Valuation and Investments in Clinical-Stage Biopharmaceutical Companies

by

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A research paper submitted for the

Rosenwald Fellowship Program

Leonard N. Stern School of Business

New York University

May 2024

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Abstract:

This paper investigates the complexities of valuing clinical-stage pharmaceutical companies. Such companies have significant uncertainty in future cash flows, depending heavily on regulatory approvals for future viability. To address this challenge, this paper develops a valuation framework that incorporates biological, epidemiological, and regulatory data to forecast future revenues and expenditures. This approach can value individual product lines or subsidiaries as well as the entire company. The paper introduces a novel statistics-based market share prediction mechanism. It also uses a decision-tree real option-based model, suitable to the highly bimodal cash flows of these companies. Finally, the study underscores the importance of mergers and acquisitions in speeding development.

Keywords: Financial Modeling, Valuation, Pre-Revenue, Biotech, Technology, Pharmaceutical, Mergers and Acquisitions

Acknowledgements:

First and foremost, I would like to thank Professor Aswath Damodaran, my research advisor, for his lectures and his guidance. His deep insights and constructive feedback have shaped both the direction and the success of my work.

I would also like to thank Professor Matthew Richardson and the entire Rosenwald Research Fellowship committee for their review and approval of my research proposal. Their guidance and encouragement made this research possible.

Finally, I extend my heartfelt gratitude to all the professors at NYU Stern School of Business. The skills and knowledge I have gained through their courses have enriched my academic journey and personal growth.

Introduction:

Clinical-stage biopharmaceutical companies do not have any approved products. They spend heavily on research and development, but do not yet have sales revenues. Their financial statements do not provide enough information to project line items into the future. Additionally, these companies often depend entirely on regulatory approval for future revenues. Yet there is a high payoff to valuing these startups. Therefore, we need a reliable framework for projecting financials like revenue, cost, and capital expenditures. Such valuation can guide investment decisions for asset managers and alternative investment managers.

Pre-revenue biopharmaceutical valuation is also important due to the accelerating activity in mergers and acquisitions. Currently, targeted-treatment breakthroughs such as Antibody-Drug Conjugates (ADCs), T-Cell Engagers (TCE), CAR-T, and derivative technologies are finding applications in oncology, immunology, and other areas. In clinical trials, they have often been shown to be more effective with reduced side effects compared to existing treatments. Established biopharmaceutical companies need to acquire these potential rivals before they reach market, otherwise, they will lose significant market share. Additionally, many established companies are reaching a patent cliff where they will lose exclusivity over products that provide a significant portion of revenue. On the other side of the deal, pre-revenue biopharmaceutical companies need funding due to their cash burn. Due to these strong synergies, we expect a boom in biopharma mergers and acquisitions.

This paper attempts to establish a practical framework to estimate future revenues and costs for the firm using sources such as biological, epidemiological, and regulatory information. We will integrate quantitative data and original analysis into our model. We will then use this framework to estimate the value of individual candidate products in the company's pipeline and the value of

the entire companies as a sum of product lines. The theoretical valuation can then be validated using observations of mature biopharmaceutical companies. We will also perform data analysis on various areas relevant to hedge funds and investments in general.

Industry and Literature Review:

The biopharmaceutical industry is fueled by advances in scientific research in fields such as molecular biology, immunology, chemistry, oncology, neuroscience, data science, and artificial intelligence. The pace of approvals has accelerated as new technologies and sources of information have proliferated.

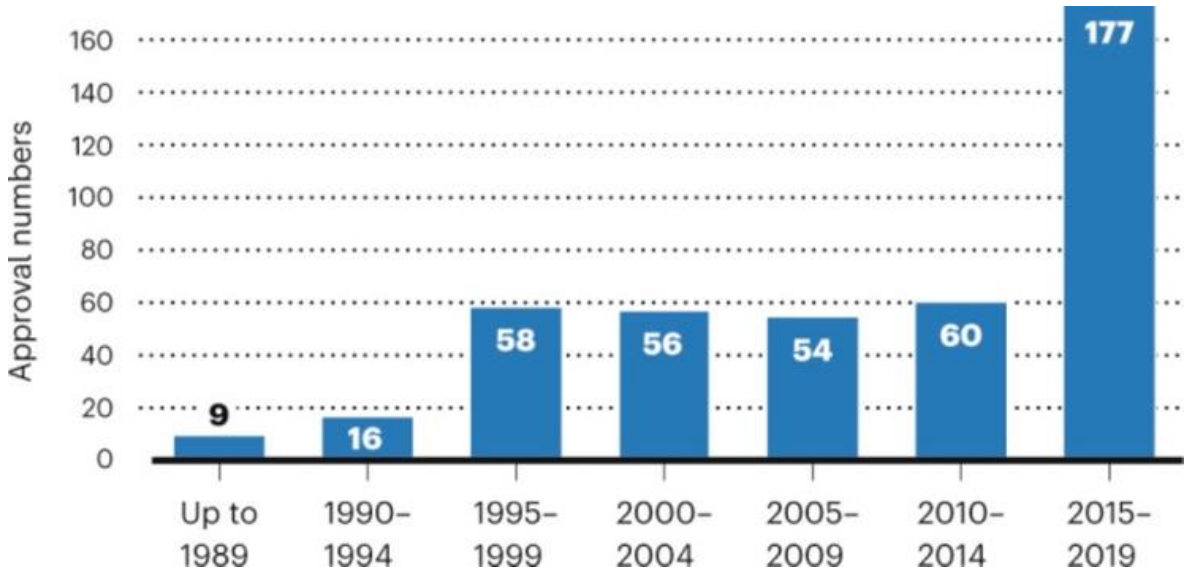


Figure 1: Walsh, Biopharmaceutical Benchmarks 2022

As of 2022, 50% of pharmaceutical sales revenue were in the US, 17% in Europe, 9% in the "Established Rest of the World", and 24% in Emerging Markets (Statista).

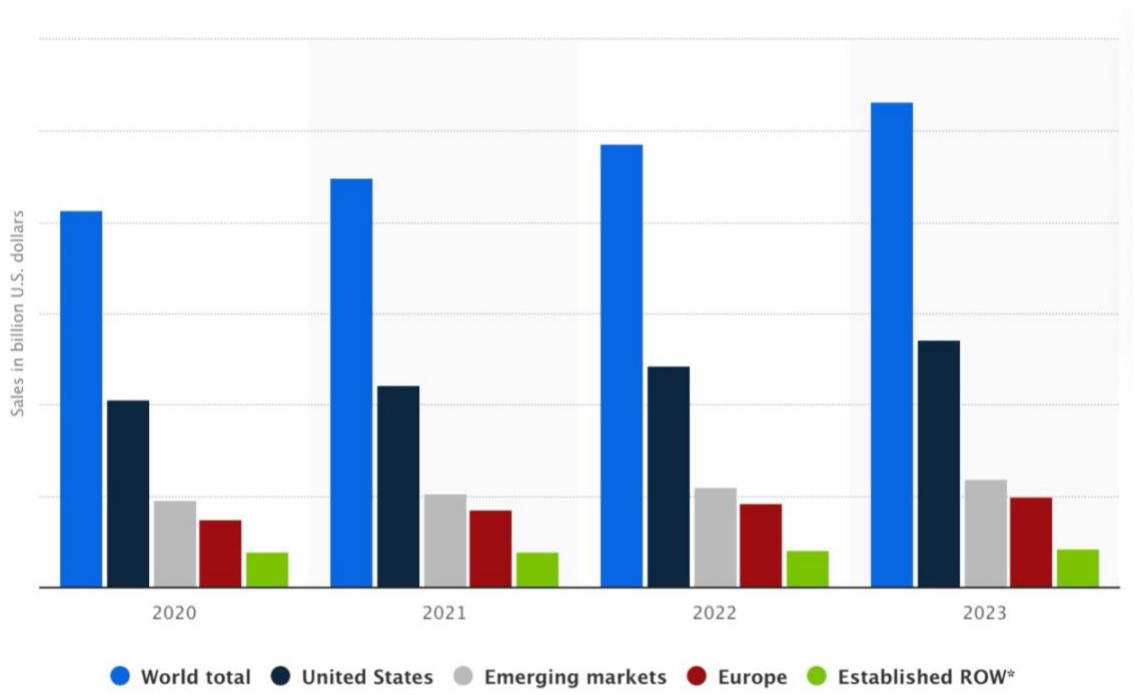
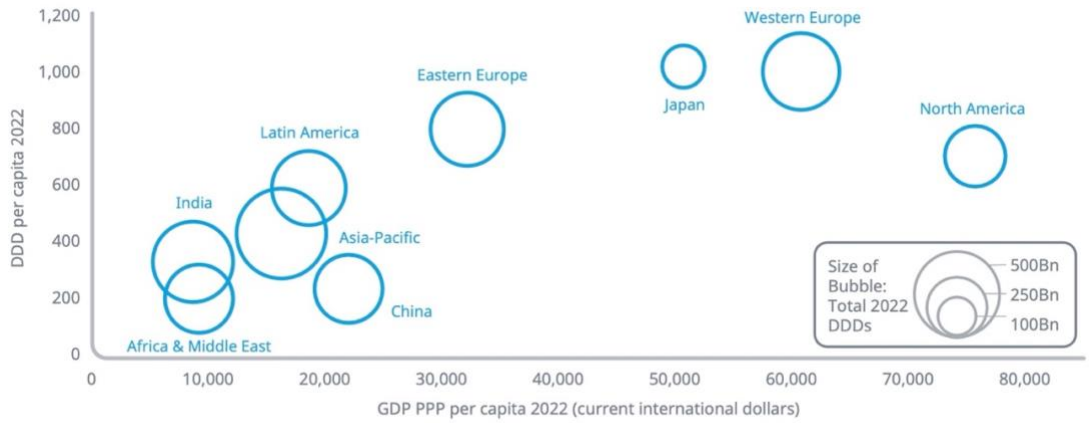


Figure 2: Statista, World Pharmaceutical Sales by Region

As of 2022, new therapies are expected to gain market share against existing treatments, and many existing treatments are expected to lose Intellectual Property protection. The IQVIA Institute predicts that US gross pharmaceutical spending is expected to be reduced by $141 billion due to Loss of Exclusivity and increase by $110B due to new brands. Furthermore, the patent cliff is already in progress, with spending effects starting in 2023. (*Global Use*, 24). On the other hand, biosimilar competition is projected to surge (*Global Use*, 39). Over 70% of pharmaceutical phase III candidates in 2021 were from small companies (CBO 4), and over 60% of biopharmaceutical trial starts were from emerging firms (Mullard).

Developed markets tend to have a higher use of medicines per capita than emerging markets. However, the US uses far less volume per capita than predicted by the trend, likely due to the high out-of-pocket cost (vs. government payment). However, developed countries' are predicted to grow more slowly than developing countries'. Specifically, overall volume is expected to grow 1.6% through 2027; this rate is only 0.1-0.4% in Western Europe, North America, Japan, and parts of Eastern Europe. Global net spending is expected to increase 3 to 6%, whereas the US net spending is expected to remain flat at a growth rate of about -1 to 2%. This discrepancy is attributable to the adoption of the US Inflation Reduction Act and the upcoming patent cliff. Regions with differing levels of development and sociocultural norms also have a differing distribution of therapeutic usage across categories. Notice that *net* spending is gross (invoice) spending minus discounts and rebates, so the gross spending is still expected to increase by $134 billion by 2027 (*Global Use,* 15-24). Key drivers of the industry are the aging population, rise in chronic diseases, and advancements in R&D technologies. The areas of highest growth are in oncology and obesity treatments. In contrast, growth in immunology treatments is expected to slow due to competition (*Global Use*, 43-46).



Source: IQVIA MIDAS, Jun 2022; IQVIA Institute, Dec 2022; The World Bank, Jul 2022; International Monetary Fund, Oct 2022.

Figure 3: from IQVIA: Defined Daily Doses per Capita/GDP per Capita.

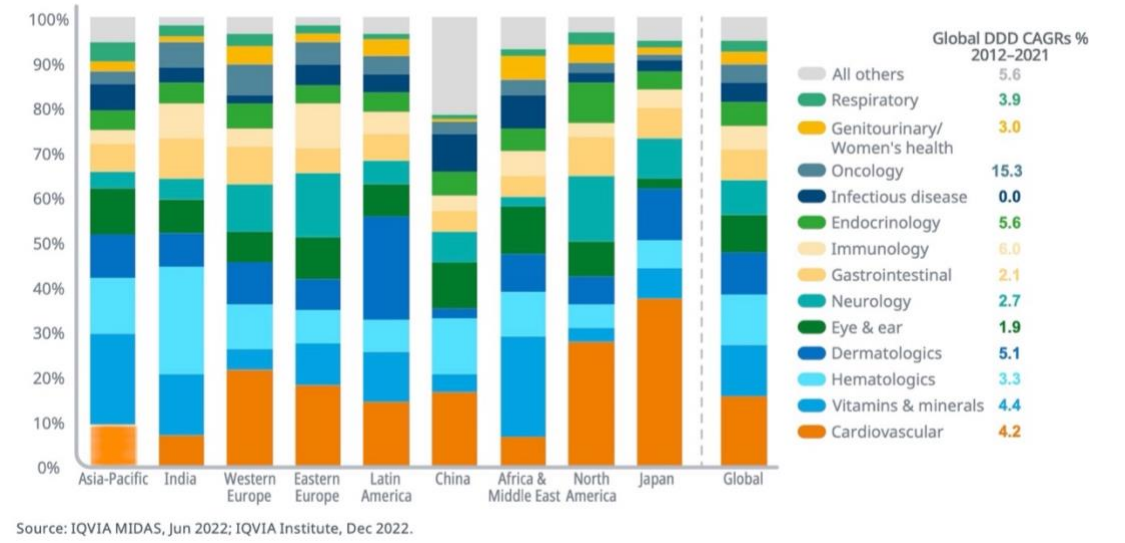


Figure 4: from IQVIA: Global Distribution of Medicine Usage.

Current hotspots in research include immunology, oncology, and weight loss (*Global Use,* 39). In particular, the treatment methods that have been receiving the most attention are Antibody-Drug Conjugates (ADC), Radioimmunotherapy (RIT), T-Cell Engagers (TCE), CAR-T, monoclonal antibodies, Immune System Reset, Tumor Infiltrating Lymphocytes, and GP-1. Biotechnology is expected to grow to 35% of all medication, with an above-average compounded spending growth rate of 7.5-10.5% (*Global Use*, 38). About 12 new biotherapeutics are projected to be approved and launched each year (*Global Use*, 48). The number of biologicals approved per year has increased dramatically in the past decade (Congressional Budget Office, 6).

We will also conduct a Porter's Five Forces analysis on the industry. Buyer power is quite strong: insurance companies can choose between multiple treatments. Many governments have already placed restrictions on prices, and the US government will also take a more active role in price setting due to the Inflation Reduction Act (*Global Use,* 27). Supplier power is very weak in many areas of research as inputs are commoditized. Intra-industry competition varies depending on the specific area and target of research. There is always the challenge of getting to market before

other players, as a certain level of brand value attaches to the first entrant (David, Robey, and Matthews, 27). There are always high barriers to entry, requiring intensive cash burn and regulatory approval before revenue generation. Finally, the threat of substitution varies based on the specific indication that research is targeting. Factors that will favor a given treatment over another are efficacy, reduced side effects, reduced discomfort on administration, affordability, and personalization.

Global Legal and Regulatory Landscape

Legal and regulatory systems have an important influence on biopharmaceutical development. As such candidate products directly interact with patients' bodies, they must pass through the gauntlet of regulatory approval. In the US, the FDA manages the drug approval process. Before testing a new drug, researchers must conduct preclinical research to prove safety and file an Investigational New Drug Application (IND). Once the IND is approved, the candidate is tested through a three-phase process, Phases I, II, and III. Each phase usually involves more patients than the last and thus uses more cash for R&D expenditures. If Phase III results indicate that the drug is safe and effective, the company files a New Drug Application (NDA) for small molecules or a Biological License Application (BLA) for biologics. This application is then reviewed and potentially approved by the FDA. Additionally, there are many programs to speed development of high-need drugs. Generally, the clinical trial procedure is similar in other jurisdictions across the world, consisting of preclinical research, preapproval, clinical trials, regulatory submission and review, and post-market surveillance.

The level of pricing, reimbursement, and medical socialization may also affect the profitability of medication. As mentioned above, regulatory changes like the Inflation Reduction Act can have an important impact on the margins of companies in the biopharmaceutical sector. On the other

hand, the federal government may increase demand by directly subsidizing purchases or providing tax breaks for "employment-based health insurance" (Congressional Budget Office 17). The federal government may also fund biomedical research directly or provide tax credits to pharmaceutical companies (Congressional Budget Office 2). As of 2019, the US Federal government contributed about 40% of "U.S. retail expenditures on prescription drugs" (Congressional Budget Office 17).

Evidence supporting the importance of policy is that over half of revenues generated by the PhRMA (Pharmaceutical Researchers and Manufacturers of America) were domestic, i.e. within the United States (Congressional Budget Office 13). Furthermore, the US pharmaceutical market makes up 30-40% of the worldwide market as of 2016 (Ellis). Heretofore, the US has had the least price-controlled and hence most favorable market for pharmaceutical manufacturers (Congressional Budget Office 23). Hence, any changes to US healthcare policy may impact the future revenues and margins of pharmaceutical companies. Additionally, policy may also influence the populations new candidates are directed at. Upon Medicare Part D implementation in 2006, new investigations targeted towards the Medicare population increased by approximately 50% (Congressional Budget Office 17-18).

Patent law has an important influence as it preserves exclusivity for developers, motivating them and their investors. Without patents, the future revenues would typically not justify the initial fixed investment. After the period of legal exclusivity, the market is directly open to competitors. This reduces prices by 80% in the US, where the initial price is the highest as there are one supplier and many buyers per product (Serra-Buriel et. al.). According to economic theory, the price should fall to the marginal cost of production once the market is open to competitors. It is

important to note that in some countries, especially emerging markets, intellectual property regulations are rather loose.

Financing Techniques:

Emerging biopharmaceutical companies have little or no revenue and thus require outside financing. These strategies include venture capital, collaborative agreements with established companies, and university research labs (Congressional Budget Office 12). PIPEs and SPACs are also common in the industry. Each of these financing channels represents a potential investment opportunity.

Which model should we use?

There are three classes of valuation models: intrinsic, relative, and contingent claim (option) valuation. Intrinsic valuation discounts future cash flows to the present. However, in the case of pre-revenue biopharmaceutical firms, we can only estimate future cash flows to a limited degree of accuracy, so not all sources approve of the DCF method. For relative valuation, since each treatment is unique, it is difficult to find comparable companies or transactions before patent expiration. Furthermore, due to the nature of new product discovery, the expected value of a product may change with clinical trials or competitive dynamics (Congressional Budget Office 13). Therefore, the preferred methodology to use for pre-revenue biopharmaceutical companies, and innovation companies in general, is option-based valuation.

What option-based valuation model is best for pre-revenue biopharmaceutical companies?

This depends on the distribution of future cash flows. Black-Scholes assumes that the prices of the underlying (in the original market model) follow a lognormal distribution. Adapting this to real options requires a lognormal, and hence continuous, unimodal distribution. However, the

underlying future revenue streams for pre-revenue biopharmaceutical companies are quite different from this assumption. They either gain significant market share in the case of regulatory approval or no market share at all (though failed projects may inform future development, *viz.* Congressional Budget Office). Furthermore, at each branching there is one branch that eliminates the possibility of approval.

Such real options are best handled with a decision tree model. Since only one branch usually leads to success, it is tempting to multiply the value of that branch by the probability of approval in a quasi-DCF and account for probability-weighted R&D expenditures. Unfortunately, this method is hard to implement adaptably in Excel and does not reflect the full optionality of clinical development processes. It is more practical to forecast cash flows in the case of success with the first year of revenue as t = 0 and input R&D expenditures into the decision tree.

What Discount Rate Should We Use?

Even with a decision tree model, we will conduct a DCF-like approach on each branch of the tree and discount back to the first node. Therefore, we need a discount rate for future cash flows. The standard cost of equity is $r_f + \beta(r_m - r_f)$. r_f is the risk-free rate; for this number, we will usually use the yield on 10-year or 30-year US bonds or the yield on a risk-free government security in the relevant currency. The equity risk premium $r_m - r_f$ for each market can be calculated as $USERP + Default\ Spread * \frac{\sigma_e}{\sigma_d}$. The second term is only applicable for companies that plan to operate in non-risk-free markets. The default spread here is the spread on bonds, estimated as the spread on a US$-denominated sovereign bond, the CDS spread minus the US CDS spread, or based on ratings. If the non-risk-free market is liquid enough, we can use statistics to calculate each specific country's relative market liquidity. Otherwise, we can use the

emerging market average for relative equity market volatility which is 1.34 as of January 1st, 2024.

Furthermore, even early investors are looking forward to the time when the company either succeeds or is acquired, as most cash flows take place after this time. Upon acquisition by a public company, the investor base will be diversified in their holdings. Therefore, we can usually use simple re-levered median betas despite the investors not being diversified today. In contrast, to value a company for sale to a private investor, we can divide beta by the correlation of the investor's portfolio with the market: $\beta_{undiv} = \frac{\beta_{div}}{\rho_{port,mkt}}$ (Damodaran, *Private Company Valuation*, 13).

In general, we will not have to weight this cost of equity with the cost of debt for pre-revenue biopharmaceutical companies, as their debt is usually negligible. Of course, this low leverage is necessitated by the low chance of a high future revenue, hence making the debt highly speculative. However, the effect of debt is easily incorporated by established methods. Furthermore, debt does not usually increase truncation risk for the entire company, as there is little to liquidate until the product goes on market. However, debt investors may take control in an event of default, thus wiping out equity holders.

Calculation of Expected Cash Flows:

The process that we need to calculate expected future cash flows will be derived from the general free cash flow to the firm methodology. We will adapt this procedure for the unique characteristics of the industry.

Revenues:

First, we will calculate revenue from its main drivers: addressable patient population, adherence, pricing, market share, and the launch curve. Addressable patient population will be derived from the disease profile: prevalence, incidence, diagnosis rates, treatment rates, and clinical trial qualification. Specifically, we can predict the percentage of patients who are diagnosed and the percentage of diagnosed patients that will use the focal product. As known in the industry, prevalence = incidence * average disease term. If we have a paucity of data on recovery rates, as in the cancer industry, there are more advanced methods to estimate current prevalence. However, these calculations vary according to the specific traits of each disease and are beyond the scope of this paper.

Furthermore, trials often move one indication at a time, and the indications tend to be quite narrow, especially for pre-revenue companies. While narrow indication definitions increase the probability of success, they can make the revenue ramp-up quite slow. Thus, we will need to segment the addressable patient population into indications. Then, we will stagger the cash flow streams over time or create separate models for each indication. We need to adjust the probability of passing each phase adjusted according to the "all indications" table in the "Regulatory Approval" section below.

Adherence, also known as compliance, refers to the percentage of doses that a patient takes or is administered relative to the amount prescribed. Adherence depends on disease severity and predicted product efficacy. Adherence also depends on the environment in which the patient receives medication; patients are far more likely to follow the treatment plan if medications are taken in-hospital or with another care provider. Information on this factor and its associations with drivers is also available from medical papers.

Pricing can be evaluated based on multiple factors including but not limited to the severity of disease, number of existing products on market, expected relative efficacy of the candidate product, and the size of the addressable market. As an example of the last factor, orphan drugs "cost five times more than non-orphan drugs" as of 2020 (Chambers, James D. *et al.*). Thus, we could use prices for similar products with similar indication severities, relative efficacies, and addressable markets to conduct relative pricing. Alternatively, we could use a supply-demand model to predict pricing. Note that average sales price, which is far lower than the end-user prices, is the price that becomes the pharmaceutical company's revenue per dose (David, Robey, and Matthews 18).

Market Share:

We can use data on the number of competitors and entrance order as well as efficacy where available to predict market share (David, Robey, and Matthews, 27). The Pharmagellan Guide predicts market share as follows:

	Share for nth entrant:				
# Medicines	1	2	3	4	5
1	100%				
2	60%	40%			
3	40%	30%	30%		
4	31%	23%	23%	23%	
5	24%	19%	19%	19%	19%

** Figure 5: From Frank, David S. *The Pharmagellan Guide*, 2016

Figure 5 indicates that the first mover has an advantage in terms of market share and the rest have less, possibly due to publicity and brand loyalty. However, since many markets such as psoriasis have many existing products, this table is no longer suitable. Additionally, we need expected values of all inputs for valuation, and this table only works for discrete numbers of market participants. Evidently, we will not find any data on a fractional number of market

participants. We can use statistics to interpolate and cautiously extrapolate from data. We will first segment the Figure 5 into two vertical categories: first mover and non-first mover. Then, we will fit a model for each segment. From inspection, we find that the market share for both first movers and non-first movers is approximately inverse-proportional to the number of products on the market, including the focal candidate. Though the basic inverse function does not fit well to the data, we can model the situation as the first mover having priority on the market share and the remaining products capturing equal market share. Specifically, we can specify:

First mover market share: $f(n) = \frac{a}{n}, n \geq 2$

Later mover market share $g(n) = \frac{1-f(n)}{n-1}, n \geq 2$

With *a* being the first-mover advantage factor and *n* being the total amount of products. Note that for the first product to market, we may have to adjust our prediction down initially to keep the predicted market share under 100%. We could directly linearize as seen in the purple line in Figure 6. $f(n) = (2-n)(1) + (n-1)\frac{a}{n}$, $1 \leq n \leq 2$. More complex and accurate functions could marginally improve the prediction; however, little impact is expected on the final valuation. This model fits very well, as seen in Figure 6.

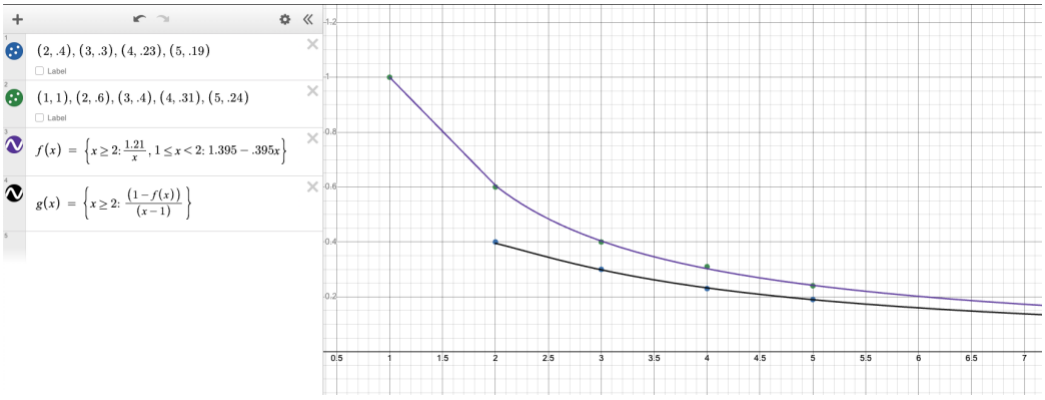


Figure 6: Plot and functional fitting of Pharmagellan Data

We can see that a ≈ 1.21 for n > 2 given the Pharmagellan summary statistics.

Since the datapoints above are summary statistics rather than "data" *per se*, they are much closer to our fitted model than they would be otherwise. While updating the model for new data, such as recent studies on market share, we will encounter many more data points that are much more widely scattered. It is only practicable to directly use data on products that have reached peak market share. Otherwise, we can reverse the effect of the ramp function that will be discussed later by dividing it out.

We could fit the model rigorously by optimizing *a* for minimum squared errors. However, an even better method is to minimize percentage differences relative to predictions, since returns are measured in percentages (*viz* Tofallis). Finally, if a product has a non-negligible chance of being first-to-market but also has a chance of being later-to-market, we may weight the probabilities accordingly. Therefore, the predicted market share in year *t* *of availability* would be:

$$p_{first}E(f(n_t)|first) + \left(1 - p_{first}\right)E(g(n_t)|not\ first)$$

Due to near-linearity between any two given observable (integer) market participant counts, we can also approximate this as:

$$p_{first}f(E(n_t|first)) + \left(1 - p_{first}\right)g(E(n_t|not\ first))$$

Notice that the number of market participants in each year depends on whether the focal product is first-to-market for a given indication.

Such a method could be dynamically modified to suit the demands of prediction. One potential optimization considers the probability of using each of the two models in determining the relative importance of accuracy. Specifically, we can simultaneously fit both functions for our

specific prediction by using the following minimization (solvable with analytical or numerical optimization):

$$\min_a p_{first}\left[\sum_{i=1}^{N(first\ mover\ products)}\ \sum_{t=0}^{tmax(i)}\left(\frac{market\ share\ (i,t)}{f(n_t)}-1\right)^2\right]+(1-p_{first})[\sum_{j=1}^{N(later\ mover\ products)}\ \sum_{t=0}^{tmax(j)}\left(\frac{market\ share\ (j,t)}{g(n_t)}-1\right)^2]$$

Notice that the probability weights are based on the assessed probability of our product being first to market. Furthermore, they do not need to be linear, as shown here. As we are minimizing a function rather than calculating an average, the probability weights can be transformed with any strictly increasing function $h(p)$, including p^2.

In fact, a generic function to fit could be:

$$\min_a h(p_{first})\left[\sum_{i=1}^{N(first\ mover\ products)}\ \sum_{t=0}^{tmax(i)}\left(\frac{market\ share\ (i,t)}{f(n_t)}-1\right)^2\right]+h(1-p_{first})[\sum_{j=1}^{N(later\ mover\ products)}\ \sum_{t=0}^{tmax(j)}\left(\frac{market\ share\ (j,t)}{g(n_t)}-1\right)^2]$$

Further research may elucidate the best transformation h to use in this case. After fitting these functions to the data, we will obtain the parameter a that should then enter both models. We can then predict the conditional market shares and weight them as previously explained. The order to market and the number of competing products should both be based on a thorough analysis of competitive dynamics in the industry.

We may also adjust for a gradual launch, depending on the specifics of the product and company. That is, we will include a gradual ramp-up to the dynamic "peak" market share within each indication. We can multiply the original prediction by this ramp factor $r(t)$.

To recap, final predicted market share in year t=

$$r(t)\left[p_{first}E(f(n_t)|first)+\left(1-p_{first}\right)E(g(n_t)|first)\right]\ where\ f(n)=\frac{a}{n}, g(n)=\frac{1-f(n)}{n-1}.$$

Note that the speed of the ramp also depends on the severity of the unmet need. That is, it depends on the severity of the disease, the number of existing treatments, and the expected relative efficacy of the candidate product. A treatment that could save patients' lives would ramp up to 100% rapidly, one that could drastically improve a patient's life would ramp up within a few years, but one that only provides minor improvement may take much longer to ramp up.

Now, we are ready to forecast revenue in the case of success. Note that revenue only occurs if all clinical trials are successful. We need to adjust the number of remaining cases for new cases, total patient count treated by *all* companies, cases resolved with treatment, and the fatality rate. Specifically, we find each year's remaining cases by incrementing the previous value of remaining cases based on the other rows or variables (depending on our implementation).

For temporary treatments: $Remaining\ cases_{\ t+1} = New\ cases + Remaining\ cases_t - (resolved\ without\ treatment + fatalities)$

For cures: $Remaining\ cases_{\ t+1} = New\ cases + Remaining\ cases_t - (total\ cases\ treated\ by\ all\ companies + resolved\ without\ treatment + fatalities)$.

Operating Costs & Expenditures

Next, we will calculate the expenditures: cost of goods sold, SG&A, R&D, and regulatory. According to S&P Capital IQ, the averages for expense percentages were as follows ("Pharmaceuticals, Biotechnology, and Life Sciences – Key Stats and Ratios"):

	This Year	5-Year Averages
Revenue	≡100%	≡100%
Implied COGS %	60.2%	59.48%
Gross Profit %	39.8%	40.52%
SG&A %	24.6%	24.44%

Figure 7: Average Biopharmaceutical Cost Margins

We can multiply the COGS % and SG&A % by the revenue for a company to find the COGS and SG&A expenses for each year after approval.

***Research and Development Expenditures*:**

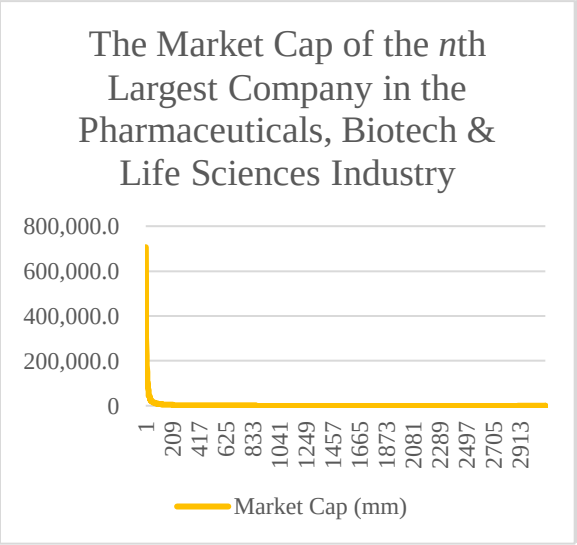
R&D and regulatory expenditures can be calculated as suggested by the data below. Furthermore, although they should be matched to revenues for general valuation purposes (*viz.* Damodaran, *R&D*), they are reported prior to revenues. We can either incorporate the cash flows directly into the valuation or we can go through the capitalization and amortization process. However, capitalization is not recognized in tax accounting. Furthermore, we are not using the margin to project reinvestment based on revenue or adjusted EBITDA since such numbers are not meaningful yet. Therefore, any such adjustments will not affect cash flows. Since we are trying to calculate cash flows, we may directly subtract expenditures from the EBITR&D from the previous step. Using the R&D capitalization process can help make adjusted EBIT margins comparable with companies outside the industry, though this step should occur separately.

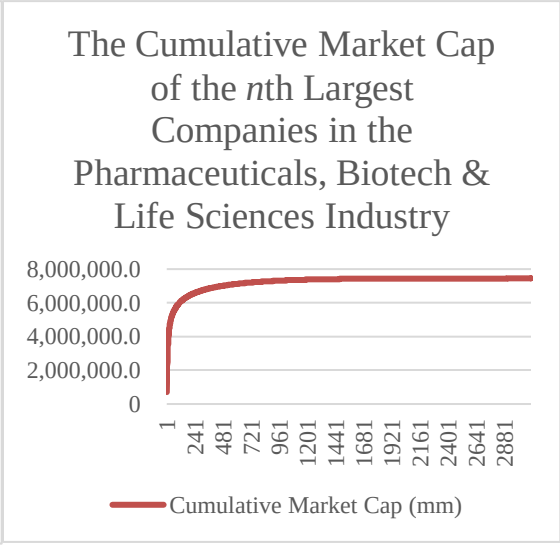
The preclinical stage takes an average of $474 million over as long as 5-6 years. Phase I trials take over $28 million over an intended time of several months. Phase II trials take $65 million over an intended time of up to 2 years, though actual time spent in Phase II is often longer, as long as 41 months. Phase III take $282 on average over an intended time of up to 4 years per approved new drug (Congressional Budget Office 15, inflation-adjusting from a 2016 study; "Step 3", FDA; Agrawal, "Accelerating Clinical Trials"). Note that the specific time and cost varies according to each product's indication, characteristics, and any special programs (Orphan Drug, Accelerated Approval) it is part of. Furthermore, there is the opportunity cost of not investing in other products. However, the use of AI may drastically reduce the costs and time spent on each stage, especially preclinical research, through both molecule discovery and trial

optimization (Agrawal, “Fast to First-In-Human”). Expenditures for each stage will only occur if the candidate passes the previous stage.

Regulatory Approval:

As of 2021, only 12% (10-14%) of drugs that enter clinical trials receive approval and go on market (Congressional Budget Office 14, 17). Specifically, the cumulative advancement rate at each phase was 100% at Phase I (by definition), 60% at Phase II, 20% Phase at III, and 12% at approval (Congressional Budget Office 15). The probability of approval also varies according to the indication: probabilities (standard errors) of success for each therapeutic area are seen in Appendix A (Wong 2019). Note that some candidates may not even reach the clinical trial stage. Therefore, even though the scale of potential revenues is immense, in most cases they are never realized. Reflective of this reality is the fact that almost all market cap is concentrated in the largest companies:





Figures 8 and 9: Data from S&P CapitalIQ

We can use the appropriate probabilities to weight the branches of the tree in our model. We may assume that only one branch of the tree contains any positive cash flows at all, but this does not account for the potential for failed candidates to inform future pipelines. Also note that the regulatory filing fee is not negligible, with the PDUFA form costing $4,048,695 as of April 2024 ("PDUFA", FDA). This negative cash flow should be included at the end of Phase III. Finally, note that news such as better-than-required clinical trial results or holds due to severe adverse events should inform changes to predicted approval rates.

Reinvestment:

Next, we will predict reinvestment using the standard technique. Non-cash working capital is 9.98% of revenue for biotechnology companies and 22.37% for pharmaceutical companies (Damodaran, "Working Capital Ratios"). However, this may change by the time our focal company reaches maturity, as the entire biotechnology industry is still in an early stage. We could use existing pharmaceutical companies' NWC/revenue percentage, but this area merits further research.

Loss of Exclusivity and Terminal Value:

The characteristics of the biopharmaceutical industry regarding loss of exclusivity and terminal value are rather unique. Due to the vast amount of information expressed in a patent application, most products face stiff competition shortly after loss of exclusivity. Prices fall an average of 80% over the course of 2-5 years. Typically, prices decrease to 55% by the first year after generic entry, and gradually decrease to 20% over the next few years. However, this decrease is highly variable across various areas and specific medications (Vondeling *et al.*). The more expensive a product is during the period of exclusivity, the more its price tends to decrease afterwards (David, Robey, and Matthews 37). This is consistent with economic theory: price should

approach marginal cost in a competitive market. The market share will also decrease as may be predicted from the number of new entrants copying the treatment. Thus, we can project revenues and variable costs to fall sharply, and the product will reach an adverse maturity. Therefore, the present value of terminal value takes up a smaller portion of the total present value of any product or pre-revenue company than in other industries.

However, several factors protect against this adversity. Firstly, the Hatch-Waxman Act (P.L. 98-417) provides five additional years of patent protection to balance the effect of extended clinical trials (Congressional Budget Office), amounting to a total of 25 years from filing. Additionally, companies often pursue a string of separate filings to extend patent protection, though this has recently come under scrutiny. Finally, biologic products such as CAR-T require a cell line, not only the information disclosed in the patent (Congressional Budget Office). This makes cell-line based therapeutics harder to copy; the price should fall by less than 80% and the market share should fall less as well.[1]

Due to the length of patent protection, we should project out 20 or more years of cash flows for biopharmaceutical companies, rather than the standard 10 years. Alternatively, we could still project out 10 years of cash flows but use the sum of an annuity and a perpetuity for the terminal value. Even more precisely, we could use an annuity, a ramp-down, and a perpetuity, but given the high level of discounting far into the future, this will not substantially change the intrinsic value. Additionally, the ramp-down rate is highly variable and dependent on the specific product market and the number of generic competitors (*viz.* Vondeling *et al.*).

[1] The patent law for biopharmaceutical products is complex; this is a high-level summary.

Expansion Options:

Upon receiving approval for the first product, the company may be able to use its cash flows to expand the product to other indications or develop more products. Developing an existing product for a new indication provides regulatory advantages over a new product, especially in oncology (Mills). In some markets, the price may also change by indication (Mills). Alternatively, a company could be acquired, in which case the cash flows contribute to the acquirer's R&D capacity. However, the development of new products is not free, and like any growth, it requires reinvestment.

Dilution:

Since pre-revenue companies require high capital expenditures, they must constantly raise additional funding. However, the dilution to existing shareholders is already accounted for in the negative projected cash flows in the first few years. The consequent reduction in present value is exactly what the new shareholders' funds pay for. Therefore, it is ***not*** necessary to account for dilution separately from the other factors.

Section Conclusion:

Thus, we can find the present value of the company or any of its products at the present time and at various milestones in the research process using standard valuation techniques. Note that since many inputs are uncertain, we can use Crystal Ball or another statistical add-on to simulate distributions, yielding a range of potential values. We can also use sensitivity analysis (known as "What-If" analysis in Microsoft Excel) to evaluate the impact of specific factors without the need for specialized software.

Truncation Risk:

Truncation risk is augmented by the high rate of cash burn without revenue. There is a risk that after a certain number of failures, biopharmaceutical companies may choose to wind down research in a certain category. This will likely lead value to drop close to zero and may result in a complete payback of remaining funds. Since the company would only suffer losses if the product does not receive FDA approval, the holding period return will always be negative in such a case.

Furthermore, as seen above, debt may increase truncation risk for equity holders. Upon discovering that a company is distressed, potential investors may refuse to provide funding. Therefore, biopharmaceutical companies may find themselves unable to recapitalize using new debt or equity, leading to a vicious cycle. It is always advisable for a pre-revenue biopharma company, like any other pre-revenue company, to maintain a cash cushion to stave off any fears of credit risk.

For equity investors, it is important to ensure that a company is not in distress before investing. Alternatively, the presence of a high debt level in a company that has recently announced positive results could be a short indicator. Specifically, the company may not be able to last until approval under the current equity holders. Though such market-friction based topics are beyond the scope of this paper, they do merit further research.

The Effect of Mergers and Acquisitions (and Partnerships)

The upcoming patent cliff and the threat of replacement makes M&A and partnership deals crucial. Furthermore, acquisition means that development no longer relies on outside funding, which might be challenging to obtain. Instead, it can rely on the new parent company's stockpile of cash and financing capabilities to fund R&D expenditures for more pipelines simultaneously.

This also means that the acquired company can be early to market and capture a larger initial market share. The effect is clearly visible in the market price. The average premium on biopharmaceutical acquisitions from 2010-2019 has fluctuated but increased in the long-term, from 47% in 2010 to 97% in 2019 (Mikulic). In contrast, many articles suggest that the average premium on all M&A deals is only about 30% (*viz* Kengelbach *et al.*).

With such attractive premiums, it is well worth investigating the factors that drive such acquisitions using public information. Major trends in the space will be an increase in "programmatic" portfolio-based acquisitions, innovation acquisitions, partnerships, digital assets, and a growing focus on emerging markets (Ascher *et al.*). Thus, biopharma startups that have a better fit with established companies' portfolios, have more innovative ideas, or develop IT are more likely to be targeted for a deal. Additionally, emerging market companies may experience better M&A prospects than in previous years.

Discussion:

Due to the low probability of approval and the high expected value conditional on approval, it is especially important to diversify. A few companies will return an astronomical multiple on invested capital, but most will return close to 0x (-100%). Furthermore, given the low probability of sufficient cash flows, debt increases the risk of equity truncation. Any concentrations greater than 5% of a portfolio would be highly speculative and not recommended. Investors may diversify across target indications, mechanisms of treatment, and stages of research.

Many of the drivers of our valuation will change from year to year. Prices and regulatory costs will change depending on the macroeconomic environment and political decisions. Furthermore, the expenditures and probabilities of success are likely to change with emerging technologies.

Therefore, this paper should be taken as a general framework, with the specific numbers to be updated regularly.

Conclusion:

The biopharmaceutical industry has the potential to transform patients' lives. However, pre-revenue biopharmaceutical companies need extensive investment before they can bring their products to market. In this paper, we have built a model for valuing such companies from underlying medical and economic fundamentals. First, we need to project out the next 10-15 years of cash flows in detail using techniques customized to the industry. Then, we can add an annuity value followed by a perpetuity after loss of exclusivity. Synergies from M&A are much more impactful than in most fields, especially in the timing of cash flows. Better funding will speed development, crucial in capturing both market share and time value, with the additional benefit of increasing access to treatment.

Appendix A

Progress and approval probabilities by indication (Wong 2019)

All Indications:

Therapeutic Group	Phase 1 to Phase 2	Phase 2 to Phase 3	Phase 3 to Approval	Overall
Oncology	57.6% (0.4%)	32.7% (0.6%)	35.5% (1.4%)	3.4% (0.2%)
Metabolic/Endocrinology	76.2% (0.7%)	59.7% (1.0%)	51.6% (1.5%)	19.6% (0.7%)
Cardiovascular	73.3% (0.8%)	65.7% (1.1%)	62.2% (1.6%)	25.5% (0.9%)
CNS	73.2% (0.6%)	51.9% (0.9%)	51.1% (1.5%)	15.0% (0.6%)
Autoimmune/Inflammation	69.8% (0.6%)	45.7% (0.9%)	63.7% (1.5%)	15.1% (0.6%)
Genitourinary	68.7% (1.7%)	57.1% (2.3%)	66.5% (3.2%)	21.6% (1.6%)
Infectious Disease	70.1% (0.7%)	58.3% (1.0%)	75.3% (1.3%)	25.2% (0.8%)
Ophthalmology	87.1% (1.3%)	60.7% (2.3%)	74.9% (3.0%)	32.6% (2.2%)
Vaccines	76.8% (1.0%)	58.2% (1.4%)	85.4% (1.4%)	33.4% (1.2%)
Overall	**66.4% (0.2%)**	**48.6% (0.3%)**	**59.0% (0.6%)**	**13.8% (0.2%)**

Lead Indications:

Therapeutic Group	Phase 1 to Phase 2	Phase 2 to Phase 3	Phase 3 to Approval	Overall
Oncology	78.7% (0.7%)	53.9% (1.2%)	48.5% (2.4%)	11.4% (0.7%)
Metabolic/Endocrinology	75.2% (1.0%)	57.0% (1.4%)	62.8% (2.1%)	21.3% (1.0%)
Cardiovascular	71.1% (1.1%)	64.9% (1.5%)	72.3% (2.1%)	26.6% (1.2%)
CNS	75.0% (0.8%)	54.5% (1.2%)	63.0% (1.9%)	19.3% (0.9%)
Autoimmune/Inflammation	78.9% (0.8%)	48.7% (1.2%)	68.6% (1.8%)	20.3% (0.9%)
Genitourinary	73.5% (1.9%)	59.2% (2.5%)	69.3% (3.5%)	25.3% (2.0%)
Infectious Disease	74.6% (0.9%)	58.0% (1.4%)	76.6% (1.7%)	26.7% (1.1%)
Ophthalmology	89.0% (1.5%)	57.6% (2.8%)	74.2% (3.9%)	30.7% (2.7%)
Vaccines	75.8% (1.4%)	57.1% (2.1%)	85.1% (2.2%)	31.6% (1.7%)
Overall	**75.8% (0.3%)**	**55.6% (0.5%)**	**67.7% (0.7%)**	**21.6% (0.4%)**

References

Agrawal, Gaurav *et al.* "Accelerating clinical trials to improve biopharma R&D productivity." McKinsey, 22 January 2024. https://www.mckinsey.com/industries/life-sciences/our-insights/accelerating-clinical-trials-to-improve-biopharma-r-and-d-productivity.

Agrawal, Gaurav *et al.* "Fast to first-in-human: Getting new medicines to patients more quickly". McKinsey, 10 February 2023. https://www.mckinsey.com/industries/life-sciences/our-insights/fast-to-first-in-human-getting-new-medicines-to-patients-more-quickly.

Ascher, Jan *et. al.* "Five ways biopharma companies can navigate the deal landscape." McKinsey, 1 February 2023. Navigating M&A deals in the biopharma industry | McKinsey.

Chambers, James. D. *et al.* "Orphan Drugs Offer Larger Health Gains but Less Favorable Cost-effectiveness than Non-orphan Drugs." Society of General Internal Medicine via NCBI, 13 April 2020. doi: 10.1007/s11606-020-05805-2

Congressional Budget Office. *Research and Development in the Pharmaceutical Industry*. April 2021. https://www.cbo.gov/publication/57126, https://www.cbo.gov/system/files/2021-04/57025-Rx-RnD.pdf.

Damodaran, Aswath. *Private Company Valuation*. NYU Stern. https://pages.stern.nyu.edu/~adamodar/pdfiles/ovhds/inv2E/PvtFirm.pdf

Damodaran, Aswath. "Working Capital Ratios by Sector." NYU Stern, January 2024. https://pages.stern.nyu.edu/~adamodar/New_Home_Page/datafile/wcdata.html.

Damodaran, Aswath. *Research and Development Expenses: Implications for Profitability Measurement and Valuation*. NYU Stern. https://pages.stern.nyu.edu/~adamodar/pdfiles/papers/R_D.pdf

David, Frank S., Seth Robey, and Andrew Matthews. *The Pharmagellan Guide to Biotech Forecasting and Valuation*. 2016.

Ellis, Lisa. "Snapshot of the American Pharmaceutical Industry." Harvard T.H. Chan School of Medicine, 14 July 2016. https://www.hsph.harvard.edu/ecpe/snapshot-of-the-american-pharmaceutical-industry/.

IQVIA Institute, *The Global Use of Medicines 2023*, 2023. https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/the-global-use-of-medicines-2023.

Kengelbach, Jens *et al.* "The 2019 M&A Report: Downturns are a Better Time for Deal Hunting." BCG, 2019. https://www.bcg.com/publications/2019/mergers-and-acquisitions-report-shows-downturns-are-a-better-time-for-deal-hunting.

Mills, M., Michaeli, D., Miracolo, A. *et al.* Launch sequencing of pharmaceuticals with multiple therapeutic indications: evidence from seven countries. *BMC Health Serv Res* **23**, 150 (2023). https://doi.org/10.1186/s12913-023-09095-2

Mikulic, Matey. "Premiums for public U.S. biopharma company trade sales 2010-2019." Statista, June 21, 2022. https://www.statista.com/statistics/1093439/biopharma-company-trade-sales-premiums-us/.

Mullard, Asher. "Shifts in the clinical trial landscape." Nature, 8 March 2024. https://www.nature.com/articles/d41573-024-00048-w.

"Pharmaceuticals, Biotechnology, and Life Sciences – Key Stats and Ratios." CapitalIQ, 6 April 2024. https://www.capitaliq.com/CIQDotNet/Lists/KeyStats.aspx?listObjectId=100886603.

"Prescription Drug User Fee Amendments." FDA. 2023. https://www.fda.gov/industry/fda-user-fee-programs/prescription-drug-user-fee-amendments.

Serra-Buriel, Miquel *et. al. Life After Patent: Drug Price Dynamics and Cost-Effectiveness Analysis*. June 2023. https://www.medrxiv.org/content/10.1101/2023.06.08.23290510v1.full.pdf.

Statista. *World Pharmaceutical Sales from 2020 to 2022, by region*. February 2024. https://www.statista.com/statistics/272181/world-pharmaceutical-sales-by-region/.

"Step 3: Clinical Research." FDA. January 2018. https://www.fda.gov/patients/drug-development-process/step-3-clinical-research.

Tofallis, Chris. *Least Squares Percentage Regression*. SSRN Electronic Journal, May 2009. doi:10.2139/ssrn.1406472.

Vondeling, Gerard T. *et al.* "The Impact of Patent Expiry on Drug Prices: A Systematic Literature Review." Applied Economic Health Policy via NCBI, 17 July 2018. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6132437/.

Walsh, Gary and Eithne Walsh. *Pharmaceutical Benchmarks 2022.* PubMed, National Library of Medicine. December 2022. https://pubmed.ncbi.nlm.nih.gov/36471135/.

Wong, Chi Heem, Kien Wei Siah, Andrew Lo. *Estimation of Clinical Trial Success Rates and Related Parameters.* Biostatistics, Oxford Academic. 31 January 2018.