VitalTransformation

The impact of health technology made simple

PRELIMINARY FINDINGS
Calculating the Value and Impact of Accelerated Approvals

June 15th
11am - 12pm

PREPARED BY

Gwen Seidl
Project Manager

Harry Bowen
Consulting Economist

Duane Schulthess
CEO

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Accelerated Approval Project

Bio Biotechnology Innovation Organization

GLOBAL CEOINITIATIVE ON ALZHEIMER'S DISEASE

Rare Disease Company Coalition

GILEAD Creating Possible

SAREPTA THERAPEUTICS

TRAVERE THERAPEUTICS

ALEXION AstraZeneca Rare Disease

Bristol Myers Squibb

Kneller II – IP Origination Project

Bio Biotechnology Innovation Organization

U.S. Chamber of Commerce Global Innovation Policy Center

NOVARTIS

GILEAD Creating Possible

Pfizer

What is an Accelerated Approval?

- "In 1992, FDA instituted the *Accelerated Approval* regulations. These regulations allowed drugs for serious conditions that filled an unmet medical need to be approved based on a surrogate endpoint."
- "A surrogate endpoint … is a … laboratory measurement, radiographic image, physical sign, or other measure that … is considered reasonably likely to predict the clinical benefit of a drug, such as an effect on irreversible morbidity and mortality (IMM)."

The Accelerated Approval (AA) pathway was implemented to help fight AIDs/HIV, and was, until recently, considered a success in addressing areas of high unmet medical needs.

https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/accelerated-approval

Overview – Building the Accelerated Approval (AA) Model

VitalTransformation

1. Vital Transformation extracted a cohort of all accelerated approvals from 2001 – 2021, both for primary (125) and secondary (81) indications that had not been withdrawn (N=206).

2. We estimated the median and quartiles of time it takes to confirm an FDA's accelerated approval for converted primary therapies (n=48), modeling the entire primary cohort (n = 93).

3. Clinical phase trial costs per drug (in constant 2013 USD) were adapted from Joseph A. DiMasi (et al.) and K. Jayasundara (et al.); annual revenues were measured in constant 2013 USDs using the CPI index; NPVs are calculated using a 11% real cost of capital.

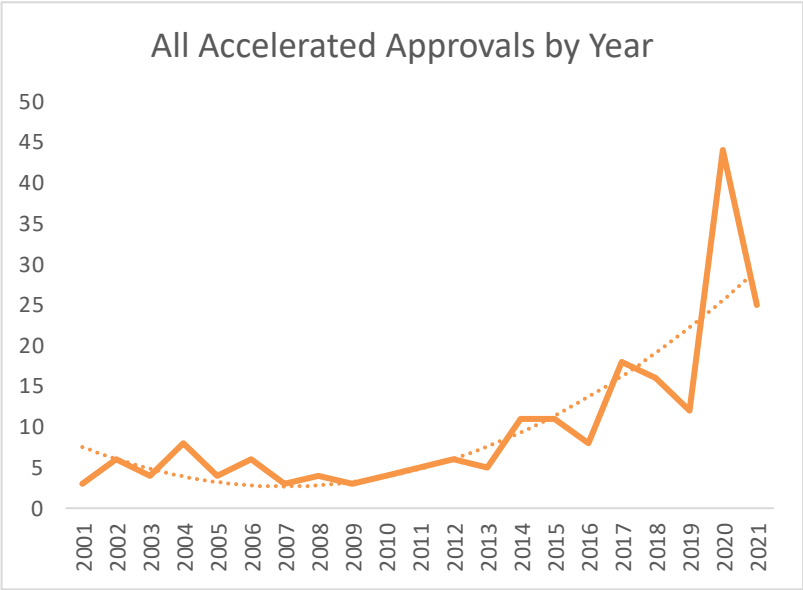
4. We allow for 11 years of revenue starting from the AA year.

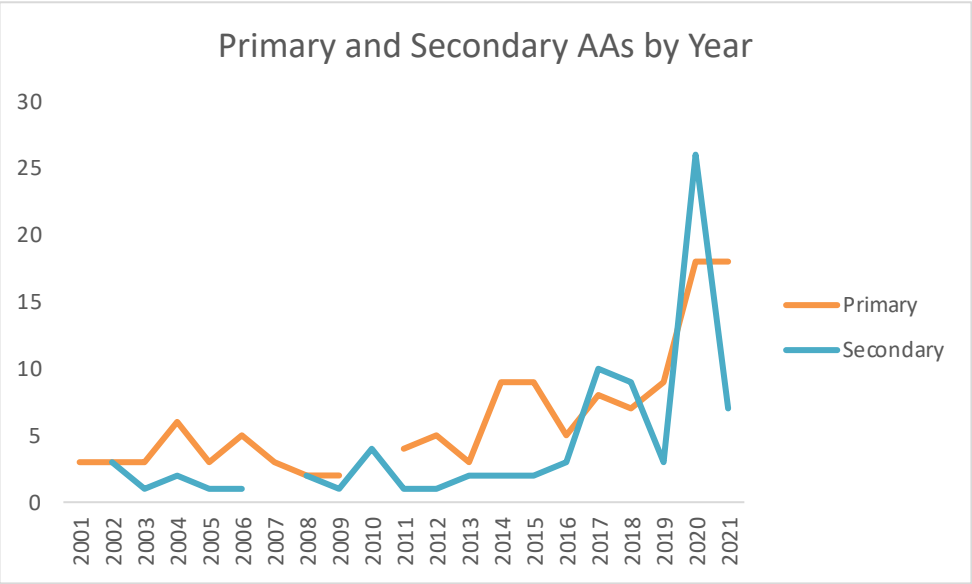
5. For therapies with no (future) revenue data, we predicted revenues by first estimating separate orphan/non-orphan revenue growth equations; the estimated growth rates where then applied using observed orphan/non-orphan mean revenue as the initial revenue value. NPVs were then computed assuming a 2, 3, 4, or 5-year delay for FDA approval.

6. We estimate the impact of trial size and secondary indications on the profitability of an asset, which ultimately impacts covered-lives due to any potential lost therapies.

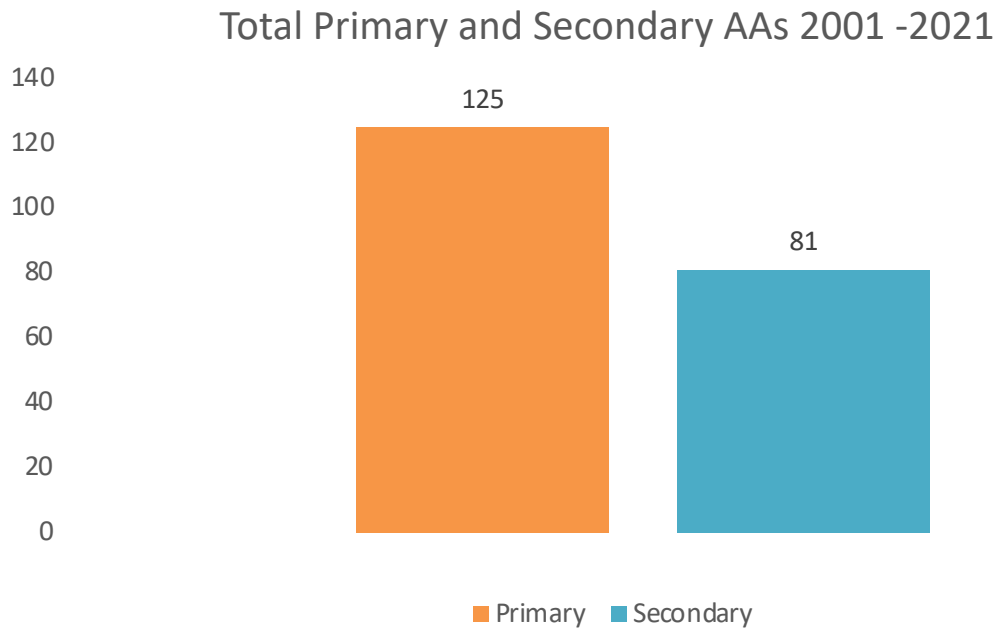
Accelerated Approvals are Increasing

2001 – 2021, n=206



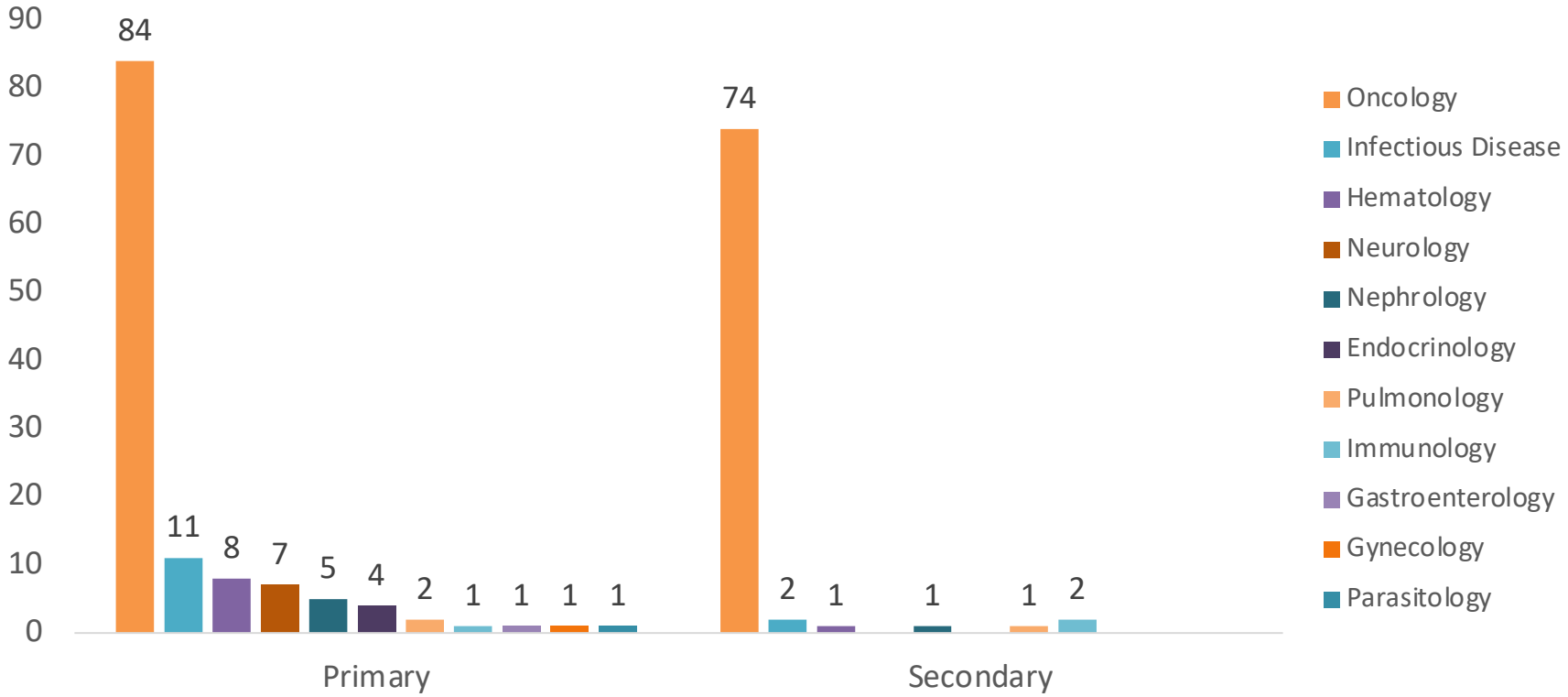


Primary Approvals are 60% of the Cohort



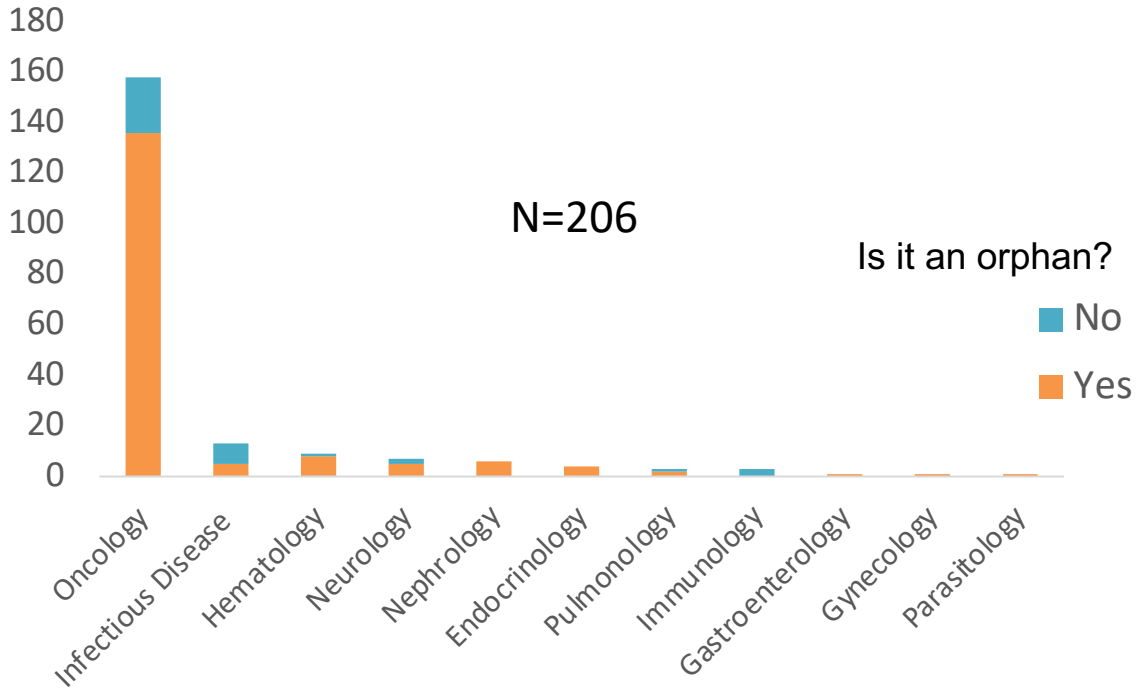
Indications by Approval Type

N=206 (oncology = 158, non-oncology = 48)



Orphan indications are 82% of our AA cohort

an orphan indication is < 200,000 persons in the US, 6 cases per 10,000



The extremely high number of orphan indications explains the need for the use of surrogate endpoints in the accelerated approval pathway.

Merits Of The Accelerated Approval Pathway Are Under Debate

Scott Gottlieb criticizes CMS in feud over Aduhelm coverage, calls out their lack of expertise

ENDPOINTS NEWS

Paul Schloesser
Associate Editor

"CMS is now using the issue of whether or not a drug is approved under regular approval versus accelerated approval as a basis potentially going forward for denying coverage to drugs."

FIERCE Pharma

"Robert Califf, President Joe Biden's pick for the top spot at the FDA, has snared the support of the Senate Finance Committee chairman thanks to a vague pledge to reform the agency's accelerated approval pathway if he's confirmed."

Oregon Scraps Closed-Formulary Plan But Seeks To Deny Accelerated Approval Drugs
By John Wilkerson / February 24, 2022 at 5:40 PM

InsideHealthPolicy
An Inside Washington news service

The Washington Times

Oregon wants to ration health care in new proposal

Government bureaucrats show their cards

"The state is seeking a federal waiver that would allow it to decline Medicaid coverage for some FDA -approved drugs… targeting medications on the… 'accelerated use' pathway"

What is behind the debate?

There is growing sentiment from some payers, academics, and state and federal policymakers that the pathway needs to be significantly altered or restrictions applied to drugs approved throught he accelerated approval pathway

Are these criticisms based in reality? Let's find out…

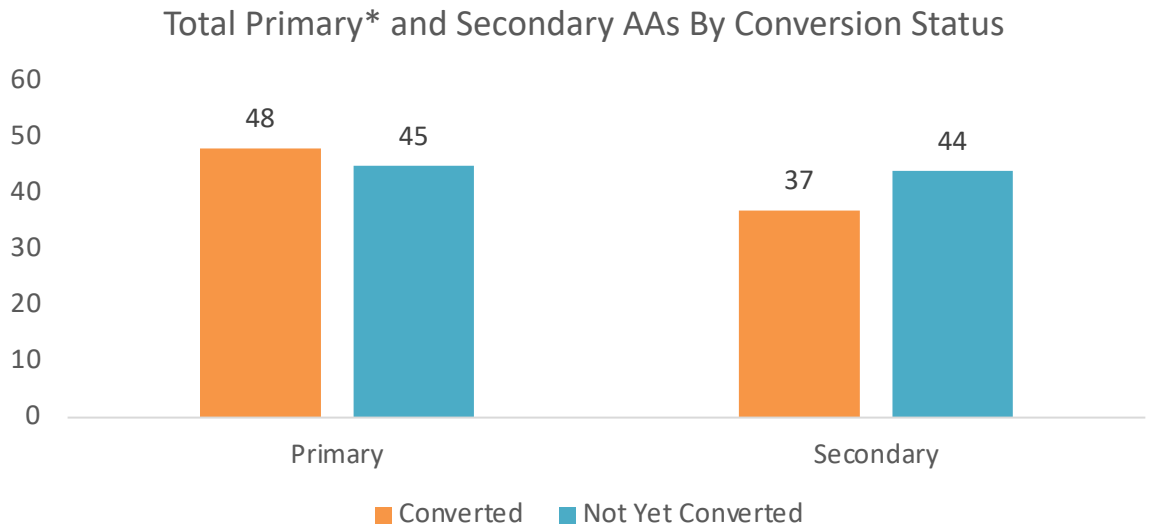
Modeling the impact of changes to the accelerated approval

what we did

Thesis: The net present value (NPV) of therapies will be negatively impacted by changes to the accelerated approval pathway that increase time to market; this will lead to the removal of therapies that treat patients.

1. We used the total patients enrolled in the confirmed primary trials as reported to FDA as the basis of our calculations.
2. We calculated the average confirmatory trial cost per patient as defined by Jayasundara et al.
3. We scaled up the lower Jayasundara costs to DiMasi's trial costs (x 2.89), giving us two points of comparison for impacts (low and high).
4. The confirmatory trial length was modeled with a delay of 2, 3, 4, and 5 years before full FDA marketing approval was granted and sales generated for the entire primary cohort (n=93) to determine the present value of any investment into an AA therapy.

Our NPV analysis focuses on primary AAs

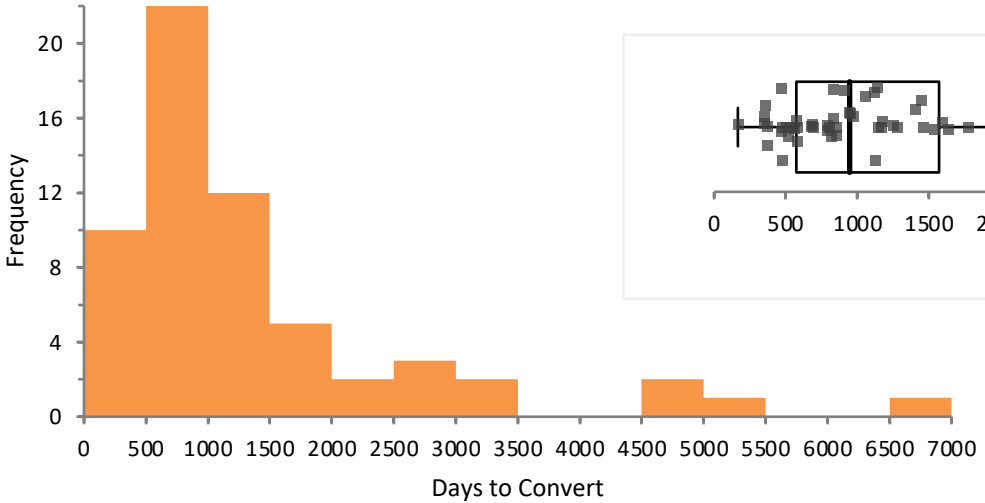


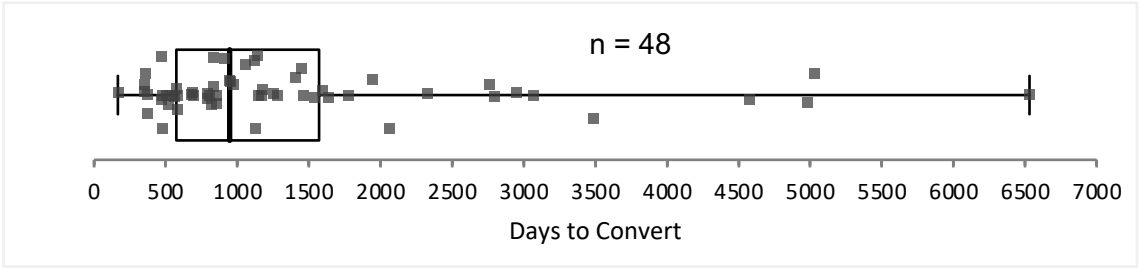
* Our 125 primary AAs are reduced by filtering those with multiple indications, repurposed off-patent therapies, and generics with AAs, leaving 93 therapies in our primary NPV cohort.

Median Years Needed to Submit Confirmatory Evidence (2001 – 2021)

i.e., FDA 'Conversion"

Conversion Time in Years				
Minimum	**1st quartile**	**Median**	**3rd quartile**	**Maximum**
0	2	3	4	18





Sources of the cost basis of our analysis

Jayasundara et al. Orphanet Journal of Rare Diseases (2019) 14:12
https://doi.org/10.1186/s13023-018-0990-4

Orphanet Journal of Rare Diseases

RESEARCH Open Access

Estimating the clinical cost of drug development for orphan versus non-orphan drugs

Kavisha Jayasundara[1*], Aidan Hollis[2], Murray Krahn[1,3,5], Muhammad Mamdani[1,4,5], Jeffrey S. Hoch[1,4,5,6] and Paul Grootendorst[1]

Contents lists available at ScienceDirect

Journal of Health Economics

journal homepage: www.elsevier.com/locate/econbase

Innovation in the pharmaceutical industry: New estimates of R&D costs☆

Joseph A. DiMasi[a,*], Henry G. Grabowski[b], Ronald W. Hansen[c]

[a] Tufts Center for the Study of Drug Development, Tufts University, United States
[b] Department of Economics, Duke University, United States
[c] Simon Business School, University of Rochester, United States

Cost basis for our analysis

Average cost per drug in constant 2013 $US Mil

	Non - Orphans					Orphans				
	Jayasundara		DiMasi			Jayasundara		DiMasi		
P1	$	20	$	58	P1	$	13	$	38	
P2	$	67	$	194	P2	$	63	$	183	
P3	$	247	$	713	P3	$	61	$	176	
	$	**334**	**$**	**965**		**$**	**137**	**$**	**397**	

Results

% of cohort with a negative NPV

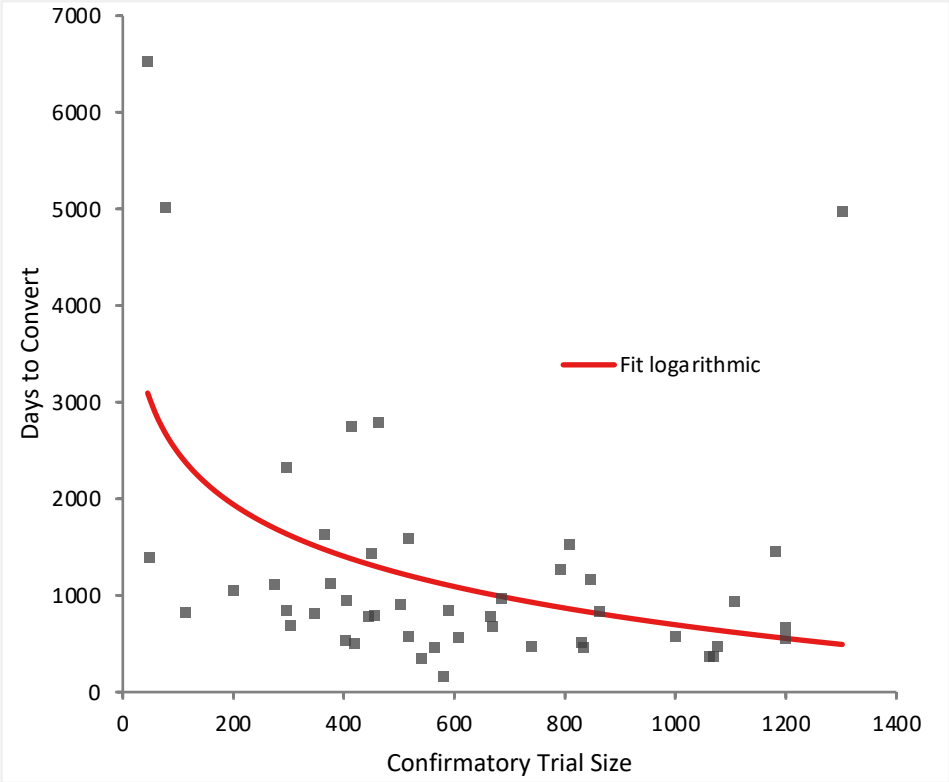
n=93

Cost Basis	2 Year Delay	3 Year Delay	4 Year Delay	5 Year Delay
Jayasundara	28%	35%	41%	51%
DiMasi	54%	65%	68%	73%

- In general, a therapy with a negative NPV is likely to either not be brought to market, or not developed at all because of the impact on continuing operations long-term (opportunity cost).
- If changes to the AA leads to a two-year delay in receiving FDA marketing approval, the percentage of therapies in our cohort with a negative NPV would rise to between 28% and 54%
- If removing AA leads to a five-year delay - which would encompass more than 80% of the AA therapies in our cohort – the percentage of therapies with a negative NPV would rise to between 51% and 73%.

Larger, shorter trials are more likely to have a positive NPV

smaller trials took longer to convert, and are more likely have a negative NPV



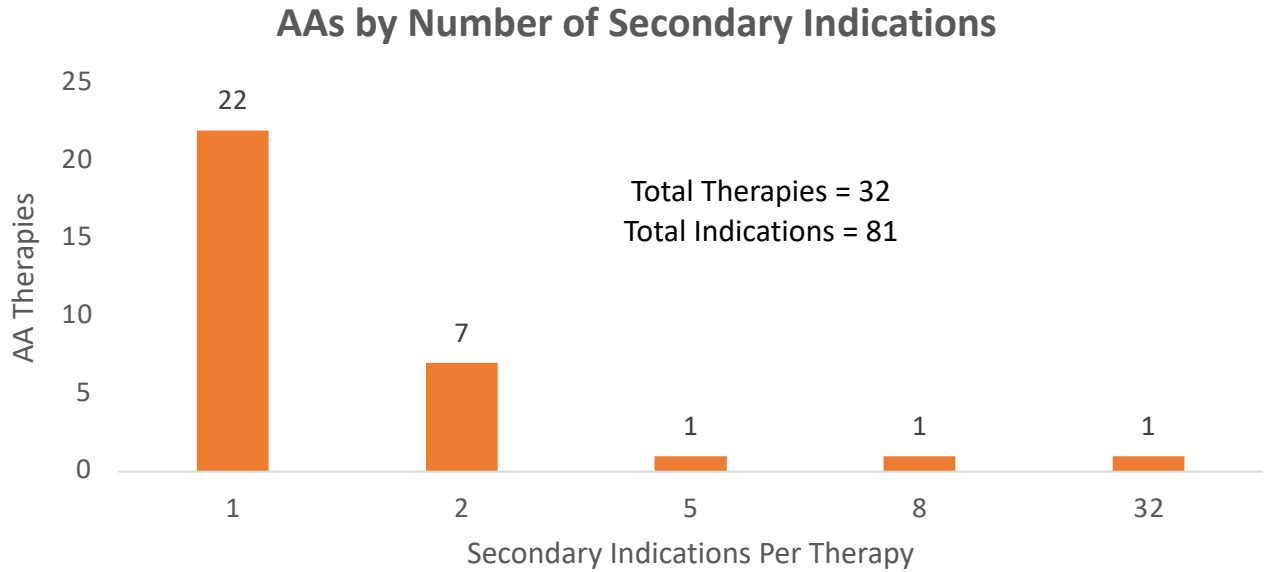
Trial size and confirmatory trial length in our cohort shows that larger, shorter trials are statistically more likely to have a positive NPV ($p < 0.0004$, $R^2 = .16$)

The size of the confirmatory trial predicts the length of time required to fulfil FDA's evidence requirements.

As most accelerated approvals are for orphan indications, our statistics show that the smaller is the number of trial participants, the longer it takes to collect the required evidence. ($p < 0.001$, $R^2 = .22$)

- Analysis excludes one clinical trial with 3360 subjects due to it being a significant outlier.

The majority of AAs have only one secondary indication

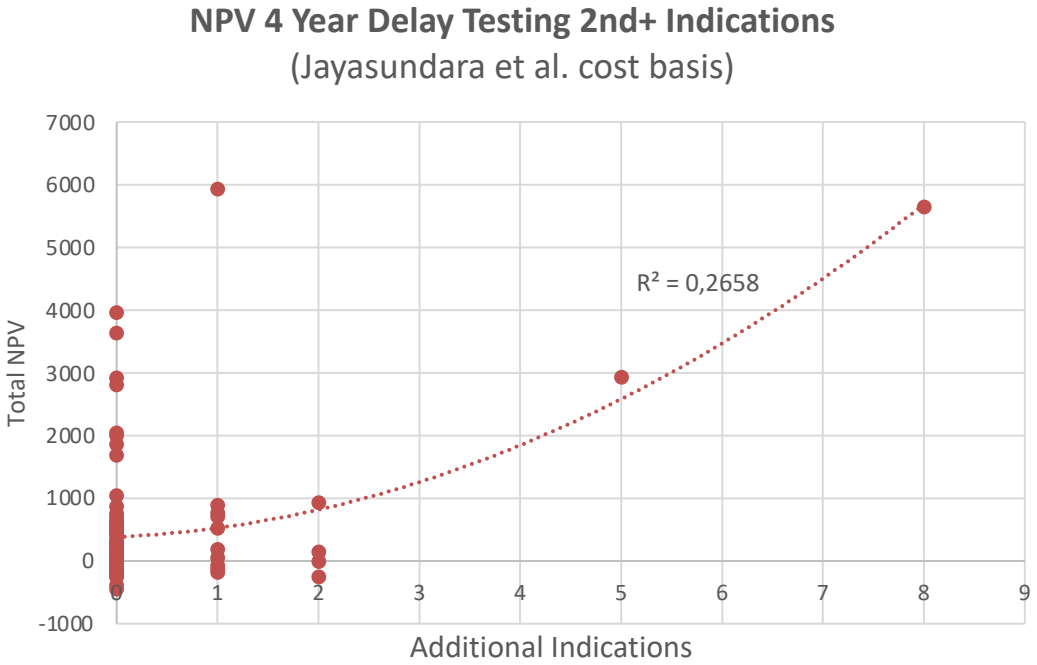


The therapies with the greatest number of secondary indications, in descending order, are Keytruda, Opdivo, and Gleevec.

All three are on the WHO's list of essential medicines, and are highly effective late stage oncology treatments.

Secondary indications are used to generate a positive NPV

Keytruda as an outlier is removed



Additional indications are shown to predict a statistically significant rise in NPV.

Unfortunately, genetically targeted therapies don't have the opportunity for secondary indications.

Rather than being a negative, the data implies that extra indications can help ensure an overall positive NPV and hence allow the primary therapy to remain in the market to treat patients.

$p < 0.0001$, N=93

Implications for Patients and US Innovation

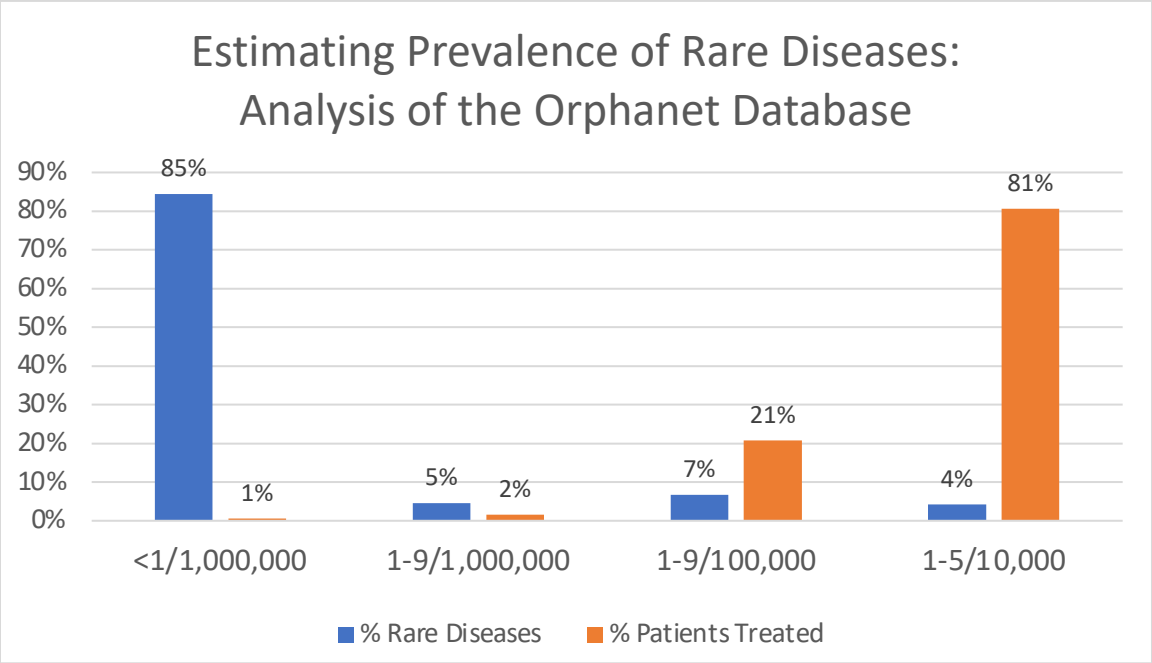
A two to four year delay due to changes to the AA will negatively impact 850,000 – 3.6 mil patients

Impact of 2 year delay on patients no longer covered		
Clinical Area	**Jayasundara**	**DiMasi**
Neurology	123,090	1,226,082
Oncology	489,126	1,189,914
Infectious Disease	123,552	160,182
Hematology	100,287	100,287
Endocrinology	13,200	13,200
Pulmonology		8,250
TOTAL	**-849,255**	**-2,697,915**

Impact of 4 year delay on patients no longer covered		
Clinical Area	**Jayasundara**	**DiMasi**
Oncology	910,602	1,942,413
Neurology	123,090	1,339,866
Infectious Disease	123,552	160,182
Hematology	100,287	111,177
Endocrinology	13,200	19,800
Gastroenterology		13,200
Pulmonology		8,250
TOTAL	**-1,270,731**	**-3,594,888**

- The above charts uses US incidence rates to estimate the total covered lives that will lose access to therapies due to potential changes to the accelerated approval pathway.
- The chart sums the total patients theoretically impacted by therapy withdrawals due to a negative NPV, based upon a two or four year FDA approval delay.
- A 2 year delay impacts 28% of our accelerated approval cohort at minimum, a 4 year delay impacts up to 68% of the therapies in our cohort.

85% of untreated orphan conditions have a prevalence of less than 1 in 1,000,000



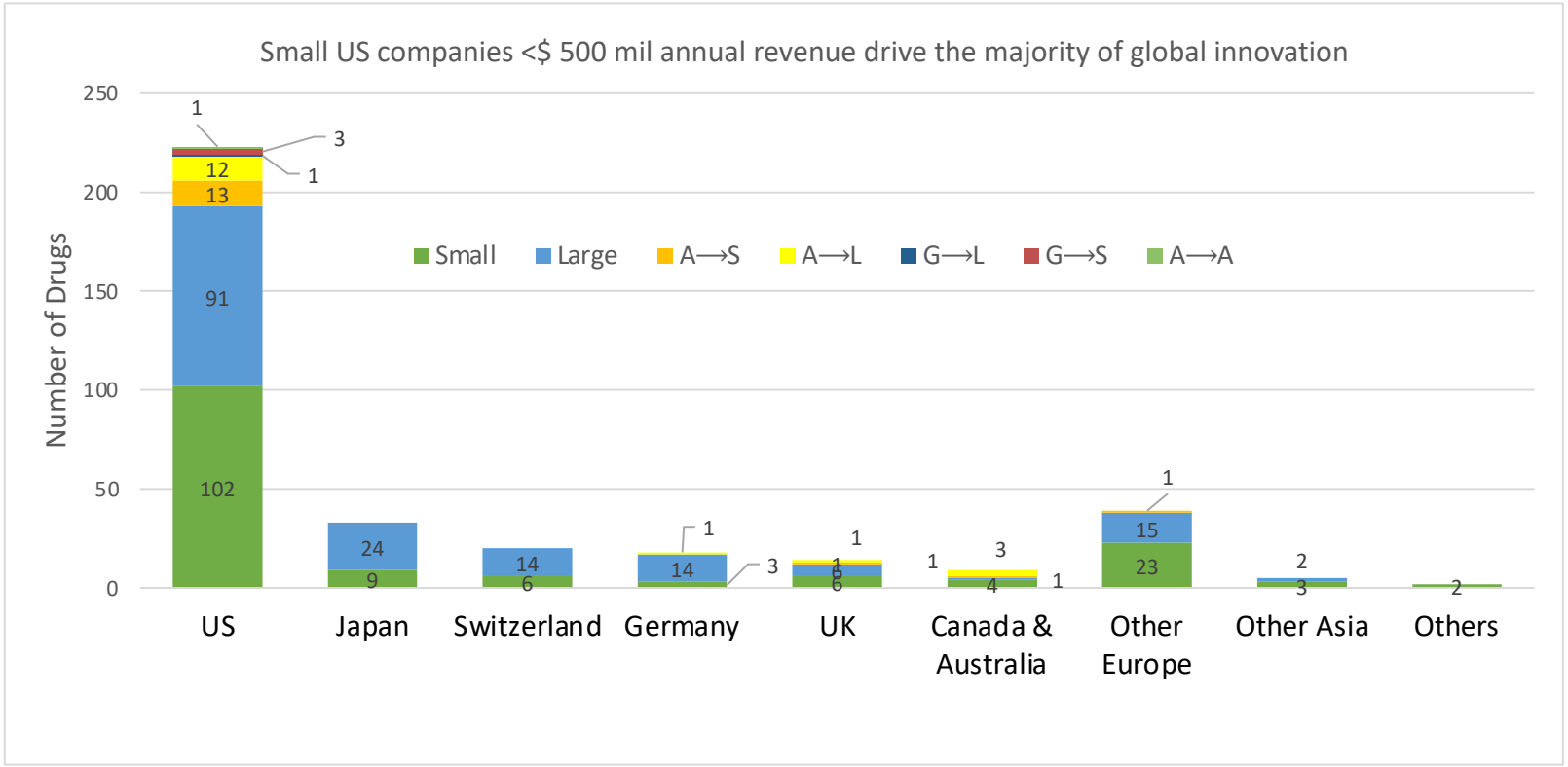
For most of the orphan conditions currently lacking treatment in the US, each condition impacts a maximum of 330 people - an incidence rate less than 1/1,000,000.

Substantial changes to the accelerated approval pathway will likely render the potential development of these therapies to treat most orphan conditions economically untenable.

https://www.nature.com/articles/s41431-019-0508-0

FDA 2011-2021 Global Drug Innovation by Origination of Core IP

NME & BLA approvals, N=363, by location of IP originator



What is the probability that a ‘blockbuster’ therapy originated in…

0	Government
8%	Academia
63%	Small Company
29%	Large Company
35%	Small -> Small
29%	Small -> Large
12%	Large -> Small
16%	Large -> Large

- The accelerated approval, being focused mostly on orphan conditions and small populations, is a way for innovative targeted therapies to come to market.
- The US currently dominates globally in small company driven innovation.
- Alterations to the accelerated approval pathway puts therapies developed by small companies at risk.

Conclusions

1. We estimate that 33% to 66% of accelerated approvals at the median delay of three years will no longer have a net positive NPV, and would be at high-risk of not coming to market or from being developed at all.

2. 82% of accelerated approvals are for orphan indications; our study generated evidence that smaller confirmatory trials take longer to meet their FDA requirements, larger and faster trials predict a positive NPV with statistical significance.

3. 85% of untreated orphan indications have incidence rates less than 1/1,000,000; changes to the accelerated approval pathway will render the development of those therapies economically untenable.

4. Secondary indications are a logical strategy for net positive NPV to retain drugs in the market; Gleevec, Opdivo, and Keytruda have the majority of those 2nd indications in oncology, but genetically targeted therapies don't have the opportunity for secondary indications.

5. The US dominates global high-value biopharma IP creation, the majority of this innovation is driven by small companies (<$ 500 mil annual revenue) who have a 63% probability of producing a given blockbuster.

6. Negatively impacting the accelerated approval pathway will lead to therapies leaving or not coming to market; we estimate these at-risk therapies address the needs of 850k to 3.6 mil patients, depending upon our cost assumptions and estimated delay time.

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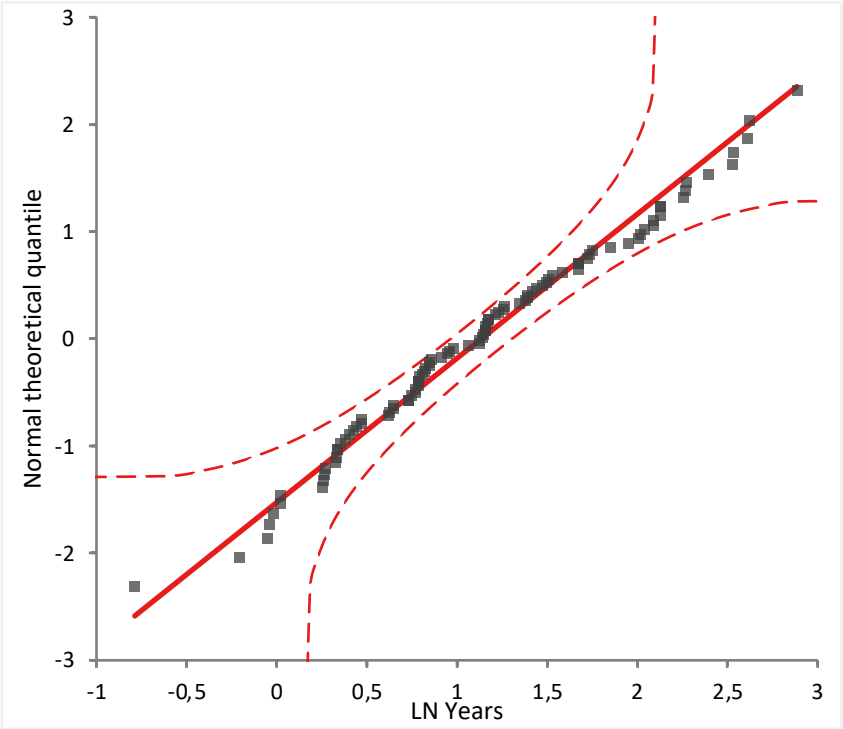
Appendix:

Ln Test for Normality All Converted (2001 – 2021)

Primary approvals



Shapiro-Wilk test

W statistic	0.99
p-value	0.3787

H0: F(Y) = N(μ, σ)
The distribution of the population is normal with unspecified mean and standard deviation.
H1: F(Y) ≠ N(μ, σ)
The distribution of the population is not normal.
[1] Do not reject the null hypothesis at the 10% significance level.

Regression results testing time to convert to confirmatory trial size

Fit

N	47
Mean of Y	6.2

Equation: P3 Trial Size = 700.5 * 0.9997 $^{\text{Days to Convert}}$

R^2	0.221
R^2 adjusted	0.203
RMSE	0.69

Parameter	Estimate	95% CI	SE	t	p-value
Constant	6.552	6.266 to 6.837	0.14169	46.24	<0.0001
Days to Convert	-2.853E-04	-4.462E-04 to -1.243E-04	7.9928E-05	-3.57	0.0009

Effect of Model

Source	SS	DF	MS	F	p-value
Difference	6.1	1	6.1	12.74	0.0009
Error	21.4	45	0.5		
Null model	27.5	46	0.6		

Multiple Regression results testing size and length of confirmatory trial to NPV

R^2	0.163
R^2 adjusted	0.144
RMSE	1839.568

Parameter	Estimate	95% CI	SE	t	p-value	VIF
Constant	2090	814.7 to 3365	641.74	3.26	0.0016	-
phase_3_length_years	-195.7	-306.4 to -85.04	55.703	-3.51	0.0007	1.06
p3_trial_size	0.7549	-0.3895 to 1.899	0.57595	1.31	0.1933	1.06

Source	SS	DF	MS	F	p-value
Difference	5.860593E+07	2	2.930296E+07	8.66	0.0004
Error	3.011771E+08	89	3.384013E+06		
Null model	3.597830E+08	91	3.953660E+06		

Regression output testing Jayasundara cost NPV to indication totals

```
------------------------------------------------------------------------------
                npv4 |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
---------------------+--------------------------------------------------------
secondary_indications |    523.641   100.1612     5.23   0.000     324.6533    722.6288
               _cons |   322.7092   111.9837     2.88   0.005     100.2341    545.1843
------------------------------------------------------------------------------

      Source |       SS           df       MS      Number of obs   =        92
-------------+----------------------------------   F(1, 90)        =     26.17
       Model |  13928422.2         1  13928422.2   Prob > F        =    0.0000
    Residual |  47904652.8        90   532273.92   R-squared       =    0.2253
-------------+----------------------------------   Adj R-squared   =    0.2167
       Total |  61833074.9        91   679484.34   Root MSE        =    729.57

------------------------------------------------------------------------------
                npv5 |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
---------------------+--------------------------------------------------------
secondary_indications |   364.9891   71.35042     5.12   0.000      223.239    506.7392
               _cons |   168.9939    79.7722     2.12   0.037     10.51249    327.4753
------------------------------------------------------------------------------
```

Probability tree for likelihood of blockbuster