Sharing R&D Risk in Healthcare via FDA Hedges*

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Abstract

Firms conducting medical research and development (R&D) face very high costs and amounts of risk, which makes financing more difficult, thus slowing down the pace of medical innovation. We analyze a new class of simple financial instruments, Food and Drug Administration (FDA) hedges, which allow medical R&D investors to better share the pipeline risk associated with FDA approval with broader capital markets. Using historical FDA approval data, we discuss the pricing of FDA hedges and mechanisms under which they can be traded, and estimate issuer returns. Using unique data sources, we find that FDA approval risk has a low correlation across drug classes, as well as with other assets and the overall market. We argue that this zero-beta property of scientific FDA risk could be a source of gains from trade, between developers looking to offload FDA approval risk and issuers of FDA hedges looking for diversified investments. We offer a proof of concept of the feasibility of trading this type of pipeline risk by examining related securities issued around mergers and acquisitions activity in the drug industry. Overall, our argument is that the use of FDA hedges to share risk between investors in medical innovation and the capital markets will ultimately spur medical innovation and improve the health of patients.

Keywords: Healthcare Finance, R&D Investments, Drug Development, FDA Approval, Idiosyncratic Risk, Risk sharing, Hedging

JEL Classification: G11, G12, G13, G22, I11, I18, K23, L65, O32

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1. Introduction

Medical product companies typically invest very large amounts of money into research and development (R&D) to develop a new treatment. For example, recent estimates suggest that the cost of developing a single new drug in the biopharmaceutical sector is $2.6 billion (DiMasi, Grabowski, & Hansen, 2014). It has been argued by Koijen, Philipson, & Uhlig (2016) that there is a significant medical R&D premium in financial health care markets that affects real health care markets, a premium whose growth is largely attributable to medical innovation. Medical product companies have the development risk of very low rates of success, not only due to the inherent scientific risk of developing new compounds for humans, but also due to the risk of the Food and Drug Administration's (FDA) regulatory approval process in the U.S. (e.g. DiMasi, Hansen, Grabowski, & Lasagna, 1991; DiMasi, Reichert, Feldman, & Malins, 2013). Significantly, this risk is borne only by those investing in the particular treatment under consideration by the FDA, and it cannot easily be shared with other investors in the general capital market. Many have argued that investors are unwilling to provide financing due to these risks, resulting in a "funding gap" and underinvestment in medical R&D that causes many potentially valuable drugs to not be realized or pursued.[6] Furthermore, there is evidence that this problem has been getting worse over time due to changes in the industry (e.g. Scannell, Blanckley, Boldon, & Warrington, 2012).

To overcome the problem of FDA-related risk, Philipson (2015a,b) suggests that financial innovation is needed, allowing those who invest in medical innovation to better share

[6] See Hall and Lerner (2010) and Kerr and Nanda (2015) for reviews of this literature.

scientific and policy-related FDA development risks with outside investors. In this paper, we empirically examine the properties of financial instruments that we refer to as "FDA hedges," which are designed to share these risks. We provide details on the pricing of FDA hedges and mechanisms by which they can be traded, and estimate issuer returns from their offer. In addition, we examine their risk characteristics, and evaluate some unique evidence that suggests these risks can be traded in capital markets.

We begin with the basic motivation behind FDA hedges, the transfer of risk. Drug developers would directly benefit from exchange-traded FDA hedges, since they would be able to transfer some of their development risks to other parts of capital markets. We therefore consider a simple form of the FDA hedge: the exchange-traded FDA binary option, which pays a fixed amount of money in the event of a trigger. Binary options are well known, and regularly traded on various exchanges.[7] In an FDA binary option, the triggering event would be the failure of a specific drug in the FDA approval process. We provide details about the pricing of such a binary option, and use historical data on drug development success rates by phase and drug type to calculate the typical price of an FDA binary option for a drug in each therapeutic area.

Having established the basic pricing of FDA hedges, we turn to a deeper analysis of their characteristics, and argue that they hold appealing properties for both buyers and sellers of the instrument. For buyers such as drug developers, FDA hedges offer a clear insurance value by paying off should a drug fail the approval process. From the perspective of sellers, we consider over-the-counter (OTC) issuers, who in the absence of exchange-traded FDA hedges

[7] One difference between bond and FDA option markets is that options do not need to be rated. This facilitates market making and trading relative to other types of structures.

might offer a portfolio of FDA contracts across developer firms. We simulate the return distribution of these portfolios by calibrating the data to historical FDA approval rates, and estimate their implied risk-reward profiles and those of other variations, based on different assumptions of the underlying contracts. We show that selling diversified pools of FDA hedges offers issuers attractive Sharpe ratios, even under the assumption that issuers are not hedging their pools on the back end.

A potentially compelling feature of FDA hedges is that they only depend on pure scientific risk, and do not aim to insure the post-approval market risk of a compound. This makes assessing the risk of these options easier, and reduces their correlation to traditional asset classes such as stocks and bonds. We argue that this increases their appeal to both buyers and sellers. To investigate the risk characteristics of FDA options, we make use of a novel dataset of project-level time-series estimates of the likelihood of eventual FDA approval for thousands of drugs and biologics. We use this data to construct a panel dataset of the implied prices and returns of FDA options if priced as predicted. We examine the nature of the risk of these synthetic FDA options, and find that the risk is largely idiosyncratic and unrelated to systematic factors.

Since the prices of these hedges are uncorrelated with the broader market or other factors, we argue that the risk associated with FDA hedges may increase the appeal of these instruments to biopharma firms, investors, and issuers. For firms engaged in drug development, the idiosyncratic risk embedded in FDA hedges will be negatively correlated with the idiosyncratic risk of the firm's stock, which may make the firm a more attractive investment by reducing this risk (e.g. Thakor, Anaya, Zhang, Vilanilam, Siah, Wong, & Lo, 2017). Alternatively, investors may purchase FDA hedges directly to offset the risk of their

own investments in biopharma firms. For issuers offering FDA options, these risk patterns may allow issuers to hedge some of the FDA option risk, thus further improving the risk-return tradeoff documented earlier. We examine how well issuers may be able to hedge the risk of offering FDA options by considering the hedge of shorting the stock of the underlying firm whose drug is going through the FDA approval process, and examining the implied value of these hedges given the prices of synthetic FDA hedges and the underlying stocks.

The main source of gains from trade may arise from the zero-beta property of FDA hedges, between issuers looking for diversified investments and developers looking to offload approval risk. Indeed, it may hold generally, provided that the inherent scientific risk of molecular efficacy in humans that drives FDA approval is not correlated with other asset classes. An even broader implication of our empirical findings is that the risk of R&D projects in general is idiosyncratic, since the value of FDA options is directly tied to their underlying R&D projects. To our knowledge, our paper is the first to provide project-level evidence of this point, which has been posited by a number of papers (e.g. Pastor & Veronesi, 2009; Fernandez, Stein, & Lo, 2012; Thakor & Lo, 2015).

A potential concern with the practical implementation of FDA hedges is that adverse selection and moral hazard related to drug development outcomes may cause the market to break down. Although economists often argue that such concerns should eliminate trade, in practice, market breakdown is often prevented through enforceable disclosure requirements that reduce informational asymmetries (e.g. IPOs). We provide a discussion of the types of disclosure requirements that would likely be adopted by markets for FDA hedges. However, we also address these tradability concerns directly by providing evidence that a form of FDA risk already trades in the current market. In particular, we argue that

several exchange-traded Contingent Valuation Rights (CVRs), issued in connection with pharmaceutical mergers, implicitly offer evidence about the market acceptance and covariance properties of FDA hedges. The fact that similar risks have been traded with great liquidity is useful evidence in favor of FDA hedges, because it negates the potential theoretical argument that trade may be infeasible due to asymmetric information between developers and issuers. We consider the price and volume data for these CVRs and examine their risk. We show that the CVR contracts have no significant exposure to the overall market or other factors, which provides further evidence that FDA hedges would be attractive as zero-beta assets to issuers interested in diversification.

Our paper is related most closely to the emerging literature on measuring and analyzing the economic implications of policy uncertainty on economic activity (Davis, 2015) by offering instruments to hedge such uncertainty. It also builds on the recent literature which argues that alternative risk-sharing arrangements between innovators and the broader capital markets are needed to mitigate underinvestment in medical innovation (e.g. Fernandez, Stein, & Lo, 2012; Fagnan, Fernandez, Lo, & Stein, 2013; Thakor & Lo, 2017). Our paper is also related to an emerging literature on the interaction between real and financial health care markets, and the importance of government risk in slowing down medical innovation (Koijen, Philipson, & Uhlig, 2016). We extend these existing literatures by proposing new financial innovations to try to limit the economic distortions imposed by policy uncertainty, and examining their empirical properties.

We start in Section 2 with a discussion of the pricing of FDA binary options, and simulate their prices given historical FDA approval rates and the time they remain in each FDA phase. In Section 3, we examine the return distributions of pools of FDA hedges offered by potential

over-the-counter issuers. In Section 4, we examine the risk characteristics of FDA hedges using a panel dataset of FDA approval probabilities, and explore how this risk may be hedged by issuers. In Section 5, we provide the proof of concept of market acceptance of FDA hedges through CVR contracts and analyze the correlation of the FDA risk with the broader market. We conclude in Section 6 with a summary of our findings and discuss future research.

2. FDA Binary Options

In this section, we consider exchange-traded FDA binary options, and we derive and calibrate prices for these options in various therapeutic areas.

2.1 Pricing Binary FDA Options

Binary options are simple contracts that are currently traded on several exchanges. We define an FDA binary option as a financial contract that is sold for a certain price, entitling the holder to be paid a pre-specified amount in the event that a certain drug fails a given phase of the FDA approval process (or the entire FDA process), and nothing in the event that it succeeds. An FDA option may be issued at the start of a given phase for the approval outcome of that phase. Without loss of generality, we assume it pays one dollar if the drug is not approved, and zero if it is.

Throughout, our pricing formulas will use actual probability estimates to compute expected values, which are then discounted at the risk-free rate. The motivation for this approach is that the risk associated with FDA approval is unlikely to be correlated with priced factors such as stock market returns or aggregate consumption. As a result, the risk inherent in FDA option payoffs should be solely idiosyncratic, in which case the equilibrium

price would be given by the expected discounted value of the payoff, discounted at the risk-free rate of return. We shall test and confirm this key property explicitly in Section 4.

Assuming that approval risk is purely idiosyncratic, the price of a binary FDA option is simply the present value of the probability of non-approval. The two uncertainties are the outcome of the approval decision itself, and the time the approval decision is made. If the approval time is distributed according the frequency $f(t)$, and the probability of non-approval is p, the price at the start of the phase is given by:[8]

$$P = \int e^{-rt} p f(t)\, dt,$$

where r is the risk-free rate. Clearly, the sooner the decision is made, and the larger the chance of non-approval, the higher is the price.

2.2 Calibrated Prices of FDA Options

We estimate the prices for binary FDA options using recent evidence on FDA approval rates. *Table 1* below reports the average historical phase failure rates for different disease groups.[9]

[8] This assumes that there is no correlation between the time of the approval decision and the chance of non-approval. If there is a dependence, we would model the probability as a non-constant function $p(t)$ of time.
[9] These failure rates are from Thomas *et al.* (2016), based upon data from 2006-2015.

Table 1: Probabilities of Phase Failure by Disease Group

The table shows the average probability of failing each phase of the FDA drug development process, broken down by disease groups. These failure rates are from data from 2006-2015, and are taken from Thomas *et al.* (2016).

	Probability of Failing Phase Conditional on Reaching It				
Disease Group	**Phase 1**	**Phase 2**	**Phase 3**	**NDA/BLA Approval Phase**	**Overall Probability of Failure**
Hematology	27%	43%	25%	16%	74%
Infectious Disease	31%	57%	27%	11%	81%
Ophthalmology	15%	55%	42%	23%	83%
Other Disease Groups	33%	60%	30%	12%	84%
Metabolic	39%	55%	29%	22%	85%
Gastroenterology	24%	64%	39%	8%	85%
Allergy	32%	68%	29%	6%	85%
Endocrine	41%	60%	35%	14%	87%
Respiratory	35%	71%	29%	5%	87%
Urology	43%	67%	29%	14%	89%
Autoimmune/immunology	34%	68%	38%	14%	89%
Neurology	41%	70%	43%	17%	92%
Cardiovascular	41%	76%	45%	16%	93%
Psychiatry	46%	76%	44%	12%	94%
Oncology	37%	75%	60%	18%	95%

Given these probabilities of failure, we calibrate the prices of the FDA binary options that pay off $1 million after a given phase if the drug fails that phase. We compute these prices for contracts structured as single-phase and multiple-phase options. For our calculations, we assume an annual risk-free interest rate of 1%.

In order to calibrate the timing of FDA decisions (*f*), we report in *Table 2* the average duration of each phase of the FDA approval process, taken from DiMasi & Grabowski (2007). The estimates for the phase lengths are different for biotech firms and pharma firms. We therefore use the average phase length for biotech and pharma firms in our calculations.

Table 2: FDA Approval Process Phase Lengths

This table shows the average length of each phase in the FDA approval process for the biotech and pharma sectors. Phase length is in months (years in parentheses). Estimates come from DiMasi & Grabowski (2007).

	Average Length of time in months (years)				
Sector	**Phase 1**	**Phase 2**	**Phase 3**	**NDA/BLA Approval Phase**	**Total Length of Time**
Biotech	19.5 (1.6)	29.3 (2.4)	32.9 (2.7)	16.0 (1.3)	97.7 (8.1)
Pharma	12.3 (1.0)	26.0 (2.2)	33.8 (2.8)	18.2 (1.5)	90.3 (7.5)
Average	15.9 (1.3)	27.65 (2.3)	33.35 (2.8)	17.10 (1.4)	94.0 (7.8)

Combining the data on approval rates and the timing of FDA decisions, *Table 3* reports the implied prices (if purchased at the beginning of the indicated phase) for single-phase FDA binary options—options that pay off $1 million if there is failure in the indicated phase, and nothing otherwise. For the purpose of simplifying our calculations and more directly conveying the intuition behind the prices of these FDA options, we do not make distributional assumptions on *f*, and treat the phase length as deterministic by using the average phase lengths from *Table 2* directly when discounting the payoffs of the options. In other words, the payoff of a single-phase FDA option in *Table 3* is given by the following formula:

$$P = e^{-rT} pX,$$

where X is the promised payoff of the option, p is the probability of non-approval, and T is the average phase length taken from *Table 2*. We use a risk-free interest rate of 1% in our calculations. In our simulation results later in this paper, we will make explicit distributional assumptions on *f* in our pricing.

Table 3: Price of Single-Phase FDA Binary Options

The table shows the prices of single-phase FDA binary options, which are issued at the start of each phase and pay off in the event of failure in that phase. Prices are in thousands of dollars.

Price of FDA Option that Pays $1m in a Given Phase ($ thousands)				
Disease Group	**Phase 1**	**Phase 2**	**Phase 3**	**NDA/BLA Approval**
Hematology	$263	$424	$243	$158
Infectious Disease	$301	$560	$266	$111
Ophthalmology	$150	$541	$406	$222
Other Disease Groups	$329	$589	$296	$114
Metabolic	$384	$536	$278	$219
Gastroenterology	$241	$628	$383	$76
Allergy	$320	$660	$278	$61
Endocrine	$406	$585	$340	$138
Respiratory	$342	$693	$281	$53
Urology	$423	$658	$278	$141
Autoimmune/immunology	$338	$667	$368	$138
Neurology	$404	$687	$414	$166
Cardiovascular	$406	$742	$433	$156
Psychiatry	$455	$746	$431	$119
Oncology	$367	$737	$583	$174

The prices of the single-phase options correspond directly to the failure rates in each phase. For example, it would cost $243,000 to buy insurance against a phase 3 failure in hematology for a $1 million insurance policy. Note that in particular, the price to purchase an option at the beginning of phase 2 to insure against phase 2 failure is significantly higher than the price to purchase options at the beginning of the other phases. This reflects the fact that the failure rates in the development process for the various disease groups are the highest in phase 2. By contrast, the prices are much lower in the final FDA approval phase, where the failure rates are the lowest.

We next calculate the prices of multiple-phase FDA binary options, which pay off if there is failure in any subsequent phase of the FDA process. We discuss the pricing of these options

in the Appendix. *Table 4* reports the prices of these options if purchased at the beginning of a given phase, thereby providing insurance against failure in any of the remaining phases.[10]

Table 4: The Price of Multiple-Phase FDA Binary Options, for Payoff in each any Subsequent Phase

This table shows the prices of multiple-phase FDA binary options, which are issued at the start of the indicated phase and pay off in the event of failure in any subsequent phase. Prices are in thousands of dollars.

Price of FDA Option that Pays $1m for Failure in Subsequent Phases ($ thousands)				
Disease Group	**Phase 1**	**Phase 2**	**Phase 3**	**NDA/BLA Approval**
Hematology	$714	$622	$358	$158
Infectious Disease	$784	$704	$344	$111
Ophthalmology	$797	$773	$531	$222
Other Disease Groups	$812	$734	$373	$114
Metabolic	$821	$726	$430	$219
Gastroenterology	$821	$778	$428	$76
Allergy	$828	$761	$321	$61
Endocrine	$843	$753	$428	$138
Respiratory	$847	$783	$318	$53
Urology	$862	$778	$376	$141
Autoimmune/immunology	$862	$807	$451	$138
Neurology	$890	$834	$507	$166
Cardiovascular	$907	$863	$517	$156
Psychiatry	$913	$860	$495	$119
Oncology	$921	$893	$650	$174

There are a few noteworthy patterns in the table. First, naturally the price to insure against *any* phase rises with non-approval rates. Second, the price of the multiple-phase option goes down as one advances to subsequent phases, since the conditional probability of the drug failing in the future goes down over time. However, the price that one would pay

[10] The details of how these prices are calculated are provided in the Appendix.

for the multiple-phase option only goes down slightly from phase 1 to phase 2, dropping much more significantly from phase 2 to phase 3, due to the high failure rates in phase 2. Since the failure rate is much higher in phase 2 relative to all other phases, most of the cost of the option in phases 1 and 2 will be to insure against failure in phase 2. Once failure in phase 2 has been averted, the price of the option drops significantly, since failure is relatively less likely going forward.

3. Risk-Reward Profile of FDA Hedges to Issuers

Having established the pricing of FDA hedges, we now further examine their characteristics in detail in order to ascertain their appeal to buyers and sellers.

For buyers, the appeal of FDA hedges stems from the insurance value of receiving a payoff when a drug fails the approval process. As a result, one of the natural purchasers of an FDA hedge will be the developing firm itself. Since the contract pays off when a drug fails, it offers the firm a chance to receive money for potential investment at exactly the time when the firm is likely to face high costs in the external capital markets.[11] This may not only spur investment, but may also reduce the need for the firm to hold ex ante precautionary savings, potentially freeing up that money for further investment. In addition, the failure of a drug may push a firm into financial distress, especially for biopharma firms with smaller drug portfolios. Since the expected future costs of financial distress are incorporated into a firm's

[11] The idea, as described theoretically in Thakor and Lo (2017), is that the market may have a very difficult time distinguishing between a bad firm/investment and a good investment for an R&D-intensive firm. This stems from the technical nature of R&D (which investors may not be able to properly evaluate) and also the low probabilities of success.

cost of capital, FDA hedges may also allow a firm to reduce its ex ante cost of capital by providing insurance against a state of financial distress.

While the insurance value of FDA hedges to drug developers is clear enough, the question remains of the value of FDA hedges to those holding the other side of the trade, i.e., the issuers. In the remainder of this section, we therefore consider the value to over-the-counter (OTC) issuers that offer FDA contracts to investors. In order to do so, we simulate the risk and return distributions of pools of FDA hedges offered by issuers.

3.1 Risk-Reward Profile of Pools of FDA Options

We first empirically investigate the risk and return tradeoff of a pool of FDA option contracts. We examine a portfolio of N contracts, each linked to a particular FDA application. If the FDA rejects the application at any t prior to the contract maturity date T, the issuer pays the insurance buyer \$1. The precise timing of the FDA's approval decision f is unknown; we model the time until an FDA decision as an exponential distribution with rate parameter λ. When the FDA reaches a decision before the contract expires, we assume that the application i is rejected with probability p_i, and in our base calculations we assume that there is no correlation between the rejection probabilities of two different applications, p_i and p_j. In other words, if each contract represents an FDA option based on the failure/success of a different drug, the probabilities of failure of each drug are independent. *A priori*, this assumption of no correlation across contracts will hold if a larger probability of one molecule working in humans does not increase the chance of another's efficacy. This assumption will likely be the case, except when molecules work within the same indication or mechanism of

action, in which case a correlation may occur.[12] In Section 5, we provide evidence that seems to suggest that the assumption of no correlation between contracts would hold in practice.

In our benchmark simulation results, we vary the number of contracts while fixing other parameters, in order to explore the potential diversification benefits of adding additional contracts to the issuer's portfolio. More specifically, we simulate portfolios of $N = 1$, $N = 10$, $N = 50$, and $N = 100$ contracts. We assume a contract maturity of $T = 5$ years, and $p_i = 30\%$. We choose a rate parameter of $\lambda = 1/3$ for the time until an FDA decision is made, in order to match a mean FDA decision time of three years. For robustness, in *Table A1* in the appendix, we provide the portfolio payout distribution characteristics for alternative choices for the size of the portfolio N, the rejection probability p_i, the correlation across draws ρ, and the arrival rate λ.

We examine the risk-return tradeoff that the issuer faces by calculating the Sharpe ratios of the portfolios. Consider an issuer who has issued N contracts priced at price $\$P$ with expected payouts $X_1, \ldots, X_N$. He invests $\$NP$ at the risk-free rate with the return:

$$R = \frac{[NP(1 + r) - \sum X_i]}{NP} = (1 + r) - \frac{\bar{X}}{P}$$

where $\bar{X} = (\frac{1}{N})\sum X_i$. The Sharpe ratio is calculated by dividing the markup by the standard deviation of the portfolio:

$$SR = \frac{\mathrm{E}[R] - r}{\sigma(R)} = \frac{P - \mathrm{E}[X]}{\sigma(\bar{X})}$$

[12] A correlation would also occur if the FDA decision-making process across molecules is tied together due to regulatory behavior. In the Appendix, we explore how our results are affected when this assumption is relaxed, and we allow for correlation between drug applications.

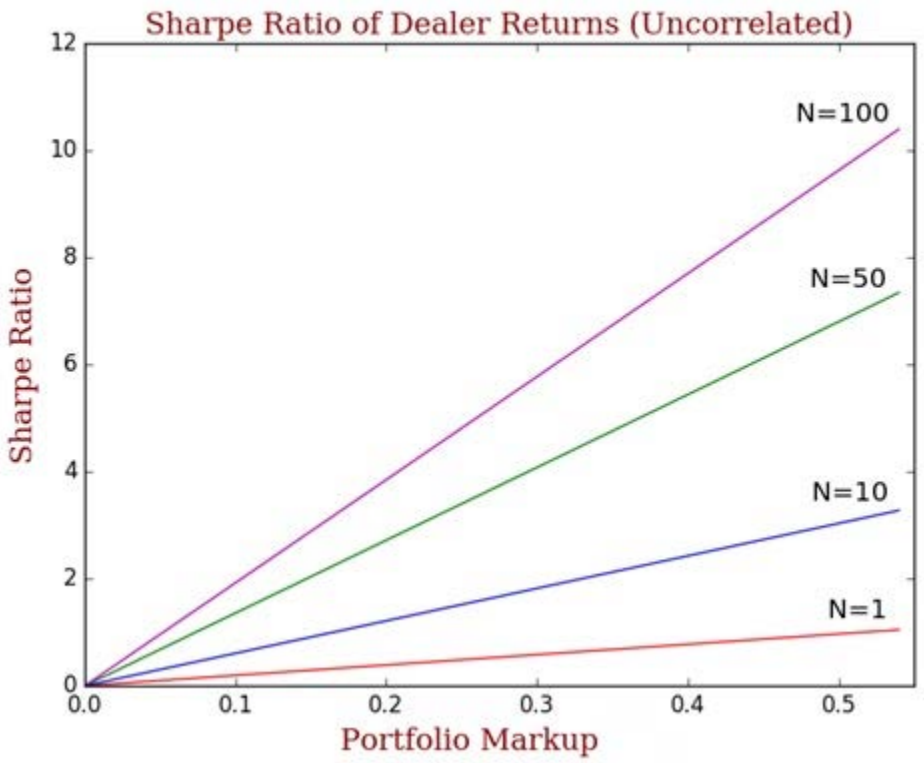
In order to calculate the Sharpe ratios in this setting, we assume contract fees of 2% of the expected payout of the portfolio, and a risk-free rate equivalent to the current five-year Treasury yield. We vary the portfolio markup, up to a maximum markup of 50% over expected portfolio return.

Figure 1 below presents the values of the Sharpe ratio for various values of N as a function of the portfolio markup. For example, for a portfolio of $N = 10$ contracts, the expected payout is estimated to be $2.04, and the standard deviation of the portfolio is estimated to be 0.449. With a price given by a 35% markup over the expected payout, contract fees of 2%, and risk-free rate of 1.22%, the Sharpe ratio is calculated to be 1.5546. As the figure shows, the Sharpe ratio intuitively improves as the markup increases, but an increase in the number of contracts also consistently improves the Sharpe ratio. Thus, in the case of independent payoffs amongst the contracts, a larger number of contracts improve the issuer's Sharpe ratio. The underlying intuition is the same as that of portfolio diversification. With any portfolio of assets, introducing uncorrelated assets will reduce the volatility of the portfolio through diversification.[13]

[13] In Section A.2 of the Appendix, we provide the results for the Sharpe ratios assuming a correlation between the contracts.

Figure 1: Sharpe Ratios

This figure plots the Sharpe ratios of dealer returns as a function of the portfolio markup % for various values of *N*, the number of contracts offered in the pool. These calculations assume no correlation between the payouts of the contracts.



3.2 Risk-Return Distributions for Disease Groups

The results above show the risk-return tradeoff faced by issuers for general pools of FDA option contracts. It is informative to examine in more detail how this tradeoff varies by the particular disease group the FDA options are based upon, since different disease groups have very different success probabilities. *Table 5* provides the expected payout, variance, and Sharpe ratio for a portfolio of FDA options based on a drug project in each respective disease group (assuming $N = 50$ contracts in the pool), using the average probabilities of failure in Phase 3 for each group that were shown in *Table 1*.

Table 5: Expected Payouts of Portfolios of $N = 50$ Contracts

This table provides the simulation results for the mean portfolio payout and variance of payout for different disease groups, assuming $N = 50$ contracts, $\lambda = 1/3$, and markup minus fees of 5%.

Disease Group	Probability of Approval in Phase III	Expected Payout	Std. dev.	Sharpe Ratio
Hematology	75%	$0.51	0.082	3.81
Infectious Disease	73%	0.50	0.079	3.97
Ophthalmology	58%	0.40	0.063	4.89
Other Disease Groups	70%	0.48	0.076	4.07
Metabolic	71%	0.64	0.077	4.09
Gastroenterology	61%	0.42	0.067	4.66
Allergy	71%	0.48	0.078	3.96
Endocrine	65%	0.44	0.071	4.44
Respiratory	71%	0.48	0.077	4.02
Urology	71%	0.48	0.077	4.03
Autoimmune/immunology	62%	0.42	0.067	4.74
Neurology	57%	0.39	0.061	5.17
Cardiovascular	55%	0.38	0.060	5.13
Psychiatry	56%	0.38	0.061	5.13
Oncology	40%	0.27	0.044	6.98

As can be seen from the table, the portfolio payouts vary between disease groups, depending on the probability of approval. In particular, the expected payouts by the issuer are higher if the probability of approval is lower (i.e. the probability that the option will pay out is higher), with the highest expected payout being in oncology. The variance of the payouts also increases as the probability of approval decreases. The Sharpe ratio for the issuer is also generally higher for disease groups with a higher probability of success. For example, issuers will find that issuing pools of FDA options are more attractive for drugs in hematology than for drugs in oncology, since drugs in oncology are more likely to fail and therefore necessitate payouts by the issuer. Overall, the relatively high Sharpe ratios for all the disease classes reinforce the notion that FDA options may be attractive for issuers. In

comparison, the Sharpe ratio of the S&P 500 SPDR ETF over the past five years was 1.32, which is substantially lower than the Sharpe ratios presented above.

While this analysis provides a view into the risk-return tradeoff faced by issuers of FDA options, it is likely to underestimate the true Sharpe ratios that are attainable, since we assume no hedging of the pool of FDA options on the back end by issuers. If issuers are able to hedge the risk of these options, their exposure to risk may be reduced even further. We explore this issue further in the next section.

4. The Risk of FDA Options

In this section, we turn to the issue of the nature of the risk of FDA hedges. FDA hedges may have additional appeal to firms, investors, and issuers if the returns to these securities are uncorrelated with the broader market or other factors, that is, if the risk of the hedge is idiosyncratic and not systematic. While it is intuitive that FDA hedges should primarily contain idiosyncratic risk, since they are directly based on the scientific risk of the underlying drug projects, it is possible that they also contain systematic risk if market conditions affect the research activities of firms, or if firms time their disclosure of results based on the market. We therefore explore whether this is empirically the case using a novel dataset of the drug approval process. Given this risk, we then discuss how this may increase the appeal of FDA hedges to buyers and issuers, and explore the circumstances under which issuers may be able to hedge the risk of FDA options.

4.1 Dataset Description

We use a novel dataset on the drug approval process from the BioMedTracker Pharma Intelligence database. This database contains detailed drug trial information for pharma and biotech companies, including historical approval success rates, development milestone events, progress updates, and most important, estimates of the likelihood of future FDA approval for individual drugs in development by each company. The database provides information on 11,587 drugs across 2,893 different companies. Although the dataset contains information on a handful of development events prior to 2000, it has full coverage from 2000 to 2016, and we therefore focus on this period for our analysis.

We use the reported likelihood of future FDA approval provided by BioMedTracker in order to construct hypothetical prices for FDA options on a wide variety of drugs. For each drug and for a given date, BioMedTracker provides an estimate of the probability that the drug will ultimately be approved by the FDA. These probabilities are updated each time there is any announcement or other development-related event related to the particular drug.[14] In order to determine the likelihood of approval (LOA) probabilities, BioMedTracker uses a combination of historical approval rates and analyst adjustments based on development events. More specifically, when a drug development project is initially started, BioMedTracker assigns it an LOA probability based on the historical approval rates of drugs in the project's particular disease group. BioMedTracker then adjusts the LOA probability for the drug each time a development event occurs. If the event conveys no relevant information as to the eventual development success of the drug, then the LOA is unchanged. However, if

[14] These include a wide variety of events broadly related to the company and drug under development, including trial results and progress updates, regulatory changes, litigation, and company news.

the event contains relevant information (for example, trial results), then the LOA is adjusted either up or down by BioMedTracker depending on whether the information is positive or negative. The magnitude of the change in LOA is determined by analysts, who evaluate the information content of the event and assign a magnitude based on pre-specified criteria.

For example, according to BioMedTracker, an event in phase 3 that "[m]et primary endpoint, but with marginal efficacy or no quantitative details; failed primary endpoint but strong potential in subgroup; some concern with efficacy vs. safety balance" will cause an increase in the LOA between 1% and 5%. In contrast, an event which posted "[m]odest Phase III results or positive results in non-standard subgroup; met primary endpoint but concerns over safety profile or study design" causes a decrease in the LOA between 1% and 5%. BioMedTracker has provided evidence that its LOA estimates have predictive ability in terms of the eventual success/failure of the drug under development. More specifically, BioMedTracker notes that from 2000-2015, 87% of drugs that were eventually approved had been classified as having an above average (relative to the disease group) LOA. Similarly, 75% of the drugs that eventually moved from phase 2 to phase 3 from 2000-2015 had been assigned an above average LOA. 80% of the drugs that were eventually suspended during the same period had a below average LOA.

4.2 Risk Exposure of FDA Options

We use this time series data of probabilities of future approval (LOA) to verify empirically whether the risk of FDA options is idiosyncratic, and thus related only to scientific risk, or systematic and related to the broader market or other factors. Specifically, we construct a time series of synthetic FDA multi-phase binary option prices using the LOA probabilities

described in the previous section. At any given time t, we set the price $F_i(t)$ of the synthetic FDA option on a given drug project i which pays off $1 if the project fails as:

$$F_i(t) = \exp(-r_t(T - t))\left(1 - LOA_{i,t}\right)$$

where LOA_t is the LOA probability at time t, r_t is the risk-free interest rate at time t, and $T - t$ is the expected duration of the contract. For simplicity, we use the expected remaining development time of the drug as a proxy for the expected duration of the contract. We estimate this using the average development times for each phase from *Table 2*.[15] As before, we use actual probabilities to compute expectations and then discount the expected value by the risk-free rate, because the risk is assumed to be purely idiosyncratic. We later provide evidence that justifies this assumption. Using this time series of constructed prices, we compute the returns for these synthetic options for all drugs in the BioMedTracker database. We exclude LOA probabilities that are either 0 (the drug has been suspended) or 1 (the drug has been approved), since there is no future development uncertainty for the drug at those time points.

With these returns, we run regressions to estimate CAPM and Fama and French (1993) 3-factor betas over the period from 2000-2016, and examine whether these betas are significant. We run these regressions at the option level, and also at the portfolio level by combining the options into an equally weighted portfolio. We first use daily data to estimate the betas. While daily data has the potential advantage of increasing the precision of the beta point estimate, one concern with using daily data in this setting is that there is typically no information on each drug between event days, and thus the return for the FDA option will be

[15] For example, for a contract currently in phase 3, we set $T - t = 4.204$ years.

zero for those days. While the lack of correlation due to few events may indeed be valuable to an issuer, for robustness we also provide the beta estimates using monthly data.

Table 6 below provides the results of these factor regressions. As can be seen from the table, the coefficients (betas) are insignificantly different from zero for the CAPM and Fama-French factors when using either daily or monthly data, as well as when running the regressions at both the option and portfolio levels. Moreover, the intercept (alpha) estimates are also insignificant. This provides empirical evidence that the risk of FDA options is idiosyncratic and unrelated to systematic factors, and thus may be valuable for diversification. More broadly, since the value of FDA options are directly tied to the underlying R&D projects, this provides evidence consistent with the idea that the risk of R&D projects in general is idiosyncratic, a point that has been posited by a number of papers (e.g. Pastor and Veronesi, 2009).

Table 6: Systematic Risk of FDA Options

This table gives the results of CAPM and Fama-French 3-factor regressions of the excess return of FDA options on the market, size, and value factors. Regressions are run at the option level or portfolio level using either daily or monthly return data from 2000 to 2016, as indicated. Robust standard errors are in parentheses, and are clustered by date when run at the option level. * indicates significance at the 10% level, ** indicates significance at the 5% level, and *** indicates significance at the 1% level.

Dependent Variable: $R_{i,t} - rf_t$

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
$(Mkt - rf)_t$	-0.0003	0.010	-0.0007	0.010	-0.059	-0.0003	-0.061	-0.029
	(0.0069)	(0.008)	(0.008)	(0.008)	(0.051)	(0.059)	(0.055)	(0.059)
SMB_t			-0.0003	0.015			0.074	0.130
			(0.012)	(0.025)			(0.062)	(0.091)
HML_t			0.002	-0.026			-0.077	-0.102
			(0.019)	(0.021)			(0.076)	(0.111)
Constant (α)	0.00003	0.00003	0.00003	0.00003	0.0008	0.0001	0.0007	0.0001
	(0.00008)	(0.0001)	(0.00008)	(0.0001)	(0.0018)	(0.0022)	(0.0018)	(0.0021)
Regression Level	Option	Portfolio	Option	Portfolio	Option	Portfolio	Option	Portfolio
Data	Daily	Daily	Daily	Daily	Monthly	Monthly	Monthly	Monthly
Obs	20,690,864	3,918	20,690,864	3,918	1,008,291	192	1,008,291	192
R^2	0.0000	0.0003	0.000	0.0012	0.0003	0.0000	0.0006	0.0460

4.3 A Direct Test of Idiosyncratic Risk

A potential concern with our factor regressions is that the lack of significance of the factors may be due to our method of discounting the payoffs of the options. In particular, if the risk of FDA approval is, in fact, not purely idiosyncratic, then our option pricing formula is incorrect. In such cases, we should be using the stochastic discount factor to compute option prices, which amounts to discounting option payoffs using risk-neutral probabilities instead of actual probabilities to compute expectations. It is therefore possible that we do not find significant correlation with priced factors because we are not properly accounting for the pricing kernel.

To address this concern, we examine whether the market return has any significant predictive power regarding the success or failure of drugs. The idea behind this test is that any correlation between FDA option returns and factors such as the market should also manifest itself in whether drugs ultimately succeed or fail (and thus whether the FDA option expires worthless or pays off). Since the success or failure is simply a binary outcome, examining whether the market return is a factor in predicting this outcome is therefore a way to test the robustness of our results above without having to discount or rely on estimation of the pricing kernel. Specifically, we run a logit regression at the drug level, where the dependent variable is a binary variable that equals one if the drug succeeded (passed U.S. regulatory approval) on the given day, and equals zero if the drug failed (development suspension) on the given day. We run this success/failure variable on the contemporaneous market return, as well as the lagged and forward 20-, 60-, and 90-day cumulative market returns.

The results of these regressions are given below in *Table 7*. As can be seen from the table, the market return is insignificant at every horizon, indicating that the market return does not have predictive power on the success or failure outcomes of drugs. This provides further evidence that the risk of FDA approval is purely idiosyncratic.

Table 7: Drug Success/Failure Outcomes and the Market Return

This table gives the results of logit regressions of drug success or failure outcomes on market returns over different time periods. The dependent variable is equal to one if the drug succeeded on the given day and zero if the drug failed on that day. The market returns are cumulative returns between the indicated lagged or forward date and the day *t*. Regressions are run at the drug level using daily data from 2000 to 2016. Robust standard errors are in parentheses, and are clustered by date. * indicates significance at the 10% level, ** indicates significance at the 5% level, and *** indicates significance at the 1% level.

Dependent Variable: Drug Success/Failure

Market Return Window:	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
Contemporaneous, *t*	-5.201								
	(4.272)								
Lagged, *t* – 1 to *t*		1.656							
		(3.182)							
Lagged, *t* – 20 to *t*			-0.214						
			(1.066)						
Lagged, *t* – 60 to *t*				-0.314					
				(0.717)					
Lagged, *t* – 90 to *t*					-0.626				
					(0.510)				
Forward, *t* to *t* + 1						-1.765			
						(3.002)			
Forward, *t* to *t* + 20							0.338		
							(1.235)		
Forward, *t* to *t* + 60								-0.127	
								(0.770)	
Forward, *t* to *t* + 90									-0.464
									(0.626)
Obs	9,678	9,678	9,678	9,678	9,678	9,676	9,628	9,553	9,474
Pseudo-R^2	0.0007	0.0001	0.0000	0.0001	0.0008	0.0002	0.0000	0.0000	0.0003

We argue that this zero-beta property of FDA hedges increases their appeal to both buyers and issuers. From the perspective of biopharma firms, FDA hedges will be *negatively* correlated with the idiosyncratic risk of the development firm's stock. The firm may appear to be a more attractive investment by reducing this risk, which has been shown to be a significant portion of biopharma firm's total risk (e.g. Thakor et al., 2017). As a result, biopharma firms may wish to purchase FDA hedges in order to attract capital from investors.

Alternatively, investors themselves may wish to purchase FDA hedges directly to offset the risk of their own investments in biopharma firms.

From the perspective of issuers offering FDA options, these risk patterns allow issuers to hedge some of the FDA option risk, thus further improving the Sharpe ratios that we previously documented. We next turn to analysis of how they may do so.

4.4 Hedging the Risk of FDA Options

In this section, we outline the extent to which an issuer of FDA risk can hedge by trading the stock of the underlying drug developer. The idea is that any significant movements in the value of the underlying project that an FDA option is based upon will also affect the stock price of the developing firm. To illustrate this in a simple manner, consider a single FDA option that the issuer hedges by shorting the underlying firm. Let the value of the firm be V before the approval decision is made, and V_1 if approved and V_0 if not approved. These approval-contingent values may be written as:

$$V_1 = X_1 + A$$
$$V_0 = X_0 + 0$$

where (X_0, X_1) are the value of the assets of the firm due to other factors than the drug under consideration, and A is the value of the drug under consideration conditional on approval (and thus equal to zero after non-approval). If X_0 and X_1 differ, there is a correlation between the approval decision and the value of the firms due to other factors. Before the approval decision, the value of the firm is:[16]

$$V = pV_1 + (1 - p)V_0$$

[16] This ignores the possibility that the stochastic discount factor may differ across the two approval states.

This equation implies that the price increase due to approval is larger when the probability of non-approval is larger. Likewise, price drops due to non-approval are smaller when the probability of non-approval is smaller.

Assume the issuer of the FDA option shorts the underlying developer to hedge the FDA option. Now consider the case when the approval decision is independent of the other factors driving firm value: $X_1 = X_0$. The payoff of the issuer hedge after non-approval is then:

$$V - V_0 + P - 1$$

The first term is positive because the firm loses value, and the second term is negative because the payout on the option is larger than the price charged for it. The payoff after approval is:

$$V - V_1 + P$$

The first term is negative because the firm gains value, and the second term is positive because of the revenue from selling the option comes without a payout.

As an example of how issuer hedging may work in practice, consider the case of Poniard Pharmaceuticals, a firm developing a lead drug known as Picoplatin, designed to tackle platinum resistance in chemotherapy. Although Picoplatin was under development for a number of different indications, one of its main indications was small cell lung cancer. According to drug trial data from the BioMedTracker, Picoplatin for small cell lung cancer was in phase 3 of the FDA approval process as of late 2009, when it had a probability of eventual FDA approval of 35%. Suppose at this point in time, an issuer had sold a multi-phase FDA binary option, which pays off in the event that the drug fails any subsequent stage of the development process, or is not approved. Ignoring discounting for simplicity, the price of an FDA option with a \$100 face value will be approximately \$100 $\times$ (1 - 0.35) = \$65.

Now, phase 3 trial data for Picoplatin for small cell lung cancer was released on 11/16/2009, and the results precipitated a drop in the likelihood of approval for the drug of 20 percentage points, from 35% to 15%. Since the drug was less likely to be approved, this in turn implied an increase in the price of the FDA option, from \$65 to \$100 × (1 - 0.15) = \$85, or a return of -30.7% from the perspective of the issuer's position. However, suppose that the issuer also had a short position in the underlying Poniard stock. In the 10 days surrounding the trial data release date, Poniard's stock posted a return of -70.8%, thus yielding a return of the short position of 70.8%.[17] As a result, on a one-for-one basis, the short position in the stock more than offsets the increased liability from the FDA option from the perspective of the issuer. A full hedge in this case would therefore involve a portfolio with a roughly 50% weight in the short stock and a 50% weight in risk-free assets.

More generally, we can use the time series of approval probability data as well as stock return data to estimate the optimal number of underlying stocks needed for issuers to hedge the risk of FDA options. Let $F(t)$ be the price of the FDA option at date t that is given by our previous formulas. Denote the underlying stock price return by $S(t)$, and let n be the number of shares of the underlying stock that issuers hold in order to hedge the FDA option. The optimal number of shares that minimizes the overall variance of the issuer satisfies the well-known formula:

$$n^* = \left(\frac{\sigma_F}{\sigma_S}\right)\rho_{F,S}$$

[17] One could alternatively examine *abnormal* returns for the stock, i.e. returns that are attributed to the idiosyncratic movement of the stock (related to the stock's fundamentals), and not to the market or other systematic factors. Doing so by calculating abnormal returns relative to the market factor yields an even larger drop of 74.8%. The very large drop may indicate that investors viewed the disappointing trial results as an indication that Picoplatin would fail some of its trials for other indications. As a result, in this case it is likely that the drug under consideration is correlated with other assets of the company.

where σ_F is the standard deviation of the FDA option price, σ_S is the standard deviation of the underlying stock price, and $\rho_{F,S}$ is the correlation between the prices of the FDA option and the underlying stock.

To more clearly illustrate how this hedging may work in practice, we obtain the approval probability data for the 30 companies in the BioMedTracker database with the lowest market capitalizations, since these companies are likely to have the fewest number of drugs or indications in development. We then obtain daily stock price data for these companies. We eliminate companies for which there are either no drug trial events, or for which there is an insufficient amount of drug trial or stock data. This leaves 19 companies for which we run our estimation results.

Using the time series data on changes in approval probabilities to estimate the prices of multiple-phase FDA binary options for different drugs, as well as stock price data for the underlying company stocks, we estimate the parameters needed to determine the optimal hedge and the implied amount of reduced variance for different drugs. The prices of the FDA options are calculated as described in Section 4.2. *Table 8* below presents the optimal hedge for various drugs. The first three columns correspond to the three parameters above, and the fourth column to the optimal number of shorted stocks. The fifth column calculates the reduction in variance enabled by optimal hedging.[18]

[18] Variances and correlations are calculated based on the sample period for which there is data for each drug. For simplicity, we assume a risk-free interest rate of 0 and we ignore the fact that the timing of the FDA approval decision is uncertain. Accounting for this uncertainty will require additional distributional assumptions.

Table 8: Optimal Issuer Hedges for FDA Options on Different Drugs

This table gives the standard deviation of the price of an FDA binary option σ_F for various drugs, the standard deviation of the researching company's stock price σ_S, the correlation between these prices $\rho_{F,S}$, the optimal number of underlying stocks to short n^* in order to hedge the option risk, and the reduction in variance implied by the hedge.

Company Name	Drug	σ_F	σ_S	$\rho_{F,S}$	n^*	Variance Reduction
Acusphere Inc.	AI-128 for Asthma	14.13	26.78	-0.42	-0.22	17%
Acusphere Inc.	CEP-33222 for Breast Cancer	15.02	26.78	-0.37	-0.21	13%
Advanced Life Sciences Holdings	ALS-357 for Melanoma	2.96	38.63	-0.54	-0.04	10%
Advanced Life Sciences Holdings	Restanza for Respiratory Tract Infections	4.07	38.63	-0.93	-0.10	82%
ARYx Therapeutics	ATI-9242 for Schizophrenia	4.32	2.27	-0.74	-1.42	53%
ARYx Therapeutics	Naronapride for Chronic Idiopathic Constipation	12.29	2.27	-0.84	-4.53	70%
ARYx Therapeutics	Naronapride for Gastroesophageal Reflux Disease	12.23	2.27	-0.84	-4.51	69%
Bone Medical Ltd	Capsitonin for Osteoporosis / Osteopenia	2.75	84.04	-0.61	-0.02	4%
Boston Therapeutics	BTI-320 for Diabetes Mellitus, Type II	0.63	84.04	-0.24	0.00	0%
Taxus Cardium	Generx for Angina	0.72	84.04	-0.25	0.00	0%
diaDexus	AIDSVAX for HIV Prevention	1.70	0.34	0.00	-0.02	1%
diaDexus	PreviThrax for Anthrax Infection (Antibacterial)	10.01	20.40	-0.81	-0.40	65%
Entia Biosciences	ErgoD2 for Renal Disease / Renal Failure	5.10	20.40	-0.73	-0.18	53%
MultiCell Technologies	MCT-125 for Multiple Sclerosis (MS)	0.27	108.04	0.57	0.00	8%
Neuro-Hitech	Huperzine A for Alzheimer's Disease (AD)	9.48	108.04	-0.51	-0.04	23%
Neurobiological Technologies	Xerecept for Cerebral Edema	1.13	0.37	0.24	0.75	0%
Nuo Therapeutics	ALD-201 for Coronary Artery Disease	11.87	0.65	-0.76	-13.86	20%
Nuo Therapeutics	ALD-401 for Ischemic Stroke	10.21	2.74	-0.94	-3.51	88%
Nuo Therapeutics	ALD-451 for Brain Cancer	4.54	1.03	-0.69	-3.02	41%
Ore Pharmaceutical Holdings	ORE10002 for Inflammatory Disorders	1.03	1.10	0.13	0.13	1%
Ore Pharmaceutical Holdings	ORE1001 for Ulcerative Colitis (UC)	0.31	1.10	0.01	0.00	0%
OncoVista Innovative Therapies	OVI-237 for Breast Cancer	0.54	1.10	-0.10	-0.05	0%
OncoVista Innovative Therapies	OVI-237 for Gastric Cancer	7.01	0.37	-0.80	-15.10	64%
OncoVista Innovative Therapies	P-AAT for Acute Coronary Syndrome (ACS)	0.54	10.67	0.29	0.01	0%
OncoVista Innovative Therapies	P-AAT for Diabetes Mellitus, Type I	2.09	10.67	0.50	0.10	1%
Poniard Pharmaceuticals	Picoplatin for Colorectal Cancer (CRC)	7.39	0.55	-0.83	-11.07	60%
Poniard Pharmaceuticals	Picoplatin for Ovarian Cancer	8.50	0.55	-0.78	-11.96	45%
Poniard Pharmaceuticals	Picoplatin for Prostate Cancer	0.84	0.55	0.20	0.31	1%
Poniard Pharmaceuticals	Picoplatin for Small Cell Lung Cancer (SCLC)	10.46	1094.51	-0.71	-0.01	8%
Poniard Pharmaceuticals	Skeletal Targeted Radiotherapy for Breast Cancer	13.53	1094.51	-0.81	-0.01	11%
Poniard Pharmaceuticals	Skeletal Targeted Radiotherapy for Multiple Myeloma	13.30	1094.51	-0.35	0.00	5%
Stromacel	UMK-121 for Liver Failure / Cirrhosis	13.44	1094.51	-0.81	-0.01	11%
Proteo	Elafin for Coronary Artery Bypass Graft (CABG)	12.66	1094.51	-0.74	-0.01	12%
Rock Creek Pharmaceuticals	Anatabine citrate for Alzheimer's Disease (AD)	0.98	1094.51	0.78	0.00	12%
Rock Creek Pharmaceuticals	Anatabine citrate for Autoimmune Disorders	2.66	1094.51	0.52	0.00	6%
Rock Creek Pharmaceuticals	Anatabine citrate for Multiple Sclerosis (MS)	0.67	352.99	0.10	0.00	0%

Rock Creek Pharmaceuticals	Anatabine citrate for Traumatic Brain Injury (TBI)	2.19	2.39	-0.21	-0.19	1%
VioQuest Pharmaceuticals	Lenocta for Anti-Parasitic and Anti-Protozoal	0.87	2.39	-0.29	-0.11	2%
VioQuest Pharmaceuticals	Lenocta for Solid Tumors	0.77	2.39	-0.29	-0.09	2%
VioQuest Pharmaceuticals	VQD-002 for Multiple Myeloma (MM)	14.63	2.39	-0.31	-1.88	3%
VioQuest Pharmaceuticals	VQD-002 for Solid Tumors	0.59	41.71	0.10	0.00	1%

In a number of cases, the resulting variance reduction is low, on the magnitude of 5% or less. There are several reasons for this. First, for some drug indications, there are only a few dates with any news, and moreover, there is no change in the probability of success for many of these dates. Because of this, the price of the FDA option will remain constant for many dates (ignoring discounting), and the variance of the FDA option will be small. This may lead to imprecise inputs into the optimal hedge calculation, and therefore a low variance reduction. Second, certain drugs or indications make up a relatively small proportion of the value of a company's overall drug portfolio. For example, a company may test a compound for efficacy in treatment areas that are different from the drug's primary target with the expectation of a low likelihood of success. The company's overall value will therefore relatively unaffected by clinical news about this indication. As a result, for these particular types of drugs or indications in development, the underlying stock of the company may not offer an ideal hedge against an FDA option issued on that drug. But as noted, for drugs or indications that make up a substantial portion of the company's portfolio, the reduction in variance can be substantial for the issuer.

5. Proof of Concept

There are several theoretical arguments about adverse selection and moral hazard that raise the concern that the trading of FDA hedges may be infeasible. For example, if there is a large degree of asymmetric information, and a firm knows more about the prospects of a drug than the market, then there may be adverse selection in the market for FDA options that could cause a market breakdown. Alternatively, it is possible that FDA options on drugs developed by smaller biotech companies may not be traded due to moral hazard and agency problems (e.g. Guedj and Scharfstein, 2004). While one could express similar concerns about many different asset classes and transactions that still trade with substantial liquidity in markets (for example, options, IPOs, and CDS contracts), it is possible that these problems may be particularly severe for certain drugs.

In such cases, FDA hedges can be structured in a way that reduces or eliminates adverse selection and moral hazard. The standard and most frequently adopted method is through enforceable disclosure requirements of private information. Just as any firm that conducts an IPO must disclose all potentially harmful information about the firm, and can be sued if it fails to do so, FDA hedges would come with similar disclosures before they are marketed. Investors would demand that material information be disclosed before the hedge is put on the exchange, similar to other insurance products such as CDS contracts. Potential disclosure issues would involve all past FDA communications, as well as past trial information. This would ensure that FDA hedges would trade future scientific and regulatory risk that cannot

be disclosed.[19] In addition, as developed theoretically by Thakor & Lo (2017), an *exchange* of FDA options between firms and investors can overcome problems of adverse selection and moral hazard, and allow additional investment into R&D.[20] Thus, the simple framework of FDA hedges that we have developed in this paper can be modified to deal with these theoretical issues.

However, to address these concerns more directly, we discuss an interesting traded instrument that provides a "proof of concept" of liquidity in markets trading FDA risks. Similar in many respects to FDA hedges, the instrument is liquid and follows predicted pricing and volume patterns. This instrument is a particular version of an exchange-traded contingent valuation right (CVR) issued in mergers and acquisitions (M&A) deals, which pays investors pre-specified amounts when certain milestones are met as part of a M&A deal structure. As these milestones many times include FDA approval decisions, these traded contracts contain implicit FDA options.

Nevertheless, one proviso should be kept in mind. Almost all current biopharma CVRs are "impure" with respect to FDA approval decisions, as they often include non-FDA related milestones in addition to FDA approvals. For example, these milestones may include sales or marketing targets. Due to these additional non-FDA milestones, the daily price movements of the CVR may be driven by other factors unrelated to FDA approval. However, this also

[19] A related concern is that insiders of companies may misrepresent their projects to investors, and trade in FDA hedges to profit from this information. However, such a concern is also present with insiders trading shares of their companies, and insider trading laws, enforced by the SEC, are already in place to prevent such actions. These same types of laws could also apply to FDA hedges.

[20] In particular, Thakor & Lo (2017) show that it is an incentive-compatible optimal mechanism for the firm to provide a put option to investors which pays off if the project fails to achieve high payoffs, and for investors to provide a put option to the firm which pays off if the project fails or provides low payoffs. These options can be viewed as types of FDA options. An exchange of these options is feasible even in the presence of significant adverse selection and moral hazard, and allows the firm to raise financing for R&D investments.

suggests that the CVR by itself is not an adequate hedge against FDA approval risk, and thus there is need for purer FDA hedges.

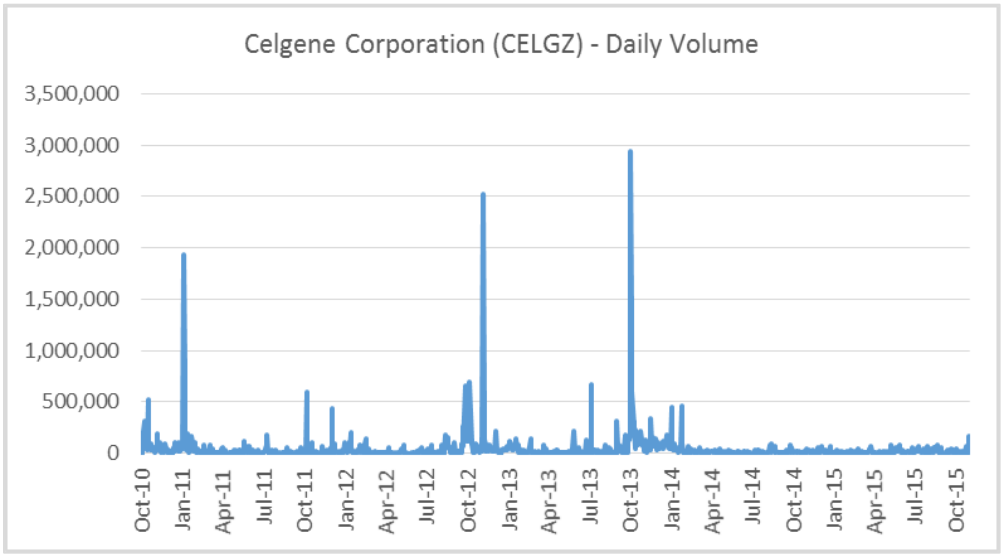
5.1 Contingent Valuation Rights with FDA Options

The contingent valuation right (CVR) is a shareholder right, often given to the selling shareholders during a merger or an acquisition, which gives the holder a cash payment if certain milestones are achieved. CVRs can be traded on the NYSE or NASDAQ, just as listed companies can be traded on these exchanges. An example of a CVR that was traded on the NASDAQ is the CVR issued by Celgene on its acquisition of Abraxis. Celgene issued the Celgene CVR contract, with the holder of the contract entitled to certain milestone and sales payments. For the milestone payments, the holder of the CVR was entitled to a fixed sum of money ($250 million divided by the number of CVRs outstanding) upon the FDA approval of the drug Abraxane for use in the treatment of non-small cell lung cancer by a certain date. In addition, the holder of the CVR was entitled to another sum of money ($400 million divided by the total number of outstanding CVR contracts) if the drug Abraxane achieved FDA approval for use in the treatment of pancreatic cancer. These milestone payments can be viewed as binary FDA options.

Figure 2 below shows the volume data of the Celgene CVR contract, while *Figure 3* shows the price data. In both figures, the top graphs show the volume or price of the CVR contract, while the bottom graphs show the volume or price normalized as a comparable percentage of the underlying Celgene stock. Notice the jump in price around October 2012, when the FDA approved Abraxane for non-small cell lung cancer, and similarly in November, after a trial that showed promise for pancreatic cancer.

Figure 2: Celgene CVR Traded Volume

This figure plots the daily trading volume of the Celgene CVR contract, CELGZ, in number of shares (top figure) and as a percentage of the number of shares traded in the underlying Celgene stock (bottom figure).



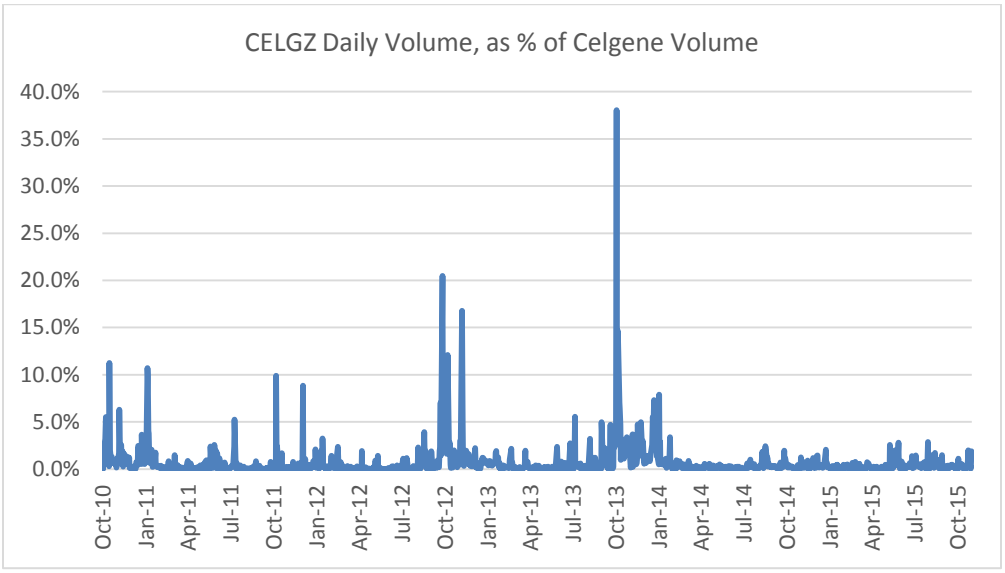


Figure 3: Celgene CVR Stock Price

This figure plots the stock price of the Celgene CVR contract, CELGZ, per share (top figure) and as a percentage of the stock price of the underlying Celgene stock (bottom figure).

Even though the price of this CVR has by and large followed the FDA's decisions, it is still an "impure" FDA hedge. For example, it is an unsecured obligation of Celgene, junior to all other claims. It is also callable by Celgene, so there is optionality embedded into it. The CVR also has sales target payments in addition to milestone payments, which may in turn carry

additional risk correlated to the overall market, but not FDA risk. These additional features generate price movements that are orthogonal to any change in the probability of FDA approval, thus counteracting the ability of the contract to act as a hedge against FDA risk.[21]

Another example is the CVR issued by AstraZeneca after its acquisition of Omthera Pharmaceuticals, Inc. in May 2013. This CVR ensured a payment for shareholders of $1.18 per share, provided that specific FDA approvals for the investigational cholesterol drug Epanova were received by July 31, 2014, and an exclusivity determination was received by September 30, 2014. An additional payment of $3.52 per share was to be paid if additional pre-specified FDA regulatory approvals were received by March 31, 2016.

5.2 Correlations and Betas for Contingent Valuation Rights

In Section 5.3, we showed that the risk in synthetic FDA hedges was idiosyncratic. We now explore whether this is also the case for CVR contracts that are actually traded. Below in *Table 9*, we report the CAPM and Fama-French betas of three CVR contracts, Celgene (CELGZ), Sanofi (GCVRZ), and Wright Medical Group (WMGIZ). We calculate these betas using both daily and monthly data, in order to ensure that the results are not due simply to a small time-series sample size. In general, the betas of the contracts are insignificant, even with features such as sales targets that may include some systematic risk.

For the Celgene CVR contract (Panel A), the market betas (columns (1) and (3)) are insignificant using both daily and monthly data. When incorporating the Fama-French factors, the market beta becomes negative and significant using daily data, but not when using monthly data—weak evidence that the Celgene CVR carries some (negative) market

[21] For this particular CVR, there were also mechanical price changes, such as a large price drop occurring in October 2013 due to the price going ex-dividend.

risk. The betas of the Sanofi CVR contract (Panel B) are all insignificant using both daily and monthly data. Finally, the betas of the Wright Medical Group CVR contract (Panel C) are all insignificant when using daily data; when using monthly data, the HML beta becomes significant. However, there are only 37 months of data available for the WMGIZ contract, and thus the significance in column (4) may be an artifact of the small sample size. Overall, the regression results show that the betas of the CVR contracts are largely insignificant, which provides additional evidence that FDA hedges are also likely to be uncorrelated with the market, and thus may have diversification appeal to investors.

Table 9: CVR Factor Regressions

This table provides CAPM and Fama-French 3-factor regressions of the excess return of CVR contracts on the market, size, and value factors. Regressions are run using either daily or monthly return data for the Celgene-Abraxane CVR contract (CELGZ) in Panel A, the Sanofi CVR contract (GCVRZ) in Panel B, and the Wright Medical Group CVR contract (WMGIZ) in Panel C. Standard errors are in parentheses. All regressions include a constant term (not reported). * indicates significance at the 10% level, ** indicates significance at the 5% level, and *** indicates significance at the 1% level.

Panel A: CELGZ Contract

Dependent Variable: $R_{i,t} - rf_t$

	(1)	(2)	(3)	(4)
$(Mkt - rf)_t$	-0.209	-0.282*	0.808	0.801
	(0.133)	(0.145)	(0.673)	(0.735)
SMB_t		0.350		-0.092
		(0.281)		(1.224)
HML_t		0.154		0.388
		(0.307)		(1.367)
Data	Daily	Daily	Monthly	Monthly
Obs	1,379	1,379	66	66
R^2	0.002	0.003	0.022	0.023

Panel B: GCVRZ Contract

Dependent Variable: $R_{i,t} - rf_t$

	(1)	(2)	(3)	(4)
$(Mkt - rf)_t$	-0.330	-0.270	-0.283	-0.568
	(0.220)	(0.238)	(0.820)	(0.888)
SMB_t		-0.345		1.068
		(0.468)		(1.534)
HML_t		0.020		1.582
		(0.508)		(1.677)
Data	Daily	Daily	Monthly	Monthly
Obs	1,257	1,257	61	61
R^2	0.002	0.002	0.002	0.026

Panel C: WMGIZ Contract

Dependent Variable: $R_{i,t} - rf_t$

	(1)	(2)	(3)	(4)
$(Mkt - rf)_t$	0.757	0.771	0.332	0.386
	(0.786)	(0.798)	(1.720)	(1.673)
SMB_t		-0.205		0.206
		(1.400)		(2.305)
HML_t		-0.186		6.723**
		(1.591)		(2.800)
Data	Daily	Daily	Monthly	Monthly
Obs	774	774	37	37
R^2	0.001	0.001	0.001	0.150

While the betas of the CVR contracts are in general not significantly different from zero, it is possible that some other type of risk is common to all these contracts. For example, there may be a systematic factor other than the market or Fama-French factors that affects the prices and returns of these contracts. One possibility is regulatory risk, potentially affecting multiple drugs simultaneously (Koijen, Philipson, & Uhlig, 2016). Another possibility is that

CVR contracts may be based on companies working in similar therapeutic areas, in which case the success of a drug specific to one company may be correlated with the success of a similar drug under development by another company.

To explore these possibilities, we examine the correlations of the daily and monthly returns for the CVR contracts. This correlation matrix is shown in *Table 10* below. The table shows that the correlations between the different contracts are very low and insignificantly different from zero, suggesting that there is no other common factor that is driving the returns of the CVRs. This provides further evidence that the risk embedded in FDA hedges is likely idiosyncratic, related to the success of the underlying drugs.

Table 10: Correlation matrix of CVR Returns

This table provides correlations between daily (Panel A) and monthly (Panel B) stock returns for the Celgene-Abraxane CVR contract (CELGZ), the Wright Medical Group CVR contract (WMGIZ), and the Sanofi CVR contract (GCVRZ). * indicates significance at the 10% level, ** indicates significance at the 5% level, and *** indicates significance at the 1% level.

Panel A: Daily Returns

	CELGZ	GCVRZ	Observations
CELGZ			1,379
GCVRZ	0.015		1,257
WMGIZ	0.009	0.001	774

Panel B: Monthly Returns

	CELGZ	GCVRZ	Observations
CELGZ			66
GCVRZ	-0.134		61
WMGIZ	-0.009	0.107	37

The insignificant betas and low correlation between contracts also underscore an important point related to the appeal of FDA hedges to OTC issuers. In particular, the Sharpe ratios to OTC issuers of pools of FDA hedges are substantially lower when the payoffs of the

contracts are correlated. These results provide further evidence that the assumption of no correlation between the payoffs of contracts is justified, and that the higher Sharpe ratios of uncorrelated contracts presented in Section 3.1 are applicable.

One alternate explanation for the low betas and covariances of these CVR contracts is their low trading volume. If the contracts are not traded, they have zero covariance with anything. (Note that even if low trading volume were the cause of the low correlation, a low correlation might still be valuable to issuers.) However, *Table 11* below gives the yearly summary statistics for the trading volume of the three CVR contracts discussed above.

Table 11: CVR Daily Trading Volume Summary Statistics

This table provides summary statistics for the daily trading volume for the Celgene-Abraxane CVR contract (CELGZ), the Wright Medical Group CVR contract (WMGIZ), and the Sanofi CVR contract (GCVRZ). All numbers represent the number of shares traded.

Panel A: Celgene CVR (CELGZ)

	Mean	Std. Dev.	p25	Median	p75
2015	17,012.6	20,114.9	3,875	10,950	20,850
2014	21,906.0	44,141.3	5,800	11,600	23,600
2013	67,625.4	216,749.9	4,225	18,000	68,075
2012	52,040.8	182,213.2	3,050	14,900	38,750
2011	35,493.7	140,553.7	2,325	8,950	28,000
2010	70,990.2	85,968.6	22,650	49,500	94,500

Panel B: Sanofi CVR (GCVRZ)

	Mean	Std. Dev.	p25	Median	p75
2015	664,032.1	2,055,218.4	110,900	235,250	516,275
2014	850,199.2	1,699,940.0	147,225	348,950	777,450
2013	1,177,137.3	4,337,753.0	74,150	237,050	624,700
2012	609,218.0	1,003,581.5	109,400	207,600	588,150
2011	2,321,230.4	4,181,025.7	529,300	1,054,800	2,424,800

Panel C: Wright Medical Group CVR (WMGIZ)

	Mean	Std. Dev.	p25	Median	p75
2015	18,037.3	47,647.4	1,100	4,300	17,700
2014	43,925.8	91,923.1	6,900	17,400	47,450
2013	108,033.8	335,577.3	10,900	33,800	88,625

As can be seen from the table, the mean daily trading volume each year is significant for all the contracts. In fact, the trading volume each year for GCVRZ is large, significantly higher than for CELGZ and WMGIZ. This table shows that there is significant trading volume for the CVR contracts, and thus the correlations and betas shown above are likely not due to illiquidity.

6. Conclusion

The high costs and risks faced by firms conducting medical R&D has been partly attributed to the risk of the regulatory approval process in medical innovation (Koijen, Philipson, & Uhlig, 2016). We investigated a new form of financial instrument, FDA hedges, which allow medical R&D investors to share the pipeline risk associated with the FDA approval process with broader capital markets. Using FDA approval data, we discussed the pricing of FDA hedges and mechanisms by which they can be traded, and simulated their risk and return distributions. We then used a novel panel dataset of FDA approval probabilities to empirically explore the nature of the risk inherent to these contracts, and showed how issuers may effectively hedge this risk. We found evidence that the risk associated with offering FDA hedges was largely uncorrelated with other asset classes. We argued that these properties of FDA hedges make them appealing to both buyers and issuers. Finally, we

offered a proof of concept that this type of risk can be traded, by examining related contingent valuation right securities issued around M&A activity in the drug industry.

We believe the type of analysis conducted in this paper is a first step in demonstrating that FDA hedges would enable better risk sharing between investors in medical innovation and capital markets. By permitting such risk sharing, financial innovations like these will encourage further medical innovation. Ultimately, FDA hedges would help accelerate the development of new medical products, and improve the health of countless future patients.

References

Davis, Steven J. "Regulatory complexity and policy uncertainty: headwinds of our own making." Becker Friedman Institute for Research in Economics Working Paper (2015).

DiMasi, Joseph A., and Grabowski, Henry G. "The cost of biopharmaceutical R&D: is biotech different?" *Managerial and Decision Economics* 28, no. 4-5 (2007): 469-479.

DiMasi, J. A., Grabowski, H. G., and Hansen, R. W. "Innovation in the pharmaceutical industry: new estimates of R&D costs." *Medford, MA: Tufts Center for the Study of Drug Development* (2014).

DiMasi, Joseph A., Hansen, Ronald W., Grabowski, Henry G., and Lasagna, Louis. "Cost of innovation in the pharmaceutical industry." *Journal of Health Economics* 10, no. 2 (1991): 107-142.

DiMasi, Joseph A., Reichert, Janice M., Feldman, Lanna, and Malins, Ashley. "Clinical approval success rates for investigational cancer drugs." *Clinical Pharmacology & Therapeutics* 94, no. 3 (2013): 329-335.

Fagnan, David E., Jose Maria Fernandez, Andrew W. Lo, and Roger M. Stein. "Can financial engineering cure cancer?." *The American Economic Review* 103, no. 3 (2013): 406-411.

Fama, Eugene F., and French, Kenneth R. "Common risk factors in the returns on stocks and bonds." *Journal of Financial Economics* 33, no. 1 (1993): 3-56.

Fernandez, Jose-Maria, Stein, Roger M., and Lo, Andrew W. "Commercializing biomedical research through securitization techniques." *Nature Biotechnology* 30, no. 10 (2012): 964-975.

Guedj, Ilan, and David Scharfstein. "Organizational scope and investment: Evidence from the drug development strategies of biopharmaceutical firms." NBER working paper 10933 (2004).

Hall, Bronwyn H., and Josh Lerner. "The Financing of R&D and Innovation." *Handbook of the Economics of Innovation* 1 (2010): 609-639.

Kerr, William R., and Ramana Nanda. "Financing Innovation." *Annual Review of Financial Economics* 7, no. 1 (2015).

Koijen, R., Philipson, T., and Uhlig, H. (2016), "Financial Health Economics", *Econometrica* 84, no 11 :195–242

Philipson, Tomas, "Hedging Pipeline Risk in Pharma: FDA Swaps and Annuities." *Milken Institute* (March 2015a).

Philipson, Tomas. "Saving Lives through Financial Innovation: FDA Swaps and Annuities." *Forbes,* (March 2015b).

Scannell, Jack W., Alex Blanckley, Helen Boldon, and Brian Warrington. "Diagnosing the decline in pharmaceutical R&D efficiency." *Nature reviews Drug discovery* 11, no. 3 (2012): 191-200.

Thakor, Richard T., Anaya, Nicholas, Zhang, Yuwei, Vilanilam, Christian, Siah, Kien Wei, Wong, Chi Heem, and Lo, Andrew W. "Just how good an investment is the biopharmaceutical sector?". Forthcoming, *Nature Biotechnology*.

Thakor, Richard T., and Andrew W. Lo. "Competition and R&D financing decisions: Theory and evidence from the biopharmaceutical industry." No. w20903. National Bureau of Economic Research, 2015.

Thakor, Richard T., and Lo, Andrew W. "Optimal Financing for R&D-intensive Firms". Working Paper, 2017.

Thomas, David W., Burns, Justin, Audette, John, Carroll, Adam, Dow-Hygelund, Corey, and Hay, Michael. "Clinical Development Success Rates". Biotechnology Innovation Organization (BIO), 2016.

Appendix A: Additional Results

A.1 Multiple-Phase Options

An FDA option may be structured to cover multiple phases of approval, so that it pays off if there is failure in any subsequent phase of the drug development process. As a simple example, consider the case where there are four discrete dates in the approval process: $t = 1$ (phase 1), $t = 2$ (phase 2), $t = 3$ (phase 3), and $t = 4$ (final FDA approval of a New Drug Application or Biologics License Application). In order to demonstrate the concept more simply, in the following we assume that each phase is the same length of time, thus removing the uncertainty related to the time when the approval decision is made. As before, we use actual probabilities to compute expected values which are then discounted at the risk-free rate due to the idiosyncratic nature of approval risk. If p_t is the probability that the FDA will approve the drug at time t, then the price of the FDA option at $t = 3$ will be:

$$P_3 = \exp(-rt)\left[(1 - p_4)X\right]$$

The option will be priced recursively at each stage. Therefore, the FDA option which has the payoff indicated by *Figure A-1* below, would be priced at the start $t = 0$ by:

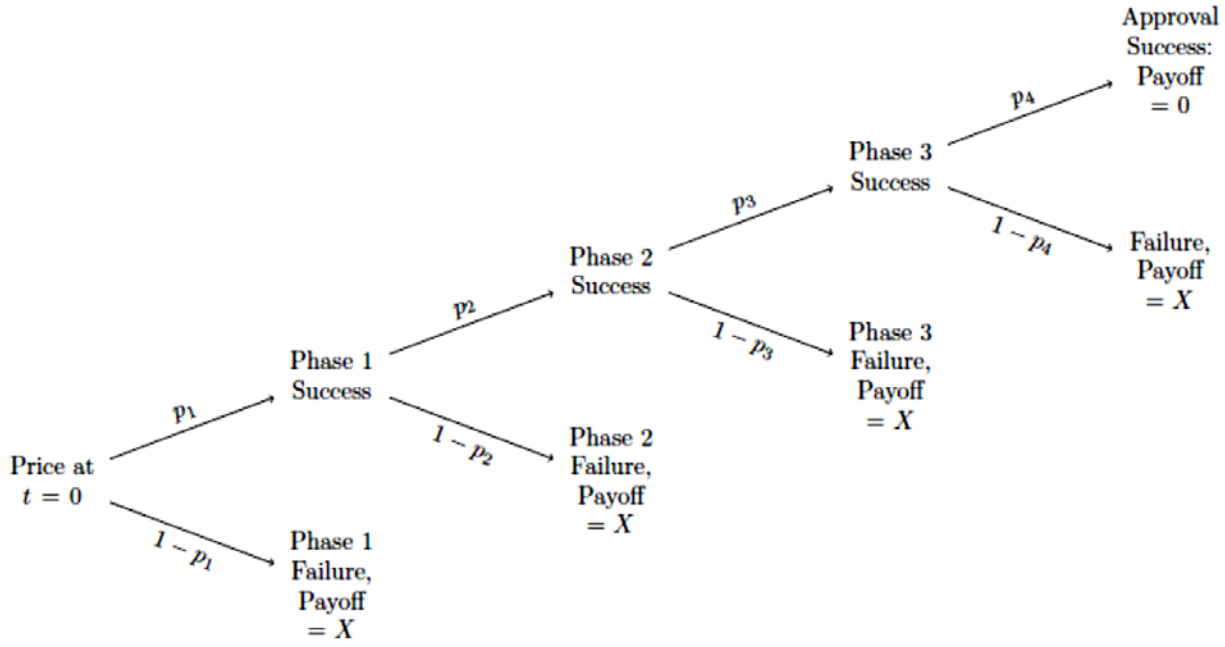
$$P_0 = \exp(-4r)\left[p_1p_2p_3(1 - p_4)X\right] + \exp(-3r)\left[p_1p_2(1 - p_3)X\right] + \exp(-2r)\left[p_1(1 - p_2)X\right] + \exp(-r)\left[(1 - p_1)X\right]$$

To give an example, suppose that a binary option is structured so that it pays off \$1,000 whenever the drug fails the approval process. Assume that the riskless interest rate is 1% per year, and that the probability of success for each phase of the development process is the same at 60%. Then purchasing this contract at $t = 3$ will cost $\exp(-0.01)[(1 - 0.60)\times 1000] = \$396.02$. Purchasing this contract at $t = 0$, however, will cost

$854.10. The high price relative to payoff reflects the fact that the contract offers full insurance: it will pay off if the drug development fails during any phase. Alternatively, one could purchase a contract offering insurance against failure in a specific phase, which would thus be valued at a lower price. This latter contract may be valuable if the risks of failure for a particular type of drug are concentrated in a specific phase. For example, the probability of success for respiratory drugs is significantly lower in phase 2 than it is in any of the other phases of the drug development process (see Thomas et al. (2016)). As a result, a binary option that pays off in the event of failure only in phase 2 may be particularly valuable to a company or an investor that is funding such a drug.

Figure A1: Payoff Diagram of a FDA Binary Option at the Start of Multiple Phases

This figure shows the payoff structure of a multiple-phase FDA binary option, when viewed at the beginning of the R&D process. In each branch, p_t indicates the probability of success.



A.2 Correlated Payoff Calculations and Results

In the analysis in Section 3 of the paper, the payoffs of the individual contracts in the pool are assumed to be independent. However, as discussed previously, it is possible that there is some correlation between the outcomes of the various contracts. In this section, we thus examine the results when relaxing the assumption of independent outcomes, and introduce a correlation of 0.3 between the payouts of the N contracts.

To explore this, we simulate the $X_1,\ldots,X_{50}$ contracts as Bernoulli random variables, and we allow for pairwise dependence between all contracts by associating each contract with a random variable Z_i that is normally distributed with mean 0 and variance 1. Z_i is associated with X_i as follows:

$$X_i = \begin{cases} 1 & \text{if } Z_i < \alpha_i \\ 0 & \text{if } Z_i \geq \alpha_i \end{cases}$$

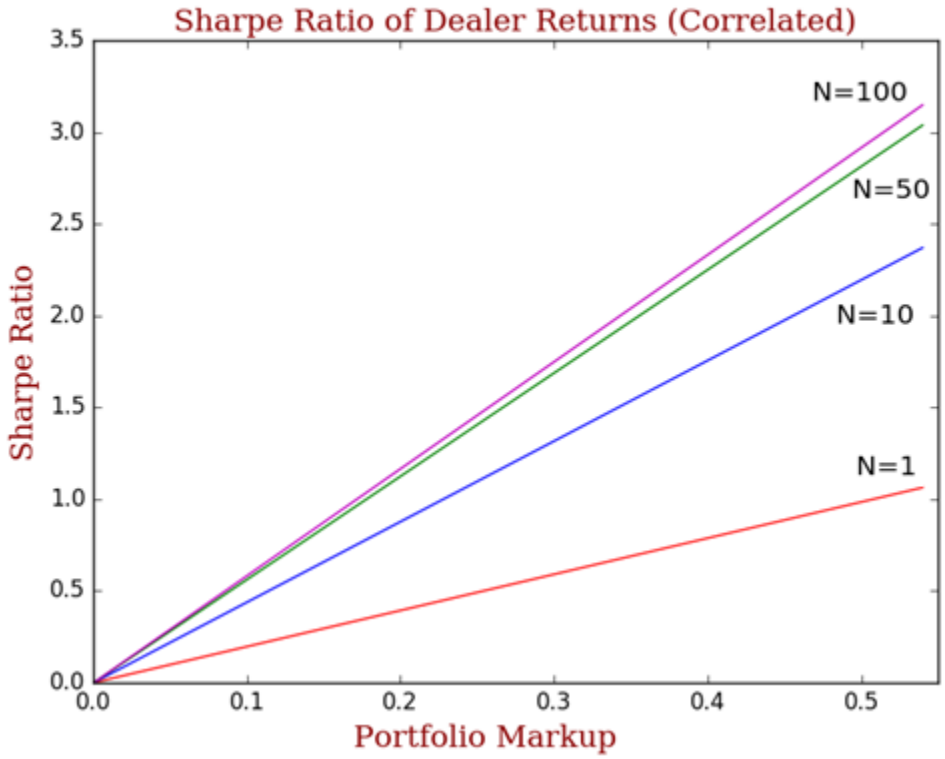
Here, letting $Z_1,\ldots,Z_{50}$ be distributed according to a multivariate standard normal distribution with covariance matrix $\boldsymbol{\Sigma}$ allows the pairwise correlation among $X_1,\ldots,X_{50}$ to be captured by the pairwise correlation among the Z_i's.

Figure A2 presents the Sharpe ratios for various values of N as a function of the portfolio markup with this correlation assumption. In this case, the Sharpe ratios are lower than the case with independent contracts. Moreover, the improvement in the Sharpe ratio is not monotonic as the number of contracts increase. In particular, while there is a large improvement in the Sharpe ratio from N = 1 to N = 10, the Sharpe ratios are very similar between N = 50 and N = 100. The correlation between the contracts reduces the Sharpe ratio because the correlation increases the standard deviation of the portfolio. Since the standard deviation enters into the denominator of the Sharpe ratio, a larger correlation will cause the

Sharpe ratio to decrease. In this case, introducing correlated assets *reduces* the diversification of the issuer's portfolio, thus reducing the Sharpe ratio. This analysis shows that the benefit of holding contracts to the issuer critically depends on both the number of contracts, and the correlation of the payouts between contracts. However, as previously discussed, a substantial correlation between contracts is not likely to hold in practice.

Figure A2: Sharpe Ratios, Equicorrelated Contracts

This figure plots the Sharpe ratios of dealer returns as a function of the portfolio markup % for various values of *N*, the number of contracts offered in the pool. These calculations assume a correlation of 30% between the payouts of the contracts.



A.3 Portfolio Payoff Simulation Results Across Varied Parameters

Table A1 below provides the portfolio payout mean, variance, and standard deviation when varying the parameters for the number of contracts N, the FDA decision arrival rate λ, the probability of payout p, and the correlation between contracts ρ. *Table A2* provides the portfolio payout mean, variance, and standard deviation for various numbers of contracts N across the different disease groups.

Table A1: Portfolio Distribution Attributes

This table provides the simulation results for the mean portfolio payout, variance of payout, and standard deviation of payout for various numbers of contracts N, arrival rate parameters λ, for various disease groups, and for probability, and varying correlation parameters. We assume a markup of 35%.

Number of Contracts	λ	Mean	Variance	Std Dev
$N = 1$	0.20	0.15	0.105	0.32
	0.25	0.18	0.117	0.34
	0.33	0.20	0.132	0.36
	0.50	0.24	0.152	0.39
	1.00	0.27	0.176	0.42
	1.50	0.28	0.185	0.43
	2.00	0.29	0.191	0.44
$N = 10$	0.20	0.16	0.011	0.10
	0.25	0.18	0.012	0.11
	0.33	0.20	0.013	0.12
	0.50	0.24	0.015	0.12
	1.00	0.27	0.018	0.13
	1.50	0.28	0.019	0.14
	2.00	0.29	0.019	0.14
$N = 50$	0.20	0.16	0.002	0.05
	0.25	0.18	0.002	0.05
	0.33	0.20	0.003	0.05
	0.50	0.24	0.003	0.06
	1.00	0.27	0.004	0.06

	1.50	0.28	0.004	0.06
	2.00	0.29	0.004	0.06
	0.20	0.16	0.001	0.03
	0.25	0.18	0.001	0.03
	0.33	0.20	0.001	0.04
$N = 100$	0.50	0.24	0.002	0.04
	1.00	0.27	0.002	0.04
	1.50	0.28	0.002	0.04
	2.00	0.29	0.002	0.04

Number of Contracts	Probability	Mean	Variance	Std Dev
	$p = 0.2$	0.14	0.097	0.31
	$p = 0.3$	0.20	0.133	0.36
	$p = 0.4$	0.27	0.158	0.40
$N = 1$	$p = 0.5$	0.34	0.175	0.42
	$p = 0.6$	0.41	0.182	0.43
	$p = 0.7$	0.48	0.180	0.42
	$p = 0.8$	0.54	0.169	0.41
	$p = 0.2$	0.14	0.010	0.10
	$p = 0.3$	0.21	0.013	0.12
	$p = 0.4$	0.27	0.016	0.13
$N = 10$	$p = 0.5$	0.34	0.018	0.13
	$p = 0.6$	0.41	0.018	0.14
	$p = 0.7$	0.48	0.018	0.13
	$p = 0.8$	0.55	0.017	0.13
	$p = 0.2$	0.14	0.002	0.04
	$p = 0.3$	0.20	0.003	0.05
	$p = 0.4$	0.27	0.003	0.06
$N = 50$	$p = 0.5$	0.34	0.003	0.06
	$p = 0.6$	0.41	0.004	0.06
	$p = 0.7$	0.48	0.004	0.06
	$p = 0.8$	0.55	0.003	0.06
	$p = 0.2$	0.14	0.001	0.03
$N = 100$	$p = 0.3$	0.20	0.001	0.04
	$p = 0.4$	0.27	0.002	0.04

	$p = 0.5$	0.34	0.002	0.04
	$p = 0.6$	0.41	0.002	0.04
	$p = 0.7$	0.48	0.002	0.04
	$p = 0.8$	0.55	0.002	0.04

Number of Contracts	Correlation	Mean	Variance	Std Dev
$N = 1$	0.00	0.20	0.133	0.36
	0.05	0.20	0.133	0.36
	0.10	0.21	0.133	0.37
	0.15	0.21	0.133	0.37
	0.20	0.20	0.132	0.36
$N = 10$	0.00	0.20	0.013	0.12
	0.05	0.20	0.019	0.14
	0.10	0.21	0.025	0.16
	0.15	0.20	0.031	0.18
	0.20	0.20	0.037	0.19
$N = 50$	0.00	0.20	0.003	0.05
	0.05	0.20	0.009	0.10
	0.10	0.20	0.016	0.13
	0.15	0.21	0.022	0.15
	0.20	0.20	0.029	0.17
$N = 100$	0.00	0.20	0.001	0.04
	0.05	0.20	0.008	0.09
	0.10	0.20	0.014	0.12
	0.15	0.20	0.021	0.15
	0.20	0.20	0.028	0.17

Table A2: Portfolio Distribution Attributes Across Disease Groups

This table provides the simulation results for the mean portfolio payout, variance of payout, and standard deviation of payout for various numbers of contracts *N*, across different disease groups.

Number of Contracts	Disease Group	Mean	Variance	Std Dev
N = 1	Hematology	0.51	0.176	0.42
	Infectious Diseases	0.50	0.178	0.42
	Ophthalmology	0.40	0.181	0.43
	Other Disease Groups	0.48	0.180	0.42
	Metabolic	0.64	0.177	0.42
	Gastroenterology	0.42	0.182	0.43
	Allergy	0.48	0.179	0.42
	Endocrine	0.44	0.182	0.43
	Respiratory	0.49	0.179	0.42
	Urology	0.48	0.179	0.42
	Autoimmune	0.42	0.182	0.43
	Neurology	0.39	0.181	0.43
	Cardiovascular	0.37	0.180	0.42
	Psychiatry	0.38	0.180	0.43
	Oncology	0.27	0.158	0.40
N = 10	Hematology	0.51	0.018	0.13
	Infectious Diseases	0.50	0.018	0.13
	Ophthalmology	0.39	0.018	0.14
	Other Disease Groups	0.48	0.018	0.13
	Metabolic	0.64	0.018	0.13
	Gastroenterology	0.42	0.018	0.14
	Allergy	0.48	0.018	0.13
	Endocrine	0.44	0.018	0.14
	Respiratory	0.48	0.018	0.13
	Urology	0.48	0.018	0.13
	Autoimmune	0.42	0.018	0.14
	Neurology	0.39	0.018	0.13
	Cardiovascular	0.37	0.018	0.13
	Psychiatry	0.38	0.018	0.13
	Oncology	0.27	0.016	0.13
N = 50	Hematology	0.51	0.003	0.05
	Infectious Diseases	0.50	0.003	0.05

	Ophthalmology	0.40	0.003	0.05
	Other Disease Groups	0.48	0.003	0.05
	Metabolic	0.64	0.004	0.06
	Gastroenterology	0.42	0.003	0.05
	Allergy	0.48	0.003	0.05
	Endocrine	0.44	0.003	0.05
	Respiratory	0.48	0.003	0.05
	Urology	0.48	0.003	0.05
	Autoimmune	0.42	0.003	0.05
	Neurology	0.39	0.003	0.05
	Cardiovascular	0.38	0.003	0.05
	Psychiatry	0.38	0.003	0.05
	Oncology	0.27	0.002	0.04
	Hematology	0.51	0.002	0.04
	Infectious Diseases	0.50	0.002	0.04
	Ophthalmology	0.40	0.002	0.04
	Other Disease Groups	0.48	0.002	0.04
	Metabolic	0.64	0.002	0.04
	Gastroenterology	0.42	0.002	0.04
	Allergy	0.48	0.002	0.04
N = 100	Endocrine	0.44	0.002	0.04
	Respiratory	0.48	0.002	0.04
	Urology	0.48	0.002	0.04
	Autoimmune	0.42	0.002	0.04
	Neurology	0.39	0.002	0.04
	Cardiovascular	0.38	0.002	0.04
	Psychiatry	0.38	0.002	0.04
	Oncology	0.27	0.002	0.04