Journal of Uncertain Systems
Vol.11, No.3, pp.205-220, 2017
Online at: www.jus.org.uk

A Robust Pharmaceutical R&D Project Portfolio Optimization Problem under Cost and Resource Uncertainty

Bo Sun[1], Ying Liu[1,*], Guoqing Yang[2]

[1] *College of Mathematics and Information Science, Hebei University, Baoding 071002, Hebei, China*

[2] *College of Management, Hebei University, Baoding 071002, Hebei, China*

Received 10 February 2017; Revised 15 May 2017

Abstract

The pharmaceutical R&D project portfolio management often needs contract research organizations (CROs) to develop a reasonable portfolio of new drug R&D project from a large set of candidates. The objective of this research is to construct a mathematical programming model to help CRO formulate its portfolio of R&D projects in uncertain situation. More specifically, the pharmaceutical R&D projects portfolio problem is managed with a zero-one integer programming model with uncertain cost and resource. Robust optimization is used in dealing with the uncertainty, and a polyhedral uncertainty set is employed to characterize cost and resource parameters. Furthermore, the robust model is transformed into a standard mixed zero-one linear programming one via duality theory and finally solved by Lingo software. A numerical experiment is conducted to demonstrate the proposed approach, and the computational results under specific values of budget levels are analyzed.

Keywords: R&D project portfolio, cost and resource uncertainty, robust optimization

1 Introduction

New drug R&D which is scrutinized at every stage of development by the Food and Drug Administration (FDA) is a lengthy process. Pennings and Sereno [27] indicated new drugs from the discovery to obtain FDA approval to market, need about 15 years time and cost more than 800 million US dollars. Drug discovery, declare clinical, clinical trials, declared production and marketing are five phases that new drug R&D must go through. Among these phases, clinical trials are the most time-consuming and investment-intensive ones and take about 6 years to complete and represent more than 50% of total pharmaceutical R&D spending [26]. A prolonged clinical testing may significantly reduce the commercial value of a drug or may even render the whole R&D project infeasible [2]. For this reason, most pharmaceutical companies will choose to outsource the clinical trials phase to CRO in order to better focus on their core business. The CRO of today is a key driver of drug development success [23].

It is well known that the choice of R&D projects is the most satisfying solution under a variety of constraints, and R&D portfolio decision is a challenging and complex decision-making task. The new drug R&D has distinctive characteristics and additional complexity compared with the product R&D in many other industrial sectors. As the new drug in the R&D process vulnerable to many uncertainties, which will likely lead to the failure of the entire R&D process. Therefore, when facing a number of new drug R&D projects options, CROs must take into account the uncertainty to make appropriate and reasonable portfolio plan to maximize the profits.

This paper focuses on the problem of selecting a portfolio of new drug R&D projects for CRO with uncertainty in cost and resource. It should be noted that obtaining the available historical data and exactly distribution information for uncertain cost and resource parameter is often difficult in actual new drug R&D project decision-making process. So it is advisable to seek a stable solution that performs well over the full range of possible parameter values. Based on this viewpoint, in this paper, we use robust optimization to

*Corresponding author.
Email: yingliu@hbu.edu.cn (Y. Liu).

study the pharmaceutical R&D project portfolio selection problem with the cost and resource volatility of each stage, and select a subset of possible candidates to maximize the total profit. Specifically, we develop a robust optimization model to hedge against the R&D uncertainty. We solve the robust 0-1 integer programming model from a conservative perspective which aims to obtain a robust solution with stable performance to resist the interference of uncertainty. According to the level of uncertainty, a sensitivity analysis are performed to assess the appropriateness of the selected new drug R&D projects portfolio. In contrast to the conventional sensitivity analysis which is ex-post and merely measures the sensitivity of the single suggested solution to small variations in parameters, the proposed parametric analysis provides a method to mitigate the sensitivity and improve the decision.

The organization of this paper is as follows. In next section, we review the related literature, briefly. In the section 3 we introduce the robust optimization concepts and techniques. In section 4, we propose a nominal R&D portfolio model. Considering the uncertainty of cost and resource parameters, robust optimization is applied in the nominal model with given uncertainty set. An example to illustrate the proposed approach is presented in Section 5 and Section 6 concludes the paper.

2 Literature Review

Benefits measurement methods, strategic management tools and mathematical programming approaches are three main research methods in R&D portfolio management literatures [1, 18, 19]. Benefits measurement methods determine the preferability figure of each project. A number of approaches, such as the merit-cost value index [18] and the analytical hierarchy process [6], have been utilized in the literature to estimate the benefit of a R&D project. The projects with the highest score may be selected sequentially. The major drawback of most benefits measurement approaches is that neither uncertainty nor resource interactions among projects can be captured. The strategic management tools, such as portfolio map [21], bubble diagram and strategic bucket method are used to emphasize the connection of innovation projects to strategy or illuminate issues of risk or strategic balances of the portfolio [9]. But this approach tends to focus on long-term strategic significance and ignore the current subtle changes in the parameters may lead to interruption of the entire project.

The mathematical programming method is one of the main approaches in the research of R&D project portfolio, which optimize some objective function(s) subject to constraints ralated to resources, project logics, costs and start-up capital. More and more complex mathematical models have been established and applied in the selection of R&D projects. R&D project portfolio selection problem in the establishment of the mathematical model can be divided into linear, nonlinear, multiobjective and so on [18]. Ghasemzadeh [15] developed a multiobjective binary integer linear model with resource limitations and interdependences among projects and comment on the issue of sensitivity of the resulting portfolio. Beaujon et al. [3] developed a mixed integer programming model to find an optimal project portfolio and studied the concept of partial funding project and the sensitivity of an estimated project value to the portfolio.

Mathematical models in most of the above-mentioned documents are generally based on deterministic data for research and analysis. However, it is well known that a key feature of R&D project portfolio issues is the high degree of uncertainty in decision-making processes such as project cost expenditures, laboratory space, human resources, etc. To cope with these uncertainties, probabilistic and fuzzy approaches have been proposed to capture the imprecision of model parameters by considering reasonable distributions. Gemici-Ozkan et al. [13] introduced a three-phase decision-support structure for the project portfolio selection process at a major U.S. semiconductor company, where the scenario structure is incorporated into a multistage stochastic programming model. Chen and Wang [8] studied a two-period portfolio selection problem. The problem was formulated as a two-stage fuzzy portfolio selection model with transaction costs, in which the future returns of risky security are characterized by possibility distributions. Kuan and Chen [20] studied the new product development projects problem and established a structure model of project risk evaluation system with fuzzy decision making trial and evaluation laboratory, then the analytical network process was used to weigh the dimension and criteria. Fernande et al. [10] proposed a non-outranked ant colony optimization II method, which incorporated a fuzzy outranking preference model for optimizing project portfolio problem. Machacha and Bhattacharya [24] modeled uncertain critical factors involved in the information system project selection by fuzzy sets and developed a fuzzy logic approach to emulate the human reasoning process and make decisions based on vague or imprecise data. However, CROs often do not get too much accurate information in R&D

project decisions, and few historical data can be used for reference, also, the resources and funds available for decision-making are very flexible [29]. So, the full distributional information about the uncertain cost and resource in R&D project portfolio problem is often unavailable. Specifically, when the imprecise parameter is affected by the noise of historic data or the ambiguity of expert's opinion, these approaches depending on the exact distribution will be invalid.

Robust optimization is a new approach that adderesses the problem of data uncertainty by ensuring the feasibility and optimality of the solution in the worst-case, which incorporates the random character of problem parameters without making any assumptions on their distributions. Robust optimization was first introduced by Soyster [28]. In his approach each uncertain parameter was considered at its worst possible value within a range, resulting in solutions that are overly conservative. El-Ghaoui et al. [14] and Ben-Tal and Nemirovski [4] introduced elliptically uncertain sets to solve the problem of overconservative problems, resulting in the problem of uncertain linear programming becoming conic quadratic robust counterpart. Bertsimas and Sim [5] developed the budget of uncertainty approach to control the cumulative conservativeness of all uncertain problem parameters. Robust optimization methods have been widely used in R&D project portfolio management. For example, Fernandes et al. [11] presented a one-period robust portfolio optimization for adaptive asset allocation, considering a data-driven polyhedral uncertainty set. They considered realistic transaction costs, out-of-sample results, obtained by applying the model for each day of the historical data (2000-2015) and updating with realized returns, indicated that the robust portfolio exhibited an enhanced performance while successfully constraining possible losses. Goh and Hall [16] considered projects with uncertain activity times that came from a partially specified distribution within a family of distributions. Hassanzadeh et al. [17] developed a multiobjective binary integer programming model for R&D project portfolio selection, where each imprecise coefficient belonged to an interval of real numbers without prior distribution details. Liu and Liu [22] discussed the project portfolio selection problem by a distributionally robust fuzzy optimization method and gained some insights into project portfolio regarding project interaction. In the selection of projects, Mild et al. [25] accounted for multiple evaluation criteria, project interdependencies, and uncertainties about project performance as well as financial and other relevant constraints and they reported how robust portfolio modeling has been used repeatedly at the Finnish Transport Agency (FTA) for bridge maintenance programming. They also developed an approximative algorithm for computing non-dominated portfolios in large project selection problems. Fliedner and Liesio [12] developed a methodology to reduce the set of possible realizations by limiting the number of project scores that may simultaneously deviate from their most likely value. By adjusted this limit, decision makers can choose desired levels of conservatism. Chen et al. [7] refined a framework for robust linear optimization by introduced a new uncertainty set that captured the asymmetry of the underlying random variables, and demonstrated the framework through an application of a project management problem.

In this paper, we develop a robust R&D project portfolio model that takes full account of the high degree of uncertainty in cost and resource which belong to polyhedral uncertainty sets. This model can help conservative decision makers make appropriate and reasonable R&D project portfolio in different uncertain R&D environments, and simulate the level of uncertainty by adjusting control thresholds to assess the appropriateness of selected projects.

3 Robust R&D Project Portfolio Model

3.1 The Nominal R&D Project Portfolio Model

In this paper, we focus on the pharmaceutical R&D project portfolio problem. Every R&D project has a specific number of development phases, each of which requires specific financial as well as human, laboratory, and several other resources. Due to the limited availability of these resources, the CRO cannot initiate all promising projects simultaneously. CRO must decide which R&D projects will be include in their optimum mix of project portfolio given their capacity constraints and profitability goals. Each project opportunity, if undertaken, will lead to a return that equals to the contract value of the project. Without loss of generality, we assume that the project once completed will immediately receive the contractual cash. To model clinical trials, we consider each phase consists of several project stages where each stage lasts for a single time period, e.g. one year. To describe our problem better, we adopt the following notations:

Table 1: The notations in R&D project portfolio problem

Notations	Definitions
n	number of projects
t_i	the start time of the project i
k_i	ith project cycle
c_{it}^{k}	the cost of the kth stage of project i in period t
$-c_{it}^{k_i+1}$	contract value of project i if complete at the beginning of period t
γ_l	the annual risk free interest rate
γ_b	the annual risk free borrowing rate
r_{its}^{k}	the number of resource type s consumed by the kth stage of project i in period t
R_t^s	amount of resource type s available in period t
T	the whole planning period
Ψ^m	set of mandatory projects
B	borrowing limit
β_t	initial fund in period t
Decision variables:	
l_t	amount of cash in account at the beginning of period t (earning interest at rate γ_l)
b_t	total liability at the beginning of period t (with interest at rate γ_b)
x_i	if project i is selected, $x_i = 1$ otherwise $x_i = 0$

Without loss of generality, we assume that financial transactions, cost spending and resource consumptions occur at the beginning of periods. The nominal R&D project portfolio problem is as follow:

$$\max \quad (l_{T+1} - b_{T+1}) \tag{1}$$

$$\text{s.t.} \quad \sum_{i=1}^{n} c_{it}^{t-t_i+1} x_i + l_t + b_{t-1}(1+r_b) \leq l_{t-1}(1+r_l) + b_t + \beta_t, \qquad t = 1, ..., T+1 \tag{2}$$

$$\sum_{i=1}^{n} r_{its}^{t-t_i+1} x_i \leq R_t^s, \qquad t = 1, ..., T;\ s = 1, ..., m \tag{3}$$

$$x_i = 1, \qquad i \in \Psi^m \tag{4}$$

$$l_t b_t = 0, \qquad t = 1, ..., T+1 \tag{5}$$

$$b_t \leq B, \qquad t = 1, ..., T \tag{6}$$

$$x_i = (0, 1), \qquad i = 1, ..., n \tag{7}$$

$$b_t, l_t \geq 0, \qquad t = 1, ..., T+1. \tag{8}$$

We formulate the objective function (1) to represent maximum profits (the account balance) at the end of the planning horizon T. At the beginning of period t, the account gains interest $l_t r_l$, pays interest $b_t r_b$, and is rolled into the next period. We use $l_t - b_t$ to represent profits in period t, which include all revenues gained from completed project, investment costs paid to undertake project phases, and interests gained from or paid to the bank. Constraint (2) is funding balance constraints, where cash in period t comes from the principal and interest from lending in period $t-1$, the amount borrowed in period t, and exogenous budget in period t. Cash is spent on lending in period t, the principal and interest related to the amount borrowed in period $t-1$ at rate r_b, and the total cost of all projects in period t. we have chosen $c_{it}^{k_i+1}$ as the negative contract value merely to simplify the writing of this equation. Constrain (3) presents all projects consumption of resources can not exceed the total number of the available resources in period t. Constraint (4) ensures the mandatory collection of some projects must be selected. Constraint (5) implies that profit and loss can not coexist at the start of time period t. Constraint (6) specifies the liability limit in each period. Finally, constraints (7) and (8) identify decision variables of the problem.

3.2 Robust Counterpart of Nominal R&D Project Portfolio Model

In the above section, we present the nominal model of the R&D project portfolio problem. In order to further describe the effects of uncertainty, in what follows, we will employ the robust optimization method as our solution approach to account for this inherent uncertainty in R&D cost estimation and resource consumption in this section.

We define the uncertain cost estimate by assuming that each uncertain parameter c_{it}^k belongs to an interval centered at its nominal value $\overline{c}_{it}^k$ and of half-length $\hat{c}_{it}^k$ but its exact value is unknown, i.e., $c_{it}^k = \overline{c}_{it}^k \pm \hat{c}_{it}^k$. We use $\zeta_{it} = |c_{it}^k - \overline{c}_{it}^k|/\hat{c}_{it}^k$ to represent the absolute deviation of the uncertain value and nominal value, and take values in [0,1]. We introduce the cost control threshold Γ_t, which is an adjustable conservative level parameter. In mathematical terms, let

$$U = \{c_{it}^k | c_{it}^k = \overline{c}_{it}^k \pm \zeta_{it}\hat{c}_{it}^k, 0 \leq \zeta_{it} \leq 1, \sum_{i=1}^{n} \zeta_{it} \leq \Gamma_t\}. \tag{9}$$

Similar to the definition of uncertain cost estimate, we model the uncertainty of resource consumption by assuming that each uncertain parameter r_{its}^k belongs to an interval centered at its nominal value $\overline{r}_{its}^k$ and of half-length $\hat{r}_{its}^k$ but its exact value is unknown, i.e., $r_{its}^k = \overline{r}_{its}^k \pm \hat{r}_{its}^k$. We use $\xi_{it}^s = |r_{its}^k - \overline{r}_{its}^k|/\hat{r}_{its}^k$ to represent the absolute deviation of the uncertain value and the nominal value and take values in [0,1]. In mathematical terms, let

$$V_s = \{r_{its}^k | r_{its}^k = \overline{r}_{its}^k \pm \xi_{it}^s\hat{r}_{its}^k, 0 \leq \xi_{it}^s \leq 1, \sum_{i=1}^{n} \xi_{it}^s \leq \Phi_{ts}\}. \tag{10}$$

Note that Γ_t and Φ_{ts} stand for the budget level of uncertainty for the cost estimation and resource consumption of all project stages occurring in period t. The budget level of uncertainty avoids overconservatism by controlling the robustness of the constraints (2) and (3) against level of conservatism. Therefore, the formulations (1)-(10) have the following robust counterpart:

$$\max \quad (l_{T+1} - b_{T+1}) \tag{11}$$

$$\text{s.t.} \quad \sum_{i=1}^{n} c_{it}^{t-t_i+1} x_i + l_t + b_{t-1}(1+r_b) \leq l_{t-1}(1+r_l) + b_t + \beta_t, \qquad t = 1, ..., T+1;\ \forall c_{it}^k \in U \tag{12}$$

$$\sum_{i=1}^{n} r_{its}^{t-t_i+1} x_i \leq R_t^s, \qquad t = 1, ..., T;\ s = 1, ..., m;\ \forall r_{its}^k \in V_s \tag{13}$$

$$x_i = 1, \qquad i \in \Psi^m \tag{14}$$

$$l_t b_t = 0, \qquad t = 1, ..., T+1 \tag{15}$$

$$b_t \leq B, \qquad t = 1, ..., T \tag{16}$$

$$x_i = (0,1), \qquad i = 1, ..., n \tag{17}$$

$$b_t, l_t \geq 0, \qquad t = 1, ..., T+1. \tag{18}$$

The cost parameter c_{it}^k and resource parameter r_{its}^k are the imprecise coefficients in the above model with $c_{it}^k \in U$ and $r_{its}^k \in V_s$, so the robust counterpart is a semi-infinite optimization problem, which has a more complicated structure than an instance of the uncertain problem itself.

3.3 Equivalent Solvable Robust Counterpart Model

The term semi-infinite arises from the observation that the constraint has to be satisfied for all possible realizations of the parameters within the given uncertainty set, i.e., an infinite number of constraints must be regarded. For a semi-infinite linear programming problem, this model can be transformed into a solvable linear programming problem by means of the duality and the robust optimization theory.

Theorem 1. *Given polyhedral uncertainty set U and V_s for the uncertain cost c_{it}^k and resource r_{its}^k, then the formulation (11)-(18) have the following solvable linear robust counterpart as*

$$
\begin{aligned}
\max\ & (l_{T+1} - b_{T+1}) \\
\text{s.t.}\ & \sum_{i=1}^{n} \overline{c}_{it}^{t-t_i+1} x_i + \sum_{i=1}^{n} p_{it}^{t-t_i+1} + \Gamma_t z_t + l_t + b_{t-1}(1+r_b) \le l_{t-1}(1+r_l) + b_t + \beta_t, \qquad t = 1, ..., T+1 \\
& z_t + p_{it}^{t-t_i+1} \ge \hat{c}_{it}^{t-t_i+1} y_i, \qquad i = 1, ..., n;\ t = 1, ..., T+1 \\
& -y_i \le x_i \le y_i, \qquad i = 1, ..., n \\
& y_i, z_t, p_{it}^{t-t_i+1} \ge 0, \qquad i = 1, ..., n;\ t = 1, ..., T+1 \\
& \sum_{i=1}^{n} \overline{r}_{its}^{t-t_i+1} x_i + \sum_{i=1}^{n} w_{its}^{t-t_i+1} + \Phi_{ts} e_{ts} \le R_t^s, \qquad t = 1, ..., T;\ s = 1, ..., m \\
& e_{ts} + w_{its}^{t-t_i+1} \ge \hat{r}_{its}^{t-t_i+1} v_{is}, \qquad i = 1, ..., n;\ t = 1, ..., T;\ s = 1, ..., m \\
& -v_{is} \le x_i \le v_{is}, \qquad i = 1, ..., n;\ s = 1, ..., m \\
& v_{is}, e_{ts}, w_{its}^{t-t_i+1} \ge 0, \qquad i = 1, ..., n;\ t = 1, ..., T;\ s = 1, ..., m \\
& x_i = 1, \qquad i \in \Psi^m \\
& l_t b_t = 0, \qquad t = 1, ..., T+1 \\
& b_t \le B, \qquad t = 1, ..., T \\
& x_i = (0, 1), \qquad i = 1, ..., n \\
& b_t, l_t \ge 0, \qquad t = 1, ..., T+1.
\end{aligned}
\tag{19}
$$

Proof. We only introduce how to deal with the balance constraint (12), the resource constraint (13) can be processed similarly.

Denote $K_t = l_{t-1}(1+r_l) + b_t + \beta_t - l_t - b_{t-1}(1+r_b)$. Let $\boldsymbol{x}^*$ be the optimal solution of formulation (19). According to the constraint maximum protected criterion, we have the following formulation:

$$
\sum_{i=1}^{n} c_{it}^{t-t_i+1} x_i^* = \sum_{i=1}^{n} \overline{c}_{it}^{t-t_i+1} x_i^* \pm \sum_{i=1}^{n} \zeta_{it} \hat{c}_{it}^{t-t_i+1} x_i^* \le \sum_{i=1}^{n} \overline{c}_{it}^{t-t_i+1} x_i^* + \sum_{i=1}^{n} \zeta_{it} \hat{c}_{it}^{t-t_i+1} |x_i^*| \le K_t, \tag{20}
$$

if and only if

$$
\max_{\zeta_{ij}} \{ \sum_{i=1}^{n} \overline{c}_{it}^{t-t_i+1} x_i^* + \sum_{i=1}^{n} \zeta_{it} \hat{c}_{it}^{t-t_i+1} |x_i^*| \} \le K_t,
$$

i.e.,

$$
\max_{\zeta_{ij}} \sum_{i=1}^{n} \zeta_{it} \hat{c}_{it}^{t-t_i+1} |x_i^*| \le K_t - \sum_{i=1}^{n} \overline{c}_{it}^{t-t_i+1} x_i^*,
$$

then formulation (20) constantly established. At optimality clearly, $y_i = |x_i^*|$, and thus we get the following formulation:

$$
\begin{aligned}
\max\ & \sum_{i=1}^{n} \zeta_{it} \hat{c}_{it}^{t-t_i+1} y_i \\
\text{s.t.}\ & \sum_{i=1}^{n} \zeta_{it} \le \Gamma_t,\ t = 1, 2, ..., T+1 \\
& 0 \le \zeta_{it} \le 1,\ i = 1, 2, ..., n;\ t = 1, 2, ..., T+1.
\end{aligned}
\tag{P2}
$$

According to the strong dual properties, we can convert the original problem into its dual problem. We introduce new variables z_t and $p_{it}^{t-t_i+1}$, and get the dual problem of the original problem (P2) as

$$\min \sum_{i=1}^{n} p_{it}^{t-t_i+1} + \Gamma_t z_t \tag{D2}$$
$$\text{s.t.} \quad z_t + p_{it}^{t-t_i+1} \geq \hat{c}_{it} y_i, \quad i = 1, 2, ..., n; \; t = 1, 2, ..., T+1$$
$$p_{it}^{t-t_i+1} \geq 0, \quad i = 1, 2, ..., n; \; t = 1, 2, ..., T+1$$
$$z_t \geq 0, \quad t = 1, ..., T+1.$$

So we have

$$\min_{p_{it}, z_t} \sum_{i=1}^{n} p_{it}^{t-t_i+1} + \Gamma_t z_t \leq K_t - \sum_{i=1}^{n} \overline{c}_{it}^{t-t_i+1} x_i^*,$$

i.e.,

$$\sum_{i=1}^{n} \overline{c}_{it}^{t-t_i+1} x_i^* + \sum_{i=1}^{n} p_{it}^{t-t_i+1} + \Gamma_t z_t \leq K_t.$$

Therefore, based on the strong duality property, the formulation (19) is proved to be the equivalent model of formulation (11)-(18).

The proof is complete. □

Formulation (19) is the robust R&D projects portfolio optimization model. Noting that the binary variable is a special case of integer variable, in this section, the proposed formulation (19) is a MILP problem which is of the same class as that of the nominal problem, and it can withstand parameter uncertainty under the model of data uncertainty U and V_s without excessively affecting the objective function. In the above model, the latent variables z_t and $p_{it}^{t-t_i+1}$ have no particular meaning but together with y_i to determine the amount by which uncertain parameter c_{it}^k deviates around $\overline{c}_{it}^k$.

4 Numerical Discussions

4.1 Statement of Problem

In this section, we present a numerical example to illustrate the validity of the proposed robust CRO portfolio optimization model in the previous section. We assume that the CRO faced with a total of 20 new drug R&D projects. At the moment, the project portfolio consists of 11 projects will undergo clinical phase I, II, III, and IV, 5 projects will undergo clinical phase I, II, III, and 4 projects will undergo clinical phase I, II. Note that each project phase may span several years and the cost takes place at the beginning of the phase. Due to the restrictions of capital and resources, 20 projects cannot be selected at the same time, thus, CRO must take into account the cost and resource uncertainty and select the appropriate R&D projects to ensure maximum profit. The data summarized in Table 2 includes the duration of the project, the cost of each phase and the value of the contract. We use notation t_i for the contract-based start year of project i presented in the last column of Table 2. According to Table 2, we calculate the end time of each project with (12, 14, 9, 10, 8, 8, 7, 6, 8, 6, 6, 5, 6, 6, 6, 5, 5, 5, 4, 3) and select the maximum value of 14 as the whole planning cycle. We assume that $s = 1, 2$, r_{it1}^k represents the raw material resource consumption, and r_{it2}^k represents the space resource consumption. Table 3 provides the consumption of two resources per year for 20 projects. In the project development process where the consumption of raw material resource is uncertain and the total is amount 150, the consumption of space resource is determined ($\Phi_{t2} = 0$) and the total amount is 8. Taking the first project as an example, $t_1 = 5$, $k_1 = 8$, $c_{1,5}^1 = 12$, $c_{1,6}^2 = 10$, $c_{1,7}^3 = 0$, $c_{1,8}^4 = 20$, $c_{1,9}^5 = 0$, $c_{1,10}^6 = 20$, $c_{1,11}^7 = 0$, $c_{1,12}^8 = 0$, $c_{1,13}^9 = -120$, $r_{1,5,1}^1 = 2$, $r_{1,6,1}^2 = r_{1,7,1}^3 = 15$, $r_{1,8,1}^4 = r_{1,9,1}^5 = 30$, $r_{1,10,1}^6 = r_{1,11,1}^7 = r_{1,12,1}^8 = 1$, $s_{1,5,2}^1 = 1$, $s_{1,6,2}^2 = s_{1,7,2}^3 = 0.9$, $s_{1,8,2}^4 = s_{1,9,2}^5 = 1.1$, $s_{1,10,2}^6 = s_{1,11,2}^7 = s_{1,12,2}^8 = 0.5$. Note that we take the contract value as the negative only for the convenience of calculation. We assume that the annual risk-free interest rates and borrowing rates are 5 percent and 14 percent. In the first three years of the start, there are 200 million dollars in start-up capital each year. The borrowing limit for each year is 200 million dollars.

In order to analyze the effect of uncertainty on the problem more effectively, we should first determine that the maximum offset of all uncertain parameter estimation is 0.5 times the nominal value, i.e., $\hat{c}_{it}^k = 0.5\overline{c}_{it}^k$, $\hat{r}_{it1}^k = 0.5\overline{r}_{it1}^k$. In the previous section we have mentioned that Γ_t and Φ_{t1} stand for the common budget of

Table 2: Annual cost for the 20 projects

Project	Length of phase				cost of phase				contract value	start time
	I	II	III	IV	I	II	III	IV		
1	1	2	2	3	12	10	20	20	120	5
2	1	2	3	4	15	20	35	120	300	5
3	1	1	2	3	13	20	50	100	320	3
4	1	3	1	3	10	5	30	75	240	3
5	1	1	2	2	15	15	110	100	310	3
6	1	1	2	3	2	10	20	30	100	2
7	1	1	3	2	10	10	40	45	290	1
8	1	1	2	2	10	15	60	100	220	1
9	1	1	3	3	10	15	45	55	280	1
10	1	1	2	2	20	80	85	100	410	1
11	1	1	2	2	15	15	25	45	280	1
12	1	2	2		10	25	30		210	1
13	1	2	3		20	35	40		260	1
14	1	3	2		20	50	75		250	1
15	1	3	2		30	55	100		230	1
16	1	2	2		10	25	30		210	1
17	2	3			30	60			160	1
18	3	2			75	180			510	1
19	2	2			90	180			480	1
20	1	2			10	50			130	1

uncertainty for all uncertain parameters of the problem in period t. In order to facilitate the calculation, we assume $\Gamma_t = \Gamma$ and $\Phi_{t1} = \Phi$. The budget level Γ and Φ are conservative level parameters. Via sensitive analysis of Γ and Φ values, we can simulate different conservatism levels and select the appropriate project portfolio for different uncertain environments.

4.2 The Influence of Conservative Level Parameters Γ and Φ

In this section, we will discuss the effect of cost conservative level Γ and resource conservative level Φ on project portfolio and objective value. Conservative level parameters Γ and Φ take value in [0,20]. We solve formulation (19) with different values of Γ and Φ by increments of 0.1 units. It should be noted that when the conservative level parameter $\Gamma = \Phi = 0$, the robust optimal value is equal to the nominal optimal value of 2330.16, and the optimal solution is $\boldsymbol{x}=$ (1,1,1,1,0,0,1,0,1,0,0,0,0,0,0,1,0,0,1,0).

In order to be able to fairly analyze the performance of robust solutions, we denote the price of robustness (PR) as the nominal optimal value (NOV) minus the robust optimal value (ROV), i.e., RP=NOV-ROV. We also calculate the objective values (OV) that decision makers use the nominal solution as substituting the nominal optimal solution in the robust model, which is reflected in the last column of Table 5, 9 and 12. In an uncertain environment, if the decision maker insists on using the nominal optimal solution and does not change, we denote the price of using the nominal solution (NP) as the NOV minus the OV, i.e., NP=NOV-OV.

4.2.1 The Influence of Single Conservative Level Parameter

We have fixed a conservative level parameter and observed the effect of the other one on project selection and objective value. So we do our numerical experiments according to the following two cases:
Case I: We assume that the cost parameter is fluctuating and the resource parameter is deterministic, i.e., $\Phi = 0$.

Table 3: Annual resources consumption for the 20 projects

Project	Annual raw material resource consumptions for the 20 projects				Annual space resource consumptions for the 20 projects			
	I	II	III	IV	I	II	III	IV
1	2	15	30	1	1	0.9	1.1	0.5
2	15	30	60	1	1.7	1	1.9	0
3	10	30	50	1	1.2	2.1	1.6	0
4	25	9	30	1	1.9	0.4	1.6	0
5	15	24	60	1	0.9	1.5	3.6	0
6	5	15	20	1	0.5	1.4	1	0
7	10	15	40	1	1	1.4	1.7	0
8	15	24	50	1	2.1	1.6	1.7	0
9	15	24	30	1	1.3	1.6	1	0
10	10	50	36	1	2.6	4	1.5	0
11	10	24	26	1	2.4	2.3	1.7	0
12	15	26	1		1.8	1.2	0	
13	10	36	1		1.9	1.9	0	
14	10	56	1		2.5	1.5	0	
15	15	56	1		2.5	1.2	0	
16	15	26	1		1.9	0.8	0	
17	30	1			1.3	0		
18	56	1			2.1	0		
19	50	1			3.4	0		
20	50	1			3	0		

Table 4: Project selection for various Γ value

Solution	Γ	Project																			
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
S1	$0 \rightarrow 0.2$	1	1	1	1			1		1							1			1	
S2	0.3	1	1	1				1					1	1			1	1			
S3	$0.4 \rightarrow 0.8$	1		1			1	1		1		1					1	1			
S4	$0.9 \rightarrow 1.7$	1		1			1	1				1	1				1				
S5	$1.8 \rightarrow 1.9$	1						1				1	1	1			1				
S6	$2 \rightarrow 2.7$				1							1	1	1			1				
S7	$2.8 \rightarrow 3.9$				1			1				1	1				1				
S8	$4 \rightarrow 20$				1			1				1	1				1				

Table 4 shows the selection of projects for adjusting the value of Γ by increments of 0.1 units in the case of resource determination. Under only the cost fluctuation condition, we can give the CRO project preference suggestion through the observation in Table 4. When the level of uncertainty is low ($\Gamma \leq 1.7$), we recommend that decision makers prefer to select projects 1, 3, 7, 16. When uncertainty is moderate ($1.8 \leq \Gamma \leq 2.7$), projects 11, 12, 13 and 16 should be given preference. When the uncertainty level is high ($2.8 \leq \Gamma \leq 20$), projects 4, 7, 11, 12 and 16 should be given preference. There is an inclination to form smaller portfolios as the uncertainty grows.

We can clearly see in Table 5 that shows the changes in ROV and OV as the cost conservative level parameter increases. It can be seen that when the external environment changes, the nominal optimal solution can no longer maximize the profit of the CRO, and may even lead to the entire decision unfeasible. Therefore, the decision makers should consider the changes in the environment and make the appropriate adjustments to the portfolio is very necessary. Table 6 shows more intuitively that if the decision maker sticks to the nominal optimal solution and does not change the strategy, it will pay more than the price of using the robust optimal solution.

Table 5: Analysis of solution (Γ)

Solution	Γ	Portfolio of selected projects	ROV	OV
S1	0→0.2	1,2,3,4,7,9,16,19	2330.16 → 2206.61	2330.16→2206.61
S2	0.3	1,2,3,7,12,13,16,17	2157.79	2144.83
S3	0.4→0.8	1,3,6,7,9,11,16,17	2117.17 →1990.41	2083.05→1831.58
S4	0.9→1.7	1,3,6,7,11,12,16	1960.69→1834.01	1767.23→1579.19
S5	1.8→1.9	1,7,11,12,13,16	1825.67→1817.39	Not Feasible
S6	2→2.7	4,11,12,13,16	1809.90→1768.51	Not Feasible
S7	2.8→3.9	4,7,11,12,16	1763.73→1738.87	Not Feasible
S8	4→20	4,7,11,12,16	1736.94	Not Feasible

Table 6: The values of RP and NP at different Γ

Γ	RP	NP
0→0.2	0→123.55	0→123.55
0.3	172.37	185.33
0.4→0.8	212.99→339.75	247.11→498.58
0.9→1.7	369.47→496.15	562.93→750.97
1.8→1.9	504.49→512.77	NO!
2→2.7	520.26→561.65	NO!
2.8→3.9	566.43→591.29	NO!
4→20	593.22	NO!

When the resources are fixed, the objective function value decreases as the cost conservative level parameter Γ increases which is shown in Figure 1. It is observed that when cost conservative level parameter $2.8 \leq \Gamma \leq 3.9$, the selected projects remain constant but the target function value continues to drop while $\Gamma \geq 4$ can impose no further decline on the objective function value 1736.94. This essentially results in a worse objective function, due to the conservative nature of the robust optimization which tends to the worst instances of the problem.

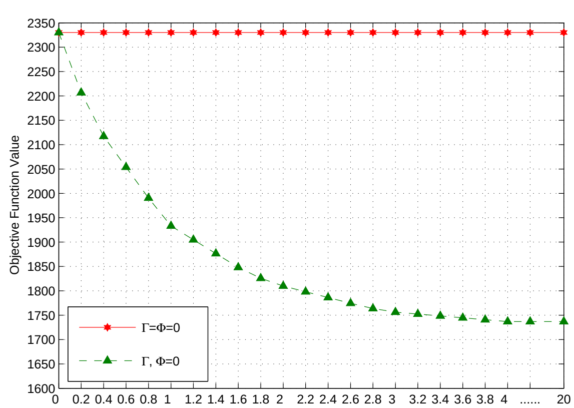

Figure 1: Objective function value versus Γ

Case II: We assume that the resource parameter is fluctuating and that the cost parameter is deterministic, i.e., $\Gamma = 0$.

Table 7 shows the selection of projects for adjusting the value of Φ by increments of 0.1 units in the case of resource determination. Under only the resource fluctuation condition, we can give the CRO project preference suggestion through the observation in Table 7. When the level of uncertainty is low ($\Gamma \leq 0.9$), we recommend that decision makers prefer to select projects 1, 2, 3, 4, 18, 19. When uncertainty is moderate ($1 \leq \Gamma \leq 2.6$), projects 1, 2, 3, 11 and 12 should be given preference. When the uncertainty level is high ($2.7 \leq \Gamma \leq 20$), projects 2, 3, 4, 11 and 16 should be given preference.

Table 7: Project selection for various Φ

Solution	Φ	Project																			
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
S1	0→0.1	1	1	1	1			1		1							1			1	
S2	0.2	1	1	1	1							1					1	1	1		
S3	0.3→0.5	1	1	1	1							1							1	1	
S4	0.6	1	1	1	1			1											1	1	
S5	0.7	1	1	1	1							1							1	1	
S6	0.8→0.9	1	1	1	1			1									1	1		1	
S7	1→1.1	1	1	1				1				1	1				1				
S8	1.2→1.6	1	1	1								1	1	1			1				
S9	1.7→2.5		1	1	1		1					1	1							1	
S10	2.6	1		1	1			1				1								1	
S11	2.7		1	1	1							1	1				1	1			
S12	2.8→20		1	1	1							1					1			1	

Table 8 shows the variation of OV and ROV with the increase of the conserved level parameter values of the resource. It should be noted that the nominal optimal value at this time is completely impractical. In conjunction with Table 9, the numerical comparison of PR and NR highlights the fact that if a decision maker does not adapt to changes in the environment and adjusts for the corresponding project, then the entire R&D portfolio will be interrupted.

Table 8: Analysis of solution (Φ)

Solution	Φ	the selected projects	ROV	OV
S1	0→0.1	1,2,3,4,7,9,16,19	2330.16	2330.16→Not Feasible
S2	0.2	1,2,3,4,11,16,17,18	2314.37	Not Feasible
S3	0.3→0.5	1,2,3,4,11,18,19	2305.13	Not Feasible
S4	0.6	1,2,3,4,7,18,19	2294.73	Not Feasible
S5	0.7	1,2,3,4,11,18,19	2305.13	Not Feasible
S6	0.8→0.9	1,2,3,4,7,16,17,19	2250.22	Not Feasible
S7	1→1.1	1,2,3,7,16,17,19	2227.28	Not Feasible
S8	1.2→1.6	1,2,3,11,12,13,16	2209.65	Not Feasible
S9	1.7→2.5	2,3,4,6,11,12,19	2166.86	Not Feasible
S10	2.6	1,3,4,7,11,19	2149.70	Not Feasible
S11	2.7	2,3,4,11,12,16,17	2143.50	Not Feasible
S12	2.8→20	2,3,4,11,16,19	2135.33	Not Feasible

Figure 2 shows that when the costs are fixed, the objective function value also decreases steadily as the resourse conservative level parameter Φ increases. So the uncertainty of resources is an extremely important factor which should be considered for decision makers in the project portfolio selection. Uncertainty of resources will directly affect decision makers to make different project choices and obtain different profits. How to choose the right combination of projects to hedge this uncertainty is particularly important.

Table 9: The values of RP and NP at different Φ

Φ	RP	NP
0→0.1	0	0→NO!
0.2	15.79	NO!
0.3→0.5	25.03	NO!
0.6	35.43	NO!
0.7	25.13	NO!
0.8→0.9	79.94	NO!
1→1.1	102.88	NO!
1.2→1.6	120.51	NO!
1.7→2.5	163.3	NO!
2.6	180.46	NO!
2.7	186.66	NO!
2.8→20	194.83	NO!

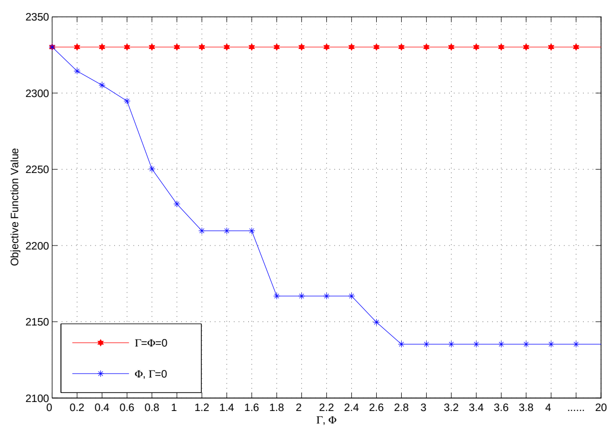

Figure 2: Objective function value versus Φ

4.2.2 The Influence of Two Conservative Level Parameter

In this section, we discuss the impact of both volatility and cost and resource conservative parameters on project selection and objective function values. In order to clear the contrast with the impact of a single parameter fluctuation, we assume that the cost and resources of the conservative level parameter are the same fluctuations, i.e., $\Gamma=\Phi$.

The portfolio of selected projects along with $\Gamma=\Phi$ by increments 0.1 is presented in Table 10. It is observed that when uncertainty is low ($\Gamma=\Phi \leq 1$), projects 1, 3, 7, 12 and 16 should be preferentially added to the optimal portfolio. When uncertainty is moderate ($1 \leq \Gamma=\Phi \leq 3.1$), projects 11, 12, 13 and 16 should be given preference. When uncertainty is high ($3.2 \leq \Gamma=\Phi$), project 7, 12, 16, 20 should be included in the R&D project portfolio.

We can see that Tables 11 and 12 show the effect on the project portfolio and target value as the two conservative level parameters increase at the same time. When the cost and resource parameters co-fluctuate, the impact on the objective function value is greater than that of a parameter fluctuation, the profit declines faster and the price paid is relatively higher. And the number of selected projects decrease as the uncertainty increases.

Table 10: Project selection for $\Gamma = \Phi$

Solution	Γ=Φ	Project																			
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
S1	0→0.1	1	1	1	1			1		1							1			1	
S2	0.2→0.5	1	1	1				1					1	1			1	1			
S3	0.6→0.8	1		1				1		1		1	1					1			
S4	0.9	1		1				1				1	1				1				
S5	1→1.6	1		1								1	1	1			1				
S6	1.7→1.9	1										1	1	1			1				
S7	2→2.3											1	1	1			1				
S8	2.4→3.1									1	1	1					1				
S9	3.2→3.9							1					1				1				1
S10	4→20							1					1				1				1

Table 11: Analysis of solution (Γ=Φ)

Solution	Γ=Φ	Portfolio of selected projects	ROV	OV
S1	0→0.1	1,2,3,4,7,9,16,19	2330.16 → 2268.38	2330.16→Not Feasible
S2	0.2→0.5	1,2,3,7,12,13,16,17	2198.85 →2075.67	Not Feasible
S3	0.6→0.8	1,3,7,9,11,12,17	2022.26→1958.88	Not Feasible
S4	0.9	1,3,7,11,12,16	1929.16	Not Feasible
S5	1→1.6	1,3,11,12,13,16	1901.58→1834.14	Not Feasible
S6	1.7→1.9	1,11,12,13,16	1806.16→1791.39	Not Feasible
S7	2→2.3	11,12,13,16	1784.80→1767.06	Not Feasible
S8	2.4→3.1	9,10,11,16	1670.87→1656.45	Not Feasible
S9	3.2→3.9	7,12,16,20	1635.32→1619.86	Not Feasible
S10	4→20	7,12,16,20	1617.92	Not Feasible

Table 12: The values of RP and NP at different $\Gamma = \Phi$

Γ = Φ	RP	NP
0→0.1	0→61.78	0→NO!
0.2→0.5	131.31→254.49	NO!
0.6→0.8	307.90→371.28	NO!
0.9	401	NO!
1→1.6	428.58→496.02	NO!
1.7→1.9	524→538.77	NO!
2→2.3	545.36→563.10	NO!
2.4→3.1	659.29→673.71	NO!
3.2→3.9	694.84→710.3	NO!
4→20	712.24	NO!

Figure 3 shows the realized value of selected portfolios with respect to different values of Γ=Φ in [0, 20]. It is intuitive that the robust objective is always a decreasing function of Γ=Φ. The non-increasing shape of the objective function verifies the fact that as uncertainty of the environment grows, the uncertain problem parameters gain more volatility. This essentially results in a worse objective function, because the conservative nature of the robust optimization which tends to the worst instances of the problem. When the conservative level parameter $\Gamma = \Phi \geq 3.2$, the robust objective value tends to decrease gently and eventually stabilizes.

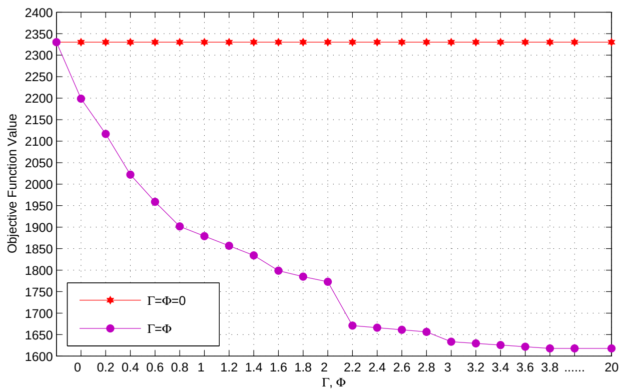

Figure 3: Objective function value versus $\Gamma \doteq \Phi$

4.3 The Results Analysis

In this subsection, we compare the effects of conservative level parameters Γ and Φ on the objective function values.

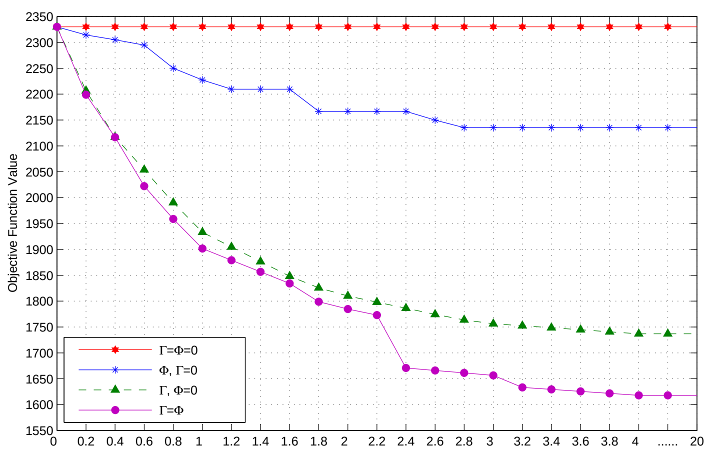

Figure 4: The objective function value in three cases

The results of the comparison in Figure 4 are shown the effect of each on the objective function values in the three cases described above. We combine the analysis of Tables 4, 6 and 8 under different parameters of the project selection and observation by Figure 4 to get the three conclusions: (i) When the cost is determined, the objective function decreases gently as the resource fluctuates. When $\Phi \geq 2.8$, the objective function value 2135.33 no longer decreases with projects 2, 3, 4, 11, 16 and 19 (six projects). (ii) When the resource is determined, the objective function declines rapidly as the cost fluctuates.When $\Gamma \geq 4$, the objective function value 1736.94 no longer decreases with projects 4, 7, 11, 12 and 16 (five projects). (iii) When the costs and resources fluctuate at the same time, the objective function will decrease drastically while $\Gamma = \Phi \geq 4$ can impose no further decline on the objective function value 1617.92 with projects 7, 12, 16 and 20 (four projects).

As the number of uncertain parameters increase, the impact on the objective function value (profit) will increase. When the uncertainty of parameters increases, there is an inclination to form smaller portfolios and the objective function value decreases. This is inevitable, because when the uncertainty of parameters increases, the look-for-feasible nature of robust optimization confronts tighter budget constraints to satisfy and fewer projects qualify to enroll the optimal portfolio. We observed that inclusion of some projects in the optimal portfolio are less vulnerable to uncertainty (some projects are always or never selected), and the remaining projects which are less sensitive to uncertainty show different behaviors under different uncertain levels. The best portfolio of projects does not necessarily include all very good projects, i.e., decision makers may not choose good projects because they are not suitable for "overall program objectives". This is a key observation to the projects portfolio selection. To summarize, the decision maker should choose the R&D project carefully while the environment fluctuates greatly.

5 Conclusions

In this paper, we develop a robust project portfolio model to determine R&D project portfolio from a pool of candidate projects that maximizes the objective value and achieves R&D strategic balance, while there is lack of reliable project information. Decision makers have more descriptive power to describe uncertain and flexible project information using robust optimization theory. The R&D project portfolio model is a very useful decision-making tool for CROs which are not usually interested in detailed data and mathematical formulas and rather decide based on descriptive and qualitative tools. In the proposed model, we consider the cost and resources which are unknown but bounded and belong to the given polyhedral sets. The original robust model is a semi-infinite programming and computationally intractable. We use the duality theorem to convert the original model into an equivalent solvable robust counterpart model. This model can help CROs make effective and rational projects combination decision in a variety of uncertain environments. Ultimately, we apply the proposed model to a pharmaceutical project selection portfolio problem, which includes incomplete information on new drug R&D cost and resource, and provide robust solutions with better performance for CROs at different conservative levels.

As a future research direction, further empirical work can be continued to ensure the practical applicability of the proposed method. When it is possible to capture more effective information about uncertain data to simulate the possibility or probability distribution of the R&D project parameters, it is more realistic to apply a fuzzy or stochastic optimization approach to the model.

Acknowledgments

This work was supported by the Social Science Foundation of Hebei Province (No.HB17GL009).

References

[1] Baker, N., and J. Freeland, Recent advances in R&D benefit measurement and project selection methods, *Management Science*, vol.21, no.10, pp.1164–1175, 1975.

[2] Bauer, H.H., and M. Fischer, Product life cycle patterns for pharmaceuticals and their impact on R&D profitability of late mover products, *International Business Review*, vol.9, no.6, pp.703–725, 2000.

[3] Beaujon, G.J., Marin, S.P., and G.C. Mcdonald, Balancing and optimizing a portfolio of R&D projects, *Naval Research Logistics*, vol.48, no.1, pp.18–40, 2001.

[4] Ben-Tal, A., and A. Nemirovski, Robust optimization-methodology and applications, *Mathematical Programming*, vol.92, no.3, pp.453–480, 2002.

[5] Bertsimas, D., and M. Sim, Robust discrete optimization and network flows, *Mathematical Programming*, vol.98, nos.1-3, pp.49–71, 2003.

[6] Brenner, M.S., Practical R&D project prioritization, *Research-Technology Management*, vol.37, no.5, pp.38–42, 1994.

[7] Chen, X., Sim, M., and P. Sun, A robust optimization perspective on stochastic programming, *Operations Research*, vol.55, no.6, pp.1058–1071, 2007.

[8] Chen, Y., and Y. Wang, Two-stage fuzzy portfolio selection problem with transaction costs, *Mathematical Problems in Engineering*, vol.2015, pp.1–12, 2015.

[9] Cooper, R.G., Edgett, S.J., and E.J. Kleinschmidt, Portfolio management for new products, *R&D Management*, vol.31, no.4, pp.361–380, 2002.

[10] Fernandez, E., Gomez, C., Rivera, G., and L. Cruz-Reyes, Hybrid metaheuristic approach for handling many objectives and decisions on partial support in project portfolio optimisation, *Information Sciences*, vol.315, pp.102–122, 2015.

[11] Fernandes, B., Street, A., Valladao, D., and C. Fernandes, An adaptive robust portfolio optimization model with loss constraints based on data-driven polyhedral uncertainty sets, *European Journal of Operational Research*, vol.255, no.3, pp.961–970, 2016.

[12] Fliedner, T., and J. Liesio, Adjustable robustness for multi-attribute project portfolio selection, *European Journal of Operational Research*, vol.252, no.3, pp.931–946, 2016.

[13] Gemici-Ozkan, B., Wu, S.D., Linderoth, J.T., and J.E. Moore, R&D project portfolio analysis for the semiconductor industry, *Operations Research*, vol.58, no.6, pp.1548–1563, 2010.

[14] Ghaoui, L.E., Oustry, F., and H. Lebret, Robust solutions to uncertain semidefinite programs, *Siam Journal on Optimization*, vol.9, no.1, pp.33–52, 2006.

[15] Ghasemzadeh, F., Archer, N., and P. Iyogun, A zero-one model for project portfolio selection and scheduling, *Journal of the Operational Research Society*, vol.50, no.7, pp.745–755, 1999.

[16] Goh, J., and N.G. Hall, Total cost control in project management via satisficing, *Management Science*, vol.59, no.6, pp.1354–1372, 2013.

[17] Hassanzadeh, F., Nemati, H., and M. Sun, Robust optimization for interactive multiobjective programming with imprecise information applied to R&D project portfolio selection, *European Journal of Operational Research*, vol.238, no.1, pp.41–53, 2014.

[18] Heidenberger, K., Dynamic project selection and funding under risk: a decision tree based milp approach, *European Journal of Operational Research*, vol.95, no.2, pp.284–298, 1996.

[19] Heidenberger, K., and C. Stummer, Research and development project selection and resource allocation: a review of quantitative modeling approaches, *International Journal of Management Reviews*, vol.1, no.2, pp.197–224, 1999.

[20] Kuan, M., and Y. Chen, Exploring a risk evaluation model for new product development project, *Journal of Uncertain Systems*, vol.9, no.3, pp.163-174, 2015.

[21] Leydesdorff, L., Heimeriks, G., and D. Rotolo, Journal portfolio analysis for countries, cities, and organizations: maps and comparisons, *Journal of the Association for Information Science and Technology*, vol.67, no.3, pp.741–748, 2016.

[22] Liu, Y., and Y.K. Liu, Distributionally robust fuzzy project portfolio optimization problem with interactive returns, *Applied Soft Computing*, vol.56, pp.655–668, 2017.

[23] Lowman, M., Trott, P., Hoecht, A., Sellam, Z., Lowman, M., and P. Trott, Innovation risks of outsourcing in pharmaceutical new product development, *Technovation*, vol.32, no.2, pp.99–109, 2012.

[24] Machacha, L.L., and P. Bhattacharya, A fuzzy-logic-based approach to project selection, *IEEE Transactions on Engineering Management*, vol.47, no.1, pp.65–73, 2000.

[25] Mild, P., Liesio, J., and A. Salo, Selecting infrastructure maintenance projects with robust portfolio modeling, *Decision Support Systems*, vol.77, pp.21–30, 2015.

[26] Mirowski, P., and R.V. Horn, The contract research organization and the commercialization of scientific research, *Social Studies of Science*, vol.35, no.4, pp.503–548, 2005.

[27] Pennings, E., and L. Sereno, Evaluating pharmaceutical R&D under technical and economic uncertainty, *European Journal of Operational Research*, vol.212, no.2, pp.374–385, 2011.

[28] Soyster, A.L., Convex programming with set-inclusive constraints and applications to inexact linear programming, *Operations Research*, vol.21, no.5, pp.1154–1157, 1973.

[29] Wang, J., and W.L. Hwang, A fuzzy set approach for R&D portfolio selection using a real options valuation model, *Omega*, vol.35, no.3, pp.247–257, 2007.