

Risk and Reward in the Orphan Drug Industry

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ABSTRACT: *Thanks to a combination of scientific advances and economic incentives, the development of therapeutics to treat rare or orphan diseases has grown dramatically in recent years. With the advent of Food and Drug Administration–approved gene therapies and the promise of gene editing, many experts believe we are at an inflection point in dealing with these afflictions. In this article, the authors propose to document this inflection point by measuring the risk and reward of investing in the orphan drug industry. They construct a stock market index of 39 publicly traded companies that specialize in developing drugs for orphan diseases and compare the financial performance of this index, which they call ORF, to the broader biopharmaceutical industry and the overall stock market from 2000 to 2015. Although the authors report that ORF underperformed other biopharma companies and the overall stock market in the early 2000s, its performance has improved over time: from 2010 to 2015, ORF returned 608%, far exceeding the 317%, 320%, and 305% returns of the S&P, NASDAQ, and NYSE ARCA Biotech indexes, respectively, and the 83% of the S&P 500. ORF does have higher volatility than the other indexes but still outperforms even on a risk-adjusted basis, with a Sharpe ratio of 1.24 versus Sharpe ratios of 1.17, 1.14, and 1.05, respectively, for the other three biotech indexes and 0.71 for the S&P 500. However, ORF has a market beta of 1.16, which suggests significant correlation to the aggregate stock market and less diversification benefits than traditional pharmaceutical investments.*

TOPICS: *Mutual funds/passive investing/indexing, security analysis and valuation, performance measurement**

The term *orphan disease* typically refers to rare conditions that affect relatively small patient populations, such as amyotrophic lateral sclerosis, chronic myelogenous leukemia, and Gaucher disease. Many are fatal or extremely debilitating. Although any single orphan disease is by definition uncommon, it is estimated that there are over 7,000 types of such diseases and that the population of Americans with an orphan disease ranges from 25 million to 30 million, exceeding the total number of US cancer patients.

Until the passage of the Orphan Drug Act (ODA) in 1983, the biopharmaceutical industry showed little interest in developing therapies for orphan indications: In the decade before the ODA, only 10 industry-sponsored orphan drugs were brought to market in the United States. However, thanks to various economic incentives created by the ODA (e.g., tax benefits, extended exclusivity, and priority Food and Drug Administration [FDA] review), combined with technological breakthroughs such as efficient whole-genome sequencing and rational drug design methods, over 600 orphan drug indications were approved by the FDA between 1983 and

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2017, based on more than 450 distinct drug products.¹ In a number of cases, fatal conditions such as chronic myeloid leukemia and Gaucher disease have been transformed into chronic but manageable conditions with the appropriate medication. Moreover, the advent of gene therapy now holds the promise of cures for certain orphan diseases, of which 80% are genetic in origin.

These factors have contributed to what many consider to be an inflection point in the treatment of orphan diseases, reflected in the financial performance of the biopharmaceutical companies producing orphan drugs. A case in point is Alexion Pharmaceuticals, a US company founded in 1992 that received FDA approval in 2007 for Soliris, a treatment for paroxysmal hemoglobinuria, a rare blood disorder. Since its initial public offering in 1996, Alexion has yielded an average compound annual return of 29% (through August 10, 2018); on May 24, 2012, the stock was added to the S&P 500 index. Of course, not all orphan drug companies are as successful, and even those companies that succeed to the point of going public still bear considerable risk. The amount of risk and whether the returns to investors are commensurate with that risk are the subjects of this study.

We propose to measure the financial performance of the orphan drug industry by constructing an index of US companies that focus exclusively on developing therapies for orphan diseases. We identify 39 such companies, construct a value-weighted return index with these companies as constituents, and investigate the statistical properties of this index, which we shall refer to as ORF. In the early 2000s, we find that orphan drug companies as an aggregate were not as attractive an investment as other drug companies; that is, ORF had worse returns with substantially higher risk. However, ORF's performance has improved over time. During the last five years, ORF has outperformed both the pharma and biotech sector indexes in terms of risk–return profile. Overall, an investment in orphan drug companies from 2000 to 2015 would have fared better than an investment in either pharma or biotech, even after adjusting for risk.²

It is useful to compare ORF to other indexes in the biopharmaceutical sector. ORF has consistently

higher volatility than the pharma index, indicating substantial risk. Although the volatility is slightly higher than that of the biotech index, it moves closely with that index. The volatility of these indexes has shown a secular decline since 2000 and also has less dispersion compared to the early 2000s. However, the higher volatility in the early 2000s may be due to the bursting of the tech bubble.

Market betas for the ORF and biotech indexes in general decreased between 2000 and 2010, spiked between 2012 and 2013, and have since been declining. The betas of the ORF and biotech indexes are quite similar over time, but when calculated over longer horizons, ORF has the higher beta beginning in 2005. The pharma index consistently posts lower betas than the ORF or biotech indexes. The conclusion is that orphan drugs carry significant systematic risk relative to the market.

In terms of downside risk, the maximum drawdowns of ORF are consistently greater in magnitude than those of the other indexes (i.e., they are more negative), showing a potential for greater tail risk of negative returns for orphan drugs. The exception is the *k*-means biotech index, which has comparable maximum drawdowns. However, the drawdowns have been smaller in magnitude (less negative) over time, indicating that there has been improvement.

INDEX CONSTRUCTION AND EMPIRICAL METHODOLOGY

Our goal is to construct an index with companies that undertake pure-play orphan drug development. We therefore define an orphan drug company as

1. a company that has an expressed and exclusive commitment to the development of orphan drugs (as determined by their mission statement);
2. a company that is devoted specifically to one or more orphan disease areas; or
3. a company whose pipeline consists only of orphan drugs.

To identify the set of constituent companies for our index, we obtain the entire history of orphan drug designations to date from the FDA's Orphan Drug Designation and Approvals database.³ From this history,

³FDA Orphan Drug Designations and Approvals Database: <https://www.accessdata.fda.gov/scripts/opdlisting/opod/>.

¹Lanthier (2017). See also Lichtenberg and Waldfogel (2003), who documented increases in consumption and longevity for individuals with less common diseases after the passage of the ODA.

²Our results are also consistent with recent evidence that suggests that orphan drug designations can serve as a positive signal for stock market investors at the time of an initial public offering; see Gorry and Useche (2018).

we identify all companies that have achieved orphan drug status for at least one product. From these companies, we manually identify the subset of companies that adhere to our definition of an orphan drug company. This yields a total of 170 companies, of which 39 are US publicly traded companies. The complete list of companies that we consider, as well as the dates for which we have data, are included in the Appendix.

For these companies, we obtain daily stock return data from the CRSP database from January 3, 2000 to December 31, 2015. We choose 2000 as our starting year because that is the first year that includes a quarter with 10 or more orphan drug companies from which we can construct our index. This provides us with a total of 59,805 daily stock return observations, which translates to 4,025 daily return observations for our index.

Using the stock return data for these companies, we construct a value-weighted total return index that is rebalanced quarterly.⁴ More specifically, at the beginning of each quarter, we calculate the weight of each company in the index as that company's proportion of the total market capitalization of all active orphan drug companies as of that date. The weights of each company vary across time, depending on the individual company's returns, until the next rebalancing date, when new companies may enter the index and the weights are readjusted. The overall return of the index is thus a weighted average of the daily returns of the constituent companies. Mathematically, the return of the index on a given date t is given by

$$R_t^{\text{ORF}} = \sum_{j=1}^N \left(\frac{Val_{j,t-1}}{\sum_{i=1}^N Val_{i,t-1}} \right) R_{j,t} \quad (1)$$

where $R_{j,t}$ is the return of stock j on date t , which is multiplied by the weight of stock j (a function of its previous-day market capitalization $Val_{j,t-1}$). Using these returns, we also calculate various risk characteristics and risk-adjusted returns of ORF over time, including the stock return volatility, Sharpe ratios, capital asset pricing model and Fama–French three-factor alphas and betas, and maximum drawdowns.

We compare the return and risk characteristics of ORF to those of broad indexes—the S&P 500 and

NASDAQ indexes—as well as widely used pharma and biotech indexes, including the NYSE ARCA Pharma, NYSE ARCA Biotech, NASDAQ Biotech, and S&P 500 Biotech.⁵ However, as noted by Thakor et al. (2017), a significant concern with comparing biotech indexes is the substantial sensitivity of their return characteristics to the inclusion of specific companies, a result of the out-sized performance of a handful of companies. Thus, for comparison we also include k -means pharma and biotech index returns taken from Thakor et al. (2017), who classified companies into the pharma or biotech sectors dynamically over time using observable characteristics via machine learning techniques.⁶

RESULTS: RETURNS

We begin by examining the returns of the ORF index compared to that of the other indexes. In Panel A of Exhibit 1, we plot the cumulative returns of ORF compared to the broad S&P 500 and NASDAQ indexes from the beginning of 2000 to the end of 2015. In terms of cumulative returns, ORF appears to slightly outperform the S&P 500 from 2000 to 2004 but then begins to underperform the S&P 500 (and slightly outperform the NASDAQ) until around 2008. After that, the performance of ORF improves substantially

⁵A possible concern with constructing these returns is that they are subject to autocorrelation. In untabulated results, we calculate the autocorrelation coefficients for each index over each year, five-year subperiods, and the entire sample period. We also perform Breusch–Godfrey LM tests and confirm that, although a few individual years have significant autocorrelation, there is no evidence of autocorrelation over the entire sample period or five-year subperiods for the orphan drug index. Similarly, for every index except for the S&P 500 and k -means biotech indexes, there is no significant autocorrelation over the entire sample. The biotech indexes, however, do have some significant autocorrelation from 2005 to 2009. Taken in total, the tests suggest that autocorrelation is unlikely to have a strong effect on our results.

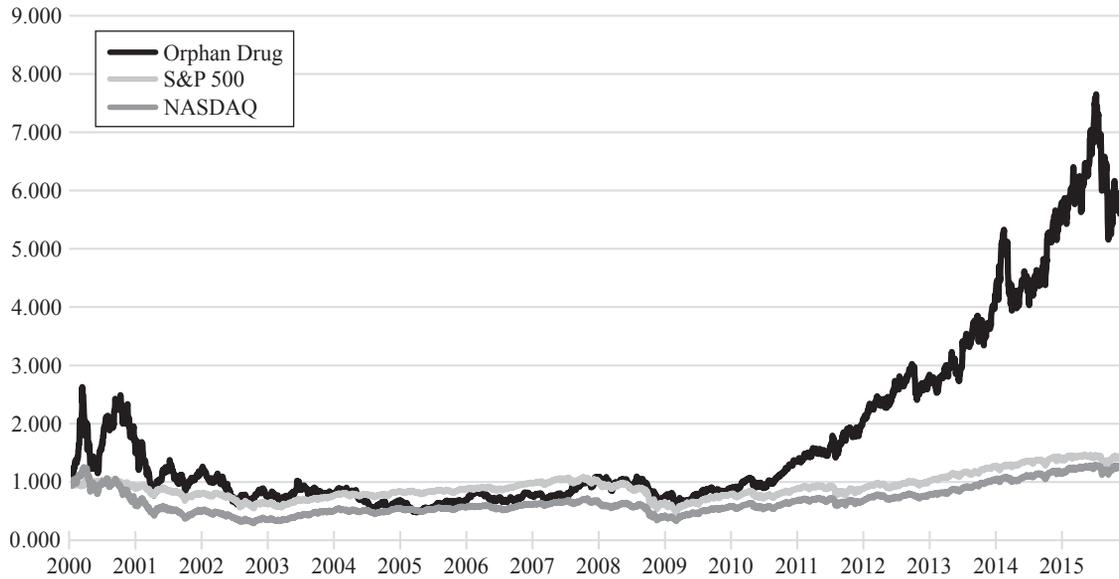
⁶More specifically, the Thakor et al. (2017) indexes are constructed to create a sample of seed companies in each year, which are classified as either pharma or biotech. The k -means machine learning algorithm then looks at all other companies in the sample in that year and calculates distances between those companies and the seed companies based on observable characteristics, such as the number of employees, research and development expenses, total asset value, intangible assets, cash holdings, sales, and company age. The classifications are recalculated for each year, and thus the classification is dynamic—a company may be biotech in one year but eventually may become pharma.

⁴The returns of our index are similar if we instead construct an equal-weighted index that is rebalanced quarterly.

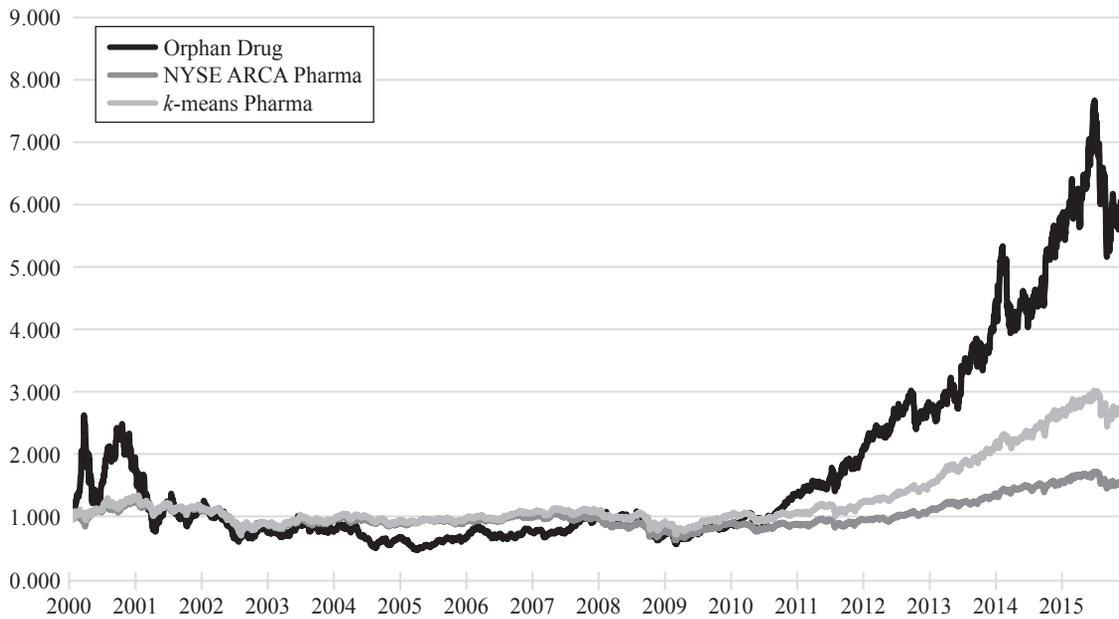
EXHIBIT 1

Cumulative Returns from 2000 to 2015

Panel A: Cumulative Returns versus Broad Indexes

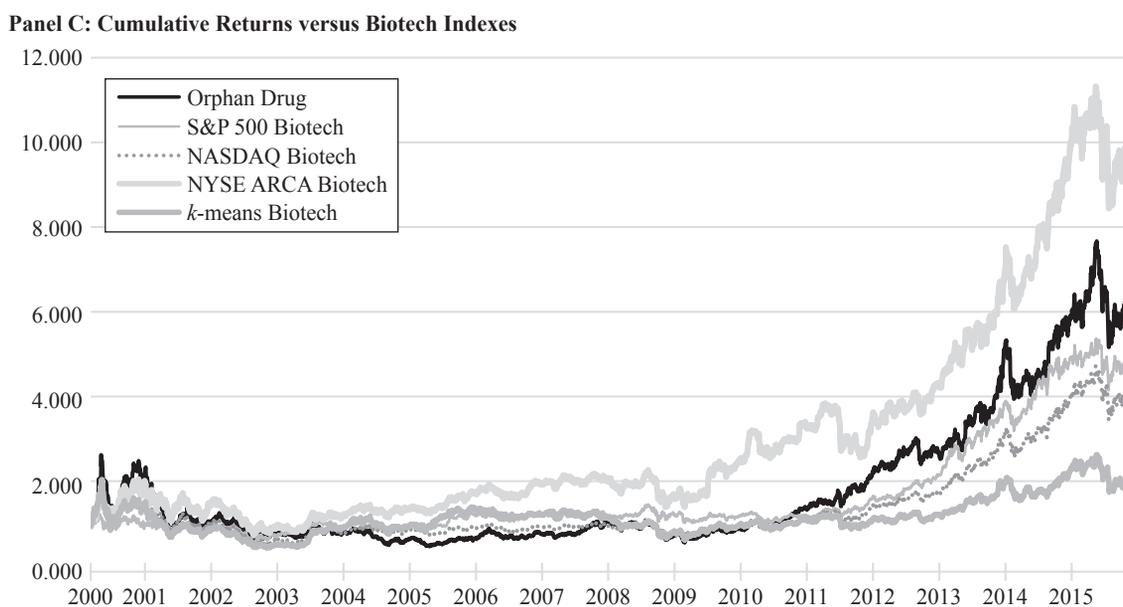


Panel B: Cumulative Returns versus Pharma Indexes



(continued)

EXHIBIT 1 (continued)
Cumulative Returns from 2000 to 2015



Notes: This exhibit provides the value over time of a \$1 investment made on January 3, 2000. Panel A compares ORF to the broad S&P 500 and NASDAQ indexes, Panel B compares ORF to pharma indexes, and Panel C compares ORF to biotech indexes.

and is greater than that of both the S&P 500 and the NASDAQ by a wide margin. For comparison purposes, a \$1 investment in ORF in the beginning of 2000 would have yielded just above \$6 at the end of 2015, whereas the same \$1 investment in either the S&P 500 or the NASDAQ would have yielded around \$1.50.

Panel B of Exhibit 1 compares the cumulative returns of ORF to those of the NYSE ARCA Pharma index and the *k*-means pharma index from Thakor et al. (2017). The performance of the ARCA Pharma and *k*-means pharma indexes is quite similar until about 2010, when the *k*-means pharma index overtakes the ARCA Pharma index. Although ORF appears to underperform these pharma indexes until roughly 2008, after 2010 it begins to substantially outpace them.

Panel C of Exhibit 1 compares ORF to four biotech indexes: the NYSE ARCA Biotech, S&P 500 Biotech, NASDAQ Biotech, and *k*-means biotech indexes. As can be seen from the exhibit, the cumulative returns from the NYSE ARCA Biotech index dominate those of the other biotech indexes and that of ORF over the entire period. In particular, a \$1 investment in the ARCA Biotech index at the beginning of 2000 would have yielded about \$10 at the end of 2015. The cumulative returns on ORF, however, stay in line with

the remaining indexes until about 2011, after which it overtakes the remaining indexes. Although the S&P 500 and NASDAQ Biotech indexes perform slightly more poorly than ORF, the *k*-means biotech index seems to post substantially lower cumulative returns.

This dramatic diversity in returns between the biotech indexes is in line with the results of Thakor et al. (2017), who pointed out that the composition of companies in a biotech index has a very strong effect on the overall picture of performance. For example, the ARCA Biotech index was originally composed of 30 constituents (the number increased in 2014), each of which was required to have a market capitalization of greater than \$1 billion and minimum average trading values. As a result, the index selects for companies with exceptionally strong performance, such as Amgen and Gilead. This selection exerts a disproportionately large effect on the pattern of realized returns, thus making the index unrepresentative of investment in the industry as a whole. Consistent with this, the cumulative performance of the other biotech indexes is much lower than that of the ARCA Biotech index, suggesting that the performance of ORF does indeed surpass that of biotech, at least over the past five years.

To more closely examine the evolution of these returns over time, Panel A of Exhibit 2 provides the

EXHIBIT 2

Yearly and Five-Year Cumulative Returns from 2000 to 2015

Panel A: Yearly

Year	Orphan Drug	S&P 500	NASDAQ	S&P 500 Biotech	NASDAQ Biotech	NYSE ARCA Biotech	NYSE ARCA Pharma	k-means Pharma	k-means Biotech
2000	69.0%	-10.1%	-39.3%	-4.8%	23.0%	62.0%	27.6%	33.1%	18.7%
2001	-27.2%	-13.0%	-21.1%	-3.7%	-16.2%	-8.5%	-14.8%	-15.9%	-23.5%
2002	-40.1%	-23.4%	-31.5%	-20.4%	-45.3%	-41.7%	-21.7%	-23.3%	-47.1%
2003	6.2%	26.4%	50.0%	28.9%	45.7%	44.9%	12.4%	13.7%	103.8%
2004	-15.1%	9.0%	8.6%	7.6%	6.1%	11.0%	-5.7%	-3.8%	-0.1%
2005	-1.4%	3.0%	1.4%	18.3%	2.8%	25.1%	1.1%	2.0%	35.2%
2006	13.4%	13.6%	9.5%	-2.7%	1.0%	10.8%	7.8%	9.6%	-8.4%
2007	39.7%	3.5%	9.8%	-3.4%	4.6%	4.3%	-2.6%	0.5%	-5.8%
2008	-30.9%	-38.5%	-40.5%	10.3%	-12.6%	-17.7%	-19.4%	-14.3%	-29.9%
2009	21.2%	23.5%	43.9%	-7.3%	15.6%	45.6%	13.3%	11.8%	16.5%
2010	53.0%	12.8%	16.9%	1.9%	15.0%	37.7%	-1.1%	3.5%	16.2%
2011	48.5%	0.0%	-1.8%	22.4%	11.8%	-15.9%	8.8%	16.1%	-9.0%
2012	32.7%	13.4%	15.9%	37.7%	31.9%	41.7%	11.0%	18.7%	12.9%
2013	53.5%	29.6%	38.3%	74.3%	65.6%	50.6%	26.7%	44.9%	51.6%
2014	36.3%	11.4%	13.4%	32.6%	34.1%	47.6%	13.8%	24.2%	20.8%
2015	12.2%	-0.7%	5.7%	5.0%	11.4%	10.9%	1.6%	5.3%	-5.0%
Entire Sample	516.0%	39.1%	23.1%	379.3%	301.5%	874.3%	53.3%	172.7%	93.6%

Panel B: Five-Year Intervals

Interval	Orphan Drug	S&P 500	NASDAQ	S&P 500 Biotech	NASDAQ Biotech	NYSE ARCA Biotech	NYSE ARCA Pharma	k-means Pharma	k-means Biotech
2000–2004	-34%	-18%	-47%	1%	-13%	39%	-10%	-6%	-2%
2005–2009	31%	-8%	4%	14%	10%	73%	-3%	8%	-5%
2010–2015	608%	83%	121%	317%	320%	305%	75%	170%	108%

Notes: This exhibit provides cumulative daily returns for the indicated time periods for each of the indexes. Panel A provides returns for each year, and Panel B provides returns for five-year intervals.

yearly compounded returns for each of the indexes. Although the NYSE ARCA Biotech index posts higher cumulative returns over the sample period at 874%, ORF outperforms all of the other indexes in a number of years. This performance has become more consistent, starting in 2010, ranging from a low of 12% in 2015 to a high of 53.5% in 2013. Examining the compounded returns at five-year intervals, Panel B of Exhibit 2 shows the broad pattern in the evolution of returns for ORF. From 2000 to 2004, the index posted returns of -34%, underperforming every index except for the NASDAQ. From 2005 to 2009, it posted returns of 31%, outperforming every index except for the NYSE ARCA Biotech, which achieved returns of 73%. Finally, in the most recent period from 2010 to 2015, ORF posted returns of 608%, substantially higher than every other index, including the biotech indexes, which had returns just over 300%.

Thus, the returns of ORF have shown a strong pattern of improvement over time and have overtaken those of all other indexes within the past few years, including the ARCA Biotech index, despite the aforementioned composition issue.

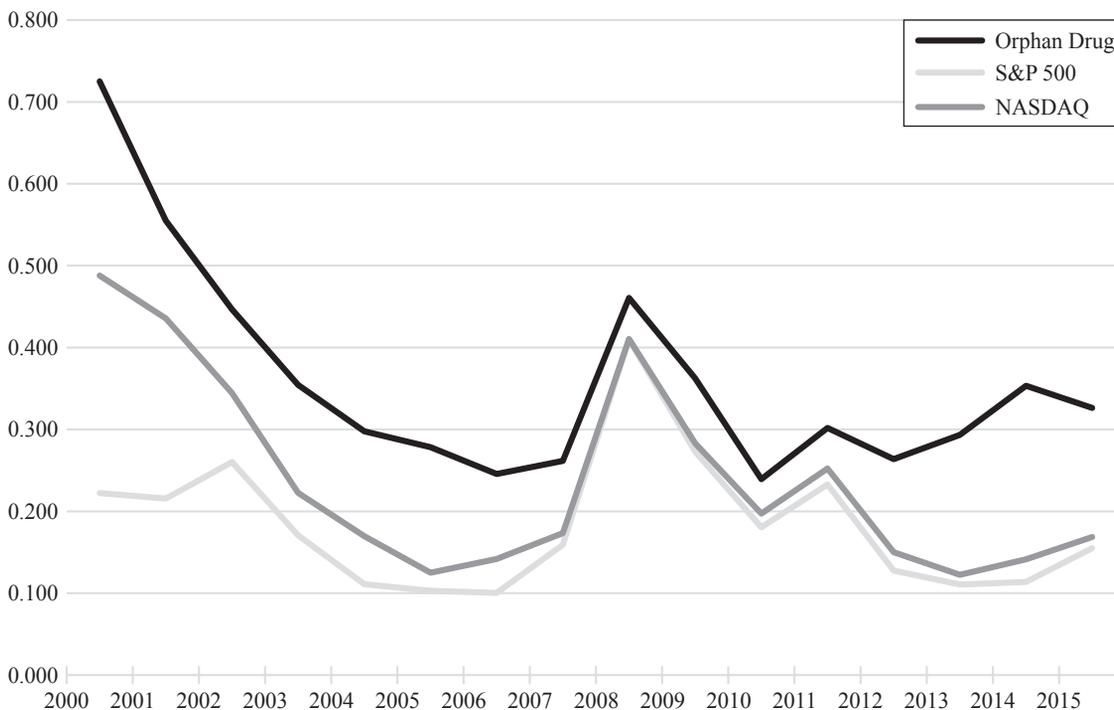
RESULTS: RISK CHARACTERISTICS

Although the previous results are suggestive of the performance of the index, they do not take into account the amount of risk taken on by an investor to realize those returns. In other words, an investor who has gained high returns may have simply been compensated for taking on a high amount of risk. We therefore compare the amount of risk carried by each index. We begin by looking at the overall risk as measured by the volatility of stock returns, and then we turn to systematic

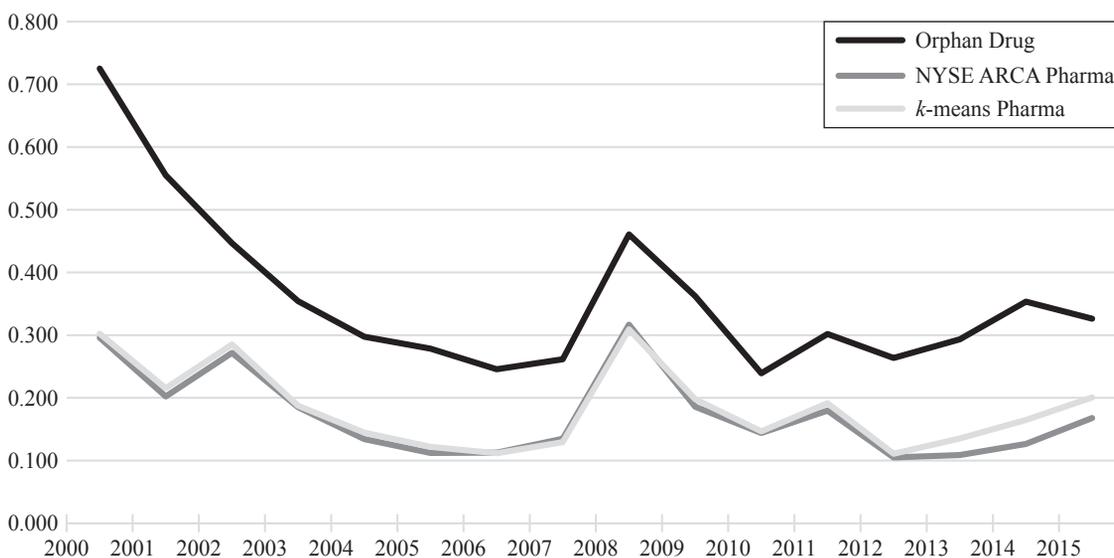
EXHIBIT 3

Yearly Volatility from 2000 to 2015

Panel A: Volatility of Returns versus Broad Indexes

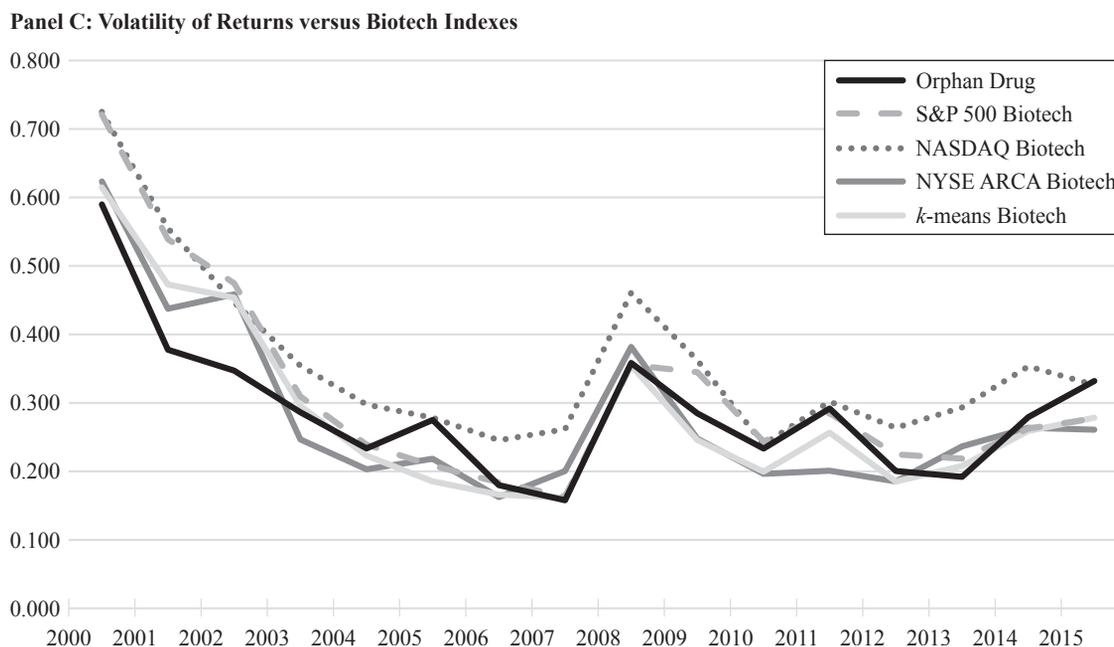


Panel B: Volatility of Returns versus Pharma Indexes



(continued)

EXHIBIT 3 (continued)
Yearly Volatility from 2000 to 2015



Notes: This exhibit provides the yearly stock return volatility for each index over time. Volatility estimates are calculated by taking the standard deviation of daily returns in each year. Estimates are annualized. Panel A compares ORF to the broad S&P 500 and NASDAQ indexes, Panel B compares ORF to pharma indexes, and Panel C compares ORF to biotech indexes.

risk as measured by beta, the tendency of movements in the index to reflect those in the market. Finally, we try to examine the downside tail risk by examining the maximum drawdowns of each index.

Volatility

The volatility of each index over time is shown in Exhibit 3. These volatilities are calculated by taking the standard deviation of each index’s returns over the indicated period. There are several noteworthy patterns. First, the volatility of each index has declined over time. Second, the differences in volatility among the indexes have also declined over time since the early 2000s. Third, the volatilities of the biotech indexes are very similar over time and higher than those of the pharma and broad indexes. Finally, ORF’s volatility is consistently substantially higher than that of the broad indexes and pharma indexes but only slightly higher than that of the biotech indexes, with which it remains closely in line. The volatility numbers in each year and for five-year periods are provided in Exhibit 4. Consistent with the pattern in Exhibit 3, ORF has a volatility of 0.38

over the entire sample period, substantially higher than that of the pharma and S&P 500 indexes (which are between 0.19 and 0.20), but only slightly higher than the biotech indexes (which range from 0.31 to 0.35). The exhibit also reinforces the pattern of decline, with ORF posting a volatility of 0.50 in the interval from 2000 to 2005, a volatility of 0.33 in the interval from 2005 to 2009, and a volatility of 0.30 in the most recent interval from 2010 to 2015. Taken together, these results imply that, although ORF appears to have substantial risk, it is generally in line with the risk found in the biotech sector.

Betas

We next examine the systematic risk of the indexes to get a sense of how much of the risk in the previous section is driven by co-movements with broader factors such as the market or economy. We do so by calculating the market betas of each index over time, controlling for the Fama and French (1993) size and value factors. These estimates over time are shown in Exhibit 5. Between 2000 and 2011, the betas for the orphan drug and biotech indexes decline from roughly 1.5 to just below 1.0,

EXHIBIT 4

Volatility Estimates from 2000 to 2015

Panel A: Yearly

Year	Orphan Drug	S&P 500	NASDAQ	S&P 500 Biotech	NASDAQ Biotech	NYSE ARCA Biotech	NYSE ARCA Pharma	k-means Pharma	k-means Biotech
2000	0.725	0.222	0.488	0.623	0.615	0.721	0.296	0.302	0.590
2001	0.555	0.216	0.436	0.438	0.473	0.539	0.202	0.215	0.378
2002	0.447	0.260	0.345	0.458	0.454	0.475	0.272	0.285	0.347
2003	0.354	0.171	0.223	0.247	0.296	0.310	0.185	0.187	0.286
2004	0.298	0.111	0.170	0.203	0.223	0.239	0.134	0.145	0.234
2005	0.278	0.103	0.125	0.218	0.185	0.208	0.112	0.122	0.275
2006	0.246	0.100	0.142	0.163	0.166	0.184	0.113	0.112	0.180
2007	0.262	0.159	0.173	0.201	0.162	0.163	0.135	0.129	0.158
2008	0.461	0.410	0.411	0.382	0.355	0.355	0.317	0.309	0.358
2009	0.362	0.273	0.283	0.248	0.246	0.345	0.186	0.198	0.285
2010	0.239	0.181	0.197	0.196	0.200	0.244	0.144	0.146	0.233
2011	0.302	0.233	0.252	0.201	0.257	0.285	0.180	0.192	0.292
2012	0.264	0.128	0.150	0.185	0.185	0.225	0.105	0.111	0.200
2013	0.293	0.111	0.123	0.237	0.208	0.219	0.109	0.135	0.192
2014	0.353	0.114	0.141	0.264	0.259	0.262	0.127	0.165	0.279
2015	0.326	0.155	0.169	0.261	0.278	0.277	0.168	0.201	0.332
Entire Sample	0.381	0.201	0.265	0.308	0.311	0.346	0.186	0.195	0.306

Panel B: Five-Year Intervals

Interval	Orphan Drug	S&P 500	NASDAQ	S&P 500 Biotech	NASDAQ Biotech	NYSE ARCA Biotech	NYSE ARCA Pharma	k-means Pharma	k-means Biotech
2000–2004	0.499	0.202	0.353	0.422	0.434	0.487	0.226	0.235	0.387
2005–2009	0.332	0.240	0.251	0.253	0.234	0.264	0.189	0.189	0.262
2010–2015	0.298	0.159	0.177	0.226	0.234	0.253	0.141	0.161	0.260

Notes: This exhibit provides volatility estimates for the indicated time periods for each of the indexes. Volatility is calculated using the standard deviation of daily returns over the indicated time periods, and the estimates are annualized. Panel A provides volatilities for each year, and Panel B provides volatilities for five-year intervals.

which is consistent with the evidence from Thakor and Lo (2015) that suggests increased competition in the biopharma sector. The betas for these indexes then spike in 2012 and 2013 but have fallen since. Overall, the betas of the orphan drug and biotech indexes appear to be very similar to each other. In contrast, the betas of the NYSE ARCA Pharma and *k*-means pharma indexes are consistently lower than the orphan drug and biotech indexes, ranging from a low of about 0.6 to a high of about 1.0. Since the mid-2000s, they have been relatively stable.

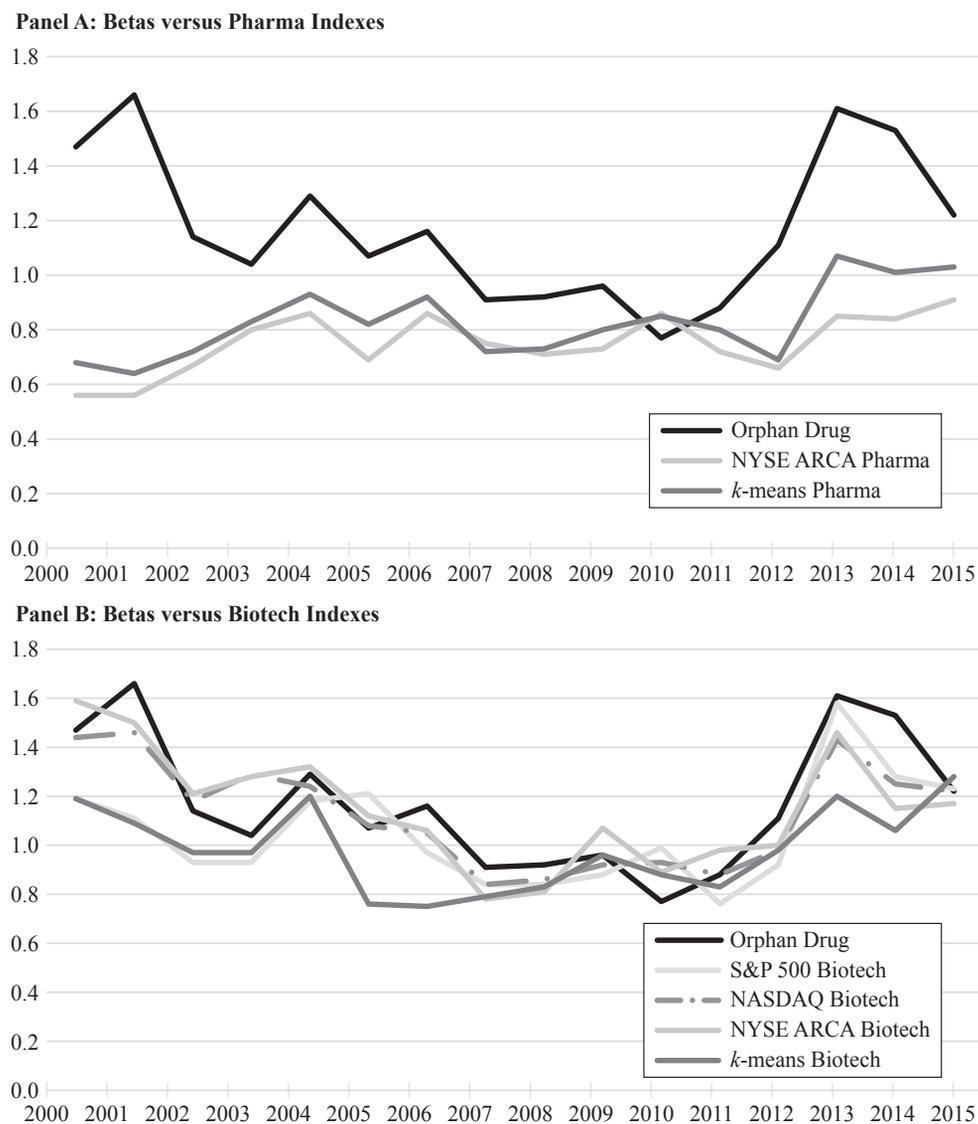
Exhibit 6 provides both yearly and five-year beta estimates. Over the entire sample period from 2000 to 2015, the beta of ORF is 1.05, which is roughly the same size as the betas of the biotech indexes. However, when calculated over five-year horizons, the betas of ORF are higher than those of all other indexes from 2005 onward, with a beta of 0.97 in 2005–2009 and a beta of 1.16 from

2010–2015. This suggests that investments in orphan drugs carry substantial systematic risk, comparable to or higher than that of the biotech sector. Although this higher systematic risk may appear puzzling at first, it is in line with evidence in previous studies that drug development has a substantial financing risk, which in turn creates systematic risk.⁷ Put differently, because the pure scientific risk involved in drug development is idiosyncratic (see Jørring et al. 2017 for recent evidence), drug development co-varies with the state of the economy due to the need for large amounts of funding for the development process. Our results show that this issue may be even more of a concern for orphan drug development.

⁷See Golec and Vernon (2009), Myers and Howe (1997), Myers and Shyam-Sunder (1996), and Thakor et al. (2017), among others.

EXHIBIT 5

Yearly Betas from 2000 to 2015



Notes: This exhibit provides the yearly market beta estimates for each index over time. Beta estimates are calculated each year and control for the Fama and French (1993) size and value factors. Panel A compares ORF to pharma indexes, and Panel B compares ORF to biotech indexes.

Maximum Drawdowns

We examine one other measure of risk to ascertain the downside risk of investments in the indexes: the maximum drawdown of returns. For an index, the maximum drawdown calculates the largest drop in the value of the index for each period. In other words, it calculates the return performance from peak to trough within a period to examine the largest possible drop in value. The maximum

drawdowns for each year, the entire sample period, and five-year intervals over the sample period are given in Exhibit 7.

The maximum drawdown for ORF is -82.5% over the entire sample period; this is consistently larger in magnitude (i.e., more negative) than that for the pharma indexes, which is between -48% and -52% . Over the entire sample period and for most years and subperiods, the maximum drawdown for ORF is also larger in magnitude than for most of the biotech indexes. However, the

EXHIBIT 6

Beta Estimates from 2000 to 2015

Panel A: Yearly

Year	Orphan Drug	S&P 500 Biotech	NASDAQ Biotech	NYSE ARCA Biotech	NYSE ARCA Pharma	k-means Pharma	k-means Biotech
2000	1.47	1.19	1.44	1.59	0.56	0.68	1.19
2001	1.66	1.11	1.46	1.50	0.56	0.64	1.09
2002	1.14	0.93	1.18	1.21	0.67	0.72	0.97
2003	1.04	0.93	1.29	1.28	0.80	0.83	0.97
2004	1.29	1.18	1.24	1.32	0.86	0.93	1.20
2005	1.07	1.21	1.08	1.12	0.69	0.82	0.76
2006	1.16	0.97	1.05	1.06	0.86	0.92	0.75
2007	0.91	0.84	0.84	0.78	0.75	0.72	0.79
2008	0.92	0.84	0.86	0.81	0.71	0.73	0.83
2009	0.96	0.88	0.92	1.07	0.73	0.80	0.96
2010	0.77	0.99	0.93	0.89	0.86	0.85	0.88
2011	0.88	0.76	0.88	0.98	0.72	0.80	0.83
2012	1.11	0.92	0.98	1.00	0.66	0.69	0.98
2013	1.61	1.58	1.43	1.46	0.85	1.07	1.20
2014	1.53	1.28	1.25	1.15	0.84	1.01	1.06
2015	1.22	1.23	1.22	1.17	0.91	1.03	1.28
Entire Sample	1.05	0.93	1.06	1.10	0.66	0.72	0.95

Panel B: Five-Year Intervals

Interval	Orphan Drug	S&P 500 Biotech	NASDAQ Biotech	NYSE ARCA Biotech	NYSE ARCA Pharma	k-means Pharma	k-means Biotech
2000–2004	1.26	1.02	1.29	1.32	0.68	0.75	1.06
2005–2009	0.97	0.87	0.89	0.87	0.72	0.75	0.83
2010–2015	1.16	1.05	1.10	1.11	0.80	0.91	1.04

Notes: Beta estimates are calculated each year and control for the Fama and French (1993) size and value factors. Panel A provides volatilities for each year, and Panel B provides volatilities for five-year intervals. All beta estimates are significant at the 1% level.

k-means biotech index has a maximum drawdown that exceeds that of ORF in a number of years and subperiods. Furthermore, during the most recent period from 2010 to 2015, the maximum drawdown for orphan drugs is -32.7% , slightly smaller (i.e., less negative) than the drawdown of the NYSE ARCA Biotech and k-means biotech indexes, which are -33.3% and -33.7% , respectively.

These maximum drawdowns indicate a substantial amount of tail risk for ORF, higher than that for the pharma indexes. Depending on the specific biotech index, the drawdowns for orphan drugs are either smaller in magnitude or comparable to those for biotech. However, it is also worth noting that these drawdowns have been decreasing in magnitude over time (becoming less negative), which may indicate that the downside risk of ORF has been diminishing over time.

RESULTS: RISK-ADJUSTED RETURNS

Having compared the risk characteristics of ORF to the other biopharma indexes, we now reexamine the performance of the index after taking into account the risk to investors. We examine two measures of risk-adjusted returns: Sharpe ratios and alphas.

Sharpe Ratios

We begin by calculating Sharpe ratios to examine the returns per unit of risk for each index. The Sharpe ratio for any given time period is defined as

$$\text{Sharpe ratio} = \frac{E[R] - r_f}{\sigma} \quad (2)$$

EXHIBIT 7

Maximum Drawdowns from 2000 to 2015

Panel A: Yearly

Year	Orphan Drug	S&P 500 Biotech	NASDAQ Biotech	NYSE ARCA Biotech	NYSE ARCA Pharma	<i>k</i> -means Pharma	<i>k</i> -means Biotech
2000	-56.7%	-35.7%	-47.1%	-49.0%	-22.0%	-15.1%	-55.2%
2001	-55.0%	-26.1%	-38.4%	-38.4%	-19.6%	-22.6%	-40.8%
2002	-50.4%	-48.5%	-54.6%	-51.0%	-37.8%	-38.7%	-53.3%
2003	-27.2%	-15.9%	-17.3%	-15.5%	-13.7%	-13.0%	-17.0%
2004	-44.5%	-14.3%	-26.4%	-20.8%	-17.2%	-18.1%	-36.5%
2005	-30.5%	-13.7%	-15.4%	-10.4%	-9.6%	-9.1%	-16.5%
2006	-28.3%	-14.9%	-20.4%	-17.7%	-6.0%	-8.6%	-18.1%
2007	-15.6%	-15.1%	-9.8%	-10.7%	-12.3%	-9.6%	-15.5%
2008	-43.1%	-28.1%	-33.1%	-38.9%	-34.2%	-30.1%	-43.5%
2009	-30.3%	-20.4%	-20.9%	-24.1%	-21.1%	-23.0%	-26.6%
2010	-16.7%	-20.5%	-18.9%	-20.6%	-17.2%	-14.4%	-23.2%
2011	-21.2%	-16.6%	-22.9%	-33.3%	-15.4%	-16.4%	-28.1%
2012	-20.5%	-9.1%	-12.7%	-12.9%	-7.9%	-7.6%	-18.1%
2013	-15.5%	-13.5%	-9.9%	-10.3%	-6.5%	-6.6%	-12.6%
2014	-26.1%	-18.4%	-21.1%	-19.6%	-9.4%	-10.0%	-26.2%
2015	-32.7%	-22.8%	-27.2%	-25.5%	-15.9%	-19.0%	-33.7%
Entire Sample	-82.5%	-60.1%	-74.7%	-65.0%	-51.8%	-48.2%	-79.3%

Panel B: Five-Year Intervals

Interval	Orphan Drug	S&P 500 Biotech	NASDAQ Biotech	NYSE ARCA Biotech	NYSE ARCA Pharma	<i>k</i> -means Pharma	<i>k</i> -means Biotech
2000–2004	-81.2%	-60.1%	-74.7%	-65.0%	-45.8%	-48.2%	-79.3%
2005–2009	-48.6%	-30.2%	-34.7%	-38.9%	-41.4%	-37.4%	-55.9%
2010–2015	-32.7%	-22.8%	-27.2%	-33.3%	-17.2%	-19.0%	-33.7%

Notes: This exhibit provides maximum drawdowns for the indicated time periods for each of the indexes. Panel A provides drawdowns for each year, and Panel B provides drawdowns for five-year intervals.

where $E[R]$ is estimated using the mean daily index return over the given time period, r_f is the risk-free rate of return, and σ is the standard deviation of the index's returns over the time period. We annualize the Sharpe ratio by multiplying by $\sqrt{252}$ because there are 252 trading days in a given year.

The Sharpe ratios for each of the indexes are provided in Exhibit 8 annually and for five-year intervals. Over the entire sample from 2000 to 2015, the NYSE ARCA Biotech index has the highest Sharpe ratio at 0.535, and ORF has the second-highest Sharpe ratio at 0.444. These Sharpe ratios are slightly higher than the ratios for the other two biotech indexes (S&P 500 Biotech and NASDAQ Biotech) but are substantially higher than the ratio of the *k*-means biotech index. This reinforces the evidence for the composition effect on the index as discussed earlier.

The Sharpe ratios of ORF are substantially higher than those of the broad S&P 500 and NASDAQ indexes

(0.118 and 0.117, respectively) as well as the ARCA Pharma and *k*-means pharma indexes (0.145 and 0.138, respectively). The pattern of Sharpe ratios over time also indicates that in its early years from 2000 to 2004, ORF (with a Sharpe ratio of 0.031) outperformed (on a risk-adjusted basis) the S&P 500 and NASDAQ broad indexes, all tested pharma indexes, and the *k*-means biotech index, which all posted negative Sharpe ratios, but it underperformed all of the other biotech indexes. From 2005 to 2009, ORF outperformed every index except for the NYSE ARCA Biotech. Finally, in the most recent period from 2010 to 2015, ORF posted a higher Sharpe ratio than all of the other indexes.

Thus, even on a risk-adjusted basis, ORF posted a consistently higher performance than the broad market or pharma indexes over the entire 15-year sample period. Its performance over time also surpassed that of biotech indexes, especially over the most recent period, when it

EXHIBIT 8

Sharpe Ratios from 2000 to 2015

Panel A: Yearly

Year	Orphan Drug	S&P 500	NASDAQ	S&P 500 Biotech	NASDAQ Biotech	NYSE ARCA Biotech	NYSE ARCA Pharma	k-means Pharma	k-means Biotech
2000	1.004	-0.628	-0.896	0.140	0.551	0.950	0.777	0.761	0.390
2001	-0.374	-0.728	-0.424	0.042	-0.224	0.031	-0.890	-0.836	-0.477
2002	-0.959	-0.956	-0.975	-0.306	-1.140	-0.936	-0.824	-0.786	-0.645
2003	0.316	1.396	1.887	1.109	1.387	1.319	0.668	0.660	0.432
2004	-0.440	0.727	0.502	0.404	0.326	0.509	-0.452	-0.421	-0.260
2005	-0.016	0.052	-0.064	0.741	0.084	1.038	-0.113	-0.103	-0.046
2006	0.445	0.860	0.383	-0.380	-0.139	0.394	0.311	0.314	0.195
2007	1.239	0.010	0.361	-0.300	0.074	0.057	-0.469	-0.489	-0.401
2008	-0.602	-1.014	-1.094	0.404	-0.247	-0.414	-0.570	-0.584	-0.504
2009	0.709	0.904	1.423	-0.185	0.709	1.255	0.761	0.714	0.496
2010	1.889	0.746	0.881	0.186	0.791	1.428	-0.017	-0.016	-0.010
2011	1.460	0.115	0.053	1.105	0.563	-0.464	0.560	0.526	0.345
2012	1.214	1.055	1.065	1.829	1.600	1.675	1.052	0.995	0.551
2013	1.608	2.399	2.710	2.470	2.533	1.983	2.227	1.791	1.262
2014	1.052	1.006	0.960	1.204	1.263	1.615	1.086	0.835	0.493
2015	0.515	0.030	0.415	0.318	0.528	0.512	0.180	0.150	0.091
Entire Sample	0.444	0.118	0.117	0.417	0.381	0.535	0.145	0.138	0.088

Panel B: Five-Year Intervals

Interval	Orphan Drug	S&P 500	NASDAQ	S&P 500 Biotech	NASDAQ Biotech	NYSE ARCA Biotech	NYSE ARCA Pharma	k-means Pharma	k-means Biotech
2000–2004	0.031	-0.222	-0.256	0.153	0.093	0.324	-0.096	-0.093	-0.056
2005–2009	0.245	-0.064	0.049	0.118	0.078	0.441	-0.085	-0.085	-0.062
2010–2015	1.243	0.713	0.833	1.166	1.141	1.047	0.729	0.639	0.397

Notes: This exhibit provides Sharpe ratios for the indicated time periods for each of the indexes. Sharpe ratios are calculated using daily returns and are annualized. Panel A provides Sharpe ratios for each year, and Panel B provides Sharpe ratios for five-year intervals.

exceeded even biotech indexes that focus on the most successful biotech companies.

Alphas

As another measure of performance after accounting for risk, we calculate alphas for each of the indexes to determine whether they posted excess returns above those predicted by exposure to risk factors. We specifically calculate the alphas using the Fama and French (1993) three-factor model, running the following regression for each index i in each time period:

$$R_i - r_f = \alpha + \beta_{mkt}(R_{mkt} - r_f) + \beta_{size}SMB + \beta_{value}HML + \epsilon_i \quad (3)$$

In Equation 3, R_i is the return of index i , R_{mkt} is the market return, SMB is the return of the size factor, and HML is the return of the value factor.⁸ The returns above those predicted by the factors is given by α , and we annualize our alpha estimates daily.

Exhibit 9 provides the estimates for alpha and indicates their statistical significance. Although the estimates for individual years are mostly insignificant, when calculated over the entire sample, the alphas are significant for ORF and the biotech indexes except for k -means, but the pharma indexes have an insignificant alpha. In line with the Sharpe ratios, the NYSE ARCA Biotech index has the highest alpha of 0.165, consistent

⁸Data for the factor returns are taken from Ken French's website: http://mba.tuck.dartmouth.edu/pages/faculty/ken.french/data_library.html.

EXHIBIT 9

Alpha Estimates from 2000 to 2015

Panel A: Yearly

Year	Orphan Drug	S&P 500 Biotech	NASDAQ Biotech	NYSE ARCA Biotech	NYSE ARCA Pharma	k-means Pharma	k-means Biotech
2000	1.239	0.420	0.886	1.712**	0.222	0.333	0.633
2001	-0.166	0.334	0.063	0.267	-0.118	-0.115	-0.147
2002	-0.106	0.232	-0.133	-0.037	0.017	0.022	-0.272
2003	-0.306	-0.001	-0.120	-0.082	-0.018	-0.042	0.351
2004	-0.253	0.019	-0.042	0.019	-0.081	-0.070	-0.130
2005	0.057	0.228	0.069	0.300*	0.012	0.034	0.475
2006	0.019	-0.091	-0.059	0.028	-0.011	0.008	-0.134
2007	0.203	-0.199	-0.086	-0.053	-0.117*	-0.096	-0.108
2008	0.029	0.690**	0.276	0.159	0.125	0.201	-0.011
2009	-0.055	-0.257	-0.107	0.095	-0.047	-0.084	-0.114
2010	0.283	-0.119	-0.055	0.137	-0.113	-0.081	-0.070
2011	0.414*	0.180	0.093	-0.180	0.068	0.131*	-0.071
2012	0.244	0.247	0.191	0.270	0.009	0.078	0.029
2013	-0.015	0.144	0.089	-0.036	0.009	0.076	0.029
2014	0.135	0.091	0.137	0.267	-0.007	0.058	0.100
2015	-0.045	-0.071	-0.029	-0.024	-0.039	-0.040	-0.145
Entire Sample	0.134*	0.128**	0.093*	0.165***	0.009	0.047	0.023

Panel B: Five-Year Intervals

Interval	Orphan Drug	S&P 500 Biotech	NASDAQ Biotech	NYSE ARCA Biotech	NYSE ARCA Pharma	k-means Pharma	k-means Biotech
2000–2004	-0.030	0.174	0.077	0.253	-0.006	0.009	0.009
2005–2009	0.075	0.041	0.016	0.117	-0.011	0.009	0.009
2010–2015	0.192*	0.104	0.093	0.091	-0.011	0.044	-0.016

Notes: This exhibit provides alpha estimates for the indicated time periods for each of the indexes. Alphas are calculated using the Fama and French (1993) three-factor model and are annualized. Panel A provides alphas for each year, and Panel B provides alphas for five-year intervals. ***Significant at the 1% level. **Significant at the 5% level. *Significant at the 10% level.

with the selection of high-performing biotech companies in the construction of the index. ORF has the second-highest alpha of 0.134, and this alpha is also significant. Although the alphas of all indexes are insignificant over the 2000–2004 and 2005–2009 intervals, ORF posts a large and significant alpha of 0.192 during the recent period of 2010–2015. This alpha is larger in magnitude than that of any other index, including those for biotech. Thus, it appears that ORF substantially outperforms the biotech indexes in terms of excess returns.

ORF performs better than every tested index except for the NYSE ARCA Biotech index from 2000 to 2015, even on a risk-adjusted basis. However, the performance of ORF has consistently improved over time and even overtakes that of the NYSE ARCA Biotech index during the most recent period.

CONCLUSION

The financial performance of an orphan drug index consisting of 39 publicly traded companies that focus solely on developing therapeutics for rare diseases is consistent with the view that we are at an inflection point in dealing with these afflictions. Although this index does reflect greater risk than aggregate stock market indexes such as the S&P 500 and the NYSE ARCA Pharma index, the average return more than compensates investors for this higher risk. Moreover, the risk is commensurate with that of biotech indexes, but the orphan drug index has outperformed significantly over the recent past.

These results may be of particular relevance to the broader set of investors who are interested in gaining exposure to recent developments in rare disease therapeutics but do not have the resources or experience to engage in stock selection.

APPENDIX

ORF CONSTITUENTS

EXHIBIT A1

Included Orphan Drug Companies

	Company Name	Start Date	End Date
1	Aegerion Pharmaceuticals, Inc.	October 22, 2010	December 31, 2015
2	Zogenix, Inc.	November 18, 2010	December 31, 2015
3	Medgenics, Inc.	April 8, 2011	December 31, 2015
4	Kamada, Ltd.	May 31, 2013	December 31, 2015
5	PTC Therapeutics, Inc.	June 20, 2013	December 31, 2015
6	Prosensa Holding N V	June 28, 2013	February 12, 2015
7	Agios Pharmaceuticals, Inc.	July 24, 2013	December 31, 2015
8	Conatus Pharmaceuticals, Inc.	July 25, 2013	December 31, 2015
9	Acceleron Pharma, Inc.	September 18, 2013	December 31, 2015
10	Ultragenyx Pharmaceuticals, Inc.	January 31, 2014	December 31, 2015
11	Auspex Pharmaceuticals, Inc.	February 5, 2014	May 5, 2015
12	Applied Genetic Technologies Corp.	March 27, 2014	December 31, 2015
13	CymaBay Therapeutics, Inc.	June 18, 2014	December 31, 2015
14	Bioblast Pharma, Ltd.	July 30, 2014	December 31, 2015
15	Sage Therapeutics, Inc.	July 18, 2014	December 31, 2015
16	Brainstorm Cell Therapeutics, Inc.	September 30, 2014	December 31, 2015
17	Bellicum Pharmaceuticals, Inc.	December 18, 2014	December 31, 2015
18	Spark Therapeutics, Inc.	January 30, 2015	December 31, 2015
19	Corbus Pharmaceuticals Hld., Inc.	April 16, 2015	December 31, 2015
20	Nivalis Therapeutics, Inc.	June 17, 2015	December 31, 2015
21	Chiasma, Inc.	July 16, 2015	December 31, 2015
22	Global Blood Therapeutics, Inc.	August 12, 2015	December 31, 2015
23	Dimension Therapeutics, Inc.	October 22, 2015	December 31, 2015
24	Strongbridge Biopharma PLC	October 2, 2015	December 31, 2015
25	Marina Biotech, Inc.	December 6, 1993	February 2, 2012
26	BioCryst Pharmaceuticals, Inc.	March 4, 1994	December 31, 2015
27	NPS Pharmaceuticals, Inc.	May 26, 1994	February 23, 2015
28	Alexion Pharmaceuticals, Inc.	February 28, 1996	December 31, 2015
29	ArQule, Inc.	October 16, 1996	December 31, 2015
30	Synageva Biopharma Corp.	October 7, 1997	June 23, 2015
31	BioMarin Pharmaceutical, Inc.	July 23, 1999	December 31, 2015
32	PlasmaTech Biopharmaceuticals, Inc.	March 30, 2000	December 31, 2015
33	Abeona Therapeutics, Inc.	March 30, 2000	December 31, 2015
34	Raptor Pharmaceutical Corp.	April 3, 2000	December 31, 2015
35	Insmmed, Inc.	June 1, 2000	December 31, 2015
36	Mast Therapeutics, Inc.	April 29, 2004	December 31, 2015
37	XTL Biopharmaceuticals, Ltd.	September 1, 2005	December 31, 2015
38	Catalyst Pharmaceuticals, Inc.	November 1, 2006	December 31, 2015
39	Amicus Therapeutics, Inc.	May 31, 2007	December 31, 2015

Note: This exhibit lists the orphan drug companies of the ORF index, as well as the date range for which we have stock data.

ACKNOWLEDGMENTS

We thank Austin Gromatzky, Joyce Hong, Manita Singh, and Kevin Wen for research assistance. Research support from the MIT Laboratory for Financial Engineering is gratefully acknowledged.

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