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The Potential Role of The Nonprofit Pharmaceutical Industry in Addressing Shortages and Increasing Access to Essential Medicines and Low-Cost Medicines

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Key Points

- We identified 11 nonprofit pharmaceutical companies that launched between 2000-2022 with mission statements aimed to enhance access to affordable and essential drugs, or resiliency in the supply chains of medical products.
- Some of these nonprofit pharmaceutical companies owned for-profit subsidiaries as a strategy to navigate a complex tax system; the majority did not have any medical products in the domestic pharmaceutical marketplace, none of them owned their own manufacturing facilities, and their financial statements suggested these tax-exempt companies were comparable in scale to for-profit small businesses and start-up companies.
- Two nonprofit pharmaceutical companies that have successfully launched medical products in the United States used different strategies for commercialization, including using contract manufacturing organizations for labeling and distribution and entering into a licensing agreement with a for-profit pharmaceutical company.
- Findings suggest that while nonprofit pharmaceutical companies hold promise in addressing drug shortages and enhancing access, their capacity and sustainability may be limited due to low production volumes, uncertainties about funding, and inexperience navigating complex tax, regulatory, and reimbursement systems.

Introduction

Americans rely on medical products, such as prescription drugs, to prevent or treat acute and chronic diseases. However, persistent high prices and shortages threaten access to lifesaving therapeutics and pose a risk to the capacity of America's health system to effectively mitigate and respond to public health emergencies and ongoing public health issues.[1,2] These market gaps in the pharmaceutical industry have attracted the adoption of different business models, such as nonprofit pharmaceutical companies, which are launched with any specified purpose other than making a profit.

The prevailing business model in the pharmaceutical industry is oriented toward the pursuit of the next blockbuster drug, defined as a drug with $1 billion or more in annual global sales.[3] For-profit companies may utilize their profits to reinvest in research and development (R&D) or deliver a high return on investment to shareholders. However, critics argue that the blockbuster model in the pharmaceutical market incentivizes a non-innovative culture that results in duplicative and nonproductive ventures targeted to populations where high revenues are guaranteed.[4] Further, some researchers have indicated that the prioritization of developing blockbuster drugs contributes to higher prices and unmet public health needs, such as shortages of older

generics and underinvestment in R&D for new antibiotics and drugs for certain rare diseases.[3-6] Researchers have proposed alternative business models to promote growth in the nonprofit pharmaceutical sector and address some of the existing market gaps.[7-10] These alternative business models include nonprofit collaborations with for-profit companies to increase manufacturing and distribution capacity, creation of nonprofit manufacturing and distribution companies, and partnering with other stakeholders to strengthen existing capability and expertise (Appendix A).

While the emergence of nonprofit companies to address market failures is not a new phenomenon in non-pharmaceutical markets,[11] there has been growing interest, including from Congress,[12] in understanding whether nonprofit pharmaceutical companies could offer solutions to the challenges of drug access and affordability.[8] Drawing from an environmental scan of the literature and key stakeholder interviews, this report examines the ways in which nonprofit pharmaceutical companies can address a number of existing gaps, including their potential role in reducing drug shortages, increasing access to essential medicines, and providing low-cost alternatives to expensive medications.

Methodology

The Office of the Assistant Secretary for Policy and Evaluation (ASPE) used a qualitative methods approach that included both an environmental scan and key stakeholder interviews. NORC, under contract with ASPE, conducted the preliminary searches and key stakeholder interviews.

Defining Nonprofit Pharmaceutical Companies

Nonprofit pharmaceutical companies are tax exempt entities that have an established presence in the pharmaceutical industry, typically pursuing R&D activities and licensing new drugs to for-profit companies. In this report, we define a nonprofit pharmaceutical company as a tax-exempt entity with a publicly disclosed goal of pursuing market authorization and commercialization of drugs to deliver low-cost medicines, including essential drugs and drugs in shortage, and broadening access to medical products. This excludes nonprofit companies that may invest in drug development to secure licensing agreements with for-profit companies and nonprofit companies that provide contract services (e.g., contract development manufacturing organizations (CDMOs)).

Environmental Scan

The environmental scan used a list of primary and secondary search terms to identify peer-reviewed and grey literature relevant to the topic areas of interest: the nonprofit pharmaceutical sector, low-cost alternatives to expensive medications, drug shortages, and access to essential medicines. The initial search terms included keywords such as (“nonprofit pharmaceutical company” OR “nonprofit biopharmaceutical sector”) AND (“generic drugs” OR “low-cost alternatives”). Appendix B describes the search terms for the preliminary searches conducted by NORC. The inclusion criteria included materials published in English between 2000 and January 2023. In addition, ASPE supplemented the preliminary searches conducted by NORC using a “snowball” approach to identify other relevant information.

Further, we cross-referenced the list of nonprofit pharmaceutical companies generated from the environmental scan with the IQVIA National Sales Perspective (NSP) dataset to gather market information such as the number of products and total sales from January 2017 to December 2022. For the identified products sold by nonprofit pharmaceutical companies in the IQVIA NSP dataset, we compared the sales volume of those products sold by the nonprofit pharmaceutical sector with the for-profit pharmaceutical sector. We note that this search resulted in the identification of one nonprofit pharmaceutical company, Civica, which indicates that

this is the only nonprofit pharmaceutical company marketing products in the United States during the period of analysis.

Key Stakeholder Interviews

To supplement the environmental scan, NORC facilitated nine (9) interviews with key informants with expertise in addressing drug shortages, increasing access to essential medicines, or providing low-cost alternatives to expensive medications. Key informants were affiliated with nonprofit and for-profit pharmaceutical companies, academic institutions, and hospitals.

Background

Brief History of Nonprofit Companies in the Pharmaceutical Industry

Nonprofit companies are tax-exempt[i] economic entities organized around missions or objectives intended to further a social cause or provide a public benefit. Nonprofit companies differ from the traditional for-profit business model, which aims to maximize profit for investors. Nonprofit companies are restricted from distributing profits to any private shareholder or individual.[13] They leverage their social mission to attract donations from private entities or funding from public entities to finance the provision of their goods and services. Many sectors, such as pharmacies, hospitals, hospices, nursing homes, and home health care, are structured with a mix of nonprofit and for-profit companies. The literature examining non-pharmaceutical sectors suggests that the co-existence of nonprofit and for-profit companies can promote competition and increase access to services for consumers.[14-16] However, little is known about the benefits and implications of these two models in the pharmaceutical industry.

Although the pharmaceutical industry is dominated by for-profit companies, nonprofit companies have a long history of advancing innovation in this industry.[17-20] The majority of their contributions has been through R&D activities,[21,22] sponsored by funding from public and private entities. Some independently conduct R&D with their endowments, royalties, donations, or other funding, while others partner with outside entities leading these activities. Philanthropic nonprofits[ii], such as the Bill & Melinda Gates Foundation and CureDuchenne, may also fund sponsored targeted R&D projects with nonprofit and for-profit companies.

Typically, nonprofit companies have not pursued commercialization activities, such as obtaining market authorization from the U.S. Food and Drug Administration (FDA), manufacturing, and distribution of pharmaceutical products.[8,17,23] The dominant approach has been for nonprofit companies to license new drugs from their R&D pipeline to for-profit companies.[8] Some experts have cited that this approach results in nonprofit companies losing the right to manufacture these drugs exclusively and for-profit companies launching new drugs with the goal to maximize profits which may result in high prices for consumers. For example, the Cystic Fibrosis Foundation (CFF), a philanthropic nonprofit organization, invested $150 million in a for-profit company to develop ivacaftor, the first drug to address the underlying cause of cystic fibrosis.[24] CFF then sold the royalty rights to ivacaftor for $3.3 billion to a for-profit company.[25] The list price for ivacaftor when it was licensed in 2012 was $294,000 per patient per year.[26] In 2019, a new combination product, Trikafta (elexacaftor/ivacaftor/tezacaftor), was released with an average list price of $322,000 per patient per year.[27] Similar examples of innovative and expensive drugs that were initially developed or financed by nonprofit companies and licensed to for-profits for commercialization include voretigene neparvovec for

[i] In some circumstances, non-profit companies are subject to taxes, such as the unrelated business taxable income (UBTI).
[ii] Philanthropic nonprofits may invest in R&D with for-profit pharmaceutical companies.

congenital blindness, tisagenlecleucel for leukemia, and bexarotene for lymphoma.[8,20] While non-exclusive licenses have been cited as a barrier, it is worth noting that licensors must also weigh factors such as costs or profitability to determine the terms of the license. For-profit pharmaceutical companies have also used business strategies such as licensing, mergers, and acquisitions to obtain access to new drugs. Researchers have reported that the share of revenues coming from innovations sourced outside of for-profit companies has grown from 25 percent in 2001 to about 50 percent in 2016.[28,29]

In this report, we focus on nonprofit companies that are pursuing commercialization activities in the pharmaceutical industry.

Profile of Nonprofit Pharmaceutical Companies, 2000-2022

Table 1 provides a profile of nonprofit pharmaceutical companies that have entered the market between 2000 and 2022 and points to a sector that is largely fragmented. The environmental scan conducted for this report identified 11 nonprofit pharmaceutical companies that met our definition in the U.S. pharmaceutical market. Their specific mission statements ranged from providing affordable medications, to enhancing access to essential medicines or those in shortage. Each mission statement identified product commercialization as one of its goals. Further, the environmental scan revealed variation with respect to the types and number of products nonprofit pharmaceutical companies provide—some focus on a specific treatment area with a handful of products, while others provide dozens of products across multiple therapeutic areas.

The nonprofit pharmaceutical companies also differ in their operations. Some engage in R&D for product development and commercialization. For example, Medicines360 engaged in R&D and commercialization of its hormonal intrauterine device (IUD) that is accessible to low-income women in public clinics across the United States (discussed in more detail in *Access to Essential)*.[10] In other cases, nonprofit pharmaceutical companies focus only on commercialization activities, such as manufacturing, distribution, and relabeling. For example, Drew Quality Group launched in 2014 with the mission to become a supplier of high-quality generic drugs that were manufactured in the United States.[30] As of March 2023, the environmental scan and key stakeholder interviewers suggest Drew Quality Group has not yet achieved this objective. Another example is Civica, which entered the market in 2018 with a focus on relabeling and distribution of generic sterile injectables.[31] While there is no one-size-fits-all approach, a common theme is the expressed desire to promote the affordability of drugs and broaden access to pharmaceutical products by engaging in commercialization activities.

All the nonprofit pharmaceutical companies we identified have an Internal Revenue Service (IRS) tax-exempt status as either a 501(c)(3) charitable organization[32] or a 501(c)(4)[iii] social welfare organization.[33] Among the 501(c)(3) charitable organizations, some are designated as public charities rather than as private foundations.[iv] By examining all of the nonprofit pharmaceutical companies' most recent IRS form 990,[34] each reported annual revenues below $20 million, with the majority reporting annual revenues below $2 million. All of the nonprofit pharmaceutical companies also reported negative annual net income, indicating expenses exceeded revenues. In contrast, research suggests that from 2000 to 2018, 35 large for-profit pharmaceutical companies reported an average annual revenue of $33 billion, and an average net income of $54 billion.[35] While nonprofit pharmaceutical companies tend to have the revenues or number of employees to be considered small businesses, the literature and many stakeholders noted that their tax-exempt status does not make them

[iii] Unlike 501(c)(3) charitable organizations, donations, or contributions to 501(c)(4) social welfare organization are not tax-deductible on federal tax returns for the entity making the donation.

[iv] Private foundations have lower levels of public involvement and scrutiny in their activities than public charities. While public charities typically receive a greater portion of their funding from public sources, private foundations are typically controlled by small groups of individuals, such as family members.

eligible for certain types of funding, such as the National Institutes of Health (NIH) Small Business Innovation Research, the Small Business Administration (SBA) loans, or even bank loans that require some expected level of revenue.

Table 1: Nonprofit Pharmaceutical Companies in the United States, 2000-2022

Name (Year Founded)	Total Revenue (Year)	Mission Statement	Conditions or Drugs Targeted	Current Drugs in U.S. Market	Associated Companies
Civica Inc. (2018)	$16,726,911, as of 2019	Provide quality generic medicines that are available and affordable to everyone.	Various conditions requiring generic sterile injectables; insulin for diabetes	Civica Rx is involved in private labeling and distribution of 60 generic sterile injectables; CivicaScript is distributing Abiraterone—used to treat prostate cancer—and plans to distribute three low-priced generic insulin by 2024.	Civica Rx, CivicaScript and Civica Foundation. While Civica Rx focuses on generic drugs used in the hospital setting, CivicaScript, a public benefit company (PBC)[v], works with pharmacy benefits managers (PBMs) and insurers to bring low-cost generics to outpatient and retail pharmacies. The Civica Foundation is a 501(c)(3) organization that provides philanthropic support to manufacture and distribute generic medications.
Drew Quality Group (2014)	less than $50,000, as of 2021	Improve society's health by being a supplier of high-quality generic drugs, manufactured in the United States.	Generic drugs	None	N/A
Fair Access Medicines (2015)	less than $50,000, as of 2021	Identify, develop, and deliver life-saving medicines to poorly served patients in the U.S. and worldwide at the lowest cost possible.	Insulin for diabetes	None	N/A
Harm Reduction Therapeutics (2017)	$1,550,000, as of 2019	Make naloxone more accessible for everyday people by combining increased funding, generating more interest in public health, and building on our years of expertise.	Naloxone for opioid overdose	None. Over-the-counter naloxone product approved in July 2023, with an expected launch date in early 2024.	N/A

[v] Public benefit companies are for-profit entities that maintain profit and public benefit objectives.

Institute for Pediatric Innovation (2006)	$34,443, as of 2020	Research and develop innovative products that will improve the health of children and support those who provide care for them.	Pediatric conditions	None. Mission focus has evolved to focus on digital health.	N/A
Medicines360 (2009)	$17,400,453, as of 2019	Catalyze equitable access to medicines and devices through product development, policy advocacy, and collaboration with U.S. and global partners.	Contraception, such as hormonal IUDs	One branded hormonal IUD, Liletta, through Actavis; over the counter emergency contraceptive through Curae Pharma360.	Medicines360's subsidiary is Curae Pharma360 Inc. which is a for-profit organization focused on improving the availability of quality generic drugs and other medicines that are in short supply. Medicines360 selected Actavis (formerly Watson Women's Health, then Allergan, and now AbbVie) as its for-profit commercial partner for a hormonal IUD.
NP2 (2019)	$340,500, as of 2020	Promote public health by developing, manufacturing, and distributing medicines for the treatment of life-threatening diseases in underserved populations.	Generic drugs for cancer	None	N/A
Odylia (2018)	$60,528, as of 2020	Accelerate the development of gene therapies for people with rare disease, changing the way treatments are brought from the lab to the clinic…to bring life changing treatments to people with genetic disease regardless of prevalence or commercial interest.	Gene therapies for rare genetic disorders	None	Odylia has partnered with Cloves Syndrome Community, SATB2 Gene Foundation, Usher 2020 Foundation, RDH12 Fund for Sight, and PTC Therapeutics
Institute for One World Health | PATH Drug Solutions (2000)	$2,972,163, as of 2018	Develop and deliver lifesaving medicines to women, children, and communities around the globe.	Drugs and vaccines for various infectious diseases, contraception, maternal and child health	An injectable contraception, subcutaneous depot medroxyprogesterone acetate (DMPA-SC), through Pfizer.	PATH selected Pfizer as its for-profit commercial partner for an injectable contraception.

Remedy Alliance Inc. (2012)	$95,600, as of 2021	Ensure harm reduction programs have sustainable & equitable access to low-cost naloxone for distribution in their communities.	Naloxone for opioid overdose	Remedy Alliance is involved in the distribution of generic naloxone.	N/A
Tutela Pharmaceutical (2020)	Less than $50,000, as of 2021	Ensure continued and affordable access of single-source medications to patients.	Single-source medications subject to discontinuation or divestiture by their manufacturers.	None. Acquired license from Astellas Pharma Inc. for active ingredient of a medication previously tested for COVID-19.	Collaborators include Zensights, Pharmafusion, Tucker Ellis, LLP, Incubate IP, and Godfrey & Kahn, SC.

Note: All general information obtained from company websites; financial information was obtained through IRS.gov.

Table 2 presents the number of products, sales, and units sold for the only nonprofit pharmaceutical company, Civica, identified in IQVIA's NSP dataset from 2020-2022, as well as the corresponding sales and units sold for the same products sold by for-profit companies. The data show that Civica sold 350 million units and $256 million in sales for 64 products. We identified 73 for-profit companies, with 20,200 million units sold and $13,900 million in sales for the same corresponding products, suggesting that sales for the one nonprofit pharmaceutical company represents about two percent of total sales and volume.

Table 2. Descriptive Statistics by Pharmaceutical Sector, United States, 2020-2022

Description	Nonprofit	For-profit
Number of companies	1	73
Number of products	64	64
Total units sold	350.2 million	20,200 million
Total sales	$255.9 million	$13,900 million

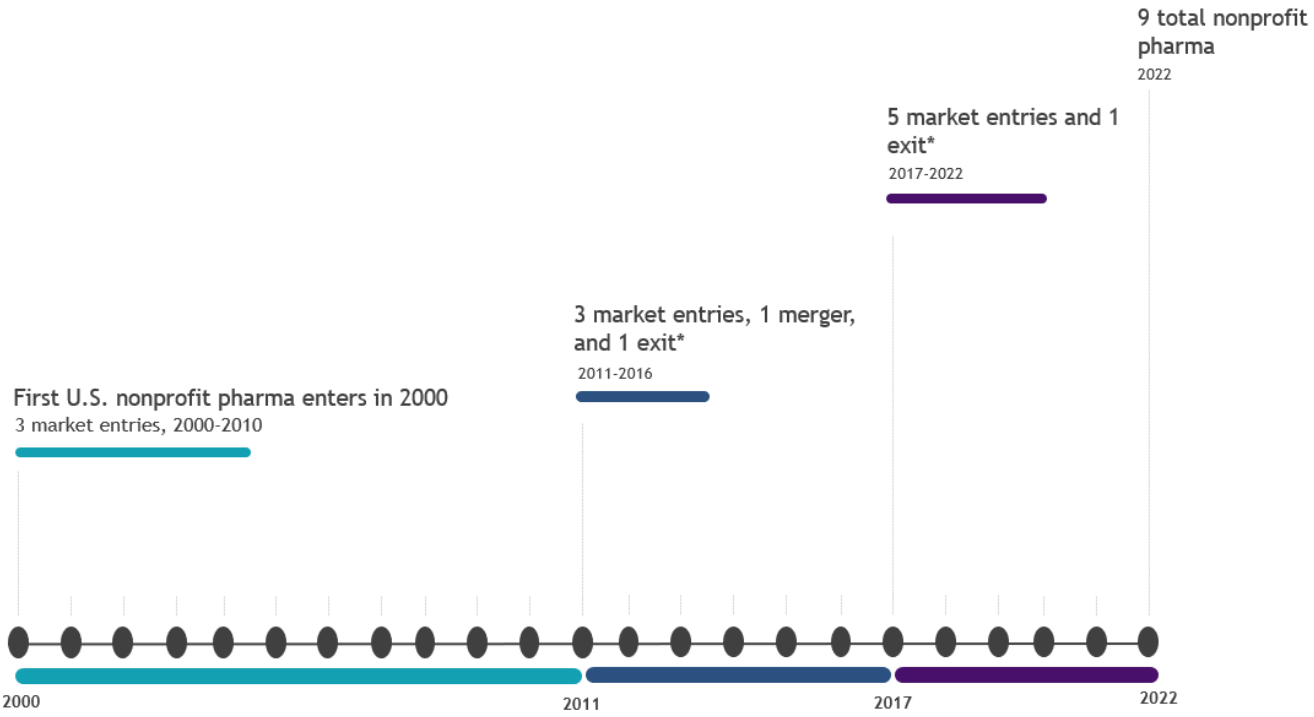
Note: A product is defined as a molecule-form-strength combination.
Source: ASPE analysis of IQVIA National Sales Perspective Data.

Market Growth

Growth in the nonprofit pharmaceutical sector was slow between 2000 and 2015, with one firm entering the market every five years, on average. Most of the growth in this sector has occurred in the last five years; on average, one nonprofit pharmaceutical company entered the market each year during 2017-2021. Out of the 11 identified companies, two are no longer operating as originally envisioned (we consider these market exits), and one merged with a global nonprofit company in 2011 (Figure 1). As of August 2023, five of the 11 nonprofit pharmaceutical companies had either received FDA marketing authorization or are distributing medical products in the United States.

The majority of nonprofit pharmaceutical companies were either in the R&D phase of medical product development or looking to secure start-up capital. As discussed above, most nonprofit pharmaceutical companies have historically outsourced the manufacturing, packaging, and labeling of their medical products to contract manufacturers. However, one nonprofit pharmaceutical company, Civica, has exhibited noticeable growth since its creation in 2018. Civica offers over 60 generic sterile injectable medications to over 1,500 hospitals through Civica Rx.[36] Further, in 2021, Civica created CivicaScript, a PBC, to offer generic drugs used in the outpatient and retail settings.[37] The Civica Foundation was also established to provide philanthropic support to manufacture and distribute generics. Civica's rapid growth has been credited to its ability to leverage the long-term commitments of its hospital and health system members to secure long-term supply contracts.[38] These supply contracts have incentivized the reentry of numerous CMOs that had excess capacity and held many of the Abbreviated New Drug Applications (ANDAs) for generic drugs that Civica labels and distributes to its members.

Figure 1: Market Growth Timeline, Nonprofit Pharmaceutical Industry, United States, 2000-2022



*Market exit refers to a shift in mission or operations that no longer covers commercialization activities.

Market Entry Strategies

Nonprofit pharmaceutical companies generally begin operations with funding from philanthropic entities or individuals, including crowdsourcing, that support their mission statement. In contrast, for-profit companies depend on raising funds through investors who expect a return on their capital. Without the expectation to sell pharmaceutical products that generate high profit, nonprofit pharmaceutical companies have a different risk tolerance and may be able to provide products with low or negative profit. However, both for-profit and nonprofit pharmaceutical companies face similar costs, timelines, regulatory oversight when developing and bringing products to market, and generate revenue from selling drug products and services.

Typically, nonprofit pharmaceutical companies focus on a single product when entering the market. Since they must demonstrate that its mission is compelling enough to motivate access to philanthropic funding, nonprofit pharmaceutical companies tend to be organized around addressing intractable market gaps that will improve social welfare, such as increasing access to medicines at affordable prices, mitigating drug shortages, or developing new drugs for rare or tropical diseases.

When selecting their target drugs, nonprofit pharmaceutical companies, like their for-profit counterparts, consider multiple factors, such as the target market size, start-up costs, regulatory requirements, and the sustainability of their business model. In interviews, stakeholders noted that nonprofit pharmaceutical companies may prefer to focus on niche drugs such as those with low start-up costs, low margins, or high volumes. Some niche markets that nonprofit pharmaceutical companies have entered are:

- **Essential drugs or drugs in shortage:** Enhancing access to affordable medications, essential or lifesaving medications, and medications that experience persistent shortages is part of the mission of many nonprofit pharmaceutical organizations. This mission can also engender trust in the market as

nonprofit pharmaceutical companies begin to be recognized for filling gaps in market demand and meeting unmet medical needs.

- **Generics:** By targeting off-patent drugs, nonprofit pharmaceutical companies can focus on products that are typically associated with low margins, as well as lower start-up, development, and regulatory costs, and lower litigation risks. These products are generally not attractive to for-profit companies due to the low margins and intense pressure to keep prices down via competition.
- **Discontinued drugs**: Nonprofit pharmaceutical companies can fill treatment gaps by focusing on medical products that have been discontinued or abandoned by for-profit companies due to low volume and profitability. These drugs represent opportunities for nonprofit pharmaceutical companies to enter the market.
- **High-volume drugs:** By targeting high-volume products like insulin, nonprofit pharmaceutical companies ensure the market can facilitate competition and business sustainability. Some of these high-volume drugs have experienced persistently high prices, despite being off patent.

Results

Low-Cost Alternatives to Expensive Drugs

Many life-saving drugs do not have low-cost alternatives, despite being off patent for an extended period of time. As a result, patients may incur debt or ration their medications, which leads to medication nonadherence and worse health outcomes.[39] In interviews, stakeholders shared that drug prices are set by for-profit companies to create shareholder value, which is typically achieved by maximizing profit. In contrast, many nonprofit pharmaceutical companies promote the affordability of medical products as a goal in their mission and vision statements. In practice, nonprofit pharmaceutical companies offer a cost-plus model that prices drugs at the level of margins that ensure their sustainability, adding a fixed percentage to the unit cost of each product.

Insulin is an example of a drug for which nonprofit pharmaceutical companies want to provide more alternatives because the global market is currently dominated by three manufacturers.[39,40] Almost a year after a nonprofit pharmaceutical company announced its two-year plan to enter the insulin market with prices set at $35 per vial, all three of the for-profit companies cut the out-of-pocket cost to a maximum of $35 per vial.[41-43] However, nonprofit pharmaceutical companies were not the only source of competitive pressure. The decision by the for-profit companies to lower insulin prices followed announcements by the state of California, in partnership with a PBC that operates a cost-plus model, to manufacture its own insulin. In addition, the Inflation Reduction Act, signed into law in August 2022, capped out-of-pocket costs for insulin at $35 per monthly prescription for Medicare enrollees beginning January 1, 2023.[39,44]

The entry of nonprofit pharmaceutical companies into markets with expensive generic drugs, few manufacturers, and high volume of sales may increase the competitive pressure for all companies to lower their prices. However, drug pricing is not only a reflection of manufacturer prices that capture the cost of R&D but also markups by intermediaries, such as PBMs, wholesalers, and pharmacies. Efforts to enhance the accessibility of affordable medications need to also consider margins that allow companies to recover their R&D costs. However, drug pricing transparency, particularly around negotiated rebates and discounts, has been a topic of debate in limiting the public's understanding of the financial arrangements dictating the profits of stakeholders in the pharmaceutical marketplace. Stakeholders shared that nonprofit pharmaceutical companies are attempting to disrupt persistently high prices for expensive medications by adopting

transparency in their financial arrangements, including disclosing the price and charging the same price for all members without volume discounts, as one of their core business strategies.

Another strategy that nonprofit pharmaceutical companies adopt to increase competitive pressure is to bring over-the-counter (OTC) alternatives to expensive prescription drugs to market. OTC drugs are typically sold at lower prices than drugs that require a prescription or that are administered in hospitals or physician offices. An example of this is naloxone, a life-saving drug used to reverse an opioid overdose, and whose price hikes[45] attracted the entry of a nonprofit pharmaceutical company, Harm Reduction Therapeutics. Although FDA encouraged sponsor applications for OTC naloxone products in 2019,[46] no existing for-profit company had submitted a New Drug Application (NDA) for OTC naloxone until two months after the nonprofit pharmaceutical company submitted its NDA in late 2022.[47,48] On March 29, 2023, FDA approved the first OTC naloxone product to a for-profit company, and sales began in the summer 2023.[49] On July 28, 2023, FDA approved Harm Reduction Therapeutics' ReVIVE, with sales beginning in early 2024.[50]

Challenges

Nonprofit pharmaceutical companies have limited capacity to offer alternatives for expensive drugs that are not off-patent or are protected by a market exclusivity. While many contribute to drug discovery and development, they typically leverage partnerships with for-profit pharmaceutical companies to commercialize their products, which creates uncertainties on the pricing model that will be used. For example, although Targretin (bexarotene), a cancer drug, was developed by nonprofit pharmaceutical companies and now has generic competitors available, it was commercialized in partnership with a for-profit company [22] and is sold for almost $30,000 for 100 capsules.[51] Relatedly, the business structure of nonprofit pharmaceutical companies with wholly owned for-profit companies has the potential to undermine their credibility regarding transparency in drug pricing. One example is CivicaScript, a subsidiary of Civica that was established as a for-profit PBC, which focuses on generic drugs distributed via retail, mail, and outpatient channels for participating pharmacies.[38]

The low levels of therapeutic concentration and market share of nonprofit pharmaceutical companies may not be sufficient to disrupt drug pricing in the pharmaceutical market for multiple reasons. First, stakeholders we interviewed noted that prices of nonprofit pharmaceutical company drugs may not be the lowest in the market at any given time because their prices are designed to create stability in the market and to be the lowest sustainable price for nonprofit pharmaceutical companies (see *Drug Shortages* for additional discussion). Second, like in the for-profit pharmaceutical sector, since list prices for drugs do not reflect markups along the pharmaceutical supply chain for each distribution channel, it is difficult to quantify the actual savings for payers and patients when there is a mix in business models. This is especially true for drugs that are administered in hospitals or physician offices because the reimbursements for those drugs are usually bundled with the reimbursement for other services.[52] Third, while OTC products tend to be low cost, OTC drugs are not covered by health insurance, which may limit the savings, number, and types of patients that could benefit from these drugs. [53]

Drug Shortages

According to the FDA, the majority of drugs in shortage are sterile injectables and older generic drugs with a median time of 35 years since first approval. [54] Root causes of generic drug shortages are the low profitability

of generic drugs and the lack of market rewards for generic manufacturers that invest in quality management maturity; shortages can also occur due to supply chain disruptions or increased demand.[vi]

The nonprofit funding model, which does not expect the same high rates of return for investors, suggests that nonprofit pharmaceutical companies may be able to sell drugs, such as generics, that are associated with low profits. However, just like any organization, nonprofit pharmaceutical companies need to balance their sustainability and cost goals. Some researchers have proposed the Health Care Utility (HCU) model, [vii] a novel governance and financing structure, to address drug shortages and persistent price hikes of generic drugs.[55] The HCU model relies on member[viii] financing to provide products and services at the lowest sustainable price. Proponents of the HCU model argue that the core tenets of the model address the factors and misaligned incentives that contribute to drug shortages.[6] The HCU model informed the business structure of Civica Rx, which provides same-price guarantees with no volume discounts, requires long-term commitments, and embeds a quality assurance process in its contracts with CMOs.[36,38] This pricing approach includes maintaining a six-month buffer supply of its products as a mitigation strategy against drug shortages or supply chain interruptions.[56] Further, Civica Rx limits its volume agreements to 50 percent of each member's total volume and establishes contracts with multiple CMOs in North America, Europe, and South Asia to increase the geographical diversity of its suppliers and mitigate supply chain risks.[36]

Challenges

In interviews, some stakeholders shared that the price of products by nonprofit pharmaceutical companies, like Civica Rx, may not be the cheapest on the market because pricing may account for the cost of investments in quality management systems to mitigate shortages. Stakeholders shared that the HCU approach to addressing drug shortages is limited because it provides drugs for its members only. The volume that nonprofit pharmaceutical companies produce may also be too low to have an impact in the broader market. Further, since many of the nonprofit pharmaceutical companies may not own the license nor manufacture their own generic drugs, some function like a group purchasing organization (GPO), and as such, they have no control over the price that patients ultimately pay.

Some stakeholders have been skeptical about the feasibility of replicating or scaling up models like that of Civica Rx for multiple reasons. First, long-term contracts may result in members paying higher prices than the lowest available market price in the short term, although the price would remain unchanged when there is a shortage. Another risk is the potential to further concentrate bargaining power in one entity and perpetuate the existing oligopoly in the pharmaceutical industry. Stakeholders shared lessons from the health care industry, which is dominated by nonprofit health systems, that suggest the nonprofit model may not always translate to maximizing social welfare. For example, research suggests that nonprofit hospitals are not more likely to provide charity care or unprofitable services than their for-profit counterparts.[57]

Access to Essential Medicines

FDA, in collaboration with other federal agencies, began developing and publishing a list of essential medicines, medical countermeasures, and critical inputs in 2020 in response to President Trump's Executive Order on Ensuring Essential Medicines, Medical Countermeasures, and Critical Inputs are Made in the United States.[58] FDA's list of essential medicines identifies those medical products that have the greatest potential

[vi] Quality management maturity measures the consistency and reliability of business processes to implement and maintain the quality of products in the marketplace, including early signals to enable actions to prevent drug shortages triggered by quality issues.

[vii] Utility is a reference to commonly shared basic goods, such as electricity and gas.

[viii] Members are customers of the HCU; for example, health systems are the customers for hospital-based drugs and health insurance companies are customers for retail drugs. Some call the HCU a "closed-system" model because only members have access to the products and services.

impact on public health and are most needed by patients for acute and urgent medical conditions. The goal of the FDA's essential medicines list is to ensure the American public is protected against outbreaks of emerging infectious diseases, chemical, biological, radiological, and nuclear threats by ensuring sufficient and reliable, long-term domestic production of these products.[59] Another list of essential medicines, managed by the World Health Organization (WHO), identifies medications that may be critical to ensure a nation's health system can meet the health care needs of its population. The WHO list of essential medicines prioritizes disease prevalence, public health relevance, and evidence on efficacy, safety, and comparative cost-effectiveness. For this report, we examine the role of nonprofit pharmaceutical companies in addressing gaps in the provision of critical medicines for both chronic and acute health conditions.[60] For purposes of the stakeholder interviews, essential medicines were broadly defined to include those in the FDA list of essential medicines and others such as oncology drugs or sterile injectables.

In interviews, stakeholders shared that nonprofit pharmaceutical companies could increase access to essential medicines by leading R&D for low volume medical products to address unmet health needs, such as rare diseases, neglected tropical diseases, and antimicrobial resistance. Examples that illustrate the potential for nonprofit pharmaceutical companies in this area include those that develop new technologies, such as Innovative Genomics Institute (IGI) that is working to develop and commercialize CRISPR gene-editing therapies to treat sickle cell disease.[61] Further, the environmental scan identified that R&D and commercialization for new antibiotics to combat antimicrobial resistance is another market gap that may be appropriate for nonprofit pharmaceutical companies.[62,63] In comparison to brand-name drugs in other therapeutic areas, new antimicrobials typically have very low volumes and low prices.[64]

Strategies to bring critical medical products to market at lower cost include identifying new uses and indications for approved and off-patent drugs, a strategy known as drug repurposing.[65] Since safety data exists for approved drugs, it has been estimated that nonprofit pharmaceutical companies can avoid approximately 40 percent of the costs for drug development by repurposing approved drugs.[66] This strategy can be effective for conditions that have few treatments available, such as rare and neglected diseases. For example, Institute for One World Health repurposed paromomycin, an off-patent drug that is no longer used as an antibiotic, to cure visceral leishmaniasis, a neglected, tropical disease.[ix]

A closely related strategy focuses on rescuing abandoned compounds for which data demonstrate safety and efficacy, but which for-profit companies do not complete development and regulatory approval due to anticipated low profitability. This market gap presents opportunities for nonprofit pharmaceutical companies. In one example, Tutela Pharmaceutical executed an exclusive license agreement for a compound that was abandoned by a for-profit company after the completion of phase 1 and 2 clinical trials.

Another market gap of interest to nonprofit pharmaceutical companies is increasing access to drugs to underserved populations by prioritizing diversity in clinical trials to ensure generalizability of evidence. For example, Medicines360 sponsored a phase 3 clinical trial for the first hormonal IUD that prioritized diversity in the enrollment of clinical trial participants. Unlike the hormonal IUD that was already available on the market at the time, this nonprofit pharmaceutical company generated safety and efficacy evidence for women of all races, women who had never given birth, overweight or obese women, and women with sexually treated infections in the United States.[10] The environmental scan identified a study that concluded that patients at a Title X clinic experienced increased uptake and decreased average payments after the introduction of the hormonal IUD.[67] This was the only example we identified of a nonprofit pharmaceutical company successfully

[ix] It is worth noting that NIH' National Center for Advancing Translational Sciences created a drug repurposes program intended to facilitate sharing of data and other resources for scientists and others interested in repurposing drugs. See https://ncats.nih.gov/preclinical/repurpose.

developing and commercializing a branded medical product for the U.S. market. While this nonprofit pharmaceutical company retained ownership of the NDA, commercialization of the medical product occurred through a licensing agreement with a for-profit company. In exchange for licensing the intellectual property of the nonprofit pharmaceutical company, the for-profit pharmaceutical company committed to prioritize commercializing the hormonal IUD, paid an upfront payment, as well as milestone payments, and continuous royalties on units sold, which are non-taxable because they are not classified as unrelated business income.[10] Retaining ownership of the license allowed Medicines360 to maintain ownership of the drug and reinvest in R&D to identify new indications. Stakeholders noted that entry by Medicines360 for an underserved market spurred additional investment and development of new products by for-profit companies. Other strategies that nonprofit pharmaceutical companies have adopted to launch their products include creating wholly owned for-profit subsidiaries, partnerships with PBCs, or selling the license to a for-profit pharmaceutical company. However, as noted above, these types of partnerships or business structures have the potential to undermine their credibility regarding transparency in drug pricing.

Challenges

Nonprofit pharmaceutical companies face challenges with repurposing off-patent drugs and rescuing abandoned compounds, including difficulty raising capital to conduct expensive phase 3 clinical trials and aligning with donor priorities.[66] For example, disulfiram, a drug approved as an anti-alcoholism drug, has been proposed as a candidate to be repurposed to treat many diseases, including various cancers, Alzheimer's disease, and COVID-19.[66,68] However, in such circumstances, prioritization of potential new indications to pursue depends on the interest of donors. While donors to nonprofit pharmaceutical companies may prioritize public benefits, it is unclear that their priorities will always align with public health needs that maximize social welfare.

Further, the risk of donor fatigue undermines the long-term sustainability of the nonprofit model. Pull incentives, wherein the government aims to reward new drug development for underserved markets by reducing the risk of insufficient future revenue streams through higher reimbursement policies, have been successfully employed to develop new hospital-based antibiotics. For example, the Centers for Medicare & Medicaid Services (CMS) have paid new technology add-on payments for novel antibiotics used in the inpatient setting.[69] However, oftentimes sales revenue from antibiotics cannot sustain a company's infrastructure costs, so other investments unrelated to sales revenue would also be necessary to ensure the sustainability of the nonprofit model for low volume medical products.[64,69]

Beyond R&D costs, nonprofit pharmaceutical companies need to raise funds for complex commercialization activities, such as manufacturing, distribution, reimbursement, and post-marketing commitments. If the nonprofit tax-exempt status was obtained based on a mission to conduct research, then sales revenue from commercialized medical products may be subject to business income taxes. Relatedly, stakeholders shared that commercial activity by nonprofit pharmaceutical companies may attract litigation and jeopardize tax-exempt status under the IRS "commerciality" doctrine.[x] Stakeholders also noted that FDA has limited experience working with nonprofit pharmaceutical companies, who may also not be aware of flexibilities available to them.

Nonprofit pharmaceutical companies adopt several strategies to navigate the complex pharmaceutical supply chains in the United States and retain tax-exempt status. However, some of these strategies may not be feasible for low-volume products. In one example, stakeholders shared that a nonprofit pharmaceutical

[x] In its determination that a business entity did not qualify as a 501(c)(3) organization, IRS stated "factors courts have considered in assessing commerciality are competition with for-profit commercial entities; extent and degree of below cost services provided; pricing policies; and reasonableness of financial reserves."

company regained ownership of a gene-therapy that was licensed to a for-profit company, likely because of claw back clauses[xi] in the licensing agreement. For several years after gaining the license for the gene therapy, the for-profit company was unable to meet the comparability[xii] requirement to scale it and terminated related development activities. While the gene therapy may be available to patients through the compassionate use program, shareholders stated that nonprofit pharmaceutical companies may not have the financial resources and expertise required to launch phase 3 trials, pay FDA user fees, maintain all of the regulatory requirements to obtain FDA approval, or meet manufacturing requirements for widespread distribution without a commercial for-profit partner.

Limitations

This report has several limitations. First, the stakeholder interviews were limited to nine experts, and as such, the findings from this report may not be generalizable to all stakeholders impacted or involved. For example, the stakeholder interviews had limited experts from the for-profit pharmaceutical industry. Further, although the environmental scan aimed to include broad terms, it is possible that our search terms and results did not capture other key topics or issues. Lastly, given the nascent nature of this sector, there was limited availability of data to quantitatively examine the role of the nonpharmaceutical companies in increasing the supply of essential and affordable drugs.

Discussion and Conclusion

The findings from this report suggest that nonprofit pharmaceutical companies have the potential to address drug shortages and enhance access to affordable and essential medicines. However, their sustainability and effectiveness may be limited due to low production volumes, a complex tax system, ineligibility for small business funding sources, and to some extent, lack of awareness of nonprofit pharmaceutical companies by the government and the public at large.

Although this report identified 11 companies in the nonprofit pharmaceutical sector, only one was captured in a database of drugs sold in the United States during 2020-2022. The data showed that the volume of this nonprofit pharmaceutical company represented about two percent of the total sales volume for the same generics sold by for-profit companies. This finding aligns with stakeholder interviews that indicated that nonprofit pharmaceutical companies currently have limited ability to fill large gaps in the market or create pressure to bring prices down due to their low production volume.

Second, the lack of profit motive for nonprofit pharmaceutical companies results in a different risk profile and set of strategies than their for-profit counterparts. Thus, nonprofit pharmaceutical companies have the potential to increase access to essential and affordable medicines. For example, their strategies to repurpose generics, pick up abandoned products, or bring OTC products to market have partly contributed to pressure on the industry to increase access to low-cost insulin products and to bring OTC naloxone products to market. Further, the focus of nonprofit pharmaceutical companies on low volume drugs necessitates the conduct of R&D or commercialization activities on essential medicines that for-profit companies may not deem commercially viable.

[xi] Claw back is a contractual provision that allows an instance of recovering assets or benefits previously given out.
[xii] Comparability requirements means demonstrating that phase 2 results are comparable to phase 3 results.

Third, while nonprofit pharmaceutical companies are governed by a different set of tax laws than for-profit companies, they are subject to the same FDA regulatory requirements and R&D costs to bring products to market. This has led nonprofit pharmaceutical companies to target products that are low cost to develop and that have a higher probability of success. In this way, some do not see nonprofit pharmaceutical companies as disruptors to the industry or a solution to the issues at hand given that many of their activities involve relabeling approved products and have low sales volume.

Fourth, although nonprofit pharmaceutical companies can leverage their tax-exempt status to seek funding from diverse sources, the complex tax environment has resulted in a mixed structure of nonprofit and for-profit companies under the same organization that blur efforts to increase transparency or ensure that drugs are affordable. Though the majority of nonprofit pharmaceutical companies have operational sizes comparable with small businesses, their tax-exempt status makes them ineligible for some types of funding from the National Institutes of Health (NIH) Small Business Innovation Research, the Small Business Administration (SBA), or even bank loans that require some expected level of revenue. Further, the diverse funding sources create challenges aligning drug development and commercialization activities of nonprofit pharmaceutical companies with public health priorities.

The literature and stakeholders have described various approaches to address some of the challenges that nonprofit pharmaceutical companies face, which can be largely divided into financial and nonfinancial incentives. Financial incentives include the establishment of a federal program or set of initiatives that could fund or provide financial support for the development and manufacturing of drugs by nonprofit pharmaceutical companies at all stages of the product life cycle—from early discovery research activities to commercialization—as well as for capital investments. Stakeholders have proposed a number of financial incentives tailored to the nonprofit pharmaceutical sector such as interest-free loans, grants, cooperative agreements, loans not requiring repayment, and advanced purchasing agreements with the government to enhance their sustainability. Stakeholders and the literature also cited other existing tools that could be leveraged to expand eligibility to the nonprofit pharmaceutical sector, including NIH's Small Business Innovation Research Grants, the Health Resources and Services Administration's (HRSA) 340B Drug Pricing Program, and advanced purchasing commitments from the Strategic National Stockpile.

In addition to the proposed initiatives discussed above, several Congressional bills have been introduced in recent years aimed at the nonprofit pharmaceutical sector. This includes Senate Bill 2257, the Expanding Access to Affordable Prescription Drugs and Medical Devices Act introduced in 2021, which included provisions for funding and low-interest loans to support nonprofit drug development and required FDA user fee waivers. Financial initiatives such as the provisions included in this bill could align eligibility with certain criteria such as manufacturing drugs that are essential, in shortage, or fulfilling a public health need. One example cited by some stakeholders was Civica's funding that allowed them to begin construction of a manufacturing facility in Virginia. This funding was awarded to Phlow Corporation, a U.S. drug manufacturing PBC, by the U.S. Administration for Strategic Preparedness and Response (ASPR) to build manufacturing capacity of essential medicines in shortage.[70,71] Stakeholders noted that Federal support would increase the financial stability of nonprofit pharmaceutical companies through funding or purchase agreements that would ensure some level of volume to be large enough to exert pressure in the industry, increase their sustainability, and also increase awareness of and trust in the nonprofit pharmaceutical sector. This support could promote market entry, competition, and expansion in this sector.

Existing literature and stakeholders have also proposed non-financial incentives to encourage growth in the nonprofit pharmaceutical sector. Specific examples included expediting FDA review of nonprofit applicant submissions or creating separate regulatory programs for nonprofit pharmaceutical companies. As noted above, these challenges are not specific to the nonprofit pharmaceutical sector. Past studies focused on the

for-profit sector have also proposed similar solutions (i.e., reduced FDA timelines, simplification of clinical trial protocols, increased interactions with FDA, improved predictability of the review process), to reduce the cost of bringing drugs to market.[72] While FDA already uses existing tools to address drug shortages that involve prioritizing and expediting review of certain applications and inspections, providing technical assistance and guidance for small companies,[73] authorizing waivers, reductions, exemptions or refunds of user fees when certain conditions are met,[74] further research is needed to understand how these existing tools can be leveraged to address issues that are specific to the nonprofit pharmaceutical sector.

Review of the literature and discussions with stakeholders identified changes to the tax code as a way to lower the entry barrier for nonprofit companies in the pharmaceutical sector. The policy proposals identified included creating tax incentives that can facilitate the transfer of patents of abandoned drugs, creating incentives for for-profit companies to partner with nonprofit pharmaceutical companies, clarifying the tax code to facilitate activities and funding mechanisms, creating a new tax-exempt designation for nonprofit pharmaceutical companies that are fulfilling a public health need, classifying drug sales of nonprofit pharmaceutical companies as non-taxable revenue, and creating protections to uphold the IRS nonprofit designation. However, stakeholders highlighted the risk of mission drift and oligopoly in the nonprofit pharmaceutical sector if regulations are not implemented to ensure accountability. Literature and stakeholders provided lessons learned from the health care industry, which is dominated by nonprofit health systems, that suggest the nonprofit model may not always maximize social welfare.

To conclude, while the nonprofit pharmaceutical sector holds promise to address drug shortages and enhance access to affordable and essential medicines, more research is needed to understand the available or potential tools that can reduce existing barriers and challenges, as well as understand their implications on competition, drug pricing, and innovation in the pharmaceutical industry.

Appendix A. Alternative Economic Models for Commercialization by Nonprofit Pharmaceutical Companies

We summarize the alternative economic models that have been proposed in literature to promote market authorization and commercialization by nonprofit pharmaceutical companies in the marketplace.

Nonprofit pharmaceutical companies as a market authorization holder leveraging the manufacturing and distribution expertise of for-profit companies

Existing literature has proposed that nonprofit pharmaceutical companies could expand their organizational capacity to pursue market authorization of new products discovered through their R&D pipeline rather than license or engage in mergers and acquisitions.[8,9,23] In this model, nonprofit pharmaceutical companies would leverage the expertise of for-profit pharmaceutical companies to maximize efficiency in production and distribution.[8] For example, nonprofit pharmaceutical companies may license new products to multiple for-profit companies for manufacturing and distribution. Further, the partnership agreements could include clauses to ensure social welfare outcomes, such as affordability and access for underserved populations, and balance the need to generate profits and sustainability. Proponents of this model state that this strategy could ensure that pricing is guided by drug affordability goals.

An important challenge to scale up this strategy is that nonprofit pharmaceutical companies may not have the expertise or financial resources to navigate clinical development activities, such as phase 3 clinical trials. Another challenge is ensuring that a nonprofit pharmaceutical company is accountable to its core mission and will not engage in misaligned actions, such as price-gouging. The participation of major donors and patients, who have a financial interest in drug affordability and accessibility, on the board of trustees may mitigate this risk.[6]

Medicines360 demonstrated the viability of this concept with the commercialization of its hormonal IUD in the United States.[10] The product was initially launched with a $82 million grant from a private philanthropic nonprofit. The total cost, including product liability insurance, of bringing the hormonal IUD to market was $73.4 million. Medicines360 partnered with Actavis, a for-profit company. However, Medicines360 retained its rights to market the hormonal IUD at a deeply discounted price to public clinics and hospitals, such as federally qualified health centers, throughout the United States. Similarly, Medicines360 retained marketing rights to sell the hormonal IUD in low- and middle-income countries.

Nonprofit pharmaceutical companies as a market authorization holder with in-house manufacturing and distribution expertise

In this model, nonprofit pharmaceutical companies would expand their organizational capacity to manage all commercialization activities, including manufacturing and distribution.[8,9] An important barrier to adopting this approach is the high start-up costs for new nonprofit pharmaceutical companies that do not have the ability to leverage the economies of scale of established for-profit companies. This is a particular problem for low-volume and new pharmaceutical products. One solution is for nonprofit pharmaceutical companies to modify this approach by outsourcing actual production to CMOs. Another solution is the potential of selling exclusive licensing of some products to raise start-up capital for internal commercialization of other products.[8]

Proponents state that this strategy could be appropriate for nonprofit pharmaceutical companies that want to target drugs that are not costly to bring to market such as old generic drugs, which have low profits and experience frequent shortages.[6] The abbreviated new drug application (ANDA) process to obtain market authorization for old generic drugs is less expensive because some of the regulatory requirements can be fulfilled with existing data on efficacy and safety. An ASPE analysis found that the average cost to develop a

generic drug was $2.4 million ($3.2 million in 2022 dollars) and time required to bring the product to market was just under five years.[75]

One example of a nonprofit pharmaceutical company demonstrating the viability of this model for old generic drugs is Civica.[38] As of March 2023, Civica Rx is distributing 60 generic sterile injectables to its members in the United States through its supply contracts with foreign and domestic CMOs. Civica is in the process of expanding to outpatient and retail pharmacies through CivicaScript. While Civica currently relies on ANDAs of its CMOs, it plans to obtain its own ANDAs for generic drugs, such as insulin, and is building a manufacturing facility in Virginia.[36,38]

Nonprofit pharmaceutical companies leveraging product development partnerships

Nonprofit Product Development Partnerships (PDPs) is another model that has proven successful for launching affordable and accessible medical products. PDPs coordinate financial and development efforts for medical product development, in partnership with for-profits, nonprofits, and public stakeholders. For example, the Global Alliance for TB Drug Development (TB Alliance) received FDA approval for pretomaid to treat extensively drug-resistant tuberculosis. TB Alliance negotiated license agreements to ensure access in low-income countries.[76] Nonprofit PDPs have resulted in bringing many medical products to market that address unmet public health needs in low- and middle-income countries.[77] PATH, a U.S.-based nonprofit, obtained FDA approval and commercialized depot medroxyprogesterone acetate (DMPA-SC), an injectable contraceptive, for the domestic market through a PDP. [77,78] Similar to the objectives of PDPs, joint academic-industry-government alliances to foster collaboration are common in the United States.[79] However, they are not formally incorporated.

Appendix B. Environmental Scan Search Terms

Primary Search Terms	Secondary Search Terms
Nonprofit pharmaceutical company	**Cost/Costly/High Cost**
Pharmaceutical Public benefit corporation	Price
Nonprofit pharmaceutical sector	Affordability
Nonprofit pharmaceutical market	Low-cost generic drugs
Nonprofit biopharmaceutical company	Low-cost alternatives
Biopharmaceutical Public benefit corporation	Low-cost substitutes
Nonprofit biopharmaceutical sector	Low-cost biosimilars
Nonprofit biopharmaceutical market	Reimbursement
Biotechnology	Payers
Nongovernmental pharmaceutical company	**Access**
Charitable organizations	Drug shortage
Tax-exempt organizations	Essential drugs/medications
	Life-threatening disease/rare disease
	Life-saving medication
	Critical drugs
	Public health emergency
	Orphan drugs
	Specific Drugs
	• Antibiotics, Antibacterials, Antimicrobials
	• Saline
	• CNS drugs

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