

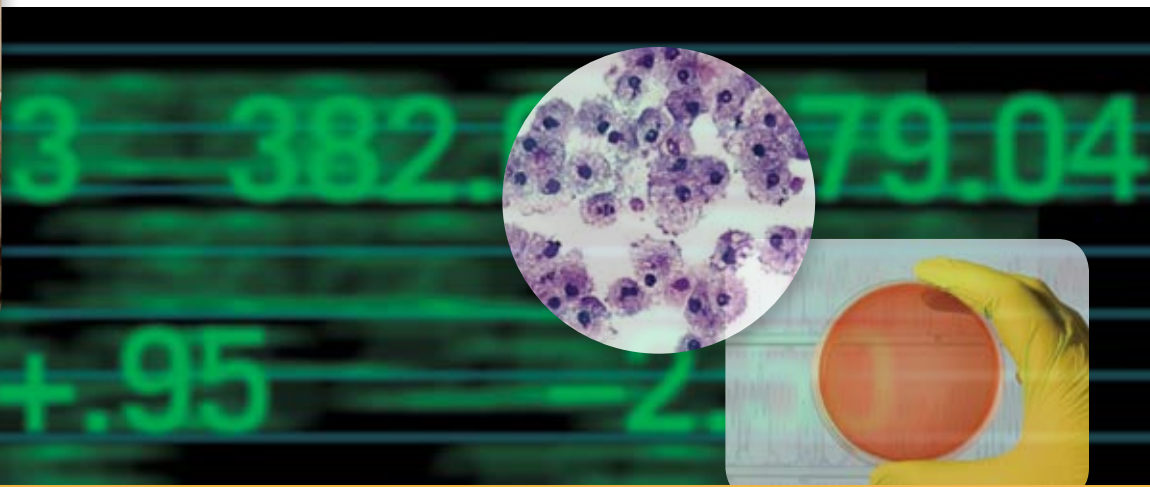
A SAFER STRATEGY:

Investing in biotech stocks is a risky business, but there's safety (as well as big rewards) in numbers.

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THE BIOTECH SECTOR is a very enticing place to put your investment dollar. After all, if a biotech company succeeds in commercializing an important drug, it can reap hundreds of millions of dollars, even billions, cheered on by its lucky investors. But the risks are many. The wise investor must weigh a given drug's potential profitability against its chances of success in clinical trials. He must balance innovation with investment security and minimize risks with an appropriately sized and diversified portfolio.





INVESTING IN BIOTECH

The sector, though historically unpredictable, has recently shown even more volatility, with valuation swings that have scared away investors. This is not a situation a sector poised for tremendous growth can afford to be in. Recent advances in *in silico* modeling, high throughput screening, the mapping of the genome, and proteomics have created more opportunities for developing new drugs than ever before.

Additionally, Big Pharma's appetite for compounds that reach proof of concept is insatiable. There will be no shortage of new drugs on the supply side. On the demand side, new emerging middle classes with more disposable income in developing areas such as China, India, Russia, and Eastern Europe offer more opportunities for newly discovered therapies, especially where a substantial unmet need currently exists.

Not to be neglected are the increasing numbers of well-off, aging, and obese baby boomers (the obesity rate has increased to 30 percent in baby boomers, compared with 19 percent in the previous generation, according to Health Canada) in developed economies who will require more diagnostics and therapies for their well-being, part of which will be paid by public health care budgets. In most developed countries, such as the United States and Canada, government health care programs cover about 40 percent of medical costs and private insurance between 40 percent and 50 percent. The rest is covered by individual cash payments.

Greater productivity, increased demand, and biopharmaceutical breakthroughs are on the horizon. With those factors come increased commercialization and marketing of medical products and services. In the context of the worldwide growth in disposable income, clarifying the risks involved results in better ways to measure and evalu-

ate them. More accurate, less volatile valuations in the biotech sector would increase the pool of willing investors and increase the overall profit of such investments.

Current Biotech Landscape

It's been said that biotech is a crapshoot. What are your chances at the biotech table? Using basic statistical analysis—primarily binomial distribution—we've attempted to shed some light on this question by investigating the risk profile of compounds in clinical development by basket size.

Simply put, the four stages of the drug development process are:

- Research and development;
- Pre-clinical testing;
- Phases I, II, and III of clinical trials;
- Filing, approval, and commercialization.

Our focus is on compounds going from phase I to phase III, in accordance with the standard business model of biotech companies, to sell or license them to Big Pharma at phase III. Throughout the article, we've used the cumulative probability of 14.9 percent, meaning that a compound will successfully pass through phases I, II, and III with a probability of 14.9 percent, unless otherwise stated.

This percentage was derived from the development probabilities, as shown in Table 1, that were obtained primarily from Dr. Joseph A. DiMasi's study "The Price of Innovation: New Estimates of Drug Development Costs," from the Tufts Center for the Study of Drug Development. These data were combined with Pharmaprojects' R&D Timelines and analysis by the Frankel Group, with some input from Decision Resources.

There are two noteworthy deviations in Table 1 from the DiMasi study. The phase I probability of 62.5 percent

TABLE 1: Tufts Study Summary

(Development probabilities of compounds successfully completing the various phases. Determined from a mix of Tufts DiMasi published data, Pharmaprojects, and analysis from the Frankel Group and Decision Resources.)

Phase	Probability of Success	Cumulative Probability
P-I	62.5%	62.5%
P-II	35.0%	21.9%
P-III	68.0%	14.9%
File	90.0%	13.4%

TABLE 2: For Baskets of Preclinical Compounds Entering Phase I, the Probability of at Least X Compounds Successfully Completing Phase III

Basket Size	1	2	3	4	5
1	14.9%	0.0%	0.0%	0.0%	0.0%
2	27.6%	2.2%	0.0%	0.0%	0.0%
3	38.4%	6.0%	0.3%	0.0%	0.0%
4	47.5%	10.7%	1.1%	0.0%	0.0%
5	55.4%	16.3%	2.6%	0.0%	0.0%
6	62.0%	22.1%	4.6%	0.6%	0.0%
7	67.7%	28.0%	7.2%	1.2%	0.1%
8	72.5%	33.9%	10.3%	2.1%	0.3%
9	76.6%	39.7%	13.9%	3.3%	0.5%

TABLE 3: For Baskets of Preclinical Compounds Entering Phase I, the Probability of at Least X Compounds Successfully Completing Phase III

Basket Size	1	2	3	4	5
10	80.1%	45.2%	17.7%	4.9%	1.0%
15	91.1%	67.7%	39.1%	17.4%	6.0%
20	96.0%	82.1%	59.0%	34.7%	16.7%
25	98.2%	90.5%	74.2%	52.3%	31.2%
30	99.2%	95.0%	84.5%	67.3%	46.9%
35	99.6%	97.5%	91.0%	78.6%	61.3%
40	99.8%	98.7%	95.0%	86.6%	73.1%

TABLE 4: For 25 Preclinical Compounds Entering Phase I, the Probability of at Least X Compounds Successfully Completing Phase III

25 Compounds	1	2	3	4	5
90% of Tufts	92.4%	71.6%	44.7%	22.4%	9.1%
Tufts	98.2%	90.5%	74.2%	52.3%	31.2%
110% of Tufts	99.8%	98.3%	93.3%	82.7%	66.3%

is supported by the other sources and is lower than DiMasi's 71 percent. We also split out the filing probability from DiMasi's combined phase III/filing category.

Excluding Big Pharma and several large biotech companies, the vast majority of biopharmaceutical companies have only a few compounds in clinical development, principally because of limited financial and scientific resources. These smaller firms were either founded as a company to develop very specific types of compounds, or they haven't raised sufficient funding to do more. As Table 2 shows, given the 14.9 percent probability of one compound's success through all phases of development, smaller baskets of compounds carry more risk for investors.

The bigger the basket size, the better the expected results. As the number of compounds in the basket increases, so does the probability of having one or more winners. A basket of four compounds gives a nearly even chance that there is at least one winner. But it also means that there is more than a 50 percent chance that there are no winners at all. And this is for four compounds.

At nine compounds, the basket starts to show a greater than 75 percent probability that we'll have one or more winners. But is this good enough? Is the risk acceptable? And what are the implications of this for companies with only one or two development projects?

Phase Success Probabilities

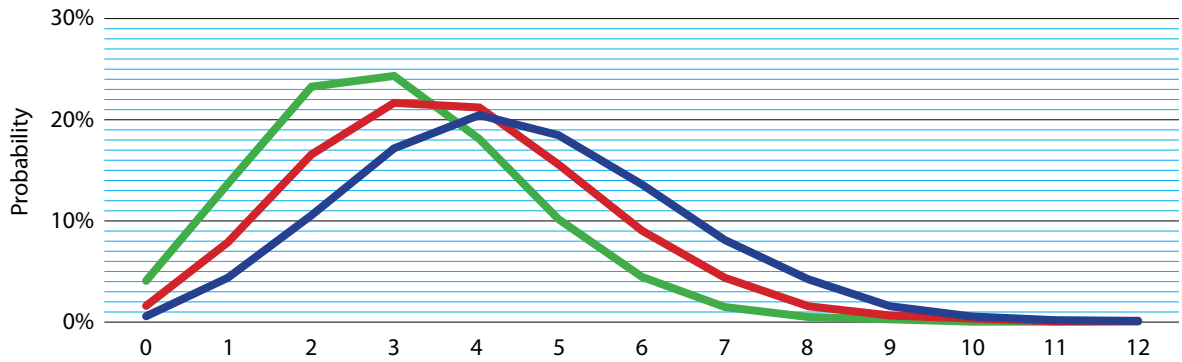
What happens where we have basket sizes that are much larger? Table 3 shows that the risk of total loss, meaning the probability of having no winners, diminishes drastically. And Graph 1 illustrates the particular smoothness of the normal curves in the 20- to 30-compound range of development projects. Where we have 25 development projects, the probability of having no winners is under 2 percent, and the chances of getting three or more winners is almost 75 percent.

The analysis so far has used 14.9 percent as the base cumulative probability of getting from phases I through III. Changing this variable has a dramatic effect on other factors in the risk calculation. Graph 2 shows the impact of a 10 percent improvement and a 10 percent degradation on a basket of 25 compounds under development, compared with the Tufts study's cumulative probability of 14.9 percent. This means each phase probability is increased by 10 percent, giving a cumulative probability of 21.8 percent instead of 14.9 percent. According to Table 4, which shows the impact on the cumulative probabilities, improving the success rates for each phase has a bigger impact in reducing risk than adding more development projects.

Going Forward

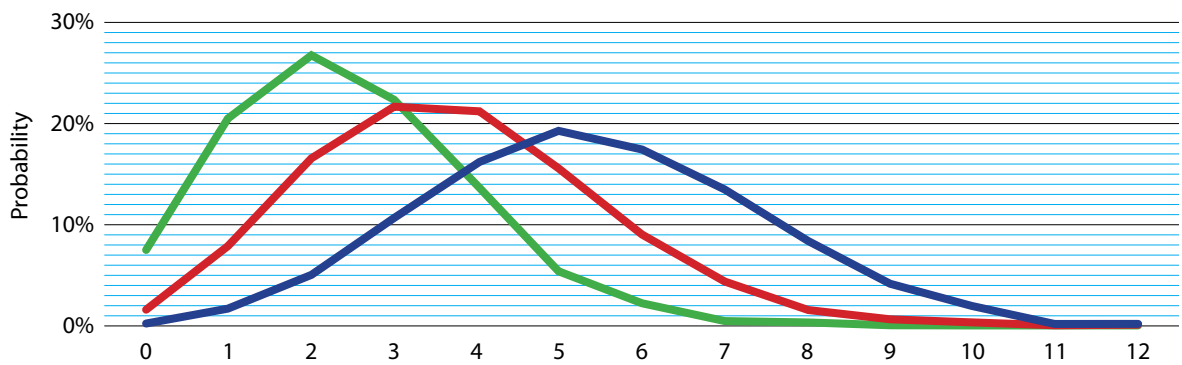
Statistical analyses like this one assume randomness and independence, and provide a way to compare basket sizes, all other things being equal. But we know that the probability of success depends not only on basket size but also on the types of compounds studied and the nature of the conditions they're meant to target. For instance, a given compound may belong to a family that has been proven to have minimal adverse effects and therefore has a much higher probability of success. Comprehensive statistics, therapeutic area, geographical region, molecular groupings by class, and so forth would be tremendously useful in further refining the evaluations.

GRAPH 1. Probabilities for Phase III Completion



20 compounds	4.0%	13.9%	23.1%	24.3%	18.1%	10.1%	4.4%	1.5%	0.4%	0.1%	0.0%	0.0%	0.0%
25 compounds	1.8%	7.8%	16.3%	21.9%	21.1%	15.5%	9.0%	4.3%	1.7%	0.6%	0.2%	0.0%	0.0%
30 compounds	0.8%	4.2%	10.6%	17.2%	20.4%	18.5%	13.5%	8.1%	4.1%	1.7%	0.6%	0.2%	0.1%

GRAPH 2. Probabilities for Phase III Completion



90% of Tufts	7.6%	20.7%	26.9%	22.3%	13.3%	6.1%	2.2%	0.6%	0.2%	0.0%	0.0%	0.0%	0.0%
Tufts	1.8%	7.8%	16.3%	21.9%	21.1%	15.5%	9.0%	4.3%	1.7%	0.6%	0.2%	0.0%	0.0%
110% of Tufts	0.2%	1.5%	5.0%	10.6%	16.3%	19.1%	17.8%	13.5%	8.4%	4.4%	2.0%	0.8%	0.2%

This study doesn't address the potential market opportunity for a given compound, the timing of its research and release, and the probability of its commercialization. These questions should be addressed in a separate study that integrates this statistical analysis, to ultimately determine risk/return levels. We're presently exploring a methodology for an actuarial valuation of compounds in clinical development in terms of probability outcomes as well as financial risk/reward elements.

We separately compared a stock-picking fund with a direct basket of compounds in development, but as expected, as long as the total number of compounds covered was the same, there was no significant statistical difference between them. For example, a stock-picking fund that has invested in a group of 10 biotech companies, which in aggregate encompasses 25 development projects in the clinic, has essentially the same chance of getting winners as a basket of 25 compounds.

There are other significant differences, though, that haven't been factored into this review. For one thing, the overheads and other related expenses for running 10 companies instead of one

differ significantly. Moreover, the general stock market risks of fickle valuations, fraudulent manipulation of stocks, and potential mismanagement are multiplied over 10 companies.

We submit that the merger of various smaller biotech entities into one provides a better risk posture for investors. Furthermore, given our results, investors interested in developing products in the clinic should invest directly in selected compounds of interest, maximizing their success and overall return on investment. The current "one in five" model, meaning that only one in five biotech companies will survive, has to go.

To prosper, the biopharmaceutical industry must consolidate its components and diversify its investment vehicles, or it's likely to lose many of its key investors to less volatile markets.

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