

Tools to Incentivize Research and Development for Pharmaceuticals – Pull Mechanisms and Differential Pricing

Kishen Anand¹ and Luca Maini^{2#}

¹Green Level High School, Cary, North Carolina, USA

²University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

#Advisor

ABSTRACT

This article is a review of the current state of pull mechanisms and differential pricing in relation to incentivizing pharmaceutical research and development. In many developing nations, there is a shortage of pharmaceuticals for their specific infectious diseases because these markets are not always viewed as profitable to firms. To combat this issue, governments and organizations need to work with firms to incentivize research and development for medications and vaccines for these diseases. Pull mechanisms are one way to achieve this goal as they only reward successful products; through the use of tax credits, patent buyouts, purchase agreements, or a combination, governments, nonprofits, and other world agencies could reward firms which makes the market more attractive to other developers too. World agencies could also use differential pricing for the same purpose. Allowing firms to charge varied prices based on specific factors like a country's real gross domestic product per capita would increase access to needed pharmaceuticals while keeping the market attractive. The synthesis of current literature shows that although these strategies have been moderately successful on their own, such as with the GAVI fund, they have also failed because of a lack of support, such as with the Vaccines for the New Millennium Act. Therefore, world organizations might need to develop new strategies, such as combining policies, to spur innovation and development.

Introduction

The costs associated with Research and Development (R&D) have been a barrier for pharmaceutical development throughout the world. Because of this, many private firms choose to invest in drugs that will serve markets that could provide large monetary returns, over drugs that could lead to public health improvements in developing countries. This inequality has led to a consensus in the industry: new mechanisms and factors are needed to stimulate R&D for diseases in developing countries (Webber & Kremer, 2001). The solutions to this problem are classified under two labels—pull mechanisms and push mechanisms.

Push mechanisms are programs that directly fund R&D, such as grants, through universities or government laboratories. Conversely, pull mechanisms are incentives that make the market more secure, which improves the possibility of a return on initial investments, by rewarding only successful outputs. While push funding is initially beneficial for the public good, by funding basic research, pull factors are the mechanisms needed to advance the development of vaccines and drugs for diseases that primarily affect developing countries (Webber & Kremer, 2001).

Because of their nature, pull mechanisms can apply to any kind of drug development. Whether it be antibiotics or vaccines, a simple pull mechanism could be a purchase contract which would confirm that a successful drug/vaccine would be purchased in some capacity. This application for pull mechanisms fights the barriers present in drug development for developing countries, since it provides a baseline revenue number through the promised

purchases. For these solutions to be effective in the actual world, cooperation from world entities (governments, firms, and international organizations) would be necessary.

While not a traditional pull mechanism, in the sense of providing a reward only when an actual product is made, differential pricing is another strategy governments and firms should consider increasing access to pharmaceuticals in developing countries (Yadav, 2010). Differential pricing is where firms can set different prices based on the average income or Gross Domestic Product of a country. The market for HIV/AIDS medications and therapies is a prime example of this policy; while there was not much variation in their price earlier, the pharmaceuticals are now priced accordingly in low-, middle-, and high-income markets (Yadav, 2010).

In this review, I will discuss pull mechanisms and their current applications, along with future uses in different markets; I will also discuss differential pricing and the consequences associated.

Pull Mechanisms

Tax Credits

In many developed nations, including the United States, left-leaning leaders have proposed tax credits for R&D and for the sales of needed pharmaceuticals. Diseases such as AIDS, Tuberculosis, and Malaria all need more research for therapies, medications, and vaccines; the tax credit given for the money made by the future sale of these products works by not only increasing the profit made for the firms, but also by lowering the price consumers must pay. To implement these credits in the capacity of a pull mechanism, they would only be given to firms that develop a successful product, which means whoever provided the tax credit would not lose money for an unsuccessful product. However, these benefits would only be possible if an organization or government would invest in the cause. While some organizations, like the Gates foundation, have shown some interest in this option, tax credits are still not as mainstream as they could be (Webber & Kremer, 2001).

Patents and How They Could Improve

Patents and other forms of idea protection, like copyright, allow for ideas to be preserved and not duplicated by others (Kremer, 1998). While this may be beneficial in some industries, Kremer shows that in the pharmaceutical industry these protections can lead to monopolies, which lead to serious issues in a market. They can lead to stagnancy in development and encourage wasteful practices like overpricing and reverse engineering to bypass the protections. While government intervention may be partly beneficial, Kremer argues developers might waste the subsidies by not providing a viable product for consumers. A combination of these two solutions allows for a protection system without monopolies and the harsh practices associated with them. Following the mechanism outlined in Michael Kremer's 1998 paper Patent Buyouts: A Mechanism for Encouraging Innovation, the government could determine a fair price to buy patents (Kremer, 1998).

On the producer's end, patent buyouts dramatically increase development and advertising incentives both before and after the patent is bought out. Before selling, firms could invest more in their patent for a large markup on the price of the patent in return. After selling, new technology, or other advances, could allow for the development of a complementary product that could be patented separately, which means the new developer could keep more of their profits. However, research shows while patent buyouts increase incentives for development, they only increase incentive for patentable development, not for testing previously patented products in different uses, or other unpatentable development. While this is an issue, examples from history (such as the developments made to the cotton gin after the government bought out its patent) show that patent buyouts do not always stop further technological development (Kremer, 1998).

In terms of governments, there are many choices in how to buy patents. Kremer describes one attractive option, which is for the government to buy the patent for the value of it in the private market, times a markup that covers the private and social impact of the patent. While this involves more of the government's volition than the current patent system, it is still much less than the volition needed to fund research through government organizations like the NIH. While the current patent system has its flaws, modifications, like those outlined above, could alleviate some of the issues while making the market a safer place for firms (Kremer, 1998).

Purchase Agreements

Purchase agreements are when a government or organization agrees to a contract that entails a guaranteed purchase amount by said organization if the firm provides a usable product. Literature shows that any firm could develop the needed product, although the amount purchased would have to be large enough to overcome the small profits if produced otherwise. This purchase amount would also have to be large enough for the firm to consider making the product available at no cost (or low co-pays) in the developing countries that need them (Webber & Kremer, 2001).

This pull mechanism is attractive because it creates market incentives for pharmaceuticals that might not have any. Purchase agreements have already been used before for other products, and as stated previously, they allow developing countries, who truly need the product, to pay much less than the initial price. Studies show, while some may be hesitant, as that large of a purchase commitment sounds too good to be true, this could easily be avoided if the buyers agree to buy other, existing medications from the same firm. In short, purchase agreements are a very beneficial option because they can provide firms with adequate profit, since developing countries could spearhead the agreements, and allow for developing countries to get what they need, with a price they can pay, all while stimulating R&D for diseases that need more attention (Webber & Kremer, 2001).

Table 1. Pull Mechanisms Summarized		
Mechanism	Benefits	Potential Drawbacks
Pull Mechanisms (Generally)	- <i>Only rewards successful outputs so investments are not wasted.</i>	- Varies.
Tax Credits	- <i>Firms can keep more of their profits;</i> - <i>The increased profits could present themselves as lower prices for consumers.</i>	- Requires Backing from big entities like government or foundations.
Patent Buyouts	- <i>Prevent monopolies and wasteful investment in reverse engineering.</i> - <i>Encourages innovation on the producer end.</i>	- Would require a whole new system to be set up in many countries.
Purchase Agreements	- <i>The country needing the medication or vaccine would pay a price that is much more affordable for them.</i>	- Needs support from a large enough buyer. - Would need to purchase a large enough amount to make the offer attractive.

Applications of Pull Mechanisms in the Real World and their Success

The Pneumococcal AMC (A Purchase Agreement)

Started by the GAVI Fund, the Pneumococcal Advanced Market Commitment (PAMC) is a purchase agreement made by the GAVI Fund to contract firms with developing a pneumococcal disease vaccine for the developing world. On average, bringing a vaccine from the developed to developing world takes ten to fifteen years, but with the support of the PAMC, the GAVI Fund has sped that process up (GAVI, 2020). As of December, thirty-first 2019, 1650 million vaccines have been contracted for use in 2025-2027 (GAVI Annual Report, 2019).

While these numbers are a monumental step towards achieving public health goals, some critics feel firms are abusing the GAVI support by agreeing on prices that developing nations cannot afford without the funds. Doctors without borders says that some of the \$1.5 billion that is being paid to pharmaceutical firms could have been used to incentivize development for more affordable products (Doctors Without Borders, 2011).

Although this is a valid criticism of the use of the GAVI Fund, the social value of the fund's effects, such as the lives saved, make the issue increasingly more complex. One significant conclusion that can be made at this time from existing literature is the GAVI Fund and the Pneumococcal Advanced Market Commitment are both examples of purchase agreements, and other pull factors, having an impact in the actual world.

Tax Credits

Many countries, developed and developing, have used tax credits for research and development in the past. While they have not been used as pull mechanisms, because they are not awarded for a finished product, the pre-established structure of their use shows that world agencies could use them as pull mechanisms in the future (Rao, 2011).

The story of the Vaccines for the New Millennium Act shows how lawmakers have responded to the use of a tax credit as a pull mechanism in a developed country. US Representative Nancy Pelosi, with support from Senators John Kerry and William Frist, new legislation that would provide a tax credit as an incentive to pharmaceutical firms to develop vaccines for infectious diseases that primarily affect developing nations. The firms could claim a credit if they sold their vaccines to international funds like the United Nations' Children Fund (UNICEF). At the time (2000), this bill was one of the first examples of a pull mechanism that increased the profitability of vaccines that might not be very profitable otherwise. While this bill had a successful initial review, the senate and the pharmaceutical industry found some issues with it; namely, many firms were not comfortable with the idea of incentives that controlled what they should focus their R&D in. Eventually, a revised version of the bill was introduced, but even without the tax credit of the previous iteration, the bill did not pass (Rao, 2011).

Based on the attitude towards the bill, the United States, if not more developed countries, was not ready for tax credits, or even other pull mechanisms, in the pharmaceutical industry.

Patent Buyouts in History

Patent buyouts have spurred innovation in many fields for years. While they have not been used in pharmaceuticals, history shows that patent buyouts have led to many advancements in the product they were used on.

One example of improvements to a product after its product was bought out is daguerreotype photography. By combining aspects of the patent system with government support by buying the patent, the French government was able to support research in the method. Since the patent was bought out, Daguerreotype photography was adopted all over the world which also put the photography method in the hands of innovators. These innovators developed many improvements to the method, which illustrates how patent buyouts can be useful (Kremer, 1998).

Patent buyouts can limit monopoly price changes and reduce the need for unnecessary reverse engineering. Kremer illustrates, in the pharmaceutical industry, patent buyouts would be a benefit to the whole world because they can ensure that developing countries have access to needed vaccines and medications without having to pay exorbitant prices or reverse engineer the product (Kremer, 1998).

Differential Pricing and its Applications

What is it?

Differential pricing is when firms charge different markets different prices based on what they can pay. In theory, this practice would allow anyone in the world to get the pharmaceuticals they need, no matter how much they could pay. Also, this practice would incentivize research and development for diseases in developing countries because the market for these certain pharmaceuticals has grown. However, full implementation of this policy is not possible because of the barriers associated with it, but partial implementation could be very beneficial, even if it has some drawbacks. Therefore, while differential pricing may be hard to achieve, literature shows that the policy could greatly benefit the developing world (Fisher & Syed, 2014).

Potential Issues in Implementation

While some countries benefit from differential pricing, developed countries sometimes implement legal regulations that ban the policy. In these countries, either the legislators or the population feel they are being treated unfairly because the price they must pay is higher than another country's. Often, these people consider pricing the goods based on what people can pay, and what makes the most profit, is price gouging. While in most cases this is immoral, most of the negative reactions are based on the idea that differential pricing is only being used to make up for variations in demand. However, when being applied to pharmaceuticals, differential pricing should focus on increasing access to medications not only for increasing profits. Therefore, implementing differential pricing must be done in a method that avoids these reactions (Fisher & Syed, 2014).

The main way a population reacts to any policy is based on how the policy is framed. Charging everyone a higher price and then providing people with rebates, coupons, or discounts is a way that this process could be framed. Compared to a system where the base price is low and then some people are charged more, the first framing method would give a better reaction, which means that more people would at least not oppose the policy, if not support it (Fisher & Syed, 2014).

In short, differential pricing is where firms price their pharmaceuticals at different prices based on the country, or category of country, it is being sold in. Studies show, while other industries may use this practice only to make up for different demands in different markets, the pharmaceutical industry can and should focus on using this tool to increase access for pharmaceuticals needed in markets where they are currently too expensive to buy, and to better incentivize R&D for these medications (Fisher & Syed, 2014).

Current Applications

One very influential example of differential pricing has been in antiretrovirals for HIV/AIDS. While there was not much variation in prices prior to 2000, a new partnership between public and private entities called the Accelerated Access Initiative (AAI) led to firms voluntarily lowering prices in developing countries. They also negotiated price offers with governments of least developed countries. This system started as a two-tiered system but later progressed into a three-tier system, because of the success of the two-tiered model. This new system offered lower prices for slightly more developed countries. Today, most firms offer two main prices for less developed countries. This system

benefited the world greatly because of the increased access of HIV/AIDS pharmaceuticals to those who need them, at prices they could better afford (Yadav, 2010). In South Africa, the number of people living with HIV with access to antiviral therapies grew from 1% in 2004 to 70% in 2019 (Databank, 2021).

In terms of other pharmaceuticals, differential pricing has been used sparingly. Most of the time, these decisions to implement differential pricing are based on the idea that the burden of diseases in developing countries increases the market size of some of their products. Therefore, if they made the products more affordable to those markets, they would be able to increase revenue while increasing awareness for their company. To apply this policy, many companies are asking consumers, health care providers, and patients what a reasonable price would be. This makes sure each price is based on what the consumers can pay rather than based on statistics that do not always accurately measure a country's realistic income, such as a real gross domestic product (RGDP) per capita. This process is an example of decentralized differential pricing (Yadav, 2010). One example of this process in action can be seen in the pricing strategy of the type two diabetes drug, Januvia®. In India, the price of one pill is \$1 USD, about one fifth the US price. Because they consulted doctors and patients before deciding on a price and launching a product, the price has been very successful. This is just another example of differential pricing benefitting both the consumers, by increasing access and affordability, and benefitting the manufacturers, by showing them the increase in demand, which serves as motivation for research and development of other possible medications they can sell for country specific diseases (Yadav, 2010).

Overall, Yadav describes that differential pricing, in its current applications, has proven to be successful in antiretrovirals (for HIV/AIDS) and other more common medications (like Januvia for type 2 diabetes). Specifically, if manufacturers work together with consumers and health care providers in their target markets, they can roll out a price that is mutually beneficial, because it increases access and affordability for consumers, while increasing revenue and incentivizing R&D for other diseases in the same market.

Concluding Thoughts

As highlighted by the death rate of neglected tropical diseases, pull mechanisms need to be used. While using individual pull mechanisms has not always proven to be effective, using a combination of various mechanisms might lead to a better result.

One such use could be a combination of tax credits for innovation and patent buyouts. Since, in a system with patent buyouts, firms could choose to invest more into their patent for a higher selling price, offering tax credits for this investment could lead to more innovation. Another option could be to provide tax credits on the revenue of purchase agreements. For some specific diseases it may be harder to make attractive offers of just tax credits or purchase agreements to firms, so combining the two might lead to more research in diseases that are not traditionally viewed as profitable. Although these examples are oversimplified generalizations, they provide ideas for how pull factors could be combined to lead to become more beneficial for consumers. Besides pull mechanisms, making differential pricing more normalized and legal, specifically for certain pharmaceuticals, could also prove to be successful in expanding the market for consumers. While developed countries would have to pay more for very specific medications, countries that need them desperately, and in higher quantities, could receive them appropriately.

In short, pull mechanisms and differential pricing have been under-used in the past of incentivizing research and development for diseases that primarily affect developing countries. International agencies, including governments and nonprofits, should take advantage of these options to make medications not only available to the countries but also make them affordable to them.

Acknowledgments

I would like to express my gratitude for my advisor, Dr. Luca Maini, at the University of North Carolina at Chapel Hill. Thanks to his advice, guidance, and general help, I was able to put together this project. I would also like to thank him for taking a chance on me, even though I did not have experience in this field, or in doing research.

References

- Antiretroviral therapy coverage (% of people living with HIV). (2021, March). [https://databank.worldbank.org/source/wdi-database-archives-\(beta\)#](https://databank.worldbank.org/source/wdi-database-archives-(beta)#).
- Cooper, M. A., & Shlaes, D. (2011). Fix the antibiotics pipeline. *Nature*, 472(7341), 32–32. <https://doi.org/10.1038/472032a>
- Cuckler, G. A., Sisko, A. M., Poisal, J. A., Keehan, S. P., Smith, S. D., Madison, A. J., ... Hardesty, J. C. (2018). National Health Expenditure Projections, 2017–26: Despite Uncertainty, Fundamentals Primarily Drive Spending Growth. *Health Affairs*, 37(3), 482–492. <https://doi.org/10.1377/hlthaff.2017.1655>
- Danzon, P. M. (1998). The Economics of Parallel Trade. *PharmacoEconomics*, 13(3), 293–304. <https://doi.org/10.2165/00019053-199813030-00004>
- Danzon, P. M. (2018). Differential Pricing of Pharmaceuticals: Theory, Evidence and Emerging Issues. *PharmacoEconomics*, 36(12), 1395–1405. <https://doi.org/10.1007/s40273-018-0696-4>
- Denti, V., & Beck, M. (2021). (rep.). *ADVANCE MARKET COMMITMENT FOR PNEUMOCOCCAL VACCINES*. Retrieved from <https://www.gavi.org/investing-gavi/innovative-financing/pneumococcal-amc>
- Fisher, W. W., & Syed, T. (2014, January). *Infection: The Health Crisis in the Developing World and What We Should Do About It*. Infection (Fisher & Syed). <https://cyber.harvard.edu/people/tfisher/Infection.htm>.
- Gilchrist, S. (2009). *Pull Mechanisms for Value-Added Technologies for Vaccines: An Evaluation of the Issues Influencing Vaccine Producer Willingness to Advance, Adopt, and Commercialize Value-Added Technologies for Vaccines for LowIncome and Lower-Middle-Income Country Markets*. PATH.
- Gonsalves, G. (2019, October 30). *Statement on the Vaccines for the New Millennium Act of 2000*. Treatment Action Group. <https://www.treatmentactiongroup.org/statement/statement-on-the-vaccines-for-the-new-millennium-act-of-2000/>.
- Kremer, M. (1998). Patent Buyouts: A Mechanism for Encouraging Innovation. *The Quarterly Journal of Economics*, 113(4), 1137–1167. <https://doi.org/10.1162/003355398555865>
- Martins-Melo, F. R., Ramos, A. N., Alencar, C. H., & Heukelbach, J. (2015). Mortality from neglected tropical diseases in Brazil, 2000–2011. *Bulletin of the World Health Organization*, 94(2), 103–110. <https://doi.org/10.2471/blt.15.152363>

- Nathan, C., & Goldberg, F. M. (2005). The profit problem in antibiotic R&D. *Nature Reviews Drug Discovery*, 4(11), 887–891. <https://doi.org/10.1038/nrd1878>
- Pneumococcal AMC*. Gavi, the Vaccine Alliance. (2020). <https://www.gavi.org/investing-gavi/innovative-financing/pneumococcal-amc>.
- Pneumococcal Vaccine is Launched in Africa, But Are Donors Getting a Fair Deal from Companies?* Doctors Without Borders - USA. (2011, February 23). <https://www.doctorswithoutborders.org/what-we-do/news-stories/news/pneumococcal-vaccine-launched-africa-are-donors-getting-fair-deal>.
- Rao, A. (2011). (rep.). *R&D Tax Credits A Tool to Advance Global Health Technologies?* (pp. 20–22). Washington, DC: Results for Development Institute.
- Scherer, F. M. (2004). The Pharmaceutical Industry — Prices and Progress. *New England Journal of Medicine*, 351(9), 927–932. <https://doi.org/10.1056/nejmhpr040117>
- Schoonveld, E. (2019, December 9). *International Price Referencing: Stacking the Deck with Lower Income Economies*. PharmExec. <https://www.pharmexec.com/view/international-price-referencing-stacking-deck-lower-income-economies>.
- Siagian, R. C., & Ayuningtyas, D. (2019). Gap analysis for drug development policy-making: An attempt to close the gap between policy and its implementation. *PLOS ONE*, 14(8). <https://doi.org/10.1371/journal.pone.0220605>
- Snyder, C. M., Hoyt, K., Gouglas, D., Johnston, T., & Robinson, J. (2020). Designing Pull Funding For A COVID-19 Vaccine. *Health Affairs*, 39(9), 1633–1642. <https://doi.org/10.1377/hlthaff.2020.00646>
- Sonderholm, J. (2009). Wild-Card Patent Extensions as a Means to Incentivize Research and Development of Antibiotics. *Journal of Law, Medicine & Ethics*, 37(2), 240–246. <https://doi.org/10.1111/j.1748-720x.2009.00368.x>
- Webber, D., & Kremer, M. (2001). *Perspectives on stimulating industrial research and development for neglected infectious diseases*. Bulletin of the World Health Organization, 735–741.
- World Health Organization. (2012, November 23). *Active pharmaceutical ingredients of ARV drugs*. World Health Organization. <https://www.who.int/hiv/amds/api/en/>.
- Yadav, P. (2010). *Differential pricing for pharmaceuticals: review of current knowledge, new findings and ideas for action*. Great Britain, Dept. for International Development.