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Production of a New Drug: A Sequential Investment Process Under Uncertainty

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Abstract - On the basis of a database of more than 80 thousand records on total retails and production costs of the pharmaceutical industry worldwide we consider four classes of drugs. We evaluate the expected profits of an investment in a new drug in the four classes of pharmaceutical products by considering the standard NPV evaluation. We compare these outcomes with the evaluation of the expected profits of the four new drugs obtained by the real option approach. Interestingly enough quite different outcomes are obtained. These results loom on the capacity of standard methods to give a reliable evaluation of real investment projects that are analogous to compound options.

Keywords: compound option, real option valuation, net present value, drugs
J.E.L. Classification: O3, L65, D92

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1. INTRODUCTION

Research and Development (R&D henceforth) have an increasing impact on corporate performance and investment returns. Starting from the mid 1990s, major areas of patent activity and innovation have been electronics, semiconductors-manufacturing processes, optics for communications and light-transmitting devices, computing, data processing and health care. Although no drug-maker is included in the top ten list of the companies which has been granted the majority of U.S. patents in 1999, the top global drug-makers lead the category of innovation which cannot be directly related to information technology. Moreover, looking at the market value of a generic pharmaceutical company, only a small fraction of it (about 50%) comes from operating profits**,** with the remainder deriving from development research in new drugs.

A report by Cambridge Healthtech Advisor (2004) puts in evidence that "54% of surveyed large pharma companies (revenues >$3B) will outsource at least 20% of ADMET in 2003 growing to 94% of companies in 2008".[1] Outsourcing can be seen as an effective tool to tackle declining productivity in discovery research and clinical trials since it allows large companies to focus on their core areas without disregarding emerging technologies and in-license products.

In the most recent years, branded pharmaceutical firms registered few new drugs and were hit by rising pressure from generic drug makers. Typically, they tried to face this new situation by increasing the price of their blockbuster products, but the effect of this market policy has been limited by the activity of scrutiny on prices, together with the threatening of legislative action by governments. In 2004, companies put about 20% of their overall revenues (amounting about $56 billion) into R&D, but they managed to have only 34 new drugs approved for marketing. However**,** pharmaceutical firms "spent a whopping $14.7 billion on marketing to health-care professionals last year, and at least $3.6 billion on direct-to-consumer advertising" (The Economist 2005, p. 69), that is one third of drug-firms sales revenues.

Summarizing, the pharmaceutical industry faces four main problems: (a) criticism for aggressive and misleading advertising, and high prices (the US Department of Commerce reports that the average market prices of the 54 leading drugs in Canada, Australia and UK are

[1] To be effective, a drug must reach its intended target and confer good Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET).

half the average prices charged for the same drugs in USA); (b) decreasing productivity in R&D (-18% with respect to 2002); (c) loss of reputation related to the safety and side-effects of some blockbuster drugs like GlaxoSmithKline (GSK) antidepressants and Merck VIOXX (a COX-2 inhibitor); (d) challenge from generic drug-makers over the blockbusters of Big Pharma such as Zyprexa, Lipitor and Plavix.

In this scenario, in which the debate involves both the business model and the drug-regulatory system, it is worth to separate from the Pharma overall business the core business, that is, the part that generates both leadership in health care field and benefits to shareholders, with the intent of providing the estimation of the correct value of R&D process in a new drug.

The production of a new drug usually involves a multistage investment process and the possibility of stopping or delaying it, thus making this investment analogous to a compound call option. The pharmaceutical firm will get revenues either if the project is completed or if the new drug patent is sold to some other firm. Being a multistage process, as soon as each stage of the production has been completed, the pharmaceutical firm has the option to go ahead or to stop the development of the new drug.

In this paper we consider the process of production of new drugs from an economic point of view and we wonder what the management's decision may be when it faces actual situations, like those summarized by the costs and revenues reported in the dataset we refer to. We compare two different evaluation methods of the likely economic performance of new drugs: the first one is based on the traditional computation of the net present value (NPV henceforth), the other rests on the Real Option Value approach (ROV henceforth). Our results show that quite different outcomes are obtained when adopting the two evaluation methods. We argue that estimating the value of the project by means of standard NPV can be misleading, since such an approach would ignore the extra-value of the project represented by its inherent optionality. The ROV, on the other hand, is devised to exploit the flexibility inherent in sequential investments characterized by technological and commercial uncertainty.[2] This flexibility stems from the possibility of discarding the project and abandoning investment initiatives at any time, when new information becomes available with the passage of time and evidence from clinical trials is gathered. This problem is very similar to that of patent valuation, of employing new natural resources, of exploiting a mine, of producing a new aircraft such as Air Bus A380 and so on.

[2] It can be stated that for every approved drug, roughly 10 thousand molecules have started development and have been abandoned along the way.

Application of the ROV to technological intensive firms under uncertainty and irreversibility has been developed in the last thirty years (Brennan and Schwartz 1985, Grossman and Shapiro 1986, McDonald and Siegel 1986, Majid and Pyndick 1987, Pyndick 1993, Trigeorgis 1996). Moreover the ROV of a drug production is not a new notion in economics (DiMasi et al. 1991, 2003, DiMasi 1995, Rogers et al 2004). But in this paper we consider an application to a very large set of real data on production costs and total revenues of pharmaceutical industry worldwide.

In order to enhance the significance of our evaluations, we start from a data set where data about production costs and revenues of several thousands drugs are collected. We then compute our valuations in four different classes, formed on the basis of certain features which are detailed in Section 2. Finally we evaluate each class using both the NPV and the ROV methods. Outcomes reported in the following sections support our contention that an evaluation method that takes into due account the existence of an option value implicit in the investment process of any R&D process is necessary to assess a correct decision.

The paper is organized as follows. Section 2 contains the description of the database, the four different classes, and illustrates the methodology used. In Section 3 the present value of drugs belonging to the four classes are evaluated by means of the ROV, and the results are discussed. Concluding remarks are in Section 4.

2. THE DATASET

The database studied in this paper is due to Fondazione Cerm, which elaborated data gathered from IMS-Health, a global health care information company, on total retails and production costs of the pharmaceutical industry worldwide. Data refer to ten years, from 1991 to 2001, and have been collected quarterly. As a result, there are at least 40 observations for each record in the retails series. The database includes 81.037 records, and each of them is about a specific drug sold in one of the following markets: U.S.A, Dutch, France, German, Italy, Spain, Portugal, Ireland, Finland, Luxemburg, Austria, Belgium, Canada, Greece, Denmark and Sweden. Each drug is considered on the basis of: its features and therapeutic class (ATC codex up to four level of detail), name of the firm that licensed the drug, and the period of its commercialization in each market. Firms involved are close to 4.000.

The implementation of a new drug production rests on a generalized routine that can be summarized as follows. The starting point is an extensive preclinical and laboratory

research that generally involves tests on mammals (animal-model) and human cells. If these tests are successful, a pharmaceutical firm requires to Public Authorities (FDA or MH) the approval to starting testing in humans. The clinical testing process is known as Investigation New Drug application (IND) and includes three different phases or stages at the end of which approval can be obtained. Often there is a post-marketing or stage four study.

Let us describe the different *phases* (stages) involved in a new drug commercialization:

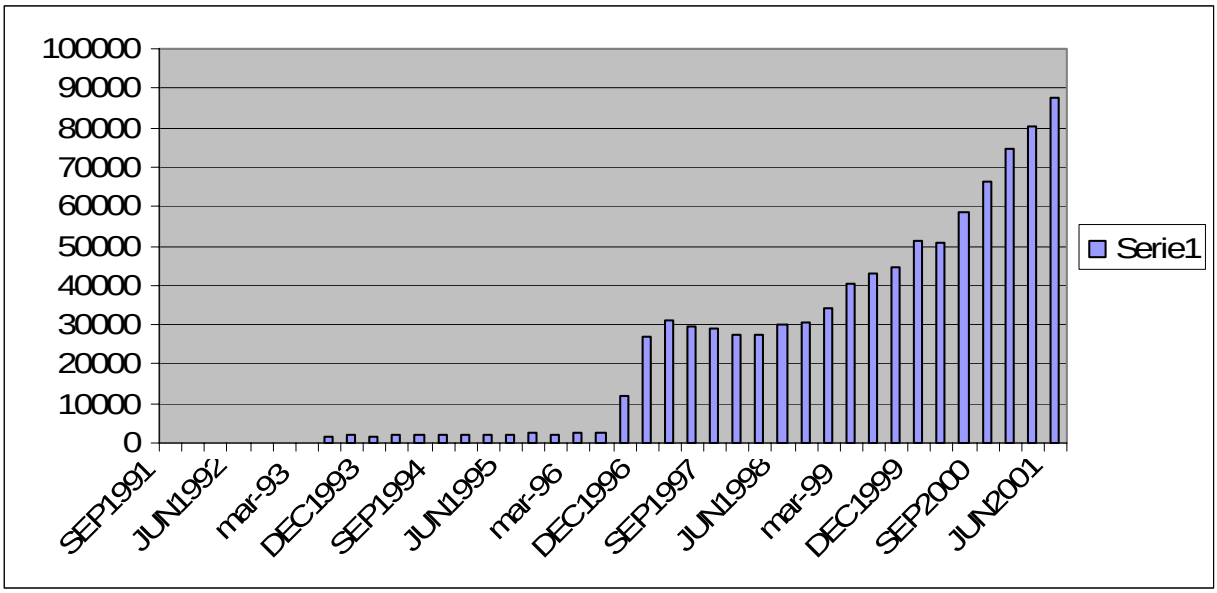
- *phase I* is devoted to the study of toxicity and safety of the new drug. There are a few tests on voluntary humans and, in general, tests last several months;
- *phase II* has to test the effectiveness of new drugs. Tests usually are conducted on a high number (several hundred) of patients and last at most two years. Trials are often random or blinded and control groups treated with placebo are involved;
- *phase III* entails large-scale tests (up to several thousand of patients) and is devoted to the assessment of new drugs effectiveness, benefits and the range of possible collateral effects. Most of the trials are random, blinded and prolonged for years. At the end of this phase firms may require Public Authorities approval to marketing of the new drug;
- *phase IV (post-marketing phase)* is devoted to obtain the following results: (a) compare the efficacy of the new drug with respect to analogous marketed compounds; (b) study the long-term effectiveness and side effects; (c) compare cost-effectiveness relative to alternative therapies.

Typically, when assessing the probability of marketing and profitability of a new drug, firms use a standard probability of 1/200, that is, one started project every two hundred is estimated to be successful[3].

In the database used, drugs are divided into four classes on the basis of their components. In principle the valuation which will be illustrated in Section 3 can be extended to any arbitrarily defined class of pharmaceutical products. Production costs are estimated on the basis of data set, which also includes total turnover for actually marketed drugs up to 2001. As an example, Figure 1 shows the turnover of a class-A drug. It is important to remark that, even if the revenues are very high, and even under the assumption that the management

[3] See for example Shockley et al. 2003, which also detail the probability of success at each stage.

can perfectly forecast the revenues, this does not imply that the rational decision for the management would be to start the production, since the likelihood of actually marketing a drug is low.



The classes are roughly described as follows.

Class A-type – This class includes drugs such as cladribine and irinotecan. Cladribine is an old drug that is going to find a new application against the multiple sclerosis. Irinotecan belongs to the group of medicines called anti-neoplastic. It has been used to treat cancer of the colon or rectum and, more recently, tested in combination with 5-fluorouracile and leucovorin (the active form of the B complex vitamin, folate, used as an antidote to drugs that decrease levels of folic acid).

Class B-type – This class includes a particular set of drugs produced by means of biotechnologies, such as monoclonal antibodies. These drugs have an application to certain specific diseases. Among them the more representative are trastuzumab (a monoclonal antibody that belongs to laboratory-made drugs designed to attack specific cancer cells that produce the HER2 protein), abciximab (anti-coagulant) or rituximab (used to treat non-Hodgkin's lymphoma).

Class C-type – This class refers to a wide set of drugs such as: rosiglitazone (for therapy of Type 2 diabetes mellitus also in combination therapy with insulin), for the large number of human cases considered, and sibutramine (anti-obesity). In this class we also put sildenafil citrate (Viagra), ropinirole (used to treat symptoms of Parkinson's disease) and rivastigmina tartrate (an Alzheimer's disease treatment).

Class D-type – In this class we consider drugs such as pantoprazole (a gastric acid pump inhibitor used and antiulcer agent) – with two ways of administration and only one oral formulation – and granisetron (an antiemetic used to prevent nausea and vomiting caused by chemotherapy and radiation therapy), with two ways of administration and three formulations.

3. THE VALUE OF OPTIONALITY

The investment decision of a pharmaceutical company is characterized by two peculiar aspects: irreversibility and uncertainty. Irreversibility breaks the temporal symmetry between the past and the future in so far as the restoration to an original natural state can be either technically impossibly or extremely expensive. This intuitive concept of irreversibility as either a technological or a physical constrain, i.e. unfeasible disinvestment, can be expressed by sunk costs. Investment expenditures in a new drug are, at a large extent, sunk costs both because they are firm specific and because a secondary market does not exist. Uncertainty, on the other hand, occurs when the consequences of each action are tied to stochastic events, whose probabilities of occurrence are either objectively or subjectively determined. The production of a new drug is a clear example of a choice conditioned on uncertain events. most of all there is uncertainty about the link between elements of the new chemical compound and a given disease, and concerning the effects of a new drug on human health (i.e. side effects).

An investment decision in a new drug can be analyzed as a sequential project that involves the ability to temporarily or permanently stop investing if the value of the completed project falls, or if the expected cost of completing the investment rises. Dixit and Pindyck (1994, p. 320) consider a sequential investment decision under uncertainty and irreversibility analogous to a financial compound option since "each stage completed (or dollar invested) gives the firm an option to complete the next stage (or invest the next dollar)". Dixit and Pindyck show that a multistage investment problem has exactly the same solution of a single-stage project. As a matter of fact if the structure of the markets is complete, or at least sufficiently complete (so that the spanning assumption is satisfied), the value of the project and the value of the option to invest (quasi-option value) are determined either by constructing a dynamic portfolio of asset (replicating portfolio) or by finding out a perfectly correlated asset and using option-pricing method. Dixit and Pindyck consider that the decision-maker faces various forms of risk, such as uncertainty over the future product prices, operating costs, future interest rates, cost and timing of the investment itself. Uncertainty is

represented as usual by a finite set of states of the world; once one of these states will be revealed as true, the option pricing will determine the optimal exercise rule of an investment. As a result there is only one opportunity value of an investment project.

At any stage then, the pharmaceutical firm has the possibility to pursue the project, as well as the opportunity (option) to postpone, to stop or to continue the research on that molecule. At the last stage, the firm will decide if marketing or not. Thus the problem of evaluating the project is formally identical to that of evaluating a *multistage option*, or *compound option*. We can then analyze the value of such a project using a real option approach, which borrows from the theory of financial option valuation.

One well known fact about option pricing is that the volatility of the underlying increases the value of the option. In real option terms, it means that when a pharmaceutical firm starts a project such as drug manufacturing, it has to take into account the fact that it is a risky business, that is a volatile business: the value of a drug could rise during pre-marketing, even for esogenous reasons, e.g. market conditions, institutional factors, technological shocks. This volatility has a value which Net Present Value (henceforth NPV) would not estimate thus leading to wrong assessment of the project value.

To assess valuation, we use the binomial tree approach of Cox, Ross and Rubinstein (1976). This approach is sophisticated enough to deal with the variability of the underlying (that is, the drug's expected revenues) and simple enough to be implemented without burdening computations. Indeed, further sophistication (e.g. a continuous time model such as Black and Scholes) is not required in this context, given the large uncertainty on costs and revenues which makes model risk negligible. We proceed as follows:

- first, we determine the initial value of the underlying, using the risk-adjusted discounted value of the expected revenues. The expected revenues are our underlying, whose volatility adds value to the multistage option;
- at every step the underlying can go up by a multiplicative factor u or down by a multiplicative factor $d = 1/u$. The choice $d = 1/u$ simplifies the analysis, since it implies a recombining tree (if you start from 1 and go first up and then down, you get again 1x u x 1/u = 1). We then compute the values of the underlying for N subsequent steps of fixed time length (say, 1 year). At step $k \leq N$, we have $(k + 1)$ possible values of the underlying;
- to assess the value of the underlying option we use backward induction, starting from step N. Denoting by S the value of the underlying, the value of the option in each of the

(N +1) possible states is $max(0, S - K(N))$ where $K(N)$ is the cost to be sustained at time N, e.g. the marketing cost, which the firm can decide to take or not;

- we then compute the underlying values in the states at time (N — 1), first taking the expected values of the option values at time N under the risk-neutral probabilities, which are functions of u, d and r, the risk-less rate;
- finally we evaluate the option values in the possible states by max (0, S-$K(N$-1)), where $K(N$-1) is the cost to be sustained at time (N-1). Iterating this backward procedure up to the initial time provides us the option value of the whole project.

The crucial parameter in the valuation procedure is the volatility σ of the underlying, from which we compute $u = e^{\sigma\sqrt{t}}$ and d=1/u, where t is the length of the time step. We then estimate the value of the project for different values of volatility, ranging from 0 % to 200 %. When assessing actual valuation, volatility can be inferred by implied or historical volatility of the market sector, e.g. of pharmaceutical stock prices. For the risk-free rate, we use r = 5% (US T-bond 30-year rate).

To show the importance of correctly estimating the value of volatility, we run the following exercise. We assume that the expected value of future revenues of an hypothetical drug is equal to 25 $ millions, which approximate the average values of revenues in the database by the probability of the drug to be successful. This number may be not adequately informative about actual revenues, but we assume that it correctly weighs the management's view about future events, because it incorporates the probability of actually marketing the drug.

Then, we use average costs of drug testing, that have been estimated separately for different departments of Research and Development: bulk manufacturing, bulk characterisation and control, pharmaceutical development, toxicology and preclinical safety, pharmacology and chemistry research, pharmacokinetic and metabolism, project management and regulatory, clinical research. Different projects imply different costs for each department. Details on the costs ($ million) are provided in *Table 1*.

Class	Pre-Clinical	Phase I	Phase II	Phase III	NDA filing	Post-Filing	NPV
A	3.77	5.73	17.57	0	1.07	2.47	4.60
B	7.14	8.54	13.50	18.68	1.07	2.47	-7.55
C	4.11	6.31	12.54	20.93	1.07	2.47	-3.26
D	6.21	10.63	15.33	28.07	1.07	3.95	-13.96

Table1: Costs $ million for each drug development step, for four typical classes of drugs

We then estimate NPV, which under our assumptions is simply given by:

$$NPV = \$\ 25 - \sum COST_i * DISCOUNT_i,$$

where $COST_i$ is the i-th cost, and $DISCOUNT_i$ is the i-th discount factor, computed with a continuously compound risk-adjusted rate of 12%. We assume that the six costs in table 1 are to be sustained at times (1,3,5,7,9,10) years, which are typical lengths for the different phases.

This simple computation is reported in the column labelled NPV in Table 1. According to the initial value of the given drug of $25 millions, and with average estimated cost for different classes, we conclude that the management would start the production of the drug only if it belongs to class A. Clearly, this approach ignores the fact that the present value of the drug can change over time. We then compute the value according to the ROV valuation method, that is evaluating the multistage compound option. *Figure 1* below shows the project values for each drug as a function of volatility. We assume that the initial expected value of the revenues is again $25 million in all classes.

Our illustrative results show that the investment in the class-A drug has a positive value even for very low volatility levels, while the investments in the other three classes of drugs have a positive value only for volatility levels well above 50%. This is not surprising, both after a peer examination of the costs structure, and because of the fact that the value is increasing with volatility, which is a well known property in standard option theory. Our results show then that the impact of volatility on project valuation is very large, a conclusion which cannot be reached within the NPV approach, which is instead volatility-neutral.

Figure 1 shows that taking into account the option which is inherent in this kind of decision making, that is applying ROV approach, all the projects may be valuable, depending on the estimated volatility of the revenues. Thus, even if illustrative, our naïve computations show that the optionality of the business makes a significant difference in assessing the value

of a drug-making project, and this difference can actually determine different managing decisions, especially in high volatility regimes.

4. CONCLUDING REMARKS

The pharmaceutical industry faces a critical stage of its evolution. The peculiarity of its production makes this industry particularly prone to the development of a new approach to evaluate investment project in new drugs. Given the risky and highly costly nature of pharmaceutical research, and the rate of commercialization of new medicines, it appears necessary to adopt an approach to evaluation able to assess the value of the optionality embedded in a project, that is the opportunity to consider future events, use future information and alter the course of the project. The ROV is the only approach able to take into account the possibility to decide whether to continue, defer, or stop a project in the future as the firm gathers more info about the costs, potential revenue, and probabilities of success of a new medicine. In this paper we compare the standard NPV approach with the ROV and obtain quite different outcomes in the valuation of four classes of drugs. Drugs expected to be unprofitable under NPV, may be estimated to be profitable under ROV, depending on the assumed volatility of the revenues. This result is reached in this paper using a big dataset which includes more than 80 thousand record about almost 4 thousand pharmaceutical firms. ROV is shown to be the only approach able to consider the value of the flexibility embedded in a compound option such as the investment project in a new drug. Then the ROV should be used to support the strategic management process of a firm that is making huge specific investment in a such uncertain scenario.

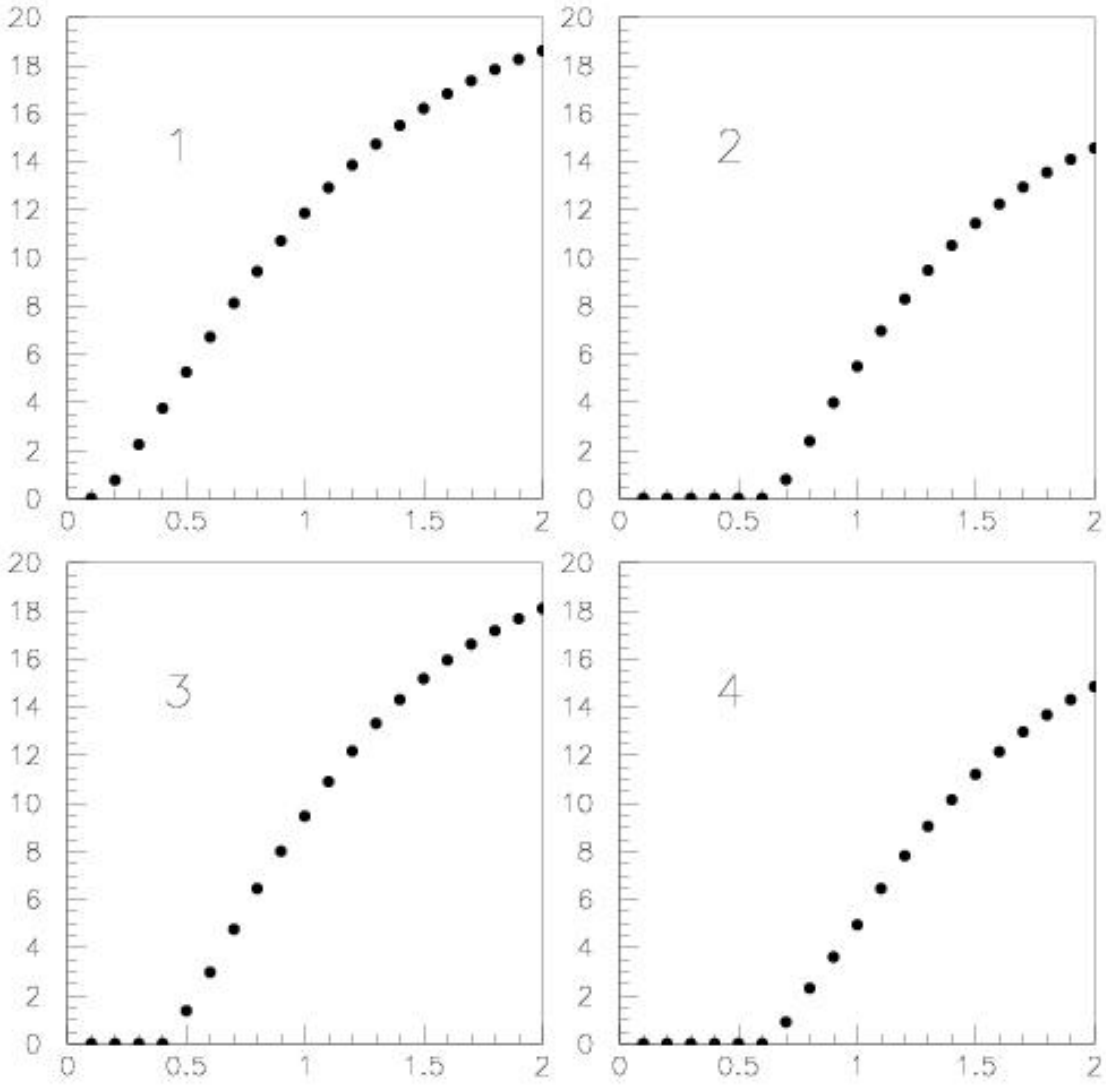


Figure 1. ROV for four typical classes of drugs

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