Putting a price on biotechnology

Many bioentrepreneurs incorrectly estimate the value of their technology by failing to account adequately for the cost, risk, and time inherent in product development.

Jeffrey J. Stewart, Peter N. Allison and Ronald S. Johnson

Venture capitalists are often wary of investing in biotechnology because bioentrepreneurs seldom provide realistic estimates of the value of their technologies. To evaluate accurately a new biotechnology, an entrepreneur must account for the future revenue from the final product, the cost and time needed to get the product to market, and the various risks faced along the way. Entrepreneurs can approach the venture community with a more rational basis for investment by expressing a biotechnology in terms of risk-adjusted net present value (*rNPV*; see "Glossary"), as discussed here. Investments, milestone payments, clinical trial costs, and royalties on sales can then be compared directly using the common currency of *rNPV*.

The numbers game

A researcher has made a scientific breakthrough that could be worth millions of dollars. To attract the investment needed to commercialize the biotechnology, the researcher must now convince venture capitalists and pharmaceutical companies of its potential. However, investors want to know what the biotechnology is worth today and will require evidence to substantiate this estimate.

Unfortunately, estimates of the value of a biotechnology are all too often clearly unrealistic. "Valuations" are typically made in the following (unrealistic) manner: "The market for our product is $2 billion per year, so if we capture only 10% of that market for 10 years, then the company is worth $2 billion today, less development costs." Perhaps as a result, the venture capital community often judges a company on the basis of its management's expertise rather than the underlying asset of real value—the biotechnology.

How, then, can we put a price tag on biotechnology? The best solution is to evaluate a biotechnology by estimating the *rNPV*. Using *rNPV*, researchers and potential investors can price the biotechnologies that they are considering selling, investing in, or acquiring. However, it should be noted that the management, science, and intellectual property surrounding a biotechnology must all be of the highest quality to interest the venture community; if any of these are seriously lacking, the biotechnology is effectively worthless.

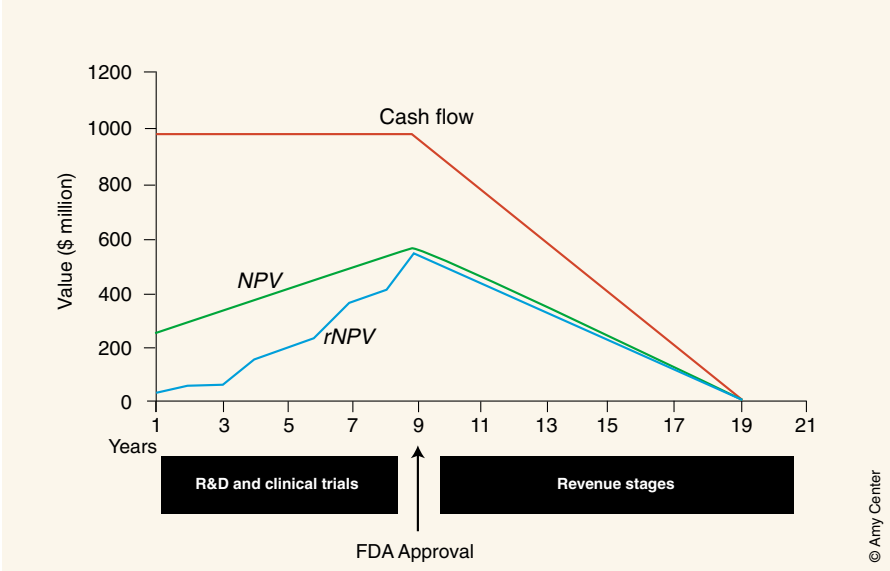


Figure 1. The value of biotechnology. Simplistic cash flows (in red), which include revenue and costs, present unrealistically high valuations for biotechnologies. A better representation is the net present value (*NPV*; in green), which discounts the revenue cash flow over time, but even the *NPV* overestimates the value of biotechnologies during all R&D stages. Risk is mitigated as biotechnologies progress through development. When this increasingly mitigated risk is taken into account, the risk-adjusted cash flow can be discounted to arrive at the risk-adjusted *NPV* (*rNPV*; in blue). The *rNPV* is an estimate of the fair price of a biotechnology. Note that *rNPV* coincides with *NPV* only once risk is mitigated.

Start at the end

The first place to start when valuing biotechnology is at the end—the projected revenue stream. The end product for most biotechnologies is a medicine, and the payoff is frequently the royalty due the biotechnology company paid from the estimated annual revenue of the product sold by a manufacturing and marketing partner (or sales of the product, if the company retains all rights). In general, annual revenues of a product are estimated using the current sales of drugs used to treat similar indications. As discussed previously[1], the take-home percentage (typically

Glossary

***NPV* (net present value):** The value of future cash flow after discounting to today's money. $NPV=x/(1+k)^n$ The net cash flow (x) is discounted annually at the discount rate (k) and is paid in n years.

Discount rate: The percentage of value that future money loses annually.

***R_0*:** Current risk mediated; the likelihood that a biotechnology will reach the market.

***R_i*:** Risk mediated after i years have passed with success.

***R_0/R_i* (risk adjustment factor):** The likelihood that a cost, revenue, milestone payment, or investment will actually materialize.

***rNPV* (risk-adjusted net present value):** The current value of a biotechnology when revenue, risk, cost, and time are all taken into account; the fair selling price of a biotechnology.

Jeffrey J. Stewart (jjs@alumni.princeton.edu), Peter N. Allison, and Ronald S. Johnson are with the life sciences investment banking firm, BioGenetic Ventures (Bellevue, WA).

Parameters for biotechnology

Average risk mitigated (when beginning the phase):	Time to complete:	Number of clinical-trial subjects:
Preclinical: 10%		
Phase 1: 20%	Phase 1: 0.5–1 year	Phase 1: 20–80
Phase 2: 30%	Phase 2: 1.5 years	Phase 2: 100–300
Phase 3: 67%	Phase 3: 3.5 years	Phase 3: 1,000–5,000
FDA approval[4]: 81%	FDA approval: 1.5 years	

Costs:

Phase 1 and 2: Clinical trials (outsourced): $8,000–$15,000 per subject
Phase 3: Clinical trials (outsourced): $4,000–$7,500 per subject
Animal studies to support phase 1: ~$500,000
Animal studies to support phase 2: ~$1 million
Animal studies to support phase 3: ~$1.5 million
FDA approval: $0.8–$1.8 million+ ($300,000 for the Prescription Drug User Fee Act II fee and the remainder for preparation of the New Drug Application (NDA); NDA-preparation costs are highly variable and depend largely on the amount and the quality of data to be presented)

Financials:

Revenue reserved for manufacturing and marketing: 40–60% (choose the high end to justify a reasonable market percentage)

Discount rate (cost of capital for biotech firms[1]; R&D risk considered separately): 20%

For "orphan drugs" (conditions affecting <200,000 people in the United States), take into account:
- Fewer clinical trials and subjects required—estimate numbers by comparing with previous trials for the indication
- 50% of clinical trial costs returned as tax credits
- Seven years of market exclusivity in the United States (even in the absence of patent protection)

divided between milestone payments and royalties on gross sales) due pre-market biotechnology developers is about 40% of gross product revenue (see "Parameters for biotechnology").

To illustrate the *rNPV* method, we have created a hypothetical scenario: A company has developed Acmed, a potential treatment for asthma. The preclinical science and intellectual property are sound, and Acmed has passed initial testing in animals and is now ready to enter phase 1 trials. The company is seeking venture funding and partnering opportunities with multinational pharmaceutical companies, so what should they charge for Acmed today?

The annual market for asthma treatments is around $5.8 billion. To estimate Acmed's market share, the product is compared with other asthma medications on the market.

Acmed payoff
$1 billion = $100 million/year for 10 years (beginning in year 9)

Competition within the asthma market is intense, and the anticipated market share for Acmed may be just 5%—a "moderate to small" share on the spectrum of market shares currently captured by pharmaceutical companies. The annual gross return of Acmed will therefore be about $290 million. Of this sum, 60% is reserved for the eventual marketing and manufacturing partner, and 5% is reserved as a royalty for the university that invented Acmed. This leaves 35%, or an annual return of about $100 million, as the royalty due the biotechnology company that develops Acmed through pre-market research and development stages.

Consultation with a patent attorney suggests that Acmed will be defended from competition for the next 18 years. The payoff for Acmed is, therefore, $100 million a year for 18 years minus the years that it takes to get the product to market. It should take eight years to carry out clinical trials and have the drug approved by the US Food and Drug Administration (FDA), and so Acmed's potential payoff for the biotechnology company is $1 billion (see "Acmed Payoff").

Acmed costs
Phase 1:
60 subjects @ $15,000 = $900,000
Phase 2 :
200 subjects @ $15,000 = $3 million
Phase 3:
2,000 subjects @ $7,500 = $15 million
Animal studies to support phase 2:
$1 million
Animal studies to support phase 3:
$1.5 million
FDA approval = $1.6 million

Total Acmed costs = $23 million

Although we have identified the theoretical payoff, the true value of Acmed is far less. Several factors consume the present value of the biotechnology in nibbles, bites, and chomps. Indeed, these factors can eat up the entire value of the biotechnology—leaving nothing for the biotechnology company or its investors. These three factors are the cost, risk, and time associated with drug development.

Factor 1—Cost

The cost of drug development can be estimated using industry standards[2,3], and any deviations from these standards must be justified. Acmed's development incurs the costs associated with additional animal studies, clinical trials, and filings to the FDA. By comparing with clinical data from currently marketed asthma drugs, it is possible to estimate how many subjects will need to be enrolled in clinical trials. Clinical trials involving asthma inhalants such as Acmed are data-intensive because multiple tests are performed over a relatively extended time period, and the trials will be conducted in the United States, so the costs for each subject will be at the top end of the range.

Overhead costs vary considerably between companies, and the value of the technology will vary in parallel. The same situation arises in other walks of life: For example, if you can repair your own house, total repair costs are lower, and the house is effectively worth more to you than it would have been to an unskilled owner. However, in this example we have left out the "overheads" and estimate Acmed's intrinsic value. The total cost of developing Acmed is $23 million (see "Acmed costs").

Factor 2—Risk

It would be grossly inappropriate simply to subtract the costs from the payoff to estimate Acmed's intrinsic value. Such a calculation would imply that each clinical trial

was a guaranteed success. Instead, clinical drug development should be regarded as a series of high-risk wagers where success in the first wager (e.g., a phase 1 trial) allows a company to make additional wagers (e.g., phase 2 and 3 trials) before reaching the ultimate payoff (e.g., a marketed drug). A company may never see the payoff, but then the company may not have to pay for a phase 3 trial. Each wager is associated with an ante (the stake or sum wagered), such as the cost of each clinical trial. The key to determining the value of the wager series is to risk-adjust both the payoff and the ante (see "Risk adjustment").

Acmed appears to be a typical pharmaceutical and is estimated to be associated with normal development risks. Each of Acmed's costs are risk-adjusted by the risk inherent to each stage (see "Risk-adjusted Acmed costs"). These risk-adjusted costs are then subtracted from the risk-adjusted payoff. Acmed's risk-adjusted costs are $8.9 million. Acmed's risk-adjusted payoff is $200 million, and so if all sales and premarket stages were completed instantaneously, the resultant risk-adjusted value of Acmed would be about $191 million.

Risk-adjusted Acmed costs

Acmed's risk-adjusted payoff PR_0 is $1 billion × 20% = $200 million

The risk-adjusted costs C_iR_0/R_i are as follows:
Phase 1: $900,000 × 20%/20% = $900,000
Phase 2: $3 million × 20%/30% = $2 million
Phase 3: $15 million × 20%/67% = $4.5 million
Animal studies to support phase 2: $1 million × 20%/30% = $670,000
Animal studies to support phase 3: $1.5 million × 20%/67% = $450,000
FDA filing: $1.6 million × 20% / 81% = $400,000

The sum of risk-adjusted Acmed costs = $8.9 million

Subtracting the risk-adjusted costs C_iR_0/R_i from the risk-adjusted payoff PR_0 as in **Equation (1)**, we calculate Acmed's current risk-adjusted value *rV*.

Acmed risk-adjusted value *rV* = $200 million – $8.9 million = $191.1 million

Factor 3—Time

A company would rather have a dollar today than a dollar tomorrow because today's dollar can be invested and earn a return, increasing its worth tomorrow. By the same argument, a dollar received tomorrow is worth less than a dollar received today. The net present value (*NPV*; see "Glossary")—a standard finance

Risk adjustment

The risk-adjusted value, *rV*, of an endeavor in which the risk changes is the payoff (*P*) times the current risk (R_0), minus each associated cost (C_i) times the likelihood (R_0/R_i) of having to pay each cost.

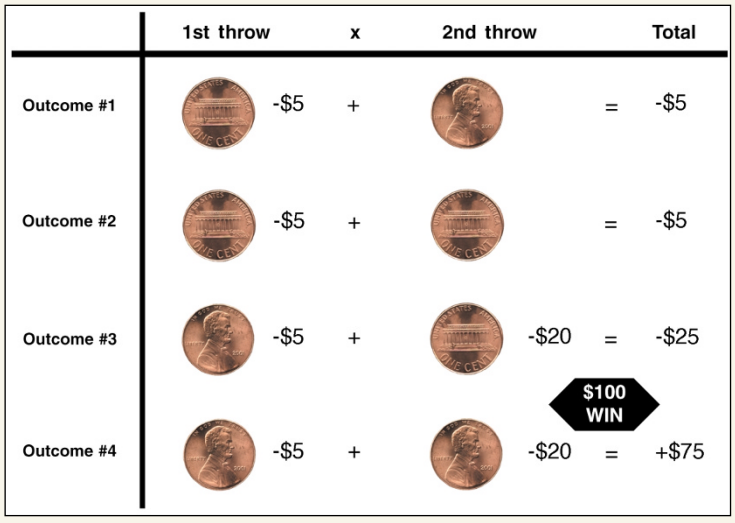
$$rV = PR_0 - \sum_{i=0}^{n} C_i R_0 / R_i \qquad \textbf{Equation (1)}$$

For example, what would be the value of the following series of coin-tossing wagers?
A coin is tossed twice. The person throwing the coin bets $5 that the first toss will come up heads. If the coin comes up heads on the first toss, he is allowed to make second wager of $20. If heads comes up a second time, the payoff is $100.
P = $100
R_0 = 25% (two tosses)
R_i = 50% (the second toss)
C_0 = $5
C_i = $20

The risk-adjusted payoff PR_0 is readily calculated as $100 × 25% = $25.
The risk-adjusted costs C_iR_0/R_i are also easily calculated. For the first ante, the risk-adjusted cost is $5 × 25% / 25% = $5. The risk-adjusted cost of the second ante is $20 × 25% / 50% = $10. The sum of the risk-adjusted costs is $15.

To calculate the current risk-adjusted value *rV* of the wager series, the risk-adjusted costs C_iR_0/R_i are subtracted from the risk-adjusted payoff PR_0.
rV = $25–$15 = **$10**

If the wager series were made many times, the bettor would net $10 on average for every time the game was played. (You can easily confirm this by averaging the four possible outcomes of flipping a coin twice.)



Acmed's *rNPV*

Acmed's *rNPV* is the *NPV* of the risk-adjusted payoff ${}_{NPV}PR_0$ minus the sum of the *NPV* of the risk-adjusted costs ${}_{NPV}C_iR_0/R_i$.

$$rNPV = {}_{NPV}PR_0 - \sum_{i=0}^{n} {}_{NPV}C_iR_0 / R_i \qquad \textbf{Equation (2)}$$

Risk-adjusted *NPV* of Acmed's payoff ${}_{NPV}PR_0$ = $23.4 million

Sum of *NPV* of the risk-adjusted Acmed costs ${}_{NPV}C_iR_0/R_i$ = $5.5 million

Acmed's *rNPV* = $23.4 million–$5.5 million = $17.9 million

equation—is what tomorrow's cash flow would be worth today.

The amount that future money loses in value each year is termed the "discount rate". Discount rates normally include many factors including risk. However, in the Acmed example, the discount rate is independent of R&D risk. We assume here that the discount rate is equivalent to the 20% internal rate of return generally expected by the primary sources of capital available to biotechnology companies—venture capitalists and large pharmaceutical companies[1]. Research and development (R&D) risk is accounted separately by development stage.

The effect of discounting can be dramatic. For example, if clinical trials began today, Acmed would not begin earning revenue for another nine years. Furthermore, the $1 billion in total revenue generated is spread out over 10 years (Acmed's has only 18 years of blocking patent life remaining). Assuming a 20% discount rate, the *NPV* of Acmed's payoff cash flow is only $117 million total (calculation not shown), and this is before any adjustment has been made for development risks. Because the payoff will not come for some time, the *NPV* of the money is much lower than one might have expected. Clearly, time is a significant factor when valuing biotechnology, especially when the brunt of clinical trial costs comes before revenue is generated. On the upside, the most expensive clinical trials take place later in development and so have significantly discounted *NPV*. In the case of Acmed, discounting reduces the pre-revenue costs of Acmed from $23 million to a present value of $12.6 million (calculation not shown).

rNPV

To calculate the true present value of biotechnologies, revenue, cost, risk, and time must be combined into a single calculation of *rNPV*. In the *rNPV* equation, Equation (2), the present value of each risk-adjusted cost is subtracted from the present value of the risk-adjusted payoff to arrive at the *rNPV* of the biotechnology.

By adding together all of Acmed's costs and risks and then discounting for time, the true *rNPV* is finally revealed. Today, Acmed is worth about $18 million (see "Acmed's *rNPV*").

Investments

The *rNPV* is the common currency for making direct comparisons of royalties and investments.

When an investment (*I*) purchases nondiluted equity (*E*) in a company, the company is increased in value by the *rNPV* of the investment ${}_{NPV}IR_0/R_i$. The percentage of the new *rNPV* now purchased by the investment is the fair value of the investment in terms of company equity.

$$E = \frac{\sum_{i=0}^{n} {}_{NPV}IR_0 / R_i}{rNPV + \sum_{i=0}^{n} {}_{NPV}IR_0 / R_i} \qquad \textbf{Equation (3)}$$

In the case of the milestone payments proposed for Acmed, the three milestones have *rNPV* of $5 million, $5.6 million, and $2.6 million. The pharmaceutical company is also assuming half the costs of clinical trials. Previously, the *rNPV* of clinical trial costs was calculated at $5.5 million. The pharmaceutical company's milestones represent an investment with an *rNPV* of $5 million + $5.6 million + $2.6 million + ($5.5 million/2) = **$15.9 million**

$$ {}_{NPV}P'R_0 = {}_{NPV}PR_0 - \sum_{i=0}^{n} {}_{NPV}IR_0 / R_i \qquad \textbf{Equation (4)}$$

In return for the *rNPV* of $15.9 million, the pharmaceutical company would fairly receive a commensurate amount of the *rNPV* of the payoff ${}_{NPV}PR_0$ (the royalty due the developers of Acmed). Acmed's ${}_{NPV}PR_0$ was previously calculated to be $23.4 million. The pharmaceutical company has purchased fairly about 68% of Acmed's royalty (which was 35% of gross revenues). This leaves a new royalty ${}_{NPV}P'R_0$ on gross revenues to Acmed's developers of **11%.**

Investment

Estimates of *rNPV* can be useful in deal-making scenarios: For example, if a company wants to raise money from investors, how much of its equity is it fair to give away in return? If a pharmaceutical company wants to pay milestones and a royalty on sales, what should this royalty be? Both investments and milestone payments can be calculated simply by reducing each to the common currency of the *rNPV*.

For example, a venture capital company is willing to invest $9 million in Acmed.

Note: A Microsoft Excel spreadsheet for calculating the rNPV is available as supplementary information in the Web Extras page of Nature Biotechnology Online (http://biotech.nature.com/ web_extras).

The spreadsheet version accounts costs by calculating the risk-added costs rather than risk-adjusted costs. Risk-added costs are C_i/R_i; R_0 is multiplied later to arrive at the risk-adjusted costs. This rearrangement of the equation yields the same rNPV.

Notwithstanding all the fancy math, the real way these tech companies are valued is based on comparables … the real value is determined on an arm's-length negotiation

Today's $9 million investment has an *rNPV* of $9 million, which is added to Acmed's *rNPV* ($18 million) to yield a new *rNPV* of $27 million. The venture capital contribution represents a third of the assets of the now-capitalized project, so a fair value for the venture capital investment would be about 33% of Acmed. (Although we will not develop this method here, the equity must be increased to account for company overheads and anticipated equity dilutions.)

In a second scenario, a pharmaceutical company is willing to in-license Acmed for milestone payments of $5 million today, $10 million on entering phase 2, $15 million on entering phase 3, and a royalty on gross sales. Also, the pharmaceutical company will split Acmed's remaining development costs. What would be a fair royalty?

By calculating the *rNPV* of each milestone and the clinical trial costs borne by the pharmaceutical company, the pharmaceutical company has made an investment with an *rNPV* of $15.9 million. In return, it would be fair to give the pharmaceutical company 68% of the $23.4 million *rNPV* of Acmed's payoff. Acmed's developers would retain 32% of the 35% R&D royalty on Acmed's gross revenue—about an 11% royalty.

Selling price versus fair value

Using the *rNPV*, the inventor and investor can arrive at a realistic value of a biotechnology (see Fig. 1). By adopting an auditable valuation approach, biotechnology companies may be able to seek debt financing even at early R&D stages. However, as Steven Burrill, chief executive officer of Burrill & Company (San Francisco, CA) cautions:"Notwithstanding all the fancy math, the real way these tech companies are valued is based on comparables ... the real value is determined on an arm's-length negotiation." Even so, knowing the underlying value of a biotechnology can be critical for getting the best deal from either side of the negotiation table. The same applies when buying or selling a house: You get the best deal when you know the house's value based on an accurate appraisal. Likewise, you can set an advantageous price by knowing the fair value of the biotechnologies—the *rNPV*.

Acknowledgments

We thank D. Constable of Hollister–Stier Laboratories (Spokane, WA), S. Litwin of the Fox Chase Cancer Center (Philadelphia, PA), M. Sanders of ProPharma Partners (Hayward, CA), S. Burrill of Burrill & Company (San Francisco, CA), and S. Trimbath and P. Wong of the Milken Institute (Santa Monica, CA), whose input was invaluable; we also thank J. Wadsack of the New Jersey Virtual Campus (Chatham, NJ) and J. Johnson (Moscow, ID), without whose support this publication would not have been possible.

1. Moscho, A. *et al.* Deals that make sense. *Nat. Biotechnol.* **18**, 719–722 (2000).
2. US Congress, Office of Technology Assessment. Pharmaceutical R&D: costs, risks and rewards, OTA-H-522. (US Government Printing Office, Washington, DC; February 1993).
3. PhRMA. The pharmaceutical industry profile 2000. Pharmaceutical Research and Manufacturers of America. http://www.phrma.org/publications/publications/profile00/
4. US Food and Drug Information Office of Planning. FY 2000 Performance Report to Congress for the Prescription Drug User Fee Act of 1992 as reauthorized and amended by the Food and Drug Administration Modernization Act of 1997 (2001). http://www.fda.gov/ope/pdufa/report2000/default.htm