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BIOTECH ASSET VALUATION METHODS: A PRACTITIONER'S GUIDE

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Biotech innovations lead to the development of life-saving drugs and vaccines. However, bringing a new drug to market is an expensive, risky, and time-consuming process. According to one survey, the probability that a drug that has completed pre-clinical trials, would successfully pass all three stages of clinical trials (the primary source of regulatory risk) and receive the FDA's approval to be commercialized was less than 12%, is expected to take nearly 10 years on average, and costs $1.4 billion (in 2013 dollars, including the cost of compounds abandoned during testing). Biotech startups, which undertake such drug development efforts, typically have no existing revenue streams, and rely heavily on venture capitalists (VCs) for funding. This requires the VC and the startup's founders to agree on the value of the drug in development (or equivalently, the startup's value as the drug in development may be the startup's only asset).

This article is a primer on the three most common valuation methods used to evaluate biotech investments (the rNPV, VC, and real option methods). As we discuss, these methods yield significantly different values because they account for a drug's regulatory risks very differently. If the VC uses one method and the startup uses another, the startup's founders may be unwilling to give the VC the equity stake it demands in exchange for its capital contribution which could stop VC funding, and potentially prevent a company from launching a life-saving drug. It is thus critical for practitioners (biotech entrepreneurs and VCs) to understand the key drivers of value using the alternative valuation methods, and the manner in which regulatory risks are considered in each method. Understanding these differences can help biotech startups reach common ground in valuation negotiations with VCs.

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Furthermore, by using a valuation method that explicitly incorporates the probabilities of success associated with each clinical trial phase (as in the rNPV method), a startup can compare bids it may receive for its biotech asset. Such bids usually include an upfront payment, and additional milestone payments that are contingent on the drug candidate successfully completing its Phase I, Phase II, and Phase III trials, and additional milestone payments associated with the drug's revenue reaching a specified level. Differences in such upfront and milestone payments across bids make it challenging for a startup to compare all bids on a apples-to-apples basis. Our practitioner's guide offers a readily implementable solution to this problem.

1 Introduction

The U.S. has the world's costliest healthcare.[1] In 2019, even before the dramatic impact of the Covid-19 epidemic on the country's health sector,[2] health-care spending in the U.S. made up 16.77% of GDP ($3.58 trillion)[3] far exceeding the shares of other developed nations. Per capita health-care spending in the U.S. was more than doubled between 2000 and 2019. The U.S.'s per capita health-care spending in 2019 ($10,661)[4] was more than double the per capita health-care spending in other developed countries such as France, U.K., Germany, and Canada.[5] Policymakers and academics have identified several reasons for the high cost of healthcare in the U.S.,[6] including limited opportunities for productivity improvements and innovations that may result in better health-care quality but do not reduce costs.[7]

The future quality and affordability of healthcare depends on new medical innovations and the development of new drugs (or new molecular entities (NMEs)).[8] Drug development, which is often undertaken by startups with no revenues from existing product sales, is a lengthy and expensive process that entails significant regulatory risks. The drug candidate must undergo pre-clinical trials *in vitro* and in animals and then typically three phases of clinical trials, each of which entails significant research and development (R&D) costs and regulatory approval from the U.S. Federal Drug Agency (FDA).[9] After successfully completing all the clinical development phases, the drug developer (company) submits a New Drug Application (NDA) to the FDA. The company can market the drug for approved uses only after its NDA is approved. According to DiMasi *et al.*'s (2016) survey, the total cost of developing a new drug to the point of marketing approval was $2.58 billion in 2013 dollars[10]; the time between the start of clinical testing and submission of an NDA was estimated to be 80.8 months[11]; and the likelihood that a drug that had reached the Phase I clinical trial stage would receive NDA approval was 11.83%.[12]

To fund such expensive drug development, biotech startups raise capital from government agencies, universities and, critically, venture capitalists (VCs). In 2021, VCs provided $36.6 billion of capital to startups in biotech and pharma startups, making this sector the third-most VC-backed sector behind software and commercial services.[13] In 2021, VCs provided more than $5 billion in first-round funding (through 296 deals) to biotech and pharma startups, making this sector second in raising first-round VC capital

that year, behind only the software sector which received $6.6 billion in 2021.[14] Between 2009 and 2021, VC funding to biotechnology companies increased by over 330%, from $1,933.4 billion to $8,336.0 billion, while VC funding to companies engaged in drug discovery increased even more, from $1,672 billion to $23,281 billion—an increase of nearly 1300%.[15]

Despite its relatively small size compared to the public equity market,[16] the VC industry has played a critical role in fostering innovation and growth in the U.S. over the last 50 years. Many VC-funded companies, such as Apple, Google, and Facebook, to name but a few, have had spectacular success.[17] Perhaps the most dramatic example of a VC-backed biotech success story is that of Moderna, a company described as a "civilization saver" for developing its Covid-19 vaccine.[18] In November 2020, only a few months after the start of the Covid-19 pandemic, Moderna, then only 10 years old, announced that it had developed a vaccine for the virus that was 94% effective. Moderna's vaccine, and another by Pfizer (a large pharmaceutical company), was a critical factor in the war against Covid, which has caused the world's worst health and economic crisis in the past century.[19] Unusually, Moderna was not just a VC-backed startup. It was *created* by VCs, as part of a VC incubator program run by Cambridge, Mass.-based Flagship Pioneering.[20]

Given their limited lives (typically 10 years), VC funds seek quick high returns on their equity investments in startups. A VC's (percentage) equity stake in a startup is calculated as its capital contribution divided by the startup's "post-money" value, which equals the sum of the VC's capital contribution and the startup's "pre-money" valuation.[21] As it is not publicly traded, the VC (and the company's management) must estimate the startup's pre-money value, accounting for the drug candidate's expected future sales, development costs and regulatory risks.[22] Such an evaluation is complex because analyzing each of these factors in turn requires an evaluation of other factors. For instance, to forecast a drug candidate's future sales one must assess, among other things:

(1) *The target market's size* using either a bottom–up or a top–down approach. The bottom–up approach "focuses on the number of patients and calculates market size by evaluating the following parameters: number of patients; number of patients receiving treatment; and price of treatment per patient." The top–down approach estimates the drug candidate's future sales by extrapolating sales of existing products in the same therapeutic class.[23]
(2) *The new drug's market share* which is affected by factors such as "competition from available treatments and products, as well as those in development; pricing; relative advantages compared with current treatments (i.e., cost/benefit analysis); dosage and formulation of the candidate; clinical evidence of efficacy and safety; and patient/physician product loyalty."[24]
(3) *The market growth rate* which depends on future competitive threats such as potential alternative treatments and entry of generic substitutes which depend on the drug's patent protection[25] and/exclusivity period.[26]
(4) *The drug's projected price* which depends on factors such as the new drug's efficacy relative to existing products; the willingness of patients and doctors to switch to the new, more expensive drug or to generic substitutes that may become available in the future; and pricing regulations and government policies.[27]

Assessing a drug candidate's expected development costs requires information about several

factors (e.g., the stage of the drug's development, and its likelihood of success) about which the company's management may be better informed that the VC.[28]

Given such information asymmetry and the significant costs and risks of drug development, VCs either avoid investing in early stage biotech companies or estimate the company's pre-money value significantly below that the company's own estimate, and correspondingly demand an equity stake[29] which the company may not find acceptable. As a result of such a difference of opinion (or "valuation gap") about the company's (or its drug candidate's) value, VC funding of a start-up's drug development efforts related to a potentially life-changing drug could stop. This could prevent a critical drug from ever coming to the market, which would be a loss to society.[30] Understanding the reasons that such a valuation gap may arise is thus critical.

This article offers a primer on commonly used methods to value biotech assets (or equivalently a biotech startup which may have only a single drug in development), namely (1) the "risk-adjusted" net present value (or rNPV method)[31]; (2) the basic VC valuation formula, which requires, as a first step, a future valuation of the company based on a valuation multiple[32]; and (3) the real options method. As we discuss, even when the VC and the startup agree about a drug candidate's expected future sales, a significant valuation gap can arise because different valuation methods account for drug development (or regulatory) risks differently. Our sensitivity analyses indicate that the size of this valuation gap depends, among other things, on the drug's current development status; each clinical trial's expected duration and cost; the phase specific success probabilities; and the valuation multiple and hurdle rate that the VC uses to value the drug.

In Sections 2 and 3, we discuss the rNPV and VC valuation methods using an illustrative example as a base case. In Section 3 we conduct sensitivity analyses using these methods which illustrates how the valuation gap (i.e., the difference in the biotech asset's value[33] under the VC and rNPV methods) at each stage of the drug's clinical development can change when the models' risk and cash flow parameters are changed. As part of our sensitivity analysis, we consider an alternative post-commercialization sales trajectory for the drug (the "peak sales" model) in which we assume that the drug's first year sales are significantly lower than in the base case, but the sales growth is significantly higher compared to the base case. In Section 4, we discuss the real option valuation method and compare its findings to the VC and rNPV methods. As we discuss, the real option method recognizes that the value of the drug's future prospects is not fixed, as assumed in traditional valuation methods, and that the company has the option to stop the drug development project at particular stages, if the cost of continuing the project at that stage is greater than the project's continuation value at that stage. Section 5 concludes.

2 The rNPV Method

Like the standard DCF method, the rNPV method also explicitly forecasts the drug's development future revenues and operating costs and calculates the asset's present value as the sum of the present values of its future cash flows, which are calculated using an appropriate cost of capital that reflects only the asset's systematic risk or beta that cannot be diversified away (i.e., the extent to which the asset's future expected cash flows are correlated with overall market returns) as the well-known Capital Asset Pricing Model ("CAPM") dictates.[34] As the illustrative example below shows, the rNPV method accounts for the drug's

regulatory risks (which are not correlated to the market) by multiplying the (1) present value of each phase-specific R&D cost by the probability of the drug reaching that phase of development; and the drug's post-commercialization value by the probability of the drug getting regulatory approval to go to market.[35]

2.1 A hypothetical example

Assume a company's NME candidate has completed its pre-clinical trials and is about to start its Phase I clinical trial (date 0). The company needs to raise $50 million of VC capital. To value the asset the company has the following model parameter values:

(1) The drug's phase success probabilities, i.e., the likelihood that the drug candidate will successfully complete a phase. If the drug fails at any phase, then its further development is expected to stop.
(2) The time required to conduct R&D at each phase or receive approval for going to market after submitting the NDA.
(3) The R&D costs at each clinical trial phase which will be incurred at the start of that phase, and the NDA submission fee.

Even though in practice these parameters can vary significantly across drugs for a host of reasons, as a starting point (the base case) the company has decided to use DiMasi *et al.*'s (2016) survey results for phase success probabilities, time to next phase (which are rounded to the nearest year) and DiMasi *et al.*'s (2016) R&D costs in 2013 dollar terms including the cost of compounds abandoned during testing, which the company has adjusted for inflation through 2022. The company's estimates of the NDA submission cost and duration of the NDA submission stage of the project rely on estimates in a 2014 study prepared for the Office of Assistant Secretary for Planning and Evaluation (ASPE).[36] The parameter estimates for these regulatory risks and R&D costs are summarized in Table 1.[37]

As Table 1 indicates, if the drug's clinical development proceeds smoothly then an NDA can be submitted in 8 years and the drug can be launched immediately after getting NDA approval, which is forecast to be about 10 years after the start of Phase I trials.[38,39]

The drug's first year of sales and profits are assumed to start 1 year after the drug gets FDA approval (i.e., 11 years from the start of Phase I trials). The drug's post-commercialization cash flow, growth rate, and the cost of capital (discount rate) are summarized in Table 2.[40]

As shown in Table 2, in the first year, the company's sales, projected operating profit (or

Table 1 Phase success probabilities, R&D costs and mean time to next phase.

Drug development phase	Phase success probability	Probability of occurrence	Di Masis Pre-Tax Median R&D Cost estimate (2013 dollars)	Inflation adjustment	Inflation adj. R&D Cost (2023)	DiMasi's Mean time to next phase estimate (months)	Mean time to next phase (in years, rounded)	Phase start date	Time to NDA submission (years)
Phase I	59.52%	100.0%	$ 17.3	1.2	$ 38	19.8	2	0	8.00
Phase II	35.52%	59.5%	$ 44.8	1.2	$ 99	30.3	3	2	6.00
Phase III	61.95%	21.1%	$ 200.0	1.2	$ 440	30.7	3	5	3.00
NDA submission	90.35%	13.1%	$ 2	0.2	$ 2	18	2	8	0.00
Approval		11.8%					10		

Table 2 Cash flow, discount rate, and growth rate assumptions.

Date of first year of sales	11
First year of sales (in millions)	$ 850
Operating cost (% of sales)	38%
Operating profit (in millions)	$ 527
Tax rate	20%
Tax (first year)	105.4
First year of after-tax cash flow (in millions)	$ 421.6
No. of years of sales	10
Annual cash flow growth rate	3%
Discount rate	10.5%

earnings before interest tax and depreciation, EBITDA), and its net earnings (after tax) are expected to be $850 million, $527 million, and $421.6 million, respectively.

Before discussing the rNPV method, for illustrative purposes, we first calculate the asset's value using the traditional discounted cash flow (DCF) or equivalently, the net present value (NPV) method (see Section 2.2). We then discuss the adjustments made to the NPV method under the rNPV method in subsection B. In sub-section C, we calculate the company's pre-money value using a standard VC valuation formula and the equity interest the VC would demand in exchange for a $50 million capital contribution, and the equity interest that you, as the company's owner would consider acceptable given your reliance on the rNPV method.

2.2 The NPV of the asset at the start of Phase I

The NPV of the asset is calculated as: (a) the present value of the project's expected future cash flows less; and (b) the present value of the R&D and NDA submission costs.

The PV of the asset's future cash flows at the start of Phase I can be calculated as the value of a growing 10-year annuity as of date 10, discounted for 10 years to the present date (start of Phase I trials) using a discount rate of 10.5%.[41]

That is, the PV of the asset's future cash flows at the start of Phase I trials (in $ millions) equals:

$$\frac{421.6}{(0.105-0.03)}\left[1-\left(\frac{1.03}{1.105}\right)^{10}\right]\left(\frac{1}{(1.105)^{10}}\right) = \$1{,}045.60. \quad (1)$$

The PVs of R&D costs at Phases I through III and the NDA submission fee at the start of Phase I equals $211.55 million are shown in Table 3.

Thus, the asset's NPV at the start of Phase I equals **$834.05 million**.[42]

Table 3 Present value of R&D and NDA submission costs at start of Phase I trials ($ millions).

	Inflation adj. R&D Cost (2023 dollars)	Phase start date	Discount rate	Discount factor	PV of R&D cost at start of Phase I
Phase I	$ 20.8	0	10.5%	1.00	$ 20.76
Phase II	$ 53.8	2	10.5%	0.82	$ 44.03
Phase III	$ 240.0	5	10.5%	0.61	$ 145.68
NDA Submission	$ 2.4	8	10.5%	0.45	$ 1.08
TOTAL					$ 211.55

However, this calculation does not consider the possibility that the drug's development may be halted before market launch if it fails to pass each clinical trial. If that occurred then the company would not incur the R&D costs for subsequent trials either. The key difference between the NPV and rNPV method[43] discussed below is that in the latter the costs and future cash flows are adjusted for their respective probabilities of occurrence.

2.3 The rNPV of the asset at the start of Phase I

As the company is already at the Phase I trial launch stage, it is reasonable to assume that the R&D cost for that stage will be incurred with a probability of 100%. However, the probability of the R&D costs being incurred at subsequent phases is contingent on the drug candidate's success through all prior trial phases. That is, as shown in the seventh column of Table 4, the probability that the company will:

- Incur R&D costs at Phase II equals 59.52%, which is the probability that the drug candidate's Phase I trial is successful (see "Phase Success Probability" column in Table 1).
- Incur R&D costs at Phase III equals 21.14%, which is the probability that the drug candidate's Phases I and II trials are both successful.[44]
- Incur the NDA submission cost equals 13.1%, which is the probability that the drug candidate's Phases I, II, and III trials are all successful.[45]

Multiplying these probabilities by the present values of the corresponding phase-specific costs yields the expected present values of the R&D and NDA submission costs shown in the last column of Table 4. The total *expected* PV of all costs of development equals **$77.91 million.**

Multiplying the PV of the asset's future cash flows at the start of Phase I ($1,045.60 million) by the probability that the drug will be commercialized (11.8%[46]) yields an expected PV of cash flows of **$123.7 million.** Subtracting the expected PV of R&D costs at the start of Phase I ($77.91 million) from this sum yields the rNPV of the asset at the start of Phase I, **$45.8 million.**

Before discussing other valuation methods, it is helpful to note that the rNPV method can help a company evaluate bids for its drug candidate from other firms with related drugs under development. Such bids usually include an upfront payment, clinical milestone payments payable once the

Table 4 Present value of expected R&D and NDA submission costs ($000s).

	Inflation adj. R&D cost (2023 dollars in millions)	Phase start date	Discount rate	Discount factor	PV of R&D cost at start of Phase I	Probability of occurrence	Expected PV of R&D cost at the start of Phase I
Phase I	$ 20.8	0	10.5%	1.00	$ 20.76	100.0%	$ 20.76
Phase II	$ 53.8	2	10.5%	0.82	$ 44.03	59.5%	$ 26.21
Phase III	$ 240.0	5	10.5%	0.61	$ 145.68	21.1%	$ 30.80
NDA Submission	$ 2.4	8	10.5%	0.45	$ 1.08	13.1%	$ 0.14
TOTAL					$ 211.55		$ 77.91

Table 5 Hypothetical bids with milestone payments.

Bids ($ millions)	*A*	*B*
Upfront	$ 5.00	$ 40.00
Phase I completion	$ 5.00	$ 2.50
Phase II completion	$ 5.00	$ 2.50
Phase III completion	$ 5.00	$ 2.50
Receipt of first year of revenue	$ 80.00	$ 20.00
TOTAL	$ 100.00	$ 67.50

drug had successfully completed its Phase I, Phase II, and Phase III trials, and a one-time, sales milestone payment payable the first time the drug's revenues reached a specified level. Differences in the upfront and milestone payments across bidders make evaluating all bids on a apples-to-apples basis challenging for startups. The rNPV method offers an easily implementable solution to this problem. For instance, consider two bids, A and B for the hypothetical drug under development we discussed above. The bids milestone payments are shown in Table 5.

Even though Bid A's total (undiscounted or risk-adjusted) payments ($100 millions) exceeds that of Bid B ($67.50 million), these numbers are not comparable as they do not account for the timing and risks associated with the various milestone payments. To compare the bids, it is necessary to calculate their rNPVs. Despite its lower total payment, in rNPV terms, Bid B is higher ($51.4 million compared to Bid A's rNPV of $41.1 million,[47] which is below the drug's rNPV.[48]

3 The VC Valuation Method

A VC's approach to valuing a startup (or a biotech asset) and correspondingly, the equity stake it would require for its capital contribution, typically involves the following steps[49]:

First, the VC determines its "exit date," when it plans to sell its stake to an acquiror or the public if the company successfully completes an initial public offering (IPO). In this case, let us assume that the VC's projected exit date is when the drug generates its first year of sales (i.e., date 11, or 11 years after the start of Phase I trials).

Second, the VC estimates the company's enterprise value (EV) *at the exit date* based on a valuation multiple, such EV to sales, EV to EBITDA, or EV to peak sales. For instance, as of January 2022, biotech companies' enterprise value (EV) to sales, and EV/EBITDA multiples were estimated by Damodaran to be 7.06,[50] and 11.29, respectively.[51] As shown in Table 2, the estimates for the company's first year sales and EBITDA are $850 million and $527 million, respectively. Thus, a VC would value the hypothetical company at about $6 billion *as of the exit date* based on the company's projected first year sales or EBITDA.[52]

Third, the VC calculates the startup's present value by discounting the estimated enterprise value at the exit date to the present date using the VC's hurdle rate or target rate of return as the discount rate. As Damodaran (2009) notes, VCs typically use a high hurdle rate of return to capture "both the perceived risk in the business and the likelihood that the firm will not survive. Since the latter is high, venture capital required rates of return tend to be much higher than the discount rates that we see used with publicly traded companies."[53] According to Damodaran (2009), VC's hurdle rates range from 50% to 70% for startups and from 35% to 50% at the second stage by when the company is generating a profit. In contrast, the actual returns that VCs had earned on average over the past 20 years (as of 2007) was far more modest (21.4% and 14.5% for early stage and later stage investments, respectively).

As the subject company in this example is at the startup stage it is reasonable to assume that the VC would use a hurdle rate of 60% which is the mid-point of Damodaran's (2009) estimate of the range of the hurdle rates that VCs use for early stage investments. Discounting the VC's estimated EV as of the exit date ($6 billion) to the present (start of Phase I trial date) using a VC discount rate of 60%, the VC's pre-money valuation of the company in PV terms is calculated as:

$$\frac{\$6000}{1.6^{11}} = \$\mathbf{34.11\ million}. \qquad (2)$$

That is, given the above parametric assumptions, according to the basic VC valuation formula, the company's value ($34.11 million) would be 26% lower than its rNPV value of $45.8 million.

Fourth, given the company's pre-money valuation estimate, if the VC contributed $50 million the company's post-money valuation would equal $84.11 million (the sum of the VC's capital contribution and the company's pre-money value), and the VC would demand a 59.4% ownership interest, calculated as the VC's capital contribution ($50 million) divided by the company's post-money valuation ($84.11 million). In contrast, given the company management's higher post-money valuation estimate of $95.8 million,[54] the company's management would consider a 52.2% stake in exchange for a $50 million capital contribution appropriate.[55]

4 Sensitivity Analyses

4.1 Changes in the drug's valuation under the rNPV and VC methods as its development progresses (base case results)

The above discussion examined the valuation of the biotech asset at the start of Phase I. Repeating those calculations (holding all parameters constant at their base case values) the drug candidate's rNPV (and VC valuation) can be calculated at the later stages of development (viz., at the start of Phase II, III, or the NDA submission date) in an analogous manner. These results are summarized in Table 6.

Three observations can be made regarding the results shown in Table 6.

First, the drug candidate's value increases under both the rNPV and VC valuation methods the further along it is in development (and correspondingly), the closer it is to commercialization.

Second, the pre-money valuation difference under the two methods widens as the drug progresses from Phase I through Phase III. The VC valuation drops from 74% of the rNPV value at Phase I to 70% at Phase III. This result follows from the fact that the rNPV valuation explicitly

Table 6 rNPV and VC valuations at later stages of the drug's development: Base case (values in $ millions).

	rNPV			VC Values	Comparison of rNPV and VC valuation	VC's Equity interest			
Development phase	Exp. PV of costs at phase launch	Expected PV of after-tax cash flows at phase launch	rnPV at Phase launch	VC Values	VC value/rNPV value	VC contribution	VC equity interest (based on VC valuation)	VC equity interest (based on rNPV valuation)	Difference
Phase I	$ 77.91	123.73	$ 45.82	$ 34.11	74%	$ 50.00	59.4%	52.2%	7.3%
Phase II	$ 117.23	253.82	$ 136.59	$ 87.31	64%	$ 50.00	36.4%	26.8%	10%
Phase III	$ 241.10	964.16	$ 723.05	$ 357.63	49%	$ 50.00	12.3%	6.5%	6%
NDA submission	$ 2.4	2099.87	$ 2,097.47	$ 1,464.84	70%	$ 50.00	3.3%	2.3%	1%

accounts for R&D costs, whereas the VC valuation method does not. Under the rNPV method, as the drug candidate completes a clinical trial phase and moves to the next phase, the R&D costs the company has incurred in the prior phase(s) are no longer value-relevant because the drug candidate's present value at any stage is based only on its expected *future* cash flows and remaining costs. In contrast, under the VC valuation method, the value of future revenues and all development costs are subsumed in the assumed valuation multiple as of the exit date, and all risks associated with the drug development project are captured by the use of a high hurdle rate. Thus, the increase in the asset's value due to a reduction in its remaining R&D costs as its development progresses is a nuance that is not captured in the VC method.[56]

Third, notwithstanding the growing difference in the company's pre-money valuation under the VC and rNPV approaches, the difference in the VC's estimated equity stake in exchange for a $50 million contribution becomes smaller as the drug's development progresses because the asset's valuation increases significantly under either method. For example, at the launch of Phase I, a $50 million VC capital contribution would imply an equity interest of 59.4% under the VC valuation method, but only a 52.2% equity interest under the rNPV method (a 7% difference). In contrast, at the NDA submission stage, a $50 million VC capital contribution would imply an equity interest of 3.3% under the VC valuation method and a 2.3% equity interest under the rNPV method (a difference of just 1%).

4.2 Changes in the drug candidate's valuation under the rNPV and VC methods as its development progresses (peak sales multiple analysis)

In the base case of our illustrative example, the first year sales were assumed to be $850 million, growing modestly thereafter for 10 years at 3% per year. However, a new drug's sales could be low in the first year, then grow rapidly to peak in 6 or 7 years, then stabilize and ultimately drop significantly as competitors enter the market and the drug loses it patent protection. Therefore, in valuing biotech assets practitioners sometimes use a variant of the sales multiple, viz., the "peak sales" multiple. To consider how the valuation gap between the VC and rNPV methods is affected under this approach, we revise the drug candidate's post-commercialization sales assumptions in the illustrative example as following:

(1) First year sales equals $170 million, or 20% of the base case first year sales estimate of $850 million.
(2) Sales growth is 100% annually for the first 6 years and then zero for the remaining 4 years of sales.
(3) The VC values the company using the same sale multiple as in the base case (7.06)[57] but applies this multiple to peak sales rather than first year sales.

Table 7 shows the drug's projected sales and after-tax cash flows under the above assumptions. As the table shows, the drug candidate's sales are expected to peak at $5,440 million in the sixth year of sales (i.e., at date 16).

Given the above set of cash flow projections, the valuation of the drug using the rNPV method and the VC method at various clinical phases is summarized in Table 8.

Comparing the results shown in Tables 6 and 8 indicates that the drug candidate's rNPV is significantly higher if sales are expected to increase rapidly in the first 6 years of production, even if the first year sales are only 20% of the base case level. For example, as shown in Table 8, the drug candidate's rNPV at Phase I is $265 million under the revised sales projections compared

Table 7 Drug candidate's projected sales and commercialization (after-tax) cash flows: The peak sales approach (in $ millions).[a]

Date	11	12	13	14	15	16	17	18	19	20
Growth rate	100%	100%	100%	100%	100%	100%	0	0	0	0
Sales	$ 170	$ 340	$ 680	$ 1,360	$ 2,720	$ 5,440	$ 5,440	$ 5,440	$ 5,440	$ 5,440
Oper. Cost%	0.38	0.38	0.38	0.38	0.38	0.38	0.38	0.38	0.38	0.38
Op. profit	$ 105.40	$ 210.80	$ 421.60	$ 843.20	$ 1,686.40	$ 3,372.80	$ 3,372.80	$ 3,372.80	$ 3,372.80	$ 3,372.80
Tax	$ 21.08	$ 42.16	$ 84.32	$ 168.64	$ 337.28	$ 674.56	$ 674.56	$ 674.56	$ 674.56	$ 674.56
After tax cash flow	$ 84.32	$ 168.64	$ 337.28	$ 674.56	$ 1,349.12	$ 2,698.24	$ 2,698.24	$ 2,698.24	$ 2,698.24	$ 2,698.24

[a] As in Table 2, the tax rate in Table 7 is assumed to be 20%.

Table 8 rNPV and VC valuations at later stages of the drug's development (peak sales version).

	rNPV			VC Values	Comparison of rNPV and VC valuation	VC's Equity interest			
Development phase	Exp. PV of costs at phase launch	Expected PV of after-tax cash flows at phase launch	rnPV at Phase launch	VC Values	VC value/rNPV value	VC contribution	VC equity interest (based on VC valuation)	VC equity interest (based on rNPV valuation)	Difference
Phase I	$ 77.91	342.95	$ 265.05	$ 47.18	18%	$ 50.00	51.4%	15.9%	35.6%
Phase II	$ 117.23	703.55	$ 586.32	$ 120.79	36%	$ 50.00	29.3%	7.9%	21.4%
Phase III	$ 241.10	2672.44	$ 2,431.34	$ 494.77	51%	$ 50.00	9.2%	2.0%	7.2%
NDA submission	$ 2.4	5820.42	$ 5,818.02	$ 2,026.56	30%	$ 50.00	2.4%	0.9%	1.6%

to $45.8 million in the base case (see Table 6). As the expected present value of costs at each phase remains unchanged from the base case when the sales projections are revised, the rNPV is significantly higher in the "peak sales" analysis compared to the base case analysis.

Applying the base case sales multiple (7.06) to the projected *peak* sales results in a significantly higher valuation under the VC method at the peak sales date ($t = 16$). But as the company does not attain its peak sales until its sixth year of production, the VC method discounts its projected future value of the company for five additional years (compared to the base case). Given the VC's high hurdle rate, the net result is that even though the VC valuations at each development phase are now higher compared to the base case, the valuation gap relative to the rNPV valuation widens. For example, the VC value at Phase I drops from 74% of rNPV in the base case to 18% under the peak sales approach. As a result, the difference in the VC's equity interest in the company under the VC and rNPV methods (for its contribution of $50 million at Phase I) widens significantly from 7.3% in the base case to 35.6% in the peak sales approach.

4.3 The impact of delays in clinical trials

We next evaluate the impact of delays in the drug's development by extending the length of each clinical trial phase and the NDA review period by 1 year, while holding all other parameter values at their base case levels. The results of this sensitivity analysis are reported in Table 9.

Comparing Tables 6 and 9, it is clear that extending the drug candidate's development time and thus delaying its commercialization reduces the

Table 9 rNPV and VC valuations at later stages of the drug's development (delayed trials).

PV			rNPV			VC Values	Comparison of rNPV and VC valuation				
PV of costs phase at launch	PV of after-tax cash flows at phase launch	NPV at phase launch	Exp. PV of costs at phase launch	Expected PV of after-tax cash flows at phase launch	rnPV at Phase launch	VC Values	VC value/ rNPV value	VC contribution	VC equity interest (based on VC valuation)	VC equity interest (based on rNPV valuation)	Difference
$ 180.71	$ 701.32	$ 520.61	$ 69.80	$ 82.99	$ 13.19	$ 5.20	39%	$ 50	90.6%	79%	11.4%
$ 215.82	$ 946.25	$ 730.43	$ 111.18	$ 188.13	$ 76.95	$ 21.32	28%	$ 50	70.1%	39%	30.7%
$ 241.61	$ 1,410.76	$ 1,169.15	$ 241.00	$ 789.63	$ 548.63	$ 139.70	25%	$ 50	26.4%	8%	18.0%
$ 2.4	$ 2,103.31	$ 2,100.91	$ 2.4	$ 1,900.34	$ 1,897.94	$ 915.53	48%	$ 50	5.2%	3%	2.6%

drug candidate's value at each phase, under the rNPV and VC valuation methods. But the gap in the pre-money valuation of the company under the two methods widens. For example, the VC value/rNPV value at Phase I is now 39% as shown in Table 9, compared to 74% to in the base case (see Table 6).

4.4 Other sensitivity analyses

We conclude this section by conducting three other sensitivity analyses. In each we assess the valuation impact of a change in a particular model parameter, while leaving all other parameter values unchanged at their base case levels, namely:

(1) *An increase in the phase success probabilities*: An increase in the phase success probabilities (at Phases I through III) by 5 percentage points, increases the rNPV values by 70% at Phase I, 36% at Phase II, and 10% at Phase III compared to the base case results presented in Table 6,[58] but does not affect the VC valuation. As a result, the VC/rNPV value ratio declines from 74% to 44%.

(2) *An increase in the cost of capital*: An increase in the cost of capital from 10.5% to 11% reduces the rNPV value but does not affect the VC valuation. As a result, the VC/rNPV value ratio increases at every phase of development.[59]

Table 10 Effect of changes in the VC's hurdle rate on the VC value/rNPV value ratio.

	VC value/rNPV value based on hurdles rates of	
	60%	59%
Phase I	74%	80%
Phase II	64%	68%
Phase III	49%	51%
NDA submission	70%	71%

(3) *A decrease in the hurdle rate*: A decline in the VC's hurdle rate estimate from 60% to 59% increases the VC's valuation at all phases but does not affect the rNPV valuations. As a result, the VC value/rNPV value increases at every phase of development as shown in Table 10.

5 The Real Option Method

The DCF method, and its variants such as the rNPV and VC methods, are commonly used in part because they are easy to implement and understand. However, such methods take a static view of the future market conditions and the management's plan, i.e., assume that the company "will follow a predetermined plan, regardless of how events unfold."[60] But in practice, a drug candidate's future prospects can change over time

(e.g., due to new side effects being observed or changes in competition). The company's management can react to such changes by re-evaluating the drug candidate's future prospects when additional R&D investments must be made, and abandoning development if additional R&D costs are not justified, given lower expectations about the drug's future prospects.

A real options valuation captures the value of such managerial flexibility, or real options the management has, which the classical DCF method (or the VC formula described above) does not.[61] Such a real options approach is used to value biotech assets[62] and more generally, investment opportunities with growth options. The real options approach "incorporate[s] both the uncertainty inherent in business and the active decision making required for a strategy to succeed."[63] In this section we value the drug candidate in our illustrative example as of Phase I (date $t = 0$) using the real options approach.[64]

5.1 Real option model parameter values

Asset value at valuation date: The first step of the real option analysis is to determine what the asset's value is as of the valuation date (Phase I launch in this example) assuming it already existed at the time and then determine the full range of the asset's possible future values till it is launched. In this case, the asset's value at the date of valuation (S_0) is assumed to be the present value of its post-commercialization cash flows which equals $1,045.60 million in our illustrative example's base case (see Equation (1)).

Future possible asset values: The asset's range of possible future values depends on its volatility. In our illustrative analysis we assume that the asset's return volatility (denoted by s) equals 30% per year.[65] As a result, according to the classic binomial option pricing model, each year the asset's value can appreciate to 1.35 times its prior value (we refer to this upside move as u) or decline to 0.74 times its prior value we refer to this upside move as d).[66]For instance:

- At $t = 1$ (or one year from the valuation date), the asset value could be either $1,411,42 million (which equals 1.35 times the current value of $1,045 million), or $774.6 million (which equals 0.74 times the current value of $1,045 million).
- At $t = 2$, the three possible asset values can be calculated as either 1.3 times or 0.74 times based on the asset's value realized at the end of $t = 1$. That is, at $t = 2$, the asset value could be either: (1) $1,905.21 million which equals 1.35 times the prior asset value of $1,411,42 million; (2) $1,045.6 million (either due to a 26% fall from the prior year's value of $1,411.42 million or a 34% rise from the prior year's value of $774.6 million); or (iii) $573.84 million (which equals 0.74 times the prior year's value of $774.6 million).

We extend this analysis for 10 years when the manager must decide whether to launch the drug, assuming that the drug candidate had reached that point of its growth trajectory. The asset's range of possible values increases over time and can be displayed as a binomial lattice or "tree" as shown in Figure 1.

Figure 1's top row denotes the date ($t = 0$ through 10). The columns at five dates (0, 2, 5, 8, and 10) are highlighted in gray as they denote five sequential decision nodes when the company has to decide if it wants to exercise a real option (i.e., whether or not to undertake Phase I trials at $t = 0$, or undertake Phase II trials at $t = 2$, or undertake Phase III trials at $t = 5$, or submit the drug's NDA at $t = 8$ or launch the drug at $t = 10$, respectively). As Figure 1 shows, by the time the drug must be launched, its value could range from $52 million to $21 billion.

0	1	2	3	4	5	6	7	8	9	10
										$ 21,001.48
									$ 15,558.28	
								$ 11,525.86		$ 11,525.86
							$ 8,538.57		$ 8,538.57	
						$ 6,325.52		$ 6,325.52		$ 6,325.52
					$ 4,686.06		$ 4,686.06		$ 4,686.06	
				$ 3,471.52		$ 3,471.52		$ 3,471.52		$ 3,471.52
			$ 2,571.77		$ 2,571.77		$ 2,571.77		$ 2,571.77	
		$ 1,905.21		$ 1,905.21		$ 1,905.21		$ 1,905.21		$ 1,905.21
	$ 1,411.42		$ 1,411.42		$ 1,411.42		$ 1,411.42		$ 1,411.42	
$ 1,045.60		$ 1,045.60		$ 1,045.60		$ 1,045.60		$ 1,045.60		$ 1,045.60
	$ 774.60		$ 774.60		$ 774.60		$ 774.60		$ 774.60	
		$ 573.84		$ 573.84		$ 573.84		$ 573.84		$ 573.84
			$ 425.11		$ 425.11		$ 425.11		$ 425.11	
				$ 314.93		$ 314.93		$ 314.93		$ 314.93
					$ 233.31		$ 233.31		$ 233.31	
						$ 172.84		$ 172.84		$ 172.84
							$ 128.04		$ 128.04	
								$ 94.85		$ 94.85
									$ 70.27	
										$ 52.06

Figure 1 Asset value tree (in $ millions).

The probability of an up or down move in the asset value: According to the CRR model, the risk-neutral probability, $\boldsymbol{p}$, of the asset value increasing to u times its previous value at any node on the binomial lattice can be calculated as a function of its volatility and the risk-free rate as reflected in the parameters u and d. In this case, given the risk-free rate value 10.5% and the u and d values of 1.35 and 0.74, respectively, $\boldsymbol{p}$ equals 61%.[67] Correspondingly, the probability of the asset value decreasing to d times its previous value any node on the binomial lattice $(\mathbf{1}-\boldsymbol{p})$ equals 39%.

5.2 Real option valuation

Given the full range of asset values at each future date, we work backwards from the last date, factoring in the investment decisions s that have to be at various stages. Such calculations provide all possible future values of the option at every node on the lattice where the company can exercise an option of continuing its development efforts by incurring R&D (or NDA submission) costs. The results of such calculations are shown in the option value tree (Figure 2).

The decision at launch stage ($t = 10$): At this stage the present values of the assets after-tax cash flows range from $21 billion (at the top, of first node) to $52 million at the bottom (11th node). As the cost of launch is assumed to be zero in the base case, if the asset reaches this stage then the company would launch the drug regardless of its valuation because even at the lowest valuation, $52 million shown at the bottom (11th) node the drug's NPV would be positive ($52 million).[68]

The value at $t = 9$: We work back from the end of year 10 to determine the asset's potential values at the end of year 9. The value at each node at $t = 9$ is calculated as the average value of the asset at the next two possible nodes, discounted back one year using the risk-free rate as the discount rate. At the top node at $t = 9$, the company recognizes that the next period the asset's value can be either $21 billion (with a probability of 61%) or $11.5 billion (with a probability of 39%), resulting in a (probability-weighted) average value of $17,280

Phase	I		II			III			NDA submission		Launch
Phase costs (millions)	$ 20.76		$ 53.76			$ 240.00			$ 2.40		$ -
Phase success prob	59.52%		35.52%			61.95%			90.35%		
											$ 21,001.48
										$ 15,558.28	
									$ 10,411.21		$ 11,525.86
								$ 7,712.43		$ 8,538.57	
							$ 5,713.17		$ 5,712.71		$ 6,325.52
						$ 2,381.79		$ 4,231.70		$ 4,686.06	
					$ 1,726.02		$ 3,134.57		$ 3,134.12		$ 3,471.52
				$ 1,244.04		$ 1,198.38		$ 2,321.43		$ 2,571.77	
			$ 262.52		$ 849.33		$ 1,719.41		$ 1,718.96		$ 1,905.21
		$ 175.96		$ 594.58		$ 548.91		$ 1,273.05		$ 1,411.42	
	$ 47.05		$ 91.67		$ 368.19		$ 942.76		$ 942.30		$ 1,045.60
		$ 50.13		$ 238.53		$ 192.47		$ 697.69		$ 774.60	
			$ -		$ 105.24		$ 516.52		$ 516.06		$ 573.84
				$ 57.55		$ -		$ 381.93		$ 425.11	
					$ -		$ 282.59		$ 282.14		$ 314.93
						$ -		$ 208.63		$ 233.31	
							$ 154.21		$ 153.76		$ 172.84
								$ 113.52		$ 128.04	
									$ 83.30		$ 94.85
										$ 70.27	
											$ 52.06
Date	0	1	2	3	4	5	6	7	8	9	10

Figure 2 Real option value tree.

million at $t = 10$, which discounted one period at the risk-free rate of 10.5% equals $15,558.28 million,[69] as shown in Figure 2. The option values at all other nodes at $t = 9$ can be calculated analogously and are reported in Figure 2.

The value at $t = 8$ (NDA submission decision): At this stage the company must decide whether it makes financial sense to submit an NDA.

To evaluate the decision at each of the nine nodes at $t = 8$, requires the following four calculations:

(1) *Calculate the expected value at the next period*: The company first discounts the expected value of the asset if the project continued, as discussed above. For instance, if the asset value had reached the top node at $t = 8$ in Figure 1 (the Asset Value Tree) then the following year its value would be either $15,558 million or $8,538 million (as shown in the first and second nodes at $t = 9$ in Figure 2), which can occur with probabilities of 61% or 39%, respectively. As before, we would calculate the (probability-weighted) average of these two possible outcomes which equals $12,801.89 million.

(2) *Calculate the present value of the project if it were to continue*: Next, the company would calculate the continuation value of the project at the node by discounting the expected value at the next period ($12,801.89 million) for one period at the risk-free rate, which equals $11,525.86 million.

(3) *Calculate the continuation value, adjusted for the technical risk at this phase*: As success at any regulatory phase of the drug's development is not guaranteed, the continuation value calculated in the previous step would have to be adjusted for the drug's likelihood of success at the NDA submission stage which equals 90.35% (as shown at the top panel of Figure 2 and Table 1). Multiplying the asset's continuation value ($11,525.86 million) by the probability of success at the NDA submission stage (90.35%) results in a regulatory-risk adjusted continuation value of $10,413.61 million.

(4) *Calculate the intrinsic value of the option to continue the project at this node by subtracting the exercise price of the real option:* To continue the project at this stage, the company would have to exercise a real option, i.e., spend the option's "exercise" price of $2.40 million (the cost of an NDA submission). The company would only do so if the option was "in the money," i.e., had a positive NPV if exercised. In this case, the option's intrinsic value equals: $(10,413.61−2.4) million or $10,411.21 million, as shown in Figure 2. As this value is positive, the company would choose to continue the project if the asset value had reached the top node at $t = 8$.

Repeating these calculations at each of the remaining eight nodes at $t = 9$ results in the values shown in Figure 2. As Figure 2 indicates, even if the asset value had declined to the lowest node at $t = 9$, the company would find it optimal to submit an NDA because even at that stage the option to continue the project would have a positive intrinsic value of $83.30 million.

In a similar fashion, the values at every node at prior time periods are calculated and reported in Figure 2.

5.3 *Option values at prior years* (1–7)

Repeating the methodology discussed above, the value of the option to continue the project, given updated values of the underlying asset, regulatory risk and R&D costs at various stages are shown in Figure 2.

In years when the company does not have to take a decision, the option's value at each node is calculated based on the first two of the four steps discussed above. In years when the company has a decision to make (highlighted in gray in Figure 2), all four of the above calculations must be performed to determine the option's intrinsic value.

Such a calculation reveals that at certain points in the drug's development, further development may be abandoned given the updated business conditions—a possibility that the traditional valuation methods ignore. For example, consider the company's decision at the fifth node at $t = 5$, (highlighted in yellow) when it must decide whether to proceed with Phase III trials.

At this node, based on the first two steps of the backward induction process discussed above, the asset's value equals $382.34 million. Multiplying that value by the probability of success at Phase III (61.95%) reduces the asset's value to $236.86 million. As the cost of continuing the project at Phase III ($240 million) is greater than the asset's remaining value, the company should optimally discontinue the drug's development at this stage. As a result, the value of the project at this stage would be zero, as shown in highlighted yellow cell in Figure 2.[70]

5.4 *Option value at* $t = 0$

Working backward along the option lattice results in two possible values at $t = 1$: $175.96 million or $50.13 million which can occur with probabilities of 61% or 39%, respectively, yielding an expected value of $126.55 million at $t = 1$, which discounted done period at the risk-free rate yields the continuation value at $t = 0$ ($113.93 million). Multiplying that continuation value by the Phase I success probability (59.52%) yields the regulatory risk-adjusted continuation value of $67.8 million. Finally subtracting the cost of exercising the option of proceeding with Phase I trials ($20/76 million) yields the option value at $t = 0$, $47.05 million, as shown in Figure 2. Note that this value is greater than the rNPV value at Phase I, $45.82 million (see Table 6). The difference of $1.23 million captures the value of managerial

flexibility, that the rNPV method ignores. The VC valuation method also ignores the value of managerial flexibility. Thus, the VC value/real option value ratio is even lower than the VC/rNPV value ratio.

The drug's real option value depends on the model's parameter values as the above discussion highlights. Two observations are in order.

(1) The greater the asset volatility, the higher is its value. For example, if volatility, s, increases from 30% to 40%, then the drug candidate's real option value at $t = 0$ increases from \$47.05 million (the base case discussed above) to \$49.66 million. This result follows from the fact that, given higher volatility, the range of possible future asset values expands[71] and the payoffs if the drug candidate is successful increase, whereas the decline in the asset's value due to greater volatility does not affect its real option value because the company can halt development, i.e., exercise its option to walk away from the project without incurring additional R&D costs.
(2) The greater the risk-free rate, the higher is the real option value because the present value of the exercise prices to be paid in the future to exercise real options at various stages falls.

6 Conclusion

Biotech innovations lead to the development of life-saving drugs and vaccines. Such development efforts are often funded by VCs. However, valuing biotech assets, such as drugs in development, are difficult because of the time and expense involved in drug development and the considerable regulatory risk that a drug candidate faces in getting FDA approval.

This article is a primer on the most common methods used in biotech valuation (the rNPV, VC and real option methods). As discussed above, different valuation models can yield significantly different valuation conclusions, primarily due to differences in the manner in which they adjust for a drug's regulatory risks. If the VC and the company cannot agree about the company's pre-money valuation (and correspondingly, the VC's appropriate equity stake in exchange for its capital contribution), then VC funding for the drug candidate's development may stop which could have significant social repercussions. A deeper understanding of the fundamental drivers of a drug candidate's value under different valuation approaches may allow VCs and entrepreneurs to objectively analyze, and resolve differences in their assessment of, the drug candidate's value given its stage of development.

Endnotes

[1] David Cutler, "The World's Costliest Health Care ... and what America might do about it," *Harvard Magazine*, May-June 2020. https://www.harvardmagazine.com/2020/05/feature-forum-costliest-health-care.

[2] According to a study by the Centers for Medicare & Medicaid Services (CMS), the COVID-19 pandemic healthcare spending in the U.S. increased by 9.7% due to the Covid-19 epidemic bringing spending to \$4.1 trillion in 2020. (See "National Health Spending in 2020 Increases due to Impact of COVID-19 Pandemic," CMS.gov, Office of the Actuary, December 15, 2021 https://www.cms.gov/newsroom/press-releases/national-health-spending-2020-increases-due-impact-covid-19-pandemic.

[3] Source: World Bank.

[4] Source: World Bank.

[5] In 2019, the per capita health-care spending in France, U.K., Germany, and Canada (in current US\$) equaled \$4,508, \$4,265, \$5,478, and \$5,083, respectively. (Source: World Bank, accessed December 11, 2023).

[6] See for example, David Cutler, "The World's Costliest Health Care ... and what America might do about it," *Harvard Magazine*, May-June 2020. https://www.harvardmagazine.com/2020/05/feature-forum-costliest-health-care.

[7] Amitabh Chandra, Cirrus Foroughi and Lauren Mostrom, 2022, "Venture Capital-Led Entrepreneurship in Health Care," Chapter 10 of The Role of Innovation and Entrepreneurship in Economic Growth (editors: Michael J Andrews, Aaron Chatterji, Josh Lerner and Scott Stern) Chicago University Press, 2022.

[8] "Certain drugs are classified as new molecular entities ("NMEs") for purposes of FDA review. Many of these products contain active moieties that FDA had not previously approved, either as a single ingredient drug or as part of a combination product. These products frequently provide important new therapies for patients. Some drugs are characterized as NMEs for administrative purposes, but nonetheless contain active moieties that are closely related to active moieties in products that FDA has previously approved." FDA. https://www.fda.gov/drugs/development-approval-process-drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products.

[9] Kellogg and Charnes (2000) describe these three clinical trial phases as follows. (1) *Phase I trial*: The drug is tested on a small group of usually healthy volunteers to obtain information about its absorption rate in the body, toxicity, metabolic effects, safe dosing ranges and the rate and manner in which it is naturally removed from the body. (2) *Phase II trial*: To obtain additional evidence of efficacy and safety the drug is tested on a larger sample of individuals who could benefit from the drug. (3) *Phase III trial*: At this final trial stage, the company tests the drug on a large scale to obtain additional evidence of efficacy. (David Kellogg and John M. Charnes, (2000), "Real-Options Valuation for a Biotechnology Company," *Financial Analysts Journal*, 56:3, 76–84, DOI: 10.2469/faj.v56.n3.2362).

[10] This estimate includes pre-human and clinical period costs (DiMasi *et al.*, 2016).

[11] DiMasi *et al.* (2016), p. 24.

[12] DiMasi *et al.* (2016), Figure 1.

[13] National Venture Capital Association (NVCA) 2022 Yearbook, (https://nvca.org/wp-content/uploads/2022/03/NVCA-2022-Yearbook-Final.pdf), p. 28.

[14] NVCA 2022 Yearbook, p. 31.

[15] NVCA 2022 Yearbook, p. 32.

[16] At the end of 2022, the US equity market's market capitalization was $52.24 trillion. This total is the sum of the aggregate market capitalizations of companies listed on the NYSE and Nasdaq, which were $2.69 trillion and $24.56 trillion, respectively. (2022 Capital Markets Fact Book—SIFMA, p. 40) In contrast, the aggregate assets under management (AUM) of all US VC funds was only $995 billion. These assets were managed by 2,889 VC firms and 5,338 VC funds in existence. Of the $995 billion of AUM, 22% (or $223 billion) was dry powder—that is, new capital that the VC funds had to deploy, while the remainder reflected the current values of existing investments. (NVCA 2022 Yearbook, p. 5).

[17] However, measuring the returns that VC funds actually generate of their investors on average (across all investments) is difficult because the values of the firms in which the VC fund invest are observable only when it goes public, receives new financing, or is acquired. As Cochrane (2005) notes, these events are more likely when the firm has experienced a good return, which introduces a "selection bias." Without controlling for such bias, Cochrane (2004) calculated VC funds' average (log) returns to be 108% per year, but only 15% after controlling for selection bias. (John H. Cochrane, 2005, "The Risk and Return of Venture Capital," Journal of Financial Economics, 75 (2005) pp. 3–52).

[18] Dan Primark and Bob Herman, (2020), "The company leading the race to a coronavirus vaccine," Axios, March 2020. https://www.axios.com/2020/03/17/moderna-coronavirus-vaccine-trial.

[19] Jeff Farrah, (2020), "Creating the Next Moderna: What VC Offers the World and 3 Public Policy Lessons," November 30, 2020, National Venture Capital Association (NVCA), https://nvca.org/creating-the-next-moderna-what-vc-offers-the-world-and-3-public-policy-lessons/.

[20] Dan Primark and Bob Herman, (2020), "The company leading the race to a coronavirus vaccine," Axios, March 2020. https://www.axios.com/2020/03/17/moderna-coronavirus-vaccine-trial.

[21] For example, if the VC's estimates the company's pre-money valuation (i.e., the company's value before including the VC's capital contribution) to be $200 million, then in exchange for a capital contribution of $100 million, the VC will require a 33% equity stake in the company, calculated as $100 million divided by $300 million. See William Sahlman (2009), "The Basic Venture Capital Formula," Harvard Business School Note 9-804-042, revised May 13, 2009; and Damodaran (2009).

[22] Jeffrey J. Stewart, Peter N. Allison and Ronald S. Johnson, (2001), "Putting a Price on Biotechnology," Nature Biotechnology, September 2001, Vol 19, pp. 813–817, see p. 813.

[23] "Drug Development Valuing the pipeline—a UK study," Mayer Brown Pharma and Biotech, March 2009, ("Mayer Brown Survey (2009)"), p. 10.

[24] Mayer Brown Survey (2009), p. 10.

[25] "A patent is a property right issued by the United States Patent and Trademark Office (USPTO) to an inventor "to exclude others from making, using, offering for sale, or selling the invention throughout the United States or importing the invention into the United States" for a limited time, in exchange for public disclosure of the invention when the patent is granted. Generally, the term of a new patent is 20 years from the date on which the application for the patent was filed in the United States." FDA, https://www.fda.gov/media/92548/download.

[26] Exclusivity is exclusive marketing rights granted by the FDA upon approval of a drug and can run concurrently with a patent or not. It prevents the submission or effective approval of ANDAs or applications described in Section 505(b)(2) of the Act, and was designed to promote a balance between new drug innovation and generic drug competition. Exclusivity is granted upon approval of a drug product if the statutory requirements are met. The length of time that FDA grants new drug exclusivity depends on the type of exclusivity. FDA, https://www.fda.gov/media/92548/download.

[27] Mayer Brown Survey (2009), p. 11.

[28] Jongmoo Jay Choi, Connie X. Mao and Arun D. Upadhyay, 2013, "Corporate Risk Management under Information Asymmetry," *Journal of Business Finance & Accounting,* 40(1) & (2), 239–271, and S. Nicholson, P.M. Danzon and S. McCullough (2005), "Biotech-Pharmaceutical Alliances as a Signal of Assets and Firm Quality," *Journal of Business*, Vol. 78, pp. 1433–64.

[29] Chandra *et al.* (2022), p. 476.

[30] Chandra *et al.* (2022).

[31] Mayer Brown Survey (2009), p. 4, and "NPV v. rNPV," Avance, p. 1.

[32] We discuss three valuation multiples that are commonly used in this context: (1) the sales multiple, (2) the EBITDA multiple, and (3) the peak sales multiple.

[33] The biotech asset refers to the drug under development.

[34] According to CAPM, the risk premium will equal the product of two numbers: $(r_m - r_f)$, the spread above the risk-free rate that investors require to invest in a well-diversified market portfolio, and the asset's beta, β (i.e., risk relative to a market portfolio). The beta measure the asset's systematic risk that investors cannot eliminate by holding the asset as part of a well-diversified market portfolio. Therefore, according to CAPM, the expected return that shareholders (or equity holders) demand for investing in shares of a company or a project (denoted as r_e) equals: $r_{f+}\,\beta(r_m - r_f)$, where $(r_m - r_f)$ denotes the market risk premium and $\beta\ (r_m - r_f)$ denotes the stock-specific risk premium ("RP") which depends on the stock's β. *See* Richard A. Brealey, Stewart C. Myers, and Franklin Allen (2017), Principles of Corporate Finance, McGraw Hill Education, p. 200.

[35] Stewart *et al.* (2001) and B. Bogdan, and R. Villiger, 2010, *Valuation in Life Sciences,* 3rd ed., Springer-Verlag, Berlin Heidelberg, p. 30.

[36] "Examination of Clinical Trial Costs and Barriers for Drug Development," Office of Assistant Secretary for Planning and Evaluation, July 2014 (ASPE, 2014).

[37] DiMasi *et al.*'s (2016) estimated phase transition probability and overall clinical approval success rates are "for self-originated new molecular entity (NME) and new therapeutically significant biologic entity (NBE) investigational compounds first tested in humans anywhere from 1995 to 2007." These estimates are based on an analysis of 1,442 self-originated compounds of top 50 pharmaceutical firms (see DiMasi *et al.*, 2016, Figure 1). DiMasi *et al.*'s (2016) estimated R&D costs at each phase are the median pre-tax "out-of-pocket clinical period costs for investigational compounds (in millions of 2013 dollars)." These costs are per approved drug and inclusive of long-term animal testing costs (see DiMasi *et al.*, 2016, Table 2). For "mean time to next phase", see DiMasi *et al.* (2016, Table 4).

[38] This figure is calculated by adding the "mean time to next phase" figures shown in the last column of TN Table 1.

[39] The R&D cost estimate as of January 2023 is estimated to be 20% higher than DiMasi *et al.*'s (2016) cost estimates which are estimated in 2013 dollars. This cumulative inflation estimate for the 10 year period (January 2013–January 2023) is based on the average annual inflation rate of 1.86% over the January 2013–January 2021 period (see St. Louis Federal Reserve Economic Data ("FRED"). https://fred.stlouisfed.org/series/FPCPITOTLZGUSA).

[40] The tax rate estimate of 20% is slightly higher than the combined (federal and state) tax rate of 19% estimated for the life science sector (Rick Fonte, 2022, "How US tax reform is testing the life sciences sector," E&Y, April 6, 2022. https://www.ey.com/en_gl/tax/how-us-tax-reform-is-testing-the-life-sciences-sector). The discount rate (or cost of capital estimate) of 10.5% is from DiMasi *et al.* (2016). The operating cost margin

of 38% results in an operating profit margin that is lightly lower than the gross margin of 62.25% for biotech sector estimated by Damodaran. https://pages.stern.nyu.edu/~adamodar/New_Home_Page/datafile/margin.html. The growth rate of 3% is estimated to equal long run inflation.

[41] Note that according to growing annuity formula the value of 10 years of cash flows starting 8.23 years from the launch of Phase I is first calculated as of one year prior to the start of the first cash flow, i.e., as of 7.23 years in the future. Therefore, this sum is further discounted (using the discount rate of 10.5%) for 7.23 years to calculate its present value at the start of Phase I.

[42] This figure is calculated as the PV of the expected cashflows after the drug is launched ($1,045.60 million) less the PV of development costs and NDA submission fee ($211.55 million).

[43] The rNPV method is commonly used to value biotech assets. See Jeffrey J. Stewart, Peter N. Allison and Ronald S. Johnson (2001), "Putting a price on biotechnology," *Nature Biotechnology,* September, 813–817.

[44] This probability is calculated by multiplying the phase success probabilities of Phases I and II provided in Table 1.

[45] This probability (13.1%) is calculated by multiplying the phase success probabilities of Phases I, II and III provided in Table 1, viz., $59.52\% \times 35.52\% \times 61.95\%$.

[46] This probability (11.8%) is calculated by multiplying the probability that the drug candidate's Phase I, II, and III clinical trials are all successful (13.1%) and that the drug candidate's NDA is then approved (90.35%).

[47] The rNPVs of the bids are calculated using the same discount rate (10.5%) as in the above example, and the same phase success probabilities (as shown in Table 1).

[48] That is, if the company accepted Bid A then it would have incurred a loss in rNPV terms.

[49] See for example, Sahlman (2009) and Damodaran (2009).

[50] https://pages.stern.nyu.edu/~adamodar/New_Home_Page/datafile/psdata.html.

[51] https://pages.stern.nyu.edu/~adamodar/New_Home_Page/datafile/vebitda.html.

[52] Multiplying the company's first year sales forecast of $850 million by the EV/Sales multiple of 7.06 yields an enterprise value estimate of $6,001 million. Multiplying the company's first year EBITDA forecast of $527 million by the EV/EBITDA multiple of 11.29 yields an enterprise value estimate of $5,949.83 million. In this analysis, the company is assumed to have no debt as in the norm in research intensive industries (see DiMasi *et al.*, 2016, p. 24).

[53] Damodaran (2009), p. 15. As shown in Damodaran's (2009) Table 2, VC's hurdle rates range from 50% to 70% for startups and from 35% to 50% at the second stage by when the company is generating a profit. In contrast, the actual returns that VCs had earned on average over the past 20 years (as of 2007) was far more modest (21.4% and 14.5% for early stage and later stage investments, respectively).

[54] This sum ($95.8 million) equals the sum of the company's pre-money valuation estimate using the rNPV method ($45.8 million) discussed above, and the VC's contribution ($50 million).

[55] This percentage is calculated as 50/(95.8).

[56] The VC method indirectly captures this declining risk because the number of periods it discounts the expected future value of the company declines as the drug's development progresses. Furthermore, the VC could use a lower hurdle rate to discount the projected future value of the company at later phases of development.

[57] In practice, the peak sales multiple is typically lower than the sales multiple applied to the first year of sales.

[58] An increase in the phase success probabilities by 5 percentage points at each phase results in a valuation of $77.91 million, $186.73 million, and $800.78 million at Phases I through III, respectively. The valuation at the NDA submission stage remains unchanged at $2,097.47 million because in this sensitivity analysis we did not change the phase success probability at that stage.

[59] The VC value/rNPV value ratio increases (i) from 74% in the base case to 88% at the Phase I stage; (ii) 64% in the base case to 71% at the Phase II stage; (iii) from 49% in the base case to 53% at the Phase III stage; and (iv) from 70% in the base case to 72% at the NDA submission stage.

[60] Timothy A. Luehrman, (1998), "Strategy as a Portfolio of Real Options," Harvard Business Review, September–October 1998 Issue.

[61] Ralph Villiger and Boris Bogdan, (2005), "Getting real about valuations in biotech," Nature Biotechnology Volume 23 Number 4, April 2005.

[62] Villiger and Bogdan (2005) and Mayer Brown Survey (2009).

[63] Luehrman (1998).

[64] The model we develop is similar to that of Villiger and Bogdan (2005).

[65] In their real option analysis of a biotech asset, Villiger and Bogdan (2005) also asset the asset's return volatility is 30% per year.

[66] These up and down moves are denoted by u and d, respectively. According to Cox *et al.*'s (1979) (CRR) classic binomial option valuation model: $u = \exp(s\sqrt{dt})$ where dt is the length of each period (one year in our model). Thus, given a volatility estimate, s, of 30%, u can be calculated as exp(.30) which equals 1.35, and following the CRR model, $d = 1/u$, or 1/1.35 which equals 0.74. (J.C. Cox, S. Ross and M. Rubinstein, (1979), "Option Pricing : A Simplified Approach," Journal of Financial Economics, Volume 7, pp. 229–263).

[67] According to the CRR model, the risk-neutral probability, $\boldsymbol{p}$, of the asset value increasing by u at any node on the binomial lattice can be calculated as $(a-d)/(u-d)$, where $a = (\exp(r_f\sqrt{dt})$ and r_f is the risk-free rate (10.5% in this example). Thus, in this example, $a = \exp(0.105) = 1.11071061$. Thus, $\boldsymbol{p} = (1.11071061 - 0.74)/(1.35 - 0.74)$, or 61%. The "risk-neutral" probability is the probability that a risk-neutral investor who expects to earn the risk-free rate on her investment (and thus discounts expected future cashflows at that rate) must assign to the "up" states of the asset tree in a world without arbitrage. Henceforth, whenever we refer to probability we mean the risk-neutral probability, unless otherwise stated.

[68] Assuming that the cost of launch is zero is analogous to assuming that any upfront launch costs may be amortized over the drug's life and is subsumed in the present value of the drug reported at each node at date 10. If instead one assumed that there is a positive upfront launch cost, then the drug would be launched at any of the 11 nodes at date 10 if the drug's value net of that launch cost was positive, otherwise the drug would not be launched.

[69] This number is calculated as ($17,280 million)/exp (0.105).

[70] In an analogous manner, it can be verified that the value at the bottom node at $t = 5$ and $t = 4$ would also be zero as shown in Figure 2.

[71] In technical terms, the u parameter value rises from 1.35 in the base case to 1.49 and the d parameter value declines from 0.74 in the base case to 0.67.

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