Orphan Drugs:

Fantastic Science,

Perfect Business Model

and

Why Policymakers Should be Concerned

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Table of Contents

Orphan Drug Act General Background

Enacted in 1983, the Orphan Drug Act (ODA) has successfully incentivized the biopharmaceutical industry to develop drugs for rare diseases – diseases which affect fewer than 200,000 people in the US. It is estimated that 7000 rare diseases affect 10 percent or more of the US population. Complementary to the ODA, subsequent federal laws[1] boosted the impact of the ODA such that today, the branded industry is fully invested in orphan drug development as its business model.[2]

Some of the very best selling drugs in the world started out as U.S. orphan drugs. While the treatment population for these global blockbuster drugs grew to millions of people, their orphan drug status and orphan drug pricing persisted.

The industry maintains that that rare disease drug development is exceptionally costly, exceptionally risky, with small market potential and that this constellation of factors justifies very high prices. The data indicate this is not a fully accurate representation of the market. Research shows that orphan drugs are as lucrative or more lucrative than non-orphan drugs, which explains why orphan drug development is the new business model and the focus for the branded drug industry.[3] It is time to examine these claims.

The ODA, multiple follow-on federal laws designed to improve the speed of drug approvals, technological and biologic science breakthroughs, and industry willingness to use the patent system in ways not in keeping with the spirit of the law, have created a business model with notably reduced financial risk.[4] The business model based on orphan drug development is so promising and lucrative that companies are moving away from drugs that treat large population diseases (such as diabetes and heart disease) to orphan drugs.[5] Most new drugs will come to market with stunningly high prices, captive, and growing patient populations, and near total ability to price beyond reason or affordability.

The industry will continue to try to convince us that rare disease drug development comes with exceptional risk of failure and that orphan drug makers are at exceptionally high risk of catastrophic financial loss. The data does not support this view.

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[1] List of subsequent federal laws to be added.

[2] DE Fagnon et al. "Financing Drug Discovery for Orphan Diseases" Drug Discovery Today. Vol 19, #5, May 2014. http://dx.doi.org/10.1016/j.drudis.2013.11.009

[3] "This marks the second Orphan Drug Designation (ODD) granted by the FDA for LP-284. The initial ODD for LP-284 was granted in January 2023, and with this most recent ODD for LP-284 announced today, a total of five orphan designations have now been granted to Lantern, with the other three granted for our drug candidate LP-184. Acquiring these orphan designations is a key element of our business model as they provide a number of benefits including seven years of market exclusivity and eligibility for expedited drug development programs. Looking forward, these designations further position Lantern to advance our discussions with biopharma companies for partnering and collaborative development opportunities." Excerpt from 11/30/2023 Lantern Pharma Press Release.

[4] Follow on laws include amendments to the ODA, Food&Drug Modernization Act 1997, Best Pharmaceuticals for Children 2002, Medicare Modernization 2003, Biologics Price & Competition 2009, Affordable Care Act 2010, FDA Safety & Innovation 2021, 21st Century Cures 2016.

[5] https://www.sanofi.com/en/media-room/press-releases/2019/2019-12-09-21-42-41-1958232 accessed 12/11/23 is an example of the trend.

Financial Benefits Unique to Orphan Drug Development

There are substantial financial benefits for orphan drug development provided by the Orphan Drug Act, which is just the beginning of the explanation as to why orphan drug development is such a strong biopharmaceutical industry business model. The benefits of the Act include the following.

- FDA grant programs for rare disease drug development.
- Seven years of broad protection from market competition.
- Waiver of FDA drug licensing fees of $4 M per drug application (2024).
- Waiver of $400,000 per drug annual FDA program fee (2024).
- Tax credit of up to 25% of clinical trial costs.
- Orphan designation is maintained even when the treatment population grows to more than 200,000.
- Companies can return many times for approval of the drug for additional disease treatments (indications) – both orphan and non-orphan.
- Ability to refuse sales of orphan drugs at federal 340B discounted prices for certain eligible hospitals. [6]

Drug companies request (and obtain) orphan designation for a drug years before the drug is ready for FDA review and approval. Early action on the designation opens up the R&D financial benefits and exemption from application fees.

Deeper Dive into Financial Benefits

FDA grants for rare disease drug treatment research and development go to a variety of entities, not just pharmaceutical companies. Federal research dollars lower the private funding needed to research and develop a rare disease product.

Tax credits for clinical trial costs also lower the net costs of go-to-market clinical trials sponsored by the drug manufacturer. This is in addition to the fundamentally lower R&D costs of orphan drugs compared to non-orphan drugs (discussed below).

Orphan Market Exclusivity lasting seven years begins once an orphan drug has been approved for market. Orphan market exclusivity applies to the first drug approved to treat a rare disease. The exclusivity is a seven year preemption on new treatments for the same disease by another company. This protection from competition is quite different than patent protection and different from biologic data protection/exclusivity, each of which is discussed below.

Patent protection lasts 20 years beginning on the date the patent is granted – years before a product is ready for FDA approval consideration. No other company can gain FDA approval for a drug that violates an active patent. Like patents, companies apply for orphan designation early in the drug development process because the designation confers financial benefits for drug development but unlike patents, the orphan exclusivity clock starts running only when the drug has been approved/licensed. Multiple

[6] Note that the 340B program administrative agency, Health Resources and Services Administration provides a list of ~5700 orphan drugs that certain hospitals may not access. The list is updated quarterly for new orphan approvals.

companies can apply for orphan designation for the same disease and be granted the designation. They can each access the financial benefits that apply during the drug development process but market exclusivity is available only to the first drug to market for the disease. After the approval of the first drug for an orphan disease, subsequent market approval applications for the orphan indication have to demonstrate some level of superiority to the orphan drug(s) already approved.[7]

Patents protect the intellectual property of the drug – new chemical entity/drug formulation/active ingredient, novel manufacturing process.[8] Manufacturers apply for patents as soon as they suspect that a molecule or manufacturing process can be patent protected. Among non-orphan drugs, another drug can be approved to treat the same disease if it does not violate active patents of an existing drug. In contrast, orphan exclusivity means a drug cannot be approved for seven years if it treats the same disease – even if the drug does not violate the patent of the first orphan to treat the disease. Patent protection may or may not outlast the orphan exclusivity depending on how many years of patent protection remain when a drug is licensed.

Biologic exclusivity applies to orphan drugs that are biologics. In addition to patent protection, biologics have data/market exclusivity that is different from, and in addition to, orphan exclusivity. The biologic market exclusivity is less expansive but lasts longer than orphan exclusivity. Biologic exclusivity means that no biosimilar application can be submitted to the FDA during the first four years the original ("reference") biologic product is on the market and no biosimilar application can be approved for the same active ingredient for another eight years.9 Biologic exclusivity, like orphan exclusivity, starts once the drug is FDA approved.10

An orphan drug can have

- seven years of robust protection from disease treatment competition.
- decades of additional patent protection on novel aspects of the drug that are developed after the drug came to market with the original patents.
- twelve years of biologic market exclusivity that protects the drug from highly similar competition.

One drug can have many orphan disease designations (such as different types of cancers or sub-categories of a general type of cancer). If the drug is the first to get to market with the additional rare disease indication, the drug will obtain another seven years of broad market exclusivity for that disease. After the market exclusivity ends for a product, another company can bring a drug to market to treat that rare disease. The second drug will also be classified as orphan. Every orphan designation after the first

[7] Orphanet. About orphan drugs. Accessed 11/2/2023. https://orpha.net/consor/cgi-bin/Education_AboutOrphanDrugs

[8] These terms have different meanings/definitions but are grouped together for purposes of this document where the distinction is not critical to topic of the paper.

[9] Pharmaceutical Patent Analyst. Vol.3 Issue 4, July 2014. https://doi.org/10.4155/ppa.14.30

[10] Biologics, like small molecule generics, rely on the clinical and other data of the original/innovator/reference drug product to speed R&D, reduce R&D costs and time to market – which helps competitor biologics and generics to come to market at a price lower than the original product.

for the same disease cannot, of course, get the broad orphan market disease specific exclusivity but can benefit from all the other financial benefits that accrue to any orphan drug.

Several companies may market orphan drugs each with multiple orphan designations that compete in the market with another orphan products with the same designations. However, drug companies generally try hard to ensure that there can be no meaningful therapeutic competition for years and years often by legal manipulation of the patent and exclusivity systems.[11]

Orphan Drug Development is Less Costly than Non-Orphan Development

By law, the FDA has several attenuated drug approval pathways: accelerated approval, priority review, breakthrough therapy, and fast track. Orphan drugs qualify for one or more of these approval pathways. Of the 37 novel drugs approved in 2022, 21 were orphan drugs; all but one of the orphan drugs qualified for at least one attenuated approval pathway.

Remarkably, there were four drugs approved in 2022 that came to market fast -- within 5 years of obtaining a patent; three of these were orphan products.[12] Fast approval means lower clinical trial costs and the drug comes to market with more years of patent protection, which is about 7-10 years for drugs without expedited review. In the case of the drugs mentioned here, they came to market with 15 years of existing patent protection.

Orphan drug clinical trials are less costly relative to non-orphan products for several reasons in addition to the expedited review. Because of the complexity of many orphan diseases (genetic, progressive, degenerative) trials can be designed and approved based on proxy outcomes – rather than direct clinical endpoints. Proxy or surrogate measures are shorter term such as tumor shrinkage, slowing disease progression, time to remission, among others. Clinical endpoints (overall survival) require longer duration trials.

In addition to data collection efficiencies, orphan trials are smaller than non-orphan trials simply because the disease is rare. Because the disease is rare, it can be difficult to have a control group, which makes the trial smaller still. This is important simply because smaller, faster trials lower the costs of orphan clinical trials relative to non-orphan trials. For non-orphan products such as vaccines, scientific rigor is more intense because the product is given to healthy people. In the case of many chronic diseases, specific outcomes (insulin control for diabetes for example) can be measured and the clinical benefits of insulin control are known. There are enough people with diabetes to conduct large, randomized trials with control groups – which are more costly. The safety and effectiveness standard is higher for non-orphan products because it can be higher and must be higher because a person with diabetes may otherwise be healthy. Trials must be longer and bigger to discern any negative effects that may not be seen in small, short term trials.

There is nothing untoward about less rigorous trials to assess the impact of a drug on a rare, life threatening disease. The important point is that the orphan approval standard can result in less costly clinical trials relative to non-orphan drugs. Additionally, there is a tax credit for up to 25 percent of

[11] See I-MAK.org for very clear explanations of patent abuse, research on drugs with decades of patent protection, and comparisons to ex-US patent protections for those same drugs.
[12] IQVIA Institute New Drug Approvals and Launches, 2022. January 2023.

clinical trial costs which further reduces costs relative to non-orphan products. Drug development costs are thought to affect price.

Actual patient overall survival is often not measured in accelerated trials.

There has been some concern about the growing use of expedited FDA review and approval, particularly for cancer treatments because of the use of surrogate outcome measures (rather than measuring longer term overall patient survival). The drugs in studies of accelerated approvals are a mix of orphan, non-orphan, biologic and small molecule. Therefore, these studies are not specific to orphan drugs.

A drug that has undergone an attenuated approval trial is generally supposed to conduct an additional or confirmatory trial. Research is showing that the rigor and completion rate of confirmatory trials may be of concern. One 2019 study looked at all 93 accelerated cancer drug approvals from 1993-2017 and their confirmatory trials.[13]

- Eight drugs were found to have no benefit in the confirmatory trial.
- Just 20 percent showed improvement in overall survival.
- 20% used the same surrogate measures in both the approval and confirmatory trial.
- 20% used a different surrogate measure in the approval and in the confirmatory trials.
- The confirmatory trials of 24 products were ongoing, delayed or pending FDA review at the time of the study.

Another recent study,[14] found that of the 38 products receiving accelerated approval between 2012 and 2017, 22 showed benefit in their confirmatory trials but only six of these products were confirmed using overall patient survival. The other 16 showed confirmed benefit using surrogate endpoints. The approved products constituted 16 percent of Medicare Part B and 2.5 percent of Medicare Part D spending. The authors contend that use of surrogate measures may not be sufficient to determine longer term clinical benefit – overall survival. These researchers and others have pointed out that while the rate of cancer drug approvals has increased, overall survival has not increased or has even declined depending on the disease. Infrequently, longer term use of a drug can demonstrate patient harm that did not appear in short studies with a limited number of participants.

Orphan Drugs Have Less Investment Risk Than Non-Orphans

Because the science is less rigorous and the drug efficacy is often measured indirectly, orphan drugs have a much higher rate of FDA approval than non-orphan drugs (22% for orphans and 11% for non-orphans).[15] This is a very significant difference and is notable for two reasons. First the industry says that orphan development is risky or riskier than non-orphan development and the opposite is true. The industry has said for almost two decades that, overall, only 10 out of 100 drugs in development get to market. Ten percent is an outdated number overall which ignores the impact of a new business model

[13] JAMA Intern Med. 2019;179(7):906-913. doi:10.1001/jamainternmed.2019.0462
[14] JAMA Health Forum. 2022;3(5):e221158. doi:10.1001/jamahealthforum.2022.1158
[15] DE Fagnon et al.

built on orphan drug development and improved clinical trial efficiencies for orphan and non-orphan drugs generally.[16]

Almost a decade ago, as the industry orphan drug development business model was gaining speed, orphans already had lifetime revenues equal to non-orphan blockbuster drugs.[17] At the time of that study, researchers attributed the revenue comparability to the exceptionally high prices of orphans relative to non-orphan drug prices.[18] The authors were certainly right. A case in point would be Trikafta, a leading rare disease drug for cystic fibrosis and is approved only to treat CF. It was the third highest revenue drug in the world in 2022 – which is due to price, not volume. Global revenue for 2022 was $8.95B and is expected to grow to $9.85B for 2023.[19]

An indicator of the level of financial risk involved in orphan drug development is the extent to which small biotechnology companies develop promising molecules and take the products all the way through clinical trials to FDA approval and market launch. In 2022, 12 of the 21 approved orphan drugs were brought to market by an emerging biotechnology company.[20] This seems to indicate the availability of capital to a growing number small biotechs. More capital, and a growing small biotech sector, can be an indicator that orphan drug development risk is manageable even for small companies. Of course, small companies may be bought by large drug makers or small companies may sell the rights to promising drugs to large companies that have the finances and ability to bear the risk. The fact that more than half of orphan drugs approved were brought to market by small biotechs is an indicator that barriers to the orphan market entry are not prohibitively high anymore.

Today's orphan drug business model is not unlike the small molecule 'salvage' therapy business model of decades past. Salvage therapy is a therapy of last resort, to be used after all other treatment options have been ruled out. Because it is treatment of last resort, the utilization is expected to be low and safety and effectiveness standards are less rigorous because death is otherwise imminent. Salvage therapies came to market priced high. But, like high-priced orphans in today's market, the salvage

[16] A 2023 op ed in MN written by the MN BIO trade association, said that the overall FDA approval rate is 12%--which speaks to the impact of new approval pathways and the growing prevalence of orphan drugs.
[17] DE Fagnon et al. Of note, drugs that begin market life as orphan are subsequently approved for additional orphan indications (enlarging the treatment population) and then non orphan indications. Humira is an orphan drug which finally faced market competition in 2023 – almost 20 years of on-market patent protection and market exclusivities. It was the top selling drug in the world with $20B in annual sales. The Fagnon analysis from 2014 was only 10 years into the 20 year Humira run and many orphan drugs have adopted the Humira playbook, making this 2014 analysis quite conservative.
[18] This older analysis may not account for the stacking of orphan and non-orphan indications for any one drug – a practice that seems to be increasing. K Miller et al. 2022 found 3,269 unique drugs that have 5,099 orphan designations, 25% of the unique drugs have multiple designations 508 drugs are FDA approved for at least one orphan indication.
[19] Vertex Earnings: Strong Demand for Trikafta/Kaftrio Drives Sales; Pipeline Continues to Make Progress | Morningstar and https://www.morningstar.com/stocks/vertex-earnings-strong-uptake-trikaftakaftrio-drives-growth-raising-fair-value-estimate-3 accessed 11/16/2023
[20] IQVIA Institute. New Drug Approvals and Launches, 2022. January 2023.

product quickly expanded to become a first line treatment option which greatly expanded utilization with no diminution in price.[21]

Global Blockbuster Products Started Market Life as US Orphan Products

An orphan product can be approved to treat more than one aspect of the same orphan disease – a disease that manifests through slightly different mutations of the same gene for instance. Orphans can be approved for multiple different orphan and non-orphan conditions.

For instance, the Hepatitis C treatment Mavyret is a non-orphan for adults but an orphan drug for children. There are 2.4 million people still living with this chronic disease in the US.[22] Biktarvy, which treats HIV, is non-orphan for adults and orphan for children.

Humira, a drug to treat about a dozen orphan and non-orphan autoimmune conditions, was the number one selling drug in the world, $21B in 2022. It had more than 20 years of in-market patent protection – far in excess of the traditional 7-10 years of in-market protection. Humira patents finally expired in 2023. It still has exclusivity for three orphan indications that expire in the next five years. Humira biosimilar competition began in 2023 but the competition is not licensed to treat the remaining pediatric orphan indications until those exclusivities expire.

Keytruda, a blockbuster cancer treatment, had global sales of $22B in 2022. Keytruda has nine approved orphan indications, and one designated but not yet approved orphan indication. Keytruda is approved for ten non-orphan uses. The first of its 53 approved patents expires in 2028. (The are 76 patent applications pending.) Orphan exclusivity ends in 2028 for three of the four most recent orphan approvals. The fourth, the most recent orphan use approval in late 2023, has no exclusivity end date posted, likely because the drug is not yet licensed to treat that condition.

For many blockbuster products, the ability to create long lasting monopolies that fend off competition is a mixture of patent thickets and orphan indications for rare diseases. It is generally thought that it is the is the rare disease approvals that give a drug great latitude in setting high prices while avoiding public criticism.

The Orphan Drug Pipeline – Trends and Future Market

In 2022, the FDA approved 103 small molecule (oral) drugs, 23 percent of which are orphan drugs and 50 percent of those received one or more types of expedited review. The FDA also approved 16 biologic drugs, 69 percent of which are orphan products and 91 percent of the orphan products received some type of priority or expedited review.[23]

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[21] This is an excellent long form article about the legal manipulation of federal orphan drug approval laws https://kffhealthnews.org/news/drugmakers-manipulate-orphan-drug-rules-to-create-prized-monopolies/ The problematic aspects of market dynamics have intensified since this article was published.

[22] Hepatitis C in the United States: One Step Forward, Two Steps Back. C del Rio and S Springer. Am J Public Health. 2021 May; 111(5): 768–769. 10.2105/AJPH.2021.306149.

[23] https://www.fda.gov/media/165826/download accessed November 2023.

A recent research project[24] compares the median launch prices of 242 approvals of New Drug Application (NDAs, small molecule products) and Biologics License Applications (BLAs, large molecule products) from 2017-2021.

Notable in the analysis

- The number of orphan drug approvals rival the number of non-orphan drugs approved.
- Biologics are more likely to be orphan products than non-orphan.
- The majority of all drugs approved (63%) were granted priority review – which is often coupled with one or more other expedited approval processes: accelerated, breakthrough, and fast track. 97 percent of orphan drugs were given priority review.
- Drugs taken for years have substantially higher median launch prices than drug treatments that are shorter term.
- There is significantly lower industry investment in prevention and diagnostic medicines as well as diseases associated with high prevalence and high mortality rates.

Excerpted Characteristics of Approved Products from Althobaiti et al.

Rx Characteristics	**Non-Orphan**		**Orphan**	
	No. (%)	Median Cost 2021	No. (%)	Median Cost 2021
Total Approvals	124 (51.2%)	$12,798.36	118 (48.8%)	$218,871.51
NDA	95 (53.1%)	$8,701.27	84 (46.9%)	$206,176,28
BLA	29 (46.8%)	$61.468.75	34 (54.0%)	$264,007.88
Treatment Rx[25]	108 (49.8%)	$18,486,88	109 (50.2%)	$230,768.11
Prevention Rx	11 (64.7%)	$2,311.92	6 (35.3%)	$71,503.98
Diagnostic Rx	4 (57.1%)	$1274.04	3 (42.9%)	$2,527.44
Priority Review	56 (36.6%)	$29,093.35	97 (63.4%)	$233,934.14
Genetic Disorders	2 (4.9%)	$290,279.77	39 (95.1%)	$274,515.15
HIV	4 (80.0%)	$37,825.76	1 (20.0%)	$36,982.36
Infectious Disease	17 (77.3%)	$3,152.25	5 (22.7%)	$3,207.95
Cancer	27 (36.5%)	$199,370.90	47 (63.5%)	$156,126.94
Transplant	0 (0%)	--	2 (100%)	$25,790.23
Other	74 (75.5%)	$9557.37	24 (24.5%)	$8411.00
Single Use	15 (75.0%)	$727.85	5 (25.0%)	$715.47
Less than 1 year	43 (52.4%)	$92,438.35	39 (47.6%)	$12,069.44
One Year or more	65 (46.8%)	$130,151.75	74 (53.2%)	$23,174.91

[24] H. Althobaiti et al. Disentangling the Cost of Orphan Drugs Marketed in the United States. Healthcare 2023, 11, 558. February 13, 2023. https://doi.org/10.3390/healthcare11040558

[25] A drug that treats a condition as distinct from a drug for prevention or diagnosis.

What the Althobaiti analysis of median launch prices *during* a 5 year period does not capture is the *growth* in launch prices *from* 2017 *to* 2022, which adds to the importance of the Althobaiti analysis.

1) The average launch price of new chronic illness medicines jumped from $2,115 in 2017 to $180,000 in 2021.[26]
2) The average launch price of new cancer medicines rose 53 percent from 2017 to $283,000 in 2022.[27]
3) The median launch price for all new medicines (chronic illness, rare disease, cancer) was $257,000 in 2022.[28]
4) Net (after rebates) prescription drug costs already consume 23 percent of our healthcare premiums.[29]

Updating the Althobaiti analysis for more recent years (2019-2022) and using mean/average launch price instead of the median price could reveal significant healthcare financing challenges.

When viewing the market with these factors in mind, it is hard to accept the idea that orphan drug development is an exceptional financial risk. In fact, the opposite seems to be true.

Nothing in the paper is meant to diminish the very important science in orphan drug development and the undeniable benefit to patients suffering from life altering and fatal neglected diseases. The issue for society is how we equitably provide coverage of and access to multi-million dollar, often lifelong, treatments for a significant portion of the US population.[30]

It may be time to confront industry threats that orphan drugs will not be developed if any cost containment is applied to them. The orphan system is clearly extremely lucrative – far too lucrative for any company to exit the market from any threat of modest cost containment.

Impact of Medicare Price Negotiation Program

The future of the orphan drug market will be affected by the new Medicare drug price negotiation program that exempts an orphan drug only to the extent it is approved for just one indication and that one indication is a rare disease. How the industry actually responds to the law and the policy is not yet clear but the industry's public-facing comment is that the Medicare orphan policy will absolutely result in the development of many fewer orphan drugs. The business decisions companies make will most likely depend on the disease, the product, and the level of existing or anticipated competition.

[26] https://www.bloomberg.com/news/articles/2022-06-07/new-drug-prices-soar-to-180-000-a-year-on-20-annual-inflation?leadSource=uverify%20wall;
[27] https://www.usnews.com/news/top-news/articles/2022-11-02/new-u-s-cancer-drug-prices-rise-53-in-five-years-report
[28] https://www.reuters.com/business/healthcare-pharmaceuticals/newly-launched-us-drugs-head-toward-record-high-prices-2022-2022-08-15/
[29] https://www.ahip.org/your-health-care-dollar-new-ahip-analysis-shows-where-it-goes/, accessed 3/15/21
[30] Drugs like Keytruda (for cancer) and Humira (autoimmune) treat many different orphan conditions *and* many other non-orphan conditions – all at the same orphan-based pricing. Orphan drugs increasingly follow this model.

The orphan drugs most likely to be impacted by Medicare negotiation are oncology therapies because cancer is probably more prevalent in our older population relative to other orphan diseases that can be deadly at younger ages. Also, the industry seems to have a particular focus on orphan cancer products. .

A company may want to develop an orphan product indicated for pediatric uses and get adult approval later. This delays the possibility that the product would be a top-spend Medicare drug for a period of years. Some companies already stagger the orphan designations/drug approvals by age cohorts which can extend the exclusivity and maximize profit.

If the orphan product is a biologic, it may be most reasonable to continue the one drug/multi-designation approach but ensure that the product has competition early enough to exempt both products from Medicare price negotiation.[31] The government has said that in order for a biologic product to be exempt from negotiation after 12 years on the market, there must be a competitor biosimilar with a high probability to be on the market before a Medicare negotiated price goes into effect. The government guidance as of June 2023 stipulates that the competition must be meaningful or robust.

The policy does not yet explicitly consider what robust competition looks like for a drug with multiple indications and remaining orphan exclusivities. A drug might be approved for multiple orphan and non-orphan uses. The biosimilar coming to market will be approved for just the treatments where exclusivity for the original (reference) product has expired. Would that qualify as robust competition and exempt both products from negotiation? Both products could continue to develop additional orphan indications. While it is very unclear at the moment, there may be a strategy that allows a drug with multiple orphan indications to continue to be exempt from Medicare negotiation so long as there is competition on at least one indication for which the drug is approved. This would allow both products to evade negotiation while developing additional orphan and non-orphan indications.

Certainly, no company will step away from the very lucrative orphan market because of the Medicare law. Trikafta is the third highest revenue drug in the world although the Cystic Fibrosis Foundation estimates that just 107,000 people in 94 countries are currently diagnosed with CF. Trikafta only treats CF and is not effective for all people with CF.

Industry has consistently warped how federal incentives for drug development and competition are used. The warped system protects industry prerogatives in the exceptionally byzantine and exceptionally profitable market. Medicare price negotiation will hopefully not produce a similar outcome.

Summary

The industry and patient groups (many of which are funded by industry) want the public to think of each extremely high priced orphan treatment as a stand-alone phenomenon and as such, price and cost should not matter. Because orphan drug development is the new prevailing business model, the more realistic way to think about orphan drugs is as an entire market segment of very high priced drugs that is projected to continue to grow quickly. Some of these products are one-time treatments but durability of

[31] https://news.bloomberglaw.com/ip-law/j-j-amgen-settle-patent-suit-on-biosimilar-of-lucrative-stelara

the treatment is not known because of attenuated clinical trials. Some of these products will be taken lifelong.

It is important to keep in mind that these life changing new products save lives, extend life, and make huge improvements to quality of life for people with rare conditions and their families. The very effectiveness of these new, wonderful treatments means people with rare conditions live longer, fuller lives. In terms of healthcare financing, this means that the patient base for these important treatments only grows over time because people with these terrible diseases live longer and the prevalence of the genetic disorder in the population does not diminish. Recent data from the Cystic Fibrosis Foundation bear this out. This is amazing progress and wonderful news for patients and their families but the growing cost is part of serious healthcare financing concerns as we hurtle into the new industry business model. A future where much of public and private spending is dedicated to the pharmaceutical industry seems unbalanced and may impede our ability to accomplish other important public policy goals, much less finance healthcare for all.

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