MIZUHO

Biotechnology Equity Research

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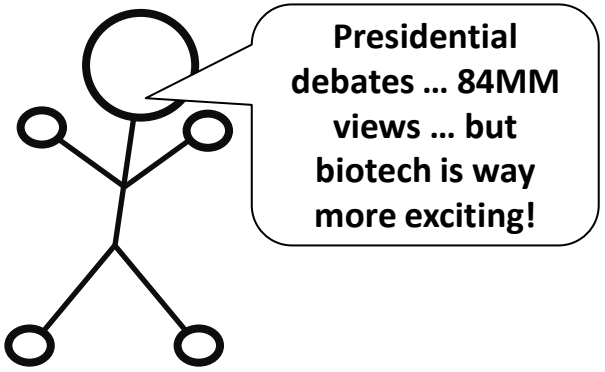
BIOTECH INDUSTRY

Initiating Coverage



Detailed Analyst Deck (DAD)

Analyses of key investor topics
Don't know the answer? Just ask DAD …

November 7, 2016

Because we know investors want and need different things, we have built 2 decks

PM Summary
(~60 pages)

Detailed Analyst Deck
(~230 pages)

Don't know the answer? Just ask DAD

YOU ARE CURRENTLY READING

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The last time many of you saw me, I was at my old shop, Evercore ISI, with my boss, friend and mentor, Mark Schoenebaum

Yep, over 5 years as an Associate has come to end. I couldn't have asked for a better teacher and kinder person to work for. Mark, thank you for everything. I hope I've made you proud. I will miss you (and the team, old and new) dearly.

Wishing you a speedy recovery …

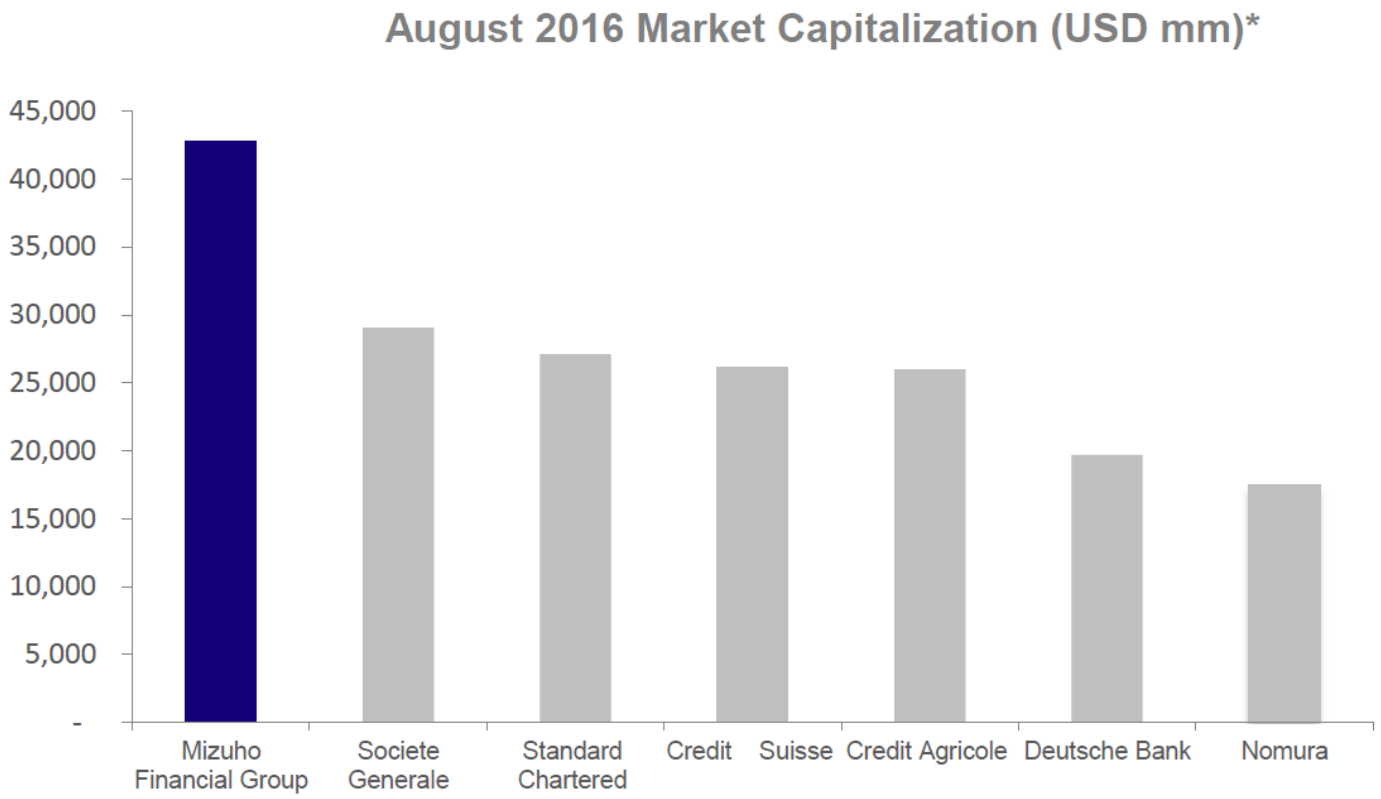
I am now at Mizuho where I will be covering the Biotechnology sector (focus on Large Cap with perhaps some SMID)

MIZUHO

+

BIOTECH

Mizuho is a large Japanese bank building its US equities biz

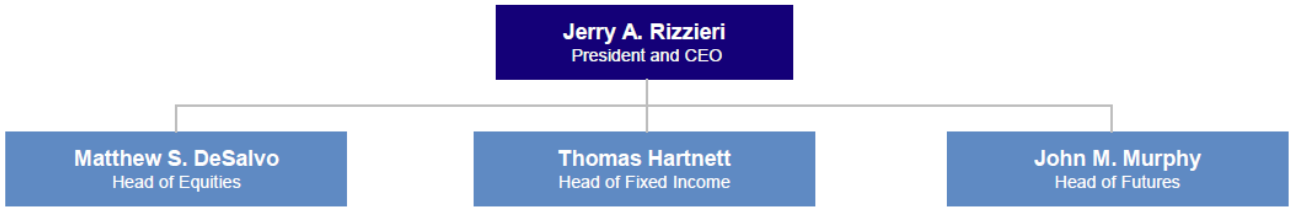


Mizuho has a US arm called Mizuho Securities USA … headed up by Jerry Rizzieri

Mizuho Securities USA CEO
Jerry Rizzieri

Here's a more detailed structure of our firm

MSUSA Organizational Structure



Equity Division

- 100+ employees servicing US, Japan and Asia ex-Japan with equity products including
  - Research
  - Sales and Trading
  - Event Driven
  - Electronic Trading
  - Convertibles
  - Corporate Access
  - Conferences
  - Equity Capital Markets

Fixed Income Division

- 180+ employees in fixed income origination, sales and trading
- Market making capabilities in EM, Corporate Credit, Securitized Products and Rates
- DCM platform is enhanced by closely coordinated effort with Mizuho Bank
- #10 in IG (ex Yankee) Issuance*
- #1 in JGBs **
- Primary Dealer in UST

Futures Division

- 30+ employees
- Client-centric, agency-only
- Premier provider of clearing and execution (voice and electronic) services around the world
- Coverage includes financials and commodities
- Operations staff of industry professional based in Chicago providing continuous global service

Mizuho Securities USA Inc. Offices

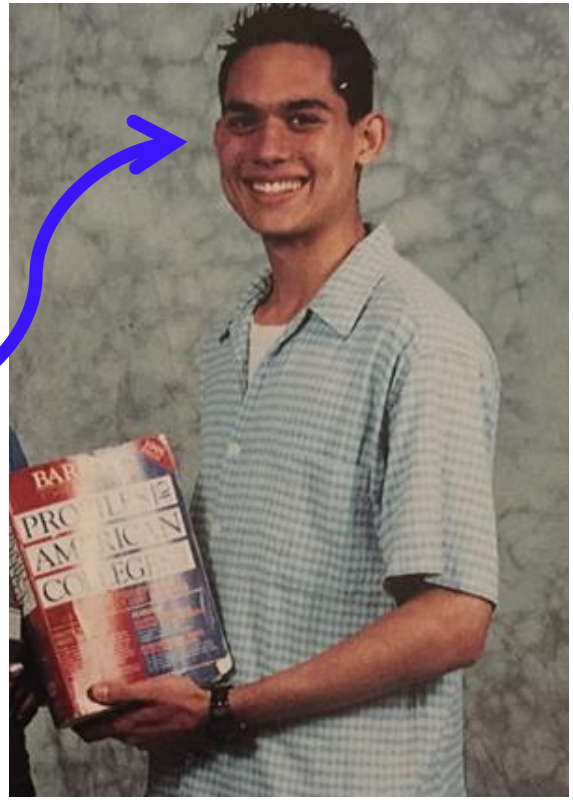
- **Atlanta** – Fixed Income, Investment Banking
- **Boston** – Equity
- **Chicago** – Equity, Fixed Income, Futures, Investment Banking
- **Hoboken** – Operations
- **Houston** – Investment Banking
- **London** - Futures
- **Los Angeles** – Fixed Income, Investment Banking
- **New York** – Equity, Fixed Income, Futures, Investment Banking
- **San Francisco** – Equity, Fixed Income

I work in this office:
320 Park Avenue (btw 50th and 51st)

My quick bio …

- Mark Schoenebaum associate (>5 years)
- Morgan Stanley investment banking (>4 yrs)
- University of Michigan BBA (2004)
- Grew up in Santa Clarita, CA (next to AMGN!) … I was so tanned back then
- Favorite sports team: Michigan Wolverines
- Fun Tidbit: half Italian / half Pakistani .. but some say I look ¼ Chinese

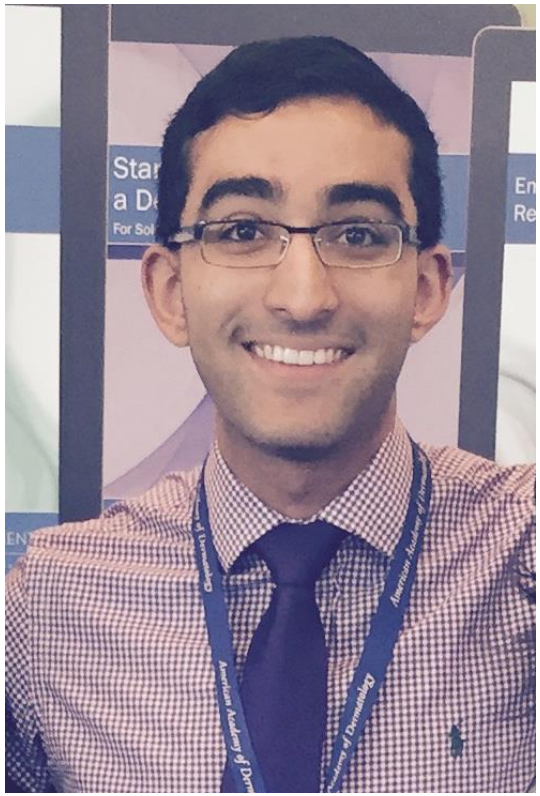
Me at 17 years old



And here's my AWESOME associate, Yusuf Anwar … he's much smarter than me

- Graduated from 8-year Coordinated BA-MD Program (accepted directly from high school)
  - Declined considerations from Cornell, Princeton and Columbia
  - CUNY Brooklyn College & Macaulay Honors College Class of 2012: B.A. Economics, Finance concentration. Summa Cum Laude. GPA 3.98. Phi Beta Kappa. Full scholarship (tuition and board).
  - SUNY Downstate College of Medicine, Class of 2016: Gold Humanism Award
- Presented at national dermatology conference (AAD) several times, & first authored several publications (JAMA Dermatology, Tele-Dermatology textbook chapter)
- 95th percentile SAT (2290) / MCAT (35) / SAT Physics (800) / Math II (800) / Chemistry (770)
- Hobbies: baseball, racquetball, programming

My associate … Yusuf Anwar



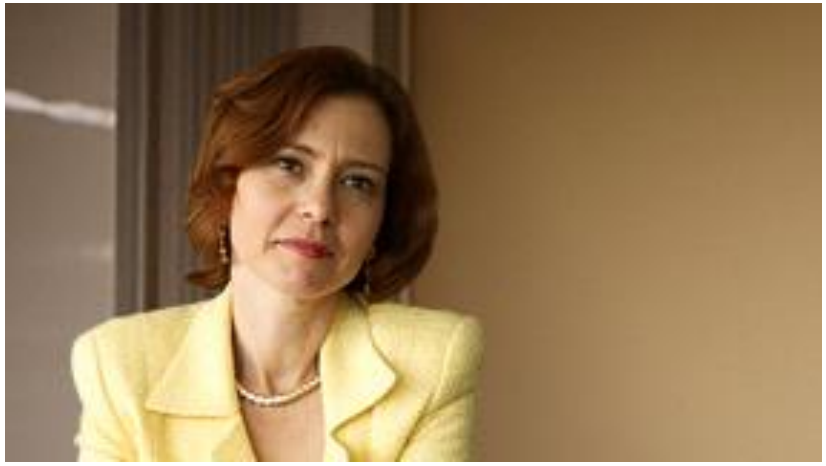
BIG THANK YOU to the folks who vouched for me to get this seat

- From my understanding at least several of you were called and vouched for me to get this seat
- I still have yet to figure out exactly who you are, but I owe you all many thanks

Also, a hearty THANKS to my FANTASTIC new bosses, who have given me the wonderful opportunity to serve you all

- Feel free to shoot them an email or call … they're great!

MATT DESALVO
Head of Equities
Matthew.DeSalvo@us.mizuho-sc.com
W: (212) 209 – 9387



SHERYL SKOLNICK
Director of Research
Sheryl.Skolnick@us.mizuho-sc.com
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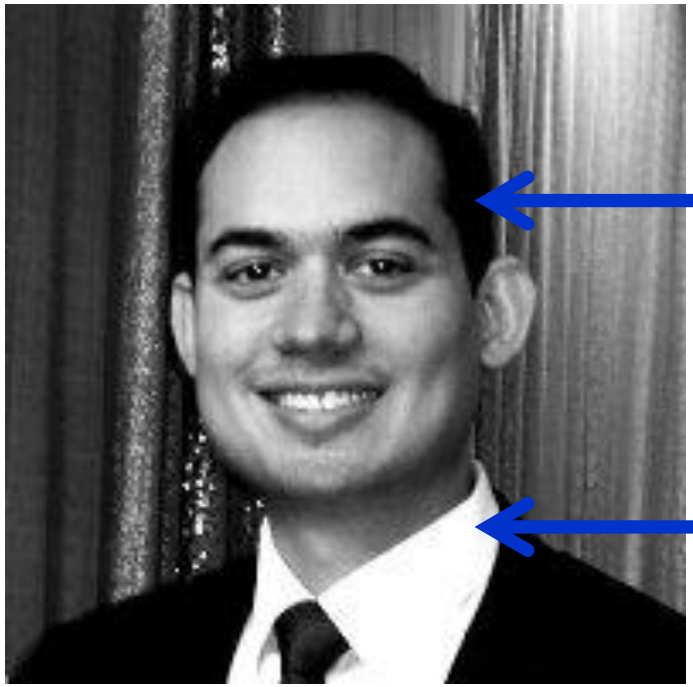
A couple things have changed since I left Evercore ISI



I got a haircut

I got shirts with collars that fit around my ENTIRE neck

But mostly things have stayed the same … I'm still your "associate" … but now you can come DIRECTLY to me

- If there is **ONE TAKEAWAY** from this entire presentation, it is this:

USE ME as your PERSONAL ASSOCIATE

I am here to make your life easier. I will work hard and do pretty much anything to earn your trust (and vote ☺)

My style … to please you …

I am human though, and I make mistakes

- I obviously try to keep mistakes to a minimum
- I am actually happy when you call me out on my errors because it gives me a chance to fix what is wrong
  - This could be as simple as a spelling typo
  - Or perhaps my math is wrong on a particular analysis
  - Or my entire thesis if just off … anything is fair game
- I spent 4 years in investment banking … and I didn't cry once … so feel free to dish it ☺ … I don't get offended … I just try to learn

I am open to your feedback anytime … negative feedback ABSOLUTELY welcome

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I have 2 email lists … high flow and low flow

- **High flow**
  - –You will get everything I write essentially
- **Low flow**
  - –Limited to just really important stuff … usually 1 email per week
  - –Opt-in for this because otherwise we can't exclude you (from high flow)

Other key folks you should know in Sales @ Mizuho

SANG YOO
HEAD OF EQUITY SALES
Sang.Yoo@us.mizuho-sc.com
W: (212) 205 – 7627

- Joined Mizuho in July 2015
- Previously at Bloomberg Tradebook, Credit Suisse, First New York, Morgan Stanley, Fox-Pitt

If you need an account set up at Mizuho this is the guy to call!!

Other key folks you should know in Trading @ Mizuho

ERIC SHENKER
HEAD OF TRADING
HEALTHCARE TRADER
Eric.Shenker@us.mizuho-sc.com
W: (212) 205 – 7657

Joined Mizuho in August 2015 from CRT (previously at Alliance Bernstein, Deutsche, Morgan Stanley)

If you need help with trading or need trading color this is the guy to call!!

NEXT WEEK in NYC (NOV 14th) … I'll be moderating a DRUG PRICING PANEL …

- **Ron Cohen, Chairman of BIO**
- **Minal Patel, Chief Strategy Officer of Horizon Blue Cross Blue Shield NJ**
- **Roger Longman, CEO of Real Endpoints**
- **Anupam Bapu Jena, Associate Professor of Healthcare Policy at Harvard Medical School**

Email me if you'd like to come!!

Table of Contents

If you're new to Biotech, do not be intimidated … you can do it!

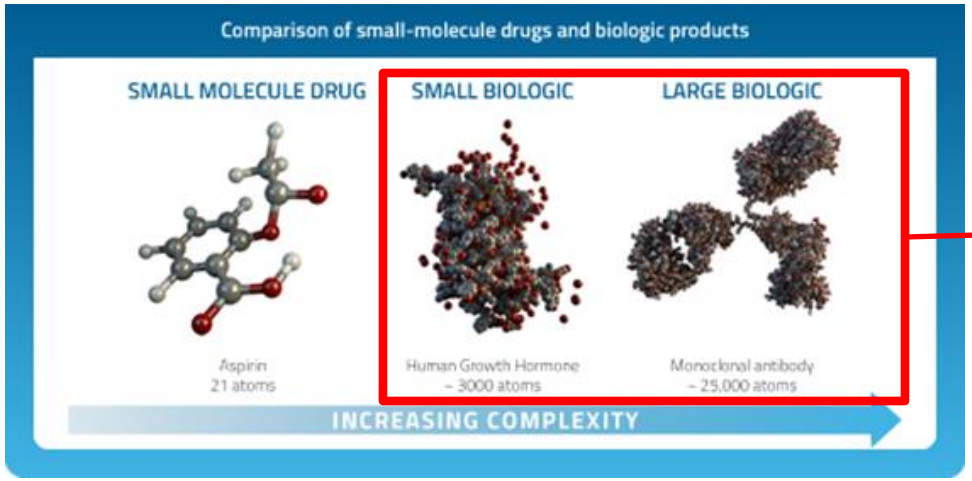
- Yes, there is "fancy" jargon
- Yes, there is science
- Yes, there are statistics
- But at the end of the day, most of the important things you'll need to do your job can be learned fairly quickly
- My job is to help you

Let's walk through the basics ➔

The Difference between Large Molecules and Small Molecules

Biotech companies historically made large molecules

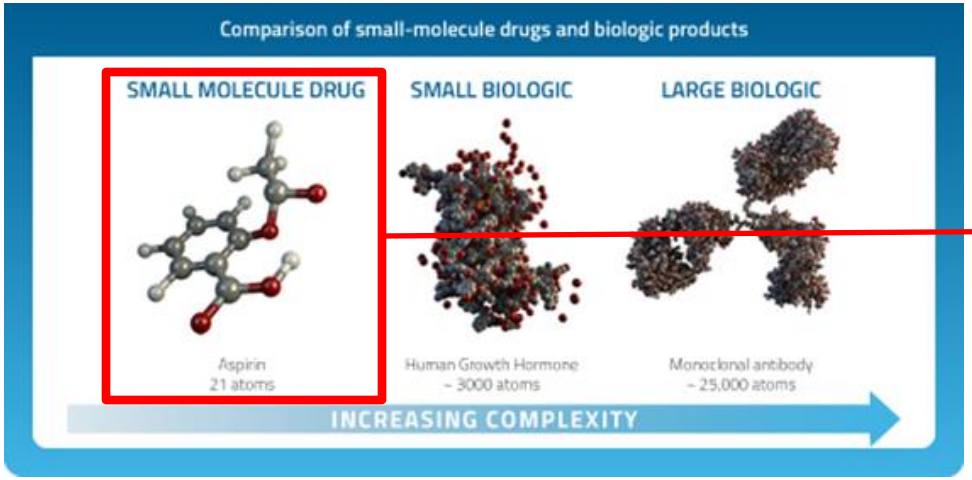
- Historically, **biotech companies** produced **large molecules**
- Another word for large molecules is **biologics**
- Large molecules are exactly that … large (by weight measurement)
- Large molecules generally are **>1,000 daltons (a unit for atomic mass)**
- Many cancer drugs (i.e., needle-in-the-vein medications) are large molecules



Sources: Pubmed, Mizuho Research

Pharma companies historically made small molecules

- Basically, these molecules are <1,000 daltons
- Most small molecules in reality are less than 500 daltons
- Oral drugs (Tylenol, aspirin, etc.) are small molecules

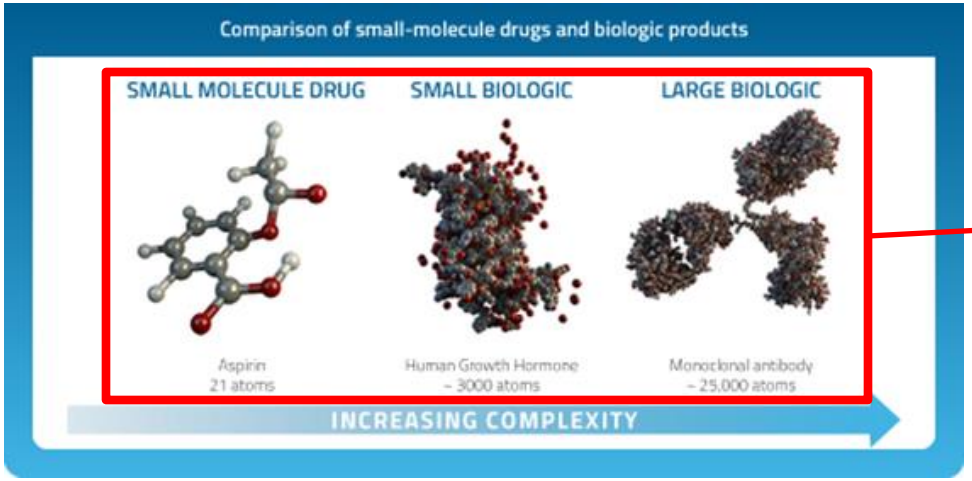


Historically, **pharma** played here

Sources: Pubmed, Mizuho Research

Today however the line between Biotech and Pharma is getting blurred

- Both biotech and pharma are developing large and small molecule drugs



Today, **biotech and pharma** are doing both

Sources: Pubmed, Mizuho Research

Another way to think about small molecule vs large molecule is bike vs airplane

SMALL MOLECULE

You could probably build a bike if you wanted to

LARGE MOLECULE

Building an airplane though would be MUCH, MUCH MORE COMPLEX …. way more parts

Small molecule drugs ➔ generic
Large molecule drugs ➔ biosimilar

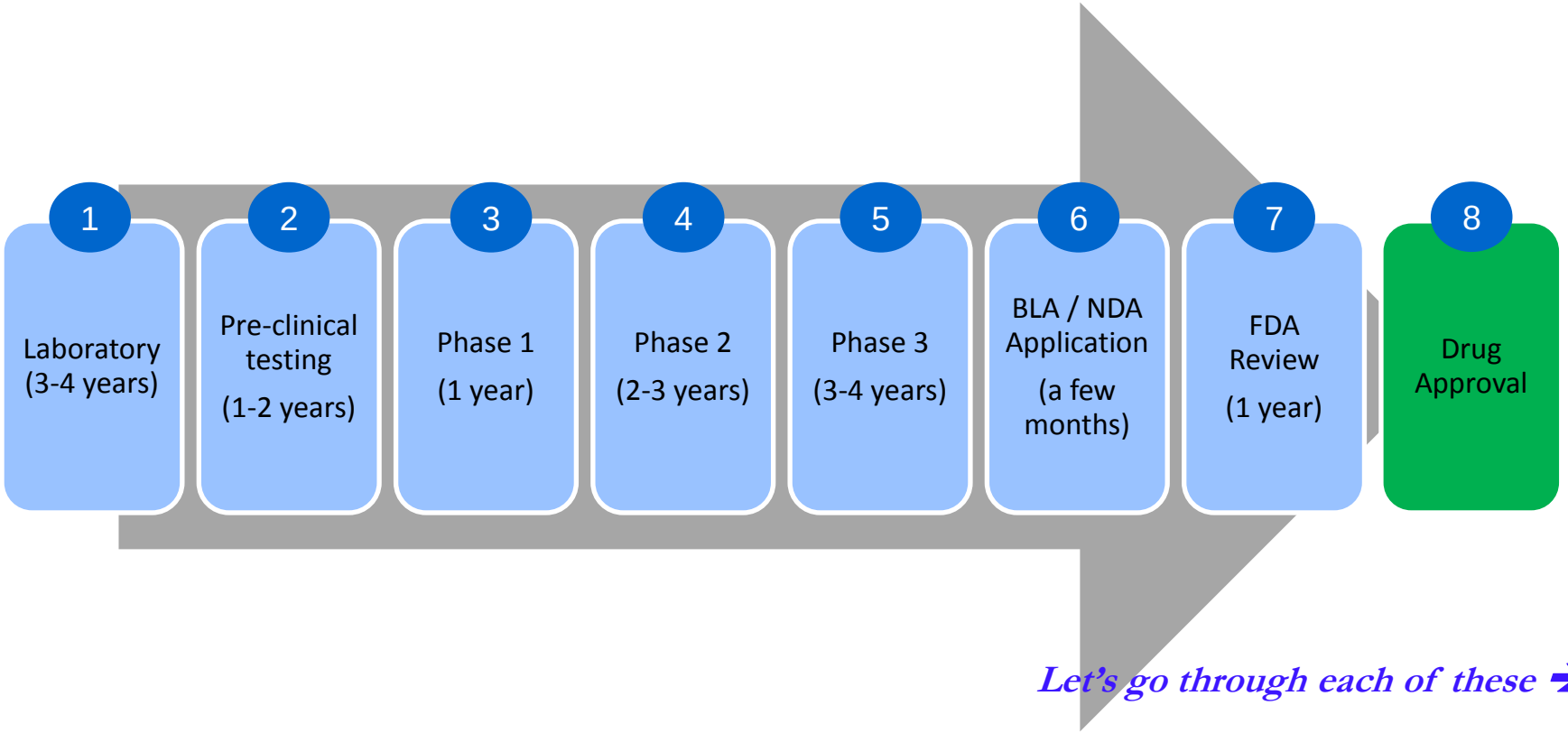
- When small molecule drugs go off patent, and other companies manufacture those drugs, the replicated form is called a **generic**
  - Small molecule drugs are easy to replicate
- Replicated large molecule drugs though are called **biosimilars**
  - Large molecules are complex
  - The best you can get is a biosimilar (the key word part here is 'similar') … in other words, not an exact replication

Large molecule drug sales post patent expiry are typically more protected vs. small molecule

- **When a generic enters the market, the branded drug can lose 80% of its sales in one year**
- **When a large molecule drug's patent expires, there isn't always a biosimilar available on the market**
  - Biosimilars approval pathway is less straightforward
  - First US biosimilar only came to market in March 2015
  - When available a doctor may be less inclined to prescribe the biosimilar vs the branded drug because it may not be necessarily **interchangeable** (with the branded drug)
  - Over time, more biosimilars will make it to market though

The Drug Approval Process

Both large and small molecule drugs have the same approval process … takes ~10-12 years

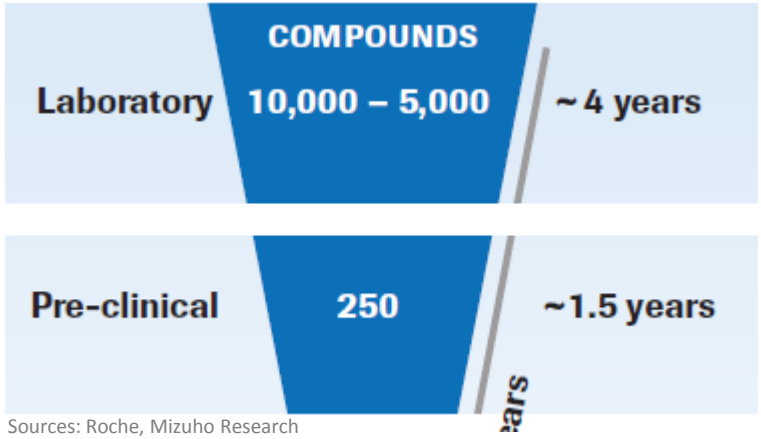


Let's go through each of these ➔

1

Laboratory … this is where new molecules are discovered

- In the lab researchers explore literally thousands of molecules for their potential
- Once a molecule has been selected, it enters preclinical testing
- To put the selection process in perspective, only 2.5 – 5% of molecules explored ever make it to preclinical testing



Sources: Roche, Mizuho Research

2

Preclinical testing means to study the drug in animals

Multiple species are used	• Rats • Mice • Monkeys • Chimps
The point of preclinical testing is to see if:	• the drug works (i.e. this is called **efficacy**) • the drug is safe (i.e. this is called **safety**)

Results don't always translate 1:1 to humans, but animals are a good first indicator to how a drug MAY work in man

3 Phase 1 is done with healthy volunteers … this is the first attempt in man … safety is key

- Because these patients are already healthy, the point of Phase 1 trials is not to see if the drug works (i.e. efficacy)
- We are trying to answer mainly one question: **IS THE DRUG SAFE?**
  - Or are there any frequent side effects (also known as **adverse events**)
- We are also trying to better understand how the drug is metabolized and excreted … this is known as a **PK/PD study**

Phase 1 trials are typically pretty simple and small

- There typically is not a placebo (pbo) arm (i.e. sugar pill or fake drug) in Phase 1 trials
- Phase 1 trials are typically 20-100 patients … very small trials

4

Phase 2 is done in sick patients … we want to see if the drug works

- This is the first time that the drug is tested in man with the particular disease that drug is intended to fight
- There are several things to look for:
  - **Efficacy** … do the drug arms separate from the pbo arm?
  - **Dose response** … does the drug work better as the dose increases?
  - **Placebo effect** … does the pbo arm move like the drug arms?
  - **Safety** … are there any **adverse events** (i.e. side effects), and do any adverse events increase with drug dose?

Phase 2 trials are usually "medium" sized and more complex than Phase 1

- Usually these trials are / have:
  - Several 100's of patients in size
  - Multiple drug arms of varying doses
  - A placebo arm (remember, this is the "fake drug" arm)

5

Phase 3 trials … this is the TRUE test of whether a drug works

- Phase 3 trials are sometimes call **pivotal trials** or **registrational trials**
- The drug company will use these trial results to apply for FDA drug approval
- The goal is to replicate what the company saw in Phase 2, but this time do it in a larger population

Phase 3 trials are "large" in size, but not necessarily more complex than Phase 2

- Trials are typically large…1,000+ patients
- By the time a company enters Phase 3, it should have a good understanding of:
  - How the drug works
  - Which dose is best (not always the highest dose as that can lead to unwanted side effects)
  - What is the target patient population
- That said, at times Phase 3 trials still have multiple drug arms (of varying doses)
- The FDA typically requires 2 phase 3 trials for approval

Once the Phase 3 trials have been completed, the company will "lock" the database

- After Phase 3 trials have been completed the drug company will **"lock"** the database (so it can't be changed) and analyze the results
  - This normally takes a couple of months
- When the database is locked, the company will **unblind** the results
  - Typically, this will be the first time typically the company will learn who was on pbo and who was on drug

6

BLA/NDA application … this is what the company submits to the FDA for review in hopes to get approved

- **NDA (New Drug Application)** … this is for small molecule drugs
- **BLA (Biologics License Application)** … this is for large molecule drugs
- The drug company submits either an NDA or BLA to the FDA
  - These applications contain data from the trials (including preclinical studies)
  - These are very detailed oriented and robust packages

7

FDA review … this usually takes about 1 year from submission

- **Standard Review** is **12 months** from submission
- If given **Priority Review** status, it's **8 months** from submission
  - The FDA may grant Priority Review to drugs that, if approved, would be significant improvements in either safety or efficacy vs the standard of care

The PDUFA date is the FDA's deadline

- The **PDUFA* date** (pronounced pŭ-dūfa) represents the deadline for the FDA to make an approval decision
  - The FDA tries to meet these deadlines 90% of the time

Original and Resubmitted Applications and Supplements:

SUBMISSION COHORT	STANDARD	PRIORITY
NME NDAs and original BLAs	90% in 10 months of the 60 day filing date	90% in 6 months of the 60 day filing date

Sources: FDA, Mizuho Research

* If you're curious, PDUFA is an acronym for Prescription Drug User Fee Act

8

Drug approval … the drug can now be given to patients … as an investor, it is important to get the FDA drug label and price

- When the drug is approved, as investors there are **2 things to look for**: **label and price**
  - The label is the prescribing information (you may recall the package insert that comes along with medication at the pharmacy)
- The label and price are usually attainable from the company the same day the drug is approved

On the label, investors will look at the language used

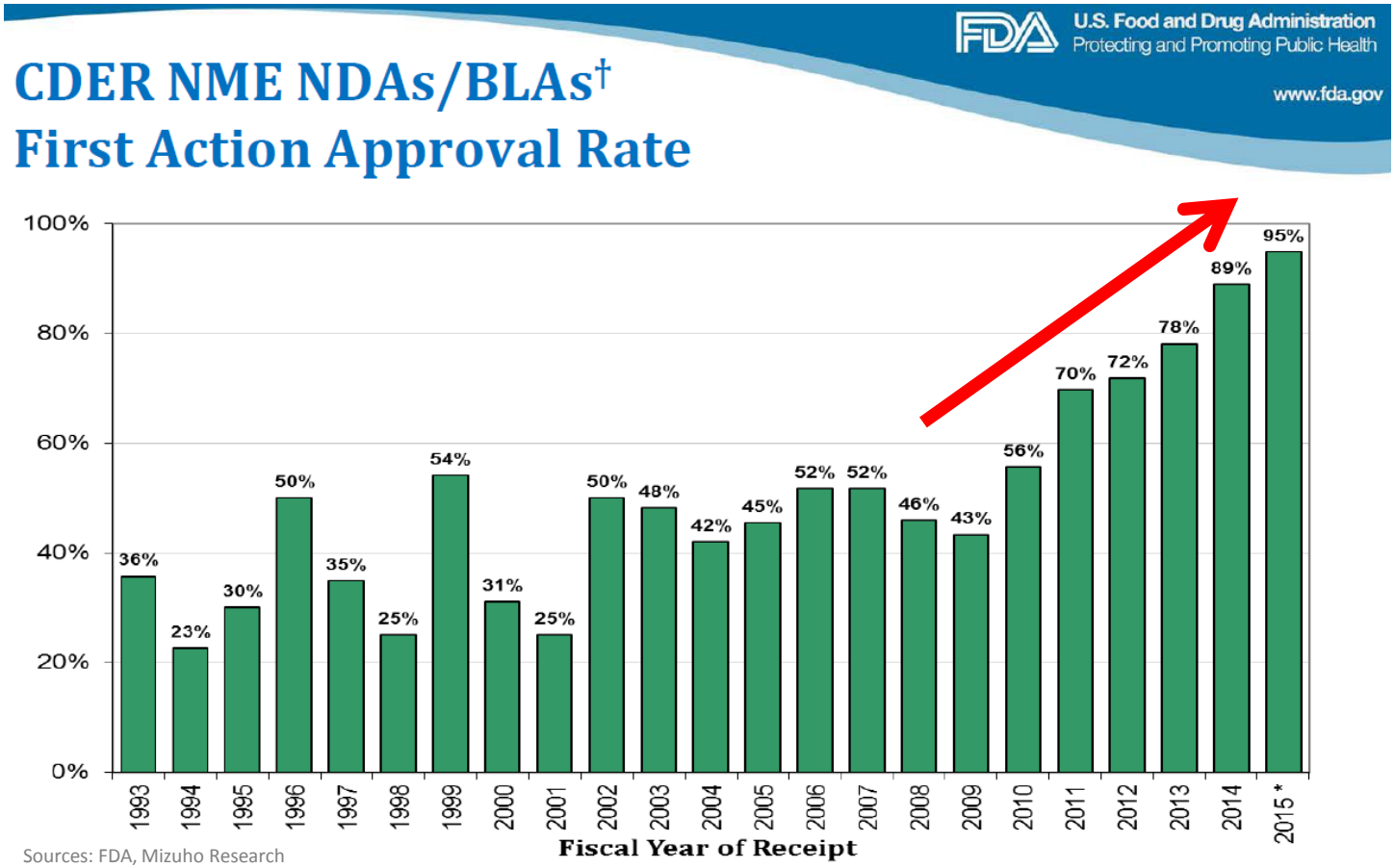
- **Label**:
  - Is the label restrictive, or as expected?
  - This can influence how the drug sells in the market because drug marketing reps can only speak to what is in the label
- It's always important to think about how the language compares to what investors had expected

The price is pretty self explanatory … it either missed, met or beat investor expectations

- **Price**
  - The drug company decides what to sell the drug for (in the US)
  - Drug pricing has become a huge debate topic … are drug prices fair and are price increases sustainable?
- It is important to know how the price compares to investor expectations
- Companies will provide the wholesale (**WAC***) price, not the net (of rebates) price
- Rebates can be significant, sometimes 40% of WAC, but drug companies rarely disclose these

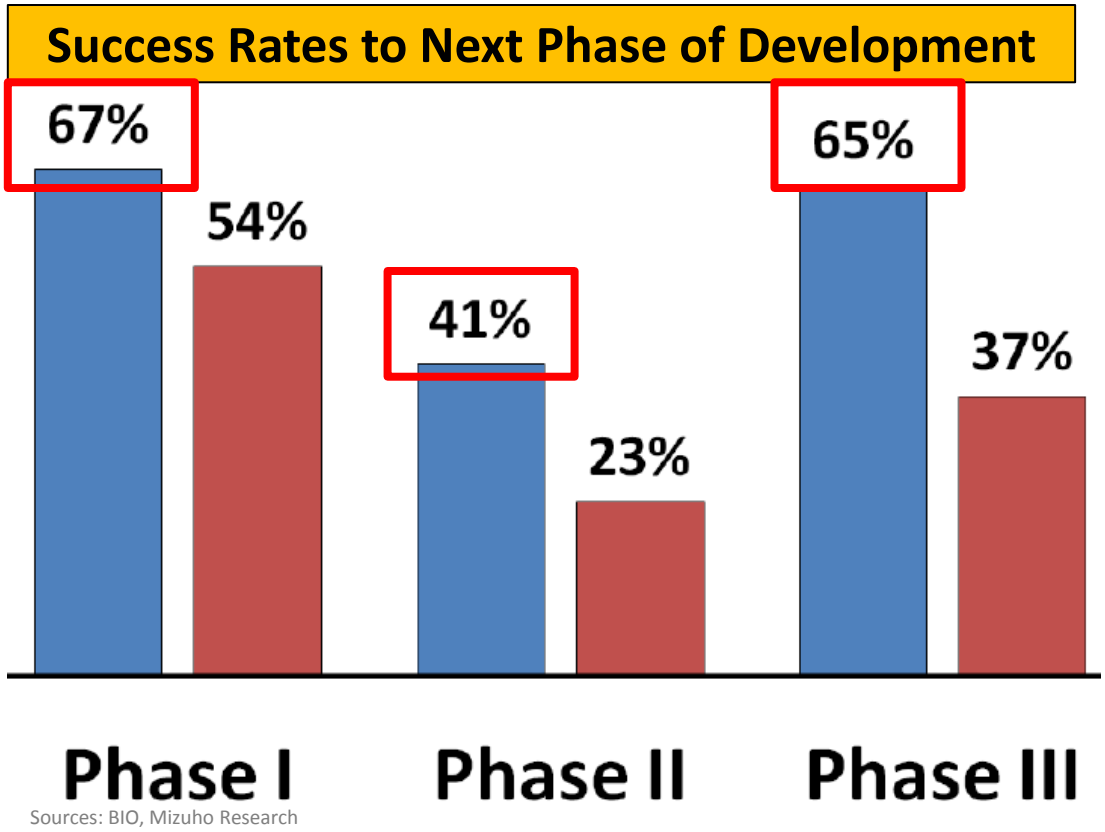
* Wholesale Acquisition Cost

Drug approval rates have increased with time … ~80-90% of applications are approved



Sources: FDA, Mizuho Research

~1 in every 5 drugs ever tested in Phase 1 makes it to application



Sources: BIO, Mizuho Research

67% * 41% * 65% = 18%
(or 1 in 5, alternatively)

Let's go through clinical trials basics ➔

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Clinical Trial Design Basics

There are several common parameters to consider when analyzing a clinical trial

1. Patient population
2. Randomization of the patient population
3. Control arm
4. Endpoints

1

Patient population … this is the target population in which the drug is being tested

- In every clinical trial there is a set of inclusion and exclusion criteria
- Patients enrolled into a particular clinical trial, must fit this criteria

The point of defining the patient population is to level the playing field, so we can isolate the effect of the drug being tested

Criteria can be as simple as age, disease and disease stage

- Criteria can include:
  - **Age**
  - **Disease** … (e.g.. Are we testing the drug in diabetics or cancer patients?)
  - **Severity of disease** … (e.g. Is this an early-staged or late-staged cancer patient?)

But it can also get more granular at times, so you have to pay attention

- One example is **line of therapy**:
  - This just means how many prior therapies has the patient had
  - There may be specific medications the patient had to fail before enrolling in the trial
- If the criteria says the patient must have failed 1 prior therapy, then the patient failed what is known as **first-line therapy**
  - Failed **two** therapies ➔ then, the patient has failed both first-line therapy and **second-line therapy**
  - Failed **three** therapies ➔ then, the patient has failed all first-line therapy, second-line therapy and **third-line therapy**

2 Randomization … this just means a computer assigns the patient to either drug or placebo

- When patients are enrolled into a clinical trial, a computer allocates them to either a drug arm or the placebo arm
- This is called **randomization**

Again, the point is to level the playing field and remove any biases from the trial … we want to know if the DRUG works on its merit

Randomization also blinds the trial

- Randomization also **blinds** the patient and researcher typically to whether the patient is getting drug or placebo
- If the trial were not randomized and blinded, the researcher could theoretically place sicker patients in the placebo arm to make the drug arm look better than it should, or he could interpret the results in a biased fashion

3

Control arm … this is the arm to which you're comparing the drug arm

- Typically in Phase 2 and 3 trials, there is a **control arm** to which you can compare the drug arm
  - If you don't have the control arm, how will you know IF the drug is working?
  - Alternatively, how will you know HOW WELL the drug is working?
- The control arm can either be:
  - **Placebo** … this is basically saline, distilled water or sugar and should have no effect on the patient
  - **Standard of care** … this is the best FDA approved therapy available today on the market
- If a standard of care exists, it is usually unethical to give patients a placebo pill because at that point you are just hurting the patient

The control arm can either be placebo or standard of care

- The control arm can either be:
  - **Placebo** … this is basically saline, distilled water or sugar and should have no effect on the patient
  - **Standard of care** … this is the best FDA approved therapy available today on the market for that particular disease
- If a standard of care exists, it is unethical to give patients a placebo pill because at that point you are just hurting the patient knowingly

4 Endpoints … this is the specific measure used in the trial to determine if the drug works

- You can have a drug arm and control arm, but without something to measure, you will not be able to tell if there is a difference between the two arms
- This measurement is called an **endpoint**
- For example, a common endpoint in:
  - diabetes trials ➔ sugar levels
  - obesity trials ➔ weight loss
  - cancer trials ➔ survival (by way of time post starting treatment)

The most important endpoint in a trial is the primary endpoint

- The most important endpoint in a clinical trial is called the **primary endpoint**
- The primary endpoint needs to show a benefit in order for the FDA to consider the trial successful
- Other measures are called **secondary endpoints**
  - These can help round the data coming out of the trial
  - They are still important to look at, but not necessarily needed for approval

Let's go through basic statistics ➔

Statistics Basics

There are 3 statistical terms that often come up in clinical trials results

1. P-value
2. Confidence Interval
3. Power

1

P-value … simply put, this is the likelihood that the trial results are due to chance

- The point of running a clinical trial is to see if a drug works vs placebo
- But of course, clinical trials are conducted in a **sample** of patients and the benefit we observe may be do to chance
- Usually trial results are considered **statistically significant** if the **p-value is less than 0.05**
  - *This means that there is less than a 5% likelihood that the benefit we're observing is due to chance (i.e. the results are very likely real, the drug works)*
  - In other words, there is <5% chance the results are a **false positive** or **Type 1 error**

The P-value is important to look at … you can't just look at the "trend" with a naked eye

- Sometimes there appears to be a benefit due to drug, but the trial did not achieve statistical significance (i.e. p-value was NOT less than 0.05)
  - In other words "the drug **trended** in the right direction" or "there was a **numerical difference** between arms"

2

Confidence Interval … this is the band of numbers where the "truth" can lie with 95% certainty (no pun intended ☺)

- In other words, let's say we run a trial and the drug benefit over placebo is 5 units … this is the **point estimate**
- What we want to know is if we were to run the same exact trial what are other potential results we could have seen with 95% certainty … these results make up the **confidence interval**

The "truth" can lie anywhere in the confidence interval

Pay attention to the width and bookends of the confidence interval

- Let's continue with our point estimate being 5 units
- Our trial may have a confidence interval of (5) – 15 units (i.e. **wide interval = bad**) or 4 – 6 units (i.e. **narrow interval = good**)
- The "truth" can lie anywhere in the confidence interval
  - A (5) unit benefit is actually not a benefit at all … the patient could actually be getting worse vs placebo!

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3

Power … this is the chance of avoiding a false negative

- **P-value** is the chance that the results are a **false positive (Type 1 error)**
- **Power** is the chance of avoiding a **false negative (Type 2 error)**
  - In other words, the trial results may indicate that the drug did not provide a benefit over placebo, but in reality the drug works

EXAMPLE:

- **Assuming a drug works, if a trial is 80% powered, 8 out of 10 times we conduct that trial we will indeed see a benefit over placebo**
- **However the remaining 2 times, the results will show no benefit**

The best way to increase the power is to increase the size of the trial

- The best way to increase the power of the trial is by increasing the number of patients in the trial (i.e. the sample size)
- As it turns out, assuming the drug works in reality, increasing the sample size of the trial also helps it hit statistical significance (or a p-value < 0.05),

In other words, it's easier to get to the truth when you test the drug on more people

The relationship between P-value and Power can be confusing, so let's break it down (1)

FIRST LET'S THINK ABOUT WHY INCREASING THE SIZE OF TRIAL REDUCES ERROR?

- P-value and power are both measures associated with the trial results being misleading (either by way of a false positive or false negative)
- To decrease the chance of error in a trial, we mentioned the best way is to increase the size of the trial

The relationship between P-value and Power can be confusing, so let's break it down (2)

Think about flipping a coin:

- You know the true odds of getting heads is 50%, and tails 50%
- But if you flip the coin only 2 times, you're leaving a lot of room for error
  - You might get heads 100% or tails 100%, but you know these aren't the true odds of a 2-sided coin
- So to decrease your chance of error, you decide to flip the coin 1,000 times (i.e. increase the sample size)
  - You still think you'll get heads 100% or tails 100%?
  - You'll probably be closer to the true odds which is 50% heads, 50% tails

The relationship between P-value and Power can be confusing, so let's break it down (3)

SECOND, LET'S THINK ABOUT HOW POWERING CAN HELP YOU REACH A P-VALUE<0.05?

- Think about your car (i.e. the drug)
  - You know your car works and can get you from where you are to your intended destination
  - But if you don't put enough gas in your car, it doesn't matter how well your car works … you probably won't get to your intended destination

The relationship between P-value and Power can be confusing, so let's break it down (4)

- Powering a trial is like putting enough gas in your car
  - If you don't put enough gas in your car, you probably will not get to your destination .. that's a false negative because you know your car works
- Getting your p-value to <0.05 is your intended destination
  - By putting enough gas in your car, you will probably get to your destination because you know your car works
  - The chance of you getting there by telekinesis is quite low
  - In other words the chance of a false positive is really low

Let's summarize … here are the key questions to answer when analyzing clinical trial results

Key Question	It's important to understand …
Which phase is the trial in?	… where the drug is in development
How many patients are in the trial and how many arms are there?	… whether the trial is powered enough to hit statistical significance … also whether we should look for dose response in efficacy and safety
Is there a control arm, and what is it?	… if will we be able to assess whether the drug is better than standard of care
What is the primary endpoint? And did it hit statistical significance?	… if the trial is successful and p-value < 0.05
What are the adverse events?	… if there is a major safety risk

Table of Contents

CONCLUSIONS first …. our key message

Biotech had an amazing run since 2009 .. Up 600-700% to the July 2015 peak

However, biotech has had a decent pullback / breather since then … down about 35% .. and **P/E valuations are at or approaching historical lows**

We believe putting the **presidential election behind us will be healthy for the sector** as it should make it easier to work with the road ahead, whatever it may be

Decent number of Phase 3 catalysts in the space for remainder 2016 / 2017

Also higher level … **we like the fundamentals of the sector** (drug pipelines, R&D productivity, "friendlier" FDA, etc.)

We believe **drug pricing pressures are a risk** more now than before, but at the same time believe the problem will result in iterative, gradual resolutions if anything … not one resolved overnight

M&A is possible, but we note **US cash balances of LC biotechs are not massive**

BOTTOM LINE: Overall though, we like the sector here … it may take another quarter or two of stabilization, but the general picture to us looks decent for 2017

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Putting Biotech's Recent Performance in Context

First let's lay out the landscape

Large-Cap Biotech is here.

Call us if you would like this in Excel … I know it's hard to see here ☺

Therapeutics Comps Summary Table

Mizuho
Salim.Syed@us.mizuho-sc.com / 212.205.7945

11/1/2016

				EPS (Non-GAAP)			P/E (Non-GAAP)				Total Revenue			EV / Total Revenue			
Ticker	Current Price ($)	Market Cap ($MM)	YTD Stock Return (%)	2015 EPS ($)	2020 EPS ($)	2015-2020 EPS CAGR (%)	NTM PE (x)	2015 PE (x)	2016 PE (x)	2017 PE (x)	2015 Sales ($MM)	2020 Sales ($MM)	2015-2020 Sales CAGR (%)	NTM EV / Sales (x)	2015 EV / Sales (x)	2016 EV / Sales (x)	2017 EV / Sales (x)
LC BIOTECH																	
AMGN	$ 141.30	105,116	(11)%	$ 10.38	$ 14.19	6%	11.4x	13.6x	12.2x	11.2x	21,662	24,560	3%	4.4x	4.7x	4.5x	4.3x
BIIB	$ 283.13	61,602	(17)%	$ 17.01	$ 26.91	10%	13.7x	16.6x	14.0x	13.6x	10,764	14,235	6%	5.4x	5.9x	5.5x	5.4x
CELG	$ 103.33	80,093	(8)%	$ 4.71	$ 12.56	22%	15.0x	21.9x	17.5x	14.6x	9,256	20,168	17%	6.8x	9.5x	7.8x	6.6x
GILD	$ 73.87	97,483	(22)%	$ 12.61	$ 11.87	-1%	6.4x	5.9x	6.3x	6.5x	32,639	27,096	-4%	3.8x	3.4x	3.7x	3.8x
ALXN	$ 132.05	29,612	(29)%	$ 4.99	$ 11.49	18%	23.8x	26.5x	28.2x	23.1x	2,604	5,909	18%	9.0x	12.2x	10.2x	8.8x
REGN	$ 344.81	35,647	(16)%	$ 12.07	$ 26.10	17%	24.3x	28.6x	31.5x	23.2x	4,104	8,923	17%	6.1x	8.7x	7.0x	6.0x
SUM		*409,553*		*$61.77*	*$102.12*						*81,029*	*100,892*					
Mean (Market Cap Weighted)			**(15)%**			**10%**	**13.3x**	**16.1x**	**14.9x**	**13.0x**			**7%**	**5.3x**	**6.4x**	**5.7x**	**5.3x**
US PHARMA																	
ABBV	$ 56.40	91,850	(14)%	$ 4.29	$ 7.59	12%	10.5x	13.1x	11.7x	10.3x	22,859	33,443	8%	4.4x	5.3x	4.7x	4.3x
BMY	$ 50.96	85,166	(14)%	$ 2.01	$ 4.72	19%	17.3x	25.4x	18.2x	17.1x	16,560	25,073	9%	4.3x	5.2x	4.5x	4.3x
LLY	$ 72.85	80,423	6%	$ 3.43	$ 6.27	13%	18.6x	21.2x	20.5x	18.3x	19,959	26,415	6%	3.9x	4.3x	4.1x	3.9x
MRK	$ 59.21	163,728	4%	$ 3.59	$ 4.98	7%	15.3x	16.5x	15.7x	15.3x	39,498	43,829	2%	4.4x	4.5x	4.4x	4.4x
PFE	$ 31.10	188,648	(0)%	$ 2.20	$ 3.17	8%	11.8x	14.1x	12.6x	11.7x	48,851	58,189	4%	3.9x	4.3x	4.0x	3.8x
SUM		*609,814*		*$17.60*	*$26.73*						*153,875*	*186,949*					
Mean (Market Cap Weighted)			**(2)%**			**10%**	**14.2x**	**17.1x**	**15.1x**	**14.1x**			**5%**	**4.2x**	**4.6x**	**4.3x**	**4.1x**
EU PHARMA																	
AZN-GB	$ 55.35	70,018	(1)%	$ 4.26	$ 6.01	7%	13.6x	13.0x	13.2x	13.7x	24,708	28,970	3%	3.7x	3.4x	3.6x	3.7x
BAYN-DE	$ 100.80	83,354	(19)%	$ 7.45	$ 10.75	8%	11.7x	13.5x	12.5x	11.5x	50,322	59,978	4%	2.0x	2.1x	2.1x	2.0x
GSK-GB	$ 19.72	96,145	17%	$ 1.12	$ 1.55	7%	15.2x	17.7x	16.3x	15.0x	35,260	40,450	3%	3.4x	3.4x	3.6x	3.4x
MRK-DE	$ 102.17	44,422	19%	$ 5.26	$ 8.80	11%	14.7x	19.4x	15.4x	14.6x	13,953	18,661	6%	3.4x	4.2x	3.5x	3.4x
NOVN-CH	$ 70.98	186,480	(24)%	$ 4.89	$ 6.61	6%	14.4x	14.5x	15.0x	14.3x	49,414	56,462	3%	3.8x	3.8x	3.8x	3.7x
NOVO.B-DK	$ 35.65	90,904	(7)%	$ 1.94	$ 3.09	10%	15.3x	18.4x	16.1x	15.2x	15,710	20,575	6%	5.1x	5.5x	5.3x	5.1x
ROG-CH	$ 228.06	196,714	(17)%	$ 13.38	$ 19.88	8%	14.4x	17.0x	15.3x	14.3x	48,097	60,989	5%	3.4x	3.7x	3.5x	3.3x
SAN-FR	$ 78.70	101,452	(5)%	$ 6.13	$ 7.64	4%	13.1x	12.8x	13.0x	13.1x	37,523	44,966	4%	2.9x	3.0x	2.9x	2.9x
SUM		*869,488*		*$44.43*	*$64.33*						*274,987*	*331,051*					
Mean (Market Cap Weighted)			**(9)%**			**7%**	**14.1x**	**15.7x**	**14.7x**	**14.0x**			**4%**	**3.5x**	**3.6x**	**3.6x**	**3.5x**
SPEC PHARMA																	
AGN	$ 209.12	82,801	(19)%	$ 13.43	$ 23.57	12%	12.9x	15.6x	15.0x	12.5x	15,071	19,796	6%	8.0x	8.4x	8.6x	7.9x
ENDP	$ 18.52	4,126	(74)%	$ 4.66	$ 6.05	5%	3.8x	4.0x	4.1x	3.7x	3,269	4,442	6%	2.8x	3.5x	2.9x	2.8x
JAZZ	$ 110.07	6,663	(33)%	$ 9.52	$ 18.06	14%	9.9x	11.6x	10.9x	9.7x	1,325	2,382	12%	4.1x	5.2x	4.6x	4.1x
MNK	$ 59.48	6,406	(40)%	$ 7.37	$ 10.90	8%	7.4x	8.1x	7.7x	7.4x	3,347	3,912	3%	3.6x	3.6x	3.6x	3.6x
MYL	$ 36.88	19,728	(35)%	$ 4.30	$ 6.59	9%	6.8x	8.6x	7.7x	6.7x	9,429	14,012	8%	2.1x	2.8x	2.4x	2.0x
TEVA-IL	$ 42.92	43,531	(26)%	$ 5.42	$ 6.65	4%	7.5x	7.9x	8.3x	7.4x	19,652	26,976	7%	2.1x	2.7x	2.4x	2.1x
VRX	$ 18.50	6,429	(87)%	$ 10.16	$ 9.67	-1%	2.5x	1.8x	2.9x	2.4x	10,447	11,061	1%	3.6x	3.5x	3.7x	3.5x
SUM		*169,685*		*$54.86*	*$81.48*						*62,539*	*82,581*					
Mean (Market Cap Weighted)			**(28)%**			**9%**	**9.9x**	**11.6x**	**11.3x**	**9.6x**			**6%**	**5.2x**	**5.7x**	**5.6x**	**5.1x**
INDICES																	
SP50	2,120		3%				16.4x	NA	18.1x	16.1x				2.1x	NA	2.2x	2.1x
NBI	2,702		(15)%				19.1x	NA	22.0x	18.6x				5.8x	NA	6.4x	5.7x
BTK	2,970		(14)%				370.9x	NA	######	166.6x				5.7x	NA	6.4x	5.6x
IBB	258		(15)%				32.4x	NA	42.5x	30.3x				5.3x	NA	5.8x	5.2x
DRG	475		(11)%				13.6x	NA	14.5x	13.4x				3.7x	NA	3.8x	3.6x
DGE	840		(16)%				NA	NA	NA	NA				NA	NA	NA	NA

Sources: FactSet, Mizuho Research

Biotech has outperformed the S&P since the 2009 bottom through the July 2015 peak

- Biotech: +600–700% (depending on the index you use)
- S&P: +200%

Sources: FactSet, Mizuho Research

Biotech has outperformed the S&P on an annual basis as well

- Double-digit **absolute** returns every year since 2010

Date	NBI (cap weighted)	BTK (equal weighted)	S&P (cap weighted)
3/9/09 – 12/31/09	+39%	+74%	+65%
2010	+15%	+38%	+13%
2011	+12%	-16%	+0%
2012	+32%	+42%	+13%
2013	+66%	+51%	+30%
2014	+34%	+48%	+11%
2015	+11%	+11%	-1%
1/1/15 – 7/20/15	+31%	+29%	+3%

Sources: FactSet, Mizuho Research

Beginning July 2015, biotech saw a downward trend

- 7/20/2015 to **12/31/2015**
  - Biotech down (14)%
  - S&P down (4)%

- 7/20/2015 to **11/04/2016**
  - Biotech down ~(35)%
  - S&P break-even

Sources: FactSet, Mizuho Research

The first downturn blip post the July 20, 2015 peak could be attributed to BIIB's guidance revision, BUT this doesn't explain the continued downtrend

Biotech down 5%

BIIB down 25%

BIIB 2Q'15 Guidance Revision

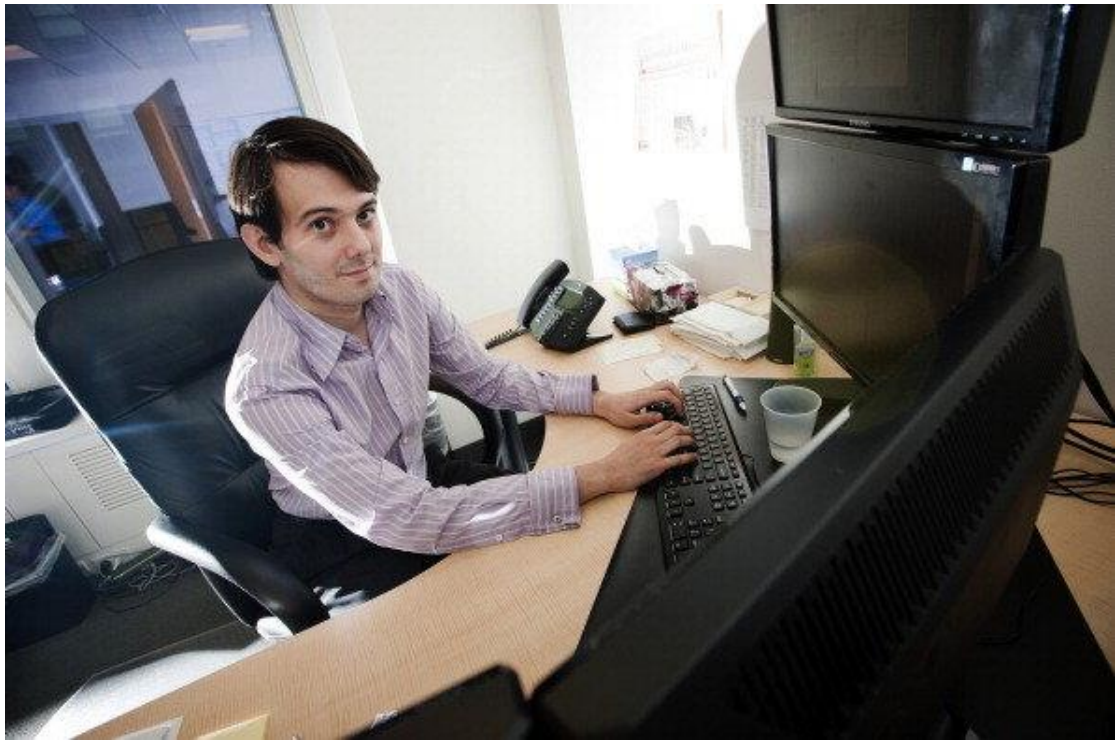
	Prior FY 2015 Guidance	Updated FY 2015 Guidance	Comments
Revenue Growth	Approximately 14 to 16%	Approximately 6 to 8%	Decrease from prior guidance change primarily due to change in estimates for Tecfidera trajectory

Sources: FactSet, Mizuho Research, BIIB

The August 2015 decline was due to macro fears: a China slowdown, lower oil prices and a possible Fed rate hike

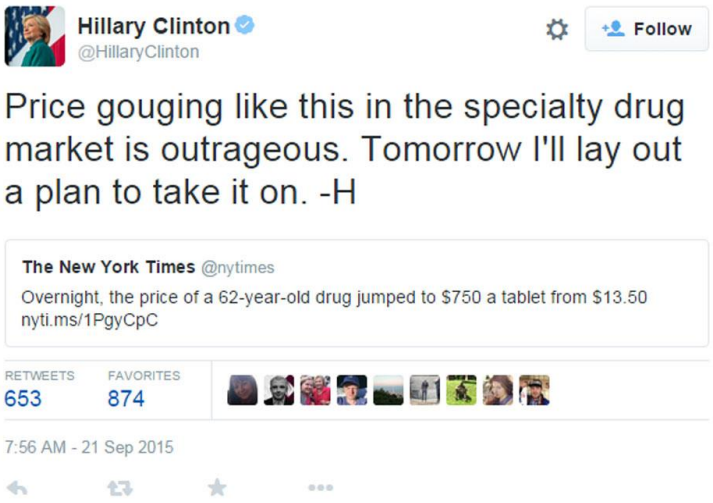
Sources: FactSet, Mizuho Research

Sept 2015, Martin Shkreli, CEO of Turing Pharmaceutics raises the price of his drug from $13.50/pill to $750/pill …. OVERNIGHT



Sources: NYT, Mizuho Research

Then Hillary Clinton tweets this and sends the NBI down (4.5)%

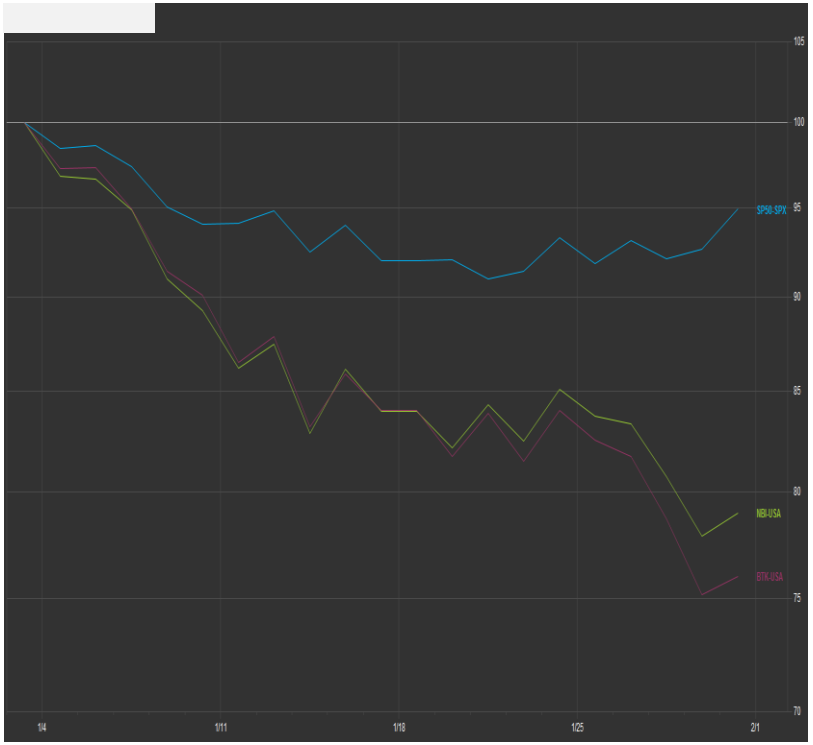


This one comment is what many street observers point to as the turning point for biotech sentiment

A weak January 2016 didn't help … S&P down (5)% … Biotech down ~(23)%

- CELG issued weaker annual guidance vs investor expectations and missed 4Q EPS
- GILD investor concerns re: HCV biz
- ALKS-5461 Phase 3 trials fail
- SRPT's eteplirsen negative briefing docs
- No IPOs in January 2016
- Continuing macro fears

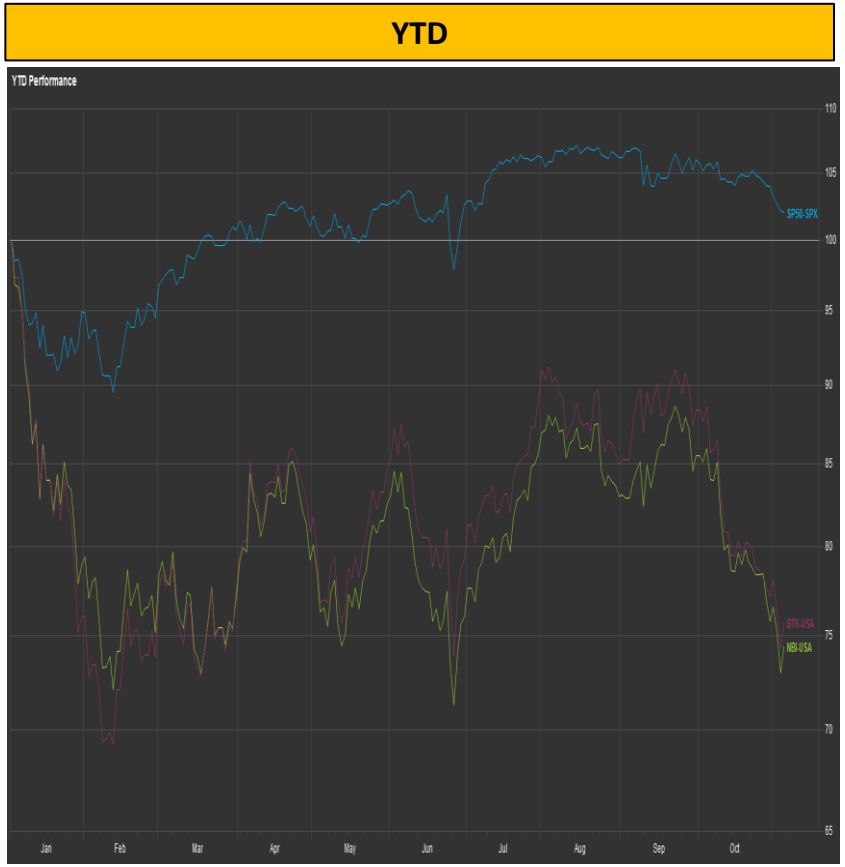
January 2016



Sources: FactSet, Mizuho Research

The remainder of the year hasn't been much better for biotech … YTD S&P up +2% … Biotech down (25)%

- Presidential elections have intensified debate on drug pricing
- Fundamentally, there also hasn't been much in terms of major clinical data in our view … at least on relative basis to what we've seen last few years

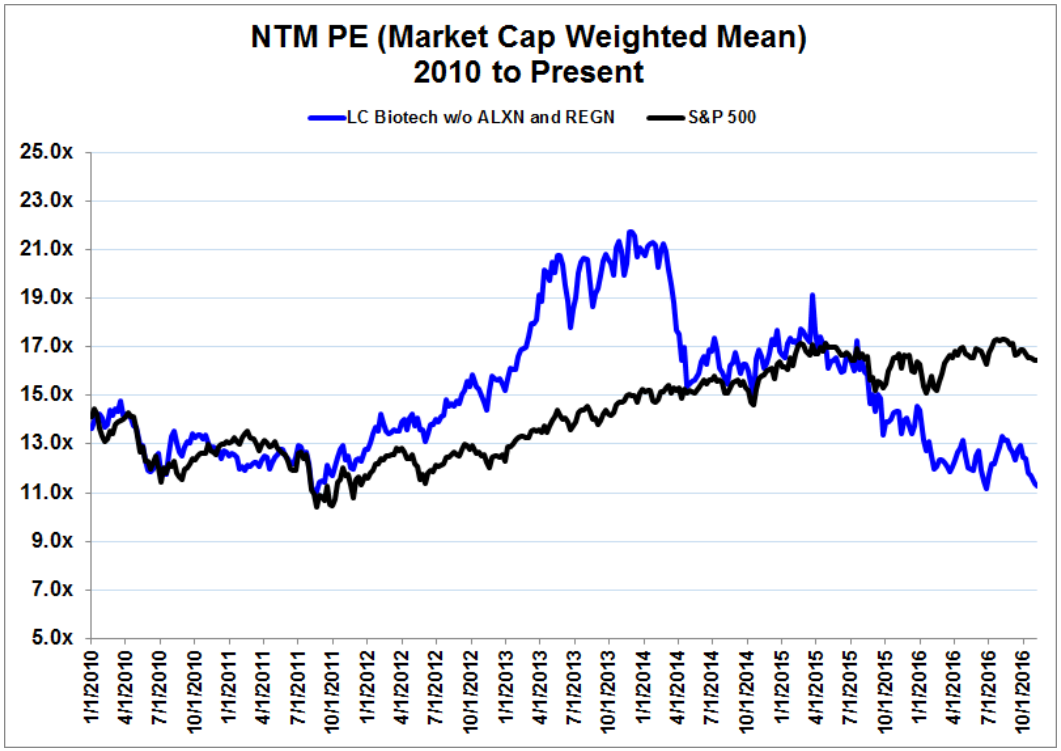


So where does that leave biotech valuations?➔

Biotech Valuations

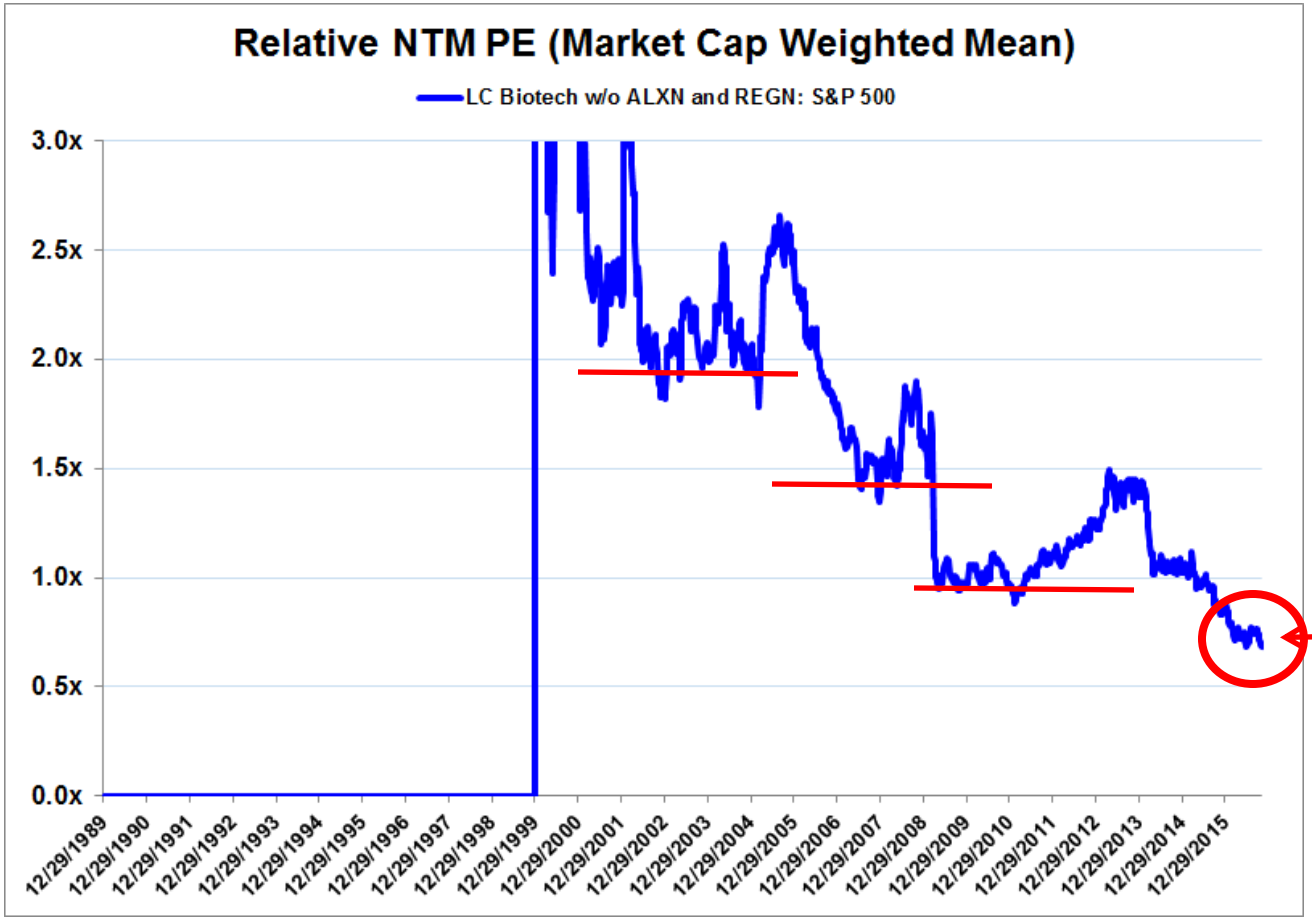
Large-cap Biotech currently trades at 11x … a 32% discount to the S&P

- The last time large-cap biotech traded below the S&P was in 2011
- **We include dead tickers: CHIR, DNA, GENZ, IMNX, MEDI**
- **We also market-cap weight our index at each point in time**



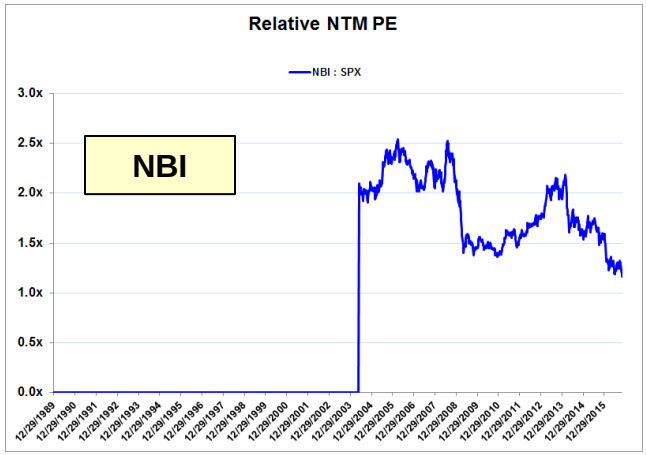
Source: FactSet, Mizuho Research

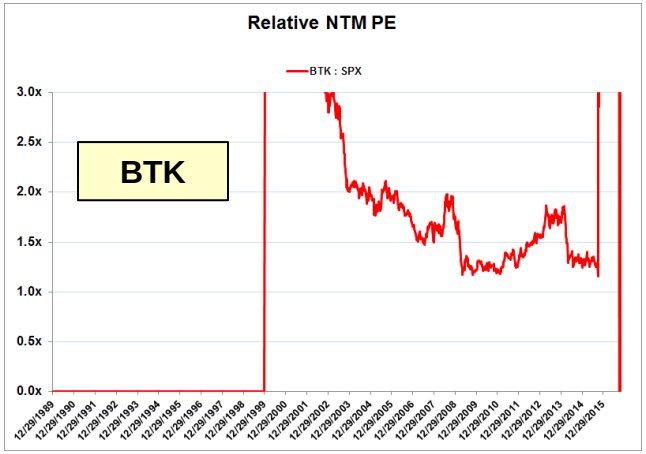
On a relative NTM P/E basis, LC Biotech is at a new low vs the S&P 500

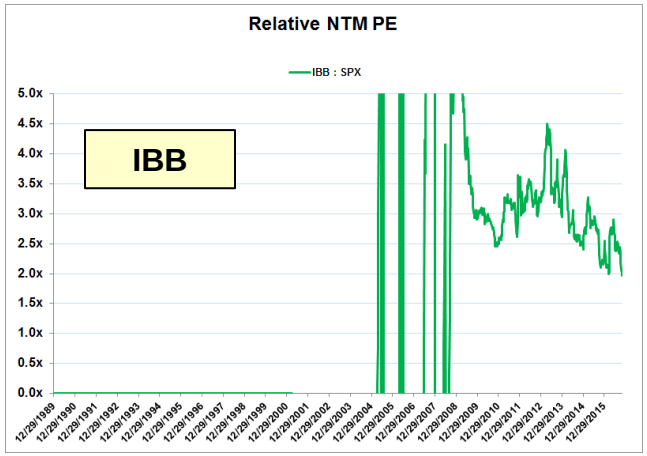


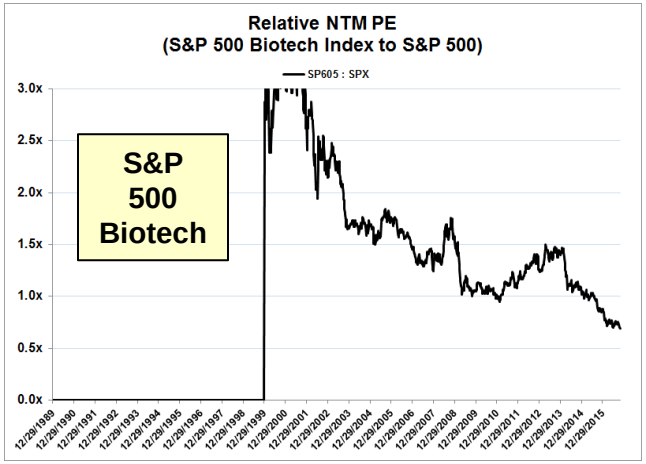
Potential bottom for the next cycle?

Here are the same charts using other biotech indexes

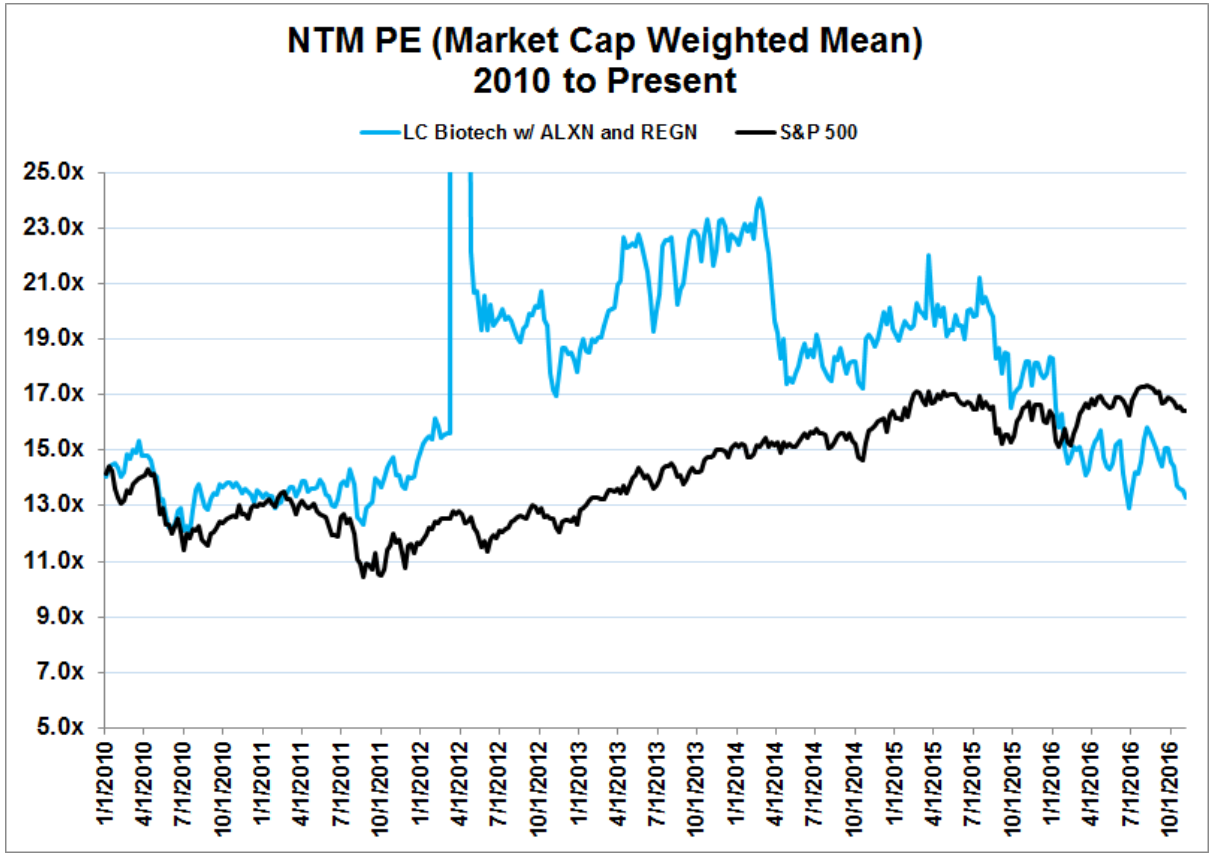








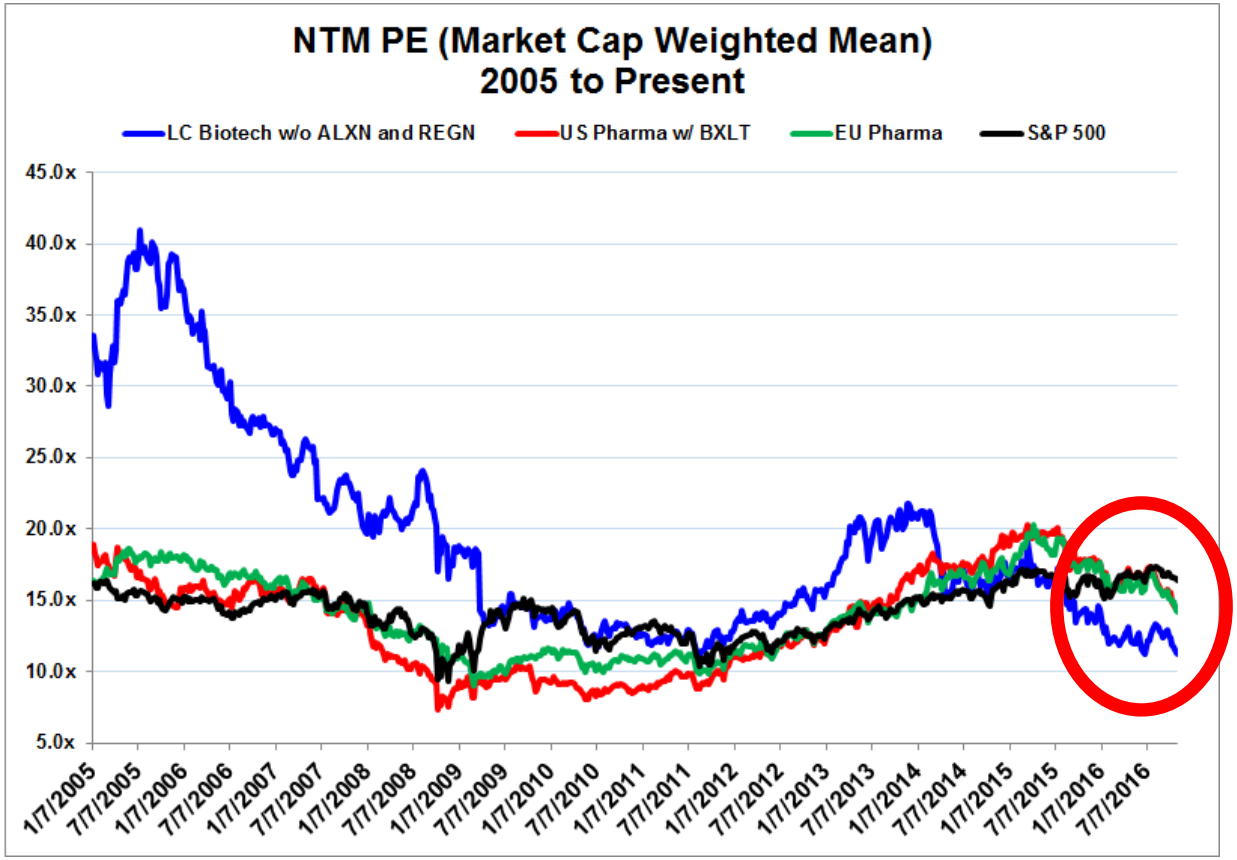
Even if we include ALXN and REGN in the index, LC biotech trades at 19% discount to the S&P



Source: FactSet, Mizuho Research

LC biotech is also trading below US and EU pharma for the first time ever

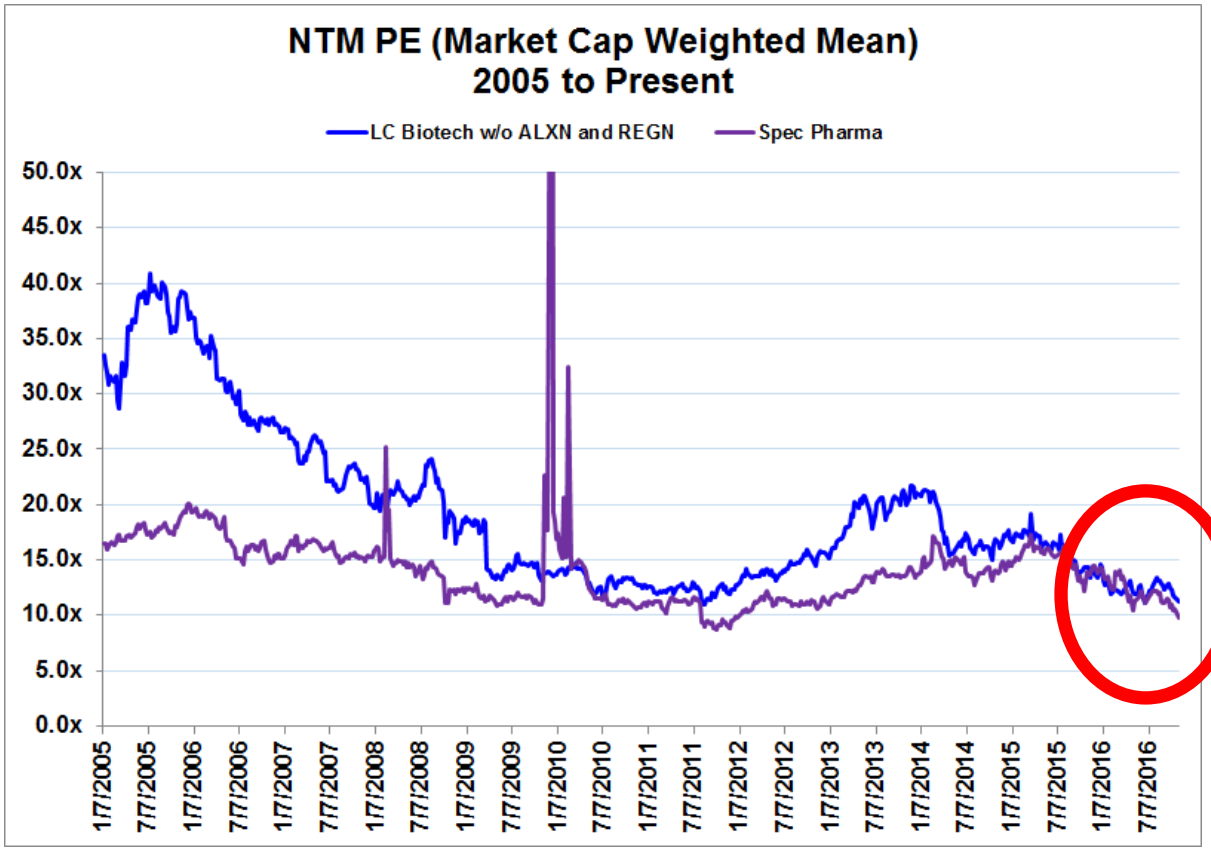
- Discount of 25% to pharma
- Again we include dead tickers in our analysis and market-cap weight valuation at each point in time



Source: FactSet, Mizuho Research

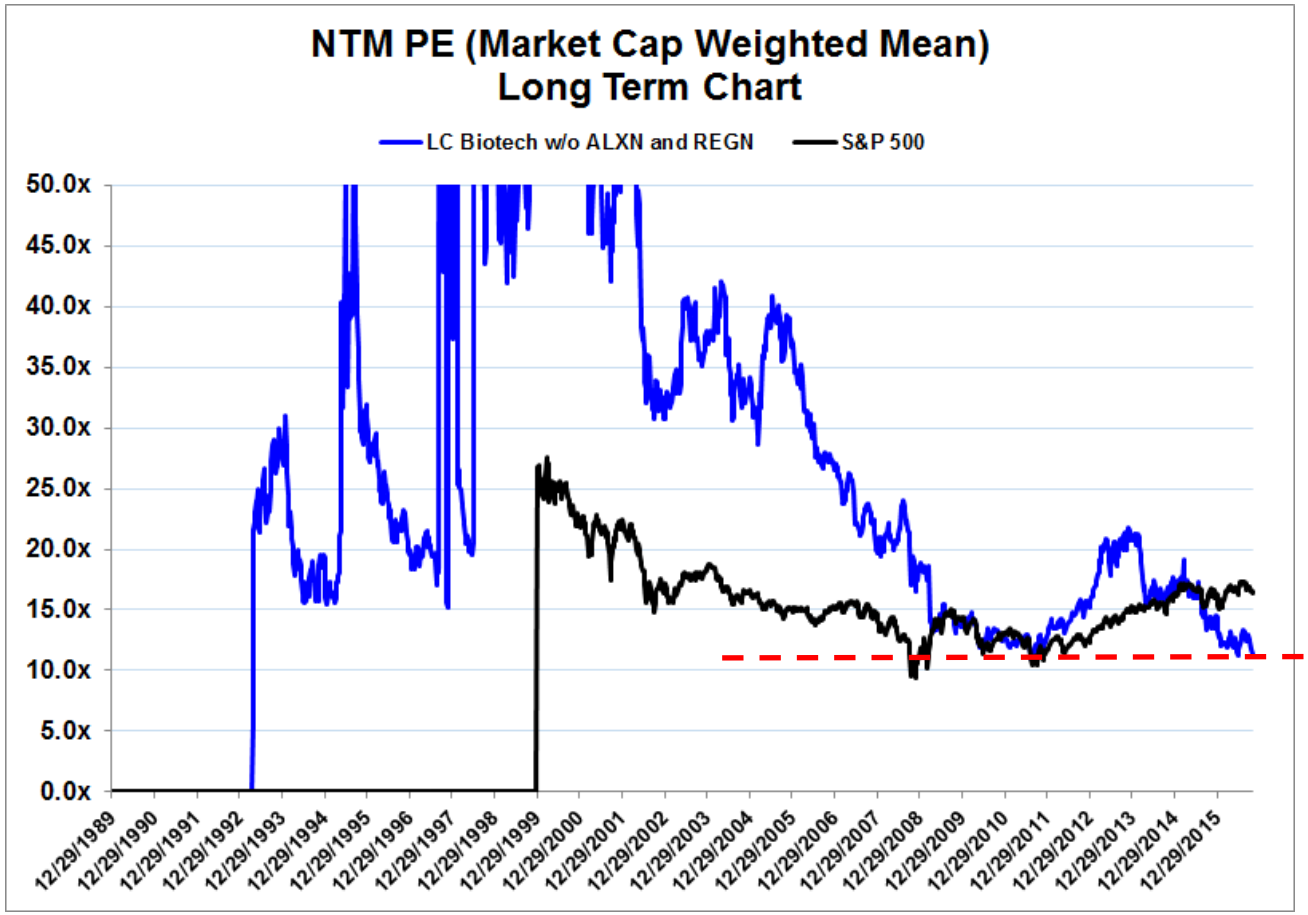
In fact, LC Biotech is now trading like Spec Pharma again

- The last time this happened was 2010



Sources: FactSet, Mizuho Research

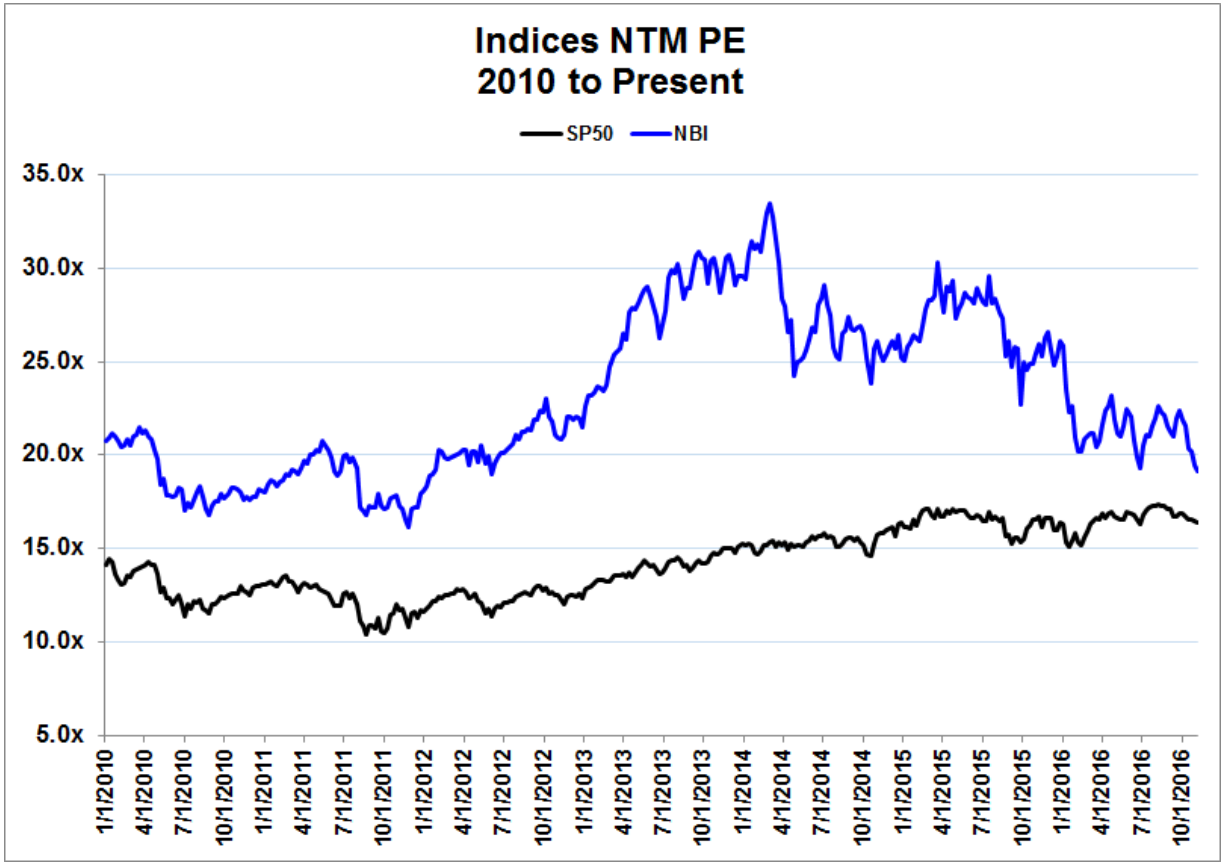
LC Biotech is actually trading at par with its all-time low of 11x



Sources: FactSet, Mizuho Research

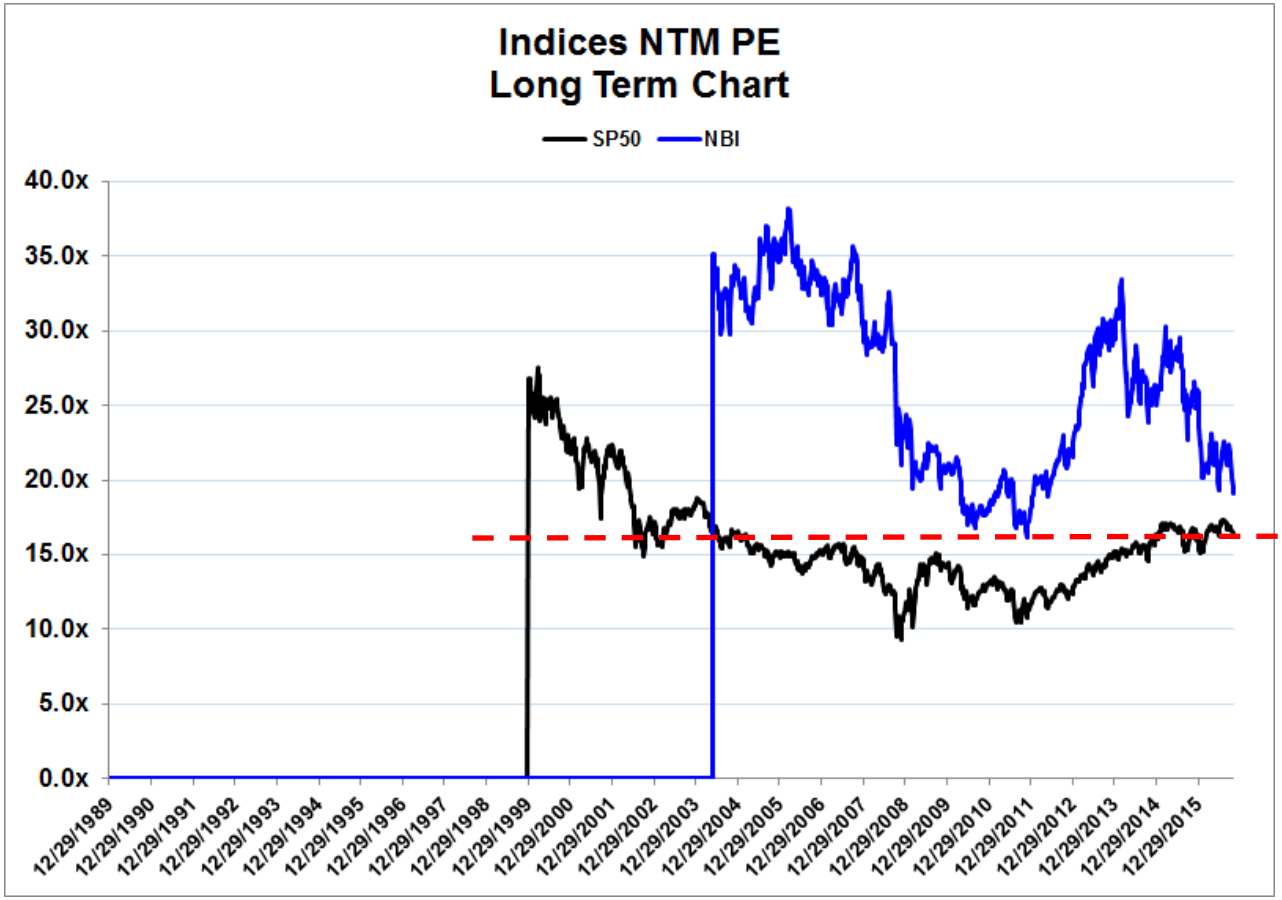
The broader biotech market still trades though at 19x, a 17% premium to the S&P

- The NBI is a market-weighted index of all biotech stocks on the NASDAQ
- 190 companies are included in the NBI



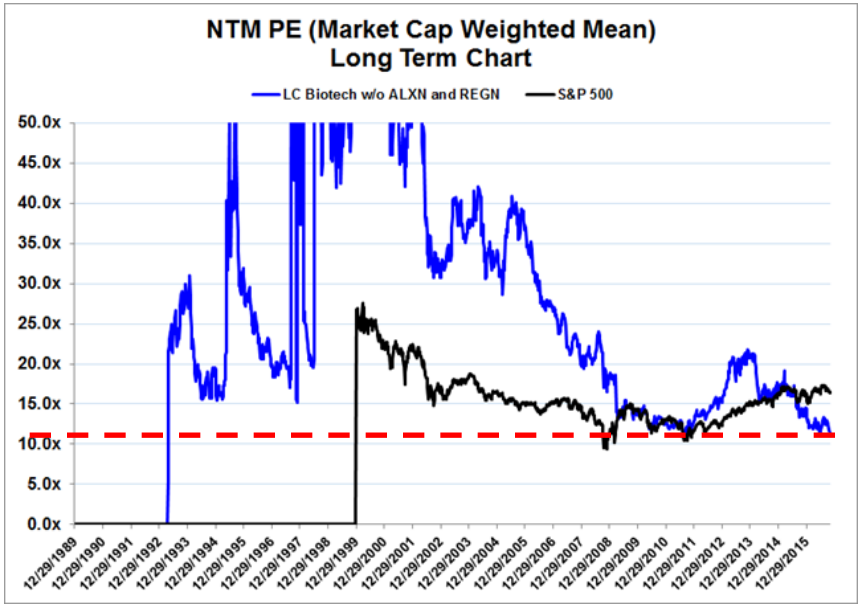
Source: FactSet, Mizuho Research

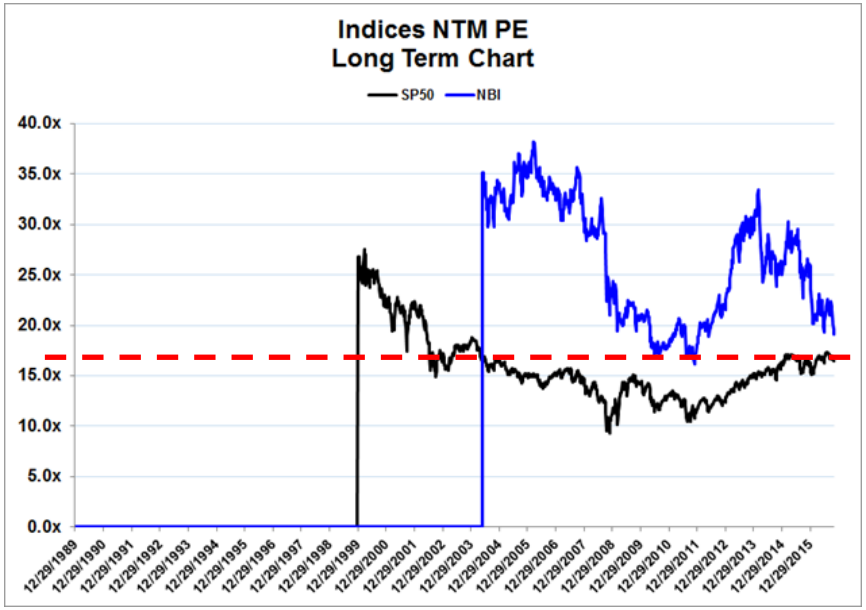
And it also trades at a 18% premium to its all time low of 16x in 2011



Source: FactSet, Mizuho Research

So we know SMID-cap biotechs aren't as cheap as Large-Cap biotechs right now



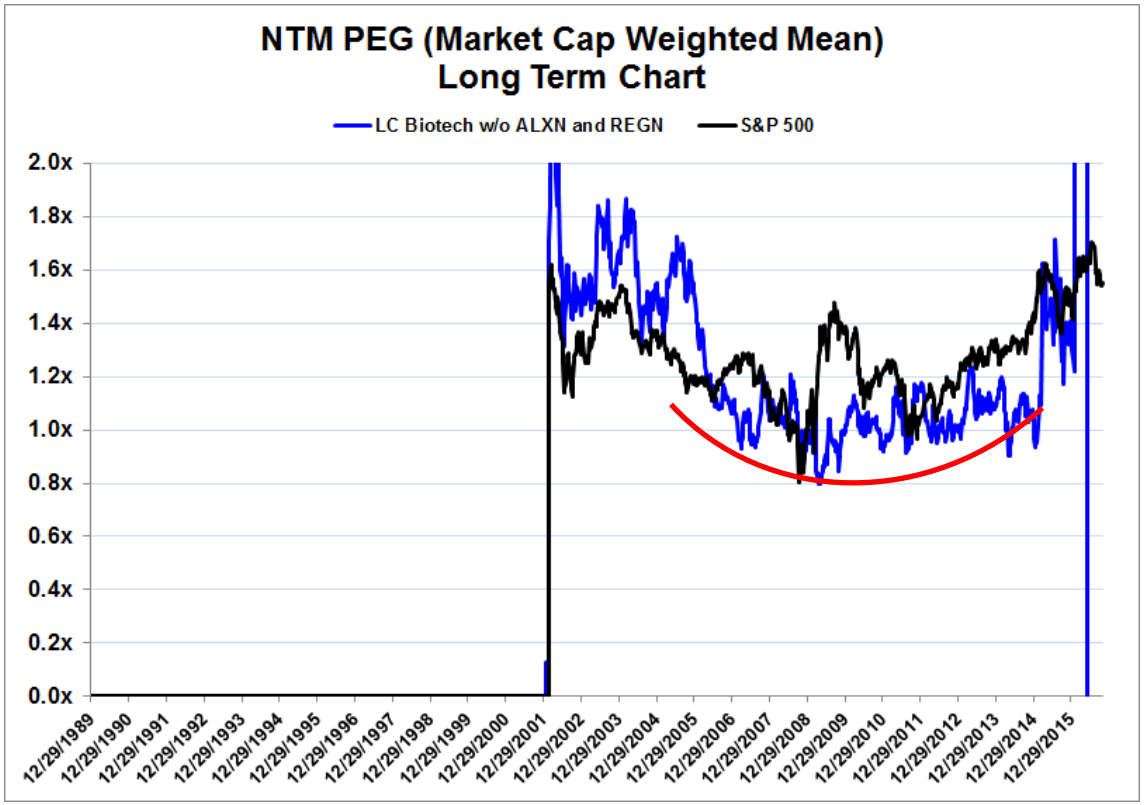


Large-cap biotech trading at par with its all-time low

Broader biotech trading at a 18% premium to its all-time low

Sources: FactSet, Mizuho Research

Biotech investors seem willing though to pay more for growth today than the 2009 trough



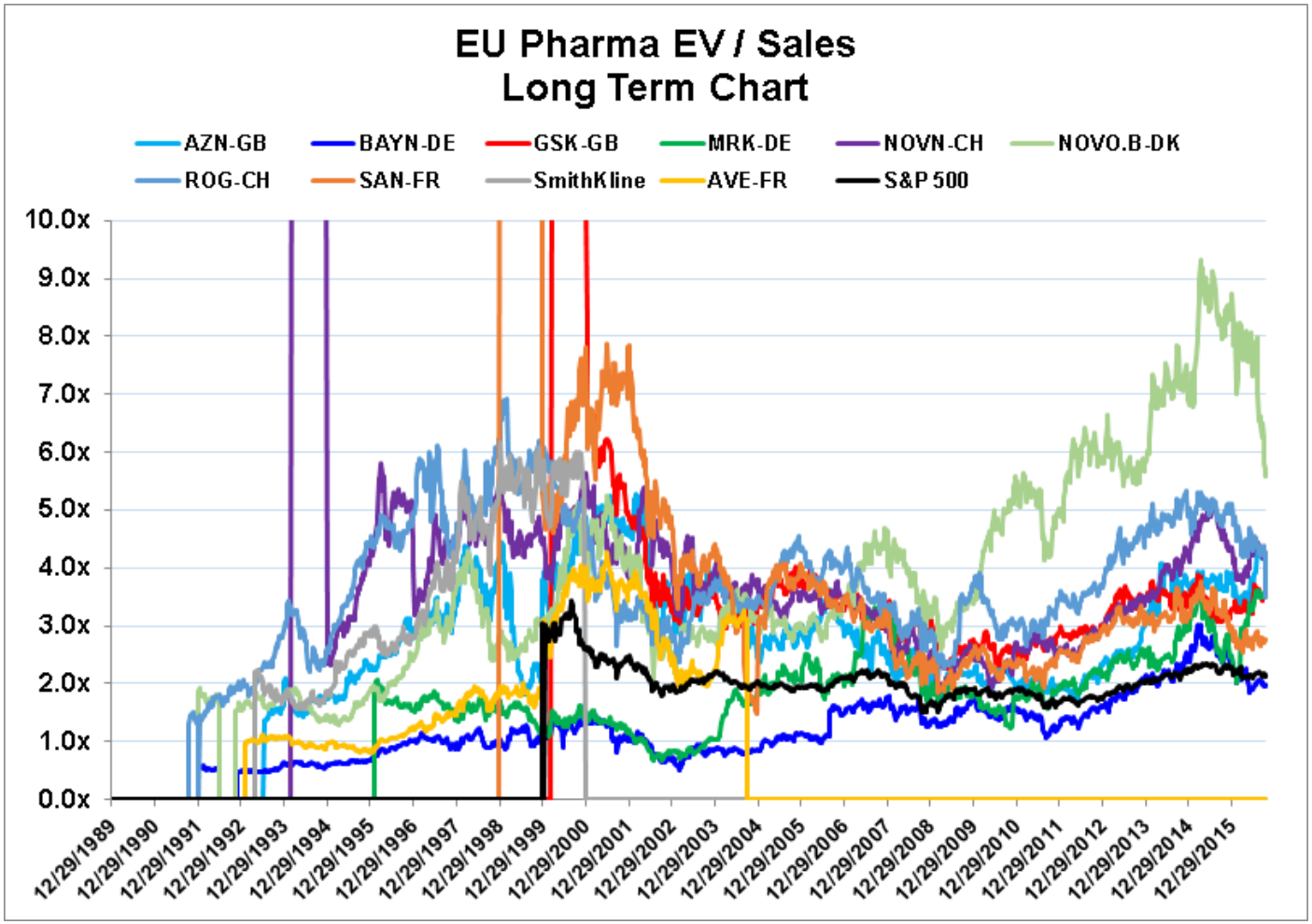
Source: FactSet, Mizuho Research

Our comps sheet is so fresh, so clean … email / call if you want it … Salim.Syed@us.mizuho-sc.com / (212) 205-7945

- We have all therapeutic sectors:
  - Biotech, US Pharma, EU Pharma, Spec Pharma
  - S&P500, NBI, BTK, IBB, DRG, DGE
- We include:
  - Dead tickers
  - **Have data all the way to 1990 (if available)**
- We calculate mean / median several ways:
  - **Market-cap weighted**
  - Equal-weight weighted
  - Aggregated data

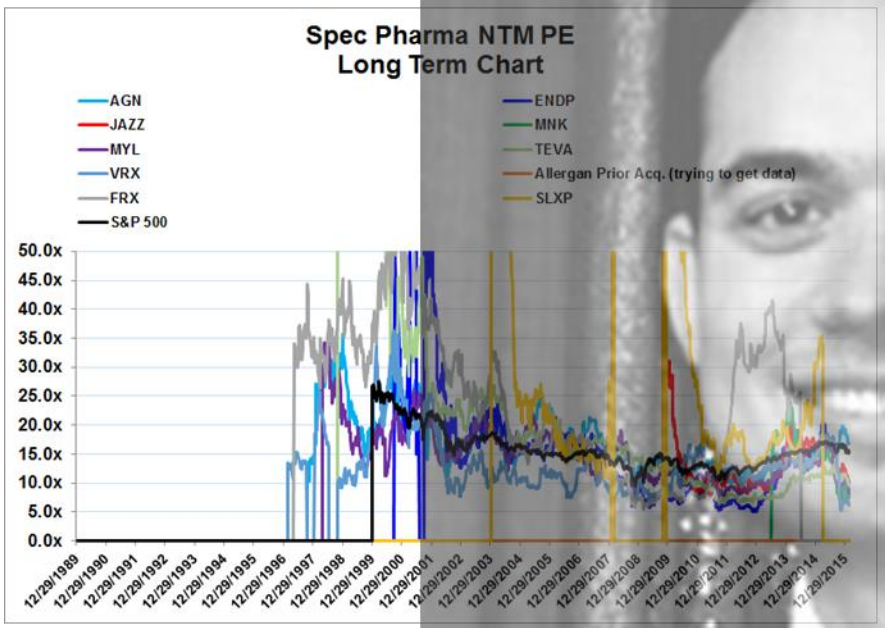
- We have all sorts of ratios:
  - NTM P/E
  - LTM P/E
  - NTM EV/S
  - NTM EV/EBIT
  - P/BV
  - NTM EV/FCF
  - NTM PEG
  - Relative P/E

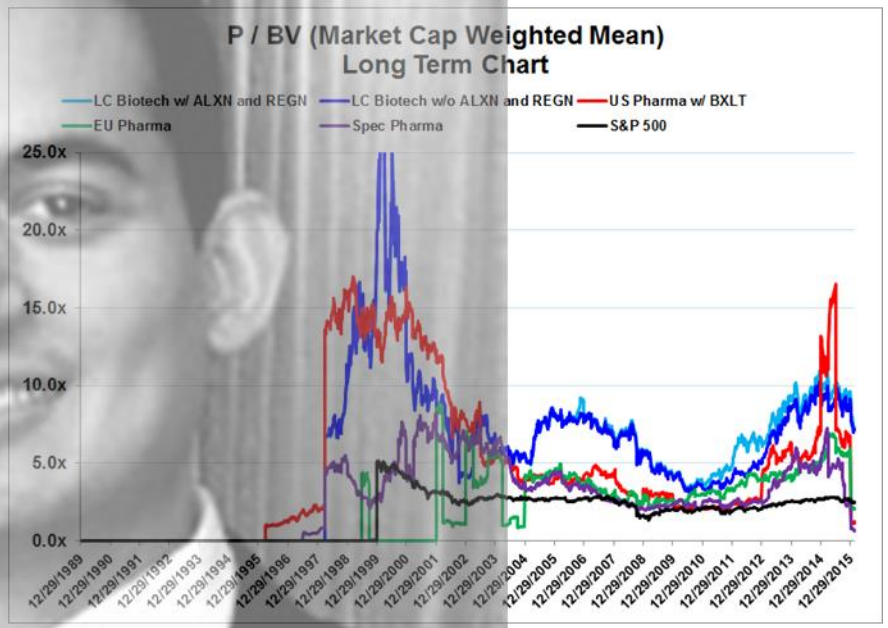
Here's a teaser:



Source: FactSet, Mizuho Research

Want more? … just let me know!





Sources: FactSet, Mizuho Research

Let's take a prospective look at biotech sector fundamentals ➔

salim.syed@us.mizuho-sc.com / W: (212) 205-7945 / C: (917) 301-9054

Prospective Look at Biotech Fundamentals

Sector fundamentals to think about …

- …how concerned should I be about all these drug pricing talks?
- …are drug pipelines healthy enough to create new sales?
- …is orphan drug spend increasing?
- …do we have a friendlier FDA today?
- …is R&D productivity increasing?
- …what will get the sector to rebound in the near-term?
- …how has biotech done historically when interest rates increase?

Let's go through these one by one ➔

Sector fundamentals to think about …

…how concerned should I be about all these drug pricing talks?

…are drug pipelines healthy enough to create new sales?

…is orphan drug spend increasing?

…do we have a friendlier FDA today?

…is R&D productivity increasing?

…what will get the sector to rebound in the near-term?

…how has biotech done historically when interest rates increase?

Many street observers deem Hillary's tweet as the turning point in biotech sentiment

- She put drug pricing on the table
- In a presidential election year, drug pricing is a very easy topic for candidates on both sides of the aisle to address
- This is especially easy to do when extreme examples like Shkreli's act arise

The discussions on drug pricing have been more intense and constant this year (than I've seen before) … so drug pricing talks can't be ignored in our view

- Seeing more comments come from CMS' Slavitt that pricing needs to be addressed
- Bernie Sander's recent tweet on insulin pricing
  - Novo and LLY both targeted by Bernie
- AMGN noted on it's 3Q'16 call that Enbrel will not see much net pricing benefit in 2017
- AGN's Brent Saunders recent "social contract" with patients
- Biosimilars seem to be become more common now … so biologics pricing now has a new element

We are also watching state government actions and state ballot proposals

- California Drug Price Act
  - This would mandate that CA state plans buy drugs at Department of Veteran Affairs prices
- Ohio Drug Price Relief Act
  - Similar to the CA act
- Some states like Massachusetts, Oregon and North Carolina are looking for ways to have drug companies disclose detailed cost / pricing information

State government actions could potentially stimulate a more heated national discourse on drug pricing essentially "forcing" the government to take action

But remember there are arguments to be made that solving this problem is not so simple

- Many players involved
- Significant legislative change usually requires continued congressional attention
- Multiple risks involved (here are a few):
  - PBMs/payors risk pushing away members who want access to drugs of their choice
  - Drug companies could theoretically shift jobs overseas to keep costs low
  - Threat to drug innovation
  - Threat to subsidized costs of medications in emerging markets

*"Exactly how we get to that in the political system that we have I think is complicated [in reference to drug price to R&D ratio], and **you may not be able to get there directly in a way that policy wonks would want."** – Ezekial Emanuel, UPenn Professor (via NYT)*

*"The ratio approach makes some sense as a tool to regulate pharmaceutical companies in an environment where it is difficult to attack price directly, says Dr. Peter Bach, the director of the center for health policy and outcomes at Memorial Sloan Kettering Cancer Center, and a vocal critic of many recent high prices attached to new cancer drugs. But he says he hopes the American system finds a way to measure and reward companies that provide medical value, **not just those that spend a lot on research.**" – Peter Bach, MSKCC (via NYT)*

We can use Hillary's proposal as an example and discuss why it's arguably ineffective as well ➔

Hillary's proposal specifically is arguably ineffective … let's discuss why ➔

(bear in mind, I'm not a Policy analyst)

HILLARY PROPOSAL
Medicare can negotiate drug prices
Reduce drug patent life
US can import drugs from price-controlled countries
Keep out-of-pocket costs <$250 / month

Hillary Proposal: Medicare can negotiate drug prices

WHY ARGUABLY INEFFECTIVE

Medicare Part D already has private-sector negotiation that stimulates natural competition. Medicare Part D was in fact designed to allow for this competition to limit drug spend.

Many regard Medicare already successful given costs are already lower than initial CMS projections.

Seniors may have to supplement their Medicare with additional insurance if formularies get narrowed in the negotiation process, which would require the law to change.

Drug companies can at least theoretically still raise price to counter any “negotiated” rebate.

In the past, Republicans haven’t been supportive of this idea

Hillary Proposal: Reduce drug patent life

WHY ARGUABLY INEFFECTIVE

Could reduce incentive for innovation leading to long-term health consequences and potential political backlash.

Also drug companies can just raise price to counter any “negotiated” rebates.

Hillary Proposal: Drug importation and keep out-of-pocket costs <$250 / month

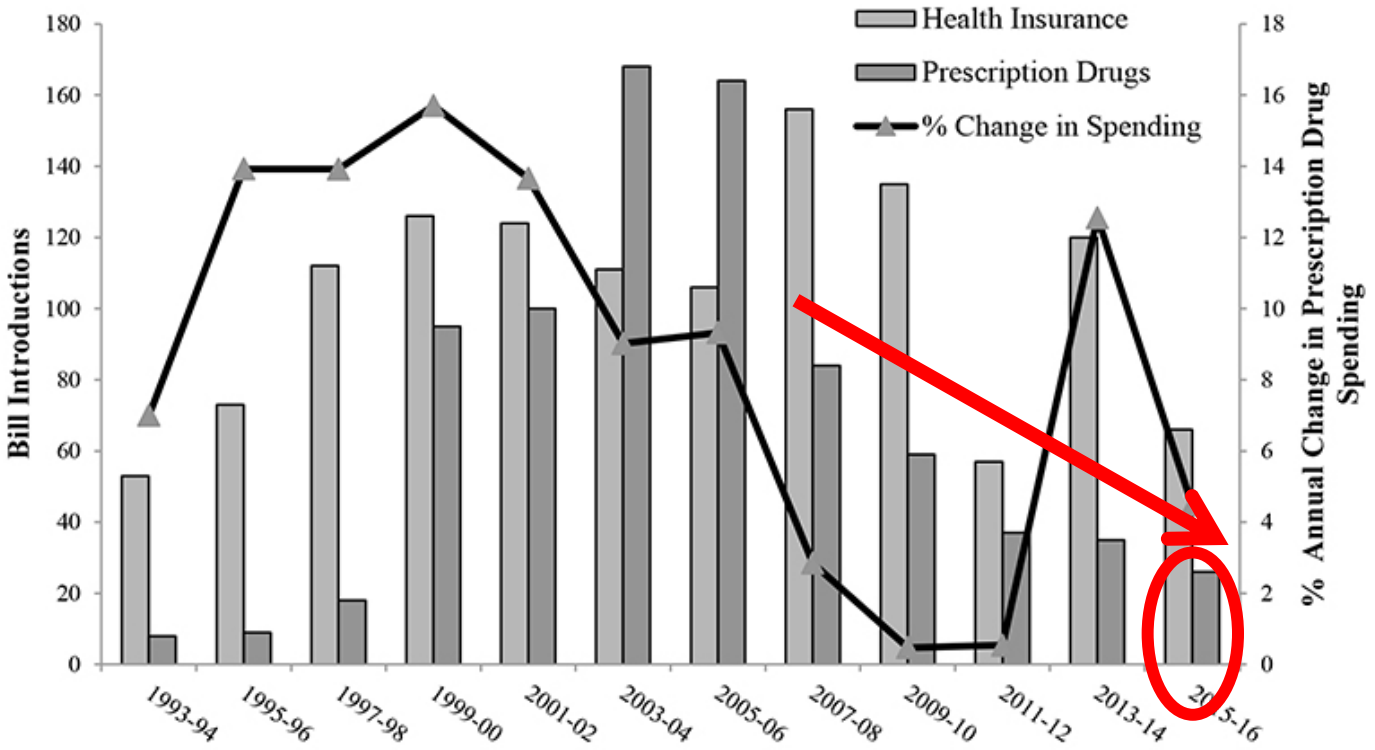
HILLARY PROPOSAL	WHY ARGUABLY INEFFECTIVE
US can import drugs from price-controlled countries	Potential supply issues given the US is a fairly large country
Keep out-of-pocket costs <$250 / month	Could in turn just increase insurance premiums

Even the CBO believes that allowing Medicare to negotiate drug prices will not accomplish much

"Some policymakers have proposed applying Medicaid's statutory rebates to drug purchases made by Part D beneficiaries who receive low-income subsidies (while retaining the existing structure of Part D in other respects). CBO expects that adopting such a policy would lower the average cost of brand-name drugs in Part D and thus reduce the federal government's costs over the first decade after the policy was adopted. But a substantial portion of those savings would probably erode over time because drug manufacturers would counter the larger rebates by raising the prices for new brand-name drugs."

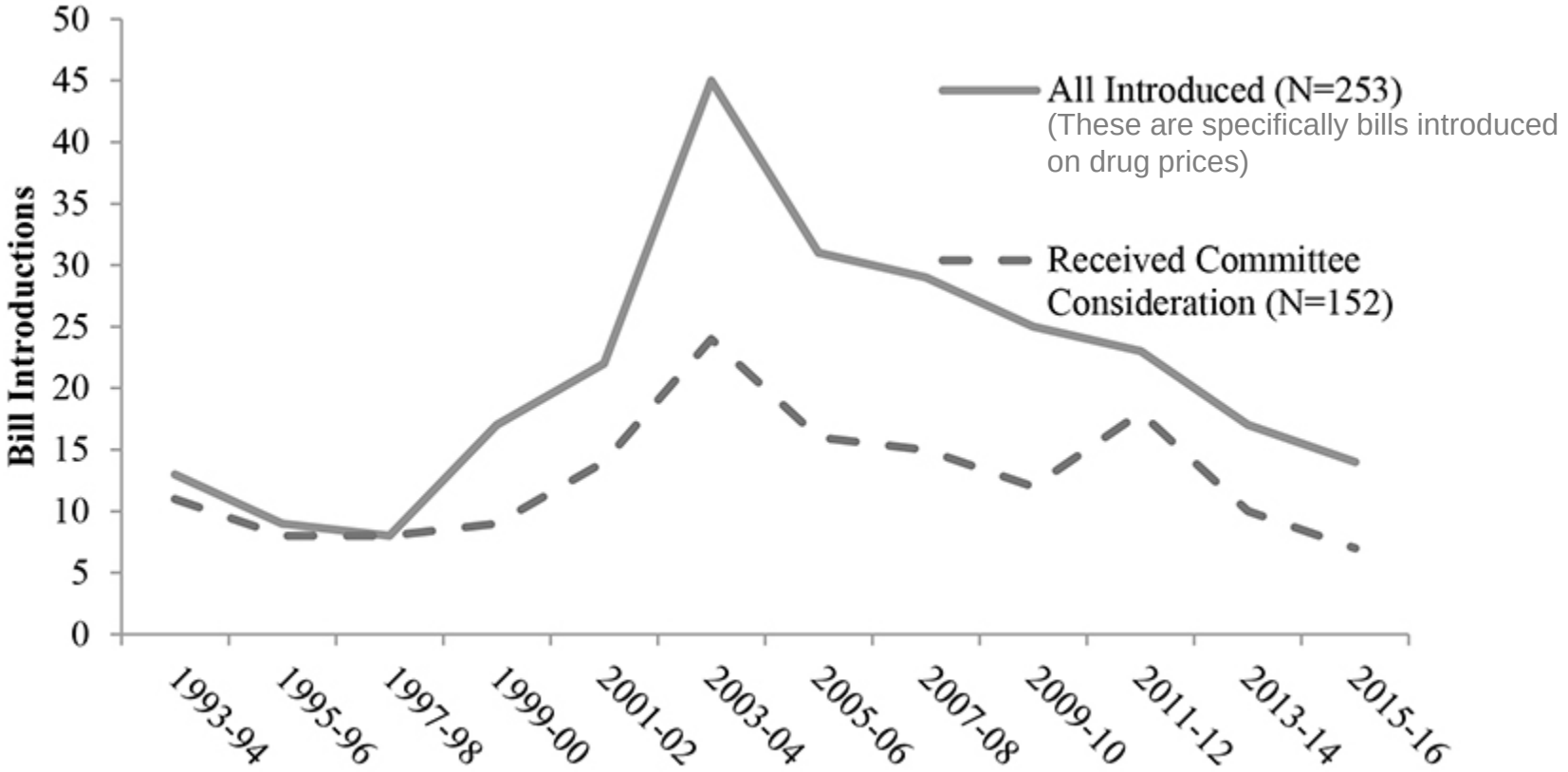
- Congressional Budget Office, July 2014

Additionally, prescription drug bills have declined significantly even in 2015 despite the noise in the political arena



Sources: Health Affairs, Mizuho Research

And only about ½ of them receive formal consideration by a congressional committee



Sources: Health Affairs, Mizuho Research

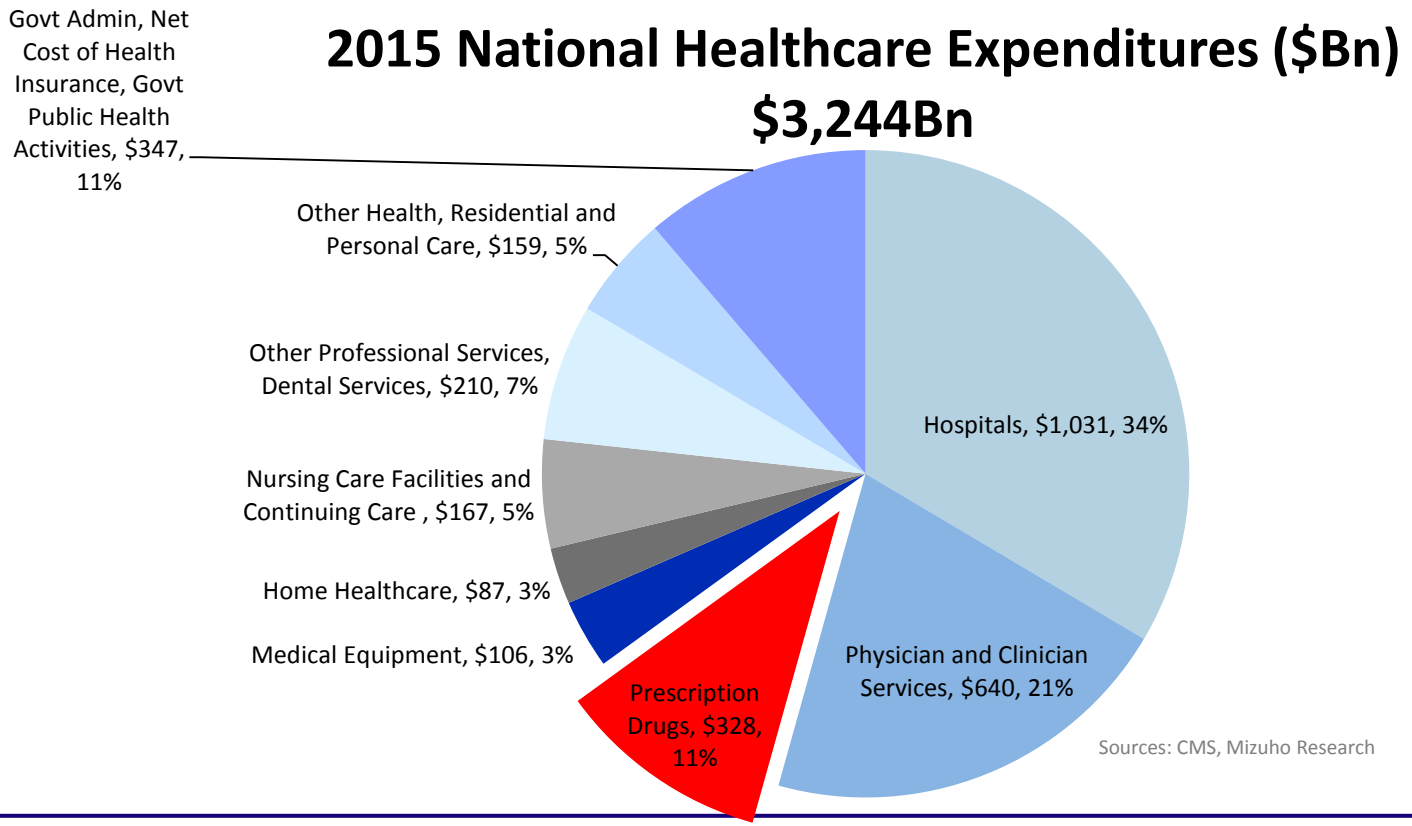
Moreover, the current bills in Congress that actually introduce lower NET drug prices have only come from Democrats or Independents … the 3 Republican bills just ask for "enhanced oversight or transparency"

Title	Sponsor	Part D Price Negotiation (N=6)	Mfr. Rebates (N=4)	Allows Imports (N=2)	Prohibits "Pay for Delay" (N=3)	Enhanced Oversight or Transparency (N=6)
Medicare Prescription Drug Price Negotiation Act of 2015 (HR 3061)	Welch (D-VT)	X				
Medicaid Generic Drug Price Fairness Act of 2015 (HR 2391)	Cummings (D-MD)		X			
Medicare Prescription Drug Price Negotiation Act of 2015 (S 31)	Klobuchar (D-MN)	X				
FEHBP Prescription Drug Oversight and Cost Savings Act (HR 2175)	Lynch (D-MA)					X
Medicare Prescription Drug Savings and Choice Act of 2015 (HR 3261)	Schakowsky (D-IL)	X				
Medicare Prescription Drug Savings and Choice Act of 2015 (S 1884)	Durbin (D-IL)	X				
Prescription Drug Affordability Act of 2015 (HR 3513)	Cummings (D-MD)	X	X	X	X	X
Preserve Access to Affordable Generics Act (S 2019)	Klobuchar (D-MN)				X	
Medicaid Generic Drug Price Fairness Act of 2015	Sanders (I-VT)		X			
Prescription Drug Affordability Act of 2015 (S 2023)	Sanders (I-VT)	X	X	X	X	X
MAC Transparency Act (HR 244)	Collins (R-GA)					X
Departments of Labor, Health and Human Services, and Education, and Related Agencies Appropriations Act, 2016 (S 1695)	Blunt (R-MO)					X
An Act Making Appropriations to Stop Regulatory Excess and for Other Purposes, 2016 (S 2132)	Cochran (R-MS)					X

Republican bills from the 114th congress

Sources: Health Affairs, Mizuho Research

Remember, we have to keep it in perspective … drug spend is only ~10% overall national health expenditures



Sources: CMS, Mizuho Research

To be clear, we do think that drug pricing is a risk (now more than before) to the sector … but we don't think that this problem will be solved overnight … we think if anything it'll be a gradual process

- **What** gets tweaked and **when**, it's not clear
- But given there are so many parties involved and a lot a stake politically and practically (i.e. no one wants to be responsible for slowing down drug innovation) … **we believe that this will be more likely than not an iterative process**

Sector fundamentals to think about …

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…what will get the sector to rebound in the near-term?

…how has biotech done historically when interest rates increase?

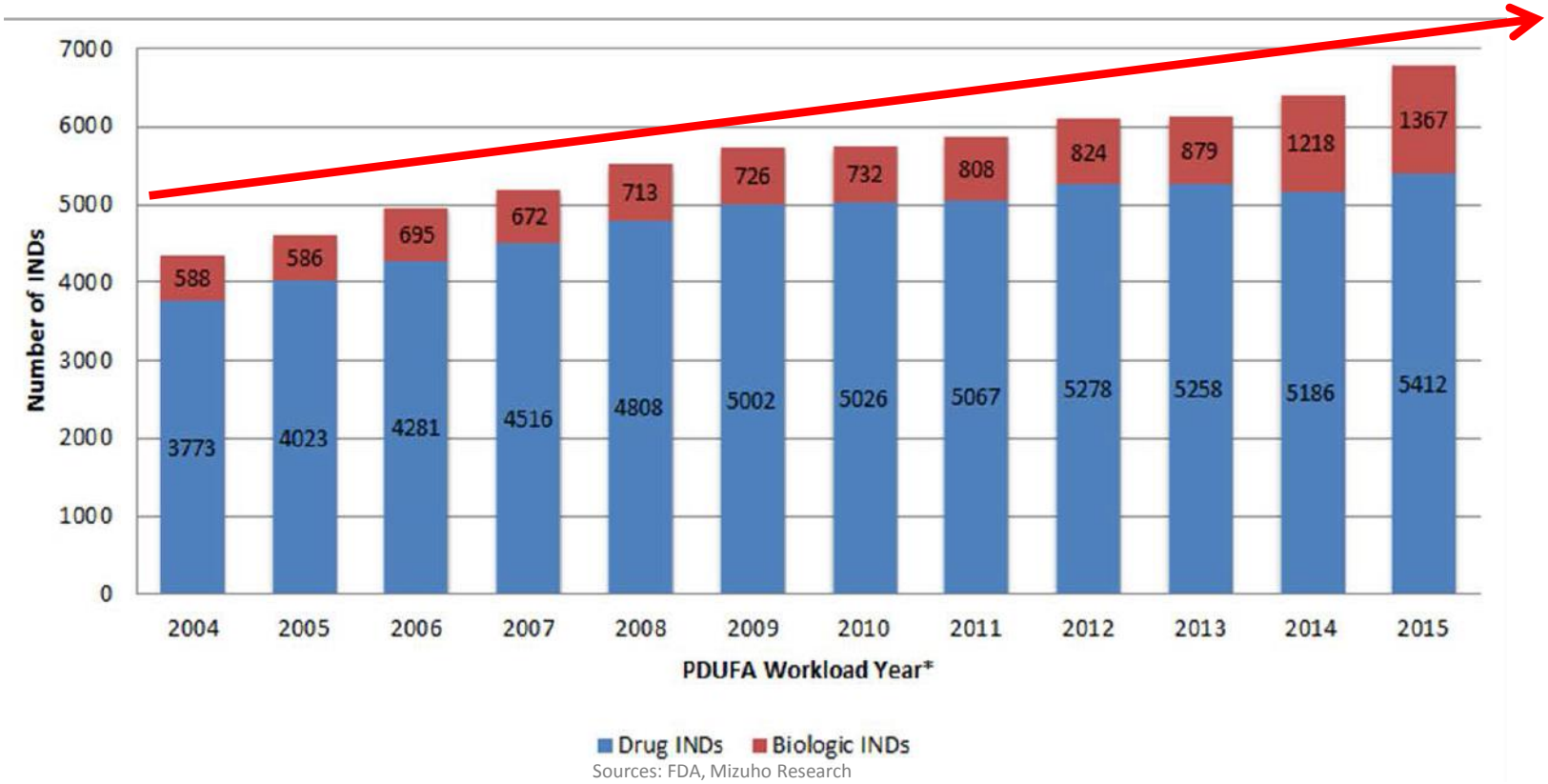
There are over 7,000 unique drugs globally in development today

Selected Diseases	Medicines in Development*
Cancers	1,813
Cardiovascular disorders	599
Diabetes	475
HIV/AIDS	159
Immunological disorders	1,120
Infectious diseases	1,256
Mental health disorders	511
Neurological disorders	1,329

*Defined as single products which are counted exactly once regardless of the number of indications pursed

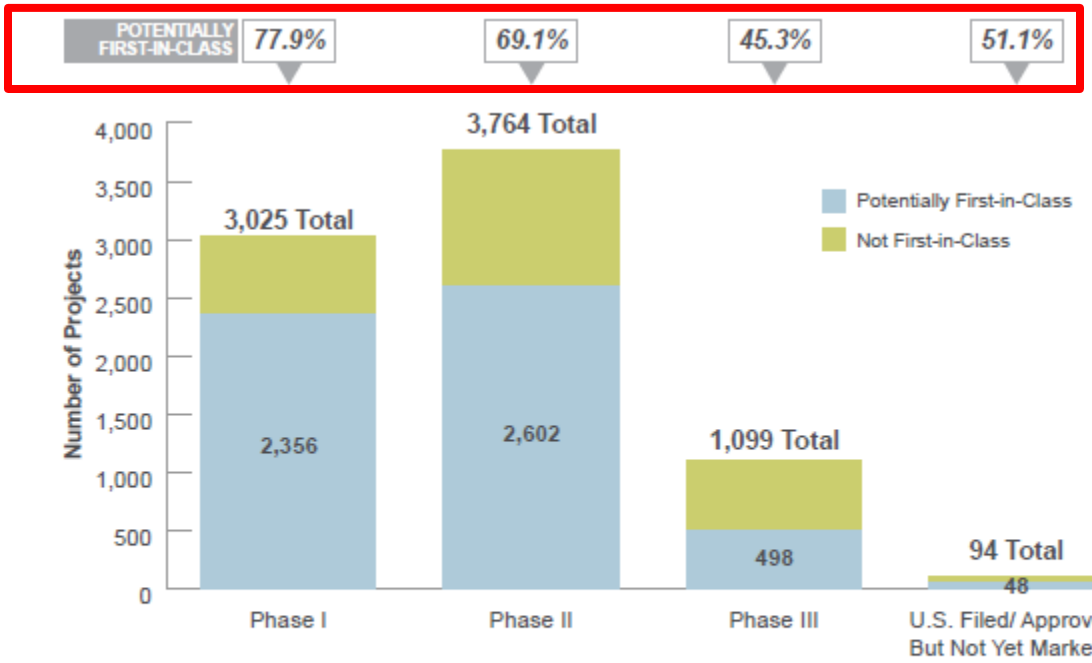
Source: Adis R&D Insight Database. Accessed February 2015.

This is more than we have seen in previous years



Sources: FDA, Mizuho Research

About 2/3 of them are potentially first-in-class medicines



Notes: Projects are limited to NMEs, as defined by EvaluatePharma. U.S. Filed/Approved But Not Yet Marketed phase projects must have a reported FDA approval date. Filed projects limited to those filed with the FDA. First-in-class defined as projects with a pharmacological class that is different from that of any marketed project/product (e.g., PPAR agonist, somatostatin antagonist, etc.) – EvaluatePharma lists 3,600+ unique "pharmacological classes." Counts by phase may include a limited number of duplicates due to co-promotion/co-development of products.

Source: Authors' calculations, using EvaluatePharma data.
Sources: Analysis Group, Mizuho Research

If “first-in-class” is a proxy for innovation, let’s try to dig into a couple therapeutic areas that have the most shots on goal

Cancer and Neurology have the most potential first-in-class "projects"

- Projects here just means unique NME-indication combinations
- About 80% of the projects for both cancer and neurology are first-in-class

Therapeutic Area	Number of Potential First-in-Class Projects by Phase					Total Potential First-in-Class Projects	Total Projects
	Preclinical / Research Project	Phase I	Phase II	Phase III	U.S. Filed / Approved But Not Yet Marketed		
Blood	137	34	52	9	2	234	373
Cancer Total	2,103	1,057	1,043	149	6	4,358	5,473
Cancer, Blood	*200*	*211*	*189*	*25*	*2*	*627*	*818*
Cancer, Miscellaneous cancer	*817*	*107*	*42*	*6*	*1*	*973*	*1,123*
Cancer, Solid tumors, Bladder	*20*	*9*	*10*	*3*	-	*42*	*56*
Cancer, Solid tumors, Breast	*103*	*37*	*83*	*7*	-	*230*	*302*
Cancer, Solid tumors, Colorectal	*71*	*41*	*58*	*11*	*1*	*182*	*226*
Cancer, Solid tumors, Lung	*83*	*54*	*109*	*18*	-	*264*	*350*
Cancer, Solid tumors, Melanoma	*51*	*49*	*65*	*10*	*1*	*176*	*193*
Cancer, Solid tumors, Prostate	*106*	*43*	*54*	*8*	-	*211*	*283*
Cancer, Solid tumors, Other	*652*	*506*	*433*	*61*	*1*	*1,653*	*2,122*
Cardiovascular	382	112	178	37	3	712	884
Diabetes	302	78	99	17	3	499	630
Gastrointestinal	168	58	85	28	3	342	481
Hepatic & biliary	43	18	21	1	-	83	112
HIV & related conditions	103	47	31	5	-	186	269
Hormone	12	2	6	2	-	22	40
Immunology	558	98	71	17	1	745	1,045
Infections	748	182	171	42	13	1,156	2,045
Miscellaneous	324	83	46	25	6	484	656
Musculoskeletal	367	80	116	26	1	590	738
Neurology	926	218	202	38	3	1,387	1,653
Psychiatry	152	66	92	21	-	331	417
Reproduction	50	18	26	12	-	106	200
Respiratory	322	86	141	28	1	578	770
Sensory organs	291	35	86	18	3	433	525
Skin	150	45	92	14	2	303	529
Surgery	28	10	13	3	1	55	72
Urinary tract	64	29	31	6	-	130	160
Total Potential First-in-Class Projects	7,230	2,356	2,602	498	48	12,734	
Total Projects	9,090	3,025	3,764	1,099	94		17,072

Notes: Projects are limited to NMEs, as defined by EvaluatePharma. U.S. Filed/Approved But Not Yet Marketed phase projects must have a reported FDA approval date. Filed projects limited to those filed with the FDA. First-in-class defined as project with a pharmacological class that is different from that of any marketed project/product (e.g., PPAR agonist, somatostatin antagonist, etc.) – EvaluatePharma lists 3,600+ unique "pharmacological classes." Counts by phase may include a limited number of duplicates due to co-promotion/co-development of products. Diabetes originally classified under "hormone" class.

Source: Authors' calculations, using EvaluatePharma data.

Sources: Analysis Group, Mizuho Research

Let's first discuss cancer ➔

Cancer cases are expected to double globally by 2050

"Cancer is rapidly becoming a global pandemic, with incidence and death rates rising in low- and middle-income countries. In **2007**, there were an estimated **12 million new cancer cases** and **7.6 million cancer deaths** globally. By **2050**, the global cancer burden is expected to grow to **27 million new cancer cases** and **17.5 million cancer deaths** per year."

- Cancer.org

Current medications have already decreased death rates (and increased life spans)

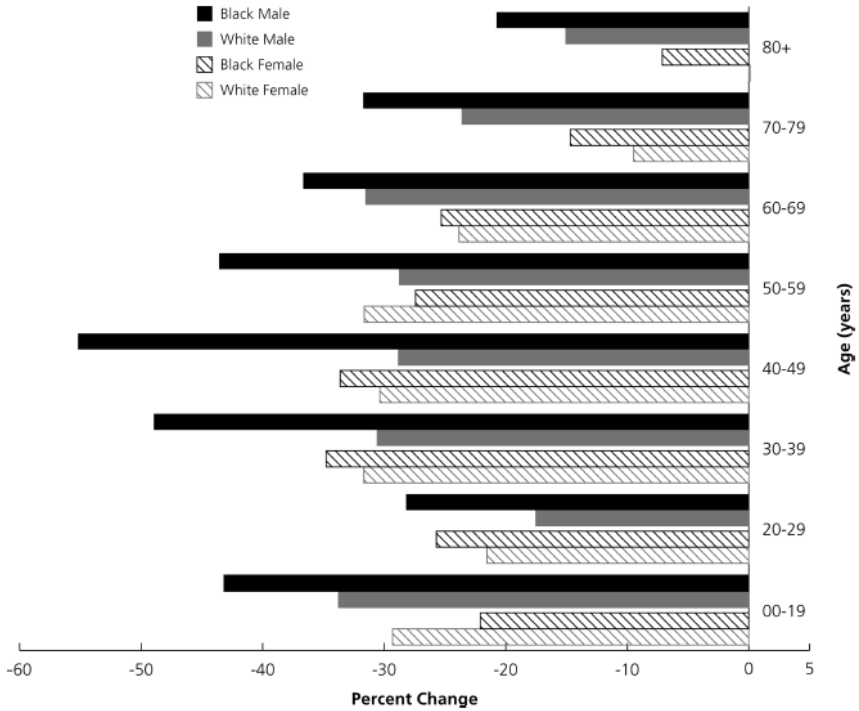
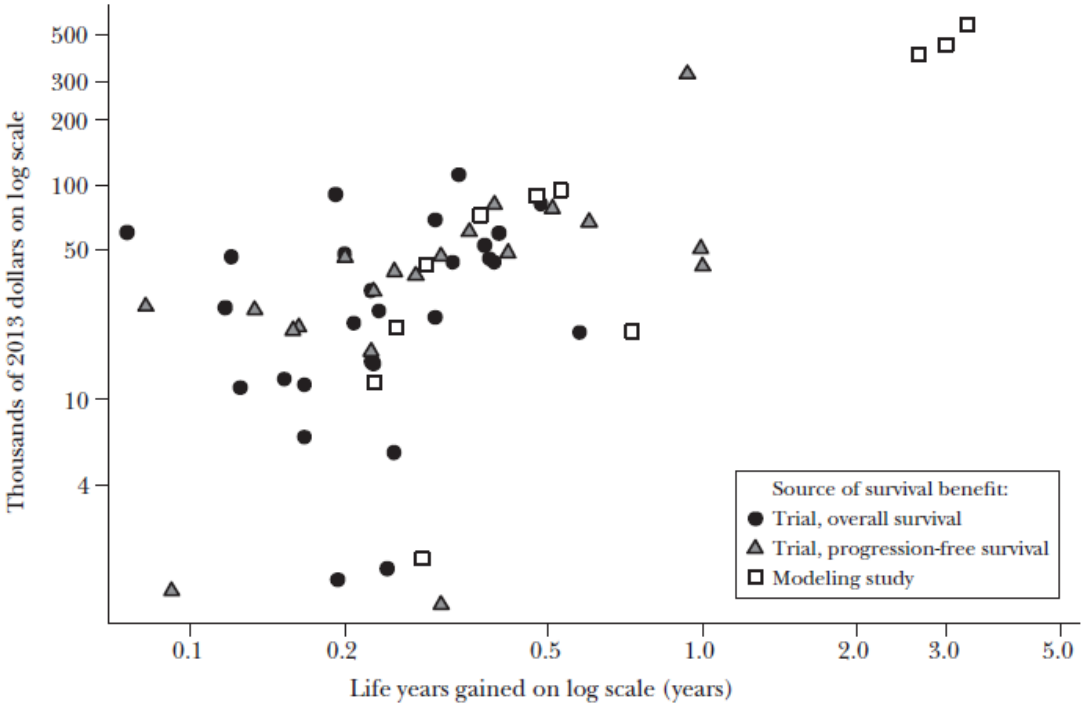


FIGURE 5. Relative Decline in Cancer Death Rates From 1991 to 2010 by Age, Race, and Sex.
The relative decline is the difference between the 2010 and 1991 rate expressed as a percentage of the 1991 rate.

Source: PubMed, Mizuho Research

Cancer patients are willing to pay for life

Figure 1
Drug Prices versus Life Years Gained

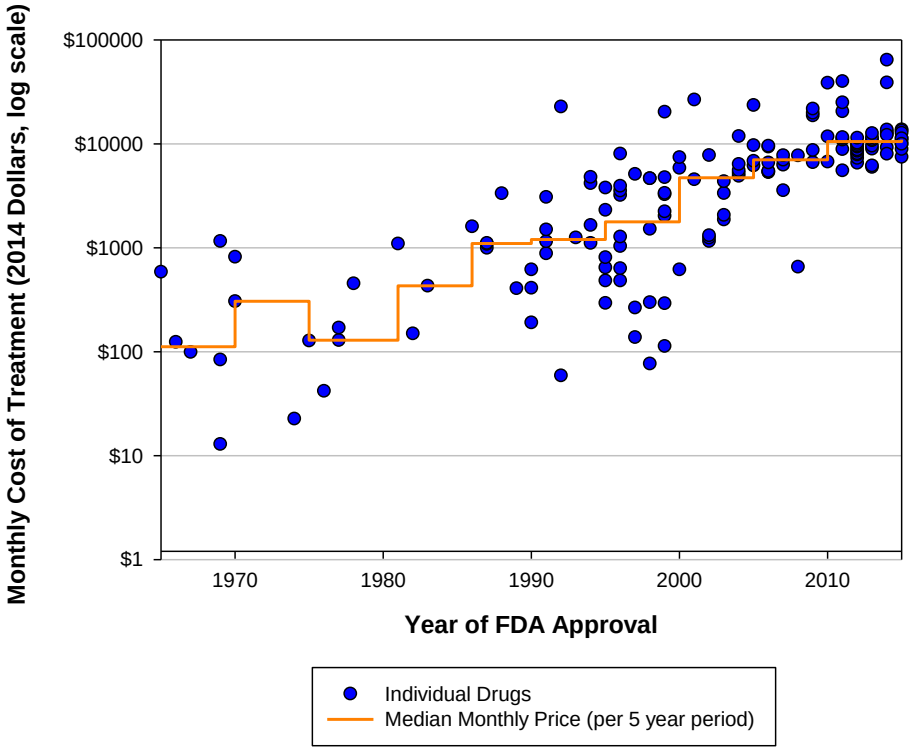


Source: Journal of Economic Perspectives, Winter 2015

Cancer drug prices continue to increase with time

Monthly and Median Costs of Cancer Drugs at the Time of FDA Approval

1965-2015



Source: Peter B. Bach, MD, Memorial Sloan-Kettering Cancer Center

Cancer pricing is protected by Medicare Part B

Given these concerns, it is worth assessing why cancer-drug prices and spending have risen so quickly. I believe the growth can be attributed primarily to a unique legislative and regulatory framework that shields cancer drugs (as well as a few other specialty drugs) from the strategies that health care payers such as Medicare typically use to hold down the price and utilization of drugs and other health care goods.

age restrictions to limit utilization. For cancer drugs that are covered under Part B, which are generally drugs that are administered in a physician's office, the law requires Medicare to cover any drug used in an "anticancer chemotherapeutic regimen," as long as the use is "for a medically accepted indication" (Table 2). The law defines

ity. Medicare has several strategies that counterbalance this profit-seeking behavior. But for cancer drugs and some other high-priced specialty drugs, these strategies have been disabled by laws and regulations that specifically constrain Medicare from making use of flexibilities that it has in other settings.

Source: NEJM 2009, Mizuho Research

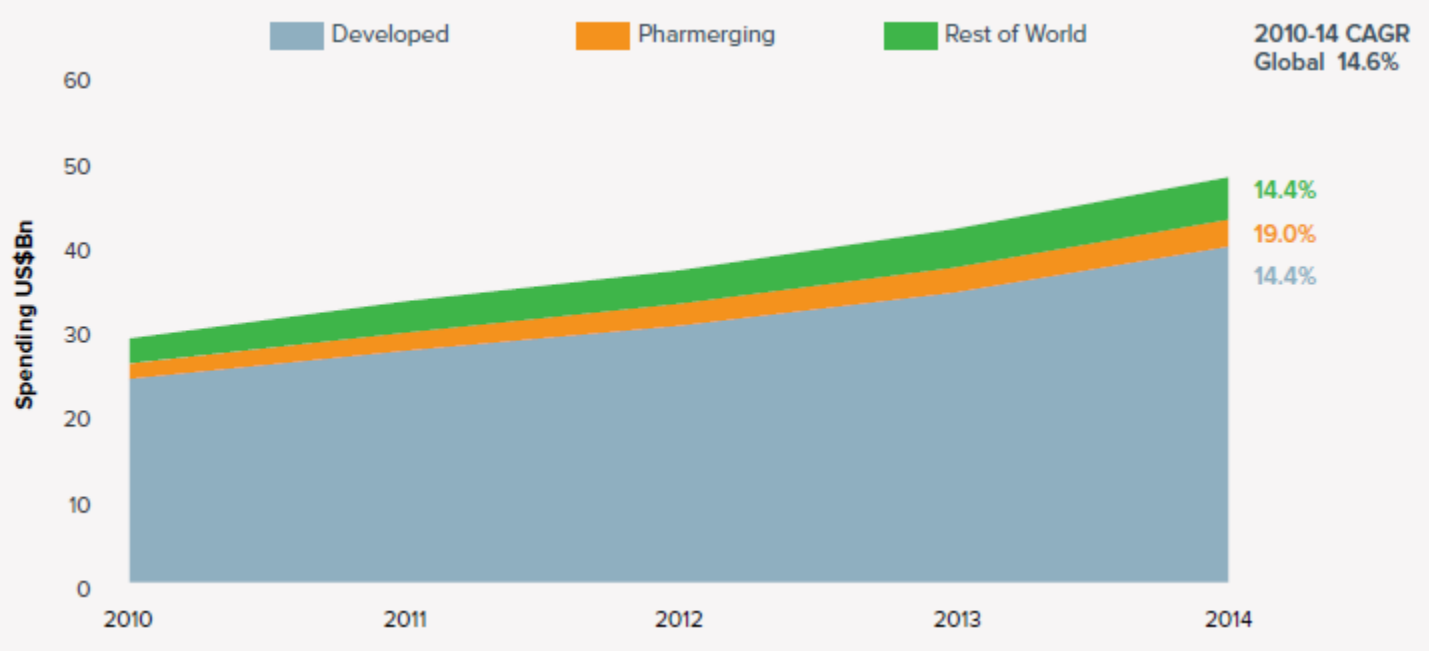
And this isn't that easy to change

Policymakers are now in a quandary. To be sure, they are worried both by the increased total costs of cancer care and by the fact that high prices are leading to higher out-of-pocket expenses for patients. Yet, it is difficult for them to discount the progress that has been made overall in the treatment of cancer and to wholly disassociate that from the high prices that innovative cancer treatments are able to capture. Progress that has

Some health economists argue for a causal link between high prices and the pace of innovation, which would suggest that efforts to reduce spending on cancer drugs would retard the pace of innovation.[27-29]

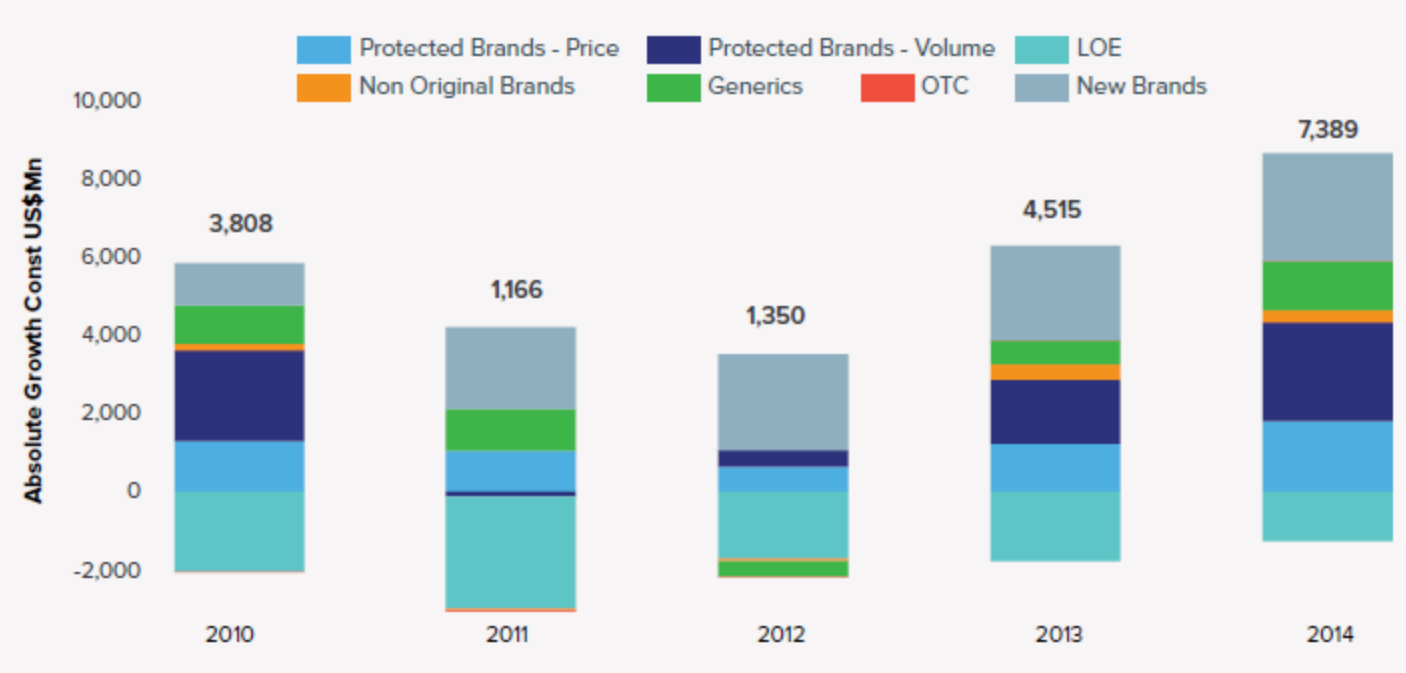
Source: NEJM 2009, Mizuho Research

Targeted cancer therapy sales have grown at a ~15% CAGR the last 4 years



Source: IMS, Mizuho Research

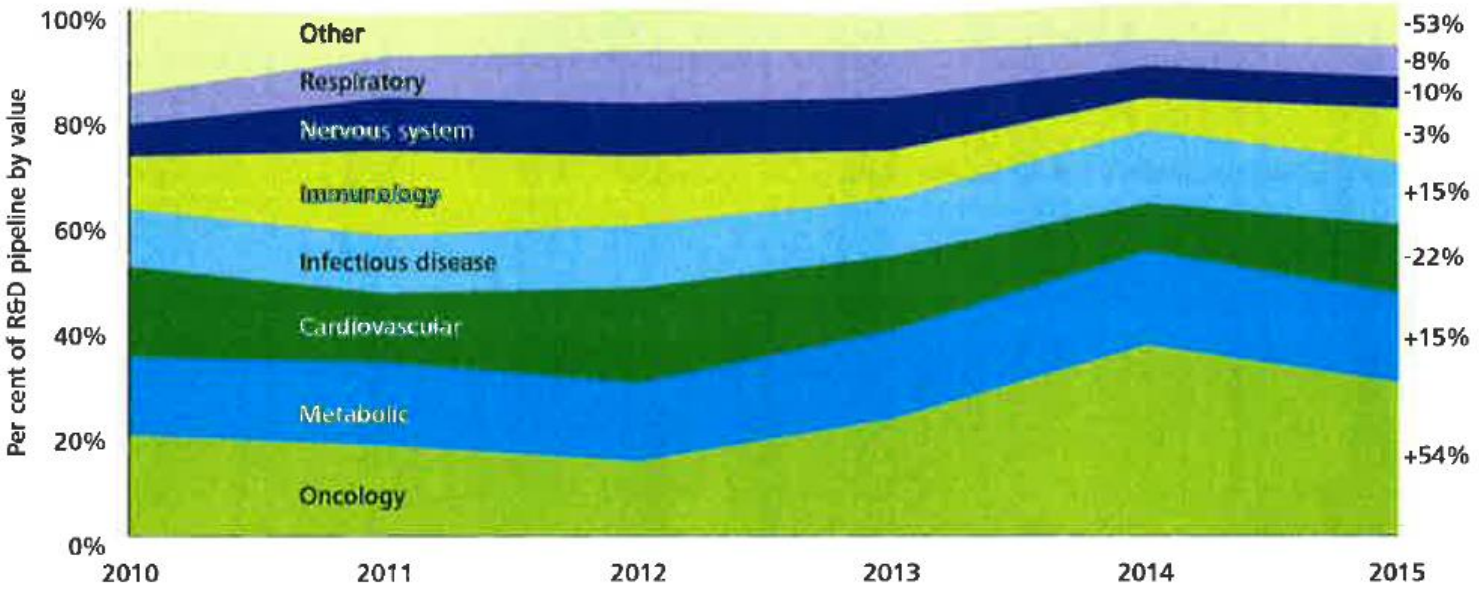
Interestingly enough most of this growth is due to new brands and volume, not price – so even if pricing policies were to change, cancer would appear to still remain a high growth area



Source: IMS, Mizuho Research

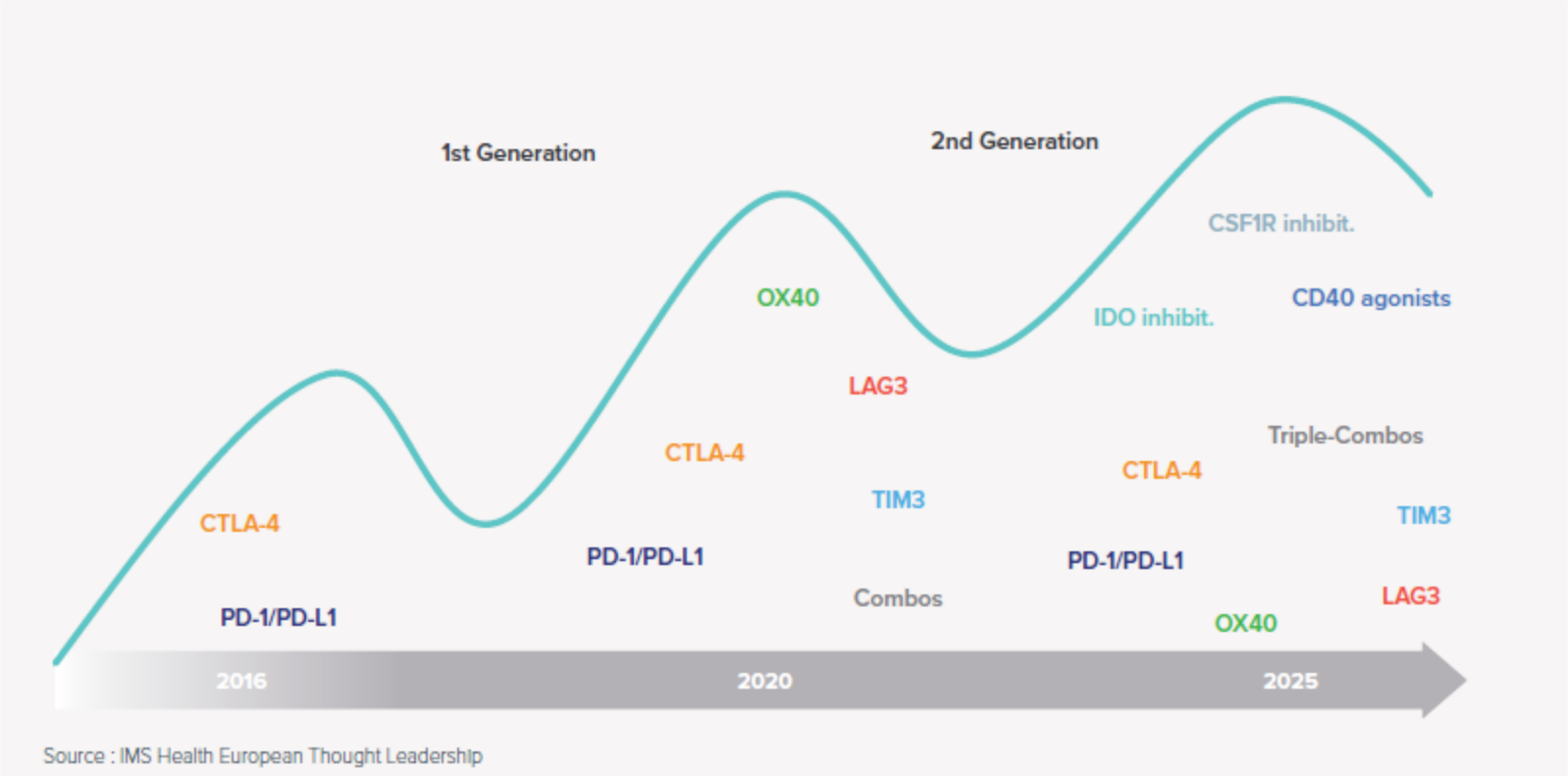
Oncology pipeline value has increased over time

Figure 7. Risk-adjusted pipeline value by therapeutic area, 2010-15



Note: Percentages reflect relative change in 2010 to 2015 pipeline composition
Source: Deloitte LLP

The emerging classes of cancer therapies are only growing



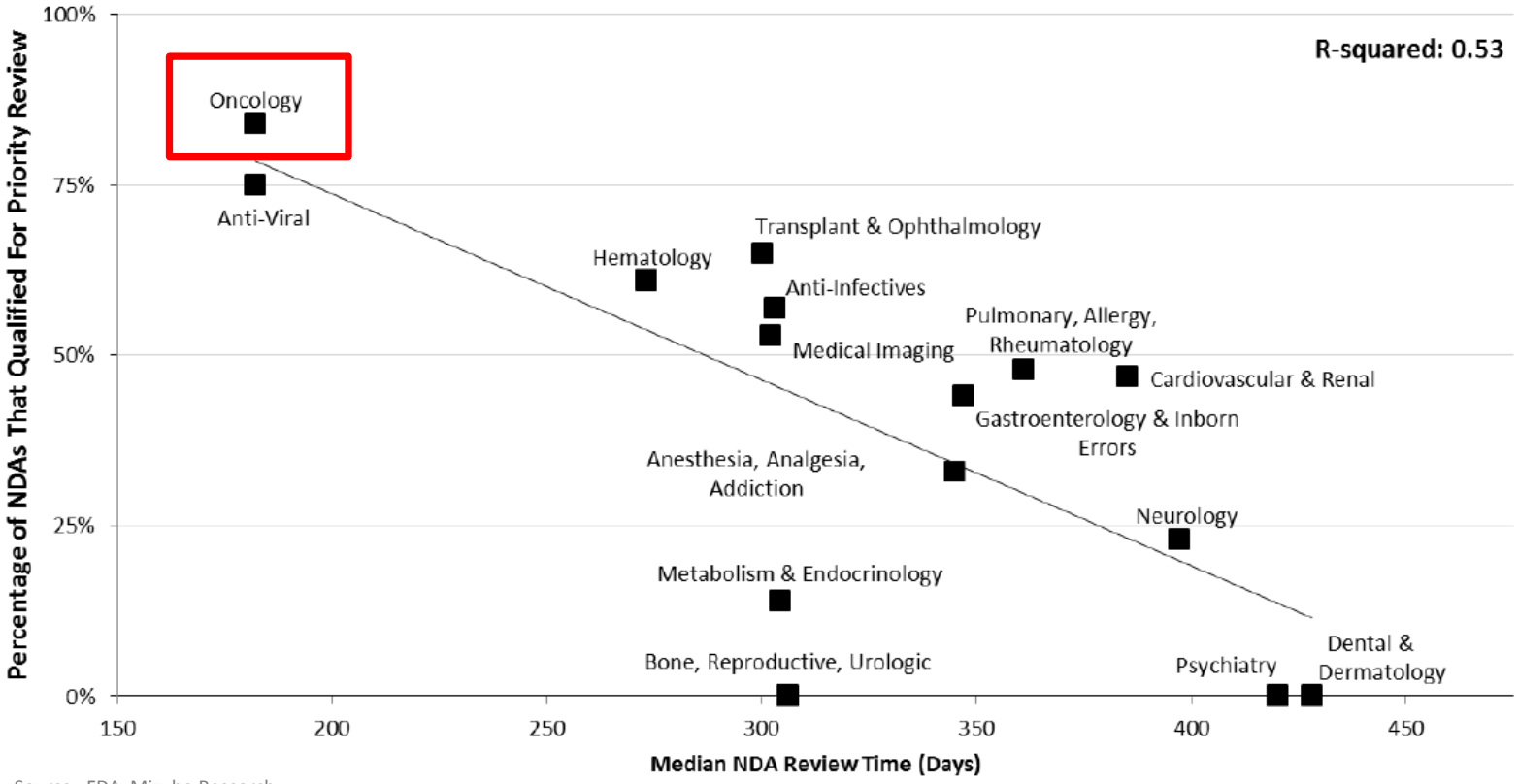
Source : IMS Health European Thought Leadership

And the pipeline is robust at all stages of development so it seems more likely than not to support a growth trend

	Number of Potential First-in-Class Projects by Phase				
Therapeutic Area	Preclinical / Research Project	Phase I	Phase II	Phase III	U.S. Filed / Approved But Not Yet Marketed
Blood	137	34	52	9	2
Cancer Total	2,103	1,057	1,043	149	6

Source: Analysis Group, Mizuho Research

The drugs that make it to an NDA should benefit from a short FDA review cycle vs drugs from other disease areas



Source: FDA, Mizuho Research

Cancer drugs should also benefit from FDA's Breakthrough Therapy Designation

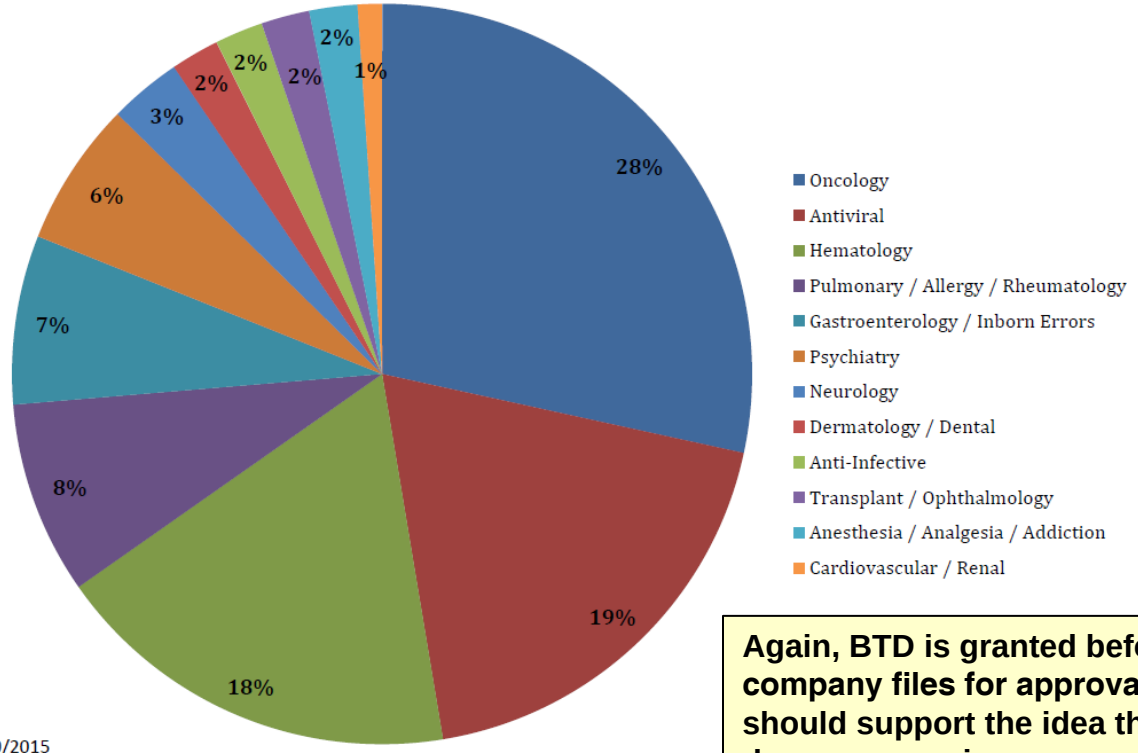
"On July 9, 2012 the Food and Drug Administration Safety and Innovation Act (FDASIA) was signed. FDASIA Section 902 provides for a new designation - Breakthrough Therapy Designation. A breakthrough therapy is a drug:

- intended alone or in combination with one or more other drugs to treat a serious or life threatening disease or condition and
- **preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies** on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development.

If a drug is designated as breakthrough therapy, FDA will expedite the development and review of such drug. All requests for breakthrough therapy designation will be reviewed within 60 days of receipt, and FDA will either grant or deny the request."

Source: FDA, Mizuho Research

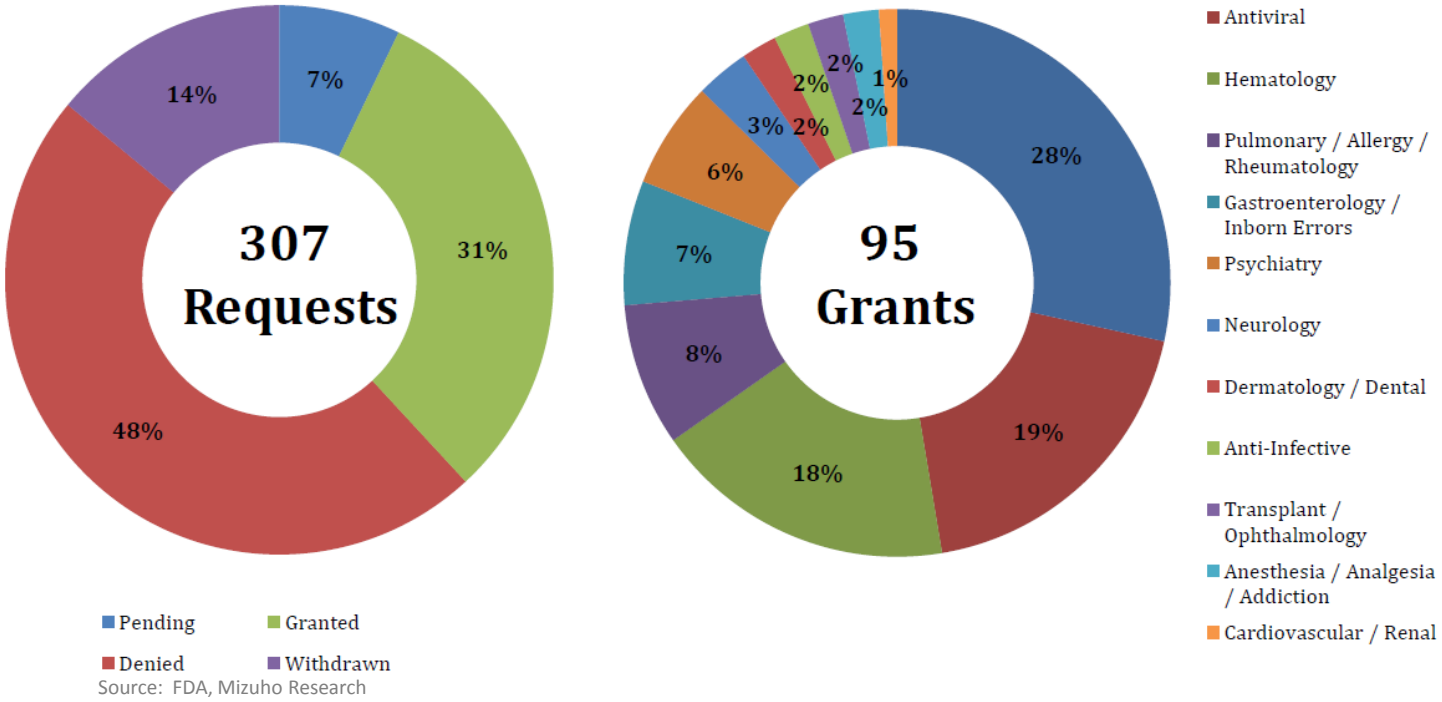
Cancer drugs have been granted the most breakthrough therapy designations since the inception of the program



)/2015
Source: FDA, Mizuho Research

Again, BTD is granted before the drug company files for approval … so this chart should support the idea that newer cancer drugs are coming

Bear in mind only 30% of BTD applications are granted … so the hurdle to get the designation is high



Source: FDA, Mizuho Research

Part of this story is also that the FDA's oncology chief's wife died of cancer … and he has evolved from "regulator" to "regulator-advocate"

F.D.A. Regulator, Widowed by Cancer, Helps Speed Drug Approval

By GARDINER HARRIS JAN. 2, 2016

Dr. Richard Pazdur, the Food and Drug Administration's oncology chief, at his home in Bethesda, Md., in November, two weeks before his wife died of cancer. Gabriella Demczuk for The New York Times

Source: NYT, Mizuho Research

Various efforts like Cancer Moonshot 2020 founded by renowned healthcare billionaire Dr. Patrick Soon-Shiong should also help new therapies come to market

LAUNCHING THE MOONSHOT FOR CANCER 2020

Announcing the Lift Off of Cancer MoonShot 2020
January 12, 2016

HISTORIC NATIONAL COALITION FORMED TO ACCELERATE NEXT GENERATION IMMUNOTHERAPY IN CANCER

LARGE PHARMA, BIOTECH, MAJOR PAYER, FORTUNE 50 COMPANY, ACADEMIA AND COMMUNITY ONCOLOGISTS JOIN FORCES TO ANNOUNCE LAUNCH OF CANCER MOONSHOT 2020 PROGRAM

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Cancer MoonShot 2020
RT @nanthealth: Some of best clinical therapies are available in #clinicaltrials. Need to expand patient access. -Jennifer Levin Carter I #CancerCenter
16 hours ago

Cancer MoonShot 2020
RT @nanthealth: .@DrPatSoonShiong's #CancerMoonShot 2020 & The National Immunotherapy Coalition keynote @BIOCOMCA about to begin. https://t.co/bCAAfMEBUT

Source: http://www.cancermoonshot2020.org/

And it doesn't hurt to have support from the federal government

Obama Takes First Step in a Cancer 'Moonshot'

By MICHAEL D. SHEAR JAN. 28, 2016

President Obama arriving at Walter Reed National Military Medical Center on Monday. Zach Gibson/The New York Times

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WASHINGTON — President Obama signed a presidential memorandum on Thursday creating a White House task force on cancer, the first step in what Vice President Joseph R. Biden Jr. has called a "moonshot" to cure the disease, administration officials said.

The president appointed Mr. Biden to lead the panel, which will include representatives from at least 13 government agencies. The group's first meeting will be on Monday, officials said.

Source: NYT, Mizuho Research

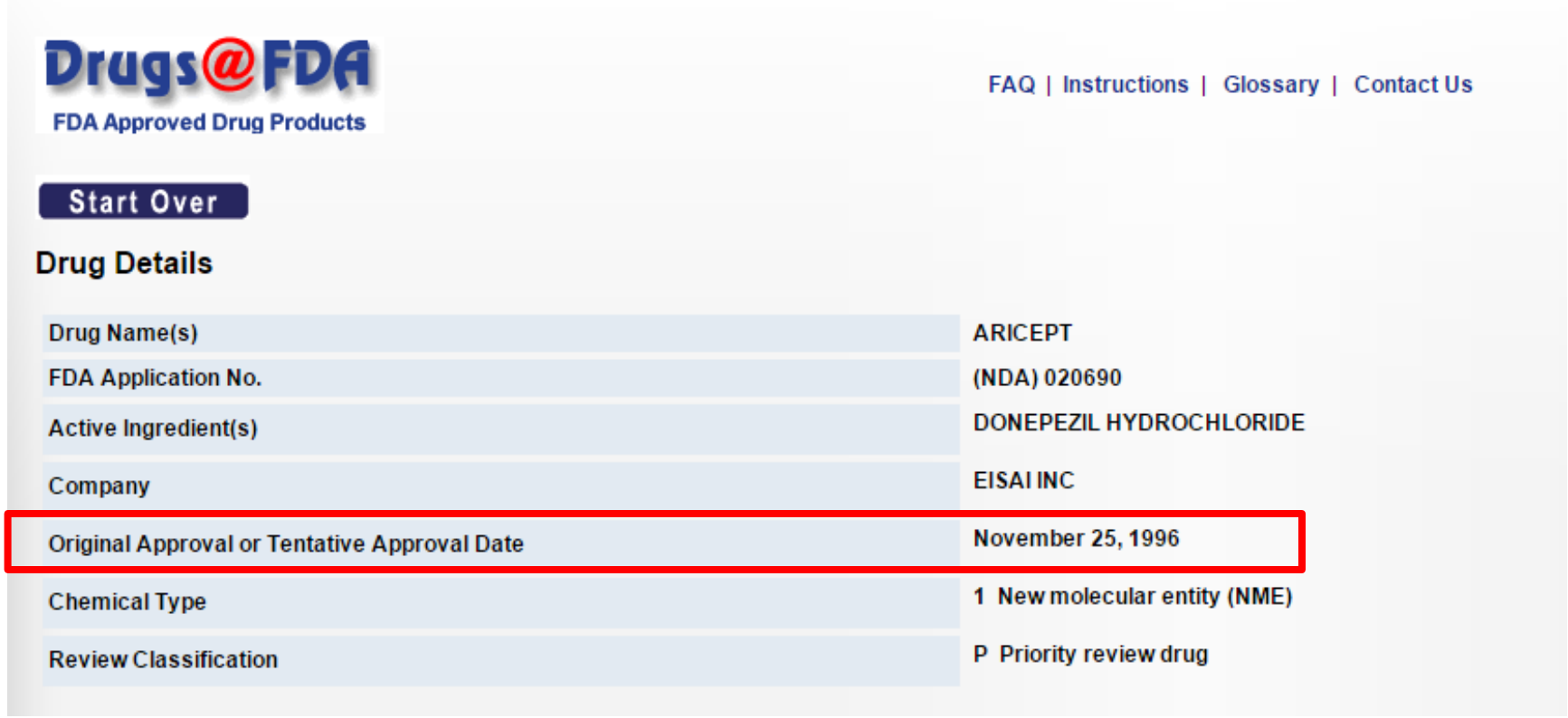
Now let's discuss Alzheimer's ➔

By 2050, Alzheimer's prevalence in the US may nearly triple

"An estimated 5.3 million Americans of all ages have Alzheimer's disease in 2015. By 2025, the number of people age 65 and older with Alzheimer's disease is estimated to reach 7.1 million — a 40 percent increase from the 5.1 million age 65 and older affected in 2015. **By 2050, the number of people age 65 and older with Alzheimer's disease may nearly triple, from 5.1 million to a projected 13.8 million**."

- Alz.org

The standard of care, Aricept, was approved 20 years ago … Alzheimer's disease needs new therapies



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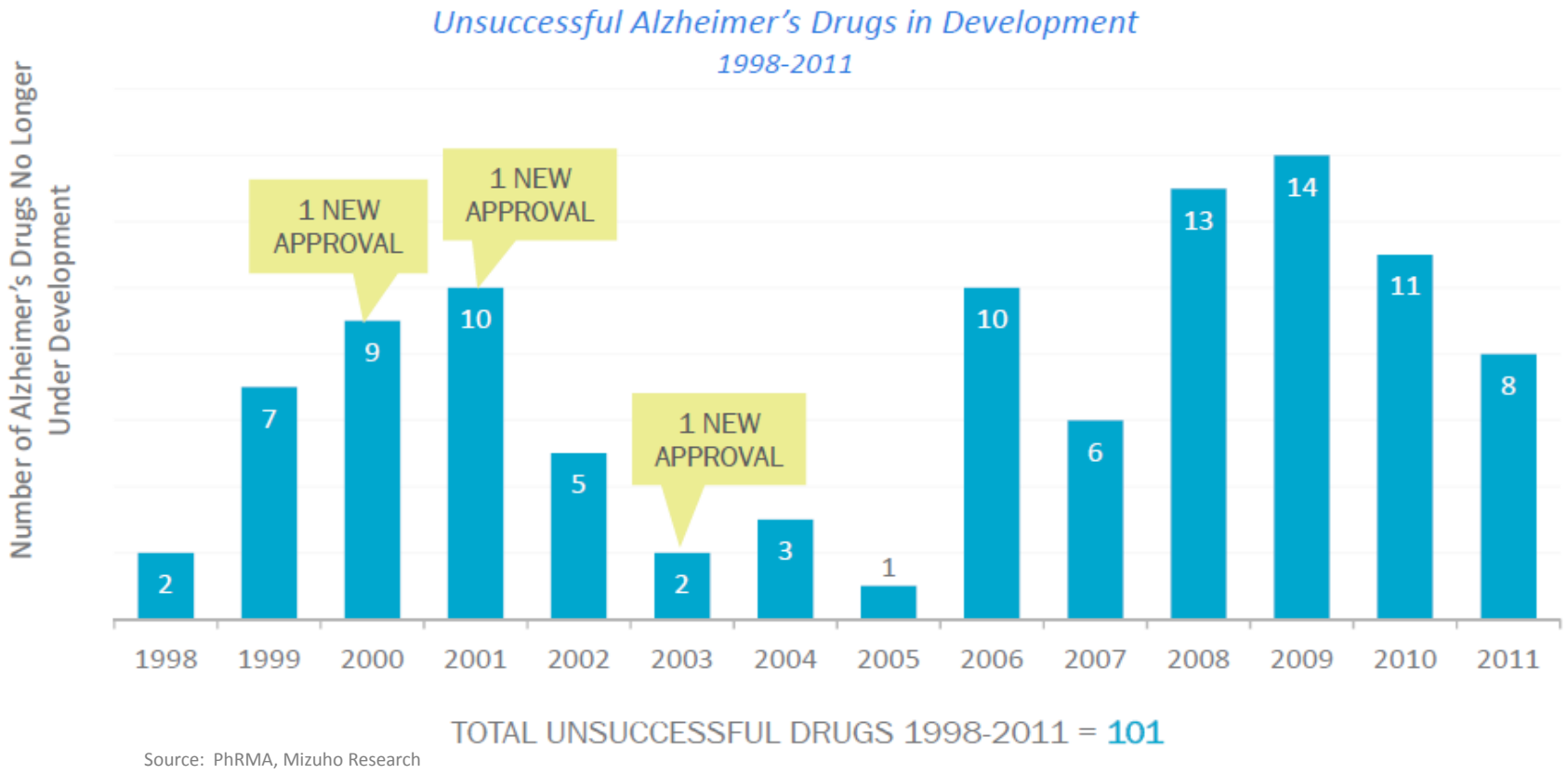
Drug Details

Drug Name(s)	ARICEPT
FDA Application No.	(NDA) 020690
Active Ingredient(s)	DONEPEZIL HYDROCHLORIDE
Company	EISAI INC
Original Approval or Tentative Approval Date	November 25, 1996
Chemical Type	1 New molecular entity (NME)
Review Classification	P Priority review drug

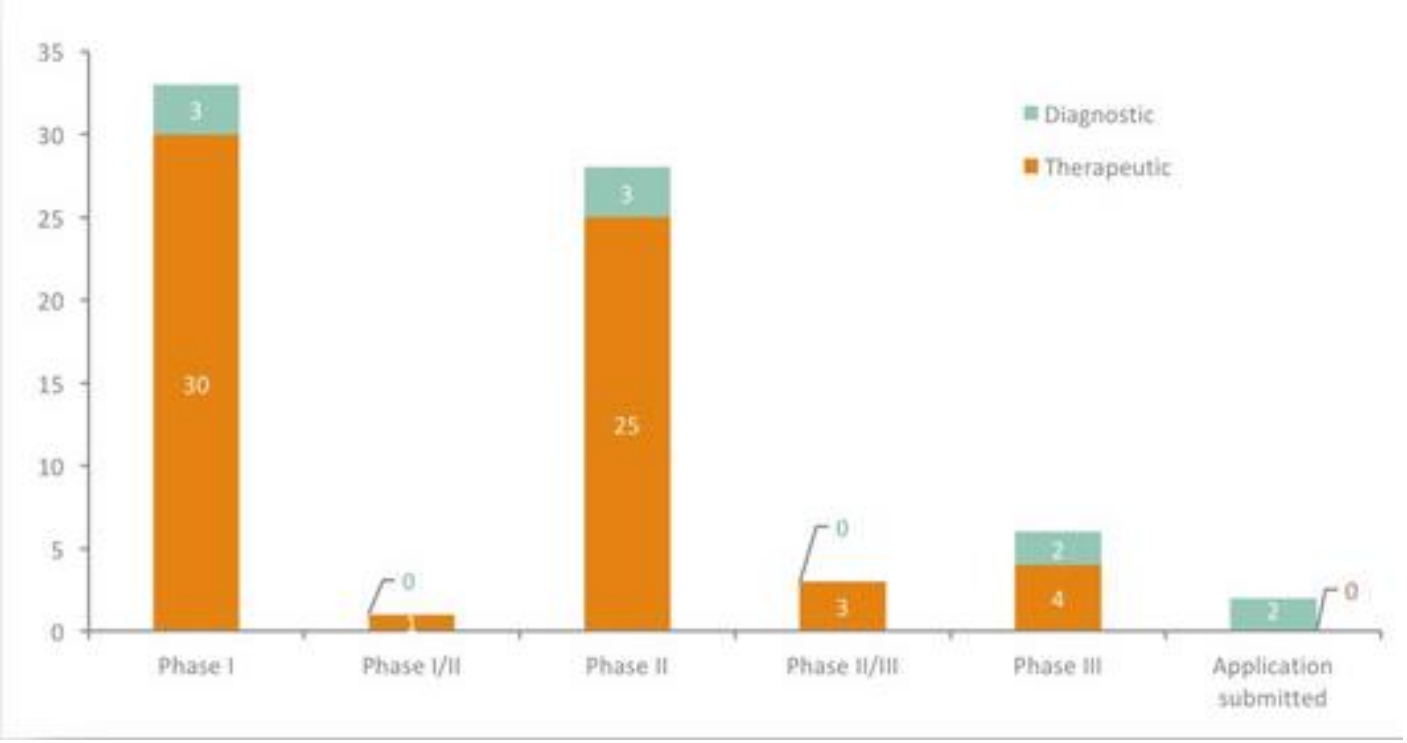
Source: FDA, Mizuho Research

Many potential Alzheimer's therapies have failed in clinical trials



Source: PhRMA, Mizuho Research

But there are dozens more of potential Alzheimer's drugs in development



Source: PhRMA, Mizuho Research

These drugs/trials have a better shot at success because as a field, researchers have learned more about how the disease works

"It has been over a decade since the last Alzheimer's drug was approved, but there is currently a **greater sense of optimism than ever before** about research into new treatments for this life-shattering disease."

-Dr. Laura Phipps, of Alzheimer's Research UK

"The recurring platitude, which has been going on forever is 'gee we're about five years away from a really effective treatment. It would be premature to say we've turned the corner but **there's a lot going on in the pipeline that is quite promising**."

-Dr. Steven Ferris, NYU Langone Medical Center in New York.

"We're at a stage now where **we understand the appropriate patient populations**"

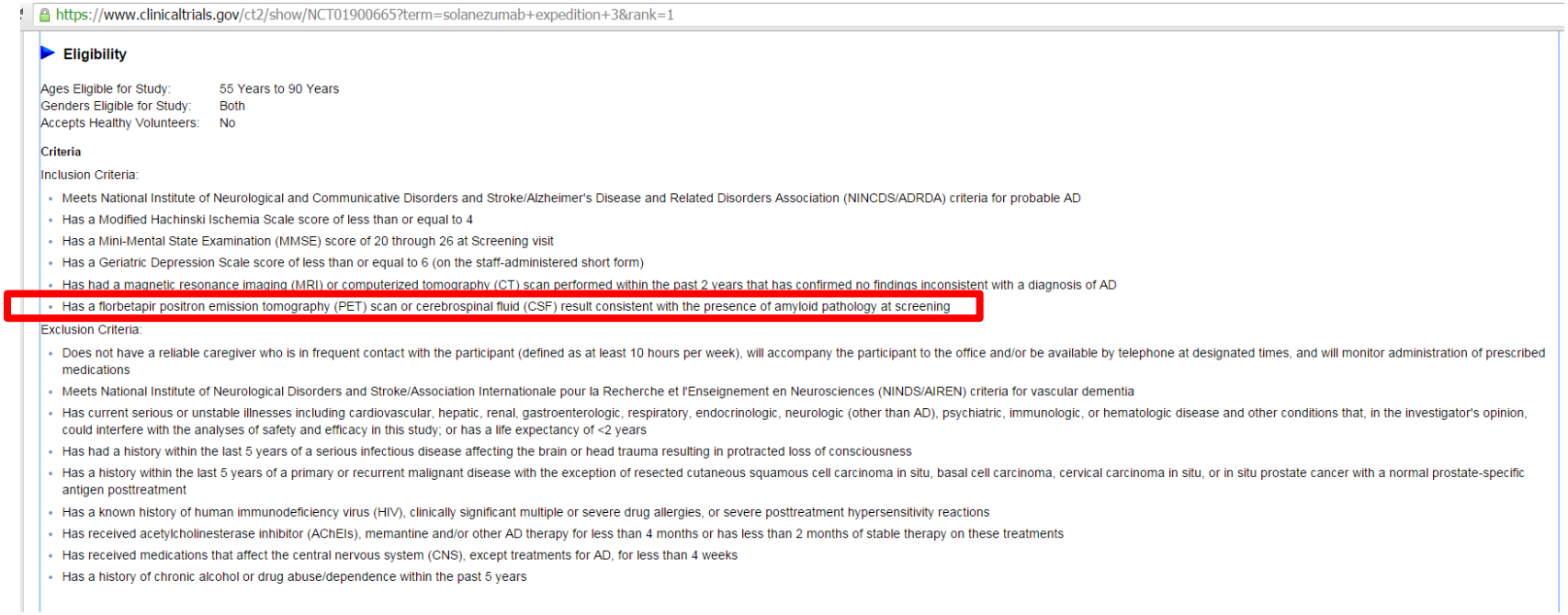
-Dr. George Scangos, Biogen CEO

This year is different because multiple mechanisms are being explored and there's a **tremendous revival of faith in the anti-amyloid approach**."

-Dr. Reisa Sperling, Center for Alzheimer's Research at Harvard Medical School

The two most discussed late-stage Alzheimer's assets today are Eli Lilly's Solanezumab and Biogen's Aducanumab

One reason why there is increased scientific optimism today is the trial population is "enriched" – this wasn't done before, and it confirms the patients have Alzheimer's pathology



https://www.clinicaltrials.gov/ct2/show/NCT01900665?term=solanezumab+expedition+3&rank=1

Eligibility

Ages Eligible for Study: 55 Years to 90 Years
Genders Eligible for Study: Both
Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:

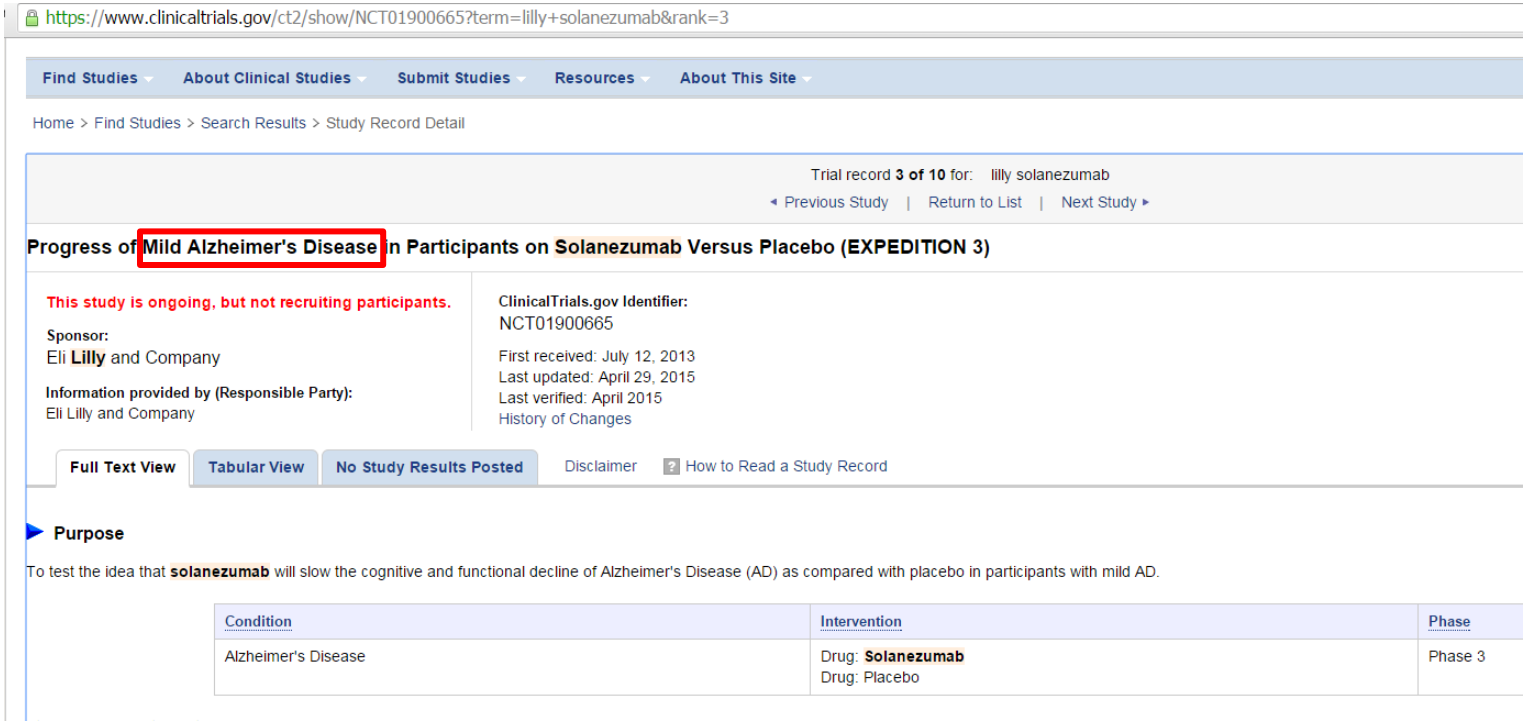
- Meets National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria for probable AD
- Has a Modified Hachinski Ischemia Scale score of less than or equal to 4
- Has a Mini-Mental State Examination (MMSE) score of 20 through 26 at Screening visit
- Has a Geriatric Depression Scale score of less than or equal to 6 (on the staff-administered short form)
- Has had a magnetic resonance imaging (MRI) or computerized tomography (CT) scan performed within the past 2 years that has confirmed no findings inconsistent with a diagnosis of AD
- Has a florbetapir positron emission tomography (PET) scan or cerebrospinal fluid (CSF) result consistent with the presence of amyloid pathology at screening

Exclusion Criteria:

- Does not have a reliable caregiver who is in frequent contact with the participant (defined as at least 10 hours per week), will accompany the participant to the office and/or be available by telephone at designated times, and will monitor administration of prescribed medications
- Meets National Institute of Neurological Disorders and Stroke/Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS/AIREN) criteria for vascular dementia
- Has current serious or unstable illnesses including cardiovascular, hepatic, renal, gastroenterologic, respiratory, endocrinologic, neurologic (other than AD), psychiatric, immunologic, or hematologic disease and other conditions that, in the investigator's opinion, could interfere with the analyses of safety and efficacy in this study; or has a life expectancy of <2 years
- Has had a history within the last 5 years of a serious infectious disease affecting the brain or head trauma resulting in protracted loss of consciousness
- Has a history within the last 5 years of a primary or recurrent malignant disease with the exception of resected cutaneous squamous cell carcinoma in situ, basal cell carcinoma, cervical carcinoma in situ, or in situ prostate cancer with a normal prostate-specific antigen posttreatment
- Has a known history of human immunodeficiency virus (HIV), clinically significant multiple or severe drug allergies, or severe posttreatment hypersensitivity reactions
- Has received acetylcholinesterase inhibitor (AChEIs), memantine and/or other AD therapy for less than 4 months or has less than 2 months of stable therapy on these treatments
- Has received medications that affect the central nervous system (CNS), except treatments for AD, for less than 4 weeks
- Has a history of chronic alcohol or drug abuse/dependence within the past 5 years

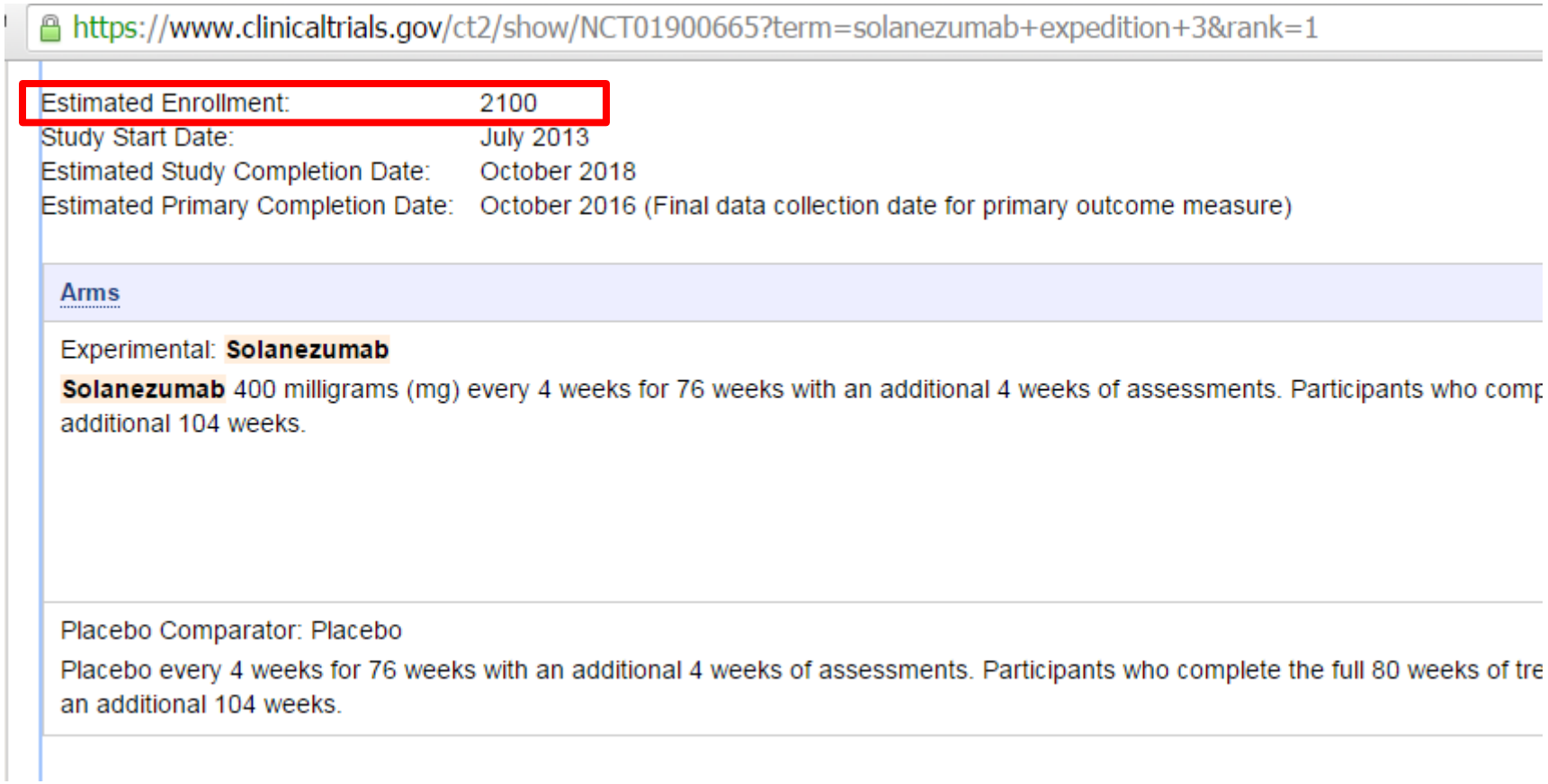
Source: clinicaltrials.gov

And its being done early-staged patients, which is where the field has gone based on previous trials and failures



Source: clinicaltrials.gov

The LLY trial is also highly powered (making it easier to be successful)



https://www.clinicaltrials.gov/ct2/show/NCT01900665?term=solanezumab+expedition+3&rank=1

Estimated Enrollment:	2100
Study Start Date:	July 2013
Estimated Study Completion Date:	October 2018
Estimated Primary Completion Date:	October 2016 (Final data collection date for primary outcome measure)

Arms

Experimental: **Solanezumab**

Solanezumab 400 milligrams (mg) every 4 weeks for 76 weeks with an additional 4 weeks of assessments. Participants who comp additional 104 weeks.

Placebo Comparator: Placebo

Placebo every 4 weeks for 76 weeks with an additional 4 weeks of assessments. Participants who complete the full 80 weeks of tre an additional 104 weeks.

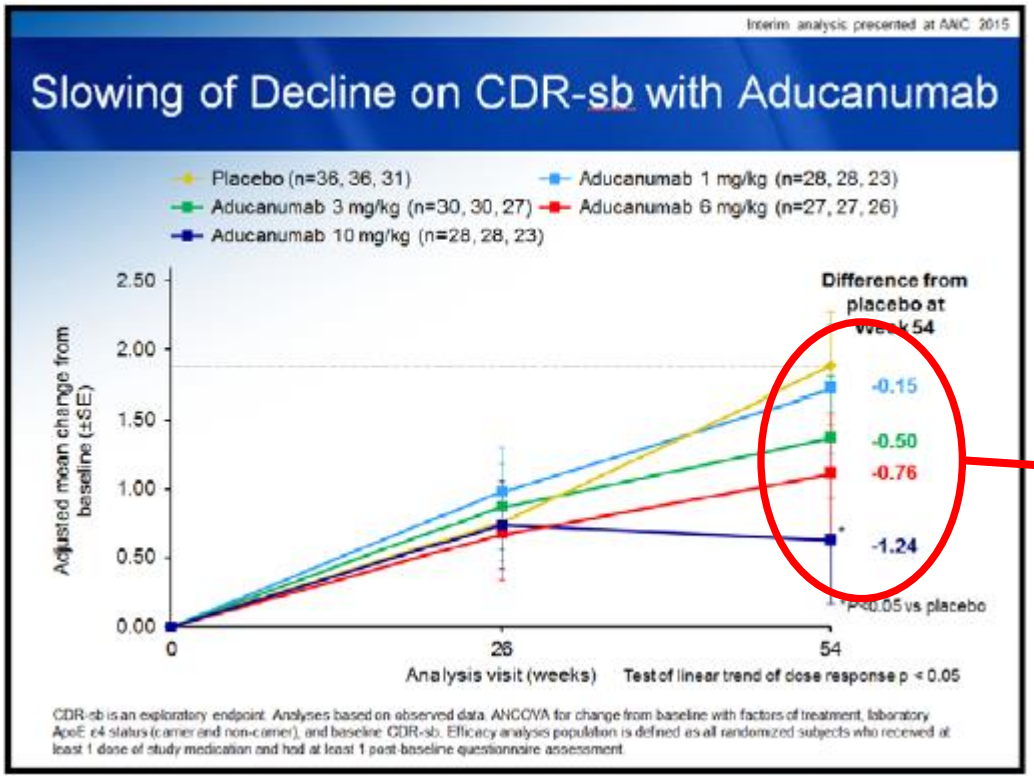
Source: clinicaltrials.gov

BIIB's Aducanumab is the first Alzheimer's drug to hit its endpoints prospectively … and this happened in Phase 1!

"Relative to placebo, the 3 mg/kg and the 10 mg/kg demonstrated a statistically significant slowing of cognitive decline on the **MMSE both with p-values <0.05**. …. Relative to placebo, the 10 mg/kg showed a statistically significant slowing of cognitive decline on the **CDR-SB with p value <0.05**."

- Neurimmune Press Release (3.20.15)

And there was a perfect dose response curve on CDR-SB (this is an important endpoint in Alzheimer's trials)



The drug worked better as dose increased

Source: BIIB, Mizuho Research

Like LLY, BIIB is also "enriching" its patient population at screening

https://www.clinicaltrials.gov/ct2/show/NCT02484547?term=biib037&rank=4

Eligibility

Ages Eligible for Study:	50 Years to 85 Years
Genders Eligible for Study:	Both
Accepts Healthy Volunteers:	No

Criteria

Key Inclusion Criteria:

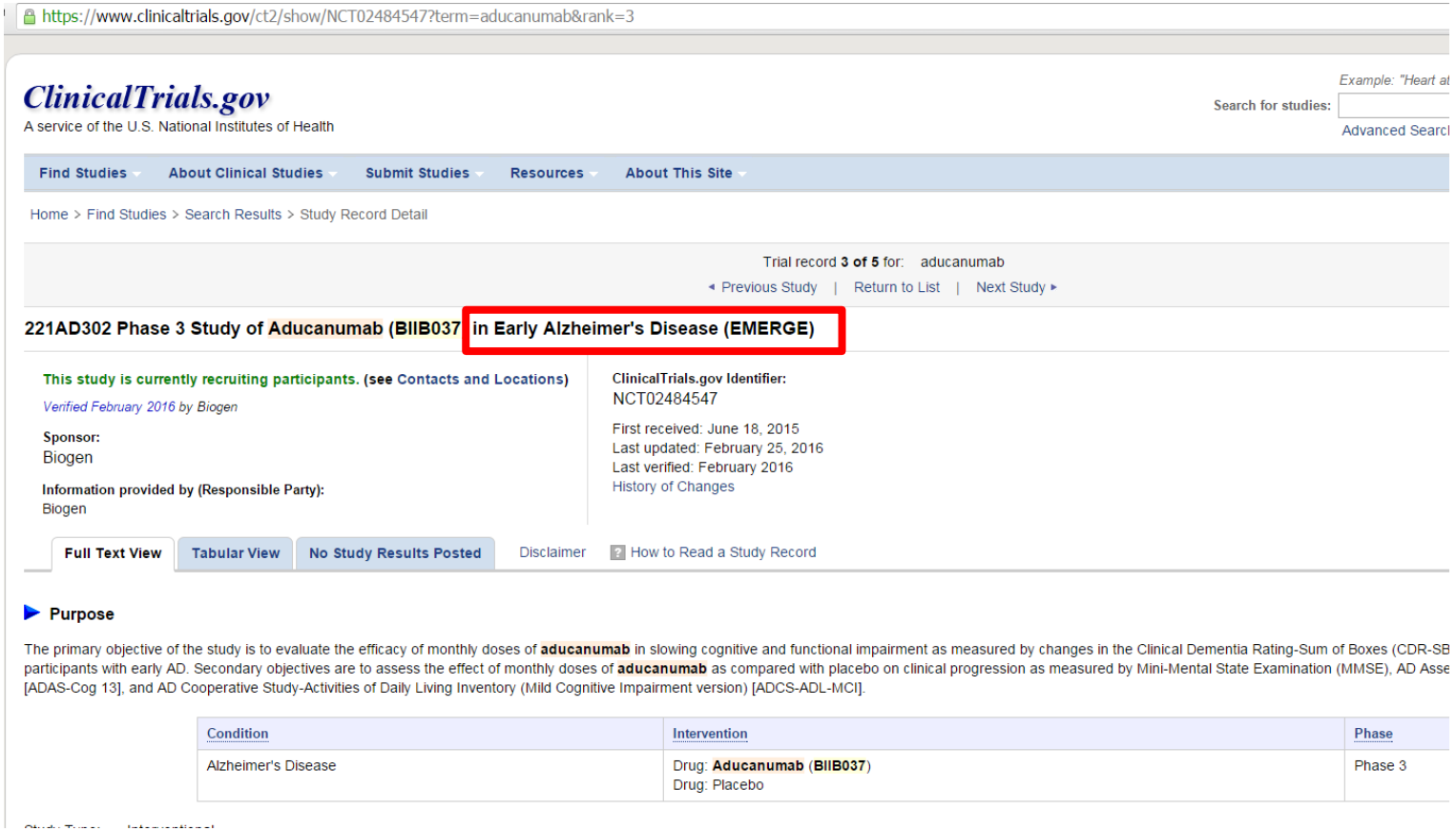
- Must meet all of the following clinical criteria for MCI due to AD or mild AD and must have:
- A Clinical Dementia Rating (CDR)-Global Score of 0.5.
- Objective evidence of cognitive impairment at screening
- An MMSE score between 24 and 30 (inclusive)
- Must have a positive amyloid Positron Emission Tomography (PET) scan
- Must consent to apolipoprotein E (ApoE) genotyping
- If using drugs to treat symptoms related to AD, doses must be stable for at least 8 weeks prior to screening visit 1
- Must have a reliable informant or caregiver

Key Exclusion Criteria:

- Any medical or neurological condition (other than Alzheimer's Disease) that might be a contributing cause of the subject's cognitive impairment
- Have had a stroke or Transient Ischemic Attack (TIA) or unexplained loss of consciousness in the past 1 year
- Clinically significant psychiatric illness in past 6 months

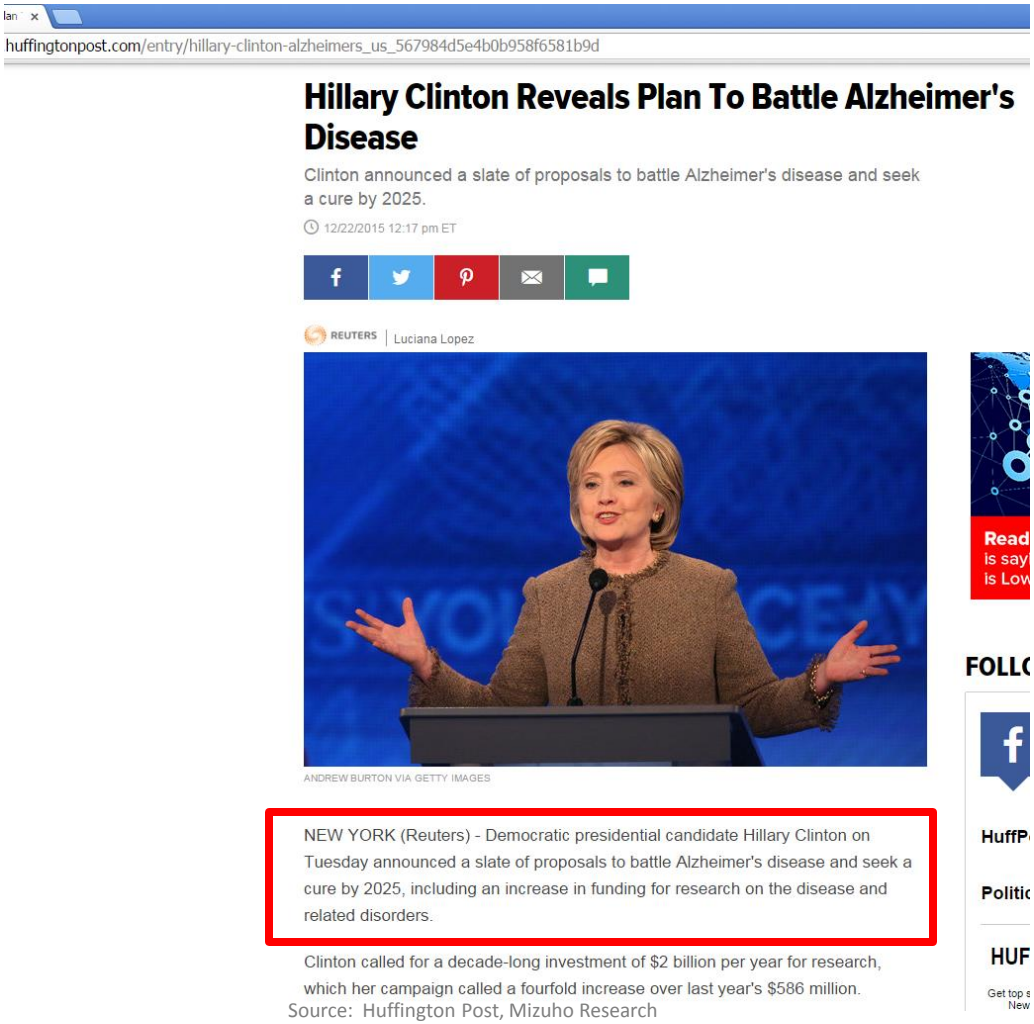
Source: clinicaltrials.gov, Mizuho Research

It's also going after early-staged patients as well



Source: clinicaltrials.gov, Mizuho Research

Again, government backing should only help



huffingtonpost.com/entry/hillary-clinton-alzheimers_us_567984d5e4b0b958f6581b9d

Hillary Clinton Reveals Plan To Battle Alzheimer's Disease

Clinton announced a slate of proposals to battle Alzheimer's disease and seek a cure by 2025.

12/22/2015 12:17 pm ET

REUTERS | Luciana Lopez

ANDREW BURTON VIA GETTY IMAGES

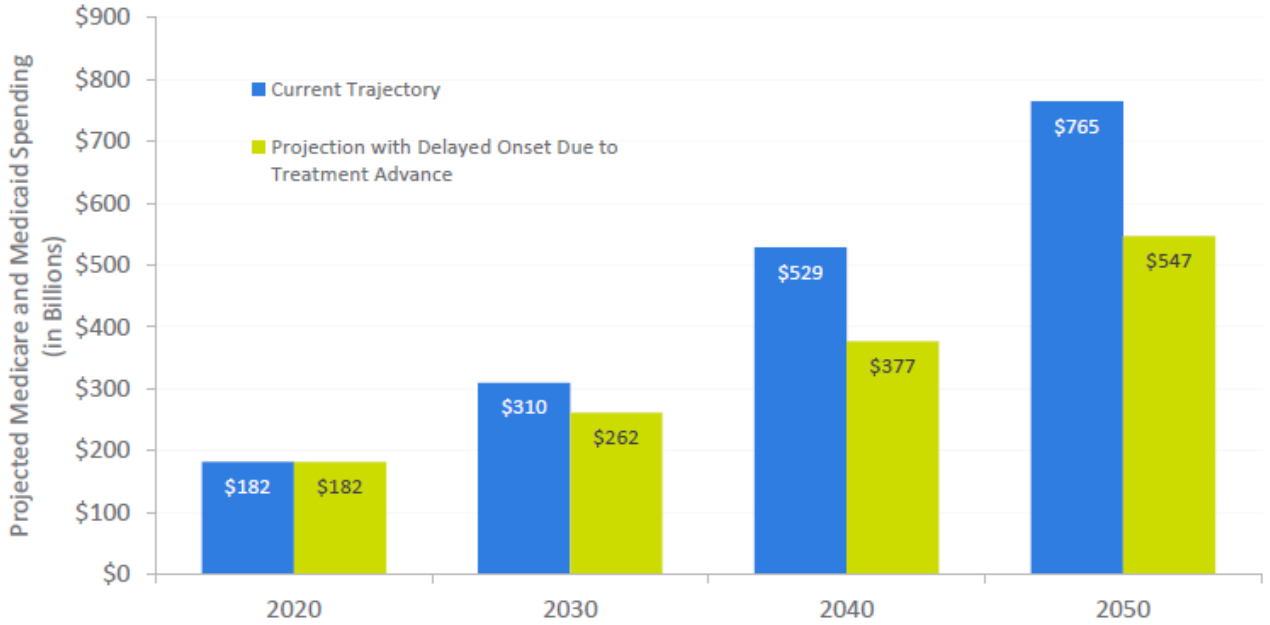
NEW YORK (Reuters) - Democratic presidential candidate Hillary Clinton on Tuesday announced a slate of proposals to battle Alzheimer's disease and seek a cure by 2025, including an increase in funding for research on the disease and related disorders.

Clinton called for a decade-long investment of $2 billion per year for research, which her campaign called a fourfold increase over last year's $586 million.

Source: Huffington Post, Mizuho Research

The government is incentivized to develop new therapies for Alzheimer's to save on Medicare and Medicaid

*Projected Annual Medicare and Medicaid Spending, With and Without New Treatment Advances (Billions)***



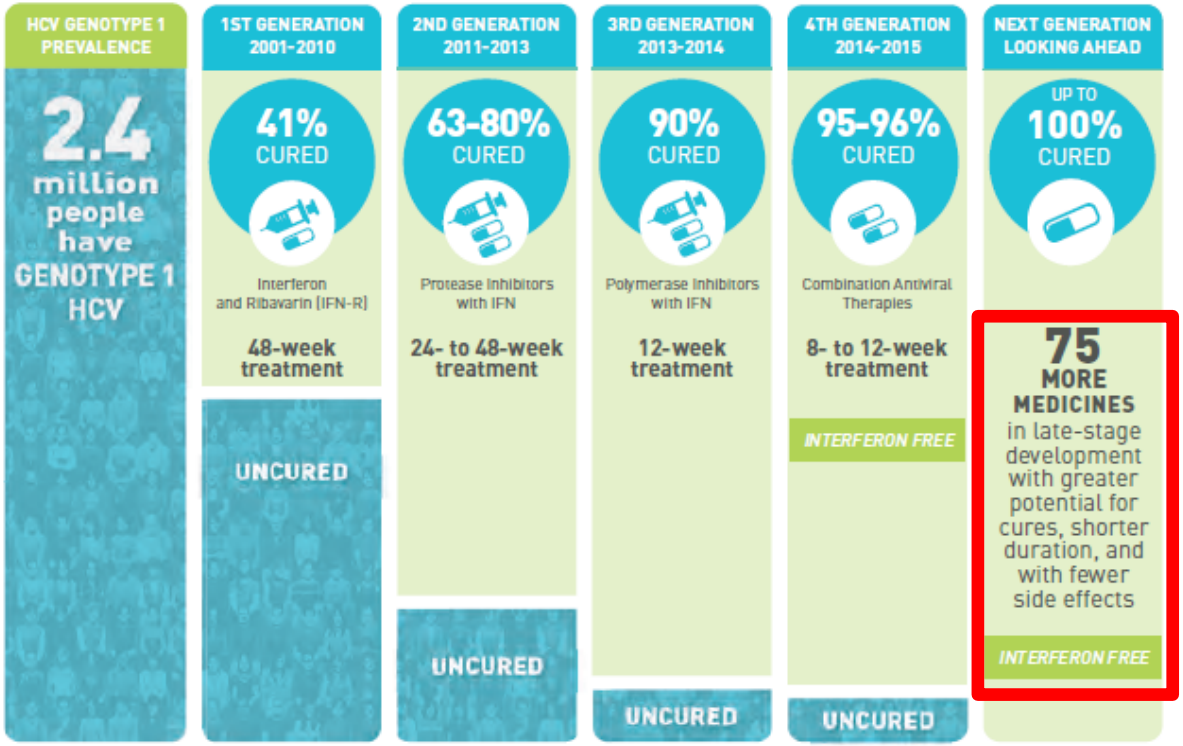
*Assumes research advances that delay the average age of onset of Alzheimer's disease by 5 years beginning in 2025

**Projected savings to Medicare and Medicaid assume research breakthroughs that slow the progression of Alzheimer's disease. This would dramatically reduce spending for comorbid conditions and expensive nursing home care.

Source: Alzheimer's Association[29]

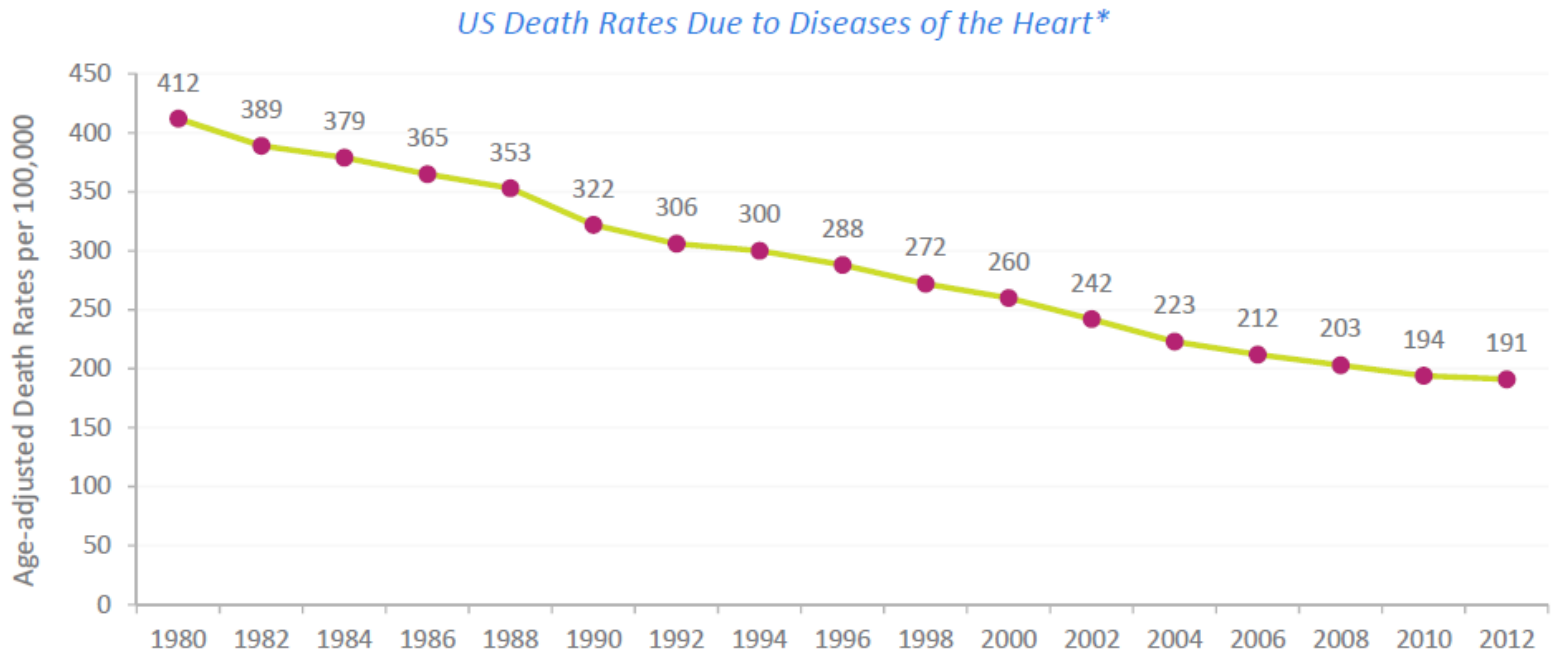
Quick tidbits on a few other disease areas ➔

HCV: Despite the recent advances, drug companies are still targeting a full 100% cure



Sources: Armstrong GL, Wasley A, Simard EP, McQuillan GM, Kuhnert WL, Alter MJ. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. *Ann Int Med*. 2008;144:705-714; Elsevier Clinical Solutions. Viral hepatitis C. ClinicalKey. https://www.clinicalkey.com/topics/gastroenterology/viral-hepatitis-c.html. Accessed March 2015.; Cure rates based upon clinical trial results reported in FDA labels for: interferon; telaprevir; boceprevir; simeprevir; sofosbuvir; sofosbuvir and ledipasvir combination; and ombitasvir, paritaprevir, ritonavir, and dasabuvir combination. US Food and Drug Administration. Center for Drug Evaluation and Research. DrugsØFDA: FDA approved drug products. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/. Silver Spring, Md.: FDA. Accessed March 2015.; Pharmaceutical Research and Manufacturers of America. Twenty-five years of progress against hepatitis C: setbacks and stepping stones. Washington, DC: PhRMA; December 2014. http://www.phrma.org/sites/default/files/pdf/Hep-C-Report-2014-Stepping-Stones_0.pdf. Accessed March 2015.

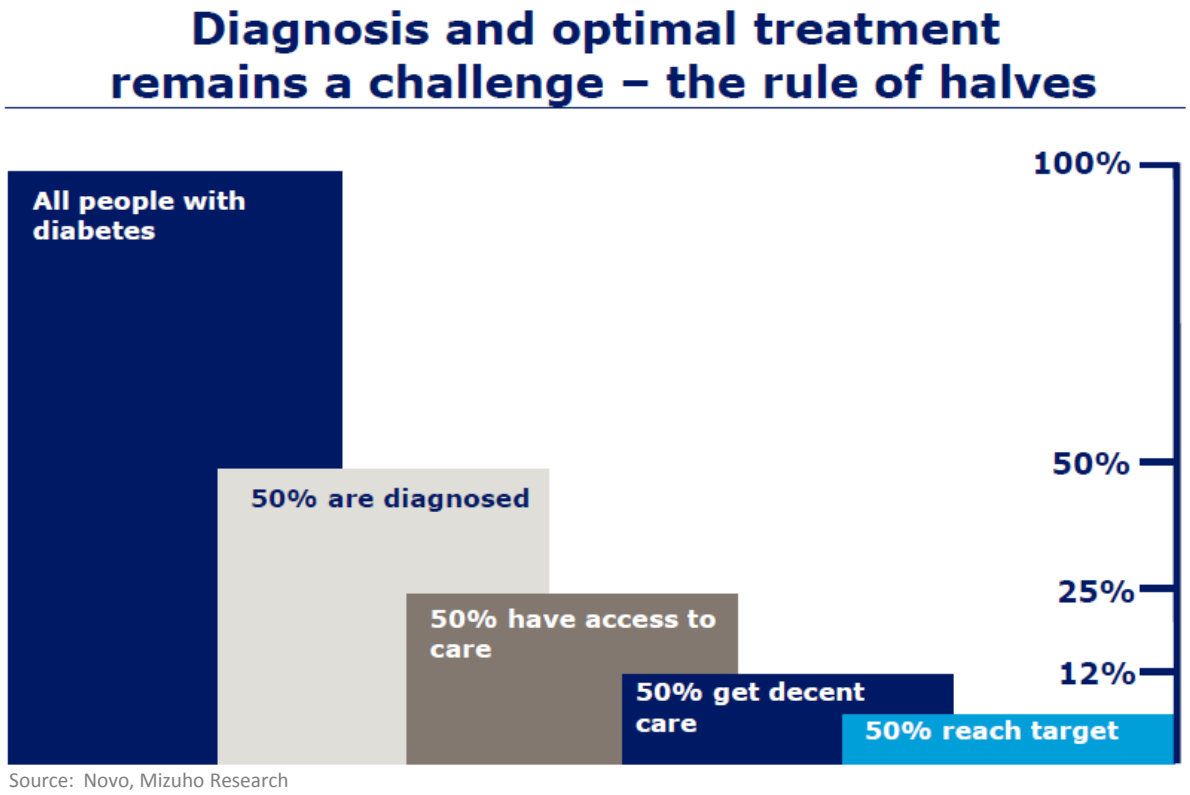
Cardiovascular: Death rates have been and are declining due to newer therapies



*Age-adjusted death rates based on Year 2000 US Standard Population. 1980-1998 causes of death are classified by the Ninth Revision International Classification of Diseases (ICD-9). Beginning in 1999, causes of death are classified by the Tenth Revision International Classification of Diseases (ICD-10).

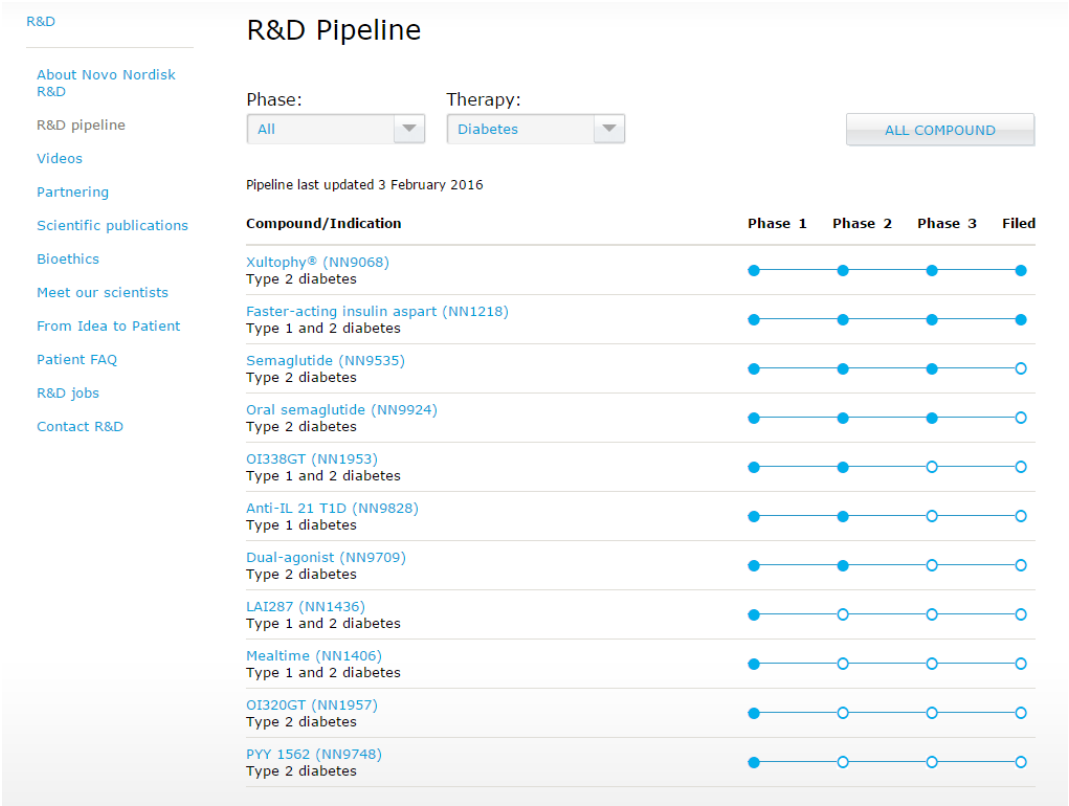
Source: CDC[23,24]

Diabetes: Some old primary care diseases like diabetes still have a lot of room for improvement (despite already being a $30Bn+ market)



Source: Novo, Mizuho Research

But even in these disease areas, there is significant work being done (at all stages of development)



Source: Novo, Mizuho Research

Sector fundamentals to think about …

…how concerned should I be about all these drug pricing talks?

…are drug pipelines healthy enough to create new sales?

…is orphan drug spend increasing?

…do we have a friendlier FDA today?

…is R&D productivity increasing?

…what will get the sector to rebound in the near-term?

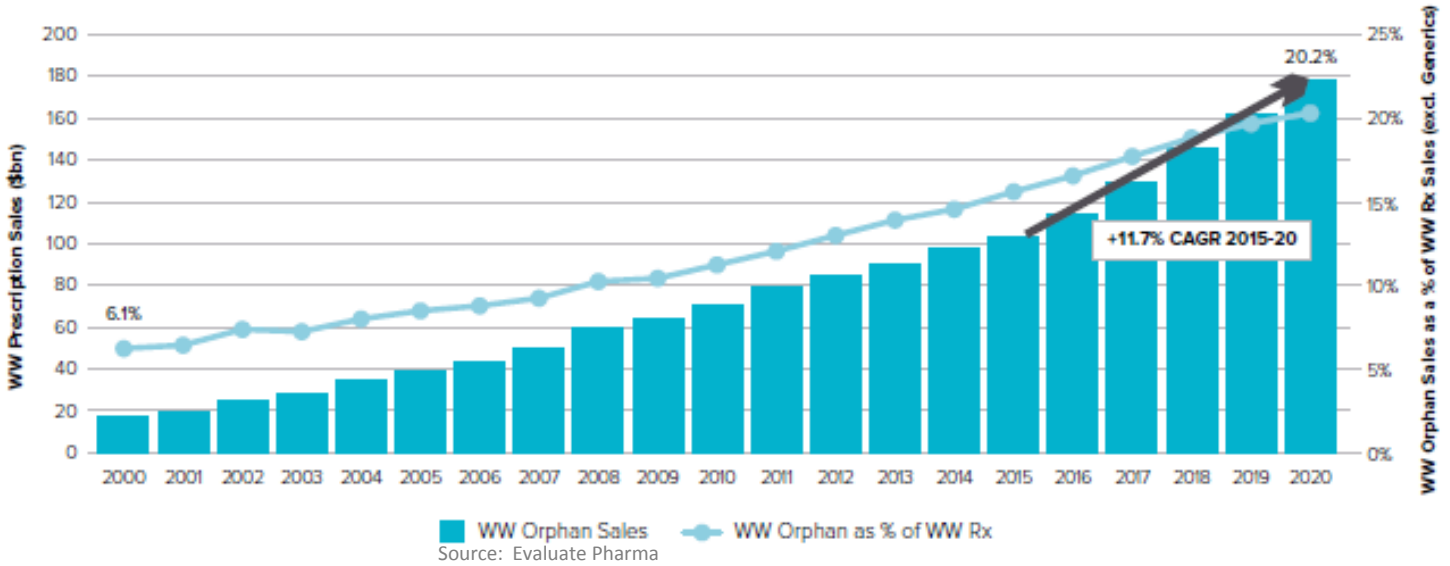
…how has biotech done historically when interest rates increase?

Orphan drugs treat rare diseases that affect fewer than 200,000 people in the US, but that doesn't mean they should be ignored (from any perspective including an investor's)

Orphan drug sales currently make up about 12.5% of WW prescription drug sales, but this number is expected to double in the next decade

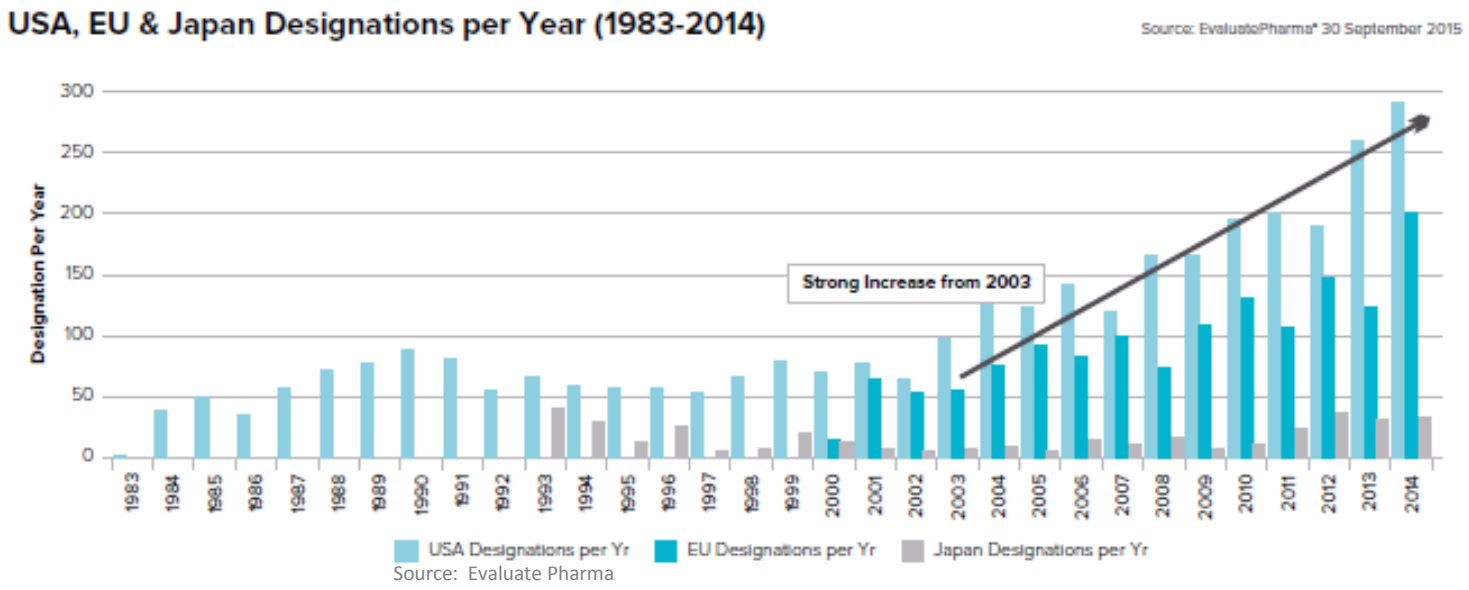
Worldwide Orphan Drug Sales & Share of Prescription Drug Market (2000-2020)

Source: EvaluatePharma® 30 September 2015



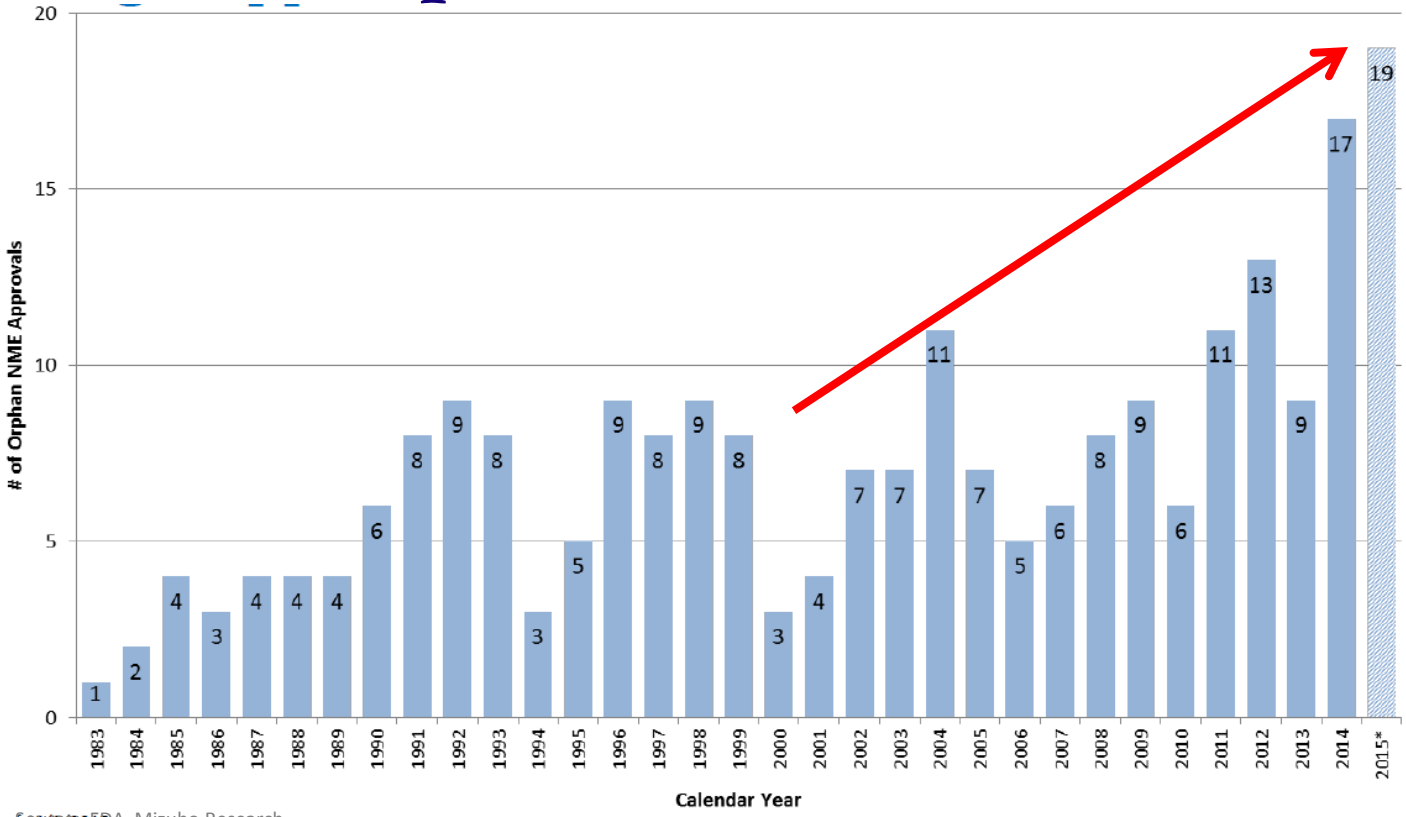
Source: Evaluate Pharma

Regulatory authorities (like the FDA) have also granted more orphan drug designations steadily over time ➔ this implies industry's interest in developing these drugs has also increased



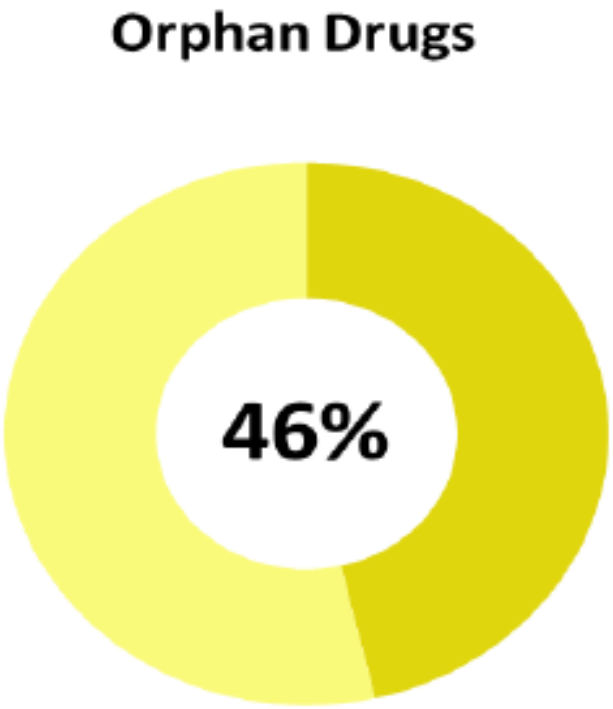
Source: Evaluate Pharma

Similarly, orphan drug approvals have increased with time and this should help drive future orphan sales



Source: FDA, Mizuho Research

In fact, orphan drugs made up about ½ of all drug approvals in 2015



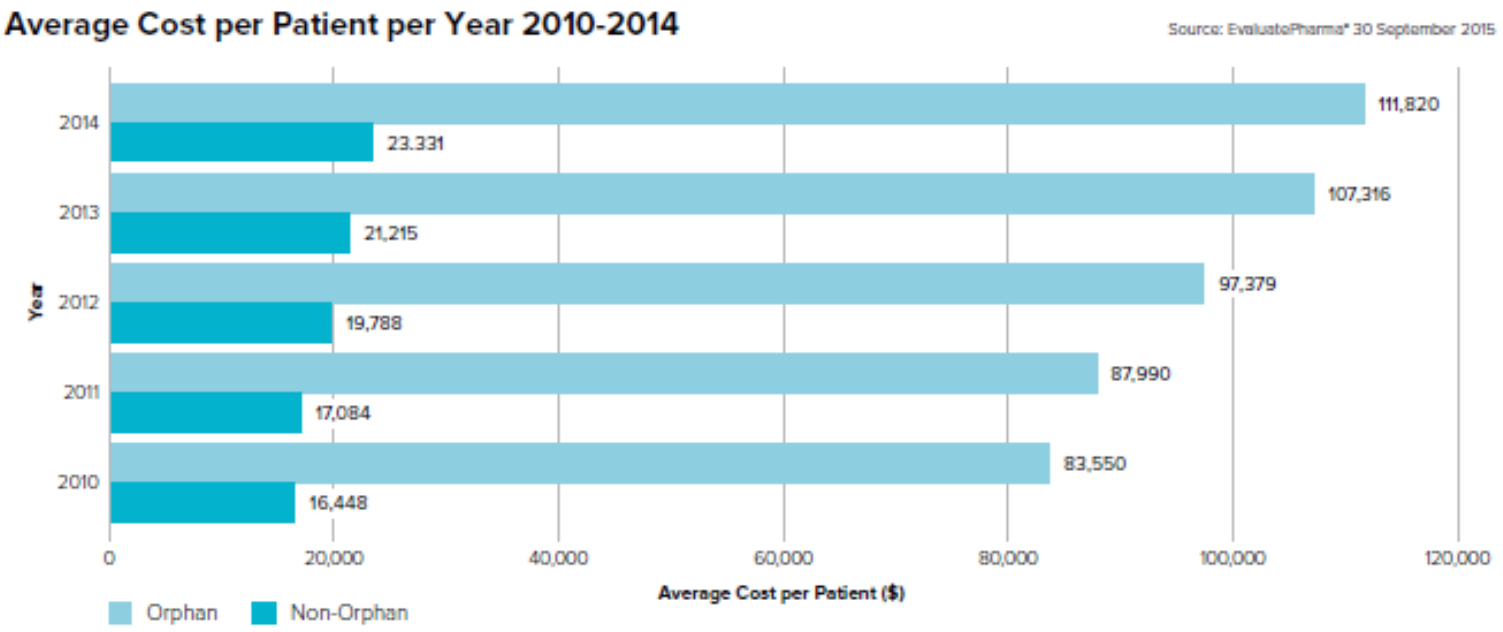
Source: FDA, Mizuho Research

Many drug companies play in the orphan drug space … so this makes sense

Rank	Company	WW Orphan Sales ($bn) 2014	2020	% CAGR 14-20
1.	Celgene	6.6	12.7	12%
2.	Novartis	11.8	12.7	1%
3.	Bristol-Myers Squibb	2.9	12.6	28%
4.	Roche	9.7	12.5	4%
5.	Alexion Pharmaceuticals	2.2	6.8	21%
6.	Pfizer	5.3	6.3	3%
7.	Vertex Pharmaceuticals	0.5	6.0	53%
8.	Merck & Co	1.1	5.9	32%
9.	AbbVie	0.2	5.8	73%
10.	Johnson & Johnson	2.0	5.7	19%
11.	Shire	2.5	4.8	12%
12.	Baxalta	3.9	4.7	3%
13.	Sanofi	3.7	4.5	3%
14.	Eli Lilly	3.1	4.0	4%
15.	Novo Nordisk	2.8	3.5	4%
16.	Amgen	2.0	3.1	8%
17.	Actelion	2.1	3.1	7%
18.	Bayer	3.9	3.0	-4%
19.	BioMarin Pharmaceutical	0.6	2.6	26%
20.	Biogen	3.1	2.5	-4%
	Total Top 20	69.9	122.8	+9.9%
	Other	27.1	55.0	+12.5%
	Total	97.0	177.8	+10.6%

Source: Evaluate Pharma

Orphan drugs command premium pricing, otherwise there would be little financial incentive for drug companies to address these rare diseases

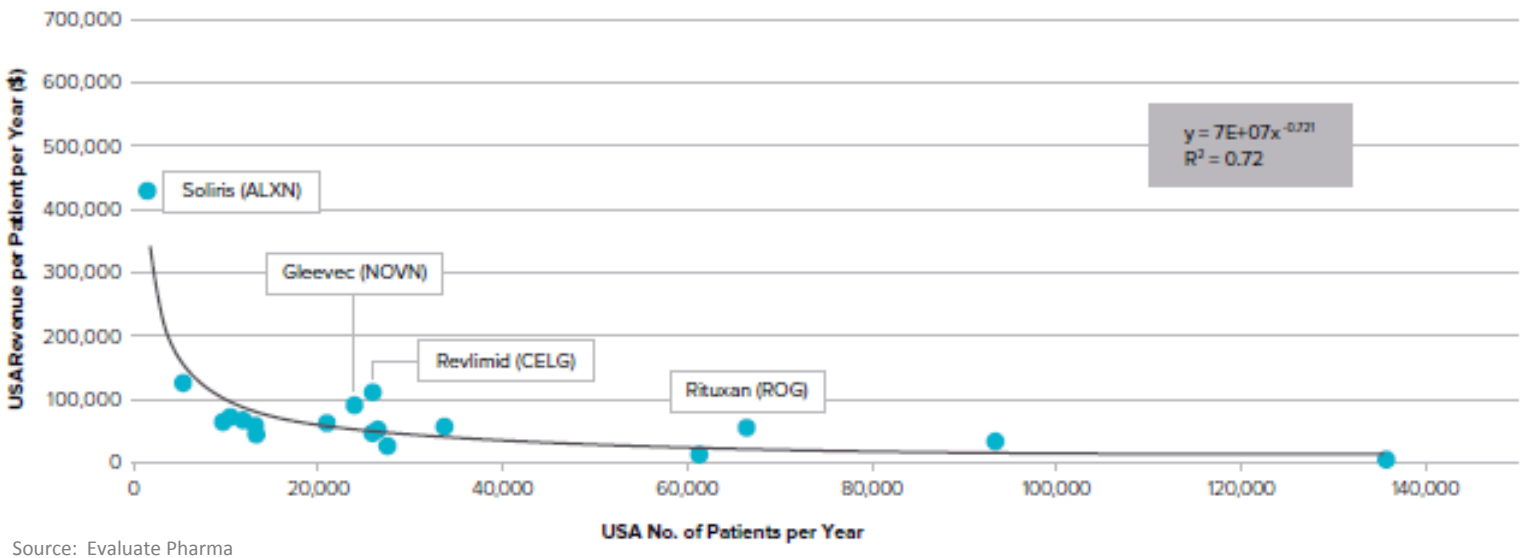


Source: Evaluate Pharma

And the fewer people there are to treat, the higher the price typically

Top 20 USA Orphan Drugs in 2014 by Sales; Revenue per Patient vs. No. of Patients Treated

Source: EvaluatePharma® 30 September 2015



Source: Evaluate Pharma

Payors typically don't attack an orphan drug's price because the particular disease that it treats makes up a small part their costs vs. other diseases

From a R&D cost perspective, orphan drug Phase 3 trials typically cost 33-50% less the non-orphan trials

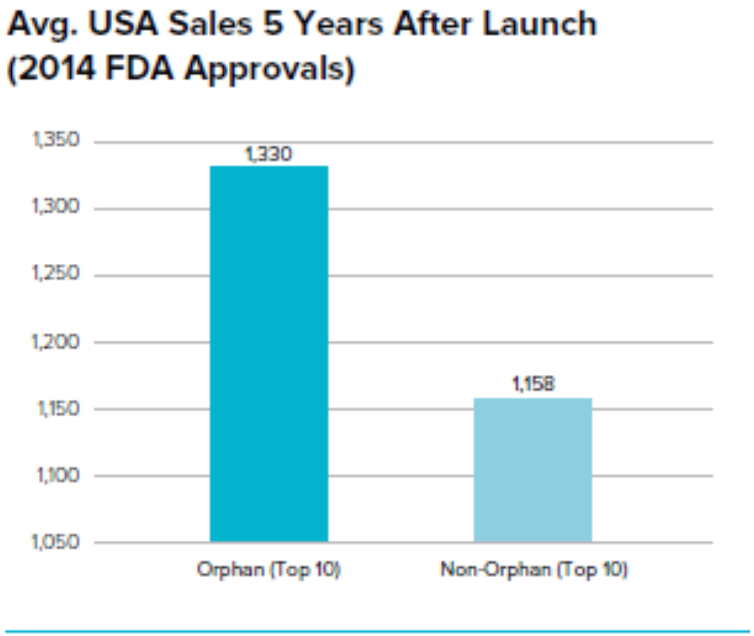
Average Phase III Trials Sizes (All New Drug Products Entering Phase III from 1 JAN 2000)

Source:

Product Type	Phase III Trial Size					Phase III Cost ($m) Estimated*		
	Median	Average	No. of Products (n=)	Total Patients	% of	Median	Average	Total
Orphan	538	761	466	354,705	10%	99	103	47,929
Non-Orphan	1,558	3,549	952	3,378,809	90%	150	193	183,543
All	921	2,633	1,418	3,733,514	100%	127	163	231,472
Orphan / Non-Orphan =	34.5%	21.4%	48.9%			65.7%	53.3%	26.1%

Source: Evaluate Pharma

Despite having cheaper Phase 3 costs, orphan drugs produce about the same if not more revenue as non-orphan drugs 5 years post launch (be careful with the scale on this chart)



Source: Evaluate Pharma

They also benefit from 7 years of market exclusivity post approval

PROTECTION FOR UNPATENTED DRUGS FOR RARE DISEASES OR CONDITIONS

SEC. 527 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT [21 USC 360cc].

(a) Except as provided in subsection (b), if the Secretary---

(1) approves an application filed pursuant to section 505, or
(2) issues a license under section 351 of the Public Health Service Act

for a drug designated under section 526 for a rare disease or condition, **the Secretary may not approve another application under section 505 or issue another license under section 351 of the Public Health Service Act for such drug for such disease or condition for a person who is not the holder of such approved application or of such license until the expiration seven years from the date of the approval of the approved application or the issuance of the license.** Section 505(c)(2) does not apply to the refusal to approve an application under the preceding sentence.

Sector fundamentals to think about …

…how concerned should I be about all these drug pricing talks?

…are drug pipelines healthy enough to create new sales?

…is orphan drug spend increasing?

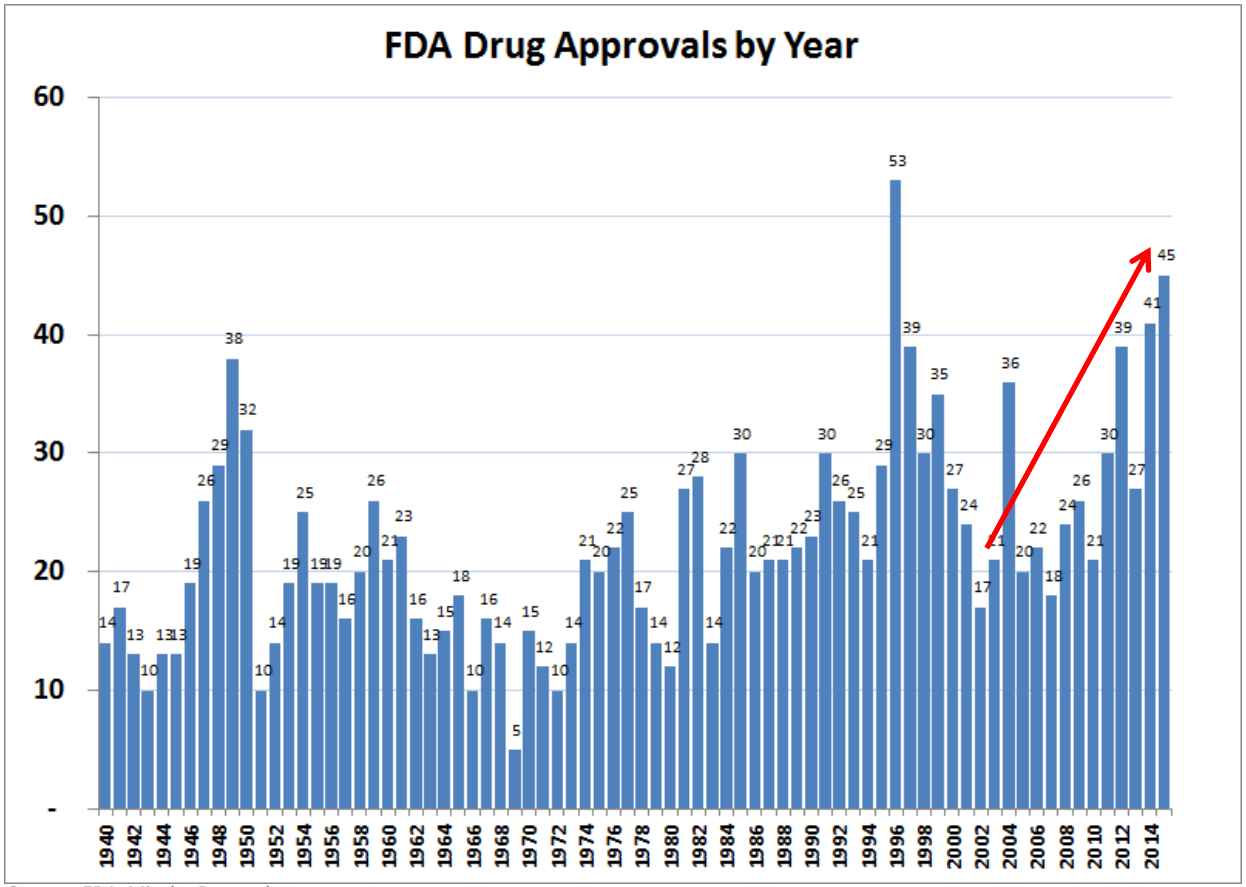
…do we have a friendlier FDA today?

…is R&D productivity increasing?

…what will get the sector to rebound in the near-term?

…how has biotech done historically when interest rates increase?

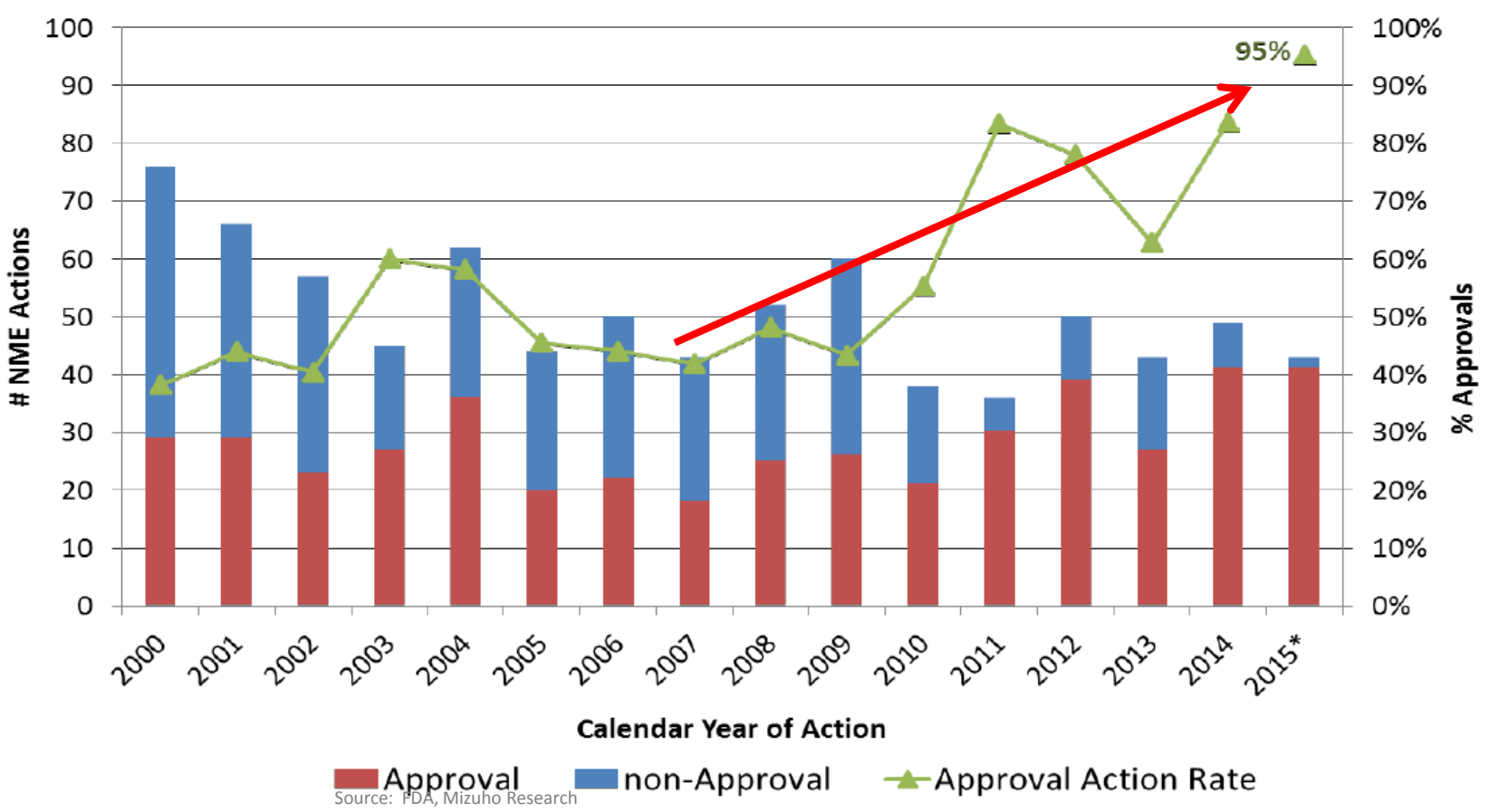
Drugs approvals have generally increased over the past decade



Source: FDA, Mizuho Research

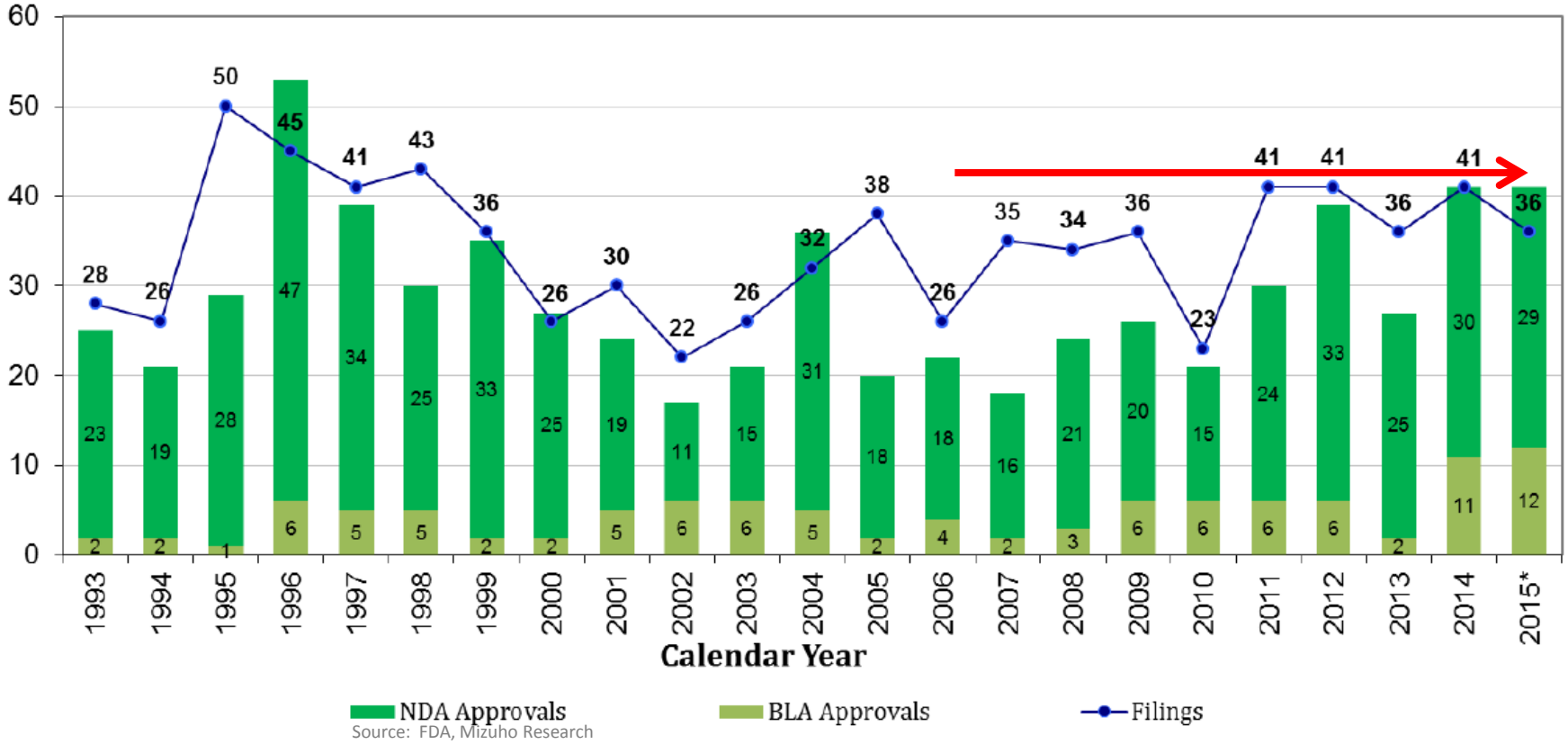
However, YTD for 2016, there have only been 19 drug approvals … doesn't take away from the overall trend, but this is much lower than 2015's 45

This is predominantly due to a greater % of NDAs getting approved …



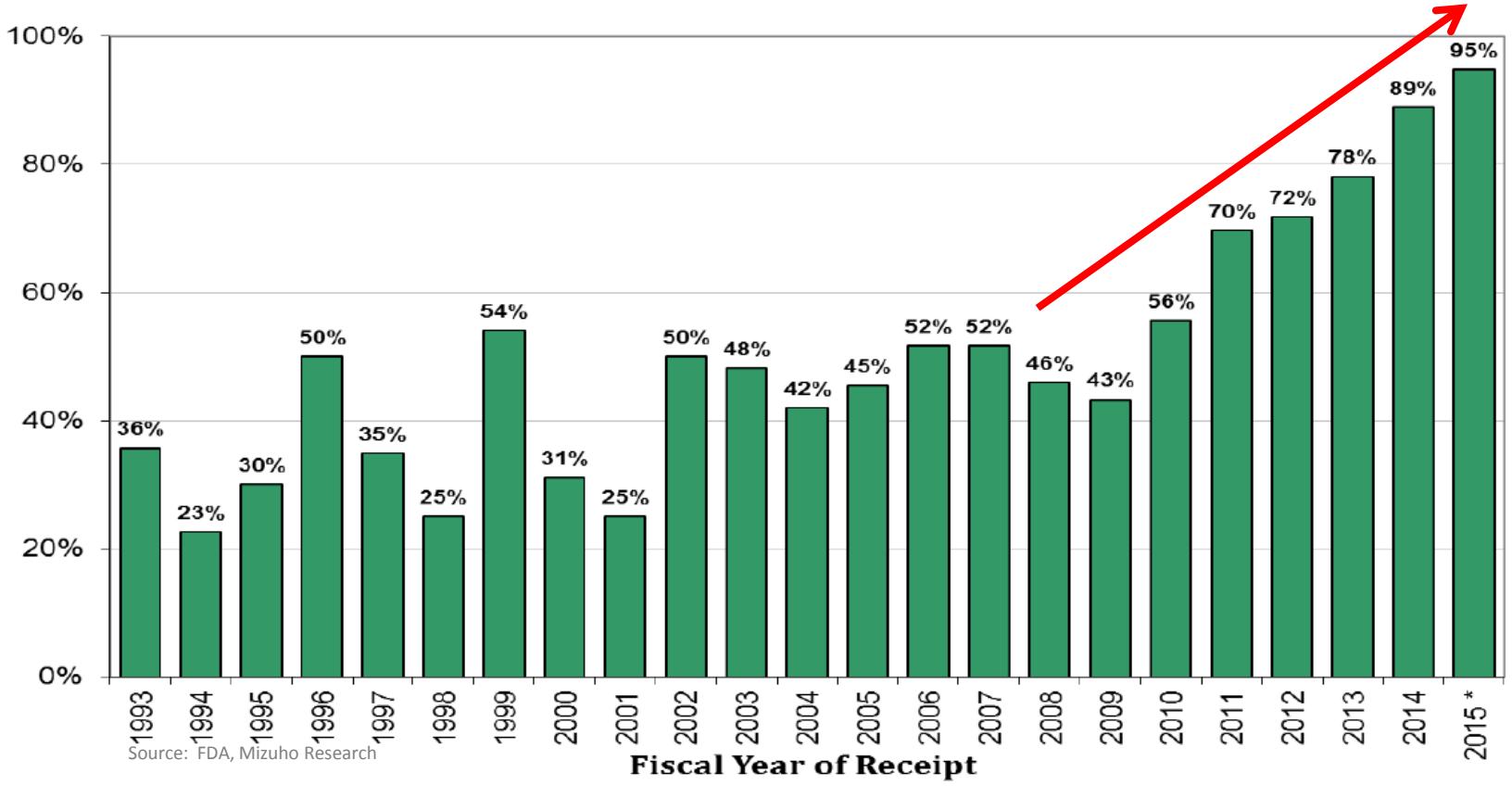
Source: FDA, Mizuho Research

… not because the number of NDA filings have significantly increased



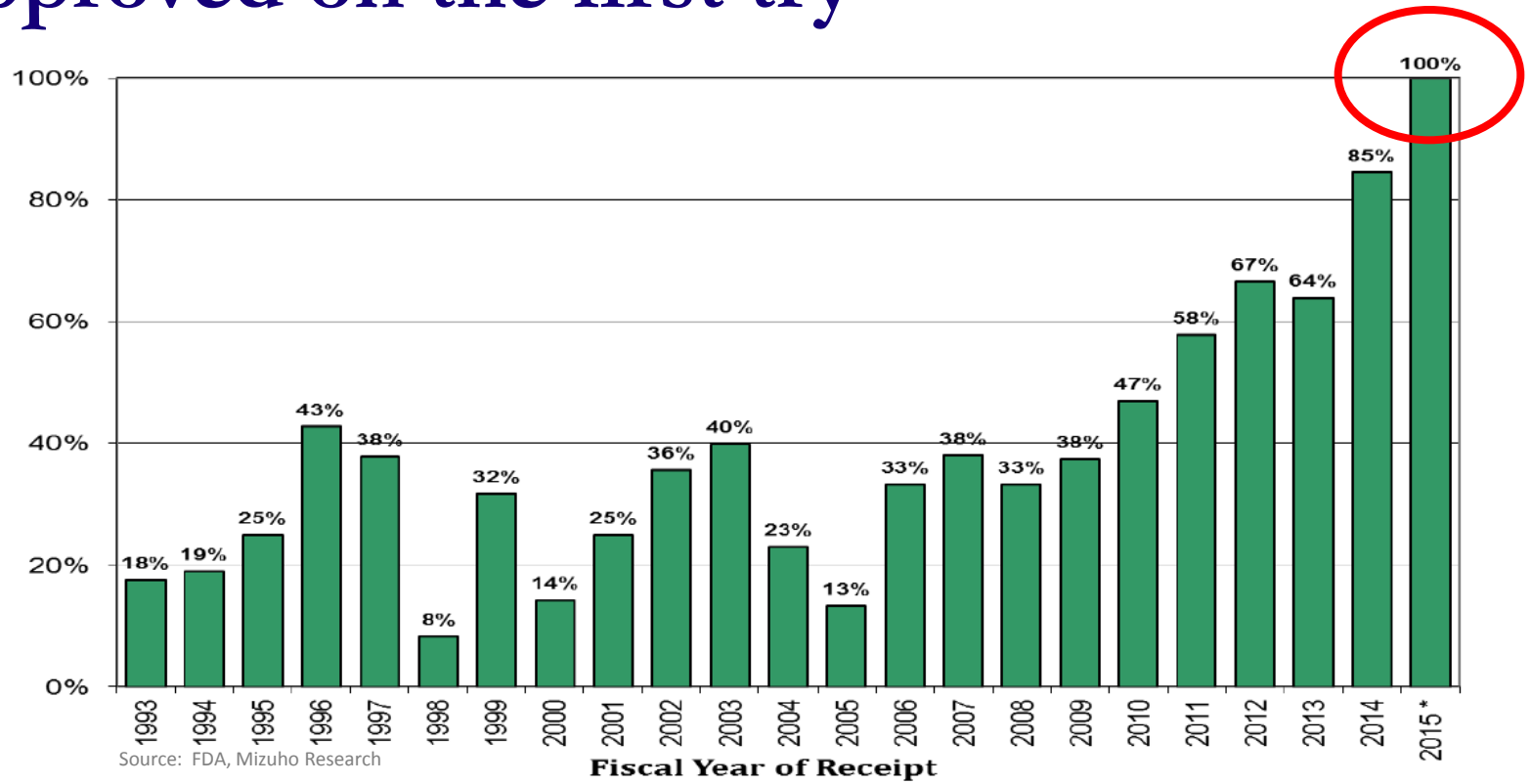
Source: FDA, Mizuho Research

The % of drugs getting approved on the first try has also increased



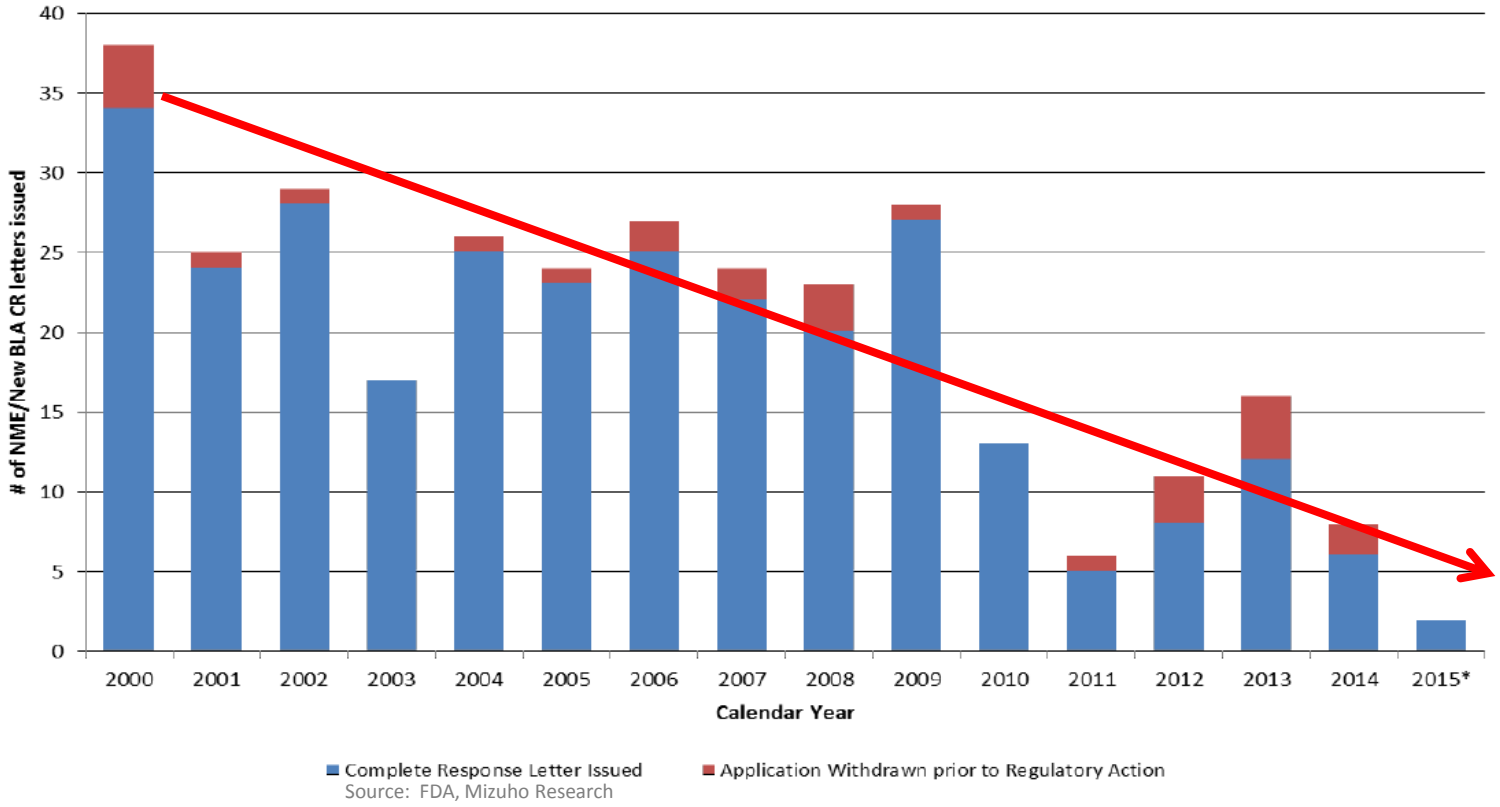
Source: FDA, Mizuho Research

In fact, 2015 was the first year more than 100% of standard NDA/BLA filings were approved on the first try



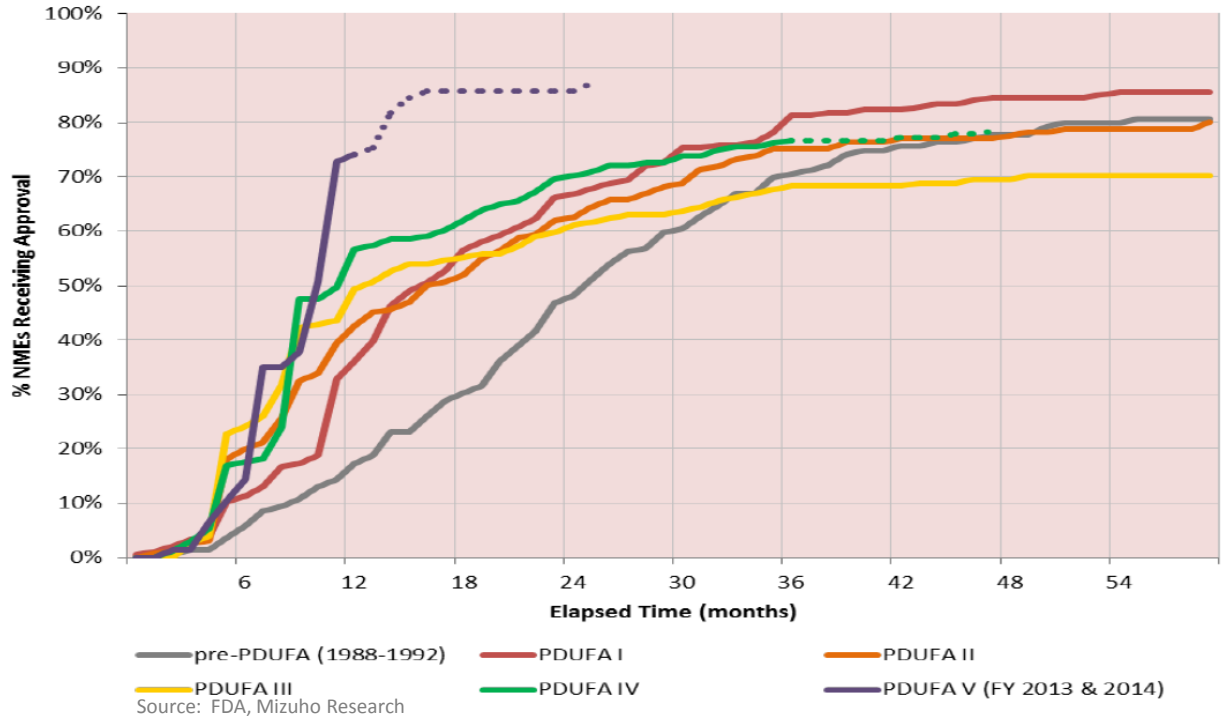
Source: FDA, Mizuho Research

By the same logic, the number of drug applications that result in a CR letter (a bad thing) have decreased



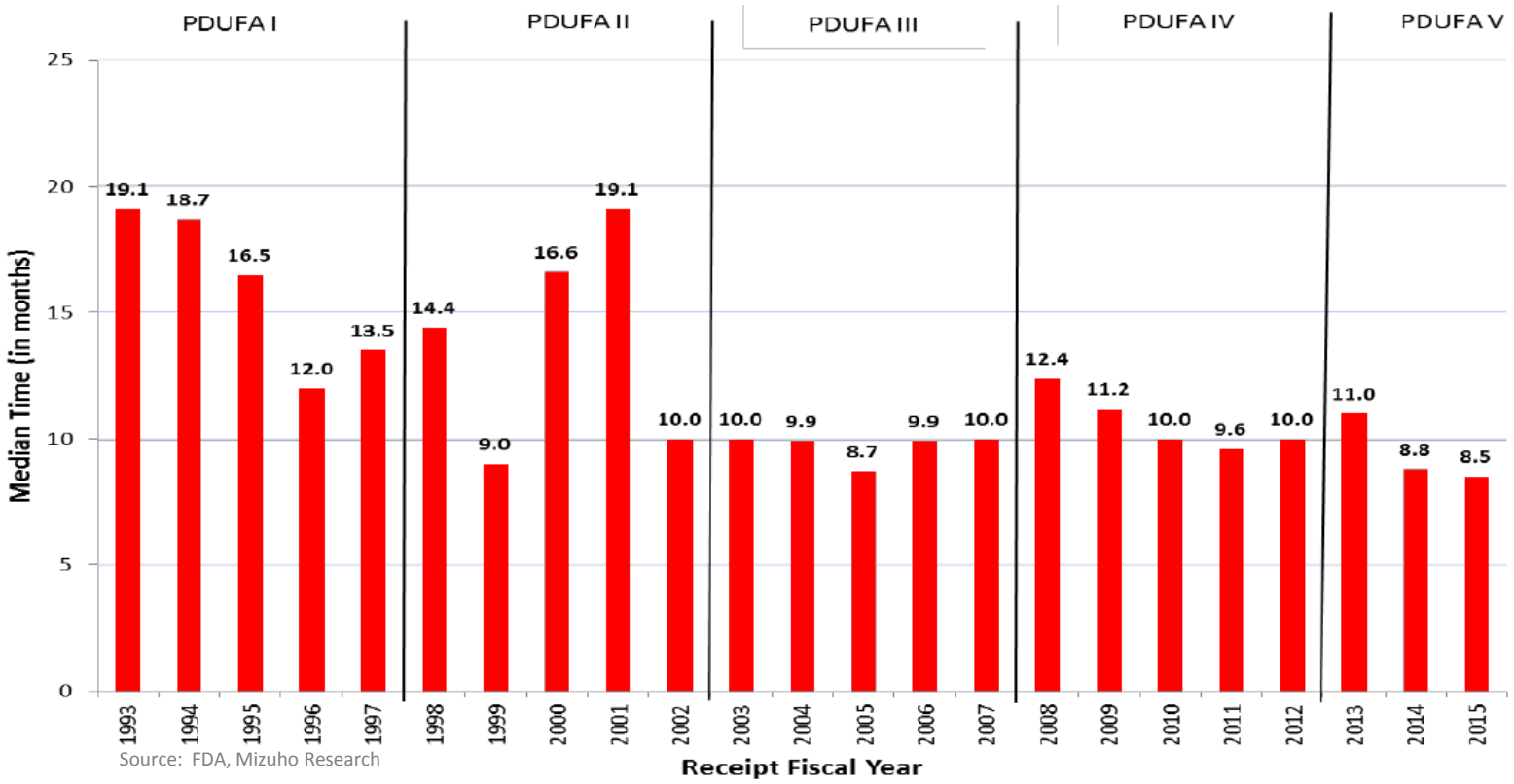
Source: FDA, Mizuho Research

Every time the FDA has introduced an updated PDUFA regime, approval rates have increased



Source: FDA, Mizuho Research

And the median time to approval has improved

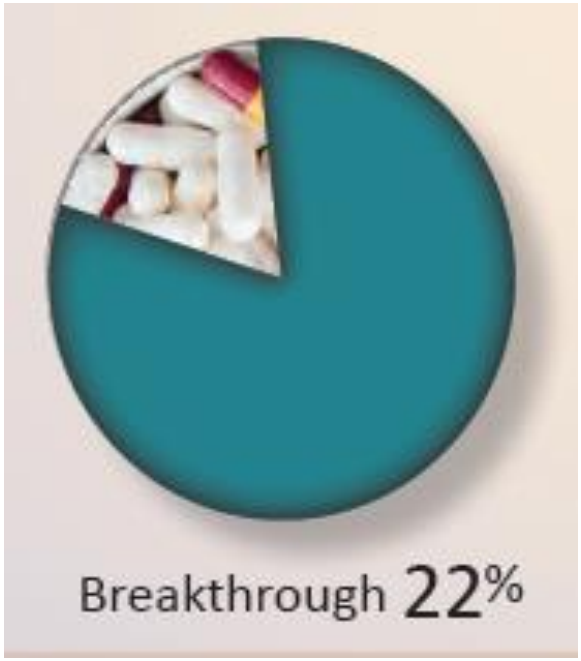


Source: FDA, Mizuho Research

% of approved drugs with Breakthrough Therapy Designation also show a favorable trend… a continuing trend should improve development and review times

2013

2015



Source: FDA, Mizuho Research

Sector fundamentals to think about …

…how concerned should I be about all these drug pricing talks?

…are drug pipelines healthy enough to create new sales?

…is orphan drug spend increasing?

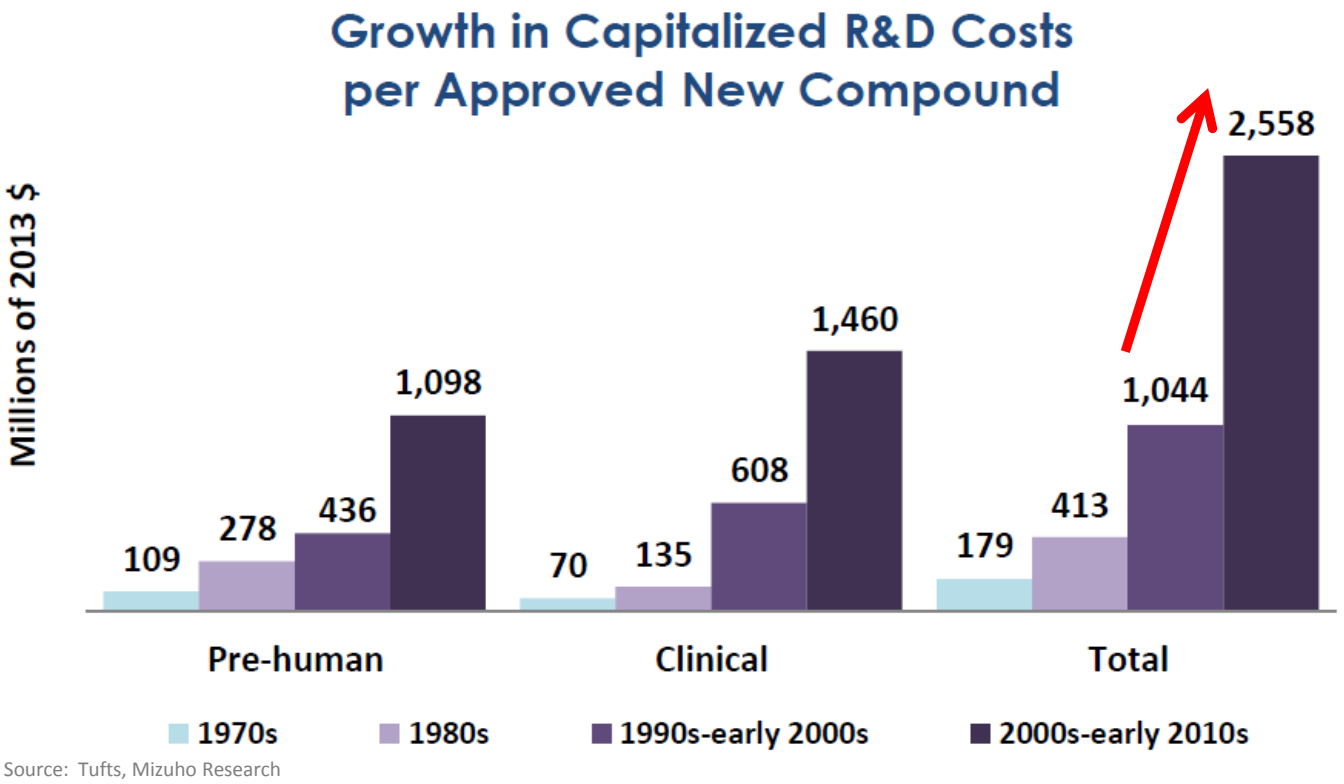
…do we have a friendlier FDA today?

…is R&D productivity increasing?

…what will get the sector to rebound in the near-term?

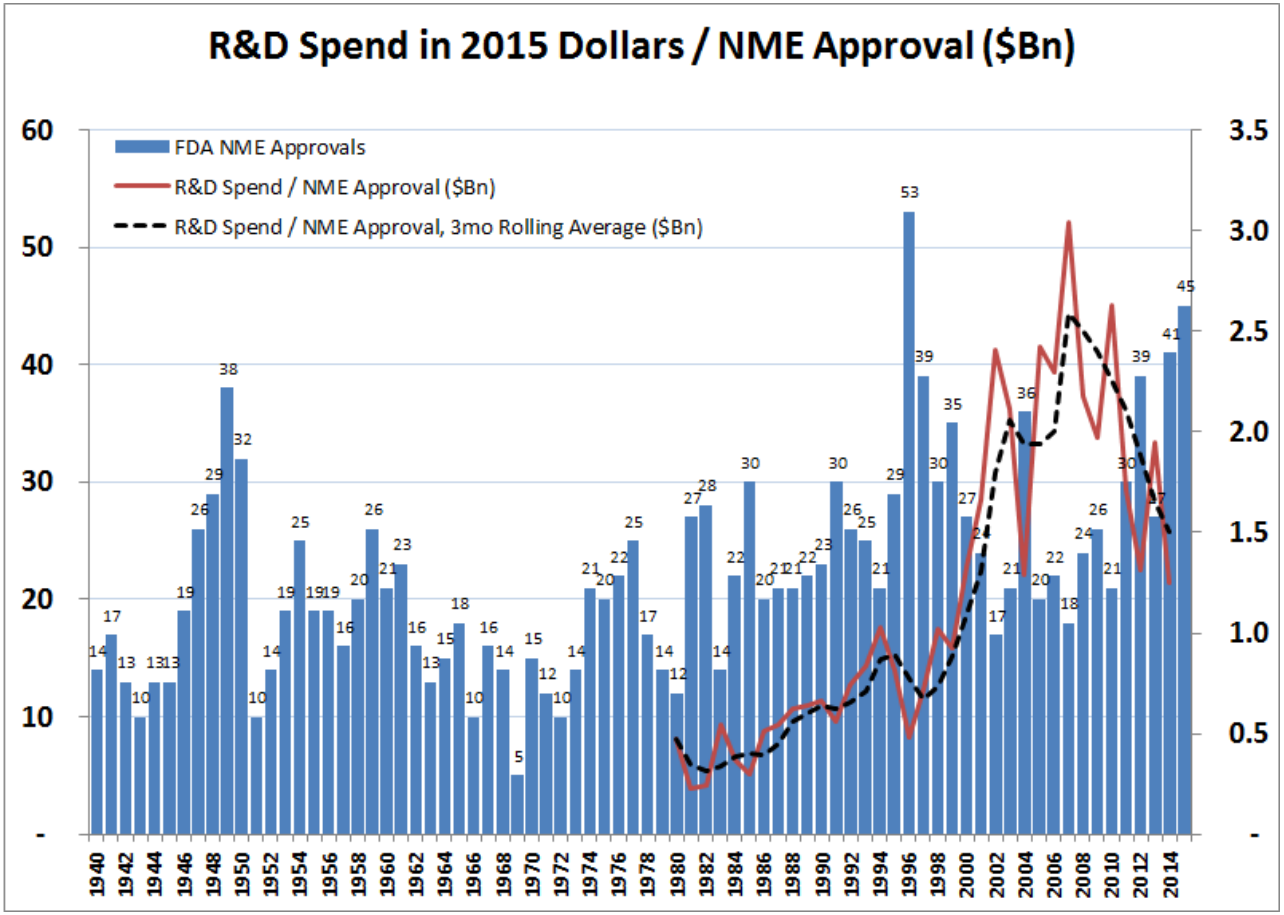
…how has biotech done historically when interest rates increase?

Sure, the R&D cost (including failures) to get a drug approved in the last decade has more than doubled to $2.6Bn



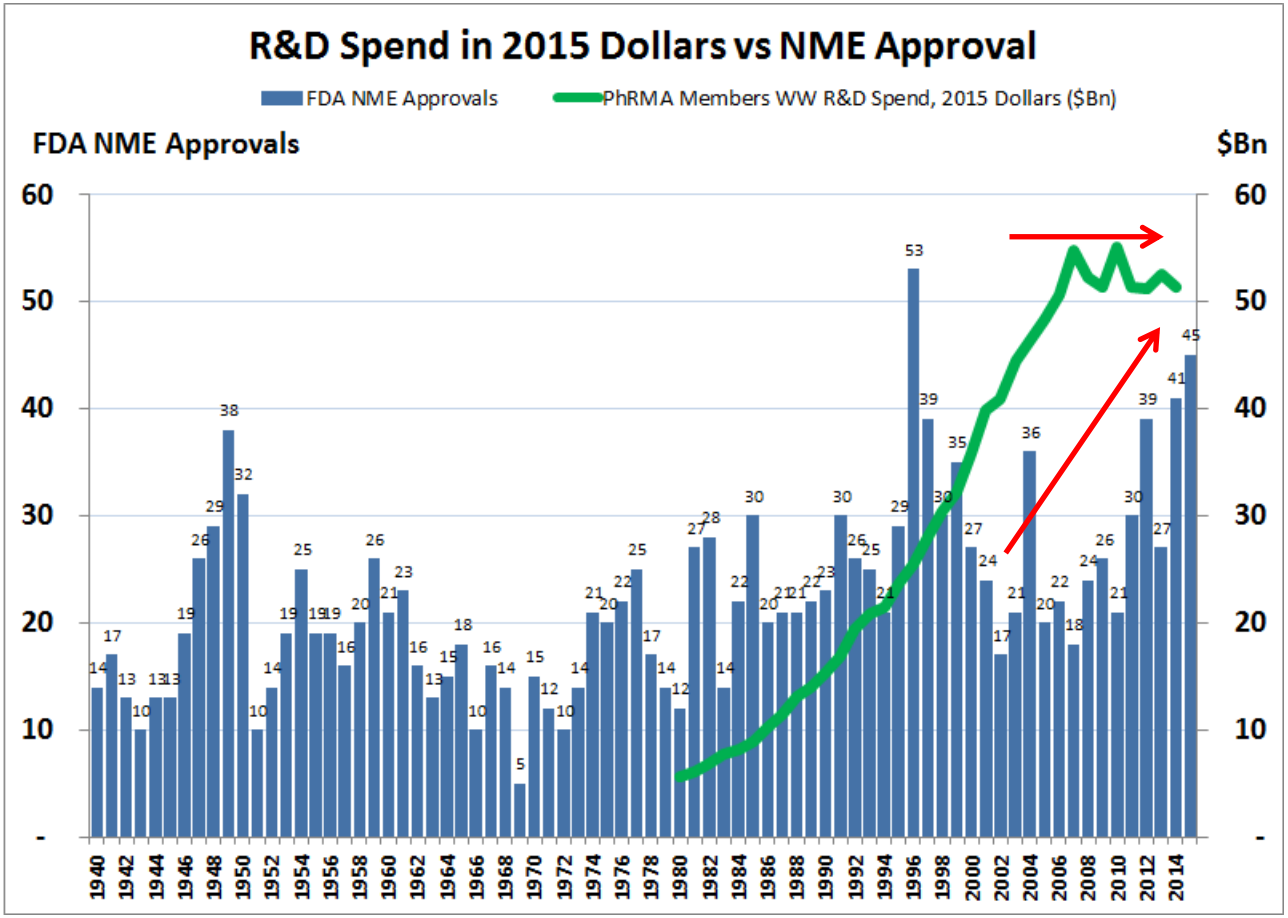
Source: Tufts, Mizuho Research

But R&D dollars spent per drug approved is decreasing ➔ more efficient spend



Source: FDA, PhRMA, Mizuho Research

In other words, R&D spend has been flat, but number of drug approvals has increased



Source: FDA, PhRMA, Mizuho Research

From a P&L management view, R&D as a % of sales has also become more efficient

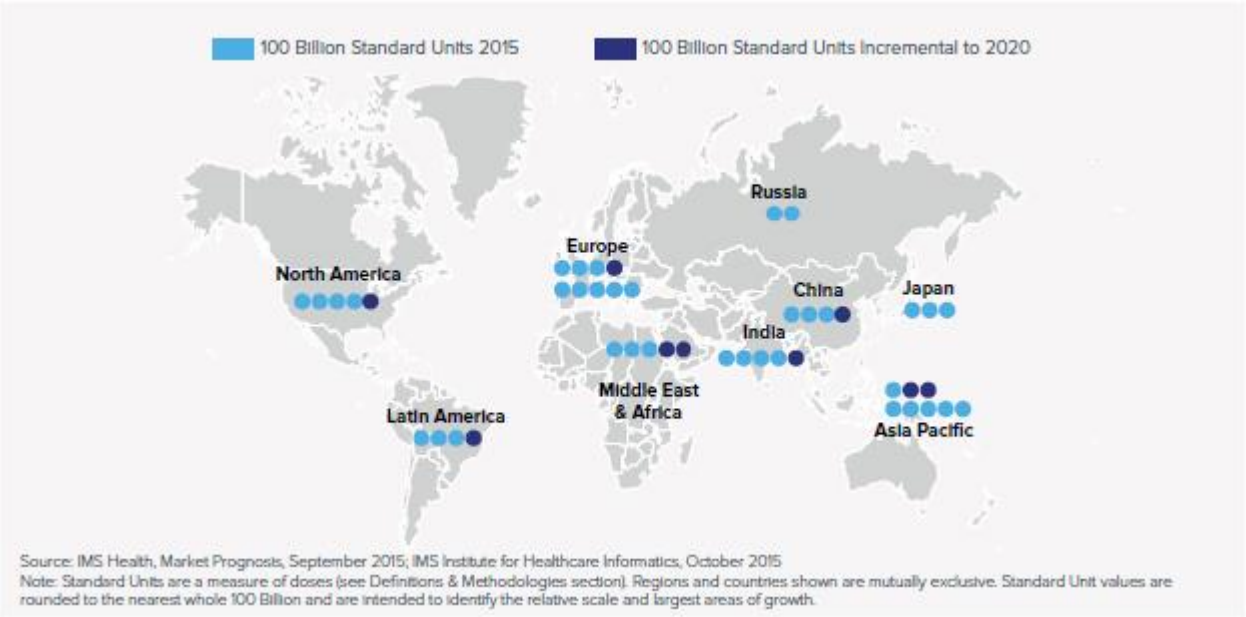
WW Prescription Sales ($bn)															
Year	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Pharma R&D Spend	108.2	119.9	129.3	127.6	128.8	136.0	135.0	137.3	141.6	140.8	143.8	147.4	151.5	155.4	159.8
Growth per Year		+10.8%	+7.9%	-1.3%	+1.0%	+5.6%	-0.8%	+1.7%	+3.1%	-0.5%	+2.1%	+2.5%	+2.8%	+2.6%	+2.8%
WW Prescription (Rx) Sales	542	599	650	665	687	728	716	723	743	734	772	816	872	926	987
R&D as % of WW Rx Sales	20.0%	20.0%	19.9%	19.2%	18.8%	18.7%	18.9%	19.0%	19.1%	19.2%	18.6%	18.1%	17.4%	16.8%	16.2%

Source: Evaluate Pharma, Mizuho Research

R&D as % of sales decreasing with time

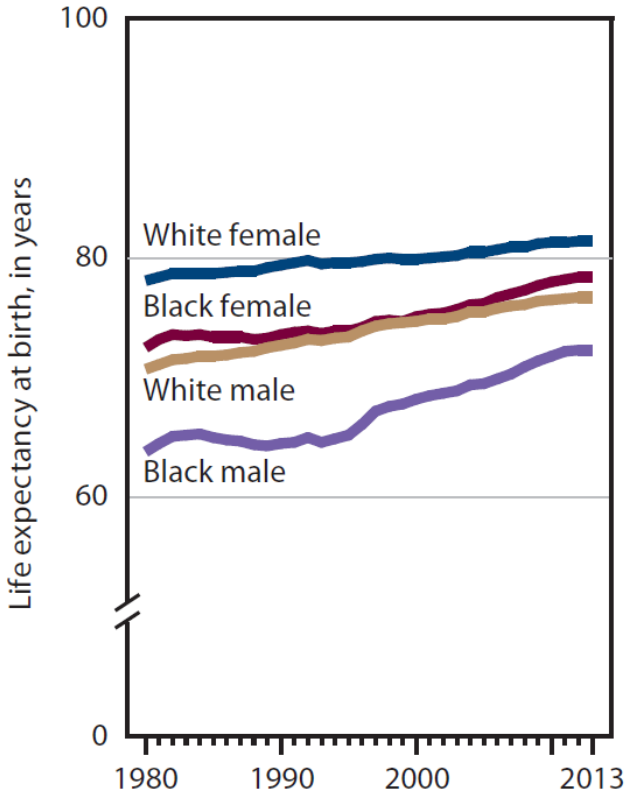
And sales likely has an long-term upward bias because drug usage is only expected to increase globally, even in the West

- More drug access
- Better medications
- Aging population
- Growing population



Source: IMS

Life expectancy is also increasing and that should arguably help drug usage (i.e. sales) as well in the long run



Source: CDC

Large molecule drugs are steadily becoming a larger part of total WW drug sales which should decrease patent cliffs gradually (arguably even with biosimilars present)

Worldwide Prescription Drug & OTC Sales by Technology (2006-2020)

Source: EvaluatePharma® 22 May 2015

Technology	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Biotechnology	14%	15%	16%	17%	18%	18%	20%	22%	23%	24%	25%	25%	26%	26%	27%
Conventional/Unclassified	86%	85%	84%	83%	82%	82%	80%	78%	77%	76%	75%	75%	74%	74%	73%
Total Rx & OTC Sales	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**

Sector fundamentals to think about …

…how concerned should I be about all these drug pricing talks?

…are drug pipelines healthy enough to create new sales?

…is orphan drug spend increasing?

…do we have a friendlier FDA today?

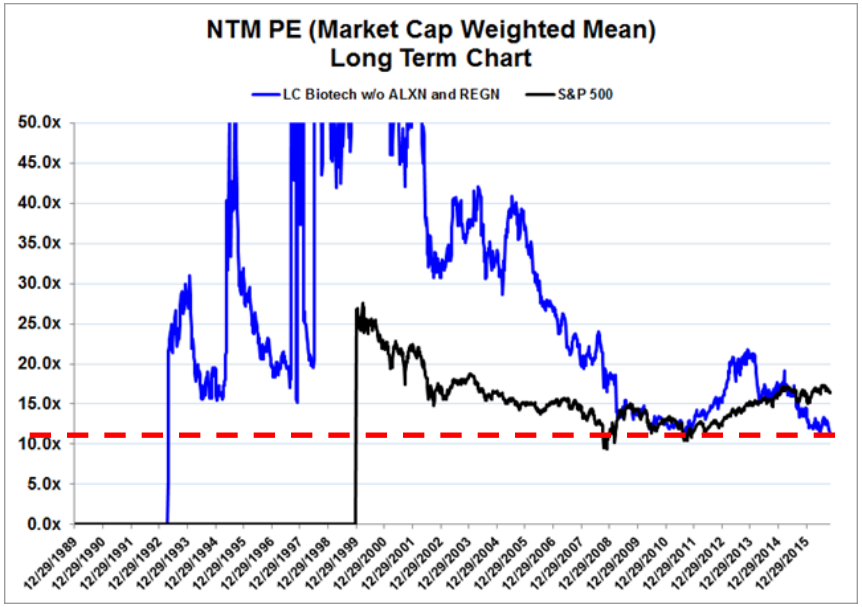
…is R&D productivity increasing?

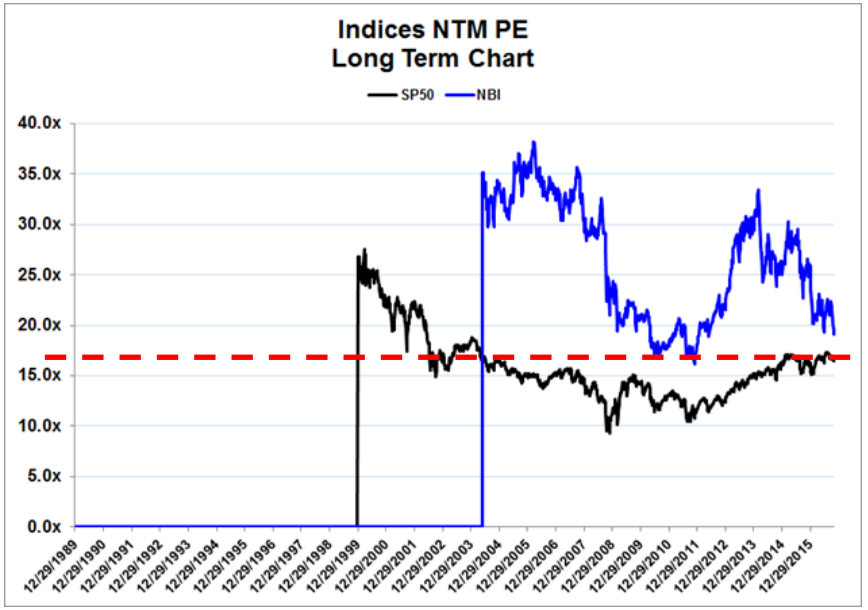
…what will get the sector to rebound in the near-term?

…how has biotech done historically when interest rates increase?

The broader biotech market has come down about 35% since its July 2015 highs

Biotech valuations are at or getting closer to achieving their historical lows





Large-cap biotech trading at par with its all-time low

Broader biotech trading at a 18% premium to its all-time low

Sources: FactSet, Mizuho Research

We are looking for a 3 things that can help turn the biotech market around

1. Positive clinical data
2. M&A
3. Clarity on the political landscape

1

Here are some important catalysts for 2016 and 2017 to watch

- LLY's Solanezumab, Phase 3 in Alzheimer's (by end 2016)
- REGN's Praluent, Phase 3 CV interim look (end Nov 2016)
- AMGN's Repatha, Phase 3 CV Outcomes data (1Q'17)
- ACOR's CVT-301, Phase 3 in Parkinson's (1Q'17)
- CELG's Ozanimod, Phase 3 in MS (1H'17)
- MRK's BACE, Phase 3 in Alzheimer's (mid-17)
- MRK's Anacetrapib, Phase 3 CV Outcomes data (mid-17)
- AXON's RVT-101, Phase 3 in Alzheimer's (2H'17)

2 With valuations where they are, M&A is on the table

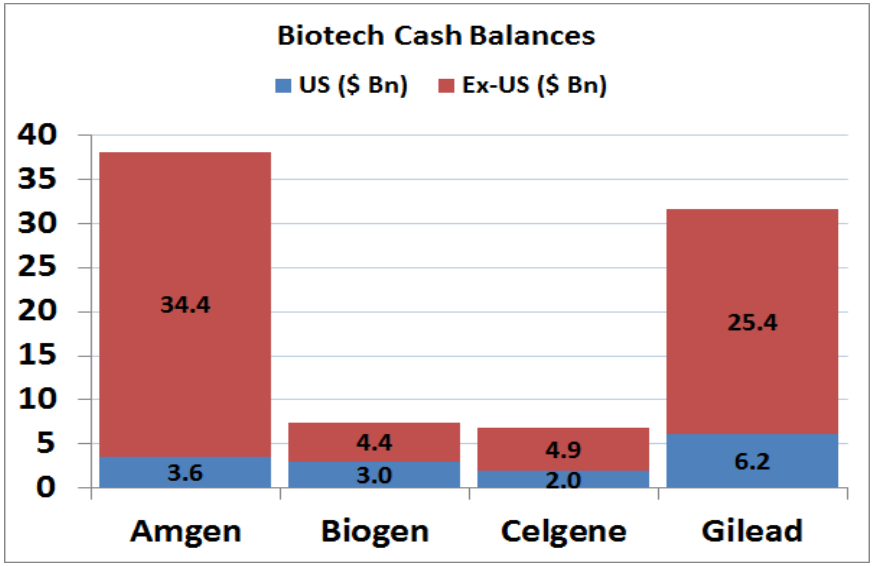
Look, if you're in a smaller biotech company, and it's pre-commercial, and you have to raise revenue, there are only a couple of ways to do that. And as it gets more difficult and less attractive to raise money from the financial markets, obviously other alternatives become more attractive. And we hope that and we believe that will all move in the favor of companies like us who are out to in-license or acquire additional compounds. So we'll see. It takes a while for that to happen. We'll take the current views of the market to hold for a while or deteriorate further. If that happens, then I believe there'll be interesting opportunities for us.

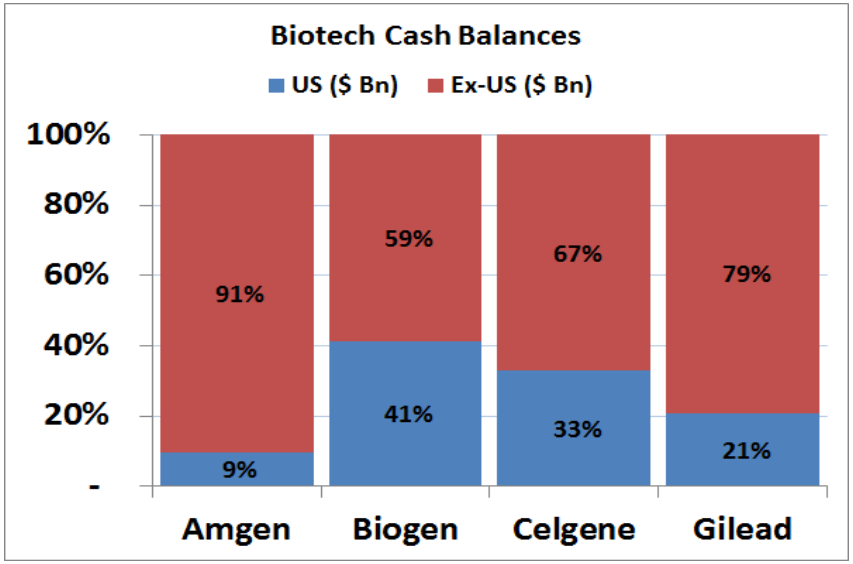
- BIIB, 1/27/16

And that's how we're thinking about it. So, we're always looking. We clearly have talked about over the past year now with the successful launch of Hep-C and with the next generation of HIV products that we've got a lot more capacity to think about M&A. And clearly to your point, with our guidance, to fuel that next level of growth...

- GILD, 2/24/16

Large cap biotech companies have a lot of cash … mostly Ex-US though…this may limit potential M&A inside the U.S.





Source: FactSet, Mizuho Research

	AMGN	BIIB	CELG	GILD
Total Debt ($Bn)	$35.3	$6.5	$14.3	$27.1
Debt to UFCF (2017)	3.3x	2.1x	2.2x	1.4x

3 Clarity on the political landscape …

- A few things to think about here:
  - Who is going to be the next president?
  - How will that person address drug pricing?
  - How much is drug pricing just a platform topic vs a post-election topic?
- We won't know all the answers on November 8th
- But the fact that we will know who will at least be president should make it easier to work with the road ahead, in our view, whatever it may be

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Sector fundamentals to think about …

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…is orphan drug spend increasing?

…do we have a friendlier FDA today?

…is R&D productivity increasing?

…what will get the sector to rebound in the near-term?

…how has biotech done historically when interest rates increase?

All caveats that come with any analysis, we wanted to point out a very important one here: we are not QUANTS, but we tried anyway to see if we could find anything useful

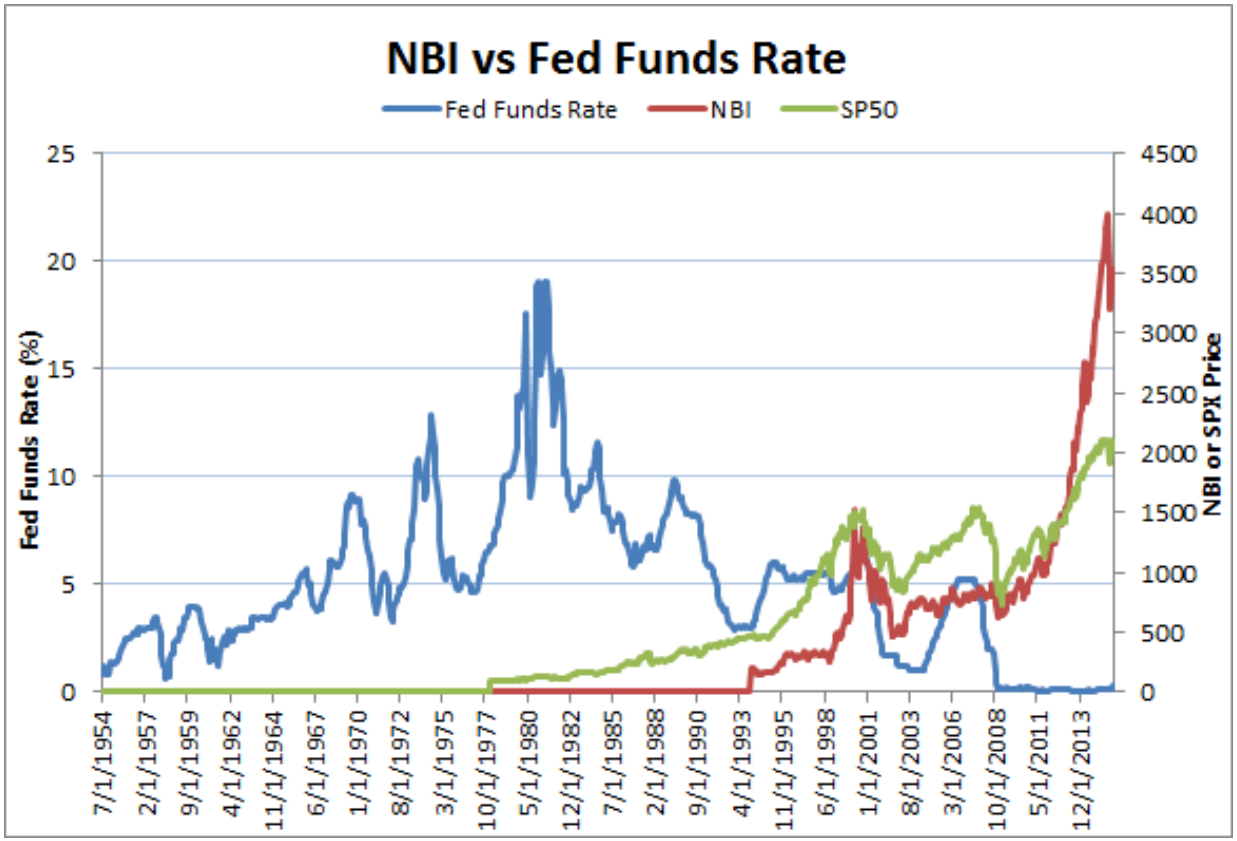
Here is our methodology (1)

- We kept it pretty simple
- We pulled **Fed funds rates by month going back to 1954**
  - This is the rate that the Fed adjusts and the one people talk about when they say "the Fed raised or decreased rates"
  - It's also the rate that banks charge each other for overnight loans
  - We looked at each month to see if the rate went up or down
- We pulled **monthly NBI price data as far back as we could … Dec 1993**
  - The NBI is the Nasdaq Biotechnology Index
  - It has 190 biotech companies … large and small
  - It's market-cap weighted
- We also pulled **monthly S&P500 price data**

Here is our methodology (2)

- Our analysis:
  - We set the performance of the NBI and SPX to a **1-month lag** vs the Fed funds rate movement
  - For example, if the Fed raised interests rates February 1, 1995 (vs January 1, 1995), we were interested in how the NBI and SPX performed between Feb 1 and Mar 1
- We looked at NBI performance on an **absolute and relative basis** to the SPX

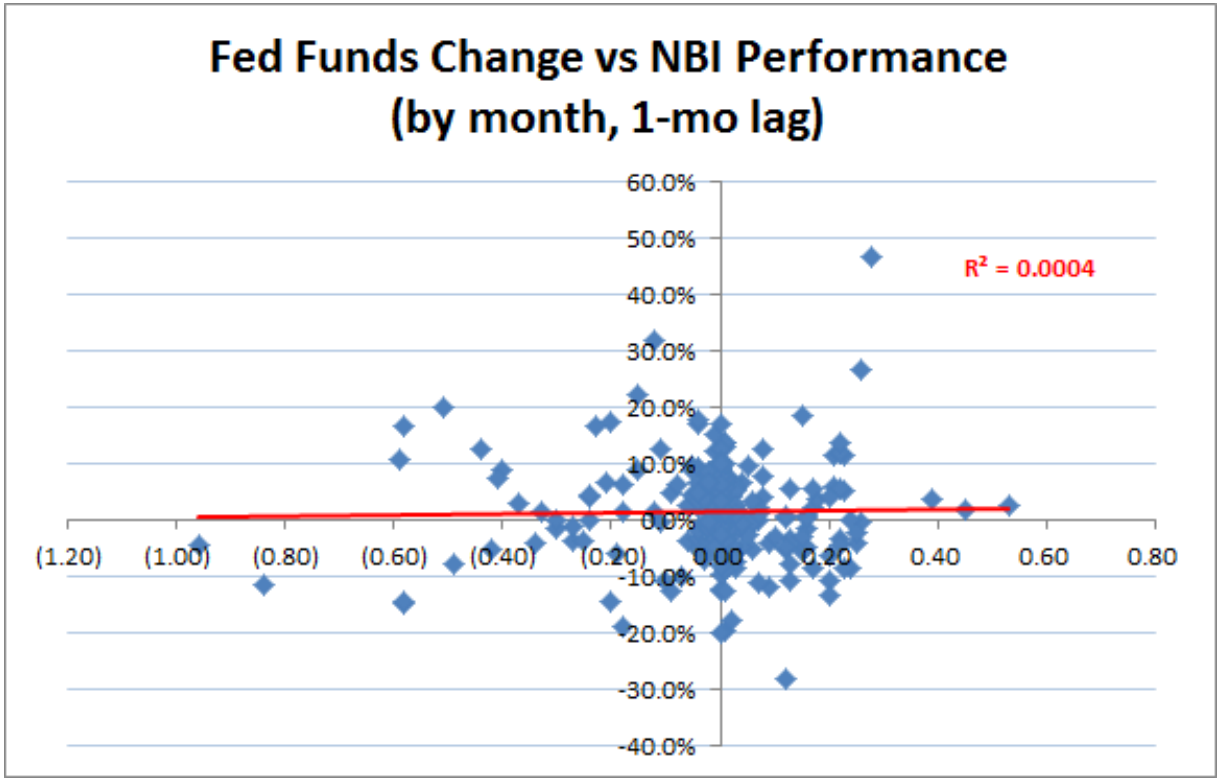
For starters, let's just look at a basic chart: Fed funds rate, NBI and SPX … over time



Source: FactSet, Mizuho Research

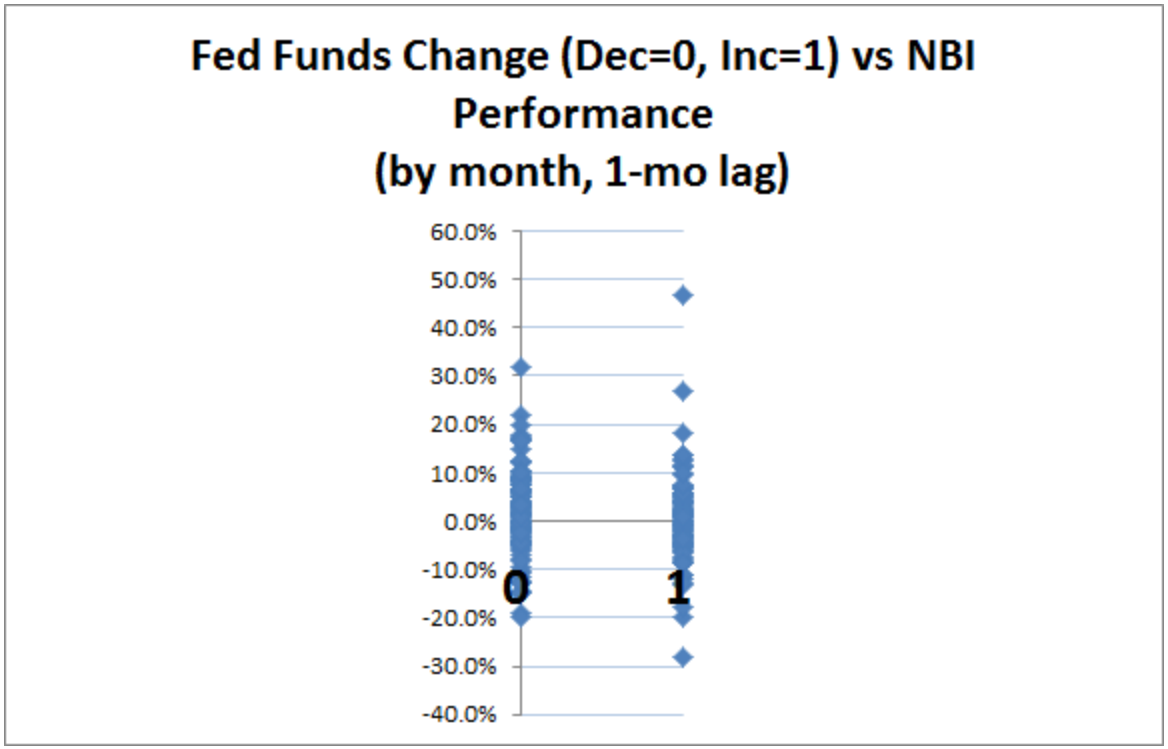
We think it's hard to take anything away from this chart, so we took a closer look at the individual data points

We compared magnitude of Fed funds rate movements to magnitude of NBI performance … no correlation



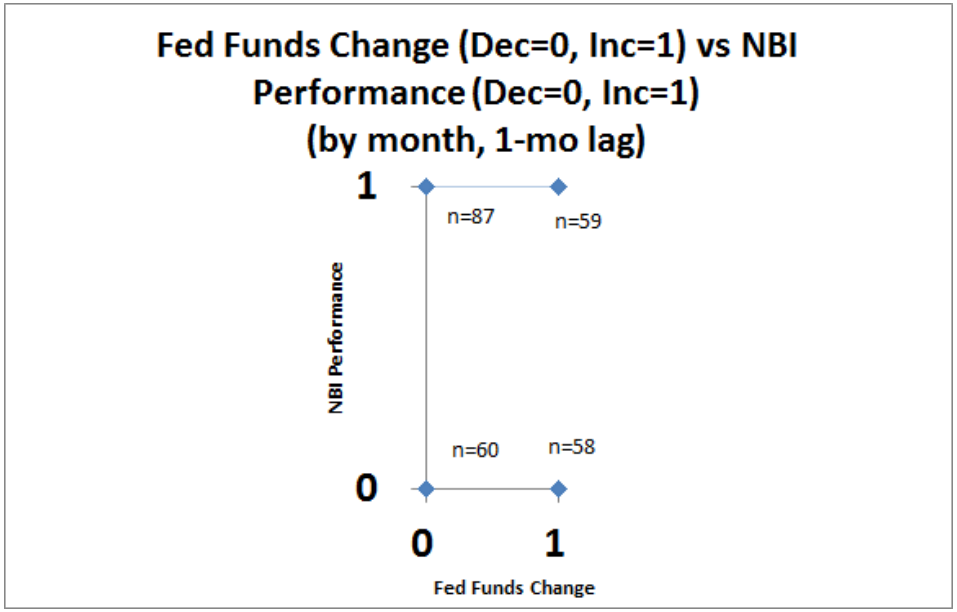
Source: FactSet, Mizuho Research

We also look at this on a binary basis … Fed funds rate either went up or down vs magnitude of NBI performance … no visible pattern



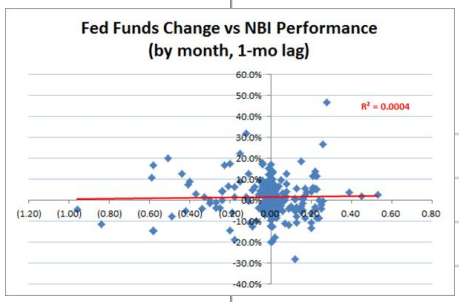
Source: FactSet, Mizuho Research

So, then we looked at both Fed funds rate and NBI performance on a binary basis … possible slight bias for an inverse relationship, but only when rates decrease … no difference in NBI performance when rates increase



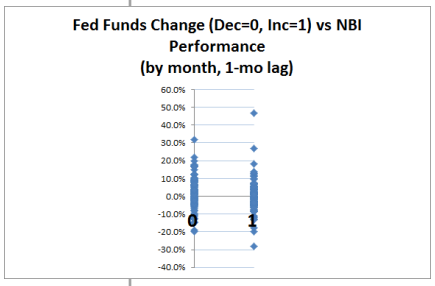
Source: FactSet, Mizuho Research

We observed similar results when we looked at NBI performance on a relative basis to the SPX … again, no correlation here



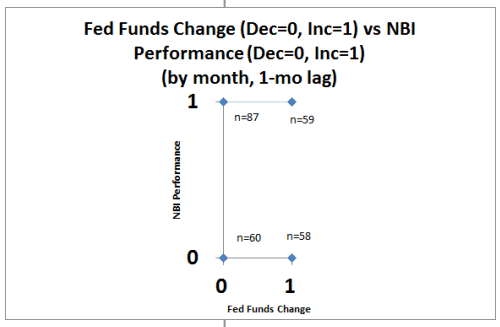
Source: FactSet, Mizuho Research

Again, no visible pattern in NBI/SPX when we looked at Fed funds on a binary basis



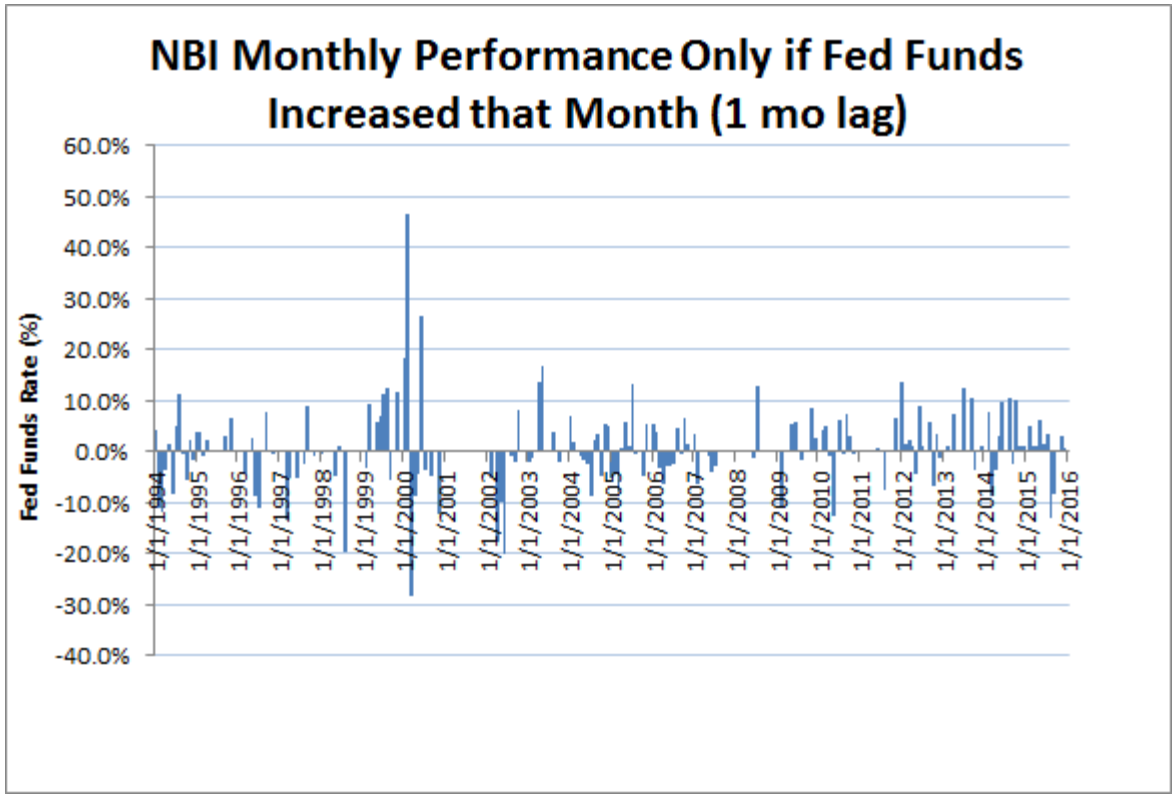
Source: FactSet, Mizuho Research

Again for NBI/SPX, possible slight bias for an inverse relationship to rate movements, but only when rates decrease … no difference in NBI/SPX performance when rates increase



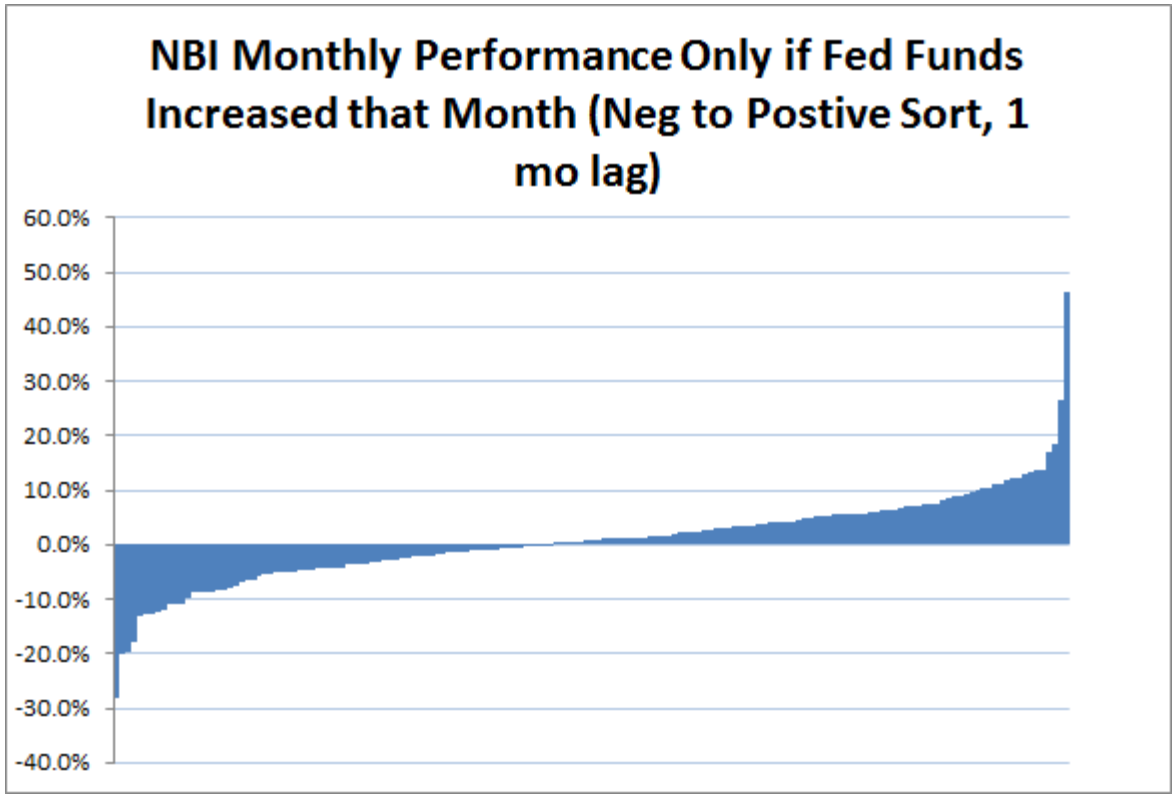
Source: FactSet, Mizuho Research

Then, we isolated NBI movements ONLY if the Fed INCREASED rates … no visible pattern



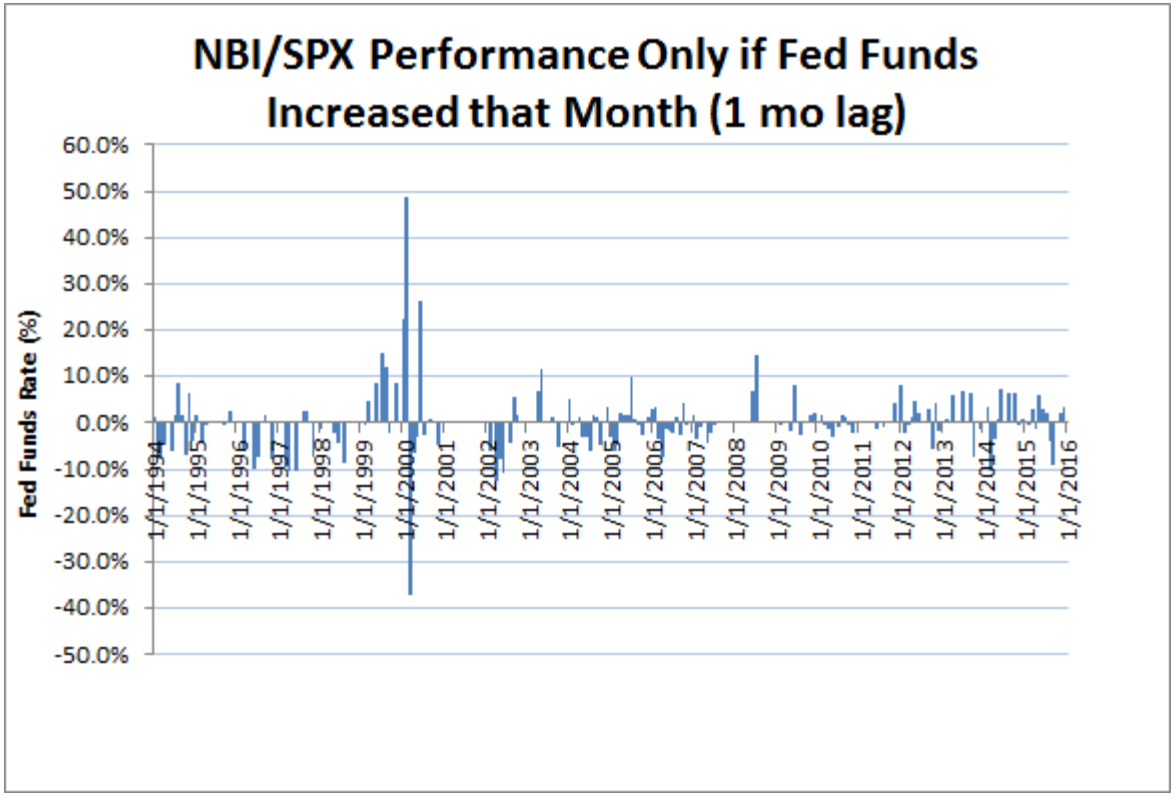
Source: FactSet, Mizuho Research

We sorted NBI performance from negative to positive to see if we could identify a trend … again, we don't see a clear pattern



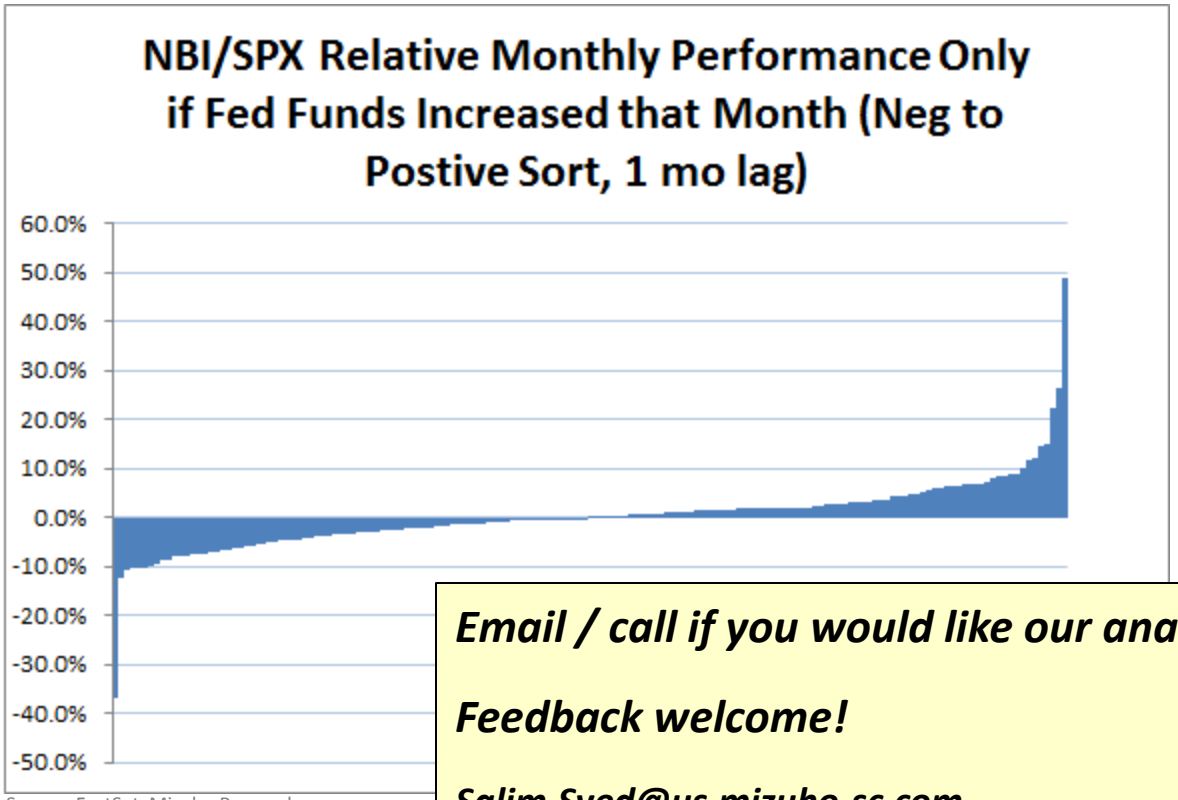
Source: FactSet, Mizuho Research

So we looked at NBI / SPX to see if there was any difference … again, we isolated results for only upward movements in interest rates



Source: FactSet, Mizuho Research

And we sorted NBI/SPX performance … again, no clear pattern when the Fed increases rates



Source: FactSet, Mizuho Research

Email / call if you would like our analysis in Excel!

Feedback welcome!

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Sanity checking our results … we think they make sense

- Most biotech investors we speak to pay very little attention to movements in Fed fund rates
- Investors seem more concerned with stock specific catalysts
- We didn't detect any visible relationship between rates and biotech stock performance in our analysis
  - Again, we aren't QUANTS
- At least superficially, this makes sense to us as stronger drivers of biotech stock performance could very well be how drug data actually look in trials or how drugs sell post approval

Biotech Sector Thoughts Conclusion

CONCLUSIONS …. our key message

Biotech had an amazing run since 2009 .. Up 600-700% to the July 2015 peak

However, biotech has had a decent pullback / breather since then … down about 35% .. and **P/E valuations are at or approaching historical lows**

We believe putting the **presidential election behind us will be healthy for the sector** as it should make it easier to work with the road ahead, whatever it may be

Decent number of Phase 3 catalysts in the space for remainder 2016 / 2017

Also higher level … **we like the fundamentals of the sector** (drug pipelines, R&D productivity, "friendlier" FDA, etc.)

We believe **drug pricing pressures are a risk** more now than before, but at the same time believe the problem will result in iterative, gradual resolutions if anything … not one resolved overnight

M&A is possible, but we note **US cash balances of LC biotechs are not massive**

BOTTOM LINE: Overall though, we like the sector here … it may take another quarter or two of stabilization, but the general picture to us looks decent for 2017

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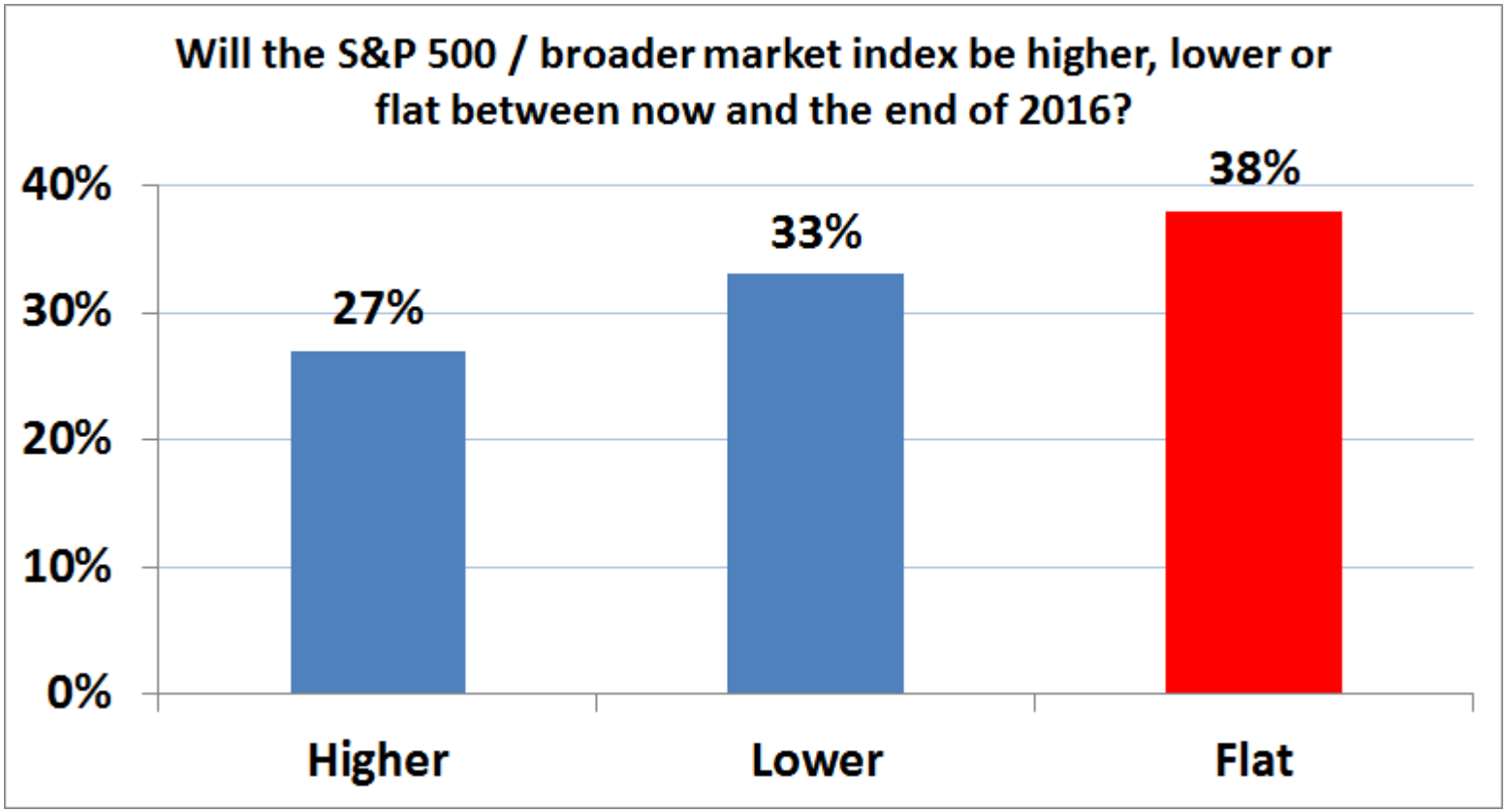
We did a mini-survey at a Boston lunch late September …

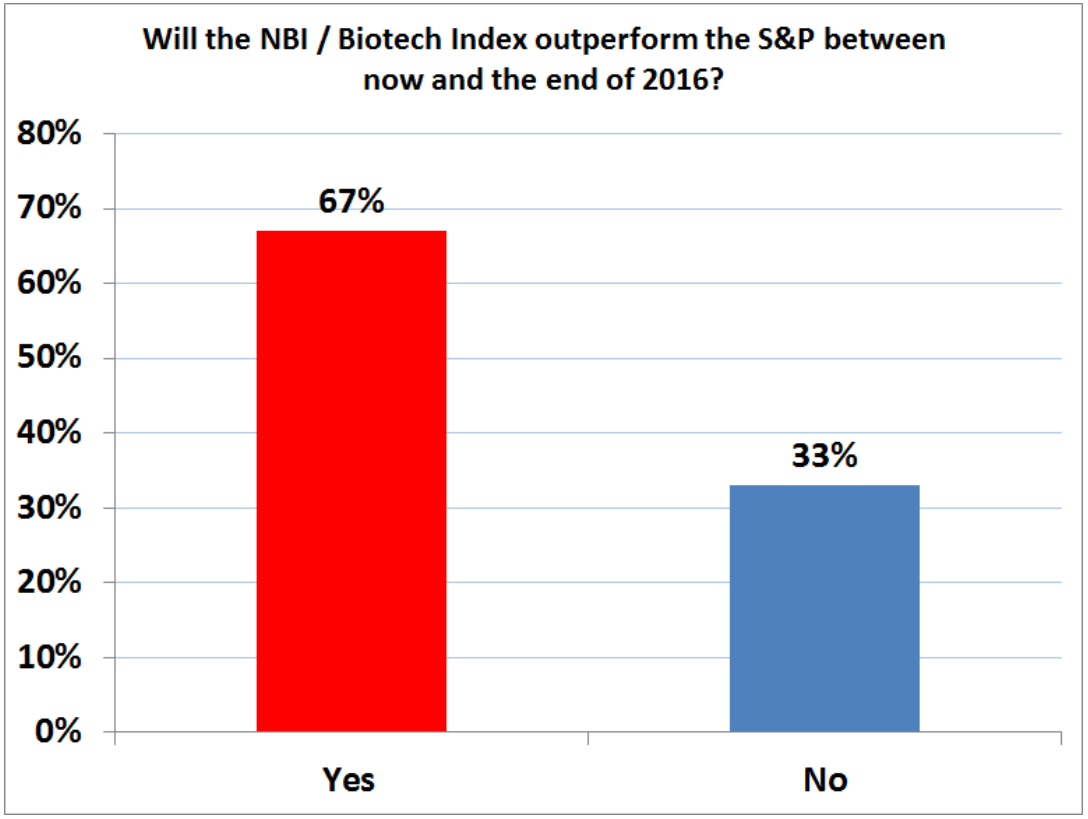
Let's look at the result ➔

Will the S&P 500 / broader market index be higher, lower or flat between now and the end of 2016?



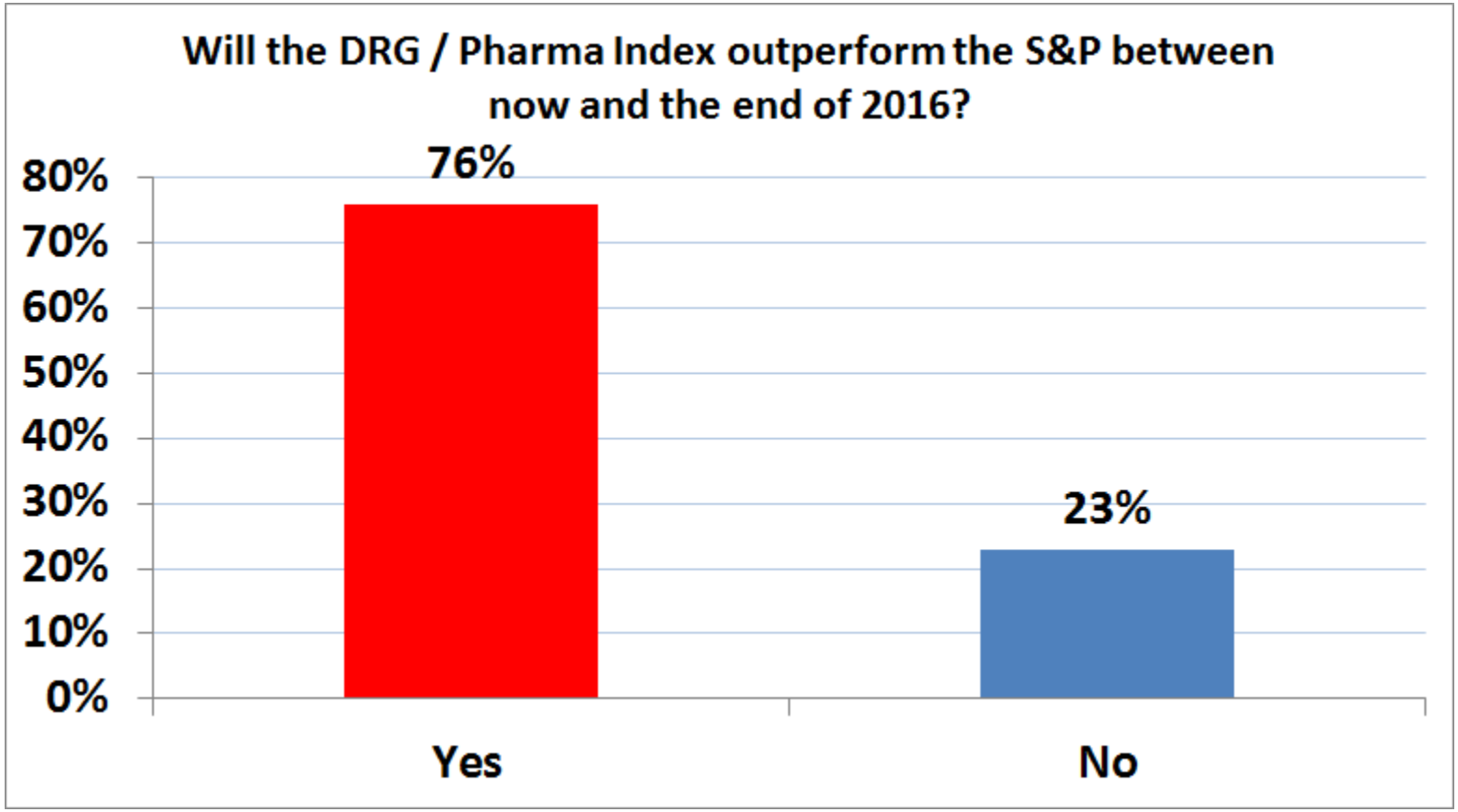
Source: Mizuho Research

Will the NBI / Biotech Index outperform the S&P between now and the end of 2016?



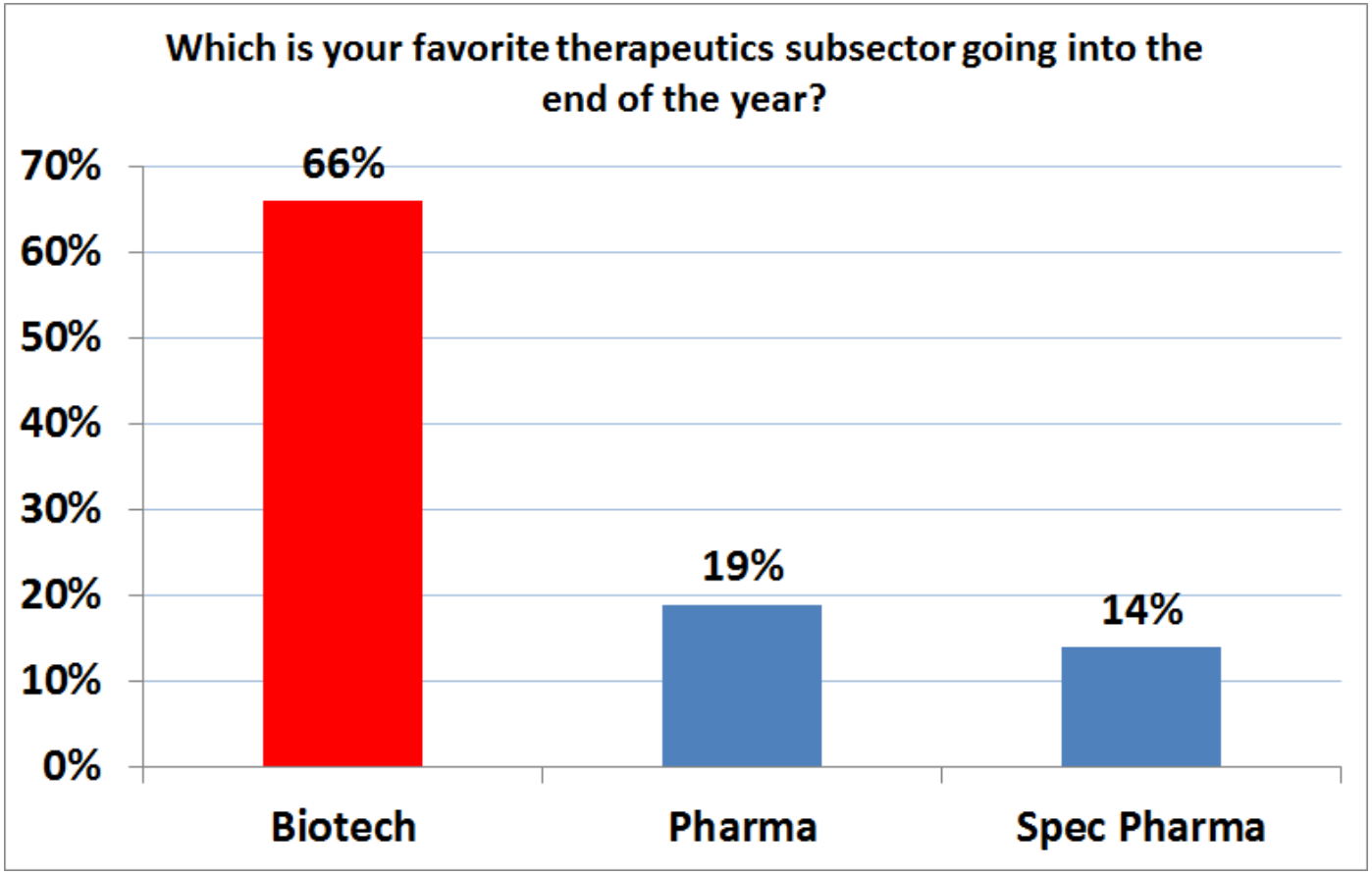
Source: Mizuho Research

Will the DRG / Pharma Index outperform the S&P between now and the end of 2016?



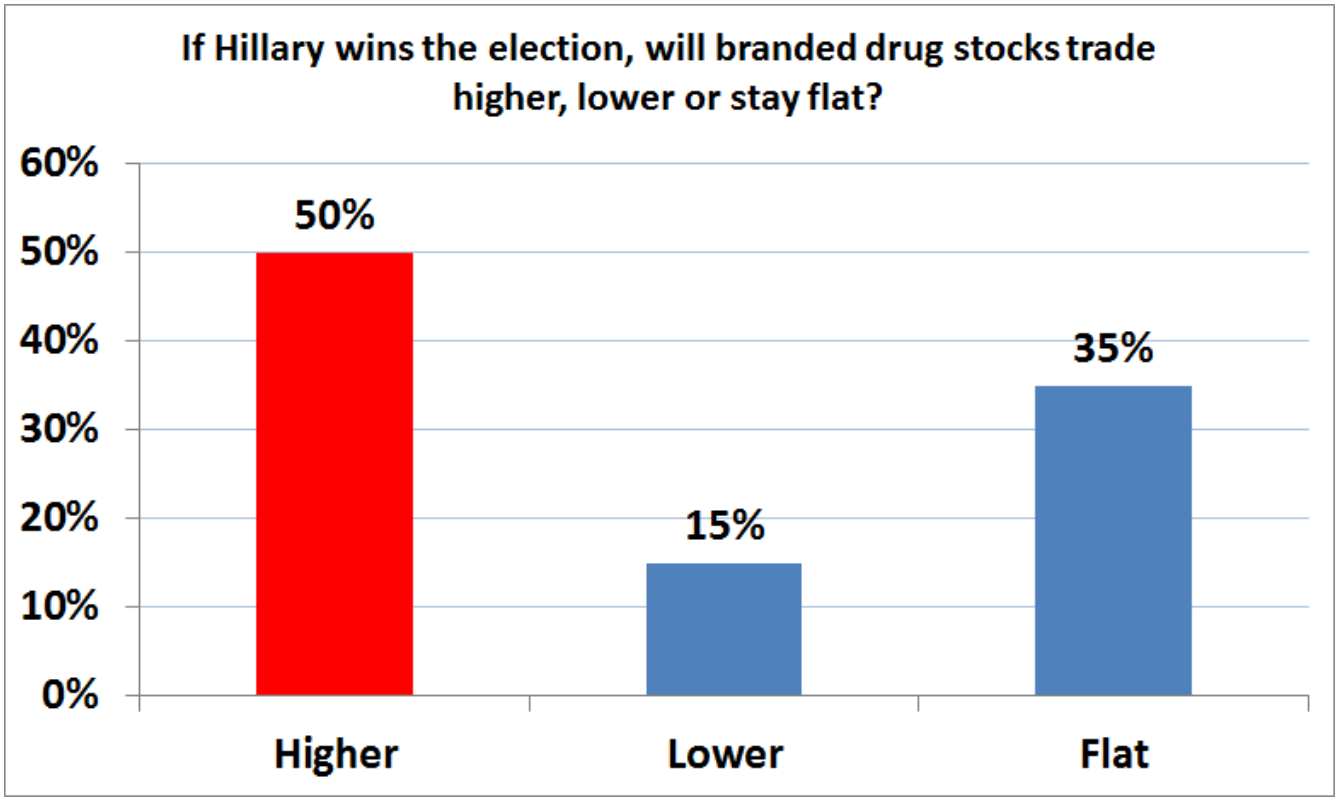
Source: Mizuho Research

Which is your favorite therapeutics subsector going into the end of the year?



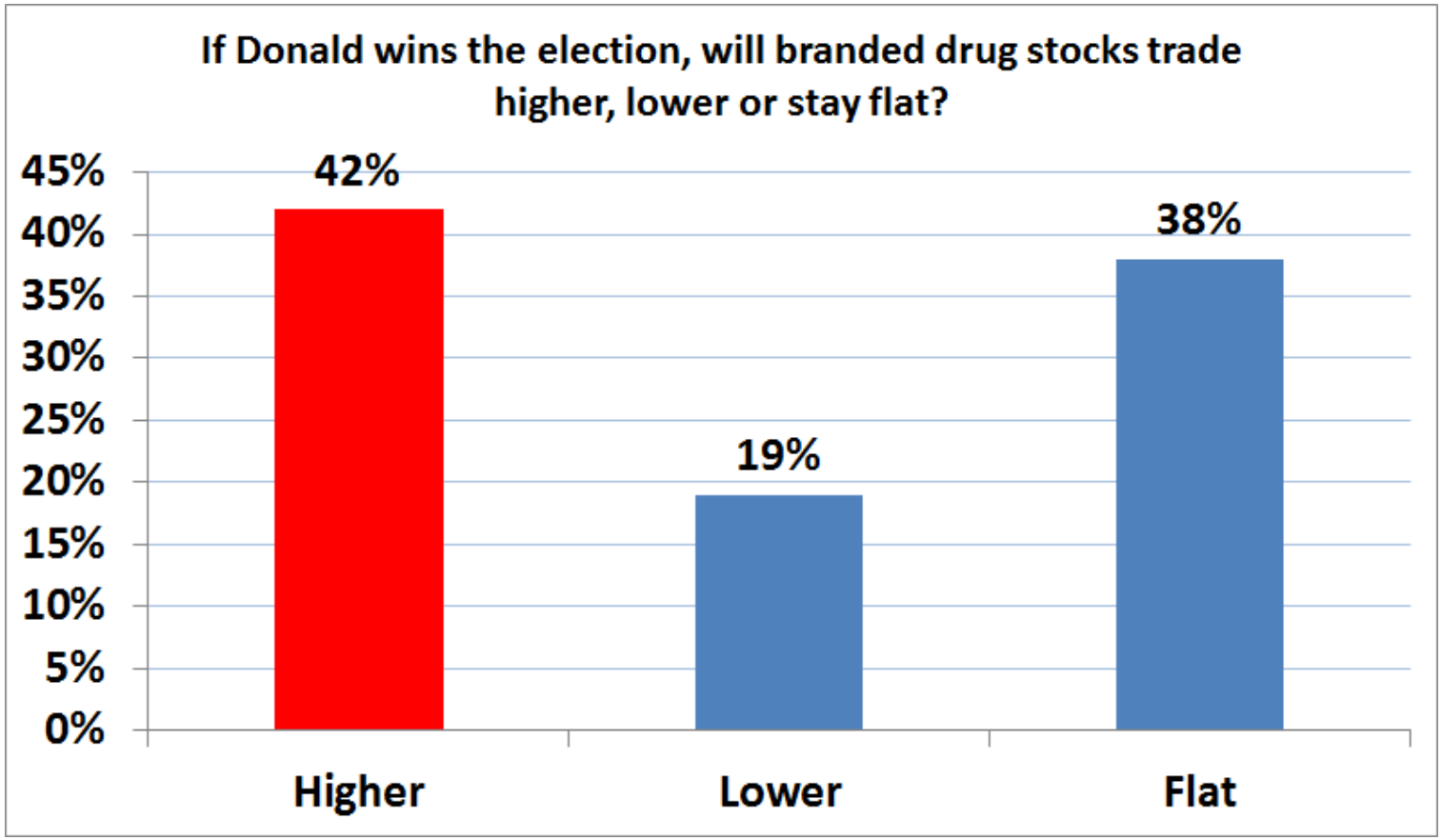
Source: Mizuho Research

If Hillary wins the election, will branded drug stocks trade higher, lower or stay flat?



Source: Mizuho Research

If Donald wins the election, will branded drug stocks trade higher, lower or stay flat?



Source: Mizuho Research

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What are we saying about AMGN?

BUY with a price target of $164

REPATHA. We like the catalysts surrounding Repatha (GLAGOV detailed data Nov 15th @ AHA) and FOURIER (CV outcomes trial 1Q'17)

VALUATION. We think the recent price decline (on 3Q'16 Enbrel commentary) may be overblown, but even if we're wrong, we will likely learn more about Repatha first

There is potential for significant upside potential – Repatha may eventually receive approval for primary prevention

We think Erenumab and Romosozumab are likely to be approved (and risk is mitigated by data thus far)

We believe Amgen can hit their 2016 and 2018 guidance.

Where do we expect pushback?

Amgen's core franchises (Neutropenia, Anemia, and Enbrel) face pressures due to competition, possible entry of biosimilars, and price. Legacy biz faces more uncertainty now. The bone and oncology franchises may not generate enough revenue to compensate in the near term.

Risk / reward is skewed down for near-term late-stage pipeline events

What are we saying about BIIB?

NEUTRAL with a price target of $290

- Stock trades above its DCF valuation but below its PE valuation
- This is arguably the "GARPy" play among the large-cap biotechs

We are Neutral, but we still think BIIB has some good programs … it may be a matter of time before we get excited again … just not now

We couldn't recommend the stock ahead of Tecfidera's upcoming litigation and several other more near-term competitor catalysts (potential pressure)

Nusinersen has largely played out in our view, but could be a new product launch in 2017 (if the drug gets approved)

- We recently got positive interim data for ENDEAR study, and the company has filed

We believe Aducanumab has a 60% shot of working in AD

- CDR-SB had perfect dose response curve in Phase 1B; dose/time dependent reduction in amyloid reduction as well

We believe BIIB will generally hit its 2016 guidance (top and bottom lines)

Where do we expect pushback?

Hasn't BIIB lost a ton of value already from it's peak? And the company just did a huge share repo in the back half of 2015.

Don't the Phase 2 drugs like LINGO and STX-100 have call-option value? So risk / reward should be skewed up, no?

Shouldn't I be buying this for the takeout potential?

What are we saying about CELG?

BUY with a price target of $130

- Stock trades above its DCF valuation but below its PE valuation
- This is a "growthy" large-cap biotech stock

We carry about a 2/3 shot of Ozanimod and GED-301 working in their lead indications

CELG has a series of potential single/double base hits in the near to medium term that can add value

CELG also has several assets that the we and the street currently assign little to no credit

- Essentially, these are largely "call options" for the company

We see minimal risk to the base business (largely Revlimid), but acknowledge the possibility of other generic filers

CELG has been an active buyer of its own stock, has historically revised its long-term guidance upward, and currently seems to believe that its 2020 guidance is conservative

- We believe CELG can hit its 2020 guidance (and 2016 guidance)

Where do we expect pushback?

The setup going into Ozanimod and GED-301 data readouts is not ideal and the clinical data we have in hand is limited

Other generic filers could arise and cut Revlimid's patent life (and much of the current base biz)

CELG is the most expensive large-cap biotech stock

What are we saying about GILD?

Buy with a price target of $88

- This is a valuation call … not a call on catalysts, etc.
- Only stock in our coverage universe that trades below our Zero Pipeline case ($81), even just on a DCF basis ($75)
- P/E currently at 6x … GILD trough PE … and >40% below biotech historical trough of 11x

Investor base business concerns are legitimate, but in our view not necessarily being weighed fairly against the revenues the company may be able to generate (even w/o HBV and NASH)

Currently very little in stock for GILD's largely early-stage pipeline

- We agree with this view and believe this presents a "call option"
- HBV and NASH failures can be replaced with external BD candidates

GILD has been an active buyer of its own stock

Management team still highly regarded in our view

Where do we expect pushback?

HCV business will suffer greater declines than your base case … pricing pressures are only getting worse and there is no guarantee GILD will be able to treat from the remaining 1.5MM diagnosed/ untreated patients (in the US)

GILD doesn't have a "real" pipeline … I don't see how the company will grow

What if management buys something I don't like or they pay too much out of desperation

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Buy:	Stocks for which the anticipated share price appreciation exceeds 10%.
Neutral:	Stocks for which the anticipated share price appreciation is within 10% of the share price.
Underperform:	Stocks for which the anticipated share price falls by 10% or more.
RS:	Rating Suspended - rating and price objective temporarily suspended.
NR:	No Rating - not covered, and therefore not assigned a rating.

Rating Distribution

(As of 11/04)	% of coverage	IB service past 12 mo
Buy (Buy)	41.89%	45.95%
Hold (Neutral)	55.85%	31.08%
Sell (Underperform)	2.26%	16.67%

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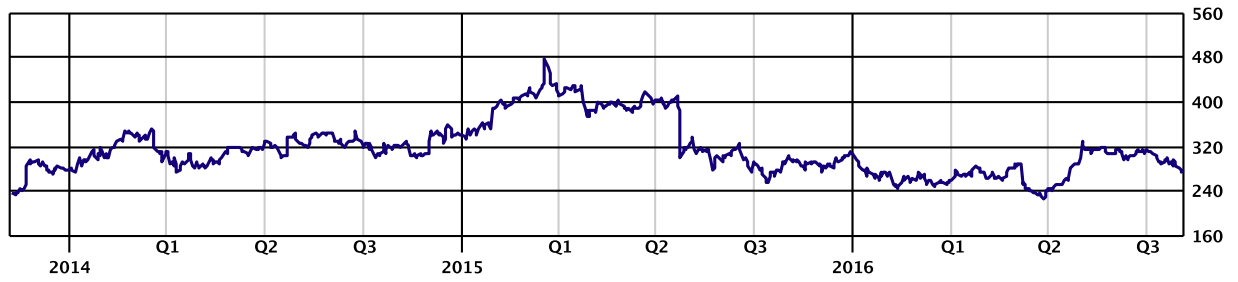
Rating and Price Target History for: Biogen Inc. (BIIB) as of 11-04-2016



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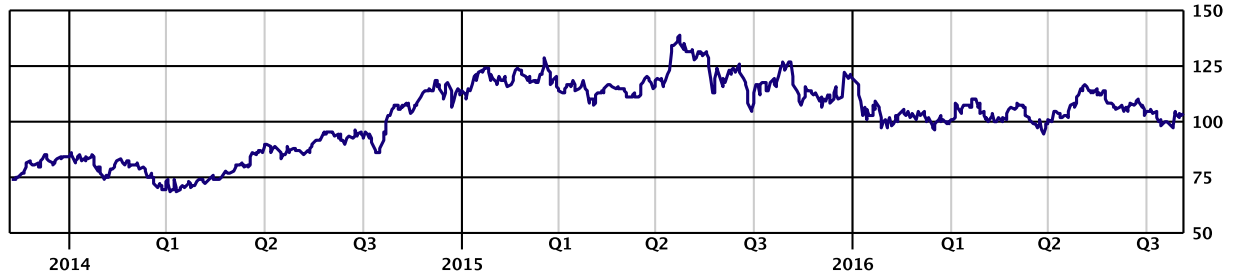

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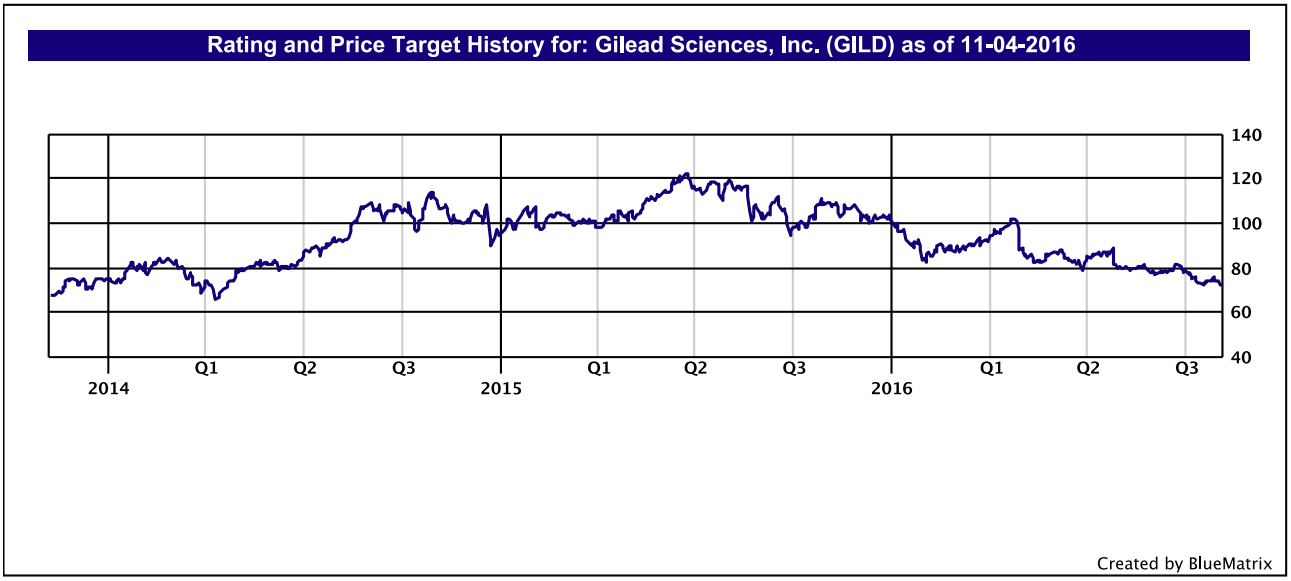

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