FOSTERING PRODUCTION OF PHARMACEUTICAL PRODUCTS IN DEVELOPING COUNTRIES[1]

William Fisher,[2] Ruth Okediji,[3] and Padmashree Gehl Sampath[4]

The residents of developing countries need pharmaceutical products at least as much as the residents of developed countries. Noncommunicable diseases (such as cancers, cardiovascular disease, and mental-health disorders), which typically are most effectively treated with drugs, are now nearly as common in developing countries as in developed countries. And communicable diseases (such as tuberculosis, HIV, and malaria), the prevention or treatment of which also typically require drugs, continue to be substantially more common in the developing world.[5]

Today, most of the drugs consumed in developing countries are imported. This is especially true of the relatively new drugs that are subject to patent protection, which typically are produced in industrialized countries. The production of generic drugs is less concentrated, but most are now manufactured in large middle-income countries (primarily India, China, and Brazil) and then exported to smaller and poorer countries.

For many years, some lawmakers, scholars, and activists have argued that firms located in each developing country (or each regional set of developing countries) should produce more of the drugs that the residents thereof need. They contend that local production would benefit the residents of those countries in two ways. First, it would create many high-paying skilled jobs and support sustainable economic development. Second, local firms could respond more quickly to the residents' changing health needs. Skeptics have responded that local production, by forfeiting economies of scale, would be less efficient and thus would raise the costs of medicines. In addition, they contend that the systems for maintaining the quality of drugs are less robust in developing countries, and thus that local production would lead to an increase in sub-standard drugs.[6]

Part I of this chapter discusses some recent developments that have altered the relative strength of these competing considerations, sharply increasing the likelihood that fostering local production in developing countries would be socially beneficial. Part II proposes five legal

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[2] Wilmer Hale Professor of Intellectual Property Law, Harvard Law School.

[3] Jeremiah Smith, Jr. Professor of Law, Harvard Law School.

[4] Senior Advisor, Global Access in Action, Berkman Klein Center, Harvard University and Visiting Professor, South African Research Chair for Industrial Development, University of Johannesburg.

[5] For data supporting these generalizations, see WHO Methods and Data Sources for Global Burden of Disease Estimates 2000-2019, WORLD HEALTH ORG. ["WHO"] (2018), https://cdn.who.int/media/docs/default-source/gho-documents/global-health-estimates/ghe2019_daly-methods.pdf?sfvrsn=31b25009_7.

[6] *Compare* Frederick Abbott and Jerome H. Reichman, "The Doha Round's Public Health Legacy: Strategies for the Production and Diffusion of Patented Medicines under the Amended Trips Provisions," *Journal of International Economic Law* 10, no. 4 (2007). with Roger Bate, "Local Pharmaceutical Production in Developing Countries: How Economic Protectionism Undermines Access to Quality Medicines," (2008); Warren Kaplan and Richard Laing, "Local Production of Pharmaceuticals: Industrial Policy and Access to Medicines," *HNO Discussion Paper 32036* (2005).

reforms and economic initiatives that could help build local pharmaceutical-production capacity and thereby save lives.

I. THE NEW GLOBAL LANDSCAPE FOR ACCESS TO MEDICINES

In the past few years, three events have strengthened substantially the case for local pharmaceutical production: the emergence of novel diseases that pose severe threats to the health of the residents of developing countries; the rise of healthcare nationalism; and revelation of the scale of the transnational trade in substandard medicines.

The Emergence of Novel Diseases

In its 2007 World Health Report,[7] the World Health Organization ("WHO") noted the unprecedented rate at which new diseases are emerging. The report identified "at least 39 new pathogens, including HIV, Ebola hemorrhagic fever, Marburg fever and SARS"[8] and cautioned that these diseases, and older well-known ones, "pose a threat to health through a combination of mutation, rising resistance to antimicrobial medicines and weak health systems."

Today, the best-known novel diseases are Ebola and COVID-19. Ebola is now fading from view but was terrifying not so long ago. Starting in 1976, when it was first discovered in humans, the disease simmered in West and Central Africa, killing a few hundred people a year.[9] Then, in 2013, it suddenly began to spread, ravaging Guinea, Sierra Leone, and Liberia, and sending tendrils into other countries.[10] A delayed but ultimately fierce public-health initiative was able to halt the outbreak, but not before 28,000 people had died.[11]

The threat that Ebola posed, particularly to the residents of African countries, is not fully appreciated. For example, Lagos, the largest city in Africa, almost experienced an outbreak. Had that happened, hundreds of thousands of people would have died.[12] Nor has the danger of an Ebola

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[7] The World Health Report 2007: A Safer Future**,** WHO (2007), https://www.who.int/whr/2007/whr07_en.pdf.

[8] *See id.* at 35–57.

[9] Jonathan Corum, *A History of Ebola in 24 Outbreaks*, N.Y. TIMES, (Dec. 29, 2014), http://www.nytimes.com/interactive/2014/12/30/science/history-of-ebola-in-24-outbreaks.html; *History of Ebola*, CTR. FOR DISEASE CONTROL & PREVENTION (CDC) https://www.cdc.gov/vhf/ebola/history/summaries.html (last visited Oct. 20, 2021).

[10] Corum, *supra* note 9.

[11] *Id*.; *see also 2014 Ebola Outbreak in West Africa – Case Counts*, CDC, http://www.cdc.gov/vhf/ebola/outbreaks/2014-west-africa/case-counts.html (last visited Oct. 20, 2021); EBOLA RESPONSE ROADMAP SITUATION REPORT, WHO, https://apps.who.int/iris/bitstream/handle/10665/137510/roadmapsitrep_5Nov14_eng.pdf (last visited Oct. 20, 2021).

[12] See Morbidity and Mortality Weekly Report, Ebola Virus Disease Outbreak - Nigeria, July–September 2014, CDC**,** https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6339a5.htm (last visited Jan. 31, 2021).

pandemic disappeared. An outbreak in the Democratic Republic of the Congo between 2018 and July of 2020 killed another 2,300 people.[13] Additional outbreaks are likely.[14]

As readers are surely aware, the COVID-19 pandemic has been far more globally devastating. As of this writing, over 650 million people have been infected and over six million have died.[15] Although the worst now seems to have passed, waves of increasingly contagious variants have kept the pandemic going.[16]

Until recently, most developing countries suffered less from the pandemic than the richest countries, but this comparison no longer holds. Peru now has the highest cumulative death rate in the world, and many other Latin American countries are not far behind.[17] Sub-Saharan African countries, which long enjoyed relatively low infection rates, are now experiencing rising rates.[18]

When one considers the impacts of COVID-19 infections and deaths on the economy and society of each country, the picture darkens further. Prior to the pandemic, the economies of most developing countries were more fragile than those of the United States or European countries. As a result, they suffered more severely from the lockdowns and the curtailments of exports and travel that the pandemic provoked.[19] For the same reason, developing countries are recovering economically more slowly than richer countries.[20]

The initial success of developing and least-developed countries (particularly in Africa) in curbing the pandemic was attributable, not to any special characteristics of their populations or climates, but rather to a combination of (a) their ability to prevent or limit the entry of potentially infected persons, (b) their foresight in imposing stringent limitations on social interactions with

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[13] *See Ebola in the Democratic Republic of the Congo, North Kivu, Ituri*, WHO, https://www.who.int/emergencies/situations/Ebola-2019-drc- (last visited Oct. 10, 2021).

[14] *See* Athalia Christie, John C Neatherlin, Stuart T. Nichol, Michael Beach & Robert R. Redfield, *Ebola Response Priorities in the Time of COVID-19*, 13 NEW ENG. J. MED. 383, 1202–04 (2020).

[15] See Center for Systems Science and Engineering at Johns Hopkins University, COVID-19 Dashboard, https://www.arcgis.com/apps/dashboards/bda7594740fd40299423467b48e9ecf6 (last visiting December 21, 2022).

[16] *See Coronavirus World Map*, NAT'L PUB. RADIO https://www.npr.org/sections/goatsandsoda/2020/03/30/822491838/coronavirus-world-map-tracking-the-spread-of-the-outbreak (last visited Dec. 1, 2021).

[17] *See Mortality Analysis*, JOHNS HOPKINS CORONAVIRUS RES. CTR. https://coronavirus.jhu.edu/data/mortality (last visited Dec. 21, 2022).

[18] *See, e.g.,* Associated Press, *South African Scientists Brace for Wave Propelled by Variant*, POLITICO, Nov. 28, 2021, https://www.politico.com/news/2021/11/28/south-africa-covid-variant-omicron-523410.; Nadia A. Sam-Agudu et al., "The Pandemic Is Following a Very Predictable and Depressing Pattern," *The Atlantic*, March 4, 2022 2022.

[19] Jonathan Wheatley, COVID-19 Curbs "Not Worth Economic Pain" for Low-Income Countries, FIN. TIMES, Sept. 6, 2020, at 1.

[20] *See Global Prospects are Improving but Performance Diverges Strongly Across Countries*, ORG. FOR ECON. COOP. & DEV. ["OECD"], https://www.oecd.org/coronavirus/en/data-insights/eo-2021-05-global-prospects-are-improving-but-performance-diverges-strongly-across-countries (last visited July 21, 2021).

which most residents complied, and (c) the low average age of their populations.[21] When governments have been unable to curtail transmission through such measures, the results have indeed been catastrophic.

The premier example is Ecuador. Early in the pandemic, one or more infected persons apparently entered Guayaquil, the principal port.[22] The resulting outbreak was fierce. The hospitals and morgues were soon overloaded. Infected doctors waited in wheelchairs for their patients to die so that they could use their ventilators.[23] Bodies piled up in the streets.[24] When a lockdown eventually managed to cap the disease in Guayaquil, it began to ravage Quito,[25] and the numbers of new cases continued to rise until May of 2021.[26]

The healthcare systems of most developing countries are no better than that of Ecuador.[27] The WHO notes that growth in the numbers of essential medical personnel, such as nurses, is barely keeping pace with population growth in most middle- and low-income countries.[28] Added to this are a shortage of doctors, prohibitive costs, and infrastructure deficits that make access to healthcare infeasible for the poorest.[29] In addition, several other conditions common in developing countries contribute to the risk that infectious diseases will spread rapidly: residences are close together (especially in the poor sectors of urban areas); most residents have neither savings nor credit and thus must work to survive; meager internet access limits opportunities to work at home;

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[21] See David Pilling, How Africa Fought the Pandemic — and What Coronavirus Has Taught the World, FIN. TIMES, Oct. 23, 2020; Anne Sooy, Coronavirus in Africa: Five Reasons Why Covid-19 Has Been Less Deadly Than Elsewhere, BBC NEWS, Oct. 8, 2020.

[22] Gonzalo Solano, After Ecuador Eased Its Lockdown, the Virus Surged in Quito, ASSOCIATED PRESS, July 29, 2020, at 2.

[23] José María León Cabrera & Anatoly Kurmanaev, Ecuador's Death Toll During Outbreak Is among the Worst in the World, N.Y. TIMES, May 12, 2020, at 3.

[24] Lucas Berti, In Ecuador, COVID-19 is Leaving a Literal Trail of Bodies, BRAZ. REP., Apr. 1, 2020, at 2.

[25] See Juan Jose Alava & Angel Guevara, A Critical Narrative of Ecuador's Preparedness and Response to the COVID-19 Pandemic, PUB. HEALTH PRAC., Nov. 2021.

[26] See Cabrera & Kurmanaev, supra note 233; Ecuador: Coronavirus Pandemic Country Profile, OUR WORLD DATA, https://ourworldindata.org/coronavirus/country/ecuador (last visited Nov. 3, 2021).

[27] See COVID -19 and the Least Developed Countries, UN DEP'T ECON. & SOC. AFFS. (2020).

[28] STATE OF THE WORLD'S NURSING 2020, WHO (2020), https://apps.who.int/iris/bitstream/handle/10665/331673/9789240003293-eng.pdf.

[29] See Sadia Ali, Healthcare in the Remote Developing World: Why Healthcare is Inaccessible and Strategies Towards Improving Current Healthcare Models, HARV. HEALTH POL'Y REV. (Nov. 10, 2016), http://www.hhpronline.org/articles/2016/11/10/healthcare-in-the-remote-developing-world-why-healthcare-is-inaccessible-and-strategies-towards-improving-current-healthcare-models.

lack of refrigeration necessitates daily shopping;[30] and limited sanitation inhibits the adoption of protective measures.[31] In combination, these factors bode ill for the Global South.

Healthcare Nationalism

The second changed circumstance is a surge of what has been called "healthcare nationalism," which is impeding the ability of developing countries to obtain the pharmaceutical products they need to meet both the new threats and the threats posed by the many diseases that have long been endemic to these countries.[32]

The situation with respect to COVID-19 is the most dire. When vaccines capable of preventing or mitigating the disease began to appear on the horizon, the governments of developed countries purchased, in advance, the bulk of the scarce supply. The government of most developing countries lacked the resources to make similar anticipatory purchases.[33] In some of the few instances in which developing countries have been able to place orders, they did not receive the promised supplies on time.[34] The COVID-19 Vaccines Global Access ("COVAX") Facility, a commendable multilateral effort to create a more equitable system for allocating scarce supplies, was unable to correct the imbalance.[35] The net result: the percentages of people in developing

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[30] See, e.g., Access Real-Time Risk Alerts from Around the World, CRISIS24 https://www.worldaware.com/covid-19-alert-nigeria-resumes-commercial-flights-some-restrictions-place; Kashlee Kucheran, Ecuador Reopens for Tourism – Everything You Need to Know, TRAVEL OFF PATH (Aug. 18, 2020), https://www.traveloffpath.com/ecuador-reopens-for-tourism/.

[31] See Matthew E. Levison, COVID -19 Challenges in Developing Countries, MERCK MANUAL (July 8, 2020), https://www.merckmanuals.com/home/news/editorial/2020/07/08/20/55/covid-19-challenges-in-the-developing-world; Terrence McCoy & Heloísa Traiano, Brazil's Densely Packed Favelas Brace for Coronavirus: "It Will Kill a Lot of People," WASH. POST (Mar. 21, 2020), https://www.washingtonpost.com/world/the_americas/brazil-coronavirus-rio-favela/2020/03/20/2522b49e-6889-11ea-b199-3a9799c54512_story.html; Yasmeen Serhan, Where the Pandemic Is Only Getting Worse, THE ATLANTIC (Aug. 6, 2020), https://www.theatlantic.com/international/archive/2020/08/coronavirus-pandemic-developing-world/614578; Brett Walton, Healthcare Facilities in Developing Countries a High Risk for Coronavirus Transmission, NEW SEC. BEAT (Mar. 23, 2020) https://www.newsecuritybeat.org/2020/03/healthcare-facilities-developing-countries-high-risk-coronavirus-transmission.

[32] *See* Kai Kupferschmidt, *"Vaccine Nationalism" Threatens Global Plan to Distribute Covid-19 Shots Fairly*, SCI. INSIDER (July 28, 2020), https://www.science.org/content/article/vaccine-nationalism-threatens-global-plan-distribute-covid-19-shots-fairly.

[33] *See* Megan Twohey, Keith Collins, and Katie Thomas, "With First Dibs on Vaccines, Rich Countries Have 'Cleared the Shelves'," *New York Times*.

[34] Rebecca Robins, *Moderna, Racing For Profits, Keeps Covid Vaccine Out of Reach of the Poor,* N. Y. TIMES (Nov, 09, 2021), https://www.nytimes.com/2021/10/09/business/moderna-covid-vaccine.html.

[35] Chelsea Clinton & Katelyn J. Yoo, *Is COVAX To Blame For Failing To Close Global Vaccination Disparities*?, Health Affairs, June 14, 2022, available at https://www.healthaffairs.org/do/10.1377/forefront.20220609.695589/; Adam Taylor, *Covax promised 2 billion vaccine doses to help the world's neediest in 2021: it won't deliver even half*

countries who are fully vaccinated remain much lower than the percentages in developed countries.[36]

The impact of the pandemic on nationalism in general and on so-called "vaccine nationalism" in particular is complex and varies significantly by country and region.[37] But there is little doubt that, in the United States at least, popular sentiment supports the principle that the government of each country should satisfy the healthcare needs of its own residents before addressing the needs of the residents of other countries.[38] That sentiment guided the U.S. government's response to the HIV pandemic,[39] has thus far dominated the actions of the Biden Administration,[40] and will surely remain influential if one of the many other infectious diseases that pose equally severe threats to the human population becomes rampant.

In sum, when confronted with future pandemics, we should expect substantial lags between the widespread introduction of therapies and vaccines in developed countries and the widespread distribution of those same drugs in developing countries. Particularly considering the weak healthcare systems of most developing countries, such lags will likely cause large numbers of unnecessary deaths.[41]

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that. Washington Post, December 10, 2021 (https://www.washingtonpost.com/world/2021/12/10/covax-doses-delivered/).

See UNICEF, "Covid-19 Vaccine Dashboard," https://www.unicef.org/supply/covid-19-vaccine-market-dashboard (last visited February 7, 2021).

[36] See, e.g., Josh Holder, *Tracking Coronavirus Vaccinations Around the World*, N. Y. TIMES (Dec. 18, 2022), https://www.nytimes.com/interactive/2021/world/covid-vaccinations-tracker.html.

[37] *See* Kashmira Gander, "U.S. Only Country to Say It Should Have Covid-19 Vaccine First in Survey," *Newsweek*, October 1, 2020; Florian Bieber, "Global Nationalism in Times of the Covid-19 Pandemic," *Nationalities Papers* (2020); Ivan Krastev, "Europe's Pandemic Politics: How the Virus Has Changed the Public's Worldview," *European Council on Foreign Relations: Policy Brief* (2020).

[38] See Justin Hughes, Biden Decision on COVID Vaccine Patent Waivers is more About Global Leadership than IP**,** USA TODAY (May 6, 2021).

[39] Kupferschmidt*, supra* note 32 ("A cocktail of powerful antiviral drugs revolutionized HIV treatment in the West in 1996, saving many lives, but it took 7 years for the drugs to become widely available in Africa, the hardest hit continent.").

[40]*See* Yasmeen Serhan, *Joe Biden's "America First" Vaccine Strategy*, THE ATLANTIC (Feb. 4, 2021), https://www.theatlantic.com/international/archive/2021/02/joe-biden-vaccines-america-first/617903.

[41] *See* Susan Michie, Chris Bullen, Jeffrey V. Lazarus, John N. Lavis, John Thwaites, Liam Smith, Salim Abdool Karim & Yanis Ben Amor, New COVID *Variants Have Changed* the *Game*, and *Vaccines Will* not be *Enough. We Need Global "Maximum Suppression*,*"* THE CONVERSATION (Apr. 5, 2021), https://theconversation.com/new-covid-variants-have-changed-the-game-and-vaccines-will-not-be-enough-we-need-global-maximum-suppression-157870; Indermit Gill & Philip Schellekens, *COVID-19 is a Developing-Country Pandemic*, BROOKINGS (May 27, 2021), https://www.brookings.edu/blog/future-development/2021/05/27/covid-19-is-a-developing-country-pandemic/.

The Prevalence of Substandard Medicines

The third changed circumstance is that the widespread distribution of low-quality medicines seriously threatens the health of residents in developing countries. This has likely been true for some time, but the scale of the problem has only recently become apparent. In 2017, the WHO, after aggregating many studies, estimated that 10.5 percent of the drugs distributed in low-income countries were either falsified or substandard.[42] In middle-income countries, the number was barely lower: 10.4 percent.[43] An even more recent and comprehensive study found the overall rate in low- and middle-income countries to be 13.6 percent and the rate in Africa to be 18.7 percent.[44]

The rates vary by type of drug. Least likely to be falsified or substandard are antiretrovirals ("ARVs") because most of them are supplied through channels closely monitored by international donors.[45] The rates for tuberculosis drugs and antibiotics are higher—somewhere between six and seventeen percent.[46] Most likely to be falsified or substandard are anti-malarial drugs.[47] In recent years, substandard vaccines have also been distributed in distressing numbers.[48]

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[42] *See* WHO, "A Study of the Public Health and Socioeconomic Impact of Substandard and Falsified Medical Products," (2017), 7.

[43] The WHO defines these two terms as follows: Falsified medical products are those "that deliberately/fraudulently misrepresent their identity, composition or source," and substandard medical products are "authorized medical products that fail to meet either their quality standards or their specifications, or both." *Id.* at 1.

[44] *See* Sachiko Ozawa et al., "Prevalence and Estimated Economic Burden of Substandard and Falsified Medicines in Low- and Middle-Income Countries: A Systematic Review and Meta-Analysis," *JAMA Network Open* 1, no. 4 (2018).

[45] WHO, *supra* note 42, at 7; Amitabh B. Suthar, William Coggin & Elliot Raizes, *Correspondence, Antimicrobial Resistance and Substandard and Falsified Medicines: The Case of HIV/AIDS*, 219 J. INFECTIOUS DISEASES 672 (2019).

[46] *See* R. Bate et al., "Substandard and Falsified Anti-Tuberculosis Drugs: A Preliminary Field Analysis," *International Journal of Tuberculoisis and Lung Disease* 17, no. 3 (2013); Theodoros Kelesidis and Matthew E. Falagas, "Substandard/Counterfeit Antimicrobial Drugs," *Clinical Microbiology Reviews* 28, no. 2 (2015): 451; K.F. Laerson et al., "Substandard Tuberculosis Drugs on the Global Market and Their Simple Detection," *The International Journal of Tuberculosis and Lung Disease* 5, no. 5 (2001); O Moses, V Patrick, and N Muhammad, "Substandard Rifampicin Based Anti-Tuberculosis Drugs Common in Ugandan Drug Market," *African Journal of Pharmacy and Pharmacology* 7, no. 34 (2013); UNITAID, "Tuberculosis Medicines: Technology and Market Landscape," (2014), 32; WHO, "Impact of Substandard and Falsified Products," 17.

[47] *See* "Impact of Substandard and Falsified Products," 7; Ozawa et al., "Prevalence and Estimated Economic Burden of Substandard and Falsified Medicines in Low- and Middle-Income Countries: A Systematic Review and Meta-Analysis."

[48] In 2018, over 200,000 doses of substandard diphtheria, pertussis, and tetanus ("DPT") vaccines produced by Changsheng Biotechnology were administered to Chinese children and over 400,000 doses of substandard DPT were sold by the Wuhan Institute for Biological Products for further administration, leading to an investigation by the national drug regulator into all vaccine producers in the country. *See* Editorial Bd., *Vaccine Scandal and Confidence Crises in China*, 392 THE LANCET 360 (2018), https://www.thelancet.com/action/showPdf?pii=S0140-6736%2818%2931695-7.

The presence of falsified and substandard medicines in the market has three serious effects. First and most obviously, patients who consume such drugs obtain either zero or reduced therapeutic benefit. This impact is especially severe in the administration of anti-malarial drugs to young children, who are especially vulnerable to the disease.[49] The most comprehensive study estimates that, globally, roughly 122,000 children under the age of five die each year in sub-Saharan Africa alone as a result of consuming falsified or substandard anti-malarials.[50] As the authors of the study concede, a good deal of uncertainty surrounds these numbers. But there is little doubt that the number of deaths is appalling.[51]

Second, when patients consume drugs that are supposed to cure them, but fail to do so, they (and their neighbors) lose faith in medical treatment. In settings where such faith is already shaky, this can diminish their willingness to consult doctors and receive treatment in the future.[52]

Finally, consumption of degraded medicines, or a course of treatment in which legitimate and falsified drugs are mixed, accelerates the emergence and spread of drug-resistant strains of the diseases in question.[53] This, in turn, both makes it harder to suppress the diseases with medicines and may diminish the effectiveness of vaccines when they finally become available.

Identifying the sources of substandard drugs in developing and least-developed countries is a difficult task. However, public-health officials in Africa and officials in various international agencies tend to believe that most substandard and falsified medicines are now coming from manufacturers in China and India.[54] Most informed observers concur.[55] Officials associated with the International Criminal Police Organization ("Interpol") are doing their best to locate and punish the firms engaged in this practice.[56] In addition, China recently increased the penalties for

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[49] *See* Vicki Brower, *Falsified and Substandard Malaria Drugs in Africa*, 17 THE LANCET: INFECTIOUS DISEASES 1026, 1026 (2017).

[50] *See* John P. Renschler, Kelsey M. Walters, Paul N. Newton & Ramanan Laxminayaran, *Estimated Under-Five Deaths Associated with Poor-Quality Antimalarials in Sub-Saharan Africa*, 92 AM. SOC'Y TROPICAL MED. & HYGIENE 119, 124 (2015).

[51] *Cf.* Sarah M. Beargie, Colleen R. Higgins, Daniel R. Evans, Sarah K. Laing, Daniel Erim & Sachiko Ozawa, *The Economic Impact of Substandard and Falsified Antimalarial Medications in Nigeria*, PLOS ONE, Aug. 15, 2019, at 1 (estimating that the consumption of poor-quality antimalarials causes 12,300 deaths a year in Nigeria).

[52] *See* Kelesidis & Falagas, *supra* note 46, at 458.

[53] *See* Bate et al., "Substandard and Falsified Anti-Tuberculosis Drugs: A Preliminary Field Analysis", supra note 46; Kelesidis & Falagas, "Substandard/Counterfeit Antimicrobial Drugs," 458 ; WHO, "Global Surveillance and Monitoring System for Substandard and Falsified Medical Products," (2017), 6.

[54] Among the few published reports identifying the sources of the bad drugs are Abigail A. Ekeigwe, *Drug Manufacturing and Access to Medicines: The West African Story*, 5 AAPS OPEN, Aug. 5, 2019, at 2, 6, https://link.springer.com/article/10.1186/s41120-019-0032-x. But informal reports are legion.

[55] *See*, *e.g.*, Roger Bate, Phake: The Deadly World of Falsified and Substandard Medicines ch. 3 (Am. Enter. Inst. Press 2012).

[56] *See Pharmaceutical Crimes Operation*, INTERPOL, https://www.interpol.int/en/Crimes/Illicit-goods/Pharmaceutical-crime-operations (last visited Oct. 13, 2021).

distributing falsified medicines.[57] Unfortunately, the large profits that can be reaped by engaging in this practice, and the difficulty of detecting defective medicines, will likely maintain the market for substandard drugs for the foreseeable future.

To summarize: (a) new diseases threaten the lives of the residents of developing countries;[58] (b) the surge in healthcare nationalism in developed countries impedes the ability of developing countries to obtain from overseas manufacturers the vaccines and drugs they need to address public-health threats; and (c) the medicines that developing countries are able to import are frequently contaminated with falsified or substandard ingredients.[59] This combination of developments sharply increases the potential benefits to the residents of developing countries of enlarging capacity for local production of pharmaceutical products.

To be sure, these changes do not neutralize entirely the objections that some economists have long made to augmentation of local production—namely, that it may forfeit economies of scale, increase the costs of drugs, and impair quality control.[60] In the remainder of this article, we will note several contexts in which those hazards remain relevant and how the governments of developing countries could, and should, meet them. But all things considered, the argument for enhancing local production is strong.

II. A FRAMEWORK TO SUPPORT LOCAL PRODUCTION

Unfortunately, increasing local production is easier said than done. The history of efforts to achieve that goal is replete with failures. In retrospect, it appears that, in most successful efforts to augment local production capacity, four conditions were present, while in unsuccessful efforts, at least one was missing. Those conditions are:

(1) Legal Authority. The local firms had clear legal rights to manufacture the drugs at issue.
(2) Technological know-how. The local firms had or were provided the technology and skills necessary to engage in the production processes in question.
(3) Financial Resources. The local companies had access to capital.

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[57] *See* Phil Taylor, *China Threatens Death Penalty for Fake Coronavirus Meds*, SECURING INDUS. 1 (Feb. 18, 2020), https://www.securingindustry.com/pharmaceuticals/china-threatens-death-penalty-for-fake-coronavirus-meds/s40/a11351/#.YP-Db-hKjSE+N14; *see also Chinese Police Seize Over 3,000 Fake COVID-19 Vaccines*, EUR. PHARM. REV. (Feb. 8, 2021), https://www.europeanpharmaceuticalreview.com/news/142118/chinese-police-seize-over-3000-fake-covid-19-vaccines/.

[58] *See* Sam Kiley*, In the Congo Rainforest, the Doctor Who Discovered Ebola Warns of Deadly Viruses yet to Come*, CNN (Jan. 5, 2021), https://www.cnn.com/2020/12/22/africa/drc-forest-new-virus-intl/index.html.

[59] *See* WHO, *supra* note 42, at 7; *see also* Ozawa, *supra* note 44, at 2.

[60] *See e.g.,* Economists Advisory Grp.: Eur. Comm'n, 4 The Single Market Review: Economies of Scale 24 (1997), http://aei.pitt.edu/85784/1/V.4.V.pdf.

(4) Reliable demand for the products. A sizeable set of customers stood ready to buy the firms' products.

The first and third factors have received considerable attention by lawmakers and scholars, but the roles played by the others have not been adequately appreciated.[61]

The second factor, the transmission of know-how, is especially critical with respect to the production of active ingredients—which is the most important and challenging dimension of the pharmaceutical manufacturing process.[62] Making and packaging pills using imported compounds is a less complex process, and the potential profits generated by those activities are lower—indeed, often too low to sustain an enterprise.[63] The greatest potential rewards, as well as the greatest benefits to public health and economic development, are associated with local production of APIs.[64] The skill levels required to begin producing APIs and to engage in sophisticated drug-development processes vary enormously but typically exceed the competence of firms in developing countries. To get off the ground, such firms usually need assistance from the enterprises already engaged in that process. The same is true for vaccines, where the production of bulk antigens remains the most daunting step to be mastered by developing country manufacturers, in general, and will be even more important in the case of new vaccine platforms.[65]

Inattention to the issue of technological know-how has had unfortunate results. When local firms have not had access to the know-how necessary to break into the lucrative and socially beneficial zone of API production, they have had difficulty staying afloat.[66] This has sometimes prompted governments to prop them up by paying exorbitant fees for the modest services that the

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[61] For a discussion of condition 1, see, e.g., Ruth L. Okediji, Legal Innovation in International Intellectual Property Relations: Revisiting Twenty-One Years of the TRIPS Agreement, 36 U. Pa. J. Int'l L. 191, 204 (2014); Carlos M. Correa, Implementing the TRIPS Agreement in the Patents Field: Options for Developing Countries, 1 Journal of World Intellectual Property, 75 (1998).

For a discussion of condition 3, see Frederick A. Abbott, Ryan Abbott, Joseph Fortunak, Padmashree Gehl Sampath & David Walwyn, *Opportunities, Constraints and Critical Supports for Achieving Sustainable Local Pharmaceutical Manufacturing in Africa: With a Focus on the Role of Finance, Final Repor*t (Fl. St. U. Coll. L., Bus. & Econ. Paper, Paper No. 21-03, 2021).

[62] UNIDO, Pharmaceutical Manufacturing Plan for Africa, at 4-5, U.N. Doc. CAMH/MIN/7(III) (2007).

[63] In the case of Tanzania, for instance, the inability to obtain technologies necessary for API production is one of the reasons for the lack of competitiveness of the eight local firms. *See* Robert M. Mhamba & Shukrani Mbirigenda, *The Pharmaceutical Industry and Access to Essential Medicines in Tanzania* 83 (EQUINET Discussion Paper Series, Paper No. 83, July 2010).

[64] *See* Kaplan & Laing, *supra* note 6.

[65] For the complexities involved in vaccine manufacturing employing next-generation vaccine platforms *see* Debby van Riel & Emmie de Wit, *Next Generation Vaccine Platforms for COVID-19,* 19 NATURE 810, 811.

[66] Abbott et al, *supra* note 61. Chapters 5 and 6 in particular discuss the difficulties faced by local firms in accessing technologies and finance that are prerequisites for competitive production. See also Gehl Sampath & Walwyn, *supra* note 61, at 11.

firms have been able to provide. That, in turn, has resulted in needlessly high drug prices,[67] prompting some commentators to insist that mercantilist industrial policy and access to medicines are incompatible.[68]

Close study of such episodes, however, reveals that the source of the problem is the limited scope of the services that the firms in question are equipped to provide, which adversely affects the ability of firms to participate in large local and international tenders.[69] This handicap, in turn, creates barriers to access the financing they need to expand and thrive. The solution is to ensure that local firms have the skills necessary to move up the value chain.[70]

The fourth factor, concerning reliable demand for products has received even less attention than the second factor but is equally important. Firms in developing countries have been reluctant to invest in manufacturing capacity absent some assurance that there will be customers able and willing to buy their products.[71] This assurance is especially important in the current environment, where generic versions of many of the drugs that the firms might consider producing are already available from Indian, Chinese, or other manufacturers.[72]

Inattention to this fourth factor can be traced in part to ways in which the debate concerning access to medicines in developing countries was reoriented by the TRIPS Agreement. Defenders of the TRIPS Agreement contended that a well-greased global market based in harmonized intellectual property protection would naturally foster technology transfers that would redound to the benefit of developing countries.[73] Critics of the TRIPS Agreement were concerned about rising

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[67] For example, a survey conducted by the WHO and the Health Action International (HAI) in Ghana in 2004, which covered fifty medicines, concluded that although the prices of generic products produced locally were lower than those of the branded versions, they were far above the international reference prices obtained from the price lists of large, generic medicine suppliers around the world. *See* EDITH ANDREWS, ANANGA YAMYOLLIA, CHARLES ALLOTEY, MARTIN AUTIN & MARTHA GYANSA-LUTTERODT, MEDICINE PRICES IN GHANA: A COMPARATIVE STUDY OF PUBLIC, PRIVATE AND MISSION SECTOR MEDICINE PRICES 41 (2004), https://haiweb.org/wp-content/uploads/2015/07/Ghana-Report-Pricing-Surveys.pdf.

[68] *See* Kaplan and Laing, "Local Production", at 6. Even in countries where local production is successful, studies have noted the lack of access to affordable medicines in local pharmacies and other outlets in the health system. On this point, *see* Wen Chen, Shenglan Tang, Jing Sun, Dennis Ross-Degnan & Anita K Wagner, *Availability and Use of Essential Medicines in China: Manufacturing, Supply, and Prescribing in Shandong and Gansu Provinces*, 10 BIOMED CENT. HEALTH SERV. RSCH. 211 (2010).

[69] Abbott et al, *supra* note 61.

[70] *See* Murray Aitken, *Understanding the Pharmaceutical Value Chain*, 18 PHARMS. POL'Y & L. 55, 55–66 (2016).

[71] Gehl Sampath & Walwyn, *supra* note 61.

[72] *See e.g.* PHARMACEUTICAL SECTOR PROFILE: NIGERIA, UNIDO 35 (2011), https://open.unido.org/api/documents/4699694/download/Pharmaceutical%20Sector%20Profile%20-%20Nigeria.

[73] See e.g. Frederick M. Abbott, Protecting First World Assets in the Third World: Intellectual Property Negotiations in the GATT Multilateral Framework, 22 VAND J. TRANSNAT'L L. 689, 698–99 (1989); see also Ruth L. Okediji, *Back to Bilateralism: Pendulum Swifts in International Intellectual Property Protection*, 1 U. OTTAWA L. & TECH. J. 125, 145 (2004).

drug prices in developing countries and emphasized mechanisms, such as compulsory licensing, that could neutralize the enhanced levels of patent protection.[74] Neither group focused on market mechanisms that could entice local producers to generate inexpensive drugs that would meet the needs of the countries' residents.

Mindful of how things have gone awry in the past, we offer below five practicable strategies that, in combination, would more effectively promote local production of pharmaceutical products.

A. *Clearing Legal Space*

As we have seen, a precondition of local production is that a firm considering making a drug has the legal right to do so. In the past, this requirement has rarely posed a significant barrier, either because the drug in question was no longer subject to patent protection (as is true of most "essential medicines") or because the patentee granted the local firm a license (as was true of the Indonesian ventures created by the Japanese firms in the 1970s). However, in the future, a developing country may wish (or need) to enable local manufacture of a new therapy or vaccine without the permission of the patent owner. If so, the government of the country will be obliged to identify some reason why, despite the TRIPS Agreement, doing so would be lawful. Most of the potential reasons have been analyzed extensively in the literature, so we simply itemize them here:

1) Several developing countries are not (yet) bound by the relevant portions of the TRIPS Agreement, either because they are not members of the World Trade Organization ("WTO")[75] or because they are classified by the Committee for Development Policy of the U.N. as "least developed countries" and thus need not comply until 2033.[76] They are therefore free to structure their national patent laws to give local firms space to engage in reverse engineering and production of drugs.
2) The Doha Declaration and article 31*bis* of the TRIPS Agreement leave developing countries considerable freedom to force patentees to grant low-royalty (nonexclusive) licenses to local firms when necessary to meet public-health emergencies.[77]
3) By following India's lead in interpreting stringently the inventive-step requirement (also known as the non-obviousness requirement), developing countries could create space for

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[74] Abbott & Reichman, *supra* note 6, at 928–29*; see also* Margo A. Bagley, *The Morality of Compulsory Licensing as an Access to Medicines Tool*, 102 MINN. L.R. 2463, 2464–68 (2018).

[75] *See WTO Members and Observers,* WTO, https://www.wto.org/english/thewto_e/whatis_e/tif_e/org6_e.htm. (last visited Oct. 2, 2021).

[76] *See WTO Drugs Patent Waiver for LDCs Extended Until 2033,* LEAST DEV. COUNTRIES PORTAL, U.N., https://www.un.org/ldcportal/wto-drugs-patent-waiver-for-ldcs-extended-until-2033/ (last visited (Oct. 21, 2021).

[77] *See, e.g.*, Germán Velásquez et al., "Improving Access to Medicines in Thailand: The Use of Trips Flexibilities," (2008), 20-23.

local firms to manufacture some so-called "me-too" drugs—that is, those that provide little or no therapeutic advantage over their predecessors.[78]

4) By refusing to follow the lead of the United States in extending the duration of patent protection to offset (partially) the time devoted to clinical trials, developing countries could empower local firms to commence manufacturing of a pioneering drug sooner than would be permissible in the United States or other developed countries.[79]

A fifth strategy has received less focus to date and thus merits closer attention. "Working requirements" consist of obligations imposed on patentees to "work" their inventions in the countries in which the patents are granted—in other words, to make the products or processes to which they apply available in those countries.[80] Such obligations were once common components of national patent statutes, but, during the twentieth century, they were abandoned by many developed countries.[81] They have not disappeared altogether, however. A few developed countries (such as the United Kingdom) still have them, and many developing countries have working requirements on their books.[82]

Working requirements come in various shapes and sizes. The more stringent ones require patentees to practice the patent within the country (for example, by manufacturing a patented product in a local plant or by granting a license to a local manufacturer); the less stringent permit patentees to satisfy the obligation by exporting to the country patented products produced elsewhere. Some are satisfied if the patent is practiced within any of a set of countries of which the country of issuance is a member. The penalties for violating the requirements range from

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[78] The latitude enjoyed by developing countries to define the inventive-step requirement is sharply contested. For a few views on this issue, see Carlos Correa, "Guidelines for Pharmaceutical Patent Examination: Examining Pharmaceutical Patents from a Public Health Perspective," (United Nations Development Programme, 2015); Eric M. Solovy and Pavan S. Krishnamurthy, "Trips Flexibilities and Their Limitations: A Rresponse to the Un Secretary-General's High-Level Panel Report on Access to Medicines," *George Washington International Law Review* 50 (2017): 103.

[79] Article 33 of the TRIPS Agreement requires that the term of patents not be shorter than "twenty years counted from the filing date." However, TRIPS neither requires that patent applications be processed within a specific period nor compels countries to extend patents to compensate applicants for the amounts of time they expend prosecuting their applications or securing regulatory approval.

[80] *See* Marketa Trimble, "Patent Working Requirements: Historical and Comparative Perspectives," *U.C. Irvine Law Review* 6 (2016).

[81] *Id.* at 487–89.

[82] *See id.* Except for a brief period in the early nineteenth century, the United States has never had a formal working requirement, but the U.S. Code still contains some provisions that put pressure on patentees to practice their inventions domestically. *See, e.g.*, 19 U.S.C. 1337 § (a)(3) (2006) (exempting from the coverage of "unfair trade practices" circumstances in which, with respect to a patented article, there exist in the United States "(A) significant investment in plant and equipment; (B) significant employment of labor or capital; or (C) substantial investment in its exploitation, including engineering, research and development, or licensing.").

forfeiture of the patent to various forms of compulsory licenses. Some penalties apply as soon as a patent issues; others take hold only after a prescribed period of time.[83]

Those countries that retain working requirements rarely enforce them.[84] One of the reasons is continued uncertainty regarding whether such requirements are compatible with the Paris Convention (the premier multilateral agreement on patent law) and the TRIPS Agreement. Only once has a dispute presenting this issue come close to authoritative resolution. During the early stages of the AIDS pandemic, one of the ways in which Brazil sought to combat the disease was by threatening to enforce a working requirement against the holders of patents on AIDS therapies. The United States formally challenged that initiative as a violation of the TRIPS Agreement but eventually backed down before the claim was resolved.[85] Since then, there have been no WTO dispute-resolution proceedings in which the issue has been presented.

In the absence of an authoritative ruling on the issue, many scholars have ventured opinions. Some contend that all working requirements violate article 27 of the TRIPS Agreement—specifically, the prohibition against discrimination on the basis of "whether products are imported or locally produced."[86] Others contend that at least the subset of working requirements that are enforced through compulsory licenses are justified by reading articles 27, 30, and 31 together or that the apparent hostility of the TRIPS Agreement to working requirements is neutralized by the more generous stance taken in article 5(A)(2) of the Paris Convention. Still others stake out compromise positions.[87]

To clear legal space for local pharmaceutical manufacturers, developing countries might make greater use of working requirements than they do at present, and they might then rely on one or more of the arguments summarized above to resist predictable attacks from adversely affected companies and countries. To be of value in the present context, such a requirement would of course

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[83] *See* Trimble, "Patent Working Requirements: Historical and Comparative Perspectives."

[84] *Id.* at 494.

[85] See Paul Paul Champ and Amir Attaran, "Patent Rights and Local Working under the WTO Trips Agreement: An Analysis of the U.S.-Brazil Patent Dispute," *Yale Journal of International Law* 27 (2002).27 YALE J. INT'L L. 365, 365–66 (2002).

[86] TRIPS Agreement, art. 27.

[87] For a range of opinions concerning the permissibility of working requirements, see Thomas Cottier, Shaheeza Lalani, and Michelangelo Temmerman, "Use It or Lose It: Assessing the Compatibility of the Paris Convention and Trips Agreement with Respect to Local Working Requirements," *Journal of International Economic Law* 17 (2014). Matthias Lamping, Reto Hilty, Dan L. Burk, Carlos M. Correa, Peter Drahos, N.S. Gopalakrishnan, Henning Grosse Ruse-Khan, Annette Kur, Geertrui Van Overwalle, Jerome H. Reichman & Hanns Ullrich, *Declaration on Patent Protection: Regulatory Sovereignty under TRIPS*, 45 INT'L REV. INTELL. PROP & COMPETITION L. 679, ¶30 (2014); Michael Halewood, R*egulating Patent Holders: Local Working Requirements and Compulsory Licenses at International Law*, 35 OSGOOD HALL L.J. 243 (1997); Kevin J. Nowak, *Staying Within the Negotiated Framework: Abiding by the Non-Discrimination Clause in TRIPS Article 27*, 26 MICH. J. INT'L L. 899 (2005); Cynthia M. Ho, *Patent Breaking or Balancing: Separating Strands of Fact from Fiction Under TRIPS*, 34 N.C. J. INT'L L. 371, 399 (2008).

have to define "working" as manufacturing the covered product locally, not merely as a willingness to export products to the country in question. Adoption (and enforcement) of such a duty would force patentees either to set up and operate a local manufacturing facility, to grant a license to a local manufacturer, or to acquiesce in unauthorized production by a local manufacturer—any of which would benefit the developing country at issue.

None of these five options, however, would do much good unless local firms could be confident that they enjoyed the legal authority to implement them. One of the main reasons that strategies like this have been infrequently employed is the uncertainty surrounding whether they could withstand opposition or sanctions from the governments of developed countries sensitive to the interests of the patentees.[88] Two legal reforms would go far to establish confidence in the legality of these strategies.

First, developing countries should create or clarify declaratory-judgment procedures that enable local firms to initiate civil suits against patentees and obtain authoritative rulings in advance regarding their rights to manufacture specific drugs. In the United States, federal courts have limited the availability of such suits because of the so-called "case or controversy" requirement derived from the U.S. Constitution,[89] but most countries (including most developing countries) have no such constitutional constraint. By exploiting this freedom, developing countries could help local firms ascertain, with minimal risk, what they can and cannot do.

The second reform, by contrast, would require a change in the law and behavior of the United States—and perhaps some other developed countries. In the past, the United States Trade Representative ("USTR") has frequently threatened or punished developing countries that invoked the TRIPS Agreement flexibilities.[90] The USTR could be required to do the opposite. Several U.S. government agencies already routinely and conscientiously provide private parties with guidance concerning the permissibility of proposed courses of conduct. For example, the Internal Revenue Service issues "private revenue rulings" to individuals or firms who want assurance concerning the tax implications of business plans, and the Federal Trade Commission indicates in advance

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[88] *See* Champ & Attaran, *supra* note 85.

[89] *See* Aetna Life Ins. Co. v. Haworth, 300 U.S. 227 (1937); MedImmune, Inc. v. Genetech, Inc., 549 U.S. 118 (2007).

[90] For descriptions of some of these threats and punishments, see Kevin Outterson, "Should Access to Medicines and Trips Flexibilities Be Limited to Specific Diseases?," *American Journal of Law & Medicine* 34 (2008): 320; Cynthia Ho, "Patent Breaking or Balancing?: Separating Strands of Fact from Fiction under Trips," *North Carolina Journal of International Law & Commercial Regulation* 34 (2009): 447-48; Jacqui Wise, "Access to Aids Medicines Stumbles on Trade Rules," *Bulletin of the World Health Organization* 85, no. 4; Horace E. Jr. Anderson, "We Can Work It Out: Co-Op Compulsory Licensing as the Way Forward in Improving Access to Anti-Retroviral Drugs," (2010), 28; Christina Cotter, "The Implications of Rwanda's Paragraph 6 Agreement with Canada for Other Developing Countries," *Loyola University Chicago International Law Revew* 5 (2008): 178, 87.

whether specific mergers would be permissible.[91] U.S. law could be amended to require the USTR to do something analogous when asked for guidance by a developing country.

Suppose, for example, that the government of Ghana were considering imposing a compulsory license or a "working" requirement on a COVID-19 vaccine. Prior to doing so, the government could submit a description of the plan to the USTR (and perhaps to either the WTO or the World Intellectual Property Organization) and request rulings from them concerning the permissibility of the initiative in question. The ideal response would consist of a published, reasoned analysis of the compatibility of the proposed initiative with TRIPS and other multilateral agreements. A more modest and practicable response, considering the limited resources and authority of the USTR, would consist of a simple statement that the agency would or would not initiate proceedings to challenge the initiative. The United States would be bound by the USTR's response, much as the IRS is bound by its "revenue rulings."

To be sure, the creation of such a mechanism would entail a significant adjustment of the USTR's responsibilities. For many years, the agency has staunchly defended the interests of the pharmaceutical firms based in the United States whenever they have objected to initiatives by developing countries to promote access to medicine.[92] To provide countries good-faith determinations of whether it intended to challenge proposed initiatives, the USTR would have to change its practices and culture considerably.

The reorientation might be justified in either of two ways. First, the USTR might be persuaded to take more seriously its current statutory charge. In its own mission statement, the agency interprets that charge as follows: "American trade policy works toward opening markets throughout the world to create new opportunities and higher living standards for families, farmers, manufacturers, workers, consumers, and businesses."[93] This statement appropriately recognizes that U.S. trade policy can and should be shaped to promote the welfare of all sectors of the U.S. population, not just businesses concerned with maximizing their export markets. In several circumstances, increasing the ability of firms in developing countries to manufacture drugs redound to the net benefit of U.S. residents.[94] For example, if augmentation of local production significantly reduced the presence of substandard antibiotics in developing countries, the resulting

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[91] *See Understanding IRS Guidance*, INTERNAL REVENUE SERV. ["IRS"] https://www.irs.gov/newsroom/understanding-irs-guidance-a-brief-primer (last visited Oct. 21, 2021); *Premerger Notification and Merger Review Process*, FED. TRADE COMM'N, https://www.ftc.gov/tips-advice/competition-guidance/guide-antitrust-laws/mergers/premerger-notification-merger-review (last visited Sept. 17, 2021).

[92] *See, e.g.*, Mike Palmedo, "Analysis of Special 301 Listings 2009-2020," (2020), https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3680332.

[93] *See Mission of the USTR,* OFF. U.S. TRADE REP. ["USTR"], https://ustr.gov/about-us/about-ustr (last visited Sept. 27, 2021). The way in which the USTR describes "the benefits of trade" is consistent with this mission statement. *See Benefits of Trade,* USTR*,* https://ustr.gov/about-us/benefits-trade (last visited Sept. 27, 2021).

[94] *See, e.g.*, *Policy Issues: Global Health*, U.S. DEP'T STATE, https://www.state.gov/policy-issues/global-health/ (last visited Dec. 6, 2021).

inhibition of the development of drug-resistant strains of bacteria would be, in the long run, hugely beneficial to everyone on the planet. Similarly, the universal provision of vaccines could lead to a speedier recovery of the global economy from global pandemics, benefiting everyone, including U.S. residents, in the long run. A preclearance system of the sort proposed above would enable the agency to identify such situations and thus to provide governments and firms in developing countries clarity concerning their authority to proceed.

The second route would be more sweeping and would likely require statutory change. Arguably, the aggressive way in which the USTR has been defining U.S. trade policy since at least 1988[95] is no longer consistent with U.S. foreign policy as a whole. The latter certainly includes some degree of attention to the welfare of the residents of the rest of the world.[96] To consistently privilege the interests of businesses based in the United States over the health of the residents of the developing world is no longer (if it ever was) compatible with the overall aspirations of the United States as a player on the world stage. It is also inconsistent with the globalized nature of scientific research today, which is characterized by transnational networks of research institutions and systems of knowledge creation, sharing, and exploitation. Adjusting to the realities of deeply integrated R&D systems requires changes, not only in the science and technology policy of the United States, but also in its trade policy. It may well be time to amend the USTR's charge to reduce the tension.

B. *Production Triangles*

In 2007, the government of Uganda catalyzed an innovative joint venture between Quality Chemicals, a local distributor with no pre-existing production capacity, and Cipla Pharmaceuticals, India's largest generic producer.[97] Cipla was given an equity share of 38.55 percent; Quality Chemicals was given 61.45 percent. The companies shared equally in the profits of the venture.[98] The government underwrote the venture by guaranteeing a twenty-three percent stake (as part of Quality Chemical's local equity) for the first plant, which was completed in 2008. The agencies responsible for the project were the Ugandan Ministry of Health and the Ugandan Investment Agency, which drew inspiration and authority from the Ugandan Drug Policy of 2002 and the Ugandan Investment Code Act of 1991.[99]

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[95] *See, e.g.*, President Obama's Trade Policy Agenda with U.S. Trade Representative Michael Froman: Hearing Before the H. Comm on Ways & Means, 113th Cong. 8 (2013) (statement of Michael Froman, USTR Representative).

[96] *See, e.g.*, *Policy Issues: Climate Crisis*, U.S. DEP'T STATE, https://www.state.gov/policy-issues/climate-crisis/.

[97] This section is based on the field work and survey conducted in Uganda by one of the authors of this paper during 2007, 2009, 2014 and 2020, tracing the development of this partnership. *See* Padmashree Gehl Sampath & Christoph Spennemann, *Case Study 8: Uganda*, *in* LOCAL PRODUCTION OF PHARMACEUTICALS AND RELATED TECHNOLOGY TRANSFER IN DEVELOPING COUNTRIES: A SERIES OF CASE STUDIES BY THE UNCTAD SECRETARIAT 261–301 (2011).

[98] *Id.* at 266.

[99] *Id.* at 266–68.

As part of the venture, Cipla Pharmaceuticals was required not only to build the plant using the blueprints of its WHO-Good Manufacturing Practices ("WHO-GMP") compliant plants elsewhere, but also to train all segments of the Ugandan staff—management personnel as well as scientists, chemists and engineers—over a period of five years.[100] The deliverables specified in the agreement included: implementation of good laboratory practices, engineering for plant maintenance, information on selecting and sourcing of raw materials, organizing supply of other inputs, and planning for contingencies in production, marketing, and distribution.[101] In addition, Cipla was expected to submit dossiers for GMP compliance to the WHO, thereby enabling Quality Chemicals to compete in international bidding processes.[102] Last, but not least, the Ugandan government agreed to purchase all products produced in the plant for a period of seven years.[103]

A few analogous ventures are currently in the works. For example, the government of Mozambique has initiated a similar venture that includes the government of Brazil (playing the roles of sponsor and patent licensor) and a local manufacturer, Sociedade Mocambique de Medicamentos.[104] But joint ventures of this sort remain highly unusual.

Such "triangular ventures" hold enormous promise for enhancing local production capacity. Their key features are:

- An experienced pharmaceutical firm, a local manufacturer, and the government of a developing country enter a long-term collaboration.
- The pharmaceutical firm provides know-how, training, guidance in creating manufacturing facilities capable of producing APIs, and advice to ensure compliance with protocols established by international organizations.
- The government provides some initial investment in the venture and, equally important, a commitment to purchase substantial quantities of the products of the venture.
- The local firm provides management, marketing, most of the personnel and much of the financing.

One of the things that makes this model promising is that in many developing countries the largest purchaser of drugs is the national government, which then distributes them through the

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[100] *Id.* at 266–67.

[101] *Id.* at 267.

[102] *Id.* at 283; *see also Making Drugs into Profit in Uganda*, BBC NEWS, April 9, 2021, https://www.bbc.com/news/world-africa-17639822.

[103] Gehl Sampath & Spennemann, *supra* note 97.

[104] *See* Giuliano Russo and Geoffrey Banda, "Re-Thinking Pharmaceutical Production in Africa; Insights from the Analysis of the Local Manufacturing Dynamics in Mozambique and Zimbabwe," *Studies in Comparative International Development* 50 (2015).

public-health system.[105] The government thus has the purchasing power necessary to provide the local firm with a sufficiently large and assured market to get off the ground. To be sure, the government's purchases are often underwritten by international donor organizations, which oversee the tender process.[106] However, those agencies typically favor increasing local production and thus would not balk at arrangements like Uganda's.

The government's purchasing power need not be wielded profligately. An unqualified commitment to purchase unlimited quantities of drugs at whatever price the local company set would obviously be inappropriate. Benchmarks and time limits can and should be employed to avoid waste.

Crucial to the feasibility of triangular ventures is the commitment by the government to empower the local firm to manufacture APIs (in the case of drugs) or antigens and adjuvants (in the case of vaccines) by supporting the venture, and also, if possible, to participate in risk-sharing.[107] As indicated above, experience has shown that the production of active ingredients of these sorts is essential to make such ventures profitable, thus minimizing and eventually eliminating the price premium that the government needs to pay for the drugs.

Of course, the details of such triangular collaborations will vary by country and product. Further experimentation as well as adjustments of ongoing projects would be necessary to determine the optimal arrangement in each jurisdiction. But triangular arrangements could go far toward boosting local production of pharmaceutical products, thereby promoting both health and prosperity in nations desperately short of both.

C. *Apprenticeships*

An alternative way to stimulate transfers of the kind of technological know-how that has proven to be critical to local-production initiatives would be to create an apprenticeship program. Hundreds of years ago, apprenticeship was a common and highly effective system for transferring technical knowledge across generations. For example, in the sixteenth and seventeenth centuries,

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[105] For example, in South Africa, the public sector provides healthcare services and medicines to almost eighty-four percent of the population. *See* Joanna C. Meyer, Natalie Schellack, Jacobus Stokes, Ruth Lancaster, Helecine Zeeman, Douglas Defty, Brian Godman & Gavin Steel, *Ongoing Initiatives to Improve the Quality and Efficiency of Medicine Use Within the Public Healthcare System in South Africa; A Preliminary Study*, FRONTIERS PHARMACOLOGY, NOV. 2017.

[106] *See, e.g.*, Henry Zakumumpa, *Beyond Donor Dollars for Health Care: How Uganda is Thinking Outside the Box,* THE CONVERSATION (Feb. 22, 2018), https://theconversation.com/beyond-donor-dollars-for-health-care-how-uganda-is-thinking-outside-the-box-89316f.

[107] *See* Gehl Sampath & Spennemann, *supra* note 97.

roughly ten percent of the population of London were apprentices, and two-thirds of adult male residents of the city had at some point served as apprentices.[108]

This system could be adapted to strengthen the technical and soft skills necessary to build capacity for local drug production. Assume, plausibly, that a U.S. or European manufacturer of a new drug or vaccine refused (or was forbidden by its national government) to export any of its products to developing countries until the needs of consumers in its country of residence were fully satisfied. Without impairing the pace of production, the firm could take on, as apprentices, scientists employed by existing or prospective pharmaceutical firms in developing countries. Working alongside the firm's managers and scientists, the apprentices would absorb crucial technical knowledge and then return to their countries of residence to set up and run similar production facilities. They would be replaced by another cohort of apprentices, who would in turn return to their countries of origin, and so forth. In this way, firms in developing countries would gain access to the most current knowledge concerning how best to produce safe and efficacious drugs.

The feasibility of such a system is strengthened by the fact that apprenticeships have long been used effectively in German chemical and pharmaceutical firms.[109] Increasingly, pharmaceutical firms in other countries are relying on them to train skilled workers.[110] To be sure, the level at which the proposed program would operate is different. Instead of training technicians,

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[108] *See* Patrick Wallis, "Apprenticeship and Training in Premodern England," *Journal of Economic History* 68 (2008).; Prak Maarten and Patrick Wallis, *Apprenticeship in Early Modern Europe* (Cambridge: Cambridge University Press, 2019).; S.R. Epstein, "Craft Guilds, Apprenticeship, and Technological Change in Preindustrial Europe," *Journal of Economic History* 58 (1998). Apprenticeship survives and indeed flourishes today in some sectors of the economy—notably, medicine in the United States (through the residency system in "teaching hospitals"); private law practice (through the "associate" system in law firms—itself a vestige of the dominant system of legal education in the eighteenth and early nineteenth centuries); boatbuilding; and in many industries in Germany. *See, e.g.,* Richard Heitmiller, Vinay K Gupta, Christopher J You, Apprenticeships: Preserving the Commitment in Surgical Education, 65 J. SURGICAL EDUC. 259, 259–62 (2008); Stan Grayson, *The Little Engine that Could – 100 Years of Beetle Cats*, WOODENBOAT, Sept.–Oct. 2020, at 24, 26–27; Lutz Raphael, "Knowledge, Skills, Craft? The Skilled Worker in West German Industry and the Resilience of Vocational Training, 1970–2000," *German History* 37, no. 3 (2019).; Dietmar Harhoff and Thomas J. Kane, "Is the German Apprenticeship System a Panacea for the U. S. Labor Market?," *Journal of Population Economics* 10 (1997): 174-75.

[109] *See* BIOSCIENTISTS, BAYER, https://karriere.bayer.de/sites/g/files/kmftyc1001/files/2019-05/EB_A4_Biowissenschaftler_180212_EN_Preview.pdf (last visited Oct. 13, 2021) (providing a description of Bayer's apprenticeship program for "bioscientists").

[110] *See, e.g*., Press Release, Ass'n Bri. Pharm. Indus., Apprenticeships Hit 4-year High in British Pharmaceutical Industry (July 1, 2018); Patrick Raleigh, *Would You Encourage Kids Into Apprenticeships?*, PROCESS ENG'G, Mar.-Apr. 2009, at 5; *PPD Announces Industry-First Apprenticeship for Clinical Research Associates*, CLINICAL LEADER (Mar. 23, 2017), https://www.clinicalleader.com/doc/ppd-announces-industry-first-apprenticeship-for-clinical-research-associates-0001; Sandeep Lahiry & Sreekanth Gattu, *Real-World Perspective on Careers of Pharmaceutical Physicians in India: A Working Report,* 11 PERSPS. CLINICAL RSCH. 150, 155 (2018); Paul Lewis, *Developing Technician Skills for Innovative Industries: Theory, Evidence from the UK Life Sciences Industry, and Policy Implications*, 58 BRIT. J. INDUS. REL. 617, 619 (2020).

the goal would be to train the scientists and managers who would be responsible for establishing and overseeing new and complex manufacturing processes. But if apprenticeship can be employed to teach advanced surgical techniques,[111] it ought to work in teaching novel pharmaceutical manufacturing methods.

Recently, the Organization for Economic Cooperation and Development ("OECD") has emphasized the importance for African countries to prioritize ways of providing African firms affordable access to technology and know-how.[112] One of the OECD's specific recommendations is that African countries should encourage leading scientists and laboratories to participate in international research consortia and should incentivize local research centers to join international research partnerships.[113] Apprenticeship programs of the sort described above would be one way of implementing this recommendation.

Creation of a system of this sort would require three things. First, mechanisms for selecting, coordinating, and supporting the apprentices would have to be established by the governments of developing countries—in much the same way that apprenticeship was regulated by the City of London in the seventeenth century. Second, to avoid corroding the primary markets of the sponsoring companies, the firms in developing countries that benefitted from this model would have to commit credibly not to export drugs to developed countries, and the governments in those countries would have to back the firms' commitment. Finally, the pharmaceutical firms would have to be persuaded to participate genuinely in the system.

The first two of these tasks would of course be the responsibility of the developing countries. Our recommendation is that they move forward on both fronts promptly. Ideally, developing countries should use the regional organizations already in place (such as the African Union) to create such systems. Not only would that be more efficient than constructing country-specific regimes, but it would also reduce the logistical challenges for the pharmaceutical firms.

The third task will likely be the hardest. There is little chance that the major pharmaceutical firms would participate in this system voluntarily. Thus far, the firms that have developed the leading COVID-19 vaccines have shown little interest in sharing any of the information or

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[111] *See* Elizabeth H. Stephens and Joseph A. Dearani, "On Becoming a Master Surgeon: Role Models, Mentorship, Coaching, and Apprenticeship," *Annals of Thorasic Surgery* (Pre-proof) (2020): 8; William Nolan, *The Making of a Surgeon* (1970).; Bennet A. Butler, Cameron M. Butler, and Terrance D. Peabody, "Cognitive Apprenticeship in Orthopaedic Surgery: Updating a Classic Educational Model," *Journal of Surgical Education* 76, no. 4 (2019).

[112] Africa's Response to COVID-19: What Roles for Trade, Manufacturing, and Intellectual Property? Organization for Economic Co-Operation and Development ["OECD"] 11 (June 23, 2020), https://read.oecd-ilibrary.org/view/?ref=134_134617-5ewrwojglf&title=AFRICA-S-RESPONSE-TO-COVID-19-What-roles-for-trade-manufacturing-and-intellectual-property [hereinafter Africa's Response to COVID-19].

[113] *Id.* at 24.

discoveries they are generating.[114] Thus, to prompt them to pass on information to scientists from the developing world, they would have to be encouraged in some way, but how?

Three possibilities seem promising. The first capitalizes on the fact that almost all of the firms in the COVID-19 vaccine race have received substantial funding from the governments of the United States or the European Union.[115] The funding provided by the U.S. government has come at various times and in various forms, but in the aggregate already exceeds $9 billion USD.[116] This amount is unprecedented, but public funding for pharmaceutical research is not; the percentage of new drugs that are fueled in part by grants from governments is large and growing.[117] In such circumstances, the governments dispensing the grants that help sustain the research could and should insist, as a condition of acceptance, that the recipients commit to participate in the apprenticeship system described above if the research leads to new products.

Second, when developing new drugs and vaccines, private pharmaceutical firms often rely upon innovations made by government scientists.[118] In some instances, this reliance may be sufficiently important that, to comply with patent law, the firm would be obliged to include the government scientists in the list of inventors in its patent applications. That, in turn, gives the government substantial leverage, which it could use to insist that the firms participate in the apprenticeship program.[119]

The third possibility capitalizes on the fact that pharmaceutical firms regularly conduct clinical trials of new vaccines and therapies in developing countries. Several trials of COVID-19

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[114] *See* Francis et al. *supra* note **Error! Bookmark not defined.** and accompanying text; Stephanie Nolen & Sheryl Gay Stolberg, *Pressure Grows on U.S. Companies to Share Covid Vaccine Technology,* N.Y. TIMES*,* (Nov. 9, 2021).

[115] *See* Lisa Cornish, *Funding COVID-19 Vaccines: A Timeline*, DEVEX (Aug. 21, 2020), https://www.devex.com/news/funding-covid-19-vaccines-a-timeline-97950.

[116] *See* Jacob S. Sherkow, Lisa Larrimore Ouellette, Nicholson Price & Rachel Sachs, *How Does Moderna's COVID-19 Vaccine Work, and Who Is Funding Its Development?*, HARV. L. PETRIE-FLOM CTR. (August 27, 2020), https://blog.petrieflom.law.harvard.edu/2020/08/27/moderna-covid19-vaccine-government-funding/; Elizabeth Cohen & Dana Vigue, *US Taxpayers are Funding Six Covid Vaccines. Here's How They Work*, CNN HEALTH (June 23, 2020), https://www.cnn.com/2020/06/22/health/us-coronavirus-vaccine-funding/index.html; *Public Citizen Tracker Finds Taxpayers Have Funded $6 Billiion in Coronavirus Treatment/Vaccine Development*, PUBLICCITIZEN (July 17, 2020), https://www.citizen.org/news/public-citizen-tracker-finds-taxpayers-have-funded-6-billion-in-coronavirus-treatment-vaccine-development; Karen Weintraub & Elizabeth Weise*, Federal Spending on COVID-19 Candidates Tops $9 Billion, Spread Among 7 Companies*, USA TODAY (Aug. 10, 2020), https://www.usatoday.com/story/news/health/2020/08/08/feds-spending-more-than-9-billion-covid-19-vaccine-candidates/5575206002/.

[117] *See, e.g.*, Rachel Barenie, Jerry Avorn, Frazer Tessema, & Aaron Kesselheim, *Public Funding for Transformative Drugs: The Case of Sofosbuvir*, 26 DRUG DISCOVERY TODAY 273 (2021).

[118] *See, e.g.*, Sheryl Gay Stolberg & Rebecca Robbins, *Moderna and U.S. at Odds Over Vaccine Patent Rights*, N.Y. TIMES, (Nov. 9, 2021).

[119] For this suggestion, we are indebted to Professor Amy Kapczynski of Yale Law School.

vaccines are already underway in African countries.[120] Such trials require the permission of the governments of the states in which they are conducted. It would be entirely reasonable for a government to condition its approval, not only upon a commitment by the firm to abide by safety requirements, as is routine, but also upon a commitment to participate in an apprenticeship program.

Fulfilling such a commitment would cost a pharmaceutical firm little. Indeed, the firm might well benefit from the insights and efforts of the apprentices. The supplies of drugs to the citizens of developed countries would in no way be impaired. And, by augmenting production capacity within developing countries, the apprenticeship system would save many lives.

D. *Quality Control*

One of the reasons for the disturbingly high number of falsified and substandard medicines in developing countries is that the governments of those countries have inadequate control over drug supplies. This is partly because, as we have seen, most medicines are imported into those countries, and, all too often, neither the foreign manufacturers nor the governments of the exporting countries are committed to ensuring that the products meet quality standards.[121] A major potential benefit of an increase in local production capacity is that it would reduce reliance on substandard foreign manufacturers and create opportunities for purging developing countries of defective drugs and vaccines.[122]

In one important respect, this benefit would be realized automatically. Currently, the introduction of substandard and falsified pharmaceutical products into the supply chains in developing countries is often triggered by stockouts—that is, exhaustion of the supply of drugs. When distributors and pharmacies are unable to meet demand for particular medicines by purchasing them through regular channels, they turn to irregular sources, which, as one might expect, contain much higher percentages of nonconforming products.[123] Displacing imports with locally produced products would decrease the frequency of such stockouts in three ways. First, the time necessary to transport products from manufacturers to distributors and retailers would of course be shorter, thus enabling quicker responses to surges in demand. Second, local production eliminates customs barriers, where batches of drugs often languish. Finally, local producers are

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[120] John N. Nkengasong et al., "Covid-19 Vaccines: How to Ensure Africa Has Access," *Nature* (2020), https://www.nature.com/articles/d41586-020-02774-8. https://www.nature.com/articles/d41586-020-02774-8.

[121] See Elizabeth Pisani, Adina-Loredana Nisstor, Amalia Hasnida, Koray Parmaksiz, Jingying Xu, Maarton Oliver Kok, Identifying Market Risk for Substandard and Falsified Medicines: An Analytic Framework Based on Qualitative Research in China, Indonesia, Turkey, and Romania, 4 WELLCOME OPEN RSCH. 70 (2019).

[122] S*ee, e.g.* Sui-Lee Wee & Javier C. Hérnandez, *Scandal Dogs AstraZeneca's Partner in China*, N.Y. TIMES (Dec. 7, 2020), https://www.nytimes.com/2020/12/07/business/china-vaccine-astrazeneca.html (demonstrating the kinds of foreign manufacturer practices that a country investing in local production could avoid).

[123] *Cf.* Harparkash Kaur et al., "Fake Anti-Malarials: Start with the Facts," *Malaria Journal* 15, no. 86 (2016): 6.

much more likely to prioritize local needs than are foreign manufacturers—and thus to ensure that scarce supplies do not end up elsewhere.

It would be a serious mistake, however, to rely entirely on these direct benefits of local production. The profits that unscrupulous suppliers can earn would remain high, and corruption in some developing countries would ensure that such suppliers could continue to ply their nefarious trade.[124] To prevent the persistence or even exacerbation of the problem, it is essential that initiatives to augment local production be married with enhanced efforts to promote quality.

Such efforts can and should be made at three levels. First, the processes for determining which pharmaceutical products are approved for sale in each country should be improved. Second, manufacturing facilities must be built, maintained, and operated in ways that ensure their products are reliable and untainted. Finally, robust systems of post-marketing surveillance must be deployed to prevent contamination of the supply chain with falsified or poor-quality medicines. Fortunately, major initiatives on all three of these levels are already underway, but they must be amplified and adequately funded.

With respect to the drug-approval process, developing countries are increasingly recognizing, and capitalizing upon, the potential benefits of regional collaborations in creating and operating counterparts to the U.S. FDA and the European Medicines Agency ("EMA"). In Africa, for example, the African Medicines Regulations Harmonization Initiative ("AMRH") is making good progress toward accelerating and improving the processes by which drugs are first approved for distribution.[125] Among its results is the African Union Model Law on Medical Products Regulation, which has now been adopted in twenty-five countries.[126] Even more promising is a treaty concluded in 2019 that, if fully implemented, would establish a continental African

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[124] *See, e.g.*, Bate et al. *supra* note 46 (discussing the wide profit margin enjoyed by pill counterfeiters in the United Kingdom).

[125] Information on AMRH can be found at *Who We Are*, AFR. UNION DEV. AGENCY -NEW P'SHIP FOR AFR. DEV. ["NEPAD"], https://www.nepad.org/programme/african-medicines-regulatory-harmonisation-amrh (last visited on Oct. 23, 2021). For reports on its progress, see Alexander R. Giaquinto et al., "Improving Access to Quality Medicines in East Africa: An Independent Perspective on the East African Community Medicines Regulatory Harmonization Initiative," *PLoS Med* 17, no. 8 (2020); Jane H. Mashingia et al., "Eight Years of the East African Community Medicines Regulatory Harmonization Initiative: Implementation, Progress, and Lessons Learned," ibid.PLOS MED., Aug 12, 2020.

[126] For the model law, *see AU Model Law on Medical Products Regulation*, NEPAD, https://www.nepad.org/publication/au-model-law-medical-products-regulation (last visited Oct. 14, 2021). For a summary of the model law, see INCREASING ACCESS TO HIGH-QUALITY, SAFE HEALTH TECHNOLOGIES ACROSS AFRICA: AFRICAN UNION MODEL LAW ON MEDICAL PRODUCTS REGULATION, AUDA-NEPAD, https://path.azureedge.net/media/documents/APP_au_model_law_br.pdf (last visited Oct. 14, 2021). For recommendations concerning its implementation at both national and regional levels, see IMPLEMENTING THE AFRICAN UNION MODEL LAW AT THE REGIONAL AND NATIONAL LEVEL, NEPAD, https://path.azureedge.net/media/documents/Implementing_the_AU_Model_Law_brief_October_2016.pdf (last visited Oct. 14, 2021).

Medicines Agency analogous to the EMA. The fifteenth instrument of ratification of the African Medicines Agency Treaty was recently deposited at the African Union Commission, and the Treaty has now entered into force.[127] It will enable considerable improvement and streamlining of the mechanisms for securing registration of new drugs in multiple jurisdictions.[128]

With respect to manufacturing quality, although few developing countries have already established systems for bringing local manufacturing facilities into compliance with the WHO's GMP certification requirements,[129] several are currently creating such systems. The UNIDO has developed a "roadmap" for countries pursuing this objective, which has already been successfully implemented in Kenya and Ghana.[130] In short, this is not an easy objective for many developing countries, but it is surely attainable.

Effective post-marketing surveillance systems have proven to be harder to implement, in part because of the ingenuity that unscrupulous counterfeiters have shown in circumventing systems for detecting their wares.[131] But technologies are now available that, in combination, enable inspectors to identify substandard or falsified medicines at any point in the distribution chain. They come in various shapes and sizes. Some facilitate tracking of products from the moment they leave the manufacturers until they are delivered to patients. Comprehensive systems of this type are now in use—or in the process of deployment—in the United States, the European Union, China, India, Brazil, Turkey, and a few other countries.[132] With sufficient funding, such systems could eventually be deployed in developing countries.

A second group of technologies does not rely on tracking, but instead uses visible or "scratchable" codes embedded in the drugs' packaging to enable consumers to verify the authenticity of pills. The purchaser of a packet uses his or her cell phone to transmit the associated

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[127] Pursuant to article 38, the Treaty entered into force on November 5, 2021.

[128] For the treaty text, *see* Treaty for the Establishment of the African Medicines Agency, February 11, 2019, https://au.int/sites/default/files/treaties/36892-treaty-0069_-_ama_treaty_e.pdf. A summary of its scope is available at *African Medicine Agency (AMA) Treaty*, AFR. Union (Feb. 5, 2020), https://au.int/en/pressreleases/20200205/25frican-medicine-agency-ama-treaty.

[129] For the WHO's GMP certification requirements, see World Health Organization, "Good Manufacturing Practices for Pharmaceutical Products: Main Principles," (2014), https://www.who.int/medicines/areas/quality_safety/quality_assurance/production/en/.

[130] *See* Kay Weyer, "A Stepwise Approach for Pharmaceutical Companies in Developing Countries to Attain Who Gmp Standards," *WHO Drug Information* 30, no. 2 (2016); UNIDO, "A Stepwise Approach for Pharmaceutical Companies in Developing Countries to Attain Who Gmp Standards," (2015), https://www.unido.org/sites/default/files/2015-09/White_paper_final_edit_content_table_print_0.pdf.

[131] *See* Inst. Medicine, Countering the Problem of Falsified and Substandard Drugs (2013), 255–89.

[132] *See* Huma Rasheed, Ludwig Höllein, and Ulrike Holzgrabe, "Future Information Technology Tools for Fighting Substandard and Falsified Medicines in Low- and Middle-Income Countries," *Frontiers in Pharmacology* 9 (2018): 2; Bernard Naughton et al., "Medicine Authentication Technology as a Counterfeit Medicine-Detection Tool: A Delphi Method Study to Establish Expert Opinion on Manual Medicine Authentication Technology in Secondary Care," *BMJ Open Access* 7 (2017).

code to the manufacturer and receives, in response, a text message indicating whether its contents are authentic. Systems of this sort include Sproxil (developed in Nigeria) and Pharmsecure (developed in Nigeria and India).[133]

Yet another set of technologies relies upon testing the chemical composition of medicines at various points in the distribution chain. They include:

- High-performance liquid chromatography ("HPLC") testing of samples in laboratories that have been qualified by the WHO to conduct such testing;[134]
- The "MiniLab," developed in the 1980s by the Global Pharma Health Fund (and subsequently updated periodically), which makes possible analogous testing in the field.[135]
- Systems that use a combination of portable scanners (relying on Raman, near-infrared, or Fourier-transform Infrared ("FTIR") spectroscopy) and portable digital libraries (containing the spectral profiles of authenticated drugs) to determine, in the field, whether pills contain the ingredients they purport to contain. Examples of initiatives of this sort include the Southern African Quality Assurance Network ("SAQAN") (a non-profit venture with initial deployments in Namibia and Malawi) and RxAll (a for-profit venture with initial deployments in five other African countries).[136]

Systems of the first two types dovetail with patent and trademark law. In other words, they facilitate detection of pills that have been produced or distributed by companies lacking legal rights to do so. They are thus dependent upon quality-control measures (of the sort discussed above) that the authorized manufacturers employ. Systems of the third type instead determine whether tested medicines have the right amount of active ingredients (and are uncontaminated by unwanted

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[133] *See* Rasheed, Höllein, and Holzgrabe, "Future Technology Tools," 3; Matthew Wall, "Counterfeit Drugs: 'People Are Dying Every Day'," *BBC News*, September 26, 2016 2016.

[134] For a description of the technology and its suitability to poor countries, see Ludwig Hoellein and Ulrike Holzgrabe, "Development of Simplified Hplc Methods for the Detection of Counterfeit Antimalarials in Resource-Restraint Environments," *Journal of Pharmaceutical and Biomedical Analysis* 98 (2014).

[135] *See, e.g.,* Ifeyinwa Fadeyi et al., "Quality of the Antibiotics—Amoxicillin and Co-Trimoxazole from Ghana, Nigeria, and the United Kingdom," *American Journal of Tropical Medical Hygiene* 92 (2015).(comparing HPLC testing and the MiniLab); Stephanie Kovacs et al., "Technologies for Detecting Falsified and Substandard Drugs in Low and Middle-Income Countries," *PLoS ONE* 9, no. 3 (2014): 8-9.; Albert Petersen, Nadja Held, and Lutz Heide, "Surveillance for Falsified and Substandard Medicines in Africa and Asia by Local Organizations Using the Low-Cost Gphf Minilab," *PLOS ONE* 12, no. 9 (2017).

[136] *See*, *e.g.*, Eillie Anzilotti, "'This Startup Built a Device to Figure out If Prescription Drugs Are Fake," *Fast Company*, https://www.fastcompany.com/90323372/this-startup-built-a-device-to-figure-out-if-prescription-drugs-are-fake.; *Instant Drug Testing*, RXALL, https://www.rxall.net. (last visited Oct. 14, 2021); Kovacs et al., "Technologies for Detection," 8.

substances) regardless of whether they have been lawfully manufactured. In most instances, the two systems will lead to the same results, but not always.

The various mechanisms currently available have features that may prove more useful in some countries than in others, depending on local factors, including the number and capacity of testing labs available, level of coordination across the responsible government agencies, expertise of testing staff, quality of telecommunications networks, transportation, and access to hospitals where drugs are distributed to patients. Regardless of the comparative advantages of any system, the point is that *some* reliable system of post-market surveillance is essential if the benefits of local production of pharmaceutical products are to be fully realized.

E. *Regional Organizations and Economic Communities*

The final strategy we propose to support local production of pharmaceutical products leverages existing but under-utilized regional frameworks to address legal and economic considerations necessary to strengthen the institutional environment in which local producers operate.

Regional integration has long been a significant feature of the international economic order. Starting with European regionalism in the 1958 Treaty of Rome, which established the European Economic Community, regionalism has gradually intensified and today is deeply entrenched in the multilateral trade system. Indeed, the idea of regional integration was codified in the General Agreement on Tariffs and Trade ("GATT"), which noted explicitly the "desirability of increasing freedom of trade by the development, through voluntary agreements, of closer integration between the economies of the countries parties to such agreements."[137]

The abiding interest in closer trade integration and liberalization has fueled sub-regional coalitions of countries politically committed to tackling economic development challenges. For many developing and least-developed countries, the formation of such regional economic communities ("RECs") was a strategic response to overwhelming development challenges that individual countries lacked resources and capacity to address. The first U.N. Economic Commission for Africa ("ECA") study on regional integration identified a number of benefits from regional integration, including increased foreign and domestic investment; increased global competitiveness; promotion of regional public goods; prevention of conflict; consolidation of economic and political reform and economies of scale.[138] These benefits, and the effectiveness of the regional institutions that support the integration process generally, offer important benefits with respect to local pharmaceutical production.

The treaties that establish RECs are especially complex (and, for our purposes, important) in sub-Saharan Africa, which boasts several regional communities, including the South African Development Community ("SADC") and the Economic Community of West African States

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[137] General Agreement on Tariffs and Trade ["GATT"] art. XXIV(4), Oct. 30, 1947, 61 Stat. A-11, 55 U.N.T.S. 194.

[138] U.N. Econ. Comm'n for Afr., Assessing Regional Integration in Africa 10–17 (2006).

("ECOWAS"), with different purposes and overlapping memberships. Without much exception, however, all RECs anticipate deeper regional integration and are largely justified by concerns relating to overcoming major constraints to competitiveness such as economies of scale in production, achieving leverage in global fora, and enhancing mutual benefit from improved growth and development. These considerations are strongly aligned with the rationale for local pharmaceutical production.

Five aspects of the RECs can be employed to increase the feasibility of enhancing local production of pharmaceutical products. The first and most obvious is scale. Not all developing countries are large enough to support commercially viable pharmaceutical manufacturing firms selling products (directly or indirectly) to domestic consumers. If they are to participate in the initiatives set forth above, they must be combined into groups that enable economies of scale. The RECs provide ready-made combinations of this sort. The populations (in millions) encompassed by the principal developing-country regional communities are set forth below: [139]

REC	**Population in Millions**
Andean Community (South America)	98
MERCOSUR (South America)	284
CARICOM (Caribbean)	18
UMA (North Africa)	102
ECOWAS (West Africa)	349
ECCAS (Centre Africa)	121
COMESA (Southeast Africa)	390
EAC (East Africa)	177
SADC (South Africa)	345
GCC (Middle East)	54
SAARC (South Asia)	1713
ASEAN (Southeast Asia)	647

With the possible exception of the Caribbean Community ("CARICOM") and the Gulf Cooperation Council ("GCC"), all of these are sufficiently large to sustain vibrant and efficient regional pharmaceutical industries.

Second, member countries of RECs typically have similar disease footprints and thus need similar portfolios of drugs.

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[139] Uwe Miesner, Contributions of Quality Infrastructure to Regional Economic Integration: Insights and Experience Gained from Technical Cooperation of PTB 1, at 8 fig. 2 (Physikalisch-Technische Bundesanstalt Discussion Paper, Paper No. 2, 2009). For a comprehensive list of regional trade agreements, see Regional Trade Agreements Database, WTO, http://rtais.wto.org/UI/PublicAllRTAList.aspx (last visited Oct. 21, 2021).

Third, freedom of trading within these blocs means that shipments of goods can move easily and quickly from a manufacturer in one member country to distributors and consumers in other member countries.

Fourth, many of the agreements underlying the RECs provide explicitly for cooperation in health matters and thus create legal frameworks that local firms can exploit. For example, article 110(1)(b) of the COMESA Treaty requires that member states cooperate in health "through the facilitation of movement of pharmaceuticals within the Common Market and control of their quality."[140] COMESA member states undertake to, among other things:

> devise and implement systems to ensure that pharmaceuticals entering the Common Market from third countries, produced in the Common Market or moving within the Common Market conform to internationally acceptable standards in terms of quality and therapeutic value;
>
> develop a national drug policy that would include establishing quality control capacities, national formularies and good procurement practices;
>
> harmonize drug registration procedures to achieve good control of pharmaceutical standards without impeding or obstructing the movement of pharmaceuticals within the Common Market;
>
> accord each other mutual recognition of drugs registered in the Common Market;
>
> co-operate, within the framework of co-operation in industrial development, in the local production of pharmaceutical products; and
>
> establish an audit team to assist local pharmaceutical industries in producing high quality products that are safe, effective, and free from harmful side effects, and to assist the Member States in controlling the standards of pharmaceuticals manufactured within their territories in conformity with the WHO Certification.[141]

Similarly, article 29 of the SADC requires that parties cooperate and assist one another in "(a) harmonization of procedures of pharmaceuticals, quality assurances and registration; (b) production, procurement and distribution of affordable essential drugs; (c) development and strengthening of an Essential Drugs Programme and the promotion of the rational use of drugs; [and] (d) development of mechanisms for quality assurances in the supply and conveyances of vaccines, blood and blood products."[142]

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[140] Treaty Establishing the Common Market for Eastern and Southern Africa art. 110(1)(b), Nov. 5, 1993, 2314 U.N.T.S. 265.

[141] *Id.* art. 110(2).

[142] Protocol on Health in the South African Development Community art. 29, Aug. 18, 1999, https://www.sadc.int/files/7413/5292/8365/Protocol_on_Health1999.pdf (entered into force on Aug. 18, 2004).

In the ECOWAS region, the West African Health Organization ("WAHO") is responsible for leading the harmonization of health policies, pooling resources, and strengthening cooperation to address health-related challenges in the subregion.[143] Like SADC and COMESA, ECOWAS adopted a Protocol to establish WAHO that gave the institution a broad policy mandate to address health matters on a regional basis.[144]

These provisions and associated regional institutions establish clear authority for policymaking and a legal framework that would enhance the viability of local pharmaceutical production, including prospects to address many of the dimensions of the initiatives described in the preceding sections of this article.

Some RECs have already experimented with stronger regional commitments to address access to pharmaceutical products. For example, a SADC Pharmaceutical Business Plan was published in 2007 with the overall goal of reducing the disease burden in the region by enhancing sustainable access to affordable, safe, and efficacious essential medicines.[145] To achieve these targets, SADC identified several strategies aligned with the region's Protocol on Health: harmonizing standard treatment guidelines and essential medicine lists; strengthening regulatory capacity, supply, and distribution of basic pharmaceutical products through ensuring a fully functional regulatory authority with an adequate enforcement infrastructure; promoting joint procurement of therapeutically beneficial medicines of acceptable safety, proven efficacy, and quality to the people who need them most, at affordable prices; and facilitating trade in pharmaceuticals within SADC.[146] Although implementation has been slow, the Pharmaceutical Business Plan provides an institutional platform on which the political commitments of states to local production of pharmaceuticals can be sustained and strengthened over time. Such action-oriented frameworks also offer important context to justify new legal or regulatory tools necessary to deploy strategic initiatives in response to public-health challenges in the region.

Even absent formal provisions on health or medicines, regional organizations may operate under more general provisions concerning free movement of goods, security, or human welfare to undertake initiatives to support local production along one of the dimensions we have described. For example, under the general purpose of eliminating technical barriers to trade, the ASEAN Pharmaceutical Product Working Group was established by the ASEAN Consultative Committee for Standards and Quality with the objective of harmonizing pharmaceutical regulations of

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[143] *See Who We Are*, W. AFR. HEALTH ORG., https://www.wahooas.org/web-ooas/en/who-we-are (last visited Sept. 18, 2021).

[144] *See* Economic Community of West African States [ECOWAS], Protocol on the Establishment of West African Health Organization, July 9, 1987, 1690 U.N.T.S. 247.

[145] *See* S. Afr. Dev. Cmty., SADC Pharmaceutical Business Plan 2007-2013, at 4 (2007).

[146] See *The SADC Pharmaceutical Programme*, S. AFR. DEV. CMTY., https://www.sadc.int/themes/health/pharmaceuticals/ (last visited Oct. 21, 2020).

member countries.[147] Harmonization of labelling standards for pharmaceutical/medicinal products in the ASEAN region was achieved in March 2006,[148] and additional harmonization initiatives remain ongoing.[149]

A comparison of provisions to support local manufacture of pharmaceutical products suggests that most RECs already have the requisite legal and policymaking authority to launch and support local production initiatives.

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[147] *See* Abhishek Tongia, "The Drug Regulatory Landscape in the Asean Region," *Regulatory Focus*, https://www.raps.org/news-and-articles/news-articles/2018/1/the-drug-regulatory-landscape-in-the-asean-region.

[148] *See* Kah Seng Lee et al., "Cross-Border Collaboration to Improve Access to Medicine: Association of Southeast Asian Nations Perspective," *Journal of Epidemiology and Global Health* 9, no. 2 (2019).

[149] Similarly, within CARICOM, the Council for Trade and Economic Development ("COTED") is charged with establishing standardization programs. *COTED Endorses Regulatory Systems for Medicines Roadmap,* CARIBBEAN CMTY. (NOV. 22, 2016), https://caricom.org/coted-endorses-regulatory-system-for-medicines-roadmap/.

FEATURES IN SELECT RECS TO ENHANCE LOCAL PRODUCTION

REC	Free movement of goods	Harmonization of medicines regulation	Pooled Procurement of medicines
ASEAN	✓	✓ (Harmonization of labelling standards for pharmaceutical/medicinal products achieved.)	×
CARICOM	✓	✓ (Caribbean Regulatory System for Medicines (CRS) which seeks, *inter alia*, to harmonize regulations for medicines and pharmaceuticals.)	✓
COMESA	✓ (Expressly provides for facilitation of movement of pharmaceuticals.)	✓ (Specifically, for medicines registration.)	×
ECOWAS	✓	✓ (Provides generally for harmonization of standards and measures.)	×
MERCUSOR	✓	×	✓ (Unclear whether this is pursuant to a legal instrument.)
SADC	✓	✓ (For harmonization of procedures of pharmaceuticals, quality assurances and registration.)	✓ (Pooled Procurement Services (SPPS) system.)

Finally, most RECs also have in place governance systems that could be employed to prevent paralyzing struggles among member countries concerning where pharmaceutical manufacturing plants will be located, which courts will have jurisdiction over the firms (particularly for triangular agreements), and which regulations are applicable.[150] In their efforts to combat the COVID-19 pandemic, the institutions responsible for the implementation of regional integration agreements have already demonstrated impressive capacity to draw on the authority provided in the relevant treaties to accomplish novel things such as standardization and deployment of common technology platforms needed to secure public trust in testing data, coordination of pooled procurement of diagnostics and other medical products, and establishment of regional lab-referral networks to assist the poorest countries that lack diagnostic capacity.[151]

In sum, in parts of the developing world, there exist large differences between countries' infrastructure, human capital, and security. These differences impede countries from relocating their pharmaceutical manufacturing capacity; therefore, organizing regional initiatives would be especially promising to remedy these issues. Even in areas (such as the South Asian Association for Regional Cooperation ("SAARC")) where individual countries are large enough on their own to sustain local industries, regional initiatives may still offer advantages such as possible manufacturing complementarity between nations and common trading tariffs.

CONCLUSION

In combination, the recent emergence of new infectious diseases, the associated surge of healthcare nationalism, and the prevalence of falsified and substandard drugs have strengthened substantially the net benefits of augmenting the capacity of developing countries to produce pharmaceutical products locally. Most previous efforts to do so have foundered. The chance of success in the future would be maximized by the adoption of five strategies: (a) clearing the legal space to ensure that local firms have the freedom to operate; (b) using "production triangles" (collaborations among developing-country governments, local firms, and developed-country pharmaceutical firms) to reduce regulatory impediments and to ensure that there exist adequate markets for locally produced products; (c) building the human capital base in developing countries through initiatives such as an international apprenticeship system to facilitate the acquisition by local firms of crucial technological know-how; (d) strengthening the legal and administrative apparatus for preventing the dissemination in developing countries of substandard and falsified drugs; and (e) relying on regional economic communities to create economies of scale and to ensure that medicines are made available to all residents of all developing countries, while also stimulating competition among networks of local firms. Initiatives that incorporate these recommendations could both save many lives and catalyze meaningful economic development.

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[150] *See, e.g., SADC Pharmaceutical Program,* S. AFR. DEV. CMTY., https://www.sadc.int/themes/health/pharmaceuticals/ (last visited Sept. 19, 2021).

[151] See Africa's Response to COVID-19, *supra* note 112, at 21.