15.482 Healthcare Finance
Spring 2017

Andrew W. Lo, MIT

Unit 4, Part 4: Portfolio Theory in a Biomedical Context

Unit Outline

- Risk & Reward
- The CAPM
- Applications
- Portfolio Theory
- Risk-Adjusted NPV

Mini-Case: Orphan Drug Portfolios

What Is An Orphan Disease?

- According to the Orphan Drug Act of 1983 (ODA), any disease that affects fewer than 200,000 individuals in the USA
- Examples: sickle cell disease (100K), GBM (100K), cystic fibrosis (30K), ALS (30K), Gaucher's (6K), hemophilia (20K), DMD (7K), PNH (0.5–1/500K), Hunter Syndrome (500), etc.
- At least 25 million Americans are afflicted with one of almost 7,000 recognized orphan diseases
- Approximately 80% of rare diseases are caused by underlying genetic defects
- Currently there 596 FDA-approved orphan drugs (as of 3/3/2017)
- But not all orphan drugs are necessarily "rare," e.g., Herceptin

What Is An Orphan Disease?

Benefits to Investors of Orphan Drug Designation (ODA):

- Tax credits of up to 50% for clinical testing costs
- Authorized expedited regulatory review (shortened times to market)
- 7-year period of marketing exclusivity that precludes FDA approval of competing drugs for the same orphan indication (exclusivity, regardless of patent protection on the compound)
- Significant pricing power
- Priority review voucher for pediatric rare diseases (8 months instead of 12, plus $2.7MM)


c&en
CHEMICAL & ENGINEERING NEWS

Feb 27, 2017

Gilead buys Priority Review Voucher from Sarepta

Deal for $125 million hints at cooler market for the incentive

By Lisa M. Jarvis

Treasure trove

Several priority-review vouchers have yet to change hands.

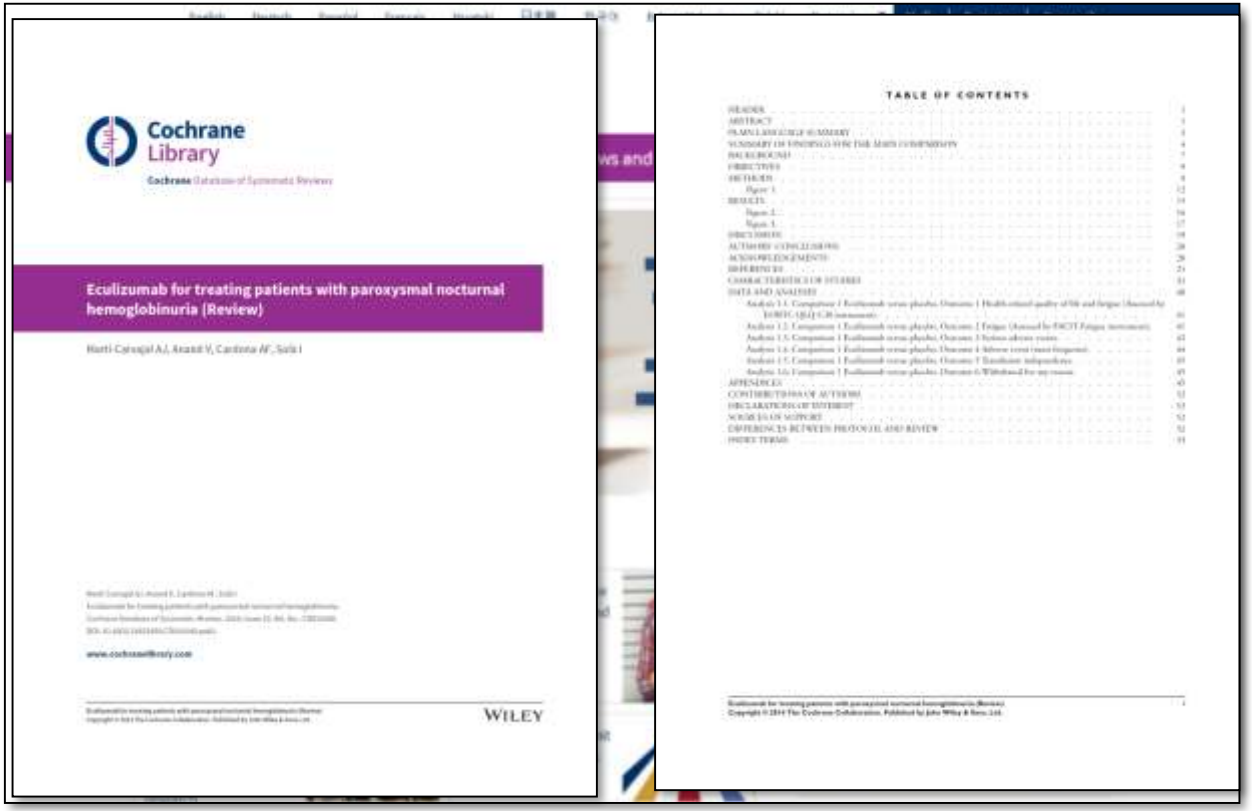
Gilead Sciences has paid Sarepta Therapeutics $125 million for a voucher that can speed up U.S. regulatory review of a new drug application. The price tag,

An Example: Alexion Pharmaceuticals

Founded in 1992 in New Haven, CT by Dr. Leonard Bell

- First drug, eculizumab (Soliris), approved for paroxysmal nocturnal hemoglobinuria (PNH) in 2007
- PNH is a blood disorder in which the body's immune system attacks its own red blood cells, causing anemia, fatigue, bone marrow failure, blood clots, stroke, and death; median survival time after diagnosis is 10–20 years.
- Bone-marrow transplant can cure the disease 50% to 70% of the time, but there are significant risks; otherwise, routine blood transfusions are needed and even then, fatigue and risk of thrombosis are still present
- With Soliris, significant reduction in transfusions, fewer blood clots, less fatigue, but no concrete evidence (yet) of significant impact on mortality

An Example: Alexion Pharmaceuticals



An Example: Alexion Pharmaceuticals

Authors' conclusions

This review has detected an absence of evidence for eculizumab compared with placebo for treating paroxysmal nocturnal hemoglobinuria (PNH), in terms of overall survival, nonfatal thrombotic events, transformation to myelodysplastic syndrome and acute myelogenous leukemia, and development and recurrence of aplastic anemia on treatment. Current evidence indicates that compared with placebo, eculizumab increases health-related quality of life and increases transfusion independence. During the execution of the included trial, no patients died. Furthermore, the intervention seems to reduce fatigue and withdrawals for any reason. The safety profile of eculizumab is unclear. These conclusions are based on one small trial with risk of attrition and selective reporting bias.

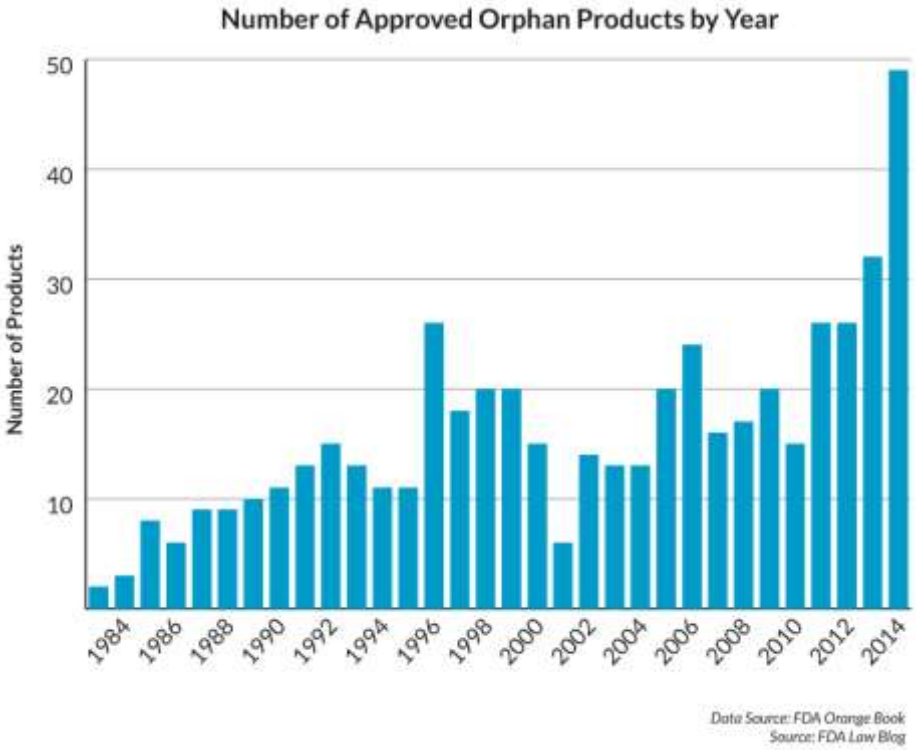
Therefore, prescription of eculizumab for treating patients with PNH can neither be supported nor rejected, unless new evidence from a large high quality trial alters this conclusion. Therefore, we urge the reader to interpret the trial results with much caution. Future trials on this issue should be conducted according to the SPIRIT statement and reported according to the CONSORT statement by independent investigators, and using the Foundation of Patient-Centered Outcomes Research recommendations.

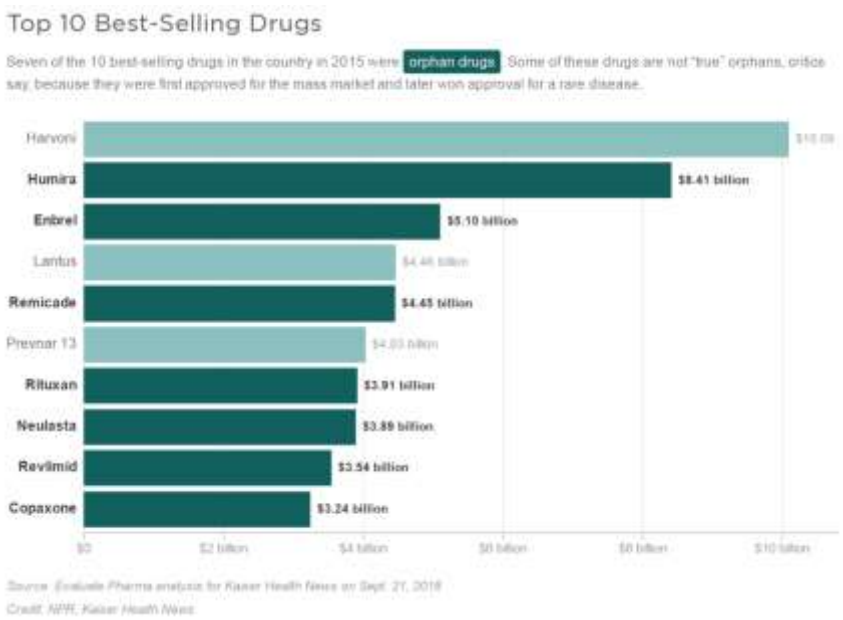
An Example: Alexion Pharmaceuticals

Alexion Business Model:

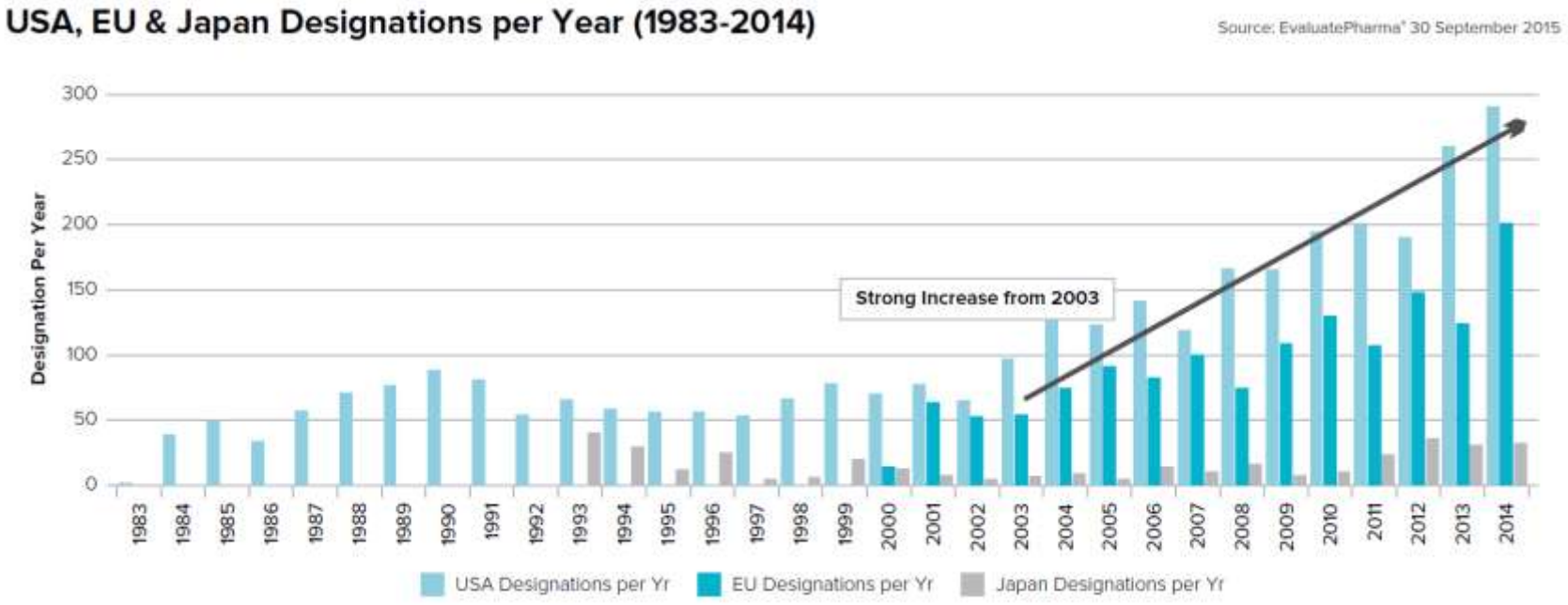
- Cost of one-year supply of Soliris in US as of 2015?:
- Second approval for Soliris as a treatment for aHUS in 2011
- Third and fourth approvals, Strensiq (for HPP), Kanuma (for LAL-D) in 2015
- 2016: $3.08 billion in sales, $13.3 billion in assets, $399 million in net income
- Current market capitalization (as of 3/3/2017): $30.3 billion
- Growth estimate, next 5 years (finance.yahoo.com 3/3/2017): 18.68%
- ALXN added to the S&P 500 in May 2012
- From 1996:03 to 2016:12, ALXN returned 20.98% with 61.0% SD, Sharpe = 0.30
- For comparison, VWRETD returned 8.11%, 15.7% SD, Sharpe = 0.35

Orphan Drug Financials





Orphan Drug Financials



- Why 2003?? Rare Disease Act of 2002 $\Rightarrow$ NIH's ORDR, NCATS

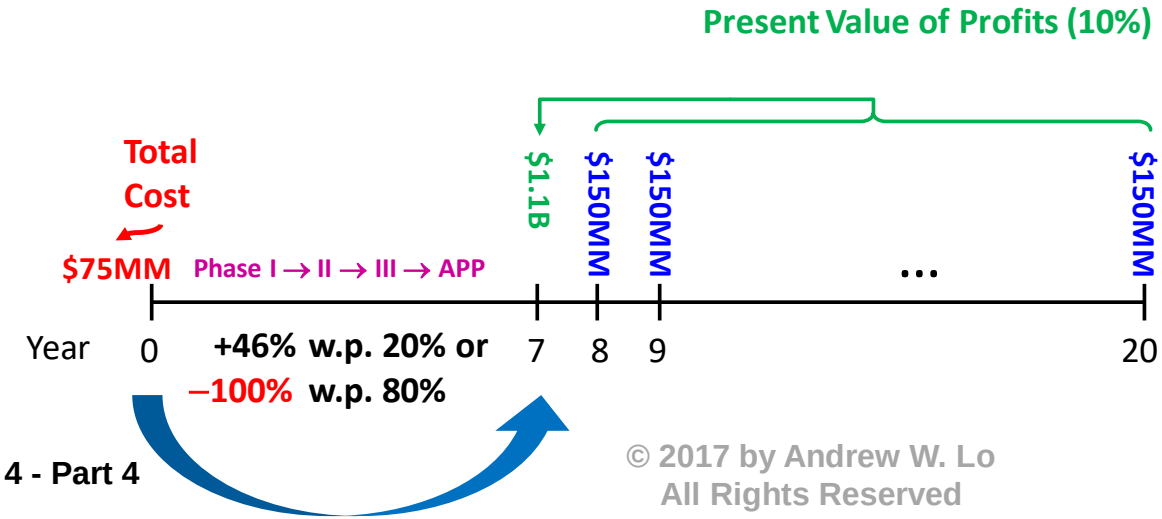
Orphan Drug Financials

$$
\begin{aligned}
\text{Total number of projects} &= m \\
\text{Cost per project} &= C \\
\text{Cost of capital} &= R \\
\text{Duration of clinical trials} &= q \\
\text{Earnings per year if approved} &= X \\
\text{Payoff per project on approval} &= Z = \frac{X}{R}\left(1 - \frac{1}{(1+R)^{20-q}}\right) \\
\text{E[NPV]} &= \sum_{k=0}^{n} \text{Prob}(H = k)(kZ) \\
\text{E}[R] &= \frac{\text{E[NPV]}}{mC} - 1 \\
\text{Annualized E}[R^a] &= \left(\frac{\text{E[NPV]}}{mC}\right)^{1/q} - 1
\end{aligned}
$$

Orphan Drug Financials

- For orphan diseases, *H* can be modeled as IID binomial
- $75MM investment, 7-year horizon
- Probability of positive payoff is 20%
- If successful, annual profits of $150MM for 13-year patent

$$\text{Prob}(H = k) = \binom{n}{k} p^k (1-p)^{n-k}$$



E[R] = 16.1%
SD[R] = 214.8%

Orphan Drug Financials

But We Can Improve The Sharpe Ratio Easily:

- Almost by definition, rare disease projects will be **uncorrelated**
- With zero correlation, we know that:

$$\text{SR}_p = \sqrt{n}\,\text{SR} = \sqrt{n}\,\frac{16.1\% - 3\%}{214.8\%} = 0.060937\sqrt{n}$$

$$= 0.19 \quad \text{for } n = 10$$

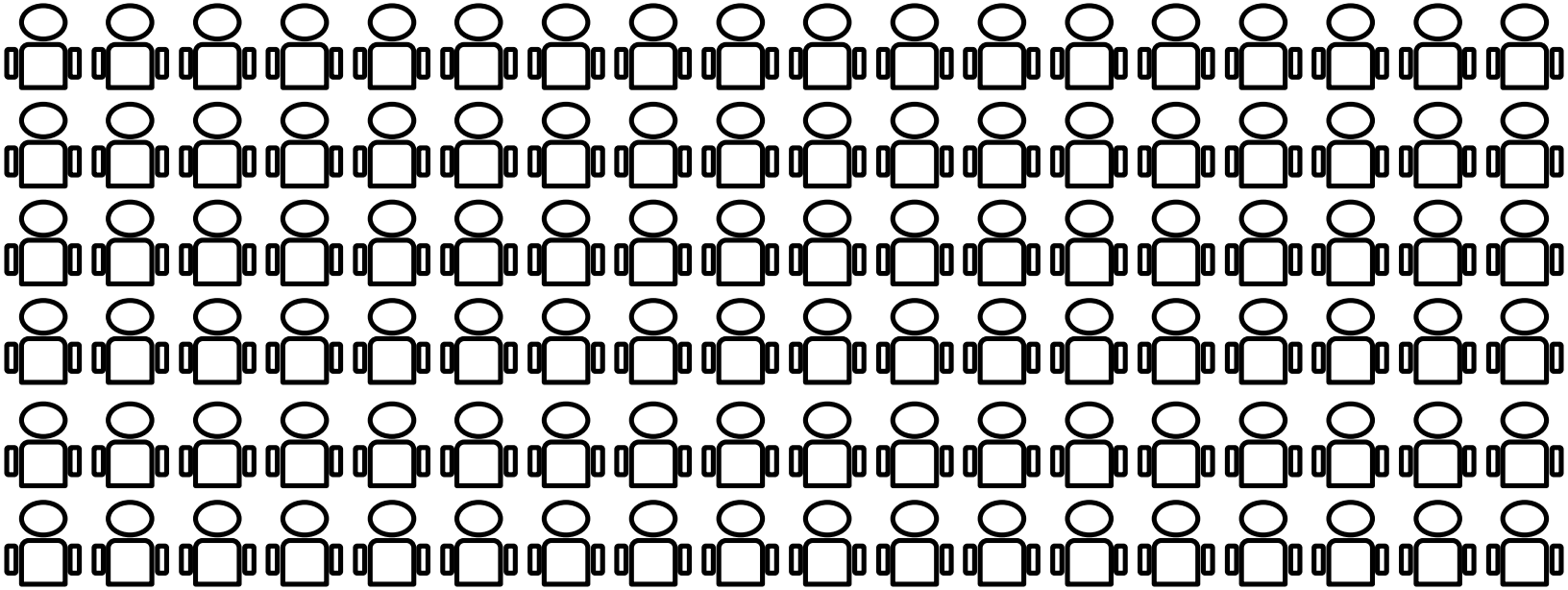
$$= 0.30 \quad \text{for } n = 25$$

$$= 0.43 \quad \text{for } n = 50$$

$$= 0.53 \quad \text{for } n = 75$$

- From 1976:11 to 2016:12, Berkshire Hathaway's Sharpe = 0.51, stock market's Sharpe = 0.40; with debt-financing, equity returns can be even higher

Divide and Conquer



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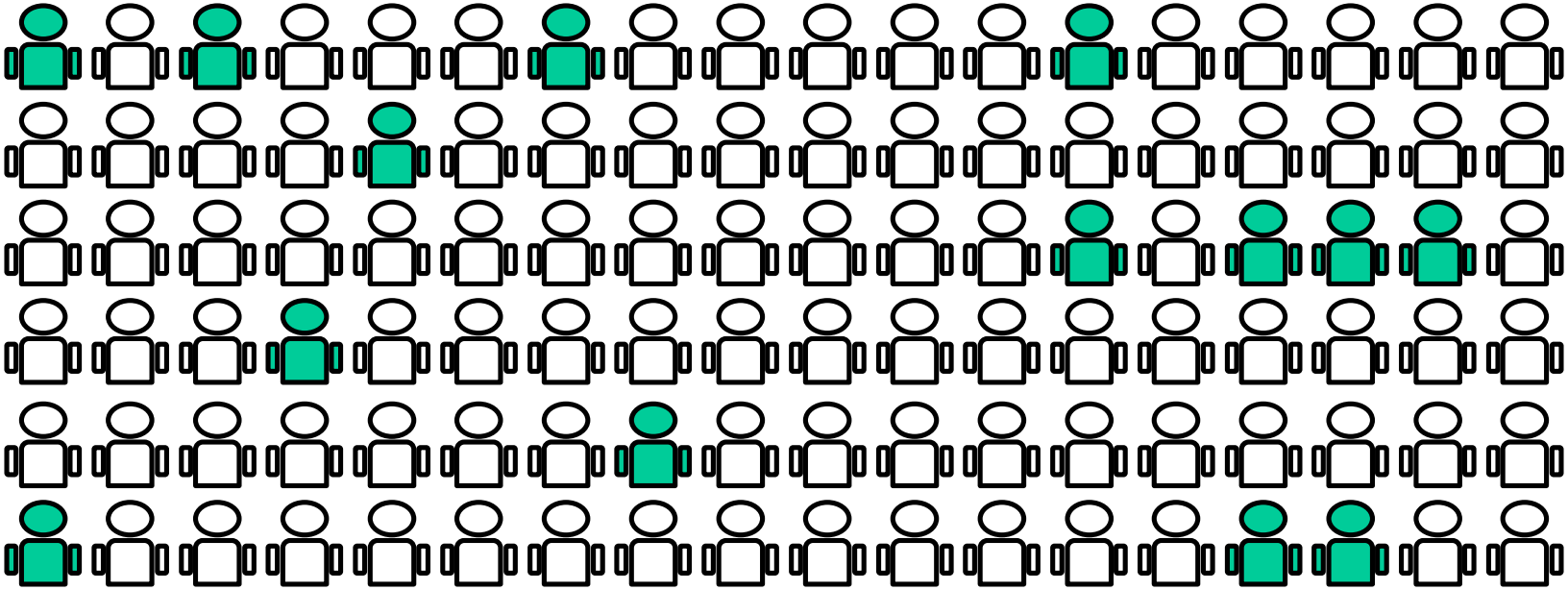

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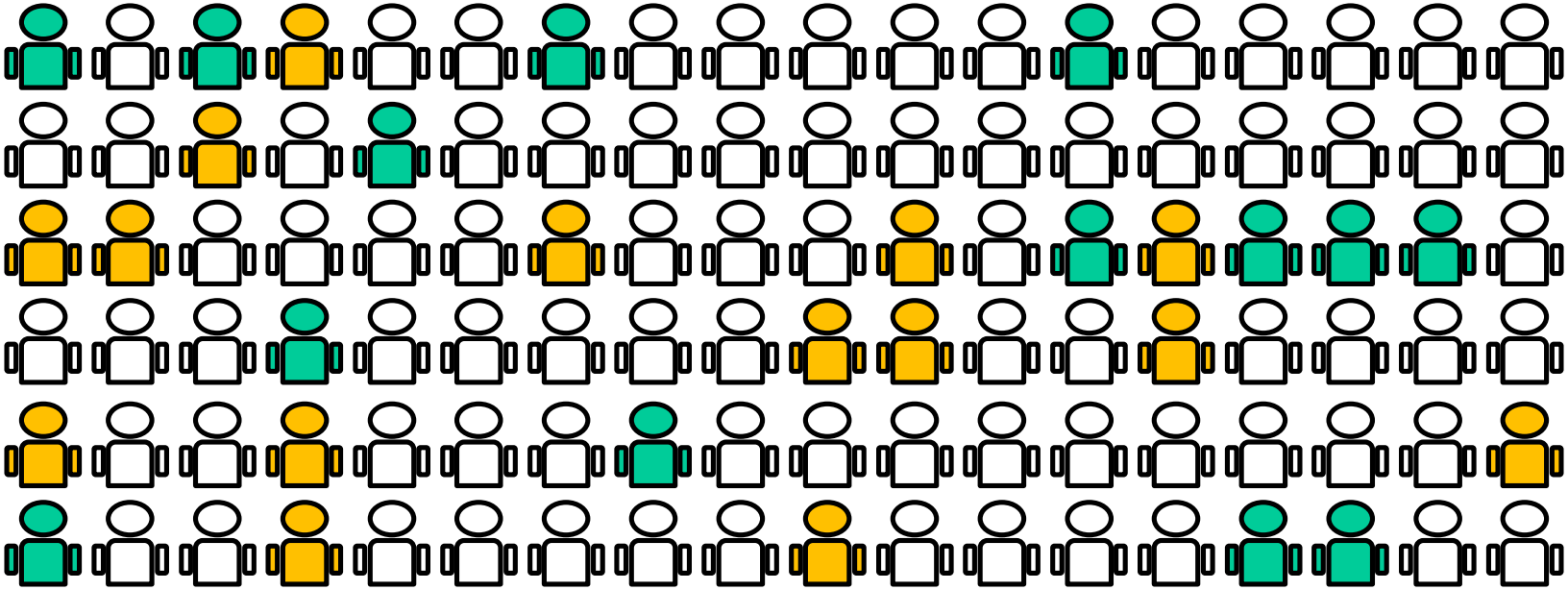

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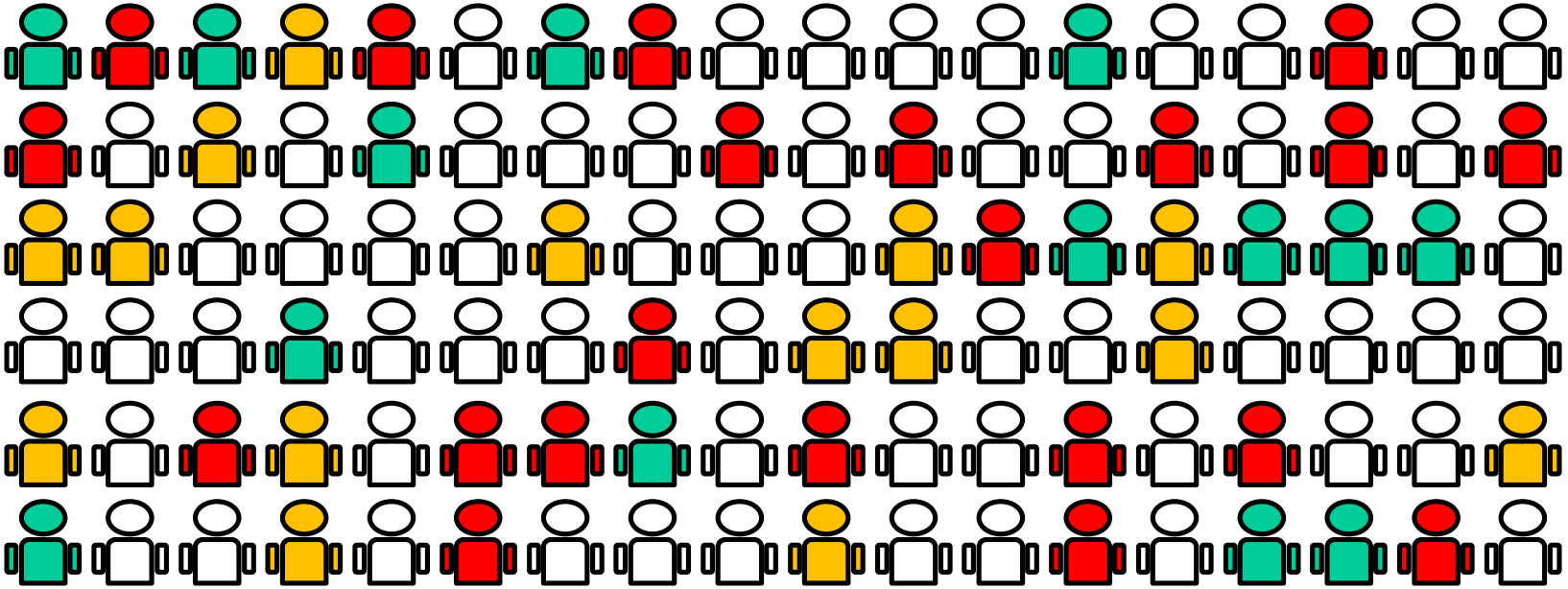

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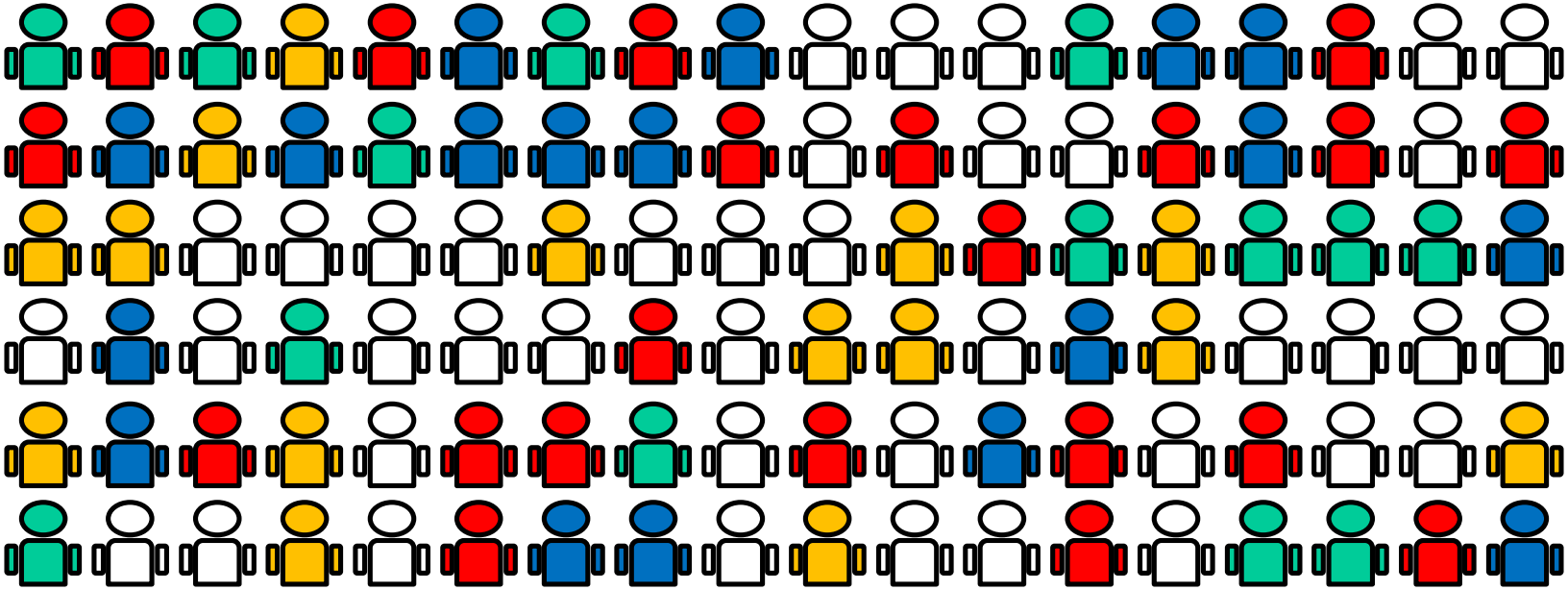


Divide and Conquer

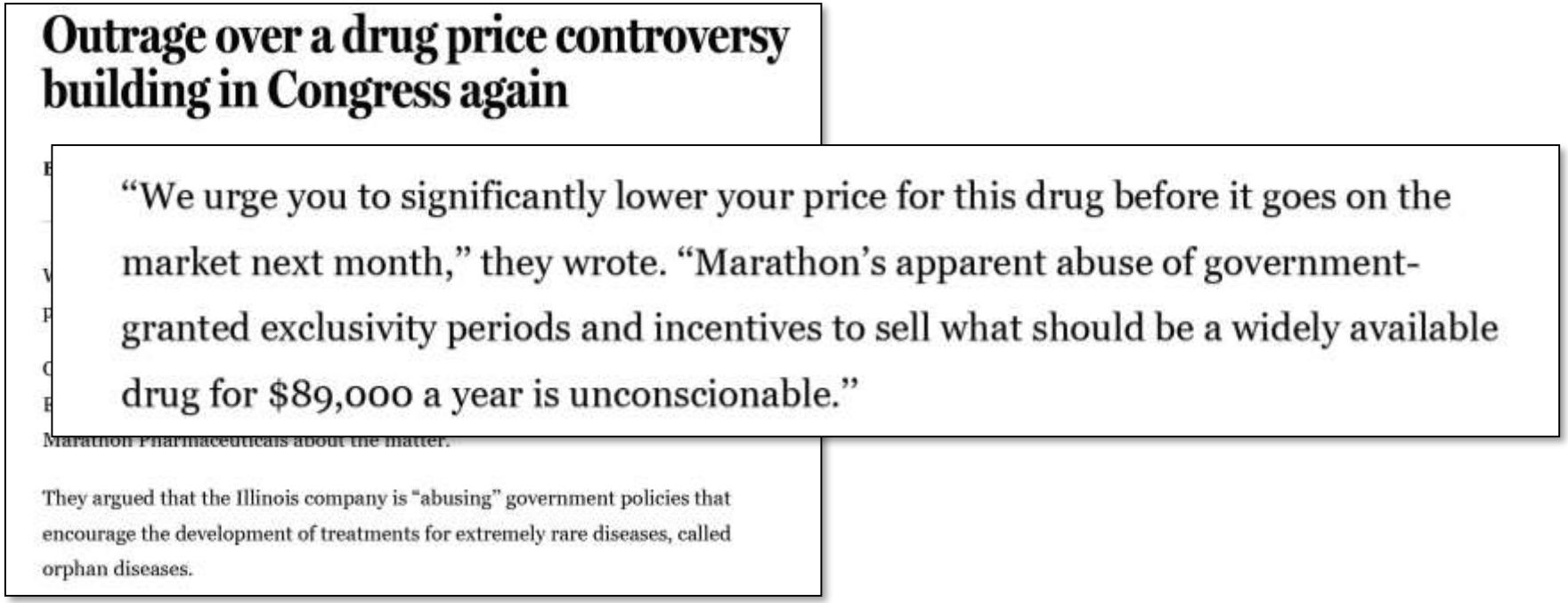
Can (and should) we "orphanize" all disease?

What About Pricing?

What About Pricing?

"Yet a Kaiser Health News investigation shows that the system intended to help desperate patients **is being manipulated by drugmakers to maximize profits and to protect niche markets for medicines already being taken by millions. The companies aren't breaking the law but they are using the Orphan Drug Act to their advantage in ways that its architects say they didn't foresee or intend.** Today, many orphan medicines, originally developed to treat diseases affecting fewer than 200,000 people, come with astronomical price tags."

What About Pricing?



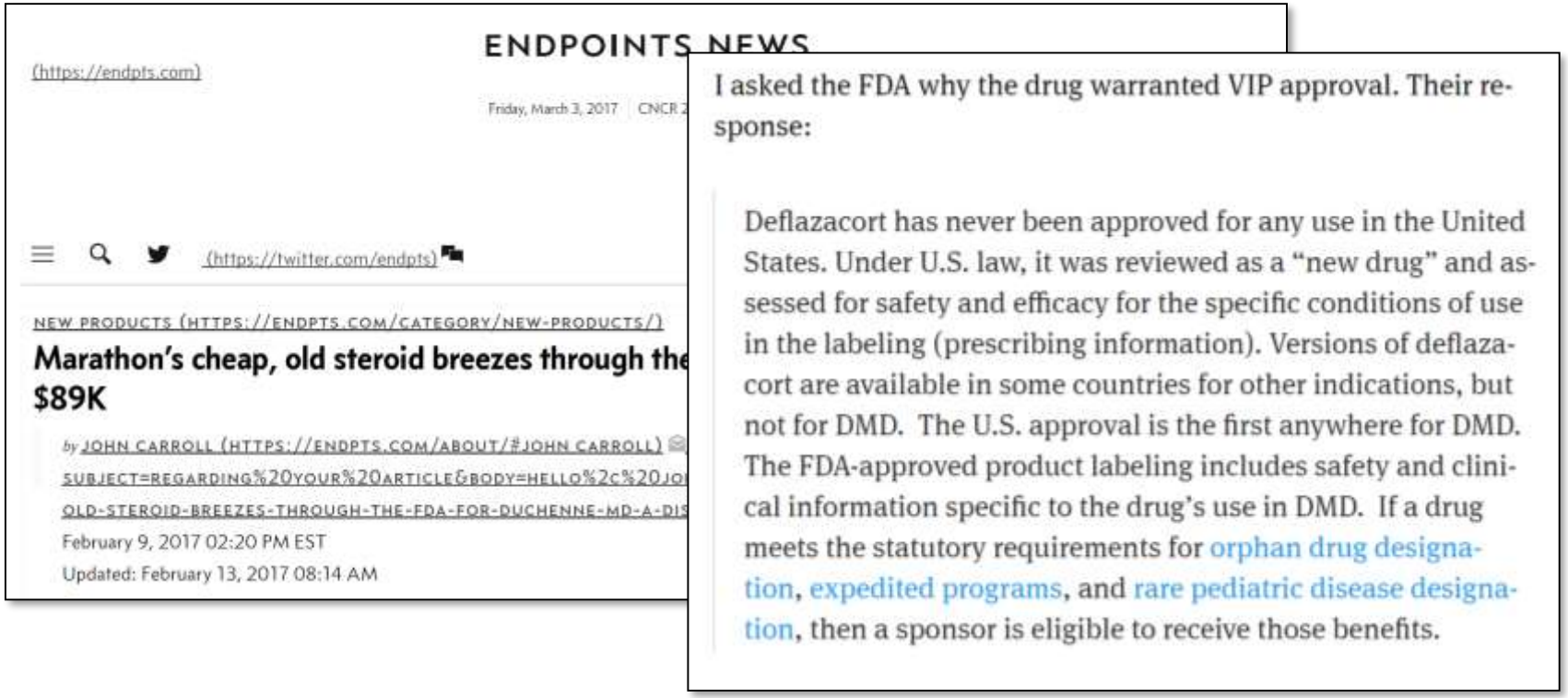
Outrage over a drug price controversy building in Congress again

"We urge you to significantly lower your price for this drug before it goes on the market next month," they wrote. "Marathon's apparent abuse of government-granted exclusivity periods and incentives to sell what should be a widely available drug for $89,000 a year is unconscionable."

Marathon Pharmaceuticals about the matter.

They argued that the Illinois company is "abusing" government policies that encourage the development of treatments for extremely rare diseases, called orphan diseases.

What About Pricing?



ENDPOINTS NEWS

(https://endpts.com)

Friday, March 3, 2017 CNCR 2

(https://twitter.com/endpts)

NEW PRODUCTS (HTTPS://ENDPTS.COM/CATEGORY/NEW-PRODUCTS/)

Marathon's cheap, old steroid breezes through the $89K

by JOHN CARROLL (HTTPS://ENDPTS.COM/ABOUT/#JOHN CARROLL)

SUBJECT=REGARDING%20YOUR%20ARTICLE&BODY=HELLO%2C%20JO

OLD-STEROID-BREEZES-THROUGH-THE-FDA-FOR-DUCHENNE-MD-A-DIS

February 9, 2017 02:20 PM EST

Updated: February 13, 2017 08:14 AM

I asked the FDA why the drug warranted VIP approval. Their response:

> Deflazacort has never been approved for any use in the United States. Under U.S. law, it was reviewed as a "new drug" and assessed for safety and efficacy for the specific conditions of use in the labeling (prescribing information). Versions of deflazacort are available in some countries for other indications, but not for DMD. The U.S. approval is the first anywhere for DMD. The FDA-approved product labeling includes safety and clinical information specific to the drug's use in DMD. If a drug meets the statutory requirements for orphan drug designation, expedited programs, and rare pediatric disease designation, then a sponsor is eligible to receive those benefits.

What About Pricing?

To be continued…