Both lead compound quality and time in this stage determine drug researchers' objective function: the better the lead compound's quality and the shorter the arrival time, the more favorable the objective function. We assume the objective function as follows:

$$p(t) = \begin{cases} a(T_e - t) + f(Y_{N(t)}^{\max} - \rho), & Y_{N(t)}^{\max} \geq \rho, \quad t \leq T_e \\ 0, & \text{otherwise} \end{cases} \quad (1)$$

where  $a$  is a known constant and  $f(x)$ , ( $0 \leq x \leq 1 - \rho$ ), is a function of  $x$ , with  $f(0) = 0$ ,  $f'(x) > 0$ , and  $f''(x) \geq 0$ . The first derivative indicates that the better a lead compound's quality (i.e., the larger the gap between a lead compound's quality effective factor and quality effective threshold), the higher the objective function. The second derivative indicates that the objective function increases at an accelerating rate as the lead compound quality improves because it is more likely that such a compound will become a blockbuster.

Then we have  $p(t) \geq 0$  for all  $t$ .

The problem becomes one of finding the optimal stopping time  $t^*$  with the best quality effective factor.

For the sake of simplification, we denote time  $\delta_i$ ,

$$\delta_i = \begin{cases} S_i, & i = 1, 2, \dots, N(T_e). \\ T_e, & i \geq N(T_e) + 1. \end{cases} \quad (2)$$

And define a function  $l(y)$ ,

$$l(y) = \int_y^1 (f(x - \rho) - f(y - \rho)) \lambda_2 e^{-\lambda_2(x-y)} dx \quad (\rho \leq y \leq 1). \quad (3)$$

We can prove that the equation

$$l(y) - \frac{a}{\lambda_1} = 0, \quad (\rho \leq y \leq 1)$$

has a unique solution  $x^*$ , c.f. Zhao and Chen [28].

Then we denote

$$\rho^* = \begin{cases} x^*, & \text{if } l(\rho) > \frac{a}{\lambda_1}. \\ \rho, & \text{if } l(\rho) \leq \frac{a}{\lambda_1}. \end{cases} \quad (4)$$

as the acceptable minimum quality effective factor (AMQ). and denote a set

$$\Lambda = \{i | Y_i \geq \rho^*\} \cup \{j | j > N_{T_e}\}. \quad (5)$$

We can derive the optimal stopping time  $t^* = \min\{\delta_i : i \in \Lambda\}$ , (c.f. [27,28]) with

- $p(t) \leq E(p(t + \Delta t) | p(t))$ , for all  $t < t + \Delta t \leq t^*$ ;
- $p(t) \geq E(p(t + \Delta t) | p(t))$ , for all  $t + \Delta t > t \geq t^*$ .

In words, for all  $t < t + \Delta t \leq t^*$ , the objective function at current time  $t$  is always smaller than or equal to the expected value of the objective function at a later time  $(t + \Delta t)$ . Thus, it would be favorable to continue the lead compound screening and optimization. For all  $t + \Delta t > t \geq t^*$ , the objective function at current time  $t$  is always larger than or equal to the expected value of the objective function at a later time  $(t + \Delta t)$ . That is, we could not expect to get a better quality lead compound after the optimal stopping time  $t^*$ . Thus, the compound screening and optimization stage should stop at time  $t^*$ . According to the definition of  $t^*$  and  $\Lambda$ , we also know that  $t^*$  is the first time that drug researchers get a quality effective factor  $Y_i$  which is no less than  $\rho^*$ . Furthermore, the definition of  $\rho^*$  tells us that it is a value no less than  $\rho$ . When  $l(\rho) \leq \frac{a}{\lambda_1}$ , AMQ  $\rho^*$  is equal to  $\rho$ . In other words, under that condition, the optimal stopping time occurs when a round generates a compound which satisfies the threshold  $\rho$ . In contrast, when  $l(\rho) > \frac{a}{\lambda_1}$ , a higher AMQ  $\rho^*$  is required by the optimal stopping policy. In the following sections, we will show how  $\rho^*$  changes according to the modifications of the relative parameters and analyze the practical meanings of this for pharmaceutical industry.

#### 4.4. Properties of acceptable minimum quality effective factor $\rho^*$

According to the definition of  $\rho^*$  and the function  $l(y)$ , we derive the following properties of  $\rho^*$ .

**Property 1.** The value of  $\rho^*$  does not depend on  $T_e$ , if the function  $f(x)$  and other parameters  $a$ ,  $\lambda_1$ ,  $\lambda_2$ , and  $\rho$  are fixed.

**Property 2.**  $(\rho^* - \rho)$  tends to decrease as  $\rho$  increases if the function  $f(x)$  and other parameters  $a$ ,  $\lambda_1$  and  $\lambda_2$  are fixed.

**Property 3.** The value of  $\rho^*$  tends to increase as  $\lambda_2$  increases, which in turn indicates that  $\text{Mean}(Y_i)$  increases, if the function  $f(x)$  and other parameters  $a$ ,  $\lambda_1$  and  $\rho$  are fixed.

**Property 4.** The value of  $\rho^*$  tends to increase as  $\lambda_1$  increases if the function  $f(x)$  and other parameters  $a$ ,  $\lambda_2$  and  $\rho$  are fixed.

In terms of an optimal stopping policy, Properties 2–4 reveal several important points. Property 2 tells us that if the quality effective threshold  $\rho$  is low, the gap between AMQ  $\rho^*$  and  $\rho$  is wide. This indicates that R&D managers and drug researchers should not be satisfied with a compound whose quality effective factor only hits  $\rho$ . They should pursue a much higher quality compound. As the value of  $\rho$  increases, the gap between AMQ  $\rho^*$  and  $\rho$  becomes smaller. In other words, managers should gradually accept a  $\rho^*$  which is closer to the threshold  $\rho$ . This means that, optimally, managers should not further expect the quality of the lead compound to be significantly higher than  $\rho$ . When  $\rho$  turns to be a high enough value,  $\rho^*$  becomes equal to  $\rho$ , which indicates that managers' best decision at that point is to accept  $\rho$  as their satisfying quality.  $\rho^*$  will be always equal to  $\rho$  as  $\rho$  further increases, since  $\rho^*$  must be greater than or equal to  $\rho$ . In the pharmaceutical industry, the quality effective thresholds for different diseases change according to factors such as the characteristics of the disease target and scientists' knowledge about the disease and the compounds. For instance, drugs aimed at curing cancers generally cause severe side effects, which in turn may cause the quality effective threshold for new anti-cancer lead compounds to be rather low. But managers and scientists may be unsatisfied with new compounds that show similar side effects. They may want to find any lead compound showing fewer side effects in curing cancer and regard it as a breakthrough. In contrast, compounds that attack other diseases' targets such as diabetes may have a different quality effective threshold altogether.

Property 3 indicates that the  $\rho^*$  tends to increase, as  $\text{Mean}(Y_i)$  increases since  $\text{Mean}(Y_i) = \frac{1}{1/\lambda_2 + 1}$ . Common sense informs this property. If in the course of a project R&D managers and drug researchers realize that the average quality of the lead compound is relatively low, then it is irrational for them to expect a higher quality lead compound in the next round. Such a low  $\text{Mean}(Y_i)$  may be due to the fact that the current level of science and technology is still not high enough to enable drug researchers to produce a better compound. In this case, it is reasonable for managers to take  $\rho$  as an acceptable quality level since it at least meets all basic toxicity and efficacy requirements. When  $\lambda_2$  increases, the average quality  $\text{Mean}(Y_i)$  increases accordingly. Thus, managers have the right to expect a better result than  $\rho$ , which implies that AMQ  $\rho^*$  increases. A higher  $\rho^*$  indicates it is optimal for managers and drug researchers to obtain higher quality compounds - to continue until they get a compound with  $Y_i$  not less than  $\rho^*$ . In other words, they should take longer to get a better result.

Property 4 tells us that  $\rho^*$  tends to decrease, as  $\frac{1}{\lambda_1}$  increases.  $\frac{1}{\lambda_1}$  is the expected elapse time for any two adjoining lead compounds. If the expected elapse time between these two leads is small, then it indicates that the waiting time for the next lead compound is short; further, the potential loss of objective function in terms of waiting time for the next compound is also small. Thus,  $\rho^*$  will be



higher, and managers and drug researchers should expect a higher quality lead compound to appear. However, if the expected elapse time is longer, then the waiting time for the next lead compound increases. In this case, the objective function becomes very sensitive to the limited remaining time of this drug research stage. The increase of  $\frac{1}{\lambda_1}$  makes it increasingly meaningless for managers to wait a longer time for a very unpredictable new result; thus, AMQ  $\rho^*$  tends to decrease. The optimal stopping policy suggests that the longer one round takes, the more likely managers will accept a lower AMQ  $\rho^*$ . By accepting a lower  $\rho^*$  under the longer elapse time, managers could save a lot of time. If the elapse time is particularly long, then AMQ  $\rho^*$  is equal to  $\rho$ , which means that managers will directly regard the quality effective threshold as acceptable, and should not pursue a higher quality.

The above four properties give basic guidelines for R&D managers and drug researchers to carry out their scientific activities and make better decisions at the lead compound screening and optimization stage.

## 5. Numerical analysis

In this section, we provide two numerical illustrations of the present model and discuss how R&D managers and scientists could use this model to make optimal decisions.

### 5.1. Relation between the parameters and $\rho^*$

This subsection explains how R&D managers should make their optimal stopping decisions according to the different levels of each parameter. Here, we assume the  $f(x)$  in the objective function  $p(t)$  is linear.

**Example 1.** Assume that  $f(x) = bx$ ,  $a = 1$ , and the total time limit  $T_e = 5$  years. We observe the change of  $\rho^*$  by changing parameters  $\rho$ ,  $\lambda_1$ ,  $\lambda_2$  and  $b$ .

Fig. 1 illustrates Property 2. Assuming  $\lambda_1 = 2$  and  $\lambda_2 = 4$ ,  $(\rho^* - \rho)$  changes when the quality effective threshold  $\rho$  changes from 0.80 to 0.96 and  $b$  changes from 5 to 29. The practical indication of the assumption ( $\lambda_1 = 2$ ) is that in the pharmaceutical industry R&D managers and scientists routinely regard one round of compound screening and optimization as lasting six months or so (i.e., the average inter-arrival time of two adjoining results is generally 0.5 of a year). We also assume that the mean of each result's quality effective factor is  $\text{Mean}(Y_i) = \frac{1}{1+1/\lambda_2} = 0.8$ . The parameter  $b$  here could be considered a factor that determines the scientific or market potential of a lead compound in R&D managers' and scientists' eyes. Practically speaking, a higher  $b$  indicates that R&D managers have higher expectations for a lead compound to become a blockbuster, whereas a lower  $b$  may reflect that the respective R&D project is not top priority. Thus, given a fixed  $(\rho^* - \rho)$ , the higher the  $b$ , the higher the objective function  $p(t)$ . If  $b$  is high (i.e., managers have high expectations for the project), managers should take a higher AMQ  $\rho^*$

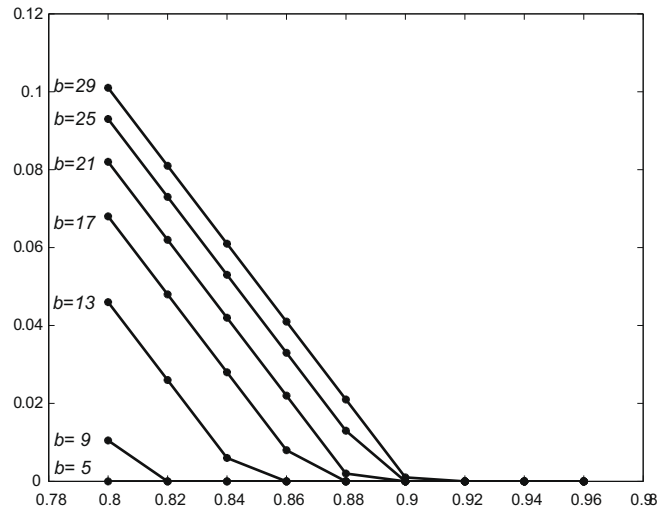


Fig. 1.  $\rho$  vs.  $(\rho^* - \rho)$  with  $\lambda_1 = 2$  and  $\lambda_2 = 4$ .

because it could significantly increase the objective function. Fig. 1 shows this property clearly. For example, as Fig. 1 shows, when  $\rho$  is equal to 0.8, the optimal stopping policy indicates that a higher  $b$  corresponds to higher  $(\rho^* - \rho)$ , i.e., higher  $\rho^*$ .

Under the optimal stopping policy, Fig. 1 also illuminates Property 2 in the sense that if the quality effective threshold  $\rho$  is low, managers should take an AMQ  $\rho^*$  which is relatively much higher than  $\rho$ , regardless of what  $b$  is. If the threshold is already high, the gap between AMQ  $\rho^*$  and  $\rho$  narrows. Taking  $b = 17$  as an example, when  $\rho = 0.8$ , the difference  $(\rho^* - \rho)$  is 0.068. This difference decreases as  $\rho$  increases, indicating that managers should take  $\rho^*$  which is much closer to  $\rho$ . For example,  $(\rho^* - \rho)$  becomes 0.008 when  $\rho$  increases to 0.86. As  $\rho$  increases to 0.88, the difference  $(\rho^* - \rho)$  becomes 0, indicating that managers should take a  $\rho^*$  which is equal to  $\rho$ . The difference is always 0 after  $\rho \geq 0.88$ .

Fig. 2 demonstrates Property 3 through the relationship between  $\bar{Y}$ , i.e.,  $\text{Mean}(Y_i)$ , and  $\rho^*$ .  $\rho^*$  changes as the mean of the quality effective factor of each result  $\text{Mean}(Y_i)$  changes from 0.75 to 0.95, - that is, changes  $\lambda_2$  from 3 to 19. At the same time we observe cases of  $b$  changing from 5 to 29. Also taking  $b = 17$  as the example, when the mean quality  $\bar{Y}$  ranges from 0.75 to 0.87, the AMQ  $\rho^*$  is always equal to 0.9 (i.e., the value of threshold  $\rho$ ), which indicates that, according to optimal stopping policy, managers should not expect a much higher quality level, even though the quality should not be too poor either. As the mean quality  $\bar{Y}$  becomes higher than or equal to 0.89,  $\rho^*$  also increases, indicating that managers should wait for a better result.

Fig. 3 depicts Property 4.  $\rho^*$  changes as the average inter-arrival time of two adjoining results  $\frac{1}{\lambda_1}$  changes from 0.3 to 1.3 years and  $b$  from 5 to 29, fixing  $\lambda_2 = 5.667$  and the quality effective threshold  $\rho = 0.9$ . This time, using  $b = 25$  as the example, we find that the optimal stopping policy suggests that managers pursue a higher quality result



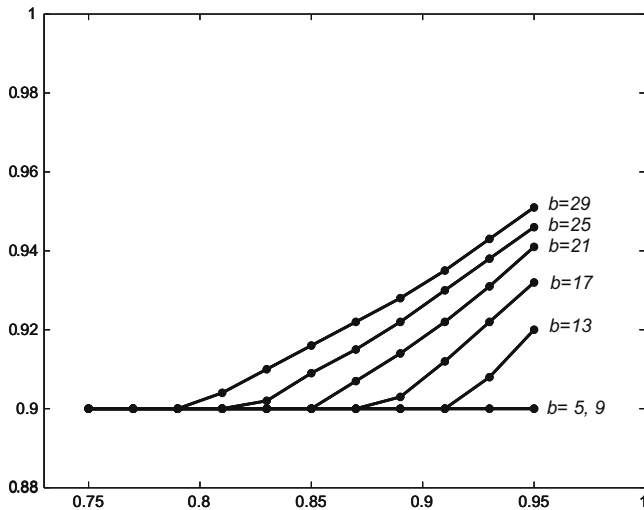


Fig. 2.  $\bar{Y}$  vs.  $\rho^*$  with  $\lambda_1 = 2$  and  $\rho = 0.9$ .

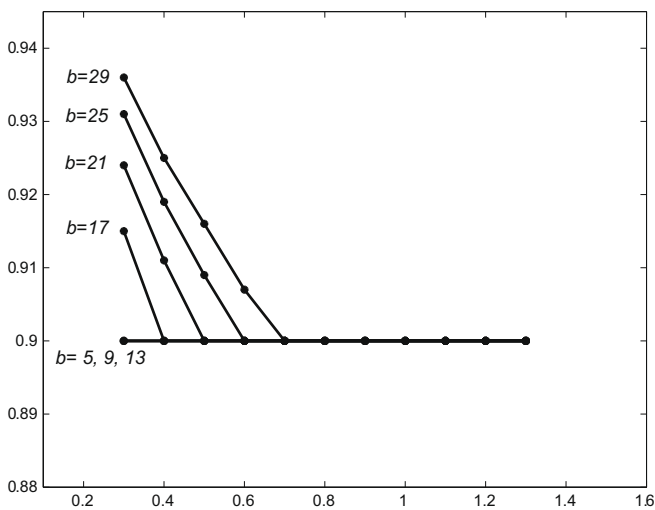


Fig. 3.  $\frac{1}{\lambda_1}$  vs.  $\rho^*$  with  $\lambda_2 = 5.667$  and  $\rho = 0.9$ .

when the elapse time of one research round is short (i.e., ranging from 0.3 to 0.6 of a year). However, as the elapse time of one round increases, AMQ  $\rho^*$  tends to decrease because it becomes increasingly difficult to create a new lead compound. In detail, in this example,  $\rho^* = 0.931$  when the time is 0.3 of a year;  $\rho^*$  decreases to 0.919 and 0.909, respectively when the time increases to 0.4 and 0.5 of a year. When the elapse time of one round is equal to or longer than 0.6 of a year,  $\rho^*$  decreases to  $\rho = 0.9$ , indicating that managers should accept the threshold as the quality level. Here, the longer elapse time suggests a situation in which the science work becomes more fuzzy, requiring the scientists to invest more time, mental efforts, and intuitive energy into their compounds.

### 5.2. Relation between the objective function and the stopping point

In this subsection, we extend our numerical example beyond linear function  $f(x)$  to other forms and consider

whether other forms are also applicable. Assuming its usability with other forms of function, our model could be applied in various pharmaceutical R&D situations.

**Example 2.** Assume  $a = 1$ ,  $T_e = 5$ . We use three different functions, i.e., linear, quadratic, and exponential, to show how the  $\rho^*$  changes by changing  $\rho$ ,  $\lambda_1$ ,  $\lambda_2$ .

- Type 1:  $f(x) = 40x$ .
- Type 2:  $f(x) = 400x^2$ .
- Type 3:  $f(x) = e^{16x} - 1$ .

The above three functions have the same value when  $x = 0$  and  $x = 0.1$ .

Figs. 4–6 together show that Properties 2–4 also hold for these three forms of function. Thus, we can confidently say that our model is widely applicable.

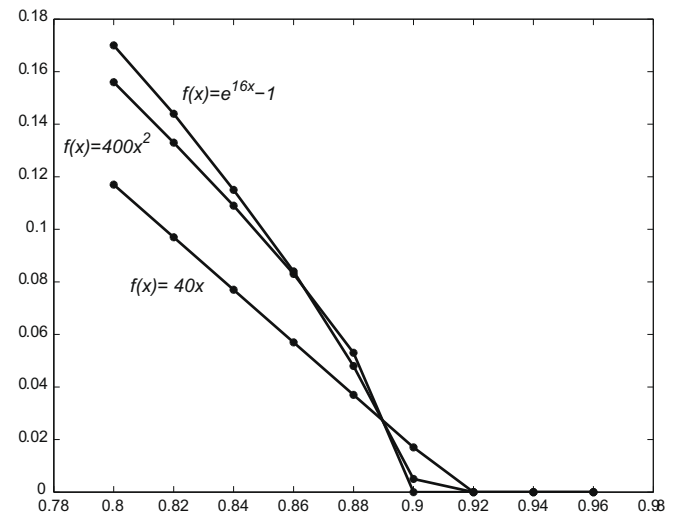


Fig. 4.  $\rho$  vs.  $(\rho^* - \rho)$  with  $\lambda_1 = 2$  and  $\lambda_2 = 4$ .

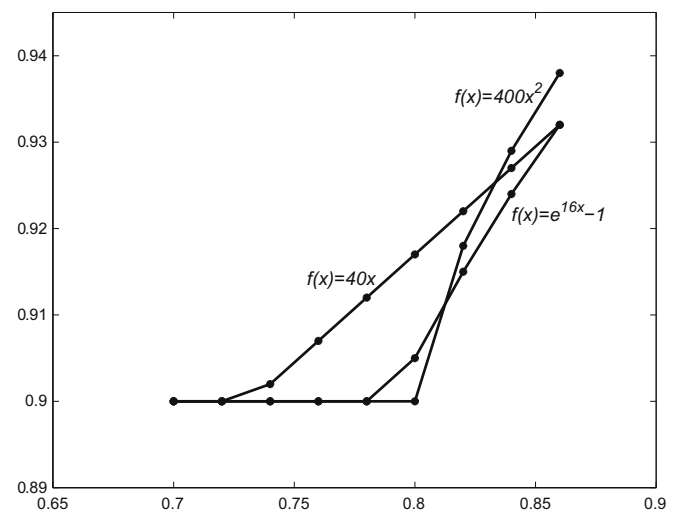


Fig. 5.  $\bar{Y}$  vs.  $\rho^*$  with  $\lambda_1 = 2$  and  $\rho = 0.9$ .

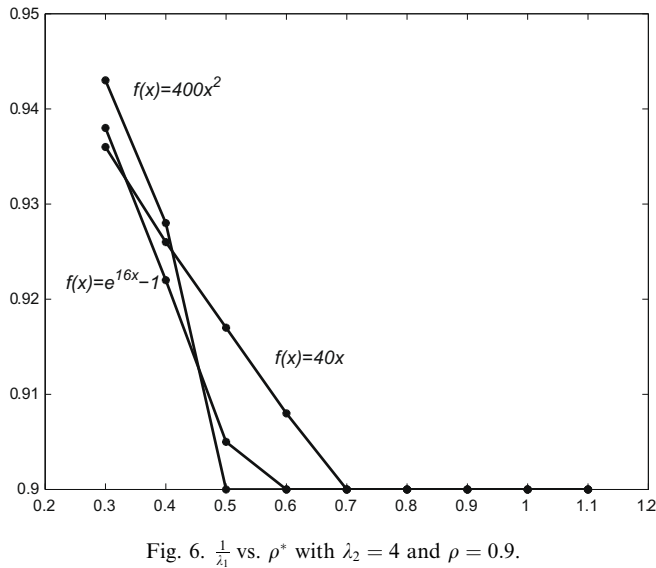


Fig. 6.  $\frac{1}{\lambda_1}$  vs.  $\rho^*$  with  $\lambda_2 = 4$  and  $\rho = 0.9$ .

### 5.3. Possible application in R&D portfolio selection

In pharmaceuticals, R&D portfolio management constitutes an extremely important tool for increasing overall R&D project value [29]. In addition to guiding R&D managers to create the best quality lead compounds in an individual project, our model also has the potential to help them compile the optimal pharmaceutical R&D portfolio through the selection of the most scientifically significant projects. Eckhause and colleagues [30] illustrate the concept of Technology Readiness Levels (TRLs) for each project vendor in their measurement of technical risks in a real options approach to R&D acquisition portfolio management; similarly, but also distinctly, our model shows the most significant scientific achievements possible (i.e., the AMQ) for individual drug research projects. A promising R&D project should have high lead compound quality and short research time. The distribution functions of quality effective factor  $Y$  differ by specific projects, and the quality effective threshold  $\rho$  depends on each individual project. Further,  $a(T_e - t)$  partially considers the potential gains from a particular project's shorter arrival time. Thus, R&D portfolio managers can select candidate projects in various ways. First, managers can examine the AMQ  $\rho_j^*$  of the  $j$ th candidate project for a portfolio. Given other conditions fixed, managers could select those projects with the highest AMQ because they will guarantee the highest portfolio quality. Second, managers can consider different projects for a portfolio by balancing the quality effective thresholds among them. For example, some projects may have low thresholds because of scientific difficulties. Managers can weigh the overall number of these projects against those with high thresholds in such a way that the portfolio will not only generate numerous drugs but also good drugs. Third, some candidate projects in a portfolio may be more marketable but also need more time for research, whereas other candidate projects are easy to develop but not very marketable. the parameter  $a$  in the

objective function could be regarded as marketability, and  $t^*$  could be regarded as research viability. Managers can optimize their portfolios' utilities by comparing projects' marketability (i.e.,  $a$ ) and research viability (i.e.,  $t^*$ ). In all, by balancing the compound quality, the arrival time, and the business factors of different projects, R&D managers can select the most appropriate portfolio candidates under limited resources and budgets.

## 6. Conclusion

This paper develops a model of optimal stopping time to describe the R&D stage of lead compound screening and optimization in pharmaceuticals. The paper illustrates pharmaceuticals as a science-based industry and describes how drug researchers can optimize their science-based work process by choosing the best stopping time for their research. More specifically, the paper aims at facilitating drug researchers' work process in such a way that they provide the best quality compounds to clinical tests. The examples illustrated here show that this model holds in different situations and applies when using different forms of functions. We built our model and designed our research questions based on comprehensive investigation of drug discovery processes in internationally recognized leading pharmaceutical companies. However, the model's applicability is not restricted to pharmaceuticals. Since this model targets specific characteristics of science work, it can also be used in other science-based industries with similar traits, such as open-source software engineering. Thus, the model's advantages include employability in real-life R&D research projects, enabling scientists and researchers to integrate their discovery process and save costs. Further research may uncover other applications and introduce economic resource allocation into the model.

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