

# ALPS Medical Breakthroughs ETF

## A primer for investors

The ALPS Medical Breakthroughs ETF (NYSE Arca: SBIO) seeks investment results that correspond (before fees and expenses) generally to the performance of the Poliwogg Medical Breakthroughs Index. That index aims to capture research and development opportunities in the biotechnology and pharmaceutical industries.



# Poliwogg Medical Breakthroughs Index: A Primer for Investors

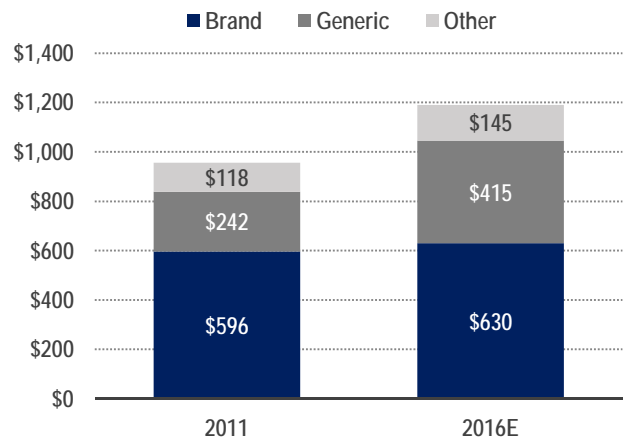
## State of Innovation

### Big Pharma: patent cliff ends era of blockbuster drugs

According to IMS HealthCare Informatics, global spending on brand name (patent-protected) drugs is projected grow less than 6% cumulatively between 2011 and 2016, while spending on generic drugs is forecast to increase more than 70% over the same time (Figure 1). This is due to the so-called “patent cliff”, in which many of the blockbuster drugs from the 1990s and 2000s have lost patent protections in the past few years, a trend which will continue through the end of the decade.

When a blockbuster drug goes off-patent, annual sales often fall 75% or more, as they are quickly replaced by much cheaper generics. Established, large drug companies (a.k.a. Big Pharma) have been left scrambling to replenish their pipelines, often by acquiring smaller, innovative biotechnology companies.

**Figure 1: Global Drug Spending**  
Brand vs. Generic 2011 & 2016E



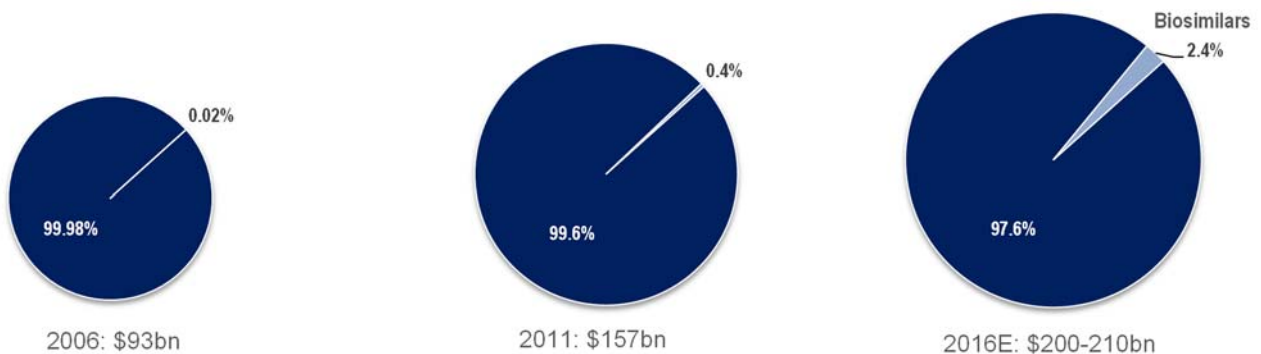
*Note: Estimates shown are based on information available at the time they are made and are subject to change. Estimates shown do no guarantee future results. Source: IMS HealthCare Informatics, IMS Market Prognosis, May 2012.*

### Biotech: rapid spending growth, limited generic competition

One area of promise is the biotechnology industry. Unlike traditional mass-market pharmaceuticals which use chemical-based synthetic products to create “small molecule” drugs, biotech therapies manipulate microorganisms like bacteria or biological substances such as proteins and enzymes to treat diseases.

IMS predicts global spending on biologics will increase from \$157 billion in 2011 to \$200-210 billion in 2016 (Figure 2), or about 30% at the midpoint. Furthermore, biosimilars — essentially biotech’s version of generic drugs — are projected to grow from less than 1% of total spending in 2011, but will still only represent about 2-3% of overall spending by 2016 based on these estimates. This makes biotech firms fertile targets for acquisition by larger firms needing differentiated therapies for which they can charge monopoly (i.e., patent-protected) prices.

**Figure 2: Global Spending on Biologics**  
2006, 2011 and 2016 Estimates



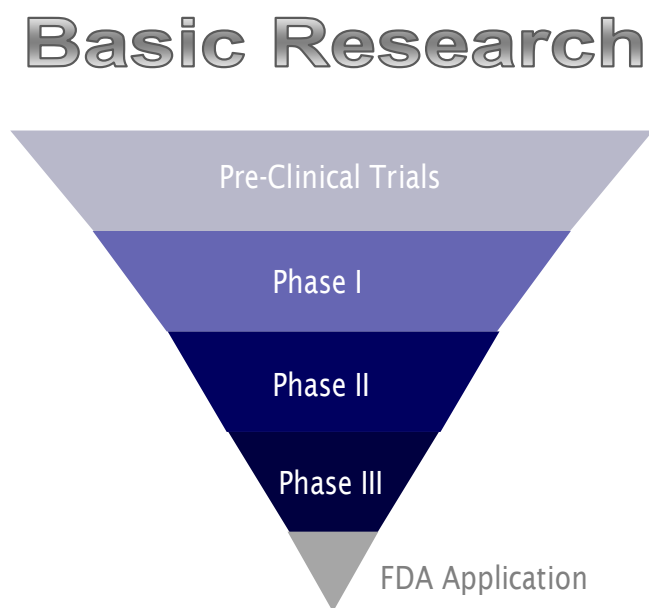
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## New Drug Development

New drug research and development—whether for biologics or traditional pharmaceuticals—is a risky, expensive, and very lengthy process. The development process looks like funnel, where at every stage the number of NMEs (New Molecular Entities) that successfully pass to the next phase decreases (Figure 3). The vast majority of NMEs tried fail to ever reach the consumer, and the ones that do have often taken a decade or more, and many millions of dollars in research and trial spending.

**Figure 3: New Drug Development Cone**



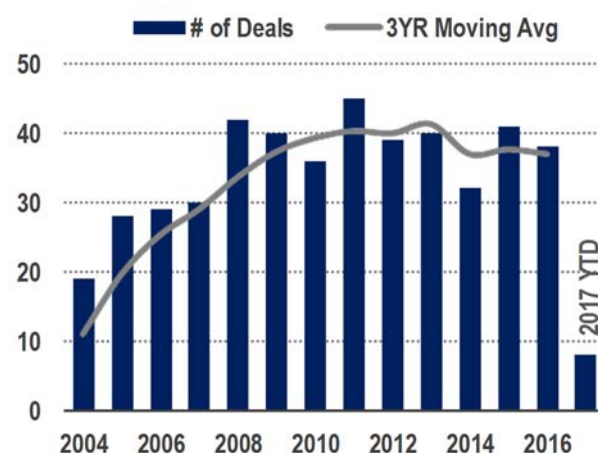
<b>Basic Research</b>	Drug discovery. Thousands of compounds tested. May take years.
<b>Pre-Clinical Trials</b>	Tests on non-human subjects to gather efficacy, toxicity info, etc. 4+ years
<b>Phase I</b>	Test of drug on healthy volunteers for safety and dose-ranging. 20-100 people and several months
<b>Phase II</b>	Testing of drug on patients to assess efficacy and safety. 100-300 participants, up to 2 years
<b>Phase III</b>	Determines a drug's therapeutic effect; at this point, the drug is presumed to have some effect. 1,000-3,000 participants, 1-4 years
<b>FDA Application</b>	About 1½ years

Sources: CERN Foundation, MD Anderson Cancer Center, Bright Focus Foundation

Given the lengthy process and high rate of failure for new drug development—combined with the fact that the era of the “blockbuster” is drawing to a close—it is difficult for large pharmaceutical companies to maintain a research and development pipeline sufficiently robust to replace revenue being lost to generic manufacturers.

In this environment, it makes sense to simply acquire promising new therapies being developed by smaller innovative biotechnology firms, through licensing arrangements or merger activity. Figure 4 shows the number of license deals completed by firms in the Poliwoogg Medical Breakthroughs Index (“PMBI”) as licensor. Data such as this is naturally bumpy, but the three-year moving average shows clearly the trend in deal activity, which nearly tripled between 2004-09 in the run-up to the patent cliff, and since appears to have leveled off but still averages about 37-40 deals per year.

**Figure 4: PMBI Number of License Deals as Licensor**



Source: BioPharm Insight. Based on current PMBI constituents as of 4/30/2017.

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## About the Index

### Description

The Poliwogg Medical Breakthroughs Index (“PMBI”) seeks to capture research and development opportunities in the pharmaceutical industry. PMBI consists of small-cap and mid-cap pharmaceutical and biotechnology stocks listed on US stock exchanges that have one or more drugs in either Phase II or Phase III US FDA clinical trials.

### Inclusion criteria

<b>Basic selection:</b>	U.S. listed biotech or pharmaceutical firm with 1 or more drugs in Phase II or Phase III FDA clinical trials
<b>Market Cap:</b>	Between \$200 million and \$5 billion
<b>Liquidity:</b>	Avg. daily volume > \$1 million
<b>Weighting:</b>	Modified market cap, max 4.5% at rebalance
<b>Sustainability:</b>	Enough cash for 24 months at current burn rate

### Index comparison

Compared to the widely-followed NASDAQ Biotechnology Index (“NBI”), PMBI is tilted to small- and mid-cap firms, which as we’ll show on the next slide is where the innovation happens, or at least where a larger portion of investors’ dollars are spent on R&D. In contrast, the companies in NBI are much larger—about 19x the market cap of their counterparts in PMBI on average—and being more established players they spend more heavily on operations.

Finally, although the two indices do have constituents in common, by weight these positions overlap by only 16.3% of each index. This means that 84.3% of exposures in one are not duplicated in the other.

	PMBI	NBI
<b>Number of constituents</b>	83	162
<b>Wgt avg. market cap</b>	\$2.2 billion	\$41.3 billion
<b>Weight of Top 10</b>	37.5%	56.5%
<b>Large cap (&gt;\$10bn)</b>	0%	61.5%
<b>Mid cap (\$2-10bn)</b>	62.0%	25.1%
<b>Small cap (&lt;\$2bn)</b>	38.0%	13.4%
<b>Overlap by weight</b>	16.3% for both	

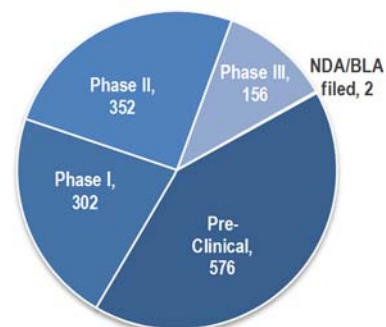
Source: AltaVista Research as of 4/30/2017. Note: PMBI is Poliwogg Medical Breakthroughs Index; NBI is NASDAQ Biotechnology Index. One cannot invest directly in an index.

### Top 10 Holdings

Company Name	Weight
IONIS PHARMACEUTICALS	4.7%
EXELIXIS	4.5%
TARO PHARMACEUTICAL INDUSTRIES	3.9%
NEUROCRINE BIOSCIENCES	3.8%
ALNYLAM PHARMACEUTICALS	3.8%
KITE PHARMA	3.7%
AKORN	3.4%
ACADIA PHARMACEUTICALS	3.4%
GALAPAGOS NV SPONSORED ADR	3.3%
BLUEBIRD BIO	3.0%

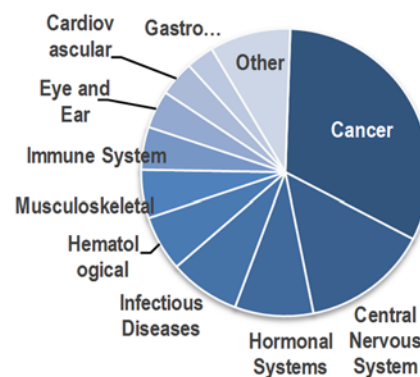
Note: As of 4/30/2017. Subject to change.

**Figure 5: PMBI Drug Development Pipeline**



Source: BioPharm Insight as of 4/30/2017

**Figure 6: PMBI Phase II Trials by Disease**



Source: BioPharm Insight as of 4/30/2017

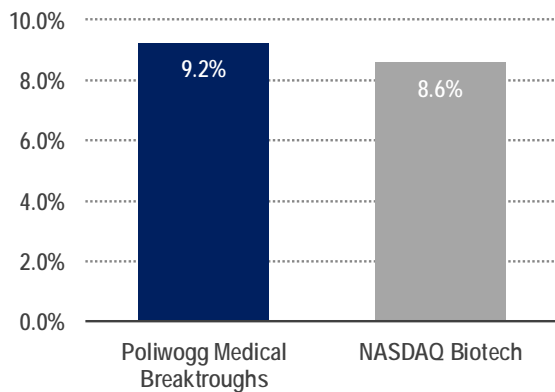
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## Index comparison

Large cap Biotech firms typically focus more on marketing and distribution, less on innovation

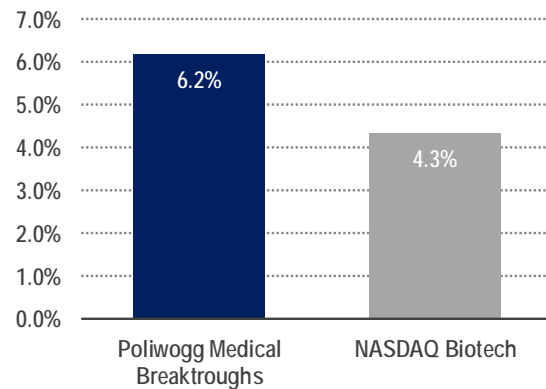
The more established firms in the NASDAQ Biotech Index spent an average of 8.6% of their market cap on non-R&D operating expenses (i.e., manufacturing, SG&A expenses, etc.) over the most recent four quarters, while the earlier-stage firms in the Poliwogg Medical Breakthroughs Index spent 9.2%, or 7% more on a relative basis. At the same time, firms in PMBI spent an amount equal to 6.2% of market cap on Research & Development, 44% more than did firms in the NASDAQ index, which spent an amount equal to 4.3% of market cap. While these differences may seem small, the results in terms of clinical trials—and therefore potential new products—is startling when measured in relation to costs to the investor.

**Figure 7: Non-R&D Operating Expense as a Percentage of Market Cap**



Source: AltaVista Research as of 4/30/2017, based on most recent four quarters data available

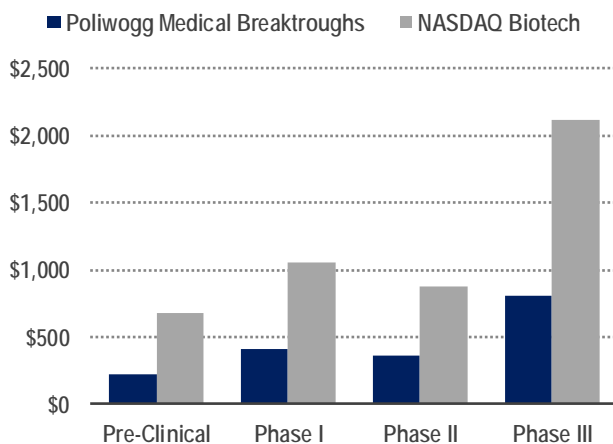
**Figure 8: Research & Development Expense as a Percentage of Market Cap**



Source: AltaVista Research as of 4/30/2017, based on most recent four quarters data available

Investors in firms in the Poliwogg Medical Breakthroughs Index may gain exposure to clinical trials for considerably cheaper than do investors in firms comprising the NASDAQ Biotech Index. For example, as of April 30, 2017 the market-cap to Phase III clinical trials ratio for firms in PMBI equated to \$802 million per clinical trial; that figure for firms in NBI was \$2.1 billion (Figure 9). On average, investors paid about 2.6x as much per clinical trial for firms in the NASDAQ Biotech Index as they did for firms in the Poliwogg Medical Breakthroughs Index.

**Figure 9: Market Cap-to-Clinical Trails (\$mns)**



Source: BioPharm Insight and AltaVista Research as of 4/30/2017

Granted, investors in firms comprising the NASDAQ Biotech Index are also acquiring more established manufacturing and distribution operations. This means products with real cash flows that are easier for investors to value and which can fund future developments—and acquisitions. This reduces their risk of failure and therefore their riskiness as investments.

Nonetheless, in terms of acquiring pure innovative potential in the form of clinical drug trials, firms in the Poliwogg Medical Breakthroughs Index were the less expense route according to the April 30, 2017 data. Investors might in some ways compare this to venture capitalists in Silicon Valley with a stable of social media start-ups hoping to strike app gold and be acquired by one of the Tech giants. In this case, striking gold with promising results from clinical trials can lead to acquisition by one of the large established players in the biotech or traditional pharmaceuticals industries.

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## Biotech Investing

### Tough industry for stock pickers

Biotechnology is a particularly difficult industry for stock pickers, making a passive index-based investment more appealing as an alternative. Among the reasons the industry is challenging for stock pickers:

**High Failure Rate:** The vast majority of new compounds fail in clinical trials, and many companies are never able to develop commercially viable products. This tends to produce more “losers” than “winners” making it unfertile ground for stock selection.

**Non-Traditional Metrics:** Biotech stocks often trade on very high (or meaningless) multiples of revenue, earnings and other traditional measures, since many companies are not profitable. They often trade on the perceived “promise” of drugs still in development.

**Specialized Knowledge:** Most investors without medical training have limited ability to assess whatever public information may exist about early trial results. Investors cannot conduct channel checks or evaluate products themselves, but must wait for unpredictable trial results.

**Extreme volatility:** Good news or bad news can result in extreme price movements, far greater than with a typical earnings surprise or disappointment.

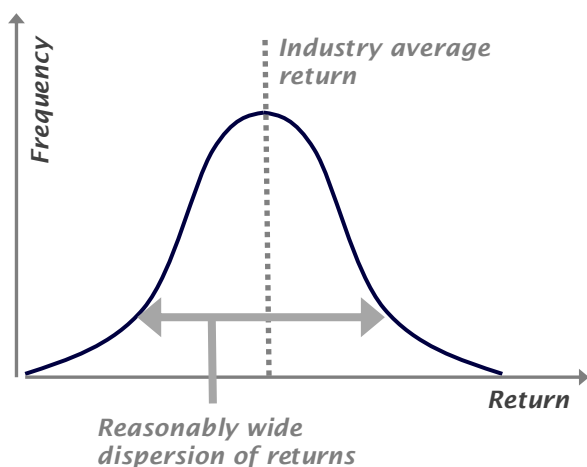
### Unfertile hunting grounds

When stock returns in an industry are reasonably well dispersed, and the distribution normal as in Figure 10 below, then investors stand at least a 50/50 chance of improving returns through stock selection.

However, that is often not the case in the biotech industry where “losers” often outnumber “winners.” Returns are not normally distributed, but rather skewed towards below-average.

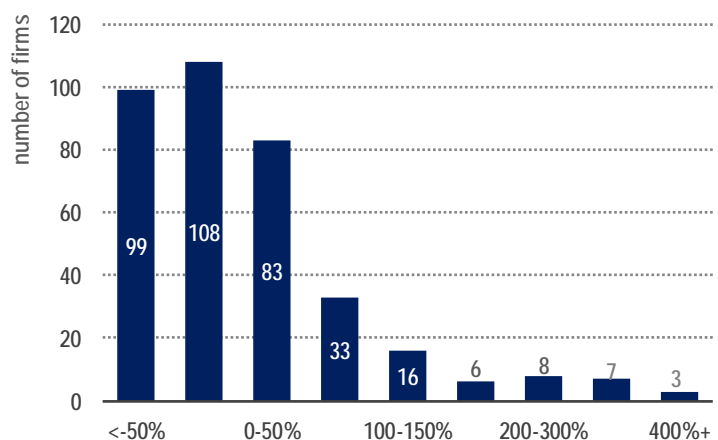
For example, the average return from all U.S.-listed Biotech firms for the one-year period ending January 31, 2017 was a gain of 11.9%, but the median return was *negative* 16.4%. Looked at another way, 236 out of 363 firms (65%) had below-average performance, making it a tough environment for stock pickers (Figure 11). This makes an index-based approach to biotech investing ideal in our opinion, where the few winners will be somewhere among the many losers.

**Figure 10: Hypothetical return distribution**  
*Normal curve*



Note: Hypothetical example for illustrative purposes only. Not based on any actual investment.

**Figure 11: Histogram of 1YR returns**  
*U.S. Biotech firms*



*Past performance does not guarantee future results.*

Source: FactSet as of 4/30/2017 for the 363 firms for which one-year total return data was available.

# Poliwogg Medical Breakthroughs Index: A Primer for Investors

## Summary



### Era of blockbuster drugs fades

Big Pharma often looks to fast-growing biotech firms to help them replace their pipelines as generics gain market share as a result of the patent cliff

### PMBI: Focuses on Innovation

The Poliwogg Medical Breakthroughs Index seeks to capture research and development opportunities in the biotechnology and pharmaceutical industries

### Ideal for Indexing

A tough environment for stock pickers makes Biotech well-suited for passive index-based investing

### Risky development process favors acquisition

New drug development being a risky, lengthy and expensive process creates an environment favorable to licensing or acquiring new drugs from smaller, R&D-focused biotech firms whose trial data shows promise

### Innovation at a Discount

Investors in firms in the Poliwogg Medical Breakthroughs Index have paid up to 62% less per clinical trial than with the NASDAQ Biotechnology Index

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## Important considerations

An investor should consider the investment objectives, risks, charges and expenses carefully before investing. To obtain a prospectus which contain this and other information call 844.234.5852 or visit [www.alpsfunds.com](http://www.alpsfunds.com). Read the prospectus carefully before investing.

Shares of Exchange Traded Funds (ETFs) are not individually redeemable and owners of the shares may acquire those shares from the ETF and tender those shares for redemption to the ETF in Creation Units only, see the ETF prospectus for additional information regarding Creation Units. Investors may purchase or sell ETF shares throughout the day through any brokerage account, which will result in typical brokerage commissions.

This fund may not be suitable for all investors.

There are risks involved with investing in ETFs including the loss of money. The Fund is considered non-diversified and as a result may experience great volatility than a diversified fund. The Fund's investments are concentrated in the pharmaceuticals and biotechnology industries, and underperformance in these areas will result in underperformance in the Fund. Investments in small and micro capitalization companies are more volatile than companies with larger market capitalizations.

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## Definitions

**Price/Earnings Ratio** represents equity securities within the Fund's portfolio, and is not intended to demonstrate Fund growth, income earned by the Fund, or distributions made by the Fund.

**Price/Sales Ratio** is the stock price divided by the sales per share for the trailing 12-month period.

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