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Evaluation of the Development of a New Drug: VIR-7831 Case Study

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Master of Science in Finance

Supervisor:
Phd, José Carlos Gonçalves Dias,
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BUSINESS
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Department of Finance

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To being with me, I am extremely grateful to my supervisor Prof. José Carlos Dias for the time, support, and patient dedicated to me during my Master's thesis and study. His knowledge and humanity have been essential to the carry out my project. I would also like to thank Mr. David Kellogg for the help and support that he provided to me without any hesitation, and despite being a complete stranger; his experience and research have inspired me since the beginning of this project. Finally, I would like to express my gratitude to my parents, my grandmother, my brother, and my old nanny. Without their undeterred encouragement and economic support in the past few years, it would have been impossible for me to complete my study.

Resumo

A Biotecnologia é uma das mais promissoras indústrias, cerca de biliões são despendidos para a investigação e desenvolvimento, todos os anos, no âmbito da descoberta, produção e comercialização de produtos biofármacos, de forma a tratar inúmeras doenças. Entender como essas investigações, poderão originar dinheiro no futuro é difícil, mas ao mesmo tempo, é essencial compreender o verdadeiro valor de uma companhia biotecnológica. O intuito deste projeto é o de estimar o valor presente, da futura comercialização de um fármaco em subdesenvolvimento. No início de 2020, a humanidade viu-se confrontada com um novo vírus, SARS-COV-2, proporcionando uma crise pandémica mundial. Face à atualidade do tópico, foi decidido elaborar um caso prático, avaliando VIR-7831, um anticorpo ao Covid-19, que a Biotécnologia VIR se encontra a desenvolver.

Palavras Chave: SARS-COV-2, Biotecnologia, Métodos de Avaliação, Estudo de Caso, VIR-7831.

Abstract

Biotechnology is one of the most promising industries, billion of dollars are expended in Research & Development every year to discover, develop, and commercialise biopharmaceutical products for treating several diseases. Understanding how those investments will generate cash flows in the future is difficult, but at the same time it is essential to understand the real value of a biotechnology company.

The aim of this project is to estimate the present value of the future commercialisation of an underdevelopment drug. In the beginning of 2020, the humanity stepped in to deal with a new virus, SARS-COV-2, that caused a worldwide pandemic crisis. Due to the actuality of the topic, it was decided to elaborate a practical case study by evaluating VIR-7831, a COVID-19 antibody that VIR Biotechnology is currently developing.

Keywords: SARS-COV-2, Biotechnology, Evaluation Methods, Case Study, VIR-7831.

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Glossary

Antigen: molecules of the Pathogen that are recognizable by the immune system.

B-Cells: immune system cells.

BSM: Black-Scholes Merton.

CAGR: Compound Annual Growth Rate.

CMC: Chemistry, Manufacturing, and Control.

DCF: Discount Cash Flow or Development Cash Flow.

ELISA Test: Immunographic test.

ENPV: Expected Net Present Value.

Epitope: part of the Antigen that bounds the antibody.

EUA: Emergency Use Authorisation.

FDA: Food and Drug Administration.

FTE: Full-time Equivalent.

GSK: GlaxoSmithKline.

Humoral Immunity System: system dedicated to the production of antibodies.

Hybridoma: cell generated by fusing Myeloma cells with B-lymphocytes.

Immunoglobin: synonym of antibody.

Interaction Affinity: straight of the boundary between the antibody and the epitope.

mAb: Monoclonal Antibody.

Memory Cells: B-cells that contain information of a previous infection.

Myeloma Cells: also known as immortal cells, are tumoral plasma cells that can replicate themselves indefinitely.

NDA: New Drug Application.

NME: New Molecular Entity.

NPV: Net Present Value.

pAb: Polyclonal Antibody.

Pathogen: viruses, bacteria, anything non recognized by the human body.

PV: Present Value.

R&D: Research & Development.

RANPV: Risk Adjusted Net Present Value.

VIR: Vir Biotechnology.

Introduction

This thesis is a Master project that intends to explain and demonstrate the difficulty of evaluating a project/investment for the development of a new drug. Since most of the evaluation methods are not suitable for estimating the intrinsic value of projects in the pharma/biotech industry (that is the core value of a biotech company), it will be used valuation models that are able to implement the risk of the different project's stages (*Risk Adjusted NPV*/*Decision Tree Model* and *Binomial Lattice Model*) for the estimation of the present value of these R&D investments.

As the applications of these methods are based mostly on assumptions and scratches taken from other research papers, due to the high level of uncertainty and the lack of public information that characterises this industry, the result will be an estimation and not an empirical result, whose purpose is to give an idea of how the developing process of a new drug can add value to the present free cash flow of a biotechnological company.

The case study analysed in this Master project takes in consideration the antibody Vir-7831, an antibody for treating SARS-CoV-2 disease that Vir Biotechnology, Inc (VIR) and GlaxoSmithKline PLC (GSK) are currently developing through a partnership.

VIR is a clinical-stage biotechnology company, specialised in developing treatments to prevent infections. Its platforms are focused on antibodies with a pipeline that includes under development products to fight hepatitis B virus, influenza A, HIV, tuberculosis, and SARS-CoV-2.

1. Main Literature Review

1.1 Traditional Project Valuation Methods

Project valuation has two main purposes: valuing investments projects, as we can understand from the name, and comparing different projects from the same investment pool (Kodukula and Papudesu, 2006). The main methods to accomplish this purpose are:

- Net Present Value;
- Risk-Adjusted Net Present Value.

1.1.1 Net Present Value

The calculation of the Net Present Value (NPV) is the approach on which are based all the others Discounted Cash Flow Models. Basically, it accounts all the investments costs and the free cash flows that the project will generate during its life, and it calculates their Present Value (PV) by discounting them for a discount factor that should represent the risk of the project (Kodukula and Papudesu, 2006), that is:

$$Project\ NPV = PV\ of\ free\ cash\ flow\ in\ production\ phase - PV\ of\ investment\ costs. \quad (1)$$

A useful formula used by Damodaran (2006) is:

$$NPV = \sum_{t_0}^{n} \frac{CF_t}{(1+r)^t} \quad (2)$$

where:

$CF =$ are the cash flow generated by the project at time t,
$r =$ is the discounting rate.

1.1.2 Risk-Adjusted Net Present Value

The Risk-Adjusted Net Present Value (RANPV), also known as Expected Net Present Value (ENPV), is used especially for the valuation of Research & Development (R&D). The possibility of failure is a great concern in R&D investments, and it needs to be taken into consideration. For this reason, by multiplying each CF_t by the estimated probability of success (or failure) it is possible to include the uncertainty in the RANPV of the project.

Furthermore, through the RANPV's probabilities it is possible to build a decision tree model that will allow the analyst to investigate the impact of operating options on the value of the project (Bode-Greuel and Greuel, 2004).

1.2 Real Option Project Valuation Methods

Real Options, as we can understand by the name, are options on real assets, and not on financial ones. This valuation method, also known as "Contingent Claim Approach", consists in having opportunities of changing investments or strategies in the future; they give the possibility to use future news/information to change the strategy of a project. We can translate this possibility of making future choices in "Managerial Flexibility", and we can give a value to that. As the traditional NPV does not have the possibility of implementing new information in the valuation model, it is common to refer it as "Static NPV", while the real option one is called "Expanded NPV". The latter has the characteristic to be of greater value, as the standards DCF methods discount the most likely future outcomes, but in reality there are more possible outcomes upside and beside that value, that we can respectively translate in profits and losses. Having this flexibility means valuating all the possible investment opportunities, and consequently making more profits and avoiding losses (Dias, 2020).
We can summarise the relationship between the two NPVs in this formula:

$$Expanded\ NPV = Static\ NPV + Flexibility. \quad (3)$$

therefore,

$$Expanded\ NPV = Static\ NPV + Optimum\ Premium\ . \quad (4)$$

This valuation method takes in account important elements, such us timing, irreversibility, and uncertainty (Dias, 2020). The most common models are:

- Black-Scholes-Merton Model;
- Lattice Model.

1.2.1 Black-Scholes-Merton Model

The Black-Scholes-Merton Model is a generalised version of the Black-Scholes Model, a free-arbitrage model that evaluates European-style options on free-dividend stocks. The new model allows stocks paying dividends thanks to the introduction of a continuous dividend yield represented by the letter q (Dias, 2020).

The BSM formula is computed as follow:

$$c_t\,(S,K,T) = S_t e^{-q\tau} N(d_1) - K e^{-r} N(d_2) \tag{5}$$

and

$$p_t\,(S,K,T) = K e^{-r} N(-d_2) - S_t e^{-q\tau} N(-d_1), \tag{6}$$

where

$$d1 = \frac{\ln\left(\frac{S_t}{K}\right) + \left(r - q + \frac{1}{2}\sigma^2\right)\tau}{\sigma\sqrt{\tau}} \tag{7}$$

and

$$d_2 = \frac{\ln\left(\frac{S_t}{K}\right) + \left(r - q - \frac{1}{2}\sigma^2\right)\tau}{\sigma\sqrt{\tau}} \tag{8}$$

where:

c_t and p_t = are respectively the European call price and the European put price,
S_t and K = are respectively the underlying asset price and strike of the option with expiration at time T,
$N(.)$ = represents the cumulative density function of the univariate standard normal distribution,
τ = is the option time to maturity,
σ = is the annualised volatility,
q = is the continuously compounded dividend.

After this explanation, we need to transform those financial option variables into real ones, in order to use the BSM model in the contingent claim approach. Table 1 shows the call option example:

Investment Opportunity	Variable	Call Option
PV of a project's expected cash flows	V_t	Stock price
Investment cost	X	Strike price
Length of time the decision can be deferred	τ	Time to expiration
Project value uncertainty	σ	Stock's volatility
Riskless interest rate	r	Riskless interest rate
Rate of return shortfall	q	Dividend yield

Table 1: Mapping an Investment Opportunity on a Project onto a Call Option. Source: Dias (2020).

1.2.2 Binomial Lattice

The Binomial Lattice, or Binomial Model, is a kind of decision tree that represent the possible evolution of underlying asset's price during the life of the option. S_0 is the present value of the underlying assets, it goes up and down, and these movements are represented by u and d. At the end of the first period the outcomes will be S_0u and S_0d. These movement will be repeated at the end of each period (for example at the end of the second period the values will be S_0u^2, S_0ud, and S_0d^2) until the last node where is represented a range of possible asset values at the end of option life. The total length of the lattice model is the option life, more time steps we include in the model, more accurate will be the option's value (Kodukula and Papudesu, 2006).

In Fig. 1 is plotted an example:

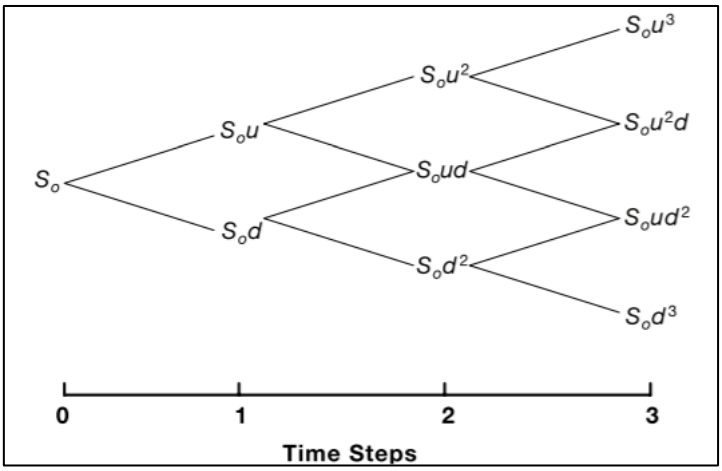


Figure 1: Three Time Steps Binomial Model. Source: Kodukula, Papudesu (2006).

The most used way to solve this model is through the *risk-neutral probabilities approach*. By applying this approach, we need to risk adjust all the cash flows in the binomial model with risk-neutral probabilities and discount them at the risk-free rate.

The risk- probability can be formulated as follow:

$$p = \frac{\exp\big((r-q)\sqrt{t}\big) - d}{u - d} \tag{9}$$

where u and d are function of the volatility of the underlying asset:

$$u = \exp(\sigma\sqrt{\delta t}) \tag{10}$$

and

$$d = \exp(-\sigma\sqrt{\delta t}) \tag{11}$$

where δt is time step decided and r is the risk-free rate (Kodukula and Papudesu, 2006).

1.3 Evaluation Methods for Biotech Projects

As reported in the paper "Real-Options Valuation for a Biotechnology Company" (Kellogg and Charnes, 2000) the best methods to evaluate the project of the development of a new drug is through the Risk-Adjusted NPV and the Lattice Model. The traditional NPV method uses inputs parameters that are fixed numbers, as they could not change in any circumstances, so is not an adequate model for the biotechnology industry. The BSM model is not suitable because projects in this kind of industry are staged (clinical trials) so there is not just a unique option, and it cannot capture the uncertainty for each one of these stages (Villinger and Bogdan, 2005).

Kellogg and Charnes (2000) decided to calculate the RANPV with the following formula:

$$RANPV = \sum \rho_i \sum \frac{DCF_{i,t}}{(1+r_d)^t} + \rho_7 \sum q_j \sum \frac{CCF_{j,t}}{(1+r_c)^t} \quad (12)$$

where:

$i = 1, \dots, 7$ = is an index of all the development stages,
ρ_i = conditional probability that stage i is not going to be a success,
ρ_7 = conditional probability of Approval,
$DCF_{i,t}$ = expected develop cash flow at stage i at time t,
r_d = development discount rate,
$j = 1, \dots, 5$ = is an index of quality for the drug,
q_j = probability of achieving the quality j,
$CCF_{j,t}$ = expected commercialised cash flow at time t for a drug of quality j,
r_c = commercialised discount rate.

When the drug will pass all the regulatory tests, phases and reaches the market, it will meet one of these five categories with respective probabilities: "Dog" with 10% probability, Below the Average with 10% probability, Average with 60% probability, Above the Average with 10% probability, and Breakthrough with 10% of probability. Furthermore, they estimated the conditional probability of success for each development trial: Discovery Stage with 60% probability, Preclinical Stage with 90% probability, Clinical Phase I with 75% probability, Clinical Phase II with 50% probability, Clinical Phase III with 85% probability, FDA Filing with 75% probability, and Post-approval with 100% of probability.

Thanks to that formula they were able to build the decision tree represented in Fig. 2:

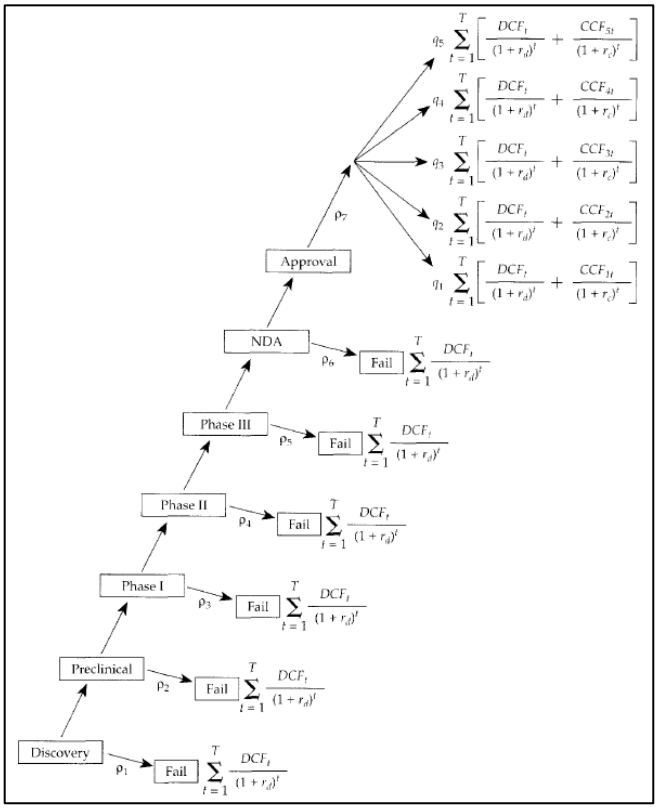


Figure 2: Decision Tree for a Pharmaceutical Development.
Source: Kellogg and Charnes (2000).

To apply the Binomial model, Kellogg and Charnes (2000) decided to calculate the initial value of the asset with the following formula:

$$A_0 = \sum q_j \sum \frac{CCF_{j,t}}{(1+r_c)^t}. \tag{13}$$

Multiplying for u (upward movement) and d (downward movement) they built the binomial tree where at the last node there is the end-branch value E_k, $k = 1, \dots, n+1$. Afterwards, they solved it with the risk-neutral probability approach. The possible payoffs are calculated with the following formula:

$$P_k = \max[E_k(\theta_t) - DCF_t, 0], \tag{14}$$

where:

θ is the success probability of year t.

Then the option values are rolled back, for each stage, until the present value:

$$V_{t,k} = \max\left\{\left[V_{t+1,k}\rho + V_{t+1,k+1}(1-\rho)\right]e^{-r\sqrt{\Delta t}}\theta_t - DCF_t, 0\right\}. \tag{15}$$

The value obtained by the two models were not significantly different, but comparing them to the stock price, it is evident an increasing difference related to the uncertainty of the trials, and, consequently, to a wide range of assumptions made by the investors.

2. Data

The data necessary to estimate the value of the project will be estimated and assumed using past studies and reports.

Regarding the success probabilities of each Development Phase, it will be used the same ones that Kellogg and Charnes (2000) have chosen. The price of the product will be assumed equal to the one of similar drugs. A deep market research and a sensitivity analysis are required to estimate the future development and commercialised cash flows.

The data necessary to understand the current status of the two companies will be found in the 10K and 10Q released by VIR Biotechnology; further information have been collected from Bloomberg platform.

3. Methodology

This Project Thesis has used two pricing models, the Risk Adjusted Net Present Value and the Binomial Option Pricing Model.

The RANPV has been built on Excel and run through a Macro (provided by Mr. Kellogg) on VBA.

The purpose of the Macro is of looping through all the scenarios of different R&D stages and the different qualities of drug (revenue), taking the results and attaching them in the Summary Sheet "TREE NPV".

The macro goes to the R&D sheet where it changes cell C49 and loops it from 1 to 7 (1 = Discovery Phase, 2 = Preclinical Phase, 3 = Clinical I, 4 = Clinical II, 5 = Clinical III, 6 = FDA Filing, and 7 = Approval). Each time it changes C49, it copies cell b23 from Cash Flow sheet (total NPV) back to Tree ENPV.

When all the different levels of development are gone it goes to the Revenue Sheet and loops cell B11 for each of the 5 levels of drug quality. Again, it copies cell B23 from Cash Flow sheet to the correct spot of Tree ENPV.

The Binomial Option Pricing Model was computed by adopting the same formulas that Kellogg and Charnes (2000) used in their paper.

The Current Value of the Asset A corresponds to the discounted value of the expected commercialisation cash flows at time zero:

$$A_0 = \sum q_j \sum \frac{CCF_{j,t}}{(1+r_c)^t}, \tag{13}$$

h is the maximum discounted commercialization cash flows at time of launch:

$$h = \text{Max}\left\{\sum \frac{CCF_{j,t}}{(1+r_c)^t}\ (1+r_c)^l\right\}, \tag{16}$$

where l is the difference between the time of the development process and the time of approbation, and r is the risk-free rate (considered as 10-years treasury bill).

The standard deviation σ of the Asset is calculated as follow:

$$\sigma = \ln(h/A)^{\frac{1}{T}}, \tag{17}$$

and the upward and downward movements:

$$u = e^{\sigma\sqrt{\Delta t}} \tag{18}$$

$$d = 1/u \tag{19}$$

where:

Δt is Tau divided by the n intervals of the Binomial Tree.

The possible payoffs are calculated as follows:

$$P_k = \text{Max}[E_k(\theta_t) - DCF_t, 0] \,, \tag{14}$$

where:

E_k are the branch end values,

θ_t are the various success probabilities at time t.

The P_k values are then rolled back using the risk neutral probabilities p and $1 - p$ to find the option values $V_{t,k}$, where:

$$p = \frac{e^{(r-q)\Delta t} - d}{u - d}, \tag{20}$$

and the equation for rolling back the option values is:

$$V_{t,k} = Max\left\{\left[V_{t+1,k}p + V_{t+1,k+1}(1-p)\right]e^{-r\sqrt{\Delta t}}\theta_t - DCF_t, 0\right\}. \tag{15}$$

4. Assumptions

4.1 Development Cost Assumptions

The following assumptions are based on the research paper "Benchmarking biopharmaceutical process development and manufacturing cost contributions to R&D" written by Farid (2020).

Pre-clinical and clinical trials are supported by Chemistry, Manufacturing, and Controls activities (CMC). Those operations are divided between Process Development and Manufacturing for Material Supply. The former includes all the costs related to bulk processing, formulation development, and the analytical effort dedicated to studies validation; the latter covers all the costs resulting from manufacturing the batches needed for guaranteeing the material supply to the trials, and the batches necessary for the regulatory review and approbation, also known as Process Validation batches.

There is an inter-dependence between the two CMCs: the developer has to establish and optimize the manufacturing plan through a series of process development activities, while ensuring its cost-effective and reproducibility. The CMCs supporting Phases I and II are focused on process scalability and productivity improvement. The activities supporting Phase III and the FDA submission are focused on characterization and validation. To avoid delays on the trials, the supporting CMC activities take place before the beginning of the relative phase, as Fig. 3 shows:

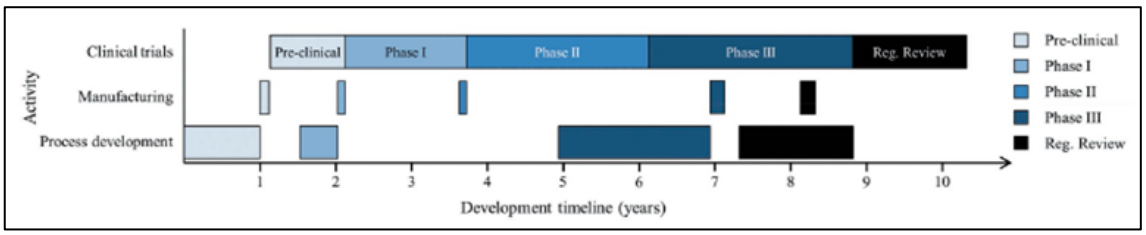


Figure 3 Timeline of Biopharmaceutical Development Activities. Source: Farid (2020).

Farid (2020) has adopted an FTE year-based approach for estimating the cost of process development activities. It was assumed a cost of 250,000 $ for every unit of FTE workload; this amount includes salary, management, and infrastructure costs. The model has been corrected for the durations of VIR-7831 trials, that resulted in a significant decrease of the process development costs.

PD Personnel	PC	Phase I	Phase III	Reg. Review (PD)	FTE Unit = $ 250,000
Project manager	1	1	2	2	
Process Scientists	3	6	10	10	
Tech-transfer	1	2	4	4	
Reg. support	0.5	1	2	10	
QC/QA	0.5	2	2	4	
Total personnel	6	12	20	32	
Duration	0.17	0.17	0.5	0.08	
Total FTE years	1.02	2.04	10	2.56	
Costs	255,000	510,000	2,500,000	640,000	

Table 2 Estimated Costs for Process Development Activities. Source: Farid (2020).

The estimation of the manufacturing activities was divided into two steps. Firstly, it was necessary to compute the doses (in kilograms) needed for each trial; it was assumed that a dose weights 0.6 g. As the phases' duration was shorter, and considering that a volunteered patient would assume a dose every two weeks, it was understood that less quantity of drug was required. The results have been corrected for the overproduction rates, as a portion of the drug candidate will be used for quality analysis, testing, and contingency inventory.

Trial	N. Patients	Doses per patient	Total N. of Doses	Clinical Demand	Over Production	Corrected Demand (g)	Corrected Demand (Kg)	Dose weight = 0.6 g
Phase I	40	1	40	24	250%	60	0.06	
Phase II	200	5	1000	600	250%	1500	1.5	
Phase III	2000	13	26000	15600	125%	19500	19.5	

Table 3 Estimation of Product Demand in Clinical Trials. Source: Farid (2020).

When the product required amount was known, it was calculated the number of batches necessary to produce that quantity. By using the batches' prices reported in the analysed paper, the final manufacturing costs were obtained (Tab.4).

Phase	Scale (L)	Titer(g/L)	Demand (Kg)	Direct Cost ($ Million)	Indirect Cost ($ Million)	Total ($ Million)	Batches
PC	500	2.5	0.5	0.43	0.14	0.57	1
Ph I	2000	2.5	0.06	0.98	0.38	1.36	1
Ph II	2000	2.5	1.5	0.98	0.38	1.36	1
Ph III	6000	5	19.5	2.51	0.61	3.12	2
Reg. Review	6000	5	19.5	2.51	0.61	3.12	2

Table 4 Estimation of Batch Cost and Number of Batches Required. Source: Farid (2020).

As revealed in Table 5, the costs of clinical trials (the core costs) were calculated by subtracting the CMC expenses from published total costs.

Cost ($ Million)	Pre-Clinical	Phase I	Phase II	Phase III	Reg. Review
Published Total Costs	6.00	18.00	48.00	180.00	48.00
Model Assumption					
Process Developmnet	1.50	1.50	-	10.00	27.00
Manufacturing	0.60	1.40	1.40	9.40	9.40
Clinical Trials	3.90	15.10	46.60	160.40	3.00

Table 5 Comparison to Published Total Costs. Source: Farid (2020).

Finally, the sum of the costs was multiplied for the numbers of projects required to complete each phase. Farid (2020) analysed three risk scenarios: average, best, and worst-case scenario. Each risk-profile represents the difficulties that the drug candidate would

incur for passing each trial, and consequently the number of projects used for each phase. As VIR-7831 has already reached the FDA review, it was decided to use the number of projects related to the best case-scenario. The final results are the assumed total costs of VIR-7831 development (Table 6).

Cost ($ Million)	Discovery (Assumed)	Pre-Clinical	Phase I	Phase II	Phase III	Reg. Review	Approval (Assumed)
Process Development	-	0.255	0.51	-	2.5	0.64	-
Manufacturing	-	0.57	1.36	1.36	6.24	6.24	-
Clinical Trials	-	3.90	15.10	46.60	160.40	3.00	-
Total	-	4.725	16.97	47.96	169.14	9.88	-
Number of projects	-	4.8	3.4	2.9	1.6	1.1	-
Total Costs	2.2	22.68	57.698	139.084	270.624	10.868	31.2
							534.354

Table 6 Estimation of Total Costs. Source: Farid (2020).

4.2 Commercialization Cost Assumptions

The commercialization costs were assumed equal to the ones that Kellogg and Charnes (2000) have used in their research, that is:

Item	Assumption	Source
Cost of revenue	25 % of the Revenue	U.S. Congress
Marketing Expense		Myers-Howe
Year 1 after Launch	100 % of the Revenue	
Year 2 after Launch	50 % of the Revenue	
Year 3-4 after Launch	25 % of the Revenue	
Year 5-13 after Launch	20 % of the Revenue	
General and Administrative Expenses	11.1 % of the Revenue	U.S. Congress
Tax Rate	35 % of the Revenue	Myers-Howe
Working Capital	17 % of the Revenue	U.S. Congress

Table 7 Commercialisation Costs. Source: Kellogg and Charnes (2000).

4.3 Probabilities Assumptions

Probabilities of Success, Conditional Probabilities that stage i is the end stage, and Drug Quality Probabilities were assumed equal to the ones used by Kellogg and Charnes (2000).

Phase	P of Success	Conditional P
Discovery	60%	40.0%
Preclinical	90%	6.0%
Phase Clinical I	75%	13.5%
Phase Clinical II	50%	20.3%
Phase Clinical III	85%	3.0%
FDA Review	75%	4.3%
Approval	100%	12.9%

Table 8 R&D Probabilities. Source: Kellogg and Charnes (2000).

Quality of Drug	Probability
Breakthrough	10%
Above Average	10%
Average	60%
Below Average	10%
Dog	10%

Table 9 Revenue Probabilities. Source: Kellogg and Charnes (2000).

4.4 Revenue Assumptions

A table with the top twenty sold biopharmaceutical products was used for assuming the possible revenue of VIR-7831.

N.	Revenues ($ Billion)	mAb	Year of approvation	Years in the Market	Recorded Year
1	18.94	Humina	2002	15	2017
2	8.34	Enbrel	1998	19	
3	7.78	Rituxan	1997	20	
4	7.77	Remicade	1998	19	
5	7.39	Herceptin	1998	19	
6	7.04	Avastin	2004	13	
7	6.72	Lantus	2000	17	
8	5.93	Eylea	2011	6	
9	5.79	Opdivo	2014	3	
10	4.53	Neulasta	2002	15	
11	4.01	Stelara	2009	8	
12	3.81	Keytruda	2014	3	
13	3.54	Prolia	2010	7	
14	3.38	Lucentis	2006	11	
15	3.31	Novolog	1999	18	
16	3.14	Soliris	2007	10	
17	2.94	Simponi	2009	8	
18	2.86	Humalog	1996	21	
19	2.75	Xolair	2003	14	
20	2.62	Aranesp	2001	16	

Table 10 The 20-Rop-Sellg Biopharmaceutical Products in 2017. Source: Walsh (2018).

As those drugs were the most profitable in 2017, they were used to calculate the Breakthrough quality revenue. The table describes for each product the annual revenue in 2017 and the year in which they reached the market. Twenty revenue historic series were built by computing those data with the Breakthrough quality CAGR used by Kellogg and Charnes (2000). Afterwards, the yearly average was calculated, and the estimated Breakthrough time series was obtained. In order to get the other four revenue sequences (Above the Average, Average, Below the Average, and Dog quality), multiplies were used to find each gross profit for the first year of commercialization. Finally, using the CAGR represented in Figure 4, all the five revenue time series were obtained.

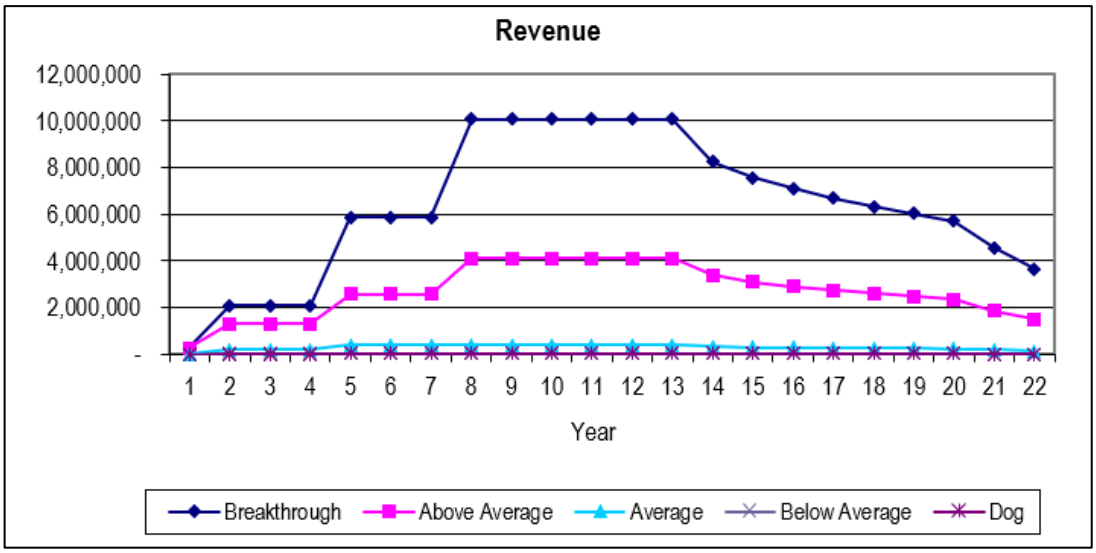


Figure 4 Revenues Streams for New Drugs by Quality Category. Source: Kellogg and Charnes (2000).

4.5 Discounting Rates Assumptions

The Discounting Rates were assumed equal to the ones used by Kellogg and Charnes (2000): 6 % for the Development Discount Rate, and 9 % for the Commercialisation Discount Rate. An inflation rate of 2% was assumed for calculating the nominal discounts rates of 8.1 % and 11.2 %.

4.6 Timeline Assumptions

Corporate's news were used to approximate the trials' timeline represented in Table 11. Due to the Emergency Use Authorization (EUA) emanated by FDA for COVID-19 epidemy, all the drugs on development for contrasting SARS-COV-2 have the right to accelerate the normal procedures. An mAb usually takes between 5 and 9 years from the Discovery to the FDA filing; VIR-7831 took 13 months for all the trials. The FDA Review duration was approximated to one month, the same time that Pfizer's COVID-19 Vaccine has taken to be approved.

Phase	Years	Months
Discovery	0.25	3.0
Pre-Clinical	0.17	2.0
Clinical I	0.17	2.0
Clinical II	0.17	2.0
Clinical III	0.50	6.0
FDA Filing	0.08	1.0
Total	**1.34**	**16.0**

Table 11 VIR-7831 Timeline.

Regarding the Commercialisation Timeline it was decided to choose 21 years as period, following what Kellogg and Charnes (2000) did.

4.7 Partnership Ratio Assumptions

A partnership between Vir Biotechnology and GlaxoSmithKline was set to develop VIR-7831. Following this agreement, VIR will be responsible for the 72.5 % of the Development Costs and the Revenue; GSK will cover (and own) the remaining 27.5 %. A fully disclosure of the Partnership Agreement can be found in the relative chapter.

5. Antibodies, a Simple Explanation

The following chapter was written inspired by the book “Basic Immunology” (Abbas, Lichtman, Pillai, 2019).

Antibodies belong to the Humoral Immunity System, more specifically they are molecules produced by B-Lymphocytes (or B-Cells) with the purpose of targeting everything that is not recognized by the human body and allowing the immune system to eliminate it (the so-called Pathogenic Agents or Pathogens).

When the B-Lymphocyte enters in contact with a Pathogen, it recognizes that through the receptors that are present on its membrane, and those receptors are antibodies themselves. So, the Lymphocyte can be considered as an antibodies’ owner, but in the late phase of its life it becomes and antibodies producer too. In more scientific terms, the antibodies are both external receptors and secreted molecules.

An antibody is a molecule composed by four polypeptide chains, two light chains (C_L) and two heavy chains (C_H), that form two regions: a variable one, whose purpose is bonding itself with antigens, and a constant part responsible for the complement activation. It has the typical Y-shape for recognizing Antigens. The antibody variable part chemically bonds itself to the epitope. The variable part is the most important one, as its variability property allows the antibody to bond itself with many different epitopes. In simple word, an efficient immune system has the capability to produce different types of antibodies against a wide range of antigens.

There are five subtypes of antibodies classified according to the type of heavy chains in the constant region, as represented in Table 12:

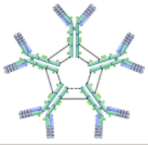
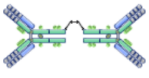
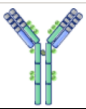
IgG	IgG is the main antibody in blood. It is the only isotype that can pass through the placenta, and IgG transferred from the mother's body protects a newborn until a week after birth. IgG widely distributed to the blood and tissue, and protects the body.	
IgM	IgM is made up of 5 antibodies. IgM has a key role in the initial immune system. It is distributed to the blood.	
IgA	Secreted IgA is made up of 2 antibodies. It is distributed to serum, nasal discharge, saliva, breast milk and bowel fluid. Breast milk protects the gastrointestinal tract of newborns from bacterial and viral infection (maternal immunity).	
IgD	IgD is present on the surface of B cells and plays a role in the induction of antibody production.	
IgE	IgE is believed to be related to immunity reactions to parasites, and has recently become known as a key factor of allergies such as pollinosis.	

Table 12 Antibodies Classification. Source: Kyowa Kirin, Na.

The power of the boundary between the antigen and the antibody is called Interaction Affinity (IA); that affinity is expressed also in constants terms, Dissociation Constant. The higher the Interaction affinity the lower is the Dissociation Constant. The Interaction Affinity is directly proportional to the number of infections. The first time that a subject will be infected by a pathogen he will be sick, so the B-lymphocyte will start to produce antibodies by dividing itself in clones; some of those clones are Memory Cells (cells which record infections' information for the immune system). The second time that the subject will be infected by the same pathogen, the antigen will activate the memory cells and the affinity will be higher, as results the symptoms will be less or lighter.

In general, antibodies are considered Polyclonal Antibodies (pAbs) by nature. They are a heterogeneous mixture produced by different B-lymphocytes clones; they can bind with many different epitopes of an antigen. In 1984, Georges Köhler, Niels K. Jerne, and César Milstein won the Noble Prize for the discovery of Monoclonal Antibodies (mAbs). They discover that each B-cell produces a specific antibody; so mAbs have a monovalent affinity and can recognize only the same epitope (Creative Diagnostic, Na).

Differently by pAbs, that are produced in live animals, monoclonal antibodies must be produced ex vivo using genetic engineering techniques. The most academic way is for producing the so-called Murine Antibodies.

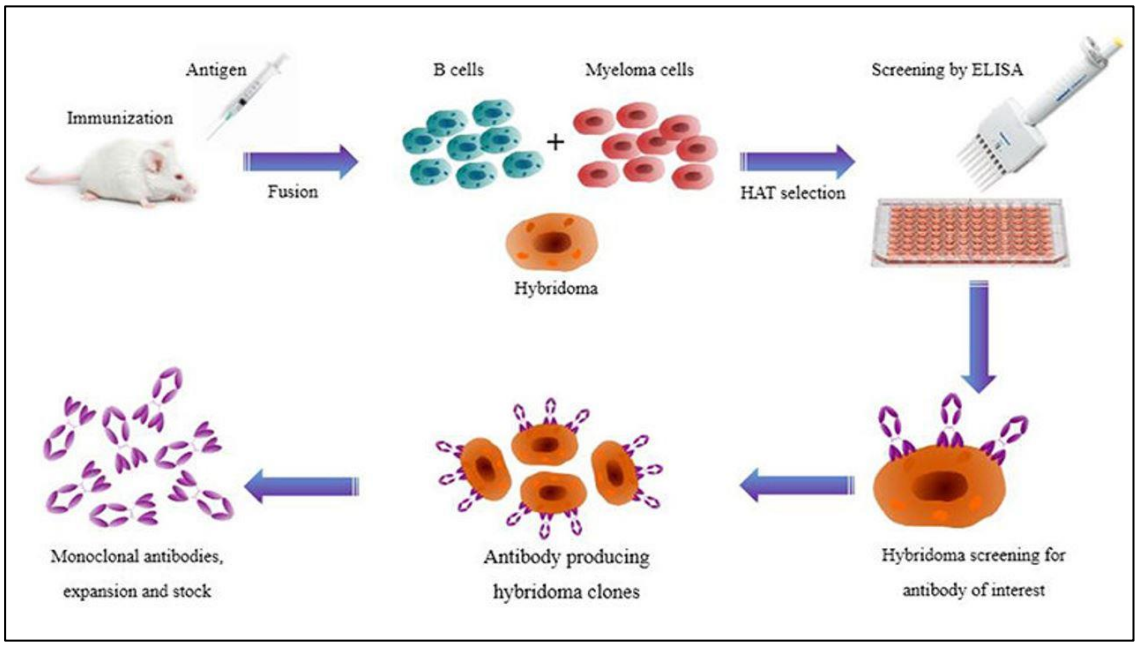


Figure 5 Murine mAb Production. Source: Liao G., Na, IBT Bioservices.

The first step is infecting a mouse with an antigen, consequently its immunity system will produce the B-cells against that antigen. The second step is drawing the B-lymphocytes

from the cells of the immune system of the mouse. Some of those cells are producing the specific antibody for contrasting the injected antigen. At this point all the B-lymphocytes are fused in vitro with Myeloma mutant lines cells creating Hybridomas, that can duplicate themselves infinitely. After a first screening, the hybridomas are selected through an ELISA test to identify which ones produce grow until the antibody of interest. The particularity of that cellular line is the capability of producing continuously the same antibody. From now on it can take the name of Monoclonal Antibody, as all the antibodies are specific for the same antigen and come from identical clones of a unique B-lymphocyte. The obtained mAb is a completely animal one, and it would be rejected by a human body. To avoid such problem, genetic engineering techniques are used to insert the variable region of the mouse in a human Immunoglobulin. Finally, the specific monoclonal antibody is ready for the pre-clinical and clinical trials.

Following the antibody domains' origins, it is possible to identify four types of mAbs in total: Murine, Chimeric, Humanised, and Human.

6. Monoclonal Antibodies Market

In 1986, the first monoclonal antibody (Orthoclone OKT3) was approved and put on the market. The growth rates related to the approbation of new mAbs and the relative sales were considerable low until 1990, year in which the first chimeric mAb was approved. After that year, humanized and human monoclonal antibodies started to be approved too; those more advanced technologies have led to an exponential increase of new products' approbations and mAb sales. In 2015, the global sales of mAb almost reached $90 billion, meaning 60% of the overall biopharmaceutical market (Levine, Cooney, 2017). In 2019, seven of the top ten selling drugs were monoclonal antibodies, as Table 13 shows:

US Product Name	Sales 2019 ($ Billion)	Type of Drug
Humira	19.60	mAb
Keytruda	11.10	mAb
Revlimid	9.40	-
Imbruvica	8.10	-
Opdivo	8.00	mAb
Eliquis	7.90	-
Eylea	7.50	mAb
Enbrel	7.20	mAb
Avastin	7.10	mAb
Rituxan	6.50	mAb

Table 13 Top Ten Drugs Sold for 2019. Source: Pharma Intelligence.

Analyzing the market data, it is evident how the revenues coming from mAbs grow faster compared to other biopharmaceutical products. As Figure 6 shows, the sales of mAb products (represented by light green, orange, and purple columns) have increased of 80% in an interval of 5 years: in 2010 sales reached $50 billion, while in 2015 they almost reached $90 billion. By contrast, the overall sales of other biopharmaceutical products have grown at a rate of 18 % (Levine, Cooney, 2017).

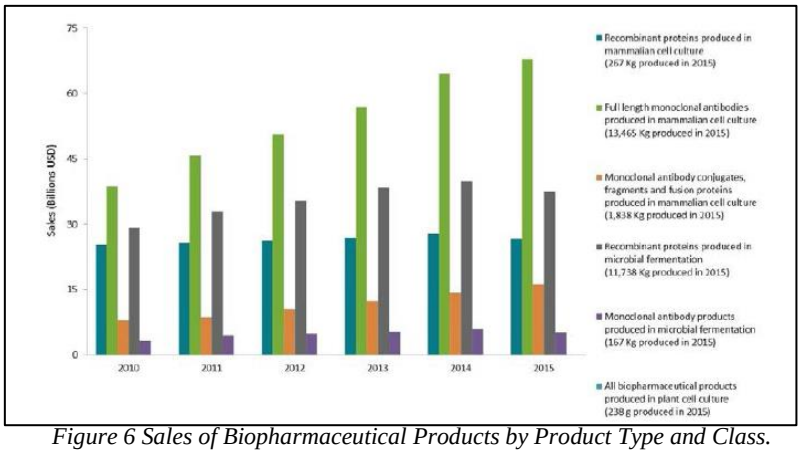


Figure 6 Sales of Biopharmaceutical Products by Product Type and Class. Source: Levine and Cooney (2017).

Analysts believe that the antibody market will grow at a compound annual rate of 9%, that could expand the market capitalization to $300 billion in 2025 (Figure 7).

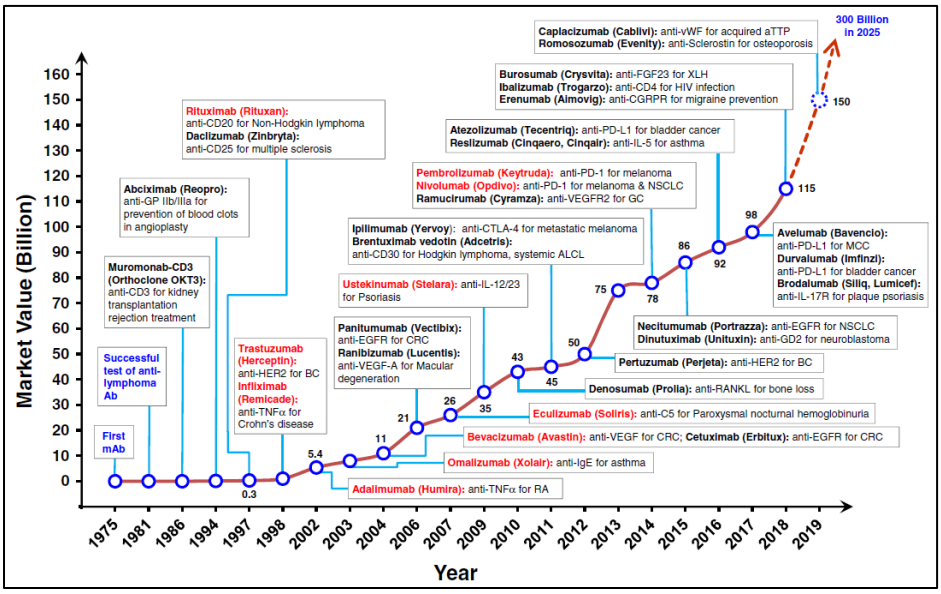


Figure 7 Timeline of Successful Development of mAbs. Source: Wu (2020).

This market is considered interesting for different factors. One reason is the so called "first-to-market" advance; monoclonal antibodies are often the first products to advance to the further clinical trial, that is due to the low risk of unexpected issues in human clinical trials (especially with the increasing trend of human antibodies). A second factor is the direct correlation between the biopharmaceutical (and pharmaceutical) market expansion and the population wellness. As there is a general increase of the worldwide population aging (including the third world countries living standards), the biopharmaceutical market is expected to grow further. Finally, the mAb cellular lines production has become more efficient and cost-effective during the time, guaranteeing the meeting of the demand (Levine, Cooney, 2017).

7. Development of a New Drug

The development of a new drug is a long process that must go through different phases before reaching the market. The following phases have been described using as main source the FDA website (2018):

- Discovery Research;
- Preclinical Research;
- Clinical Trial I;
- Clinical Trial II;
- Clinical Trial III;
- FDA Drug Review.

7.1 Discovery Research

This is the phase where a New Molecular Entity (NME) is discovered. Potential candidates can be discovered through new insights into a disease process, tests of molecular compounds, further analyses on existing treatments, and the implementation of new technologies.

At this this stage, thousands of NMEs can be potential candidates, but after early testing just a small number is going to proceed to the next phase.

Once a promising compound is found, experiments are conducted to gather information regarding its metabolization properties, its potential benefits and mechanism of action, its best dosage, its side effects, and other possible collateral effects depending by groups of people and interaction with other drugs.

7.2 Preclinical Research

The purpose of this research is understanding the toxicity level of the candidate NME. There are two types of Preclinical Research:

- In Vivo;
- In Vitro.

Usually, the PC studies are not large, they need to identify information on the dosing and toxicity levels. After analysing the results, the researchers will decide if testing the new drug on human patients.

7.3 Clinical Trial I

The fist clinical trial is conducted on a small number of volunteers (between 20 and 100) with the purpose of testing the safety and the dosage of the NME. Usually, it takes several months.

7.4 Clinical Trial II

The second clinical trial consists in testing the candidate drug on hundreds of patients with the target disease. The purpose is testing its efficacy and its side effects. The duration could take from a minimum of months to a maximum of 2 years.

7.5 Clinical Trial III

The third clinical trial the NME is tested on thousands of patients (up to 3,000) with the scope of analysing efficacy and monitoring adverse reactions. The duration could take up to 4 years.

7.6 FDA Drug Review

If all the previous phases were successful, the drug developer can submit a New Drug Application (NDA) to FDA.

The NDA must include all the possible information regarding the candidate drug: directions for use, drug abuse and safety information, patent information and so on.

If the FDA review team will find the candidate product safe and effective for the addressed disease, it will finally give its approval.

8. Vir Biotechnology

8.1 Company Profile

VIR Biotechnology Inc. is a clinical stage immunology company based in San Francisco operating in the Biotechnology & Medical Research sector. It was founded in 2016 by Robert Nelsen and Vicki Sato and it was listed in Nasdaq Stock Exchange in 2019. The company, with a Market Capitalization of $5.411 B and a price per share of $37.20 (recorded on the day 21 of July 2021), is currently managed by George A. Scangos (CEO), Howard Horn (CFO), and Phil Pang (CMO).

The main mission is combining immunologic insights with cutting-edge technologies to treat and prevent serious infectious diseases. The approach is divided as follow: identifying the limitation of the immune system in fighting a specific pathogen, studying the vulnerabilities of that pathogen, and understanding why previous therapies have not worked. After that, new technologies (that are analysed in the next paragraph) are used, individually or combined, to develop new effective therapies and biopharmaceutical products.

8.2 Technologies and Pipeline

Following the information reported in VIR Biotechnology 10-K (2021), the company is working on biopharmaceutical products to contrast SARS-COV-2 (COVID-19), HBV, Influenza A, and HIV. VIR uses four technology platforms for developing their products:

- Antibody Platform: using rare immune response in people that are protected from infectious diseases to treat resistant or quick evolving pathogens through engineered fully human antibodies.
- T Cell Platform: using the immunology of human cytomegalovirus (HCMV), a common virus in human, as a vector for vaccines to treat infections that are resistant to current vaccine technologies.
- Innate Immunity Platform: creating therapies to develop high barrier resistance in patients. The purpose is to produce a drug for treating multiple diseases thanks to the leveraging of innate immunity.
- siRNA Platform: inhibiting pathogen replication to eliminate key host factors necessary for pathogen survival.

In the following table it is represented the products pipeline of VIR Biotechnology:

Drug	Platform	Disease	Phase	Collaboration
VIR-7831 (Early Treatment)	Antibody	SARS-COV-2	FDA Filing	GSK
VIR-7831 (Prophylaxis)	Antibody	SARS-COV-3	Preclinical	GSK
VIR-7832	Antibody	SARS-COV-4	Clinical I	GSK
VIR-2218	siRNA	HBV	Clinical II	Alnylam
VIR-2218-IFN-α	siRNA	HBV	Clinical II	Alnylam
VIR-3434	Antibody	HBV	Clinical I	-
VIR-2218 + BRII-179	siRNA	HBV	Clinical II	Alnylam - Brii
VIR-2482	Antibody	Influenza A	Clinical I	-
VIR-1111	T Cell	HIV	Clinical I	B&MG Foundation

Table 14 VIR Biotechnology Pipeline. Source: VIR Biotechnology, 2021.

8.3 Financials

Looking at the balance sheet of the company, it is evident an increase of the Total Assets from $512.1 million to $918.8 million; the most significant change is the increase of $353.4 million (from $383.4 million in 2019 to $736.9 million in 2020) in Cash, Cash Equivalents, and Short-term Investments item. As reported in the 10-K, VIR has financed their operations mainly through sales of common stock and convertible preferred securities, and payments received from grant and collaboration agreements. In April 2020, VIR issued 6,626,027 shares of common stock to GSK at a price per share of $37.73, for an approximate purchase price of $250.0 million. In July 2020, VIR completed a follow-on offering of common stock and issued 8,214,285 shares for a net profit of $323.2 million (Vir Biotechnology, 2021).

The Income Statement reports an increase of $68.3 million in Total Revenue for the year 2020. As VIR at the moment does not have any approved products, its revenue only consists of Grant Revenue, revenue originated by grant agreements with government and private organization, and License and Contract Revenue, revenue generated by license rights and R&D services. The increase in Total Revenue is mainly justified by the $43.3 million of revenue from the license granted to GSK, and $22.7 million of revenue generated by Brii Bio's option exercise to obtain exclusive rights for developing and commercialize compounds arising from VIR-2218 in China. Research and Development expenses were respectively $302.4 million and $148.5 million for the years 2020 and 2019. This change is mainly related to the following factors: an increase of $79.4 million in Licenses, Collaborations and Contingent Consideration Expenses, an increase of $21.0 million in clinical Trial Expenses (mainly allocated for VIR-7831, VIR-2218 and VIR-3434 trials), an increase of $18.8 million in Contract Manufacturing Expenses, and an

increase of $14.3 million Other Research and Development Expenses. Finally, the Net Income is -$298.7 million compared to -$174.7 million recorded at the end of 2019 (Vir Biotechnology, 2021).

The Cash Flow Statement reports $190.9 million of Net Cash used in Operating Activities for the year 2020, the net loss of $298.7 million was partially offset by a decrease in Net Operating Assets of $29.5 million and Non-cash Charges of $94.0 million. In 2020 the Net Cash used in Investing Activities was $9.9 million. This consisted primarily of $403.8 million in Investments purchases and $6.5 million in Property and Plant Equipment purchases, partially offset by $400.3 million in proceeds received from matured investments. Financing Activities used $529.5 million of Net Cash in 2020, consisting in proceeds coming from the issuance of common stock to GSK ($206.7 million) and the $323.2 million related to the follow-on offering (Vir Biotechnology, 2021).

Looking at the financial statements it is obvious that using the classic valuation methods (DCF, Multiplies, EV and so on) is meaningless: as the company is young, the net incomes are still negative and calculating growths rates and multiples would not be economically significantly. Nevertheless, a relevant correlation between R&D investments and stock price was identified. Despite the even more negative net income recorded in 2020, the stock price followed an opposite path: on 31/12/2019 the price for a VIR stock was $12.575, on 31/12/2020 it was $26.78, for a total appreciation of 113%. That was due to the increase of R&D investments: more money spent in research means more present costs, but at the same time more investments in R&D increases the investors' expectation for future profits (in a best-case scenario).

8.4 VIR-7831

VIR Biotechnology has selected 14 mAbs or mixtures of mAbs as possible candidates to fight SARS-COV-2. The one that this thesis is taking into consideration is the most promising VIR-7831 (also known as GSK 4182136 due to its partnership with GlaxoSmithKline). For discovering and developing VIR-7831, the VIR's team has started by analysing S 309, an antibody that was recorded and studied in a SARS-COV-1 survived patient in 2003. The team has found out that S 309 bounds itself to the epitope shared by COV-1 and COV-2. That epitope is located in the Spike Protein, that is the protein through the SARS-COV-2 enters into the human cells. S 309 was engineered at

the DNA level to improve its pharmacokinetic properties. The Dissociation Constant recorded VIR-7831 is 0.21 nanomolar, that guarantees a high Interaction Affinity (Hebner C. M., 2021).

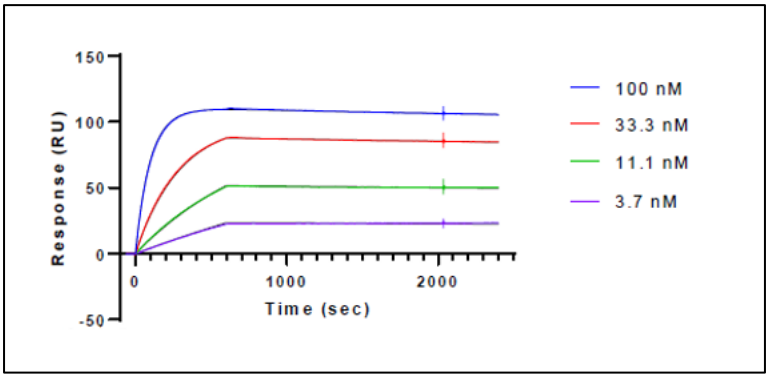


Figure 8 Interaction Affinity Analysis. Source: Hebner (2021).

VIR Biotechnology (2021) has defined its mAb as a "fully human dual action monoclonal antibody". As its origins come from S 309 there is no animal domain inside the antibody, that increases its success probability in the clinical trials. Moreover, it is defined as Dual Action because it has the potential to block the virus entry into sane cells and to purify the infected ones. At the moment VIR-7831 is being evaluated by FDA for its approbation, after its success in the previous trials.

9. Preliminary Collaboration Agreement

On April 5 2020, Vir Biotechnology and GlaxoSmithKline Biologicals entered in a Preliminary Collaboration Agreement with the purpose to unite their technologies and resources to develop antibodies, vaccines, and functional genomics products.

9.1 Collaboration Products

The products that are going to be developed in this collaboration agreement are regrouped in three macrofamilies:

- *Antibody Products*: any monoclonal antibodies developed against any coronavirus under the Antibody Program.
- *Vaccine Products*: any vaccines that are developed under the Vaccine Program.
- *Functional Genomics Products*: any products included in the Functional Genomics Program based on the results of the genomics screens conducted under the same program.

During the Initial Development Term, Vir and/or its affiliates will not create any antibodies against SARS-COV2 or other coronavirus; or conduct any functional genomics screens for SARS-COV2 or any coronavirus to discover new targets to develop; both cases are except for pursuant to collaboration. The same terms are valid for GSK and/or its affiliates.

If during the Initial Development Term, either Party or its Affiliates wishes to pursue a new program that falls in one of the above-mentioned obligations, such Party has to offer the possibility to include that specific program under the Collaboration. If the other Party declines the expansion of the subscribed Collaboration, the offering Party shall have the right to pursue that specific program outside the collaboration, regardless of its obligations.

9.2 Lead Party

Depending on each Collaboration Program Agreement, the party designated as Lead Party in accordance with a development pan will be primarily responsible for Development, Regulatory, and/or Manufacturing in accordance with the Development Plan. The Lead Party shall have the right of making the final decision under the specific Collaboration

Program, except for budget increases and assignment of activities to the other Party; in this scenario such Party will have to express its consent. Under the Antibody Program, VIR will be the Lead Party for any Antibody Products until the first filing is submitted for Regulatory Approval. After that, GSK will become the Lead Party for such Antibody Program.

9.3 Collaboration Programs

9.3.1 Antibody Program

This will be the first Collaboration Program to be pursued by the Parties, improving the VIR's ongoing activities. As mentioned above, VIR will be the Lead party for the Development and clinical Manufacturing activities related to the Antibody Program. GSK will be primarily responsible for the Commercialization and Commercial Manufacturing activities. The two companies will share the development costs for the activities under the Antibody Development Plan as follows:

- VIR will be responsible for the 72.5 % of the Development Costs,
- GSK will bear the remaining 27.5 %.

9.3.2 Vaccine Program

The Vaccine Program will use both technologies of VIR and GSK. GSK will be the Lead Party of this program while the research part will be conducted mainly by VIR. If the research proves to be successful, the party has the option to continue the program and enter the development phase. If GSK decides to stop the research or development of a candidate vaccine, VIR can take the project forward. The two companies will share the development costs for the activities under the Vaccine Development Plan as follows:

- GSK will bear the 72.5 % of the Development Costs,
- VIR will be responsible for the remaining 27.5 %.

9.3.3 Functional Genomics Program

The program will start after the adoption of the Development Plan for the Functional Genomics Products. GSK will be the Lead Party and it will have the main responsibility for the Development and Manufacturing activities under the Functional Genomics Program. VIR and GSK will respectively bear 50 % of the development costs.

9.4 Manufacture and Supply

For each Collaboration Program the Parties will jointly choose an appropriate manufacturing strategy, taking in consideration each Party's manufacturing capability. As written above, regarding the Antibody Program VIR will be the Lead Party for the clinical manufacturing activities, while GSK shall be responsible for the commercial manufacture.

9.5 Commercialization and Collaboration Products

The Parties will share any profits and/or losses arising from any Collaboration Program in the same Development Costs ratio as stipulated under that specific Collaboration Program.

In general, the Lead Party for the Development Plan will continue to act as Lead Commercialization Party (LCP) for such Collaboration Program, that will act under an arranged commercial plan and budget.

Regarding the Antibody Program instead, GSK will assume the role of Lead Commercialization Party for any Antibody Products and will be responsible for booking all sales of each of those Antibody Products.

GKS will be responsible for each commercialization activities worldwide concerning each Collaboration Products. Moreover, it will put efforts to commercialize each Collaboration Products in United States, European Union, and United Kingdom following the local regulatory approvals.

9.6 Opt-Out Right

Both Parties will have the right, at each specified milestone (called "Opt-Out Points"), to exercise the Opt-Out of its obligation. The Party that wants to stop funding a specific Collaboration Product, shall continue to be liable for its allocation of costs. If a party decides to exercise its Opt-Out right outside a milestone, it will be forced to continue to co-fund the Development Costs until the next Opt-Out Point will occur.

In the scenario in which a Party decides to exercise its Opt-Out Right, the other Party will have the right to choose either to:

- continue unilaterally the program, and substitute the sharing of future net profits with Royalties to Opt-Out Party, and a percentage of Sublicence Revenue from such Collaboration Product,
- cease of founding such Collaboration Product. In this case there will be negotiations for the divestment of the specific Collaboration Product. Any costs and revenues arising from the out-license shall be share in the same ratio used for the costs of the related Development Program.

9.7 Intellectual Property

The ownership of the products developed under the Collaboration Program will follow the United States patent law. Based on the terms and conditions of the Collaboration Agreement:

- VIR will grant to GSK:
    - A co-exclusive worldwide sublicensable license under the VIR Licensed Technology and VIR Program Technology to develop and manufacture products arising from the Collaboration Program;
    - An exclusive worldwide sublicensable license under the VIR Licensed Technology and VIR Program Technology to commercialize any products developed under the Collaboration Program.
- GSK will grant to VIR:
    - A non-exclusive worldwide sublicensable license under the GSK Licensed Technology to develop and manufacture any Collaboration Products in accordance with the Collaboration Agreement;
    - A co-exclusive worldwide sublicensable license under the GSK Program Technology to develop and manufacture any product arising from this Collaboration Agreement.

10. Results Discussion

Comparing the results (Table 15), it is evident how the traditional NPV method is completely unrealistic and biased for the valuation of the development of a drug, and consequently for the evaluation of a biotechnology company. The probabilities of trials' success are not considered to evaluate the Development NPV, and only the Average Quality revenue, as it is the most probable, is considered to calculate the Commercialisation NPV. By not considering all the possible outcomes the result is significantly lower compared to the other two methods.

Method	Result
Traditional NPV	15,442
Risk Adjusted NPV	44,240
Strategic NPV	68,780
Flexibility Value	24,540

Table 15 Final Results.

By contrast, the other two methods give a more reliable present value. The risk adjusted NPV (RANPV) takes into consideration different revenue scenario, each one was corrected for its occurrence probability (Dog 10%, Below Average 10%, Average 60%, Above Average 10%, and Breakthrough 10%). Regarding the Development present value, the NPV is calculated for each stage of the R&D process (VIR-7831 stops at Preclinical trial, VIR-7831 stops at Clinical Phase I, and so on) and it is multiplied for the relative conditional probability that the current stage would be the end stage for VIR-7831.

The Lattice Model considers the same revenue assumptions by using the commercial NPV of the risk adjusted NPV method as the value of the asset (A) at time 0. As it has been already explained in the Methodology chapter, after computing all the asset values in the Lattice Model, those are solved back for the risk-neutral probability; the formula is then adjusted with the probability of success of each trial.

The RANPV and the Lattice Model give two values that are bigger compared to the traditional NPV. The difference between those two values ($24,540 thousands) is the Flexibility Value. As in the Binomial Model it is included an option, that is the right to decide if proceeding with the next R&D phase or stopping the trials, there is an added value. By taking off this option value, the strategic NPV equals the Risk Adjusted NPV.

11. Conclusion

Both models work, but some considerations have to be done. The Lattice Model is efficient if the candidate drug is at an early stage, but as it starts to be closer to the Regulator Review the values become less realistic. More specific information (not included in the Lattice Model inputs) will guarantee a more accurate result. Furthermore, the flexibility guaranteed by the option starts to lose meaning as the drug come closer to the market launch. After the Clinical Phase II success probabilities become more optimistic and the option loses value; moreover, from a more empirical point of view, that option would not be exercised anyway as too much time and money has already been spent, so it is not realistic that the project would be suddenly quit. By the contrary, the Risk Adjusted Net Present Value has a more pragmatic application; more accurate inputs increase the reliability of the results, consequently the result will be more accurate.

As VIR-7831 does not reach the market yet, only time will tell us which model has given a more realistic result.

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Annex A

Traditional Net Present Value

For computing the traditional NPV it was decided to calculate separately two Net Present Values, the Development NPV and the Commercial NPV.

To calculate the first one, it was built an investments time series (2.34 years) where all the cash flows (the expenses for each development phase) were corrected for an inflation rate of 2%. After that, all the cash outflows were discounted for the Development Nominal Discount Rate of 8.1% and the Pre-partnership Development NPV, $-390,765 thousands, was obtained. The final Development Net Present Value, $-283,305 thousands, was found by multiplying the result for the partnership ratio 72.5%.

Regarding the Commercial NPV, it was assumed the average quality revenue as the unique one (due to its high probability). After correcting the future cash inflows (24 years) for an inflation rate of 2%, they were discounted for the Commercial Nominal Discount Rate of 11.2% and Pre-partnership Commercial NPV, $412,064 thousands, was obtained. The final Commercial NPV, $ 298,746 thousands, was calculated by multiplying the result for the partnership ratio 72.5%.

The traditional NPV, $15,442 thousands, was obtained by subtracting the Development NPV to the Commercial one; no probabilities of success were used to correct the results (it was assumed 100% of success rate).

Annex B

Risk Adjusted NPV

For computing the Risk Adjusted NPV (also known as Expected NPV) it was decided to calculate separately two Net Present Values, the Development NPV and the Commercial NPV. As shown in the first table, it was computed the NPV for each development phase; for doing that the cash flows were first corrected for an inflation rate of 2% and then discounted for the Development Nominal Discount Rate of 8.1%. This procedure was done, in an incremental way, for each of the phases (from 1 to 6).

Phase Numbers	Phase Type	P of End Point	NPV
1	Discovery	40%	-
2	Pre Clinical	6%	-15,284
3	Phase I	14%	-51,366
4	Phase II	20%	-132,084
5	Phase III	3%	-277,837
6	FDA Filing	4%	-283,305
7	Approval	13%	770,517
Expected NPV			**44,240**

Regarding the phase number 7 (the Approval), it was calculated the Commercial NPV for the revenue deriving from each drug quality (using the Commercial Nominal Discount rate of 11.2%). From the results was subtracted the Development NPV $283,305 thousands (that is the NPV of FDA Filing as it includes all the previous development phases). The results, shown in the table below, were then multiplied for their relative occurrence probability and summed to each other (a sum of the products). The Expected NPV of Approval, $770,517 thousands, is so obtained.

Number of Quality	Quality of Drug	Probability	NPV
1	Dog	10%	-252,817
2	Below Average	10%	-248,633
3	Average	60%	15,442
4	Above Average	10%	2,316,658
5	Breakthrough	10%	5,797,316
Expected NPV of Approval			**770,517**

Lastly, a second sum of the products was done with the values of the first table, where each phase NPV was first multiplied for its relative Probability of End Point and then summed to the others. The Expected NPV (or RANPV) of $44,240 thousands was so obtained.

Annex C

Binomial Option Pricing Model

To replicate the Binomial Option Pricing Model the following inputs were calculated and used:

Lattice Model Inputs	
A	1,053,822
h	7,008,477
σ	181%
r	1.64%
tau	1.08
Δt	0.08
exp(-r*dt)	0.99863
u	1.68851
d	0.59224
exp(r*dt)	1.00137
p	0.37320
1-p	0.62680

Where A and h are respectively the discounted value of expected commercialization cash flow at time 0 and maximum discounted commercialization cash flow at time of the launch, both fount in the RANPV model.

It was decided to use 0.08 as Δt to have a model with thirteen interval, the same number of the months assumed for the development of VIR-7831.

After the computation of the Monthly Value Tree, obtained by multiplying A for u and d, the possible payoffs are calculated using the equation 14:

$$P_k = \text{Max}[E_k(\theta_t) - DCF_t, 0]$$

Where DCF are the Development Cash Flows corrected for the Development Nominal Discount Rate 8.1%.

That becomes:

$$P_k = \text{Max}[E_k * (0.75) - 11{,}827\ ,0]$$

The payoffs were the rolled back for the risk neutral probabilities to find the option value $V_{0,0}$; it was used the equation 15:

$$V_{t,k} = Max\{\left[V_{t+1,k}p + V_{t+1,k+1}(1-p)\right]e^{-r\sqrt{\Delta t}}\theta_t - DCF_t, 0\}$$

For example, the equation to find $V_{12,1}$ would be:

$V_{12,1} = Max\{[716{,}742{,}674 * 0.3132 + 251{,}387{,}426 * 0.6268] * 0.99863 * 0.85 - 48{,}766, 0\}$ = 360,760,946

By applying the equation 15 to all the intervals, a Strategic Net Present Value of $68,780 thousands was obtained.

In the next page is possible to see the Binomial Option Pricing Model tables.

Phase	Discovery	Preclinical		PC I		PC II		PC III						FDA Filing
Year	0	0.08	0.17	0.25	0.33	0.42	0.50	0.58	0.67	0.75	0.83	0.92	1.00	1.08
Schedule of Investment		11,340	11,359	28,944	28,992	70,003	70,118	45,553	45,628	45,703	45,779	45,854	45,930	11,085
Yearly Value Tree	1,053,822	1,779,387	3,004,510	5,073,141	8,566,041	14,463,832	24,422,302	41,237,262	69,629,464	117,569,933	198,517,819	335,199,004	565,986,330	955,672,668
		624,114	1,053,822	1,779,387	3,004,510	5,073,141	8,566,041	14,463,832	24,422,302	41,237,262	69,629,464	117,569,933	198,517,819	335,199,004
			369,625	624,114	1,053,822	1,779,387	3,004,510	5,073,141	8,566,041	14,463,832	24,422,302	41,237,262	69,629,464	117,569,933
				218,906	369,625	624,114	1,053,822	1,779,387	3,004,510	5,073,141	8,566,041	14,463,832	24,422,302	41,237,262
					129,645	218,906	369,625	624,114	1,053,822	1,779,387	3,004,510	5,073,141	8,566,041	14,463,832
						76,781	129,645	218,906	369,625	624,114	1,053,822	1,779,387	3,004,510	5,073,141
							45,472	76,781	129,645	218,906	369,625	624,114	1,053,822	1,779,387
								26,931	45,472	76,781	129,645	218,906	369,625	624,114
									15,949	26,931	45,472	76,781	129,645	218,906
										9,446	15,949	26,931	45,472	76,781
											5,594	9,446	15,949	26,931
												3,313	5,594	9,446
													1,962	3,313
														1,162

Probabilities	100%	100%	90%	100%	75%	100%	50%	100%	100%	100%	100%	100%	85%	75%
Schedule of Investment	0	0.08	0.17	0.25	0.33	0.42	0.50	0.58	0.67	0.75	0.83	0.92	1.00	1.08
Intervals	0	1	2	3	4	5	6	7	8	9	10	11	12	13
Option Value Tree	68,780	172,323	408,893	945,865	1,808,315	4,329,279	7,573,256	26,005,898	44,151,155	74,758,570	126,408,350	213,588,246	360,760,946	716,743,415
		7,280	49,961	182,813	480,661	1,335,997	2,519,072	8,937,837	15,331,590	26,096,492	44,242,023	74,849,714	126,499,770	251,388,167
			0	0	52,112	290,158	746,335	2,951,271	5,223,223	9,028,431	15,422,458	26,187,636	44,333,443	88,166,365
				0	0	0	131,016	851,503	1,677,747	3,041,865	5,314,092	9,119,574	15,513,878	30,916,861
					0	0	0	135,669	434,183	942,097	1,768,616	3,133,009	5,405,511	10,836,789
						0	0	0	31,001	205,610	525,052	1,033,241	1,860,035	3,793,770
							0	0	0	0	88,876	296,754	616,472	1,323,455
								0	0	0	0	38,434	180,296	457,000
									0	0	0	0	27,309	153,094
										0	0	0	0	46,500
											0	0	0	9,113
												0	0	0
													0	0
														0

Annex D

Vir Biotechnology Financial Statement

Vir Biotechnology Inc (VIR US) - Income Statement						
In Millions of USD except Per Share **12 Months Ending**	**FY 2018** **12/31/2018**	**FY 2019** **12/31/2019**	**FY 2020** **12/31/2020**	**Last 12M** **12/31/2020**	**Y 2021 Est** **12/31/2021**	**Y 2022 Est** **12/31/2022**
Revenue	**10.7**	**8.1**	**76.4**	**76.4**	**304.0**	**424.5**
+ Other Revenue	10.7	8.1	76.4	76.4		
Gross Profit	—	—	—		**285.2**	**397.3**
+ Other Operating Income	0.0	0.0	0.0	0.0		
- Operating Expenses	129.4	186.1	373.3	373.3		
+ Selling, General & Admin	29.1	37.6	70.9	70.9		
+ General & Administrative	*29.1*	*37.6*	*70.9*	*70.9*		
+ Research & Development	100.2	148.5	302.4	302.4		
+ Other Operating Expense	0.0	0.0	0.0	0.0		
Operating Income (Loss)	**-118.7**	**-178.0**	**-297.0**	**-297.0**	**-175.8**	**-64.3**
- Non-Operating (Income) Loss	-2.3	-3.5	1.6	1.6		
- Interest Income	*2.5*	*6.5*	*2.8*	*3.3*		
+ Foreign Exch (Gain) Loss	0.0	0.0	0.0			
+ Other Non-Op (Income) Loss	0.2	5.1	4.5	4.9		
Pretax Income (Loss), Adjusted	**-116.4**	**-174.5**	**-298.6**	**-298.6**	**-188.3**	**-140.7**
- Abnormal Losses (Gains)	0.0	0.0	0.0	0.0		
Pretax Income (Loss), GAAP	**-116.4**	**-174.5**	**-298.6**	**-298.6**	**-188.3**	**-140.7**
- Income Tax Expense (Benefit)	-0.5	0.2	0.1	0.1		
+ Current Income Tax	0.0	0.2	0.1			
+ Deferred Income Tax	-0.5	0.0	—			
Income (Loss) from Cont Ops	**-115.9**	**-174.7**	**-298.7**	**-298.7**	**-351.3**	**-419.3**
- Net Extraordinary Losses (Gains)	0.0	0.0	0.0	0.0		
+ Discontinued Operations	0.0	0.0	0.0	0.0		
+ XO & Accounting Changes	0.0	0.0	0.0	0.0		
Income (Loss) Incl. MI	**-115.9**	**-174.7**	**-298.7**	**-298.7**		
- Minority Interest	—	0.0	0.0			
Net Income, GAAP	**-115.9**	**-174.7**	**-298.7**	**-298.7**	**-351.3**	**-419.3**
- Preferred Dividends	0.0	0.0	0.0	0.0		
- Other Adjustments	0.0	0.0	0.0	0.0		
Net Income Avail to Common, GAAP	**-115.9**	**-174.7**	**-298.7**	**-298.7**	**-351.3**	**-419.3**
Net Income Avail to Common, Adj	**-115.9**	**-174.7**	**-298.7**	**-298.7**	**-189.3**	**-141.6**
Net Abnormal Losses (Gains)	0.0	0.0	0.0	0.0		
Net Extraordinary Losses (Gains)	0.0	0.0	0.0	0.0		

Source: Bloomberg

Vir Biotechnology Inc (VIR US) - Balance Sheet			
In Millions of USD except Per Share 12 Months Ending	FY 2018 12/31/2018	FY 2019 12/31/2019	FY 2020 12/31/2020
Total Assets			
+ Cash, Cash Equivalents & STI	98.4	383.4	736.9
+ Cash & Cash Equivalents	47.6	109.3	436.6
+ ST Investments	50.8	274.1	300.3
+ Accounts & Notes Receiv	0.0	0.0	0.0
+ Inventories	0.0	0.0	0.0
+ Raw Materials	0.0	0.0	0.0
+ Work In Process	0.0	0.0	0.0
+ Finished Goods	0.0	0.0	0.0
+ Other Inventory	0.0	0.0	0.0
+ Other ST Assets	19.3	19.6	35.5
+ Derivative & Hedging Assets	0.0	0.0	0.0
+ Misc ST Assets	19.3	19.6	35.5
Total Current Assets	**117.8**	**403.0**	**772.4**
+ Property, Plant & Equip, Net	12.3	16.3	79.9
+ Property, Plant & Equip	14.0	21.1	89.1
- Accumulated Depreciation	1.7	4.8	9.2
+ LT Investments & Receivables	0.0	24.3	0.0
+ LT Investments	—	24.3	0.0
+ Other LT Assets	61.5	68.5	66.5
+ Total Intangible Assets	53.9	52.6	50.8
+ Goodwill	*16.9*	*16.9*	*16.9*
+ Other Intangible Assets	*36.9*	*35.7*	*33.8*
+ Derivative & Hedging Assets	0.0	0.0	0.0
+ Misc LT Assets	7.7	15.8	15.7
Total Noncurrent Assets	**73.8**	**109.1**	**146.4**
Total Assets	**191.6**	**512.1**	**918.8**

Liabilities & Shareholders' Equity			
+ Payables & Accruals	21.0	32.4	78.4
+ Accounts Payable	6.5	5.9	5.1
+ Other Payables & Accruals	14.5	26.5	73.3
+ ST Debt	0.0	0.0	3.6
+ ST Borrowings	0.0	—	0.0
+ ST Lease Liabilities	0.0	—	3.6
+ ST Finance Leases	*0.0*	—	—
+ ST Operating Leases	—	—	*3.6*
+ Other ST Liabilities	18.9	26.8	17.1
+ Deferred Revenue	8.8	6.2	6.5
+ Derivatives & Hedging	0.0	12.4	0.0
+ Misc ST Liabilities	10.1	8.2	10.6
Total Current Liabilities	**39.9**	**59.2**	**99.1**
+ LT Debt	1.0	0.0	66.6
+ LT Borrowings	1.0	—	0.0
+ LT Lease Liabilities	0.0	—	66.6
+ LT Finance Leases	*0.0*	—	—
+ LT Operating Leases	—	—	*66.6*
+ Other LT Liabilities	20.7	28.9	36.3
+ Accrued Liabilities	0.0	0.0	0.0
+ Pension Liabilities	—	0.0	0.0
+ Deferred Revenue	6.6	12.7	3.8
+ Derivatives & Hedging	0.0	0.0	0.0
+ Misc LT Liabilities	14.1	16.3	32.5
Total Noncurrent Liabilities	**21.7**	**28.9**	**102.8**
Total Liabilities	**61.6**	**88.1**	**201.9**
+ Preferred Equity and Hybrid Capital	309.1	0.0	0.0
+ Share Capital & APIC	14.7	793.1	1,385.3
+ Common Stock	0.0	0.0	0.0
+ Additional Paid in Capital	14.7	793.1	1,385.3
- Treasury Stock	0.0	0.0	0.0
+ Retained Earnings	-193.8	-368.5	-667.2
+ Other Equity	0.0	-0.6	-1.3
Equity Before Minority Interest	**130.0**	**423.9**	**716.9**
+ Minority/Non Controlling Interest	0.0	0.0	0.0
Total Equity	**130.0**	**423.9**	**716.9**
Total Liabilities & Equity	**191.6**	**512.1**	**918.8**

Source: Bloomberg

Vir Biotechnology Inc (VIR US) - Cash Flow Statement

In Millions of USD except Per Share 12 Months Ending	FY 2018 12/31/2018	FY 2019 12/31/2019	FY 2020 12/31/2020	Last 12M 12/31/2020
Cash from Operating Activities				
+ Net Income	-115.9	-174.7	-298.7	-298.7
+ Depreciation & Amortization	2.8	4.5	5.4	5.4
+ Non-Cash Items	6.7	30.4	68.0	68.0
+ Stock-Based Compensation	5.1	8.7	27.6	27.6
+ Deferred Income Taxes	-0.5	0.0	—	
+ Other Non-Cash Adj	2.1	21.7	40.4	40.4
+ Chg in Non-Cash Work Cap	12.3	10.1	34.3	34.3
+ Inc (Dec) in Accts Payable	1.5	1.0	-0.8	-0.8
+ Inc (Dec) in Other	10.9	9.1	35.1	35.1
+ Net Cash From Disc Ops	—	0.0	0.0	0.0
Cash from Operating Activities	**-94.1**	**-129.6**	**-190.9**	**-190.9**
Cash from Investing Activities				
+ Change in Fixed & Intang	-9.9	-8.9	-6.4	-6.4
+ Disp in Fixed & Intang	0.0	0.0	0.2	0.2
+ Disp of Fixed Prod Assets	*0.0*	*0.0*	*0.2*	*0.2*
+ Disp of Intangible Assets	*0.0*	*0.0*	*0.0*	*0.0*
+ Acq of Fixed & Intang	-9.9	-8.9	-6.5	-6.5
+ Acq of Fixed Prod Assets	*-9.9*	*-8.9*	*-6.5*	*-6.5*
+ Acq of Intangible Assets	*0.0*	*0.0*	*0.0*	*0.0*
+ Net Change in LT Investment	0.0	0.0	0.0	0.0
+ Dec in LT Investment	0.0	0.0	0.0	0.0
+ Inc in LT Investment	0.0	0.0	0.0	0.0
+ Net Cash From Acq & Div	0.0	0.0	0.0	0.0
+ Cash from Divestitures	0.0	0.0	0.0	0.0
+ Cash for Acq of Subs	0.0	0.0	0.0	0.0
+ Cash for JVs	0.0	0.0	0.0	0.0
+ Other Investing Activities	-50.5	-247.2	-3.5	-3.5
+ Net Cash From Disc Ops	—	0.0	0.0	0.0
Cash from Investing Activities	**-60.4**	**-256.2**	**-9.9**	**-9.9**
Cash from Financing Activities				
+ Dividends Paid	0.0	0.0	0.0	0.0
+ Cash From (Repayment) Debt	0.0	3.3	-4.2	-4.2
+ Cash From (Repay) ST Debt	0.0	3.3	—	
+ Cash From LT Debt	0.0	0.0	—	
+ Repayments of LT Debt	0.0	0.0	—	
+ Cash (Repurchase) of Equity	14.8	444.9	534.0	534.0
+ Increase in Capital Stock	14.8	444.9	534.0	534.0
+ Decrease in Capital Stock	0.0	0.0	0.0	0.0
+ Other Financing Activities	10.1	1.1	-0.3	-0.3
+ Net Cash From Disc Ops	—	0.0	0.0	0.0
Cash from Financing Activities	**25.0**	**449.2**	**529.5**	**529.5**
Effect of Foreign Exchange Rates	0.0	0.0	0.0	0.0
Net Changes in Cash	**-129.6**	**63.5**	**328.7**	**328.7**

Source: Bloomberg