Michigan Journal of International Law

Volume 43 | Issue 1

2022

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https://doi.org/10.36642/mjil.43.1.fostering

FOSTERING PRODUCTION OF PHARMACEUTICAL PRODUCTS IN DEVELOPING COUNTRIES

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INTRODUCTION

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.[1]

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.[2] 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 and flexibly 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 registering and maintaining the

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Suggestions made by Yochai Benkler, Urs Gasser, Felix Oberholzer-Gee, James Mickens, Margo Seltzer, Rebecca Tushnet, and Jonathan Zittrain considerably improved the paper. Francisco Collantes provided expert research assistance.

1. 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.

2. 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.

quality of drugs are less robust in developing countries, and thus that local production would lead to an increase in sub-standard drugs.[3]

As suggested by this debate, the problem of how best to facilitate access to medicines in developing countries is complex. What is clear, however, is that the existing system of pharmaceutical drug development and distribution is severely deficient with respect to the needs of developing countries.

In this article, we examine challenges to and potential benefits of local production as a response to the persistent deficit of affordable, high-quality pharmaceutical drugs in developing countries. Given the manifest underpreparedness for the COVID-19 pandemic in high-income countries, addressing the supply of vaccines to low-income countries and preparing for the next pandemic seems particularly urgent. We propose specific initiatives to improve the viability of local production consistent with well-established rules and precepts in industrial policy, trade policy, and human rights. An advantage of our approach is that it avoids the need for new modifications of the multilateral intellectual-property agreements that plagued efforts to address access to medicines during the HIV/AIDS pandemic and its aftermath. We conclude that enhanced local production of pharmaceuticals is necessary both to mitigate global public-health risks and to capture more fully the benefits of liberalized trade and regional integration. The proposals we advance address the salient concerns of both proponents and critics of local production.

Part I of this article discusses some recent developments that have altered the relative strength of the competing considerations, sharply increasing the likelihood that fostering local production in developing countries would be beneficial. Part II traces the checkered history of efforts to foster local production, distilling from the narrative some lessons concerning when such efforts have succeeded and when they have failed. Part III uses those lessons to propose five legal reforms and economic initiatives that might be employed to build local pharmaceutical production capacity to harness existing legal authority in regional treaties.

As we will try to show, adoption of the combination of legal and economic reforms we outline would clearly benefit the residents of developing countries. It is less clear that the slate of initiatives would provide a net benefit to the residents of developed countries. Indeed, shifting some capacity to the developing world to produce pharmaceutical products would likely

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3. *See* Frederick Abbott & Jerome H. Reichman, *The Doha Round's Public Health Legacy: Strategies for the Production and Diffusion of Patented Medicines under the Amended Trips Provisions*, 10 J. INT'L ECON. L. 921, 923–87 (2007) (discussing advocacy of augmented local production); *see also* ROGER BATE, CAMPAIGN FOR FIGHTING DISEASES, LOCAL PHARMACEUTICAL PRODUCTION IN DEVELOPING COUNTRIES: HOW ECONOMIC PROTECTIONISM UNDERMINES ACCESS TO QUALITY MEDICINES (2008); Warren Kaplan & Richard Laing, *Local Production of Pharmaceuticals: Industrial Policy and Access to Medicines* (The World Bank, Health, Nutrition & Population Discussion Paper No. 32036, 2005) *(*discussing skepticism of augmented local protection).

somewhat diminish the manufacturing jobs available in some developed countries, such as the United States, where production is currently concentrated. Whether that loss would be offset by the various ways in which the residents of developed countries would benefit from the improvement in overall global health and the associated acceleration of the global economic recovery is unclear.[4] However, any net economic losses suffered in developed countries would pale beside the number of lives saved in the developing world.[5]

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: first, the emergence of novel diseases that pose severe threats to the health of the residents of developing countries; second, the rise of healthcare nationalism; and third, the revelation of the scale of the transnational trade in substandard medicines. We address each of these events below, describing in brief the historical context, scope of the problem, and implications in the wake of the COVID-19 pandemic.

A. *The Emergence of Novel Diseases*

In its 2007 World Health Report,[6] the World Health Organization ("WHO") observed 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" 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."[7]

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

4. *But cf. Ending The COVID-19 Pandemic: The Need For A Global Approach*, WHO (2020), https://www.who.int/news/item/03-12-2020-global-access-to-covid-19-vaccines-estimated-to-generate-economic-benefits-of-at-least-153-billion-in-2020-21 (highlighting a recent study that suggests that the economic benefits over the next five years of an equitable system for distributing vaccines in all countries would be roughly $466 billion U.S. dollars, radically exceeding the total estimated cost of $38 billion U.S. dollars required to implement it).

5. *See Coronavirus: The economic impact – 10 July 2020*, U. N. Indus. Dev. Program (July 10, 2020), https://www.unido.org/stories/coronavirus-economic-impact-10-july-2020.

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

7. *See id.* at 35–57

and Central Africa, killing a few hundred people a year.[8] Then, in 2013, it suddenly began to spread, ravaging Guinea, Sierra Leone, and Liberia, and sending tendrils into other countries.[9] A delayed but ultimately fierce public-health initiative was able to halt the outbreak, but not before 28,000 people had died.[10] The threat that Ebola posed, particularly to the residents of African countries, is not fully appreciated. For example, Lagos, Nigeria, the largest city in Africa, with over twenty-one million residents, almost experienced an outbreak. Had that happened, hundreds of thousands of people would have died.[11] Furthermore, the danger of an Ebola pandemic has not disappeared. An outbreak in the Democratic Republic of the Congo between 2018 and July of 2020 killed another 2,300 people.[12] Additional outbreaks are likely.[13]

As readers are surely aware, the COVID-19 pandemic has been far more globally devastating. As of this writing, over 250 million people have been infected and over five million have died. Cold weather and the emergence of increasingly infectious variants of the virus are driving a fourth major wave of cases.[14]

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.[15] Sub-Saharan African countries,

8. 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).

9. Corum, *supra* note 8.

10. *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).

11. *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).

12. *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).

13. *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).

14. *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).

15. *See Mortality Analysis*, JOHNS HOPKINS CORONAVIRUS RES. CTR. https://coronavirus.jhu.edu/data/mortality (last visited Dec. 1, 2021).

which long enjoyed relatively low infection rates, are now severely threatened by new variants.[16]

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.[17]

For the same reason, developing countries are expected to recover economically more slowly than richer countries. The United States, China, and Russia already have per-capita gross domestic products ("GDPs") that exceed the levels they enjoyed prior to the pandemic. The economies of most other advanced countries will hit this milestone by the middle of 2022, while those of most poorer countries will not do so for another year or two.[18]

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 which most residents complied, and (c) the low average age of their populations.[19] 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.[20] 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.[21] Bodies piled up in the streets.[22] When a lockdown eventually managed to cap the disease in Guayaquil, it began to

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16. *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.

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

18. *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).

19. *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.

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

21. 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.

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

ravage Quito,[23] and the numbers of new cases continued to rise until May of 2021.[24]

The healthcare systems of most developing countries are no better than that of Ecuador.[25] 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.[26] Added to this are a shortage of doctors, prohibitive costs, and infrastructure deficits that make access to healthcare infeasible for the poorest.[27] 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; lack of refrigeration necessitates daily shopping;[28] and limited sanitation inhibits the adoption of protective measures.[29] These

23. *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.

24. *See* Cabrera & Kurmanaev, *supra* note 21; *Ecuador: Coronavirus Pandemic Country Profile*, OUR WORLD DATA, https://ourworldindata.org/coronavirus/country/ecuador (last visited Nov. 3, 2021).

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

26. STATE OF THE WORLD'S NURSING 2020, WHO (2020), https://apps.who.int /iris/bitstream/handle/10665/331673/9789240003293-eng.pdf; (The global shortage of nurses is estimated to be 6.6 million in 2016, with "[a]n estimated 5.3 million (89%) of that shortage concentrated in low- and lower middle-income countries." The greatest gaps in density of nursing personnel to population are in in the African, South-East Asia and Eastern Mediterranean regions and some countries in Latin America.).

27. *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.

28. *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/.

29. *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.

factors have compounded the impact of the Delta variant across Africa and Asia.[30] The most recent outbreak, provoked by the Omicron variant, poses an even more severe threat to the global south .[31]

B. *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. Drugs that appear capable of suppressing the disease are rapidly emerging. In the United States, the Food and Drug Administration ("FDA") granted an emergency-use authorization for a monoclonal antibody therapy that has shown promise in reducing the severity of COVID-19 infections.[33] Even more importantly, vaccines developed by Pfizer, Moderna, AstraZeneca, Gamalaya Institute, and Johnson & Johnson have proven to be both safe and efficacious. As a result, eight vaccines are now included in the World Health Organization's emergency use listing, and twenty-eight vaccines are approved for use by at least one national regulatory authority.[34]

The vaccine manufacturers have been expanding their capacity. Forecasts of manufacturing capacity for 2021 ranged between 9.5 and thirteen

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30. *See* Gabriele Steinhauser & Joe Parkinson, *Delta Variant of COVID -19 Surges Across Unvaccinated Africa*, WALL ST. J. (Jun. 28, 2021), https://www.wsj.com/articles/delta-variant-of-covid-19-surges-across-unvaccinated-africa-11624896315.

31. *See* Meru Sheel, *Could the Omicron Variant Have Been Avoided? It Could Set Back Vaccine Successes Around the World*, THE GUARDIAN (Nov. 29, 2021), https://www.theguardian.com/commentisfree/2021/nov/29/could-the-omicron-variant-have-been-avoided-it-could-set-back-vaccine-successes-around-the-world. *See* Selene Ghisolfi, Ingvild Almås, Justin Sandefur, Tillmann von Carnap, Jesse Heitner & Tessa Bold, *Predicted COVID -19 Fatality Rates Based on Age, Sex, Comorbidities, and Health System Capacity*, (Center for Glob. Dev. Working Paper, Paper No. 535, 2020), for examples of some predictions based on some of the listed variables concerning likely fatality rates in developing countries.

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 Coronavirus (COVID-19) Update: FDA Authorizes Monoclonal Antibody for Treatment of COVID-19*, FOOD & DRUG ADMIN., (Nov. 09, 2020), https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-monoclonal-antibody-treatment-covid-19.

34. *See COVID-19 Vaccine Market Dashboard*, U.N. CHILDREN'S FUND ["UNICEF"], https://www.unicef.org/supply/covid-19-vaccine-market-dashboard (last visited Nov. 24, 2021).

billion doses.[35] This would be sufficient to vaccinate most people globally (calculated as two doses per person).[36] However, it remains unclear as we near the end of the year to what extent these self-projections by large companies have materialized.[37] Meanwhile, the bulk of the supplies generated to date have been purchased by the governments of developed countries. The government of most developing countries lack the resources to make similar anticipatory purchases.[38] In some of the few instances in which developing countries have been able to place orders, they have not received the promised supplies on time.[39] The COVID-19 Vaccines Global Access ("COVAX") Facility, a commendable multilateral effort to create a more equitable system for allocating scarce supplies, has not been able to correct the imbalance.[40]

The net result: for the foreseeable future, most of the scarce supply of the vaccines will go to the residents of the United States or other developed countries. This situation has not gone unnoticed. Many activists and some government officials have advocated massive investments in drug manufacturing capacity combined with a commitment to make the products produced from such investments available with priority to developing countries.[41] But thus far such calls have gone largely unheeded. Barring substantial modifications of the policies of developed countries, "most people in low-income countries will be waiting until the end of 2022 or early 2023 for COVID-19 vaccinations."[42]

This forecast is not likely to change materially any time soon. 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

35. Andrew Taylor, Elina Urli Hodges, Jasmine Chigbu, Genevieve Muñoz, Blen Biru & Krishna Udayakumar, Deciphering the Manufacturing Landscape for Covid-19 Vaccines (Duke Glob. Health Innovation Ctr. Issue Brief, 2021).

36. *See Vaccine Manufacturing*, LAUNCH & SCALE SPEEDOMETER, https://launchandscalefaster.org/covid-19/vaccinemanufacturing (last visited Oct. 20, 2021).

37. *See* Padmashree Gehl Sampath, *Covid-19 Vaccines and the Case for a New Global Health Diplomacy*, 29 HARV. PUB. HEALTH REV. (2021) https://harvardpublichealthreview.org/29-article-gehlsampath/#_ftn1.

38. *See* Megan Twohey, Keith Collins & Katie Thomas, *With First Dibs on Vaccines, Rich Countries Have* "*Cleared the Shelves*," N.Y. TIMES (Dec. 18, 2020), https://www.nytimes.com/2020/12/15/us/coronavirus-vaccine-doses-reserved.html.

39. 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.

40. *See* UNICEF, *supra* note 37.

41. *See, e.g.,* Stephanie Nebehay*, G20 Leaders Urged to Provide Funds for COVID-19 Drugs, Vaccines, Tests,* REUTERS (Nov. 19, 2020), https://uk.reuters.com/article/uk-health-coronavirus-g20/g20-leaders-urged-to-provide-funds-for-covid-19-vaccines-drugs-tests-idUKKBN27Z2Q6?il=0.

42. *Will Low-Income Countries Be Left Behind When Covid-19 Vaccines Arrive?,* DUKE GLOB. HEALTH INST. (Nov. 9, 2020), https://globalhealth.duke.edu/news/will-low-income-countries-be-left-behind-when-covid-19-vaccines-arrive.

region.[43] 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.[44] That sentiment guided the U.S. government's response to the HIV pandemic,[45] has thus far dominated the actions of the Biden administration,[46] 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, we should expect a substantial lag between the widespread introduction of COVID-19 therapies and vaccines in developed countries and the widespread distribution of those same drugs in developing countries– and similar lags when we confront future pandemics. Particularly in light of the weak healthcare systems of most developing countries, such lags will likely give rise to large numbers of unnecessary deaths.[47]

C. *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

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43. *See* Kashmira Gander, *U.S. Only Country to Say It Should Have Covid-19 Vaccine First in Survey*, NEWSWEEK (Oct. 1, 2020), https://www.newsweek.com/us-covid-19-vaccine-survey-first-country-1535570; Florian Bieber, *Special Issue Article, Global Nationalism in Times of the Covid-19 Pandemic,* NAT'YS PAPERS (2020); Ivan Krastev & Mark Leonard, *Europe's Pandemic Politics: How the Virus Has Changed the Public's Worldview*, EUR. COUNCIL ON FOREIGN RELS. (June 2020).

44. Justin Hughes, *Biden Decision on COVID Vaccine Patent Waivers is more About Global Leadership than IP*, USA TODAY (May 6, 2021) ("During its first 100 days, the Biden administration was laser focused on vaccinating Americans. Critics complained about how unequal the global vaccine rollout was (and is), but Biden understood that whether you're an autocrat or a democratically-elected leader, your first duty is to protect your own citizens.").

45. 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.").

46. *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.

47. *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/.

in low-income countries were either falsified or substandard.[48] In middle-income countries, the number was barely lower: 10.4 percent.[49] 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.[50]

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.[51] The rates for tuberculosis drugs and antibiotics are higher—somewhere between six and seventeen percent.[52] Most likely to be falsified or substandard are anti-malarial drugs.[53] In recent years, substandard vaccines have also been distributed in distressing numbers.[54]

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,

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48. *See* WHO, A STUDY OF THE PUBLIC HEALTH AND SOCIOECONOMIC IMPACT OF SUBSTANDARD AND FALSIFIED MEDICAL PRODUCTS 7 (2017).

49. 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.

50. *See* Sachiko Ozawa, Daniel R. Evans, Sophia Bessias, Deson G. Haynie, Tatenda T. Yemeke, Sarah K. Liang & James E. Herrington, *Prevalence and Estimated Economic Burden of Substandard and Falsified Medicines in Low- and Middle-Income Countries: A Systematic Review and Meta-Analysis*, 4 JAMA NETWORK OPEN 1 (2018), https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2696509.

51. WHO, *supra* note 48, 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).

52. *See* Roger Bate, Paul Jensen, Kimberly Hess, Lorraine Mooney & Julissa Milligan, *Substandard and Falsified Anti-Tuberculosis Drugs: A Preliminary Field Analysis*, 17 INT'L J. TUBERCULOSIS & LUNG DISEASE 308 (2013); Theodoros Kelesidis & Matthew E. Falagas, *Substandard/Counterfeit Antimicrobial Drugs*, 28 CLINICAL MICROBIOLOGY REVS. 443, 451 (2015); Kayla Laerson, A.S. Kenyon, Tom A. Kenyon, Thomas Layloff & N.J. Binkin. S*ubstandard Tuberculosis Drugs on the Global Market and Their Simple Detection*, 5 THE INT'L J. TUBERCULOSIS & LUNG DISEASE 448 (2001); Moses Ocan, *Substandard Rifampicin Based Anti-Tuberculosis Drugs Common in Ugandan Drug Market,* 7 AFR. J. PHARMACY & PHARMACOLOGY 2428 (2013); UNITAID, TUBERCULOSIS MEDS.: TECH. & MKT. LANDSCAPE 32 (2014), WHO, *supra* note 48, at 7.

53. *See* WHO, *supra* note 48, at 7.; Ozawa et al., *supra* note 50.

54. 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.

who are especially vulnerable to the disease.[55] 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.[56] 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.[57]

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.[58] In the context of a pandemic, such vaccine skepticism exacerbates an already perilous public-health situation.

Last but not least, 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.[59] 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.[60] Most informed observers concur.[61] Officials associ-

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

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

57. *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 the consumption of poor-quality antimalarials causes 12,300 deaths a year in Nigeria).

58. *See* Kelesidis & Falagas, *supra* note 52, at 458.

59. *See* Bate et al., *supra* note 52, at 310; Kelesidis & Falagas, *supra* note 52, at 458; Sachiko Ozawa, Deson G. Haynie, Sophia Bessias, Sarah K. Laing, Emery Ladi Ngamasana, Tatenda T. Yemeke & Daniel R. Evans, *Modeling the Economic Impact of Substandard and Falsified Antimalarials in the Democratic Republic of the Congo,* 100 AM. SOC'Y TROPICAL MED. & HYGIENE 1149, 1149 (2019). The two factors emphasized in the text – failure to complete courses of treatment, and the presence of falsified and substandard drugs – are the most widely accepted explanations for the emergence of drug resistance in Tuberculosis. Some scientists, however, contend the causes are more complex. *See* Keertan Dheda, Tawanda Gumbo, Neel R Gandhi, Megan Murray, Grant Theron, Zarir Udwadia, G B Migliori & Robin Warren, *Global Control of Tuberculosis: From Extensively Drug-Resistant to Untreatable Tuberculosis,* 2 LANCET RESPIRATORY MED. 321, 324 (2014); WHO, GLOBAL SURVEILLANCE AND MONITORING SYSTEM FOR SUBSTANDARD AND FALSIFIED MEDICAL PRODUCTS 1, 6 (2017).

60. 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

ated with the International Criminal Police Organization ("Interpol") are doing their best to locate and punish the firms engaged in this practice.[62] In addition, China recently increased the penalties for distributing falsified medicines.[63] 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;[64] (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.[65] 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.[66] 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. THE HISTORY OF LOCAL PRODUCTION INITIATIVES

The roots of the current low manufacturing capacity in most developing countries, particularly in sub-Saharan Africa, lie in colonial-era policies designed to secure export markets for European goods and to ensure that the

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AAPS OPEN, Aug. 5, 2019, at 2, 6, https://link.springer.com/article/10.1186/s41120-019-0032-x. But informal reports are legion.

61. *See*, *e.g.*, ROGER BATE, PHAKE: THE DEADLY WORLD OF FALSIFIED AND SUBSTANDARD MEDICINES ch. 3 (Am. Enter. Inst. Press 2012).

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

63. *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/.

64. *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.

65. *See* WHO, *supra* note 48, at 7; *see also* Ozawa et. al., *supra* note 50, at 2.

66. *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.

colonies produced and exported agricultural commodities and minerals needed by European countries.[67] Despite some early successes in the 1920s, (in countries such as Congo, Zimbabwe, and Kenya), industrialization efforts in most colonial economies remained largely subject to the dynamics of the external markets to which they were structurally linked, creating limited opportunities for firms to respond to local needs.[68]

By the 1960s and 1970s (when most African countries first secured independence), many developing countries were characterized by underdeveloped infrastructure, limited capital savings, and lack of access to technologies.[69] Many of the countries in Africa and in the Americas initiated import-substitution policies,[70] but those policies failed quickly and had lingering adverse effects, particularly as international development agencies imposed strict structural adjustment requirements in exchange for access to capital.[71] A number of the conditions that marked these early industrialization efforts in developing countries—like limited qualified human capital, a weak entrepreneurial class, and lack of access to relevant technologies—remain persistent features of the current challenge of access to medicines.[72]

The complexity of modern processes for pharmaceutical manufacturing makes these longstanding limitations especially problematic. Producing a drug suitable for delivery to consumers typically involves the following steps:

(a) production of the active pharmaceutical ingredient ("API") that gives the drug its efficacy;

(b) production of the "excipients," the inactive ingredients that provide the vehicle or medium for the drug;

(c) combining APIs and excipients;

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67. *See* DANIEL R. HEADRICK, POWER OVER PEOPLES. TECHNOLOGY, ENVIRONMENTS AND WESTERN IMPERIALISM: 1400 TO THE PRESENT 8 (Princeton Univ. Press 2010).

68. This is explored at length in scholarship that explores the notion of center-periphery relationships in global trade. *See* GUNNAR MYRDAL, ECONOMIC THEORY AND UNDERDEVELOPED REGIONS 104 (1971); *see also* U.N. Dep't Econ. Affs., *The Economic Development of Latin America and its Principal Problems*, U.N. Doc. E/CN.12/89/Rev.l (Apr. 27, 2015).

69. *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.

70. Import substitution is an industrialization strategy employed by countries to facilitate the manufacture of capital goods by local companies. *See* GUNNAR MYRDAL, AN INTERNATIONAL ECONOMY: PROBLEMS AND PROSPECTS 268 (1956).

71. *See* Farhaad Noorbaksh & Alberto Paloni, *Structural Adjustment Programs and Industry in Sub-Saharan Africa: Restructuring or De-Industrialization?*, 33 J. DEVELOPING AREAS 549, 566–67 (1999).

72. *See* PADMASHREE GEHL SAMPATH, RECONFIGURING GLOBAL HEALTH INNOVATION 3 (2009); *see also* MAKING MEDICINES IN AFRICA: THE POLITICAL ECONOMY OF INDUSTRIALIZING FOR LOCAL HEALTH 1 (Maureen Mackintosh et al. eds., 2016).

(d) formulating the drug in final dosage form;

(e) packaging those formulations.[73]

These steps can be performed by different firms in different places. The most difficult and expensive stage of pharmaceutical drug production is typically the first–the production of the API. It is usually achieved through either chemical synthesis, fermentation, or extraction from biological materials. All three processes require considerable skill and advanced technologies. Partly for that reason, it is widely believed that the benefits—to both public health and economic development—of performing these processes locally are highest with respect to API production and diminish as one proceeds down the list.[74]

The multidimensional character of pharmaceutical manufacturing, plus the limitations of the available data, make it impossible to describe precisely the degree to which global pharmaceutical manufacturing capacity has been geographically concentrated over time. But as suggested above, all observers agree that most developing countries had little to no manufacturing capacity during the twentieth century.[75]

The exceptions to this situation arose from one of two circumstances. First, on occasion, pharmaceutical firms located in industrialized countries engaged in collaborations with firms in developing countries—either by entering into joint ventures with them or simply through outsourcing production in ways that involved the transfer of technology.[76] For example, in the 1970s, some Japanese pharmaceutical firms established factories in Indonesia. These included PT Takeda Indonesia ("Takeda"), PT Eisai Indonesia ("Eisai"), PT Tanabe Indonesia ("Mitsubishi Tanabe Pharmaceuticals"), PT Otsuka Indonesia ("Otsuka") and PT Meiji Indonesia ("Meiji").[77] Technology-transfer arrangements associated with these deals not only helped the local firms establish manufacturing capacity for formulations, but also supported the expansion of product portfolios over time and helped local companies meet the quality standards needed for export markets.[78]

Second, a few developing countries deliberately refused to extend patent protection to pharmaceutical products, thereby insulating local firms

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73. *See* Kaplan & Laing, *supra* note 3, at 3.

74. *Id.*

75. Karen Lashman Hall, *Pharmaceuticals in the Third World: An Overview* 36 (Population, Health & Nutrition Dep't, World Bank, Note No. 86-31, 1986).

76. U. N. Conf. on Trade and Dev. ["UNCTAD"] Secretariat, Local Production of Pharmaceuticals and Related Technology Transfer in Developing Countries: A Series of Case Studies by the UNCTAD Secretariat, at 8–9, U.N. Doc. UNCTAD/DIAE/PCB/2011 (2011).

77. *Id.*

78. *See* Richard Husada & Raymond R. Tjandrawinata, *The Healthcare System and the Pharmaceutical Industry in Indonesia*, in THE NEW POLITICAL ECONOMY OF PHARMACEUTICALS: PRODUCTION, INNOVATION AND TRIPS IN THE GLOBAL SOUTH 134, 140, 141 (Hans Löfgren & Owain David Williams eds., Palgrave Macmillan 2013).

from patent infringement suits, or even the presence of foreign competition.[79] The premier example was India, whose robust generic industry and economic progress during the 1970s was partly attributable to the combination of a large domestic market and a patent regime directed at encouraging pharmaceutical innovation for domestic public welfare.[80]

In sum, by late 1970s, a few developing countries contained firms that participated in some aspects of drug-making, but most developing countries did not. The sequence of efforts to alter this situation is described below. We classify them into early local production efforts (the first wave), and a reinforced set of local production initiatives by countries around the turn of the century (the second wave). We discuss the progress made until now in vaccine manufacturing separately, because the vaccines market has evolved differently.

A. *The First Wave*

Although desultory efforts to augment local pharmaceutical production capacity occurred as early as the 1960s, it was not until the late 1970s that the issue attracted widespread attention.[81] The most important source of its

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79. *See* Shamim S. Mondal & Viswanath Pingali, *Competition and Intellectual Property Policies in the Indian Pharmaceutical Sector*, 42 VIKALPA: J. FOR DECISION MAKERS 61, 62 (2017); William S. Greene, *The Emergence of India's Pharmaceutical Industry and Implications for the U.S. Generic Drug Market* 2–3 (U.S. Int'l Trade Comm'n, Paper No. 2007-05-A, 2007).

80. The Indian Patent Act of 1970 only allowed for process patents of seven years and did not grant product patents. The Patents Act, 1970, § 53 (India). This was based on a Report on the Revision of the Patent Law submitted by the Patent Law Amendment Commission in 1959, which noted that while non-Indian nationals held eighty to ninety percent of India's patents at the time, ninety percent of the patented products were not manufactured in the Indian territory. Patents thus allowed foreign companies to block the production of their patented drugs in India, leading to the stagnation of the Indian domestic pharmaceutical industry. *See* SHRI JUSTICE N. RAJAGOPALA AYYANGAR, GOV'T OF INDIA, REPORT ON THE REVISION OF THE PATENT LAW 274, 285 (1959). For a more general discussion of the impact of the 1970 Patent Act on the growth of the domestic pharmaceutical sector in India, *see* PADMASHREE GEHL SAMPATH, EMERGING ASPECTS OF ACCESS TO MEDICINES AFTER 2005: PRODUCT PATENT PROTECTION AND EMERGING STRATEGIES IN THE INDIAN PHARMACEUTICAL SECTOR 21– 22 (WHO, 2005), https://www.who.int/intellectualproperty/studies/PadmashreeSampathFinal.pdf?ua=1; *see also* Juan He*, Indian Patent Law and Its Impact on the Pharmaceutical Industry: What Can China Learn from India*, *in* INNOVATION, ECONOMIC DEVELOPMENT, AND INTELLECTUAL PROPERTY IN INDIA AND CHINA, ARCIALA SERIES ON INTELLECTUAL ASSETS AND LAW IN ASIA 251, 266 (Kung-Chung Liu & Uday S. Racherla eds., 2019).

81. Paragraph 23 of the of the Report of the International Conference on Primary Health Care states that "[p]rimary health care requires the development, adaptation, and application of appropriate health technology that people can use and afford, including an adequate supply of low-cost, good quality essential drugs, vaccines, biologicals and other supplies and equipment, as well as functionally efficient supportive healthcare facilities." WHO & U.N. Children's Fund, *Rep. of the International Conference on Primary Health Care,* ¶23, WHO Doc. CF/HST/1985-034/Anx.04/07 (Sept. 6–12 1978). This report prompted the recognition of the need to build local production in low- and middle-income countries World Health As-

enhanced visibility was a series of meetings in 1978 at the WHO, culminating in Resolution 31.32 of the Thirty-First World Health Assembly. The key passages of that resolution provided:

> The Thirty-first World Health Assembly . . . [r]ecognizing the importance of an adequate supply of essential drugs and vaccines to meet the real health needs of the people, through the implementation of national programs of health care; . . . Considering that local production of essential drugs and vaccines is a legitimate aspiration which developing countries have expressed on many occasions, and that considerable progress has been achieved in some countries; Considering that the establishment of a pharmaceutical industry in countries where it does not exist requires transfer of appropriate technology and investment, and that most developing countries cannot afford this without international cooperation; . . . Requests the Director-General: . . . (4) to ensure collaboration with the United Nations Development Programme, the World Bank and regional development banks and funds, the United Nations Children's Fund and the United Nations Industrial Development Organization with a view to ensuring that technical expertise and financing are made available to interested countries for establishing, wherever feasible, local production corresponding to their health needs, it being understood that financings should be independent of the source of technology; . . .

The subsequent Alma Ata Declaration on Primary Health Care, signed by 134 member states of the WHO, also emphasized the advantages of local production.[82]

Spurred by these initiatives, several United Nations ("U.N.") agencies began to address the question of local production. Discussions focused on stimulating technology transfer[83] and building domestic production capaci-

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sembly Res. 31.32 (May 23, 1978), *reprinted in* WHO, THIRTY-FIRST WORLD HEALTH ASSEMBLY: VERBATIM RECORDS OF PLENARY MEETINGS 451 (May 8–24, 1978).

82. WHO & UNICEF, *Rep. of the International Conference on Primary Health Care,* ¶93, WHO Doc. CF/HST/1985-034/Anx.04/07 (Sept. 6-12, 1978) states, in pertinent part that:

> In developing a supply system, consideration has to be given both to cost and to national and local production as part of overall development. For example, it may be cheaper to buy certain items abroad, but economically more productive in the long run to produce them within the country. This principle may also apply to the alternatives of national purchasing and local production.

83. UNCTAD, Compendium of International Arrangements on Transfer of Technology: Selected Instruments, U.N. Doc. UNCTAD/ITE/IPC/Misc.5 (2001); UNCTAD, Transfer of Technology, U.N. Doc. UNCTAD/ITE/IIT/28 (2001); UNCTAD, Facilitating the Transfer of Technology to Developing Countries: A Survey of Home Country Measures, U.N. Doc. UNCTAD/ITE/IPC/2004/5 (2004).

ties at the firm and sector level.[84] Efforts by developing countries to use tax rebates, subsidies, and grants for research and development to incentivize local production intensified.[85]

The results were disappointing. As of 1990, only five developing countries—India, Brazil, Mexico, Egypt, and Argentina—had established significant local capacity for pharmaceutical production. [86] A few others, such as Colombia, and Jordan, have since followed suit.[87] Reasons for this disappointing outcome include, but are not limited to: poor institutional support, low access to technologies, low degrees of industrial infrastructure, a lack of technical skills, and low finances available to private firms in these countries.[88] A 1986 report by the World Bank concluded that only around eleven percent of global pharmaceutical production was being undertaken in developing countries, while over eighty percent occurred in six industrialized countries.[89]

B. *The Second Wave*

At the turn of the century, there was a second round of initiatives in the developing world. Some occurred at the national level. For example, the Government of Uganda enacted a National Drug Policy in 2002.[90] One of its objectives was "to maximize appropriate procurement of locally produced essential drugs" and to "encourage local pharmaceutical manufacturers to produce essential drugs at competitive prices and encourage procurement agencies to source available essential drugs locally in order to support the local industry."[91] Uganda's subsequent National Strategic Plan (2007–2012)

84. *See* U. N. INDUSTRIAL DEVELOPMENT ORGANIZATION ["UNIDO"], BOOSTING PHARMACEUTICAL PRODUCTION CAPACITY (2019), https://www.unido.org/sites/default/files/files/2019-01/Boosting_Pharmaceutical_Production.pdf (tracing the history of UNIDO's work in this area).

85. *See e.g.,* Michael Kremer*, Pharmaceuticals and the Developing World,* 16 J. ECON. PERSPS. 67 (2002). *see also* ROGER BATE, LOCAL PHARMACEUTICAL PRODUCTION IN DEVELOPING COUNTRIES: HOW ECONOMIC PROTECTIONISM UNDERMINES ACCESS TO QUALITY MEDICINES, 3-4 (Int'l Pol'y Network, 2008).

86. Hall, *supra* note 75.

87. *See* UNCTAD, Local Production of Pharmaceuticals and Related Technology Transfer of Pharmaceuticals, 89, 193, U.N. Doc. UNCTAD/DIAE/PCB/2011 (2011).

88. *Id.*

89. Hall, *supra* note 75, at 35. For a slightly higher estimate, see Edward Elgar, Robert Ballance, János Pogany & Helmut Forstner, The World's Pharmaceutical Industries: An International Perspective On Innovation, Competition, And Policy 24–25 (1992) (concluding that 20% of local production occurs in the developing world).

90. MINISTRY HEALTH, NATIONAL DRUG POLICY (Oct. 2002) (Uganda), http://lbrary.health.go.ug/sites/default/files/resources/Uganda%20National%20drug%20Policy%202002.pdf.

91. *Id.* § 3.5.

proposed local production of HIV/AIDS drugs as a priority.[92] Similarly, in 2016, Ethiopia offered firms a range of incentives to encourage local pharmaceutical production.[93] Its government invested in a "Health Sector Development Plan" and partnered with the WHO to launch the National Strategy and Plan of Action for Pharmaceutical Manufacturing Development, which emphasized domestic production and the strengthening of the country's national medicine regulatory system.[94]

Other initiatives arose at the regional level. For example, in 2005, African heads of states pressed the African Union to boost pharmaceutical production on the continent.[95] The ultimate outcome was the Pharmaceutical Manufacturing Plan for Africa ("PMPA"), adopted in 2008.[96] Since then, the African Union Conference of Ministers of Industry ("CAMI") has prioritized the local pharmaceutical sector as a potential driver of industrial development and incorporated the PMPA into the Accelerated Industrial Development of Africa ("AIDA") Plan of Action.[97] This initiative has led to the creation of a reasonably detailed menu of tactics from which African countries are encouraged to draw when seeking to boost local manufacturing capacity.[98] The menu includes:

1. a Good Manufacturing Practice ("GMP") road map and associated risk assessment of WHO's Essential Medicines List ("EML");

2. a syllabus for developing the human resources required for the long-term sustainability of the industry;

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92. UGANDA AIDS COMM'N, THE NATIONAL HIV AND AIDS STRATEGIC PLAN (2020) (updating and replacing the 2011-2014 National HIV & AIDS Strategic Plan).

93. *See* TSIGE GEBRE-MARIAM, KEDIR TAHIR & SOLOMON GEBRE-AMANUEL, MAKING MEDICINES IN AFRICA 65–84 (Maureen Mackintosh, Geoffrey Banda, Paul Tibandebage and Watu Wamae, 2016).

94. *Drive to Increase Local Production of Drugs Presents Vast Opportunities for Ethiopian Pharmaceuticals*, AFR. HEALTH (June 4, 2016), https://africa-health.com/news/drive-to-increase-local-production-of-drugs-presents-vast-opportunities-for-ethiopian-pharmaceuticals.

95. Janet Byaruhanga, How Africa can Manufacture to Meet its own Pharmaceutical Needs: The Pharmaceutical Manufacturing Plan for Africa Provides a Roadmap, AFR. RENEWAL (Sept. 4, 2020), https://www.un.org/africarenewal/magazine/september-2020/how-africa-can-manufacture-meet-its-own-pharmaceutical-needs.

96. Afr. Union, Fourth Ordinary Session: Decisions and Declarations, Nos. Assembly/AU/Dec.55-72 (IV), Assembly/AU/Decl.1-2 (IV) (Jan. 30–31, 2005).

97. *See Review of Policies and Strategies for The Pharmaceutical Production Sector In Africa*, U.N. ECON. COMM'N FOR AFR. & AFR. UNION (May 2020), https://archive.uneca.org/publications/review-policies-and-strategies-pharmaceutical-production-sector-africa.

98. PHARMACEUTICAL MANUFACTURING PLAN FOR AFRICA, AFR. UNION (2012), https://au.int/sites/default/files/pages/32895-file-pmpa_business_plan.pdf.

3. a Business Linkages Platform (which would also assist companies in establishing relationships with local, regional, and international players in order to increase product ranges, mobilize investment, etc.); and

4. technical assistance to enable regulators to devise and implement organizational development plans.[99]

Prior to the COVID-19 pandemic, the African Union had already cited the need to "formulate a plan of action . . . to facilitate increased drug manufacturing in the region and to bolster research and development ('R&D')."[100] In the wake of the pandemic, there have been increased calls at the national, regional, and multilateral level for local production in Africa,[101] along with unprecedented healthcare-related inventions by domestic inventors.[102] Some notable inventions include a digital inventory to monitor the availability of ventilators and respirators in hospitals, developed by Lifebank (a Nigerian health-care technology and logistics start-up); a contactless solar-powered handwashing station developed by a young entrepreneur in Ghana; a mobile sprayer produced by Nigeria's Agency for Science and Engineering Infrastructure ("NASENI");[103] and a ventilator produced in Egypt using designs developed originally by Medtronic that had been released (complete with technical information, printed circuit board drawings and 3-D CAD files) via a stylized open-source license.[104] Alongside these innovations were policy initiatives aimed at strengthening overall regional capacity for drug production. Recently, ten African countries, led by Ethiopia, asked the WHO

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99. *Id.*

100. *Measures to Boost Drug Production, Scientific Research Highlighted in AU Summit*, GLOB. INSIGHT (Oct.15, 2007), https://ihsmarkit.com/country-industry-forecasting.html?ID=106597556.

101. Kerry Cullinan, *African Countries Appeal for WHO Support for Expanded Local Production of Medicines, Diagnostics & Vaccines*, HEALTH POL'Y WATCH (Jan. 22, 2021), https://healthpolicy-watch.news/african-countries-who-local-production-medicines-vaccines/.

102. *COVID-19 Spurs Health Innovation in Africa*, WHO REG'L OFF. FOR AFR. (Oct. 29, 2020), https://www.afro.who.int/news/covid-19-spurs-health-innovation-africa. *See also* U.N.D.P., AFRICA INNOVATES: 50 HOMEGROWN AFRICAN INNOVATORS TACKLING COVID-19, U.N. DEV. PROGRAMME (2020), https://reliefweb.int/sites/reliefweb.int/files/resources/Africa%20innovates%20-%2050%20homegrown%20African%20innovations%20tackling%20COVID-

103. *See* Aneta Felix, *Onu to Unveil First Nigerian-Made Ventilator Today*, TV360 NIGERIA (Apr. 7, 2020), https://www.tv360nigeria.com/onu-to-unveil-first-nigerian-made-ventilator-today/ (reporting that NASENI also produced the first locally made ventilators.); *see also* Yomi Kazeem, *Tech Startups are Joining Nigeria's Fight Against Coronavirus*, QUARTZ AFR. (Mar. 30, 2020), qz.com/africa/1828438/coronavirus-nigerian-tech-startups-step-up-to-assist-government/; *see also* Zaina Adamu, *A Solar-Powered Hand-Washing Basin Encourages Personal Hygiene in Ghana Amidst Coronavirus*, CNN (May 11, 2020), http://edition.cnn.com/2020/05/09/africa/ghana-coronavirus-handwash/index.html.

104. *Our Ventilator Specifications. Your Ingenuity,* MEDTRONIC, https://www.medtronic.com/us-en/e/open-files.html (last visited Oct. 21, 2021).

"for support to develop 'national policies and evidence-based comprehensive strategies and plans of action for local production.'"[105]

Finally, several international agencies, both governmental and nongovernmental, have expressed support for local production initiatives.[106] For example, in 2007 the European Parliament issued a resolution urging increased pharmaceutical-related transfers of technology and capacity-building for local production of medicines in developing countries in line with Element 4 of the Global Strategy Plan of Action ("GSPoA").[107] This has led to expanded assistance activities from agencies such as the United Nations Industrial Development Organization ("UNIDO"), the United Nations Development Program ("UNDP"), and the United Nations Conference on Trade and Development ("UNCTAD").[108]

These various second-wave initiatives have had some impact. For example, Ethiopia continues to invest in institutional, policy, and structural changes to enhance access to medicines and overall healthcare.[109] In 2007, Ethiopia founded the Pharmaceutical Fund and Supply Agency ("PFSA") to manage the country's supply chain and determine strategic plans to improve the availability of medicines throughout the country. In 2010, PFSA implemented the Integrated Pharmaceuticals Logistics System ("IPLS") to improve the management of pharmaceutical supplies through more refined record keeping, storage, and availability. IPLS provided trainings to improve communication between supervisors and suppliers to better monitor stocks of supplies. By 2014, the availability of essential medicines in Ethiopia had increased from sixty-five percent to eighty-nine percent, nearly

105. *See* Cullinan, *supra* note 101.

106. Local production of pharmaceuticals has been a longstanding emphasis of the United Nations Industrial Organization. *See* BATE, *supra* note 85.

107. Implementation, Monitoring and Evaluation for GSPOA, WHO Dep't Pub. Health, Innovation & Intell. Prop. (2010), https://www.who.int/phi/documents/MEforWHA.pdf?ua=1.

108. *Id.* (identifying UNCTAD as a stakeholder for action on the issue of transfer of technology in local production of pharmaceuticals and health products in developing countries, culminating in a series of reports and technical assistance activities). *See, e.g.,* UNCTAD, Toolbox for Policy Coherence in Access to Medicines and Local Pharmaceutical Production, U.N. Doc. UNCTAD/DIAE/PCB/2017/2 (2017). Producing pharmaceutical-sector development strategies for implementation in a wide range of countries (such as Ghana, Vietnam, Kenya and Zimbabwe) has been central to UNIDO's work in recent years. *See* FORMULATING NATIONAL STRATEGIES FOR PHARMACEUTICAL SECTOR DEVELOPMENT, UNIDO (Mar. 1–2, 2018), https://www.unido.org/sites/default/files/files/2018-03/Shahid%20Hasan_UNIDO_%20Sector%20Development%20Strategies_01032018_Bonn.pdf.

109. *See* Elizabeth Annis & Hannah Ratcliffe, *Strengthening Primary Health Care Systems to Increase Effective Coverage and Improve Outcomes in Ethiopia,* PRIMARY HEALTH CARE PERFORMANCE INITIATIVE, improvingphc.org/strengthening-primary-health-care-systems-increase-effective-coverage-and-improve-outcomes-ethiopia (last visited Oct. 21, 2021); *see also Drive to Increase Local Production of Drugs Presents Vast Opportunities for Ethiopian Pharmaceuticals*, AFR. HEALTH (June 4, 2016), https://africa-health.com/news/drive-to-increase-local-production-of-drugs-presents-vast-opportunities-for-ethiopian-pharmaceuticals.

reaching the Health Systems Development Programme goal of 100%. Ethiopia is currently working to expand its warehouse and cold-chain capacity for storing and distributing pharmaceuticals and has introduced larger trucks to distribute supplies in an integrated supply chain. Health facilities at all levels are now able to monitor their supply and demand and adjust supply requests accordingly.[110] This progress is in addition to the prioritization of the pharmaceutical sector in Ethiopia's Growth and Transformation Plan II.[111]

In Africa at large, there are now roughly 600 firms engaged in the production of pharmaceutical products. Especially large numbers can be found in Nigeria (157), Ghana (thirty-three), and Morocco (forty).[112] These numbers are misleading, however. The majority of these firms are not manufacturing APIs; instead, they are either combining imported APIs and excipients or simply repackaging imported combinations. API production remains heavily concentrated in China, with some capacity in the United States, India, and Japan.[113]

Even the success stories turn out, upon close examination, to be discouraging. For example, starting in 1989, the government of Ghana offered local pharmaceutical manufacturers several financial incentives, including

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110. AFR. HEALTH, *supra* note 109.

111. *See* INVESTING IN ETHIOPIA: THE FUTURE PHARMACEUTICAL HUB OF AFRICA, ETH. INV. COMM'N (Mar. 2018), https://www.unido.org/sites/default/files/files/2018-03/Aida%20Bayissa%2C%20Ethiopian%20Investment%20Commission_01032018%20Bonn.pdf. One of the authors served as an advisor to the Ethiopian government at the time of the second Growth and Transformation Plan, which introduces the concept of pharmaceuticals.

112. *See* Michael Conway, Tania Holt, & Adam Sabow, *Should Sub-Saharan Africa Make its Own Drugs?*, MCKINSEY (Jan. 10, 2019), https://www.mckinsey.com/industries/public-and-social-sector/our-insights/should-sub-saharan-africa-make-its-own-drugs.

113. *Id.* Estimates suggest that China accounts for forty percent of all global API production, having driven out many other countries from the API business by competing on cost margins. *See* Tom Hancock & Wang Xueqiao, *China Drug Scandals Highlight Risks to Global Supply Chain*, FIN. TIMES (Aug. 6, 2018), https://www.ft.com/content/38991820-8fc7-11e8-b639-7680cedcc421. Approximately eighty percent of all APIs to make drugs in the USA are estimated to be imported from China and India, but India itself depends on China for up to seventy-five percent of its own API supply. Yanzhong Huang, *U.S. Dependence on Pharmaceutical Products from China*, COUNCIL FOREIGN RELS. BLOG (Aug. 14, 2019), https://www.cfr.org/blog/us-dependence-pharmaceutical-products-china. The United States still produces a significant share of global APIs and supplies twenty-eight percent of its own needs. *Safeguarding Pharmaceutical Supply Chains in a Global Economy: Hearing Before H. Comm. on Energy & Com., Subcomm. on Health*, 116th Cong. (2019) (Testimony of Dr. Janet Woodcock, Dir. U.S. Food & Drug Admin. Ctr. for Drug Evaluation & Rsch). India accounts for seven percent of global API production as of 2020. Jerin Jose Cherian, Maju Rahl, Shubhra Singh, Sanapareddy Eswara Reddy, Yogendra Kumar Gupta, Vishwa Mohan Katoch, Vijay Kumar, Sakthievel Selvaraj, Payal Das, Raman Raghunathrao Gangakhedkar, Amit Kumar Dinda, Swarup Sarkar, Puroshottambhai Devshibhai Vaghela & Balram Bhargava, *India's Road to Independence in Manufacturing Active Pharmaceutical Ingredients: Focus on Essential Medicines*, ECONS., May 3, 2021, at 2.

an exemption from corporate taxes in the first three years after establishment, exemption of import duties on sixty-six important ingredients, and an import ban on forty-four medicines that were earmarked for local production. [114] Thanks to these incentives, the country was able to develop a relatively large local pharmaceutical sector. [115] Several estimates suggest the pharmaceutical sector has a thirty percent share in the market. [116] However, this achievement obscures the limited product choice amongst local companies, low capacity utilization, and low technological capacity, resulting in an inability to manufacture APIs or expand production into new therapeutic categories. [117] South Africa took a different tack, relying on competition law to try to force international pharmaceutical firms to grant licenses to local manufacturers. [118] Although it had some impact, it too has failed to enhance the capacity of local firms to produce their own APIs.

C. *Vaccine Manufacturing*

The vaccine sector has developed differently. Since 2000, a significant percentage of global vaccine production has shifted to some developing countries. According to the WHO, of the eighty-four vaccine manufacturers worldwide, sixty-five are located outside of the European Union and the United States. [119]

This statistic is especially striking because most vaccines have complex components, requiring larger scale and more advanced facilities to produce than small-molecule medicines. [120] Vaccine manufacturing typically in-

114. *See* David Nguyen-Thanh & Christoph Strupat, *Is the Burden Too Small? Effective Tax Rates in Ghana* 6 (RUHR Econ. Papers, Paper No. 389, 2013); ARIANE MCCABE, ANDREAS SEITER, AISSATOU DIACK, CHRISTOPHER H. HERBST, SHEILA DUTTA, & KARIMA SALEH, PRIVATE SECTOR PHARMACEUTICAL SECTOR SUPPLY AND DISTRIBUTION CHAINS: GHANA, MALI AND MALAWI 16–17 (World Bank, 2009), https://pdfs.semanticscholar.org/4b7c/82b2d7ead291d498faff43d9d020e138aa77.pdf.

115. MCCABE ET AL., *supra* note 114, at 16.

116. *Id.* at 36.

117. ANDREAS SEITER & MARTHA GYANSA-LUTTERODT, POLICY NOTE: THE PHARMACEUTICAL SECTOR IN GHANA 12 (World Bank, Nov. 2009).

118. *See, e.g.*, UNCTAD'S INTELL. PROP UNIT, NOTE ON HAZEL TAU & OTHERS V. GLAXOSMITHKLINE, BOEHRINGER INGELHEIM & OTHERS, 2002: SOUTH AFRICAN COMPETITION COMMISSION, COMPETITION COMMISSION CASE NO. 2002SEP226, at 1, https://unctad.org/ippcaselaw/sites/default/files/ippcaselaw/2020-12/Hazel%20Tau%20SA%20Competition%20Commission%20v.%20GSK%20BI%20et%20al%202002.pdf ("The complainants alleged that the respondents had both abused their dominant positions by charging excessive prices for their patented ARVs to the detriment of consumers, in violation of section 8(a) of the South African Competition Act.") (last visited Dec 6, 2021).

119. *Market Information for Access to Vaccine*, UNCTAD DEP'T IMMUNIZATION, VACCINE & BIOLOGICALS, https://www.who.int/immunization/programmes_systems/procurement/mi4a/platform/module1/en/ (last visited Nov. 16, 2020).

120. *See, e.g.*, Roxanne Khamsi, *If a Coronavirus Vaccine Arrives, Can the World Make Enough?*, NATURE (Apr. 9, 2020), https://www.nature.com/articles/d41586-020-01063-8; Julie Steenhuysen & Kate Kelland, *Vaccine Makers Face Biggest Medical Manufacturing Chal-*

volves: (a) bulk production of purified antigens; (b) formulation using adjuvants that enhance immune responses, stabilizers to enhance potency, and preservatives for multi-vial preparations; and (c) packaging and distribution. [121] The know-how needed to engage in bulk antigen production is more challenging than that needed for pharmaceutical production for several reasons. Antigens, although comparable to APIs in the drug-production process, require a range of biological competencies, and need highly specialized production facilities that are dictated by the vaccine/s in question.[122] Often, they cannot all be produced with the same methods or the same kinds of equipment, or even in the same facility.[123] The antigens at the heart of the newest vaccines are especially difficult to produce.[124] In addition, the regulatory processes applicable to vaccines are more stringent than those for most therapies, requiring producers even of generic versions to conduct clinical trials to demonstrate safety and efficacy.[125]

These barriers are sometimes exacerbated by intellectual property rights. In contrast to the older vaccines, which have long been outside of patent protection,[126] the newest vaccines enjoy generous shields. Perhaps most importantly, the new vaccine platforms for COVID-19 (mRNA and DNA)

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lenge in History, REUTERS (June 25, 2020), https://www.reuters.com/article/us-health-coronavirus-vaccines-manufactu/vaccine-makers-face-biggest-medical-manufacturing-challenge-in-history-idUSKBN23W1ND; CORMAC O'SULLIVAN, PAUL RUTTEN, & CASPAR SCHATZ, WHY TECH TRANSFER MAY BE CRITICAL TO BEATING COVID-19 (McKinsey, July 2020), https://www.mckinsey.com/~/media/McKinsey/Industries/Pharmaceuticals%20and%20Medical%20Products/Our%20Insights/Why%20tech%20transfer%20may%20be%20critical%20to%20beating%20COVID%2019/Why-tech-transfer-may-be-critical-to-beating-COVID-19-vF.pdf.

121. Phillip L. Gomez & James M. Robinson, *Vaccine Manufacturing*, *in* PLOTKIN'S VACCINES 52 (Stanley A. Plotkin et al. eds., 7th ed. 2017).

122. *See, e.g.,* Morgan Brisse, Sophia M. Vrba, Natalie Kirk, Yuying Lian, & Hinh Ly, *Emerging Concepts and Technologies in Vaccine Development*, FRONTIERS IMMUNOLOGY, Sept. 2020, at 1.

123. Stanley Plotkin, James M. Robinson, Gerard Cunningham, Robyn Iqbal, & Shannon Larsen, *The Complexity and Cost of Vaccine Manufacturing – An Overview*, 35 VACCINE 4064 (2017).

124. *See* Richard Strugnell, Fred Zepp, Anthony Cunningham, & Terapong Tantawichien, *Vaccine Antigens*, 1 UNDERSTANDING MOD. VACCINES PERSPS. VACCINOLOGY 61, 70–71 (2011). Vaccine antigens refer to either whole live pathogens (modified to reduce their virulence), individual pathogen components (such as protein or polysaccharides), or the genetic material of the pathogen (that is, "naked" DNA/RNA) which can direct the production of the vaccine antigen in the recipient. *Id.* at 64.

125. UNIDO & WHO, WHITE PAPER: ESTABLISHING MANUFACTURING CAPACITY FOR VACCINES 7 (2017). *See also* Fernando Gomollón, *Biosimilars: Are They Bioequivalent?*, 32 DIGESTIVE DISEASES 82, 82–87 (2014).

126. MARTIN FRIEDE, PRESENTATION AT THE WORLD HEALTH ORGANIZATION TECHNOLOGY TRANSFER WORKSHOP, INTELLECTUAL PROPERTY AND LICENSE MANAGEMENT WITH RESPECT TO VACCINES (2010), https://www.who.int/phi/news/Presentation15.pdf.

are protected by multiple patents, and the associated manufacturing processes and genomic information are protected through trade secrets.[127]

What accounts for the expansion of vaccine manufacturing in the developing world despite this combination of impediments? In retrospect, two factors seem to have been crucial. The first was a deliberate effort by the Global Alliance for Vaccines and Immunizations ("GAVI"), the United Nations Children's Emergency Fund ("UNICEF"), and the Gates Foundation to diversify the sources of the vaccines they purchase and then distribute to developing countries.[128] The result was that several developing-country vaccine manufacturers were encouraged to participate in global procurement processes.[129] One recent manifestation of the benefits of such vaccine manufacturing capacity in developing countries was the decision by AstraZeneca (UK and Sweden) to license the Serum Institute of India to manufacture AstraZeneca's COVID-19 vaccine.[130] Since then AstraZeneca has signed agreements for production with Fiocruz (Brazil), BioKantai (China), Liomont (Mexico) and Siam Bioscience (Thailand), apart from several companies in high income countries.[131]

The second factor was a few influential technology-transfer agreements. For example, technologies necessary to produce conjugate Hib (Haemophilus influenzae type B) vaccines were transferred by the Netherlands Vaccine Institute ("NVI") to three Indian manufacturers and by GlaxoSmithKline ("GSK") to a Brazilian manufacturer.[132] Similarly, in the late 1990s, the technology underlying the recombinant Hepatitis B vaccine was transferred to the Republic of Korea, India, and Brazil.[133] Both resulted in sharp drops in the prices of the vaccines in the developing world. The WHO estimates that, between 1990 and 2010, eleven developing countries actively partici-

127. Mario Gaviria & Burcu Kilic, *A Network Analysis of COVID-19 mRNA Vaccine Patents*, 39 NATURE BIOTECH. 546, 546–48 (2021); *see also* Ana Santos Rutschman, *The COVID-19 Vaccine Race: Intellectual Property, Collaboration(s), Nationalism and Misinformation*, 64 WASH. UNIV. J.L. & POL'Y 12, 19 (2020); Ana Santos Rutschman, *The Intellectual Property of Vaccines: Takeaways from Recent Infectious Disease Outbreaks*, 118 MICH. L. REV. ONLINE 170 (2020).

128. *See* Shawn A. N. Gilchrist & Angeline Nanni, *Lessons Learned in Shaping Vaccine Markets in Low Income Countries: A Review of the Vaccine Market Segment Supported by the GAVI Alliance*, 28 HEALTH POL'Y & PLAN. 838, 838–40 (2013).

129. *Id.* at 841.

130. *See AstraZeneca Takes Next Steps Towards Broad and Equitable Access to Oxford University's COVID-19 Vaccine*, ASTRAZENECA (June 4, 2020), https://www.astrazeneca.com/media-centre/press-releases/2020/astrazeneca-takes-next-steps-towards-broad-and-equitable-access-to-oxford-universitys-covid-19-vaccine.html.

131. *See Vaccine Manufacturing*, *supra* note 36.

132. Michael Beurret, Ahd Hamidi, & Hans Kreeftenberg, *Development and Technology Transfer of Haemophilus Influenzae Type B Conjugate Vaccines for Developing Countries*, 30 VACCINE 4897–4906 (2012).

133. WHO, INCREASING ACCESS TO VACCINES THROUGH TECHNOLOGY TRANSFER AND LOCAL PRODUCTION 8–13 (2011).

pated in vaccine technology-transfer agreements.[134] India was the recipient of technology in twenty-six such agreements, followed by China (eighteen) and Brazil (ten).[135] The net effect was a significant expansion of the manufacturing capacity of countries in the developing world.[136]

Once again, however, the situation turns out to be less encouraging than it first appears. Most of the vaccines manufactured in developing countries today use older or generic vaccine technologies and consequently generate only modest profits.[137] As a result, although in unit terms, seven companies from developing countries account for eighty percent of all vaccine sales,[138] before the pandemic, four companies producing branded products dominated the global market, estimated at $30.6 billion U.S. dollars in 2018.[139] Pfizer's Prevenar Vaccine for pneumonia, Sanofi's Vaxigrip for Influenza, Pfizer's Prevnar13 vaccine for pneumonia, Merck's Gardasil for the Human Papillomavirus ("HPV"), and GSK's Shingrix vaccine for shingles accounted for the bulk of these revenues.[140] The COVID-19 vaccine manufacturing landscape recently prepared by the Coalition for Epidemic Preparedness Innovations ("CEPI") confirms this capacity divide. The landscape shows that the capacity to manufacture more complex vaccines (using DNA and viral vector technologies) is highly restricted worldwide, and lists India as the only country in the developing world currently with the capacity to manufacture vaccines that rely on such technologies.[141]

Recent developments underscore to some extent the difficulties in navigating intellectual property rights in new vaccines and shed some light on how they might impact the sector. The WHO has set up a COVID-19 Technology Access Pool ("C-TAP") to facilitate the sharing of technologies for

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134. *Id.* at 11–12.

135. *Id.* at 12.

136. Donald P. Francis, Yu-Ping Du, & Alexander R. Precioso, *Global Vaccine Supply. The Increasing Role of Manufacturers from Middle Income Countries.* 32 VACCINE 5259 (2014).

137. Older vaccines, such as the HiB vaccine, can also be subject to intellectual property protection, but these have not posed significant barriers for technology transfer. *See* WHO, *supra* note 133, at 6; FRIEDE, *supra* note 126, at 5.

138. UNCTAD DEP'T IMMUNIZATION, VACCINE & BIOLOGICALS, *supra* note 119.

139. Padmashree Gehl Sampath & Jon Pearman, *Local Production of COVID-19 Vaccines: A Strategy for Action*, GLOB. POL'Y J. (Aug. 23, 2021), https://www.globalpolicyjournal.com/articles/health-and-social-policy/local-production-covid-19-vaccines-strategy-action.

140. *Id.* at 4–5. Other estimates report that Merck's Gardasil alone generated more than $3 billion USD in 2018. *See* Trefis Team & Great Speculations, *Merck's $3 Billion Drug Jumped to 4x Growth over Previous Year*, FORBES (Oct. 4, 2019), https://www.forbes.com/sites/greatspeculations/2019/10/04/mercks-3-billion-drug-jumped-to-4x-growth-over-previous-year/?sh=3fca61986294.

141. COALITION FOR EPIDEMIC PREPAREDNESS INNOVATIONS, COVID-19: MANUFACTURING SURVEY RESULTS ANALYSIS 4, 7 (2020) (comparing capacity for vaccine technologies by country). For a comparison of capacity across different vaccine technologies, see discussion *supra* p. 4.

COVID-19 treatments, including vaccines, but private companies have preferred to enter into voluntary licensing arrangements.[142] The mRNA Hub Initiative of the WHO, in partnership with the Government of South Africa, to promote the first mRNA production facility for COVID-19 vaccines in Africa[143] was launched without the support of larger companies willing to share technology for vaccines.[144] Although it was initially envisaged that Pfizer-BioNTech would join the initiative to transfer technology to the Biovac Institute of South Africa, many of the intellectual property and technology transfer issues related to the deal are yet to be sorted out.[145]

D. *The TRIPS Agreement*

The adoption in 1995 of the Agreement on Trade Related Aspects of Intellectual Property Rights ("TRIPS Agreement") had a profound impact on international debates concerning local production of pharmaceutical products. The principal source of the perturbation was article 27(1), which provides:

> 1. Subject to the provisions of paragraphs 2 and 3, patents shall be available for any inventions, whether products or processes, in all fields of technology, provided that they are new, involve an inventive step and are capable of industrial application.[146] Subject to paragraph 4 of article 65,[147] paragraph 8 of article 70[148]

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142. Emily Baumgaertner, *Vaccine Companies and the US Government Snubbed WHO Initiative to Scale up Manufacturing*, L.A. TIMES (Apr. 30, 2021), https://www.latimes.com/world-nation/story/2021-04-30/vaccine-companies-and-the-u-s-government-snubbed-who-initiative-to-scale-up-global-manufacturing; *see also* Ed Silverman, *Pharma Leaders Shoot Down WHO Voluntary Pool for Patent Rights on Covid-19 Products*, STAT (May 28, 2020), https://www.statnews.com/pharmalot/2020/05/28/who-voluntary-pool-patents-pfizer/.

143. WHO, *Establishment of an mRNA Hub to Scale up Vaccine Manufacturing*, WHO: NEWS ROOM (Apr. 16, 2021), https://www.who.int/news-room/articles-detail/establishment-of-a-covid-19-mrna-vaccine-technology-transfer-hub-to-scale-up-global-manufacturing.

144. The WHO's media briefing on June 21, 2021 estimated that vaccines could be produced in South Africa "within nine to [twelve] months" if a big pharma partner does indeed come forward. *See* Kerry Cullinan, *South Africa to Become Africa's First mRNA Vaccine Manufacturing Hub – WHO Asks Big Pharma to Support Scaleup*, HEALTH POL'Y WATCH (June 21, 2021), https://healthpolicy-watch.news/africas-first-mrna-hub-to-be- set-up/.

145. David Mckenzie & Jeevan Ravindran, *Pfizer-BioNTech to Start Producing COVID-19 Vaccines in South Africa in 2022*, CNN (July 21, 2021), https://edition.cnn.com/2021/07/21/africa/covid-vaccine-manufacture-pfizer-africa-intl/index.html.

146. A footnote to this sentence provides that, "[f]or the purposes of this Article, the terms 'inventive step' and 'capable of industrial application' may be deemed by a Member to be synonymous with the terms 'non-obvious' and 'useful' respectively." Agreement on Trade-Related Aspects of Intellectual Property Rights ["TRIPS"] art. 27(2) n.5, Apr. 15, 1994, Marrakesh Agreement Establishing the World Trade Organization, Annex 1C, 1869 U.N.T.S. 299 (1994) [hereinafter TRIPS Agreement].

147. Paragraph 4 of article 65 provides that

> and paragraph 3 of this article, patents shall be available and patent rights enjoyable without discrimination as to the place of invention, the field of technology and whether products are imported or locally produced.[149]

The main purpose and effect of this provision was to compel developing countries, such as India, to extend patent protection to pharmaceutical products and thus to strengthen the ability of the major pharmaceutical firms to control global markets for products based on their innovations.[150]

The critics of the TRIPS Agreement argued that it would damage developing countries in two related ways. First, as soon as a developing country complied with the Agreement, pharmaceutical firms would use their enhanced rights to shut down generic manufacturing of compounds covered by the firms' patents.[151] Even if the pharmaceutical firms then expanded sales of authorized versions of those compounds in the country in question, the prices on these versions would be high and poor residents would be unable

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> To the extent that a developing country Member is obliged by this Agreement to extend product patent protection to areas of technology not so protectable in its territory on the general date of application of this Agreement for that Member, as defined in paragraph 2, it may delay the application of the provisions on product patents of Section 5 of Part II to such areas of technology for an additional period of five years.

Id. art. 65(4).

148. Paragraph 8 of article 70 provides that:

Where a Member does not make available as of the date of entry into force of the WTO Agreement patent protection for pharmaceutical and agricultural chemical products commensurate with its obligations under Article 27, that Member shall:

> (a) notwithstanding the provisions of Part VI, provide as from the date of entry into force of the WTO Agreement a means by which applications for patents for such inventions can be filed;
> (b) apply to these applications, as of the date of application of this Agreement, the criteria for patentability as laid down in this Agreement as if those criteria were being applied on the date of filing in that Member or, where priority is available and claimed, the priority date of the application; and
> (c) provide patent protection in accordance with this Agreement as from the grant of the patent and for the remainder of the patent term, counted from the filing date in accordance with Article 33 of this Agreement, for those of these applications that meet the criteria for protection referred to in subparagraph (b).

Id. art. 70(8).

149. *Id.* art 70(3).

150. Prior to the TRIPS Agreement, at least forty developing countries did not offer patent production for pharmaceutical processes and related products. *See* Pascale Boulet, Jos Perriens, Françoise Renaud-Théry & Germán Velasquez, *Pharmaceuticals and the WTO TRIPS Agreement: Questions and Answers*, U.N. PROGRAMME ON AIDS/WHO (2000).

151. *See e.g.*, Pradeep Agarwal P Saibaba, *TRIPS and India's Pharmaceuticals Industry*, 36 ECON. & POL. WKLY. 3787, 3787 (2001).

to afford the medicines they needed.[152] The critics contended that this adverse impact would become especially severe when both India and China, where many of the generic manufacturers were located, were forced to comply with article 27.[153] Second, the critics predicted that the few developing countries that had succeeded in creating local manufacturing capacity would lose it—and other developing countries, struggling to achieve sustainable scale, would be unable to gain it. [154] The loss of market share by Argentinian companies in the immediate aftermath of the TRIPS Agreement lent credibility to these predictions.[155]

Especially worrisome to some commentators was the risk that both of these effects would further undermine incentives to invest in treatments for infectious diseases (such as malaria and tuberculosis).[156] Developing countries are highly vulnerable to these diseases, but they are less prominent in developed countries, thus receiving less attention from major pharmaceutical firms primarily concerned with lucrative markets.[157]

Such concerns figured prominently in the efforts of developing countries and their advocates to identify, expand, and exercise "flexibilities" in the TRIPS Agreement.[158] Major battles in that war included:[159]

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152. *Id.*; *see also* Jerome H. Reichman, *Compulsory Licensing of Patented Pharmaceutical Inventions: Evaluating the Options*, 37 J.L. MED. & ETHICS 247, 247–63 (2009).

153. *See* CHERI GRACE, A BRIEFING PAPER FOR DFID: UPDATE ON CHINA AND INDIA AND ACCESS TO MEDICINES (U.K. Dep't For Int'l Dev't, Nov. 2005), https://assets.publishing.service.gov.uk/media/57a08ca5e5274a27b200131d/Update-on-China-an-India-and-Access-to-Medicines.pdf (studying the impact of India's and China's accession to TRIPS on pharmaceutical supplies to Africa); BISWAJIT DHAR & K. M. GOPAKUMAR, POST-2005 TRIPS SCENARIO IN PATENT PROTECTION IN THE PHARMACEUTICAL SECTOR: THE CASE OF THE GENERIC PHARMACEUTICAL INDUSTRY IN INDIA (Nov. 2006), https://unctad.org/system/files/official-document/ictsd-idrc2006d2_en.pdf (examining the supply of HIV/AIDS drugs to Africa after India's compliance with TRIPS in 2005).

154. Argentine companies that controlled over sixty percent of the local pharmaceutical market lost substantial ground to foreign firms soon after ratification of the TRIPS Agreement. *See* Andrés López, *Innovation and IPR in a Catch-up Falling Behind Process: The Argentine Case*, *in* INTELLECTUAL PROPERTY, DEVELOPMENT AND CATCH-UP: AN INTERNATIONAL COMPARATIVE STUDY 266–67 (Richard R. Nelson, Akira Goto et al. eds., 2010).

155. *Id.*

156. *See* Carlos M Morel, Tara Acharya, Denis Broun, Ajit Dangi, Christopher Elias, N K Ganguly, Charles A Gardner, R K Gupta, Jane Haycock, Anthony D Heher, Peter J Hotez, Hannah E Kettler, Gerald T Keusch, Anatole F Krattiger, Fernando T Kreutz, Sanjaya Lall, Keun Lee, Richard Mahoney, Adolfo Martinez-Palomo, R A Mashelkar, Stephen A Matlin, Mandi Mzimba, Joachim Oehler, Robert G Ridley, Pramilla Senanayake, Peter Singer & Mikyung Yun. *Health Innovation Networks to Help Developing Countries Address Neglected Diseases*, 309 SCI. 401 (2005).

157. Ellen 't Hoen, *TRIPS, Pharmaceutical Patents and Access to Essential Medicines: Seattle, Doha and Beyond,* 3 CHI. J. INT'L L. 27 (2002).

158. *See* UNCTAD Secretariat, *The TRIPS Agreement and Developing Countries*. U.N. Doc. UNCTAD/ITE/1 (1996); WHO, *Globalization and Access to Drugs: Perspectives on the*

- The struggle between the United States and Brazil prompted by Brazil's threat to impose compulsory licenses on HIV-related patents that were not "worked" in Brazil;[160]
- The effort (ultimately unsuccessful) by pharmaceutical firms to limit the ability of the government of South Africa to curb the prices of patented HIV drugs;[161]
- The effort, begun by the African Group[162] in 2001, to force the TRIPS Council to explore the relationship between the TRIPS Agreement and public health—an effort that ultimately concluded with the Doha Declaration, which clarified the right of all member states to interpret the Agreement in light of their domestic public-health circumstances,[163] and later a formal amendment of the Agreement.[164]
- Several efforts by the WHO to augment countries' abilities to manage pharmaceutical products to address health emergencies, culminating in the adoption of the GSPoA at the World Health Assembly of 2008, which proposed a series of actions to promote the transfer of technology and production of health products in developing countries.[165]

WTO/TRIPS Agreement (Revised), WHO Doc. WHO/DAP/98.9 (1999)); Carlos M. Correa, *Implementing the TRIPS Agreement in the Patents Field: Options for Developing Countries*, 1 J. WORLD INTELL. PROP. 75 (1998).

159. Additional detail concerning each is available: *See* 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).

160. See Decreta No. 9.279, de 14 de Maio de 1996 art. 68, Diário Oficial da União [D.O.U.] de 15.05.1996 (Braz.); U.S. Request for Consultations, Brazil –Measures Affecting Patent Protection, WT/DS199/1 (June 8, 2000), https://www.wto.org/english/tratop_e/dispu_e/cases_e/ds199_e.htm; see also Paul Champ & Amir Attaran, Patent Rights and Local Working Under the WTO TRIPS Agreement: An Analysis of the U.S.-Brazil Patent Dispute, 27 Yale J. Int'l L. (2002).

161. *See* Ed Vulliamy, *How Drug Giants Let Millions Die of AIDS,* THE GUARDIAN (Dec. 18, 1999); *see also* Nabila Ansari, *International Patent Rights in a Post-Doha World,* 11 INT'L TRADE L.J. 57, 61 (2002).

162. A list of the member countries of the African Group is available at *Groups in the Negotiations*, WTO, https://www.wto.org/english/tratop_e/dda_e/negotiating_groups_e.htm (last visited Dec. 6, 2021).

163. World Trade Org. ["WTO"], *Declaration on the TRIPS Agreement and Public Health, Nov. 14, 2001,* WT/MIN(01)/DEC/2 (Nov. 20, 2001); *see also* CARLOS M. CORREA, IMPLICATIONS OF THE DOHA DECLARATION ON THE TRIPS AGREEMENT AND PUBLIC HEALTH 2 (WHO, 2002), https://www.who.int/medicines/areas/policy/WHO_EDM_PAR_2002.3.pdf.

164. *See Factsheet on Amendment to the Agreement on Trade-Related Aspects of Intellectual Property (TRIPS)*, WTO, https://www.wto.org/english/tratop_e/trips_e/tripsfacsheet_e.htm (last visited Oct. 21, 2021).

165. *See* World Health Assembly Res. 61.21, *reprinted in* WHO, SIXTY-FIRST WORLD HEALTH ASSEMBLY: DECISIONS AND RESOLUTIONS 31 (May 19–24, 2008); COMM'N ON

- Fraught deliberations in major international fora and within the vast network of non-governmental organizations that ultimately led to various global initiatives, including a 2016 report by the United Nations High-Level Panel on Access to Medicines, which urged all World Trade Organization ("WTO") member countries to "make full use of the policy space available in article 27 of the TRIPS Agreement" and not to interfere with efforts of other member countries to do so.[166]

Partly because of these various efforts to curtail the impact of the TRIPS Agreement, the worst fears of its critics have not been realized. By and large, the developing countries that had developed robust manufacturing capacities prior to TRIPS—above all, India and Brazil—have managed to keep them, partly through shrewd and aggressive use of the "flexibilities" described above.[167] But of the countries that lacked significant manufacturing capability prior to the adoption of the Agreement, Bangladesh is the only one that managed to build a sizeable export-oriented pharmaceutical sector.[168] In Bangladesh, TRIPS flexibilities, a protected national market, and a number of other provisions aimed at strengthening local production enabled the expansion of the domestic pharmaceutical sector to diversify into numerous therapeutic categories including vaccines.[169] Today, the Agreement continues to limit the ability of most developing countries to expand local production capacity.

E. *Lessons*

Some general guidelines lurk in this history. In retrospect, it appears that, in most successful efforts to augment local production capacity, four

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INTELL. PROP. RTS., INTEGRATING INTELLECTUAL PROPERTY RIGHTS AND DEVELOPMENT POLICY (Sept. 2002), World Health Assembly Res. 56.27, Intellectual Property Rights, Innovation & Public Health (May 28, 2003); World Health Org., *Rep. of The Inter-Governmental Working Group On Public Health, Innovation and Intellectual Property*, WHO Doc. A61/9, (May 19, 2008).

166. U.N. SECRETARY-GENERAL, REP. OF THE UNITED NATIONS SECRETARY-GENERAL'S HIGH-LEVEL PANEL ON ACCESS TO MEDICINES (Sept. 14, 2016), https://static1.squarespace.com/static/562094dee4b0d00c1a3ef761/t/57d9c6ebf5e231b2f02cd3d4/1473890031320/UNSG+HLP+Report+FINAL+12+Sept+2016.pdf.

167. WORLD HEALTH ORGANIZATION, LOCAL PRODUCTION FOR ACCESS TO MEDICINES: DEVELOPING A FRAMEWORK TO IMPROVE PUBLIC HEALTH (2011), https://www.who.int/phi/publications/Local_Production_Policy_Framework.pdf; Okediji, *supra* note 159, at 199.

168. *See* Padmashree Gehl Sampath, *Pharmaceutical Manufacturing in Bangladesh: A Success Story- What Can We Learn*? 1, 2–3 (Fed. E. Afr. Pharm. Mfrs. Advoc. Series, Paper No. 1, 2019); MUSTAFIZUR RAHMAN & SHERAJUM MONIRA FARIN, WTO DECISION ON TRIPS AND PUBLIC HEALTH: A WINDOW OF OPPORTUNITY FOR BANGLADESH'S PHARMACEUTICAL INDUSTRY (May 2018).

169. *Id.*

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

The first and third factors are obvious and have received considerable attention by lawmakers and scholars.[170] By contrast, the roles played by the second and fourth factors have not been adequately appreciated.

Know-how is especially critical with respect to the production of active ingredients—which, as we have seen, is the most important and challenging dimension of the manufacturing process.[171] Making and packaging pills using imported compounds is a less complex process, and the potential profits generated by those activities are low—indeed, often too low to sustain an enterprise.[172] The greatest potential rewards, as well as the greatest benefits to public health and economic development, are associated with local production of APIs.[173] 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 develop-

170. For a discussion of condition 1, see, e.g., Okediji, *supra* note 159; Correa, *supra* note 161. 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).

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

172. 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).

173. *See* Kaplan & Laing, *supra* note 3; Hall, *supra* note 75 and accompanying text.

ing country manufacturers, in general, and will be even more important in the case of new vaccine platforms.[174]

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.[175] This has sometimes prompted governments to prop them up by paying exorbitant fees for the modest services that the firms have been able to provide. That, in turn, has resulted in needlessly high drug prices,[176] prompting some commentators to insist that mercantilist industrial policy and access to medicines are incompatible.[177]

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.[178] It adversely affects the ability of firms to participate in large local and international tenders. 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.[179]

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.[180] This assurance is especially important in the current

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174. 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.

175. Abbott et al., *supra* note 170. 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 170, at 11.

176. 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.

177. *See* Kaplan & Laing, *supra* note 3; Hall, *supra* note 75. 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); GEHL SAMPATH, *supra* note 72, at 207.

178. Abbott et al, *supra* note 170.

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

180. Gehl Sampath & Walwyn, *supra* note 170.

environment, where generic versions of many of the drugs that the firms might consider producing are already available from Indian, Chinese, or other manufacturers.[181]

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.[182] Critics of the TRIPS Agreement were concerned about rising drug prices in developing countries and emphasized mechanisms, such as compulsory licensing, that could neutralize the enhanced levels of patent protection.[183] Neither group focused on market mechanisms that could entice local producers to generate inexpensive drugs that would meet the needs of the countries' residents.

III. A Framework to Support Local Production

Building on the historical record outlined above, this section outlines five practicable strategies that, in combination, would more effectively promote local production of pharmaceutical products.

A. *Clearing Legal Space*

As indicated above, 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).[184] 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

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

182. *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).

183. Abbott & Reichman, *supra* note 3, 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).

184. *See* UNCTAD Secretariat, *supra* note 76, at 124, 189.

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")[185] 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.[186] 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.[187]

(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 local firms to manufacture some so-called "me-too" drugs—that is, those that provide little or no therapeutic advantage over their predecessors.[188]

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185. The nonmember countries can be subdivided into two loosely separated groups: the "observers," which are obliged (at least in theory) to begin negotiations for WTO membership within 5 years of becoming observers; and the non-observing non-members, most of which have not yet expressed interest in membership. The observers are: Algeria, Andorra, Azerbaijan, Bahamas, Belarus, Bhutan, Bosnia and Herzegovina, Comoros, Curacao, Equatorial Guinea, Ethiopia, the Holy See, Iran, Iraq, Lebanon, Libya, Sao Tome and Principe, Serbia, Somalia, South Sudan, Sudan, Syria, Timor-Leste, and Uzbekistan. The non-observing non-members are Eritrea, Kiribati, Kosovo, Marshall Islands, Micronesia, Monaco, Nauru, North Korea, Palau, Palestine, San Marino, Turkmenistan, and Tuvalu. *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).

186. *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).

187. *See, e.g.*, Germán Velásquez, Bill Aldis, Karin Timmermans, Cecilia Oh, Kiyoshi Adachi, Roger Kampf & Xavier Seuba, Improving Access to Medicines in Thailand: The Use of Trips Flexibilities 20–23 (Knowledge Ecology Int'l, 2008), https://www.keionline.org/misc-docs/thaimissionreportfeb08.doc; SISULE F. MUSUNGU & CECILIA OH, THE USE OF FLEXIBILITIES IN TRIPS BY DEVELOPING COUNTRIES: CAN THEY PROMOTE ACCESS TO MEDICINES? 18–19 (WHO Comm'n on Intell. Prop. Rts., 2005); Ellen 't Hoen, Jacquelyn Veraldi, Brigit Toebes & Hans V. Hogerzeil, *Medicine Procurement and the Use of Flexibilities in the Agreement on Trade-Related Aspects of Intellectual Property Rights, 2001–2016,* 96 BULL. WORLD HEALTH ORG. 185 (2018).

188. 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

(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.[189]

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.[190] Such obligations were once common components of national patent statutes, but, during the twentieth century, they were abandoned by many developed countries.[191] 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.[192]

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 forfeiture of the patent to various

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FROM A PUBLIC HEALTH PERSPECTIVE (U.N. Dev. Programme, 2015), https://www.undp.org/content/dam/undp/library/HIV-AIDS/UNDP_patents_final_web_2.pdf; Eric M. Solovy & Pavan S. Krishnamurthy, *TRIPS Flexibilities and Their Limitations: A Rresponse to the Un Secretary-General's High-Level Panel Report on Access to Medicines*, 103 GEO. WASH. INT'L L. REV. 50 (2017).

189. Article 33 of the TRIPS Agreement requires that the term of patents not be shorter than "twenty years counted from the filing date." TRIPS Agreement, *supra* note 146, art. 33. However, TRIPS neither requires that patent applications be processed within a specific period of time nor compels countries to extend patents to compensate applicants for the amounts of time they expend prosecuting their applications or securing regulatory approval.

190. *See* Marketa Trimble, *Patent Working Requirements: Historical and Comparative Perspectives*, 6 U.C. IRVINE L. REV. 483 (2016).

191. *Id.* at 487–89.

192. *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.").

forms of compulsory licenses. Some penalties apply as soon as a patent issues; others take hold only after a prescribed period of time.[193]

Those countries that retain working requirements rarely enforce them.[194] 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. As was mentioned in Part II of this article, 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.[195] The United States formally challenged that initiative as a violation of the TRIPS Agreement but eventually backed down before the claim was resolved.[196] 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."[197] 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.[198]

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 summa-

193. *See* Trimble, *supra* note 190, at 486–87.

194. *Id.* at 494.

195. *See* discussion *supra* Part II(D).

196. *See* Paul Champ & Amir Attaran, *Patent Rights and Local Working under the WTO Trips Agreement: An Analysis of the U.S.-Brazil Patent Dispute*, 27 YALE J. INT'L L. 365, 365–66 (2002).

197. TRIPS Agreement, *supra* note 146, art. 27.

198. For a range of opinions concerning the permissibility of working requirements, see Thomas Cottier, Shaheeza Lalani, & Michelangelo Temmerman, *Use It or Lose It: Assessing the Compatibility of the Paris Convention and Trips Agreement with Respect to Local Working Requirements*, 17 J. INT'L ECON. L. 437 (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).

rized 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 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.[199] 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,[200] 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.[201] 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

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199. *See* Bagley, *supra* note 183, at 498.

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

201. For descriptions of some of these interventions, see Kevin Outterson, *Should Access to Medicines and Trips Flexibilities Be Limited to Specific Diseases?*, 34 AM. J.L. & MEDICINE 279, 301 (2008); Cynthia Ho, *Patent Breaking or Balancing?: Separating Strands of Fact from Fiction under TRIPS*, 34 N.C. J. INT'L L & COM. REGUL. 371, 447–48 (2009); Jacqui Wise, *Access to AIDS Medicines Stumbles on Trade Rules*, 85 BULL. WORLD HEALTH ORG 342 (2006); Horace E. Jr. Anderson, *We Can Work It Out: Co-Op Compulsory Licensing as the Way Forward in Improving Access to Anti-Retroviral Drugs*, 16 B.U. J. SCI. & TECH. L. 167, 193 (2010); Christina Cotter, *The Implications of Rwanda's Paragraph 6 Agreement with Canada for Other Developing Countrie*s, 5 LOY. UNIV. CHI. INT'L L. REV. 177, 178–87 (2008).

"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 whether specific mergers would be permissible.[202] 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, in light of 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.[203] 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."[204] This

202. *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).

203. *See, e.g.*, Mike Palmedo, *Analysis of Special 301 Listings 2009–2020*, (Shamnad Basheer IP/Trade Fellow White Paper, 2020).

204. *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) ("Trade is critical to America's prosperity—fueling economic growth, supporting good jobs at home, raising living standards and helping Americans provide for their families with affordable goods and services . . . Trade expansion benefits families and businesses by: Supporting more productive, higher paying jobs in our export sectors; Expanding the variety of products for purchase by consumers and business; Encouraging investment and more rapid economic growth. Trade

statement appropriately recognizes that U.S. trade policy can and should be shaped to promote the welfare of all sectors of the population, not just businesses concerned with maximizing their export markets. As noted earlier in this article, it is not certain that increasing the ability of firms in developing countries to manufacture drugs will always directly benefit the United States, but surely the resultant improvements to public health and economic development in those countries would *sometimes* redound to the net benefit of U.S. residents.[205] For example, if augmentation of local production significantly reduced the presence of substandard antibiotics in developing countries, the resulting inhibition of the development of drug-resistant strains of bacteria would be, in the long run, hugely beneficial to everyone on the planet, including U.S. residents. 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[206] is no longer consistent with U.S. foreign policy as a whole. The latter certainly includes some de-

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keeps our economy open, dynamic, and competitive, and helps ensure that America continues to be the best place in the world to do business").

205. *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) ("To protect the American people, our home, and our way of life, the United States actively works to prevent, detect, and respond to infectious disease threats. Outbreaks of infectious disease do not respect national boundaries. Halting and treating diseases at their points of origin is one of the best and most economical ways of saving lives and protecting Americans. The U.S. National Security Strategy and U.S. National Biodefense Strategy prioritize U.S. efforts to build global health security capacity. The United States leads internationally, collaborating with countries to invest in basic health care systems and address infectious diseases such as HIV/AIDS, malaria, Ebola, Zika, and influenza.").

206. *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).

> As President Obama has made clear, our focus must be to promote growth, create American jobs and strengthen our middle class. USTR can contribute to this effort in three important ways: First, by opening markets around the world so we can expand our exports; second, by leveling the playing field so that our people can compete and win in the global economy; and third, by ensuring that the rights and trade rules we have fought so hard for are fully implemented and enforced.
>
> Trade policy, negotiated and enforced vigorously to reflect both our interests and our values, gives our workers, farmers and ranchers, our manufacturers and service providers, our innovators, creators, investors in businesses of all sizes the best chance to compete around the world.

gree of attention to the welfare of the residents of the rest of the world.[207] 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.[208] 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.[209] 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.[210]

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.[211] The deliverables specified in the agreement included: implementation of good laboratory practices, engineering for plant maintenance, information on selecting and

207. *See, e.g.*, *Policy Issues: Climate Crisis*, U.S. DEP'T STATE, https://www.state.gov/policy-issues/climate-crisis/ ("Bold action to tackle the climate crisis is more urgent than ever. The record-breaking heat, floods, storms, drought, and wildfires devastating communities around the world underscore the grave risks we already face. Through our actions at home and our leadership abroad, the United States is doing its part to build a zero-carbon future that creates good jobs and ensures a healthy, livable planet for generations to come.").

208. This section is based on the field work and survey conducted by one of the authors of this paper in Uganda 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).

209. *Id.* at 266.

210. *Id.* at 266–68.

211. *Id.* at 266–67.

sourcing of raw materials, organizing supply of other inputs, and planning for contingencies in production, marketing, and distribution.[212] In addition, Cipla was expected to submit dossiers for GMP compliance to the WHO, thereby enabling Quality Chemicals to compete in international bidding processes.[213] Last, but not least, the Ugandan government agreed to purchase all products produced in the plant for a period of seven years.[214]

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.[215] But joint ventures of this sort remain highly unusual.

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

1) An experienced pharmaceutical firm, a local manufacturer, and the government of a developing country enter into a long-term collaboration.
2) 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.
3) The government provides some initial investment in the venture and, equally important, a commitment to purchase substantial quantities of the products of the venture.
4) The local firm provides management, marketing, most of the personnel and much of the financing.[216]

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

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212. *Id.* at 267.

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

214. Gehl Sampath & Spennemann, *supra* note 208.

215. *See* Giuliano Russo & Geoffrey Banda, *Re-Thinking Pharmaceutical Production in Africa; Insights from the Analysis of the Local Manufacturing Dynamics in Mozambique and Zimbabwe*, 50 STUD. COMPAR. INT'L DEV. 50 (2015). The contributions made by the Brazilian government parallel those made by Cipla in the Uganda model: "The Government of Brazil committed to providing funds for staff training and capacity building, equipment, technical assistance, raw materials, design of the factory and management." Giuliano Russo & Geoffrey Banda, *Re-Thinking Pharmaceutical Production in Africa; Insights from the Analysis of the Local Manufacturing Dynamics in Mozambique and Zimbabwe*, 50 STUD. COMPAR. INT'L DEV. 258, 265 (2015). The contributions by Mozambique are even more substantial than those made by the government of Uganda: "The Government of Mozambique took responsibility to purchase the infrastructure for the factory, to undertake rehabilitation works, and for the factory's recurrent expenditures, including local staff's salaries, and to purchase drugs from SMM." *Id.*

216. *See* Gehl Sampath & Pearman, *supra* note 139.

which then distributes them through the public-health system.[217] 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.[218] However, those agencies typically favor increasing local production and thus would not balk at arrangements like Uganda's. Moreover, 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.[219] 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. To see how this might work requires a bit of background.

In early modern Europe, the apprenticeship system emerged as a highly effective mechanism for transmitting technical knowledge. During this period, if an individual wanted to learn a skilled trade (for example, baking or

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217. 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.

218. *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.

219. *See* Gehl Sampath & Spennemann, *supra* note 208.

metalworking), he did not go to school or read a book; he became an apprentice to a master in that trade. The form of such apprenticeships varied significantly by region, but the most successful and influential variant was the model formalized (partly by law and partly by custom) in London, and then mimicked in many other English cities.[220] In brief, an apprentice worked for a minimum of seven years, the termination of which had to be after the apprentice turned twenty-four years old. The master provided the apprentice training, food, and housing—but usually not wages. The apprentice, in turn, provided labor—which, over the course of the apprenticeship, gradually became increasingly skilled. Masters were required to register apprenticeship indentures (that is, contracts) with city authorities. An apprentice who completed his term of service frequently set up shop on his own, became a freeman of the city, and eventually took on apprentices of his own. This system was widely used. In the sixteenth and seventeenth centuries, 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.[221]

Apprenticeship during this period had several social and economic functions, including the socialization of unruly adolescents, the maintenance of class hierarchies, and, in conjunction with the guild system, limiting the supply of skilled labor and thus sustaining the prices that skilled laborers could charge. Historians continue to debate the relative importance of these functions.[222] But on one issue there is little disagreement: The apprenticeship model proved a highly effective mechanism for preserving and transmitting technical information.[223] After the industrial revolution, apprenticeship was displaced in most fields by other forms of technical training (or by no training at all), but it 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.[224]

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220. *See* PRAK MAARTEN & PATRICK WALLIS, APPRENTICESHIP IN EARLY MODERN EUROPE (Cambridge Univ. Press, 2019).

221. *See* Patrick Wallis, *Apprenticeship and Training in Premodern England*, 68 J. ECON. HIST. 832 (2008).

222. *See, e.g.*, *id.* at 832–33.

223. *See, e.g.*, Stephen R. Epstein, *Craft Guilds, Apprenticeship, and Technological Change in Preindustrial Europe*, 58 J. ECON. HIST. 684 (1998).

224. *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*, 37 GER. HIST. 359 (2019).; Dietmar Harhoff & Thomas J. Kane, *Is the German*

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 own 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.[225] Increasingly, pharmaceutical firms in other countries are relying on them to train skilled workers.[226] To be sure, the level at which the proposed program would operate is different. Instead of training technicians, 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,[227] 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

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Apprenticeship System a Panacea for the U. S. Labor Market?, 10 J. POPULATION ECON. 171, 174–75 (1997).

225. *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").

226. *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).

227. *See* Elizabeth H. Stephens & Joseph A. Dearani, *On Becoming a Master Surgeon: Role Models, Mentorship, Coaching, and Apprenticeship*, ANNALS THORASIC SURGERY, June 1, 2021, at 8; WILLIAM NOLAN, THE MAKING OF A SURGEON (1970); Bennet A. Butler, Cameron M. Butler & Terrance D. Peabody, *Cognitive Apprenticeship in Orthopaedic Surgery: Updating a Classic Educational Model*, 76 J. SURGICAL EDUC. 931 (2019).

prioritize ways of providing African firms affordable access to technology and know-how.[228] 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.[229] 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, in order to avoid corroding the primary markets of the sponsoring companies, the firms in developing countries who 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 discoveries they are generating.[230] 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 Un-

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228. 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].

229. *Id.* at 24.

230. *See* Francis et al. *supra* note 136 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) *("*Moderna accepted $2.5 billion in taxpayer money to develop its Covid-19 vaccine. But officials in the U.S. and overseas are having trouble persuading the company to license its technology.").

ion.[231] 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.[232] 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.[233] 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.[234] 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.[235]

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 vaccines are already underway in African countries.[236] 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

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231. *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.

232. *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 Billion in Coronavirus Treatment/Vaccine Development*, PUBLIC CITIZEN (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/.

233. *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).

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

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

236. John N. Nkengasong, Nicaise Ndembi, Akhona Tshangela & Tajudeen Raji, C*ovid-19 Vaccines: How to Ensure Africa Has Access*, NATURE (Oct. 6, 2020), https://www.nature.com/articles/d41586-020-02774-8.

firm to abide by safety requirements, as is routine, but also upon a commitment to participate in the 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.[237] 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.[238]

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.[239] Displacing imports with locally produced products will decrease the frequency of such stockouts in three ways. First, the time necessary to transport products from manufacturers to distributors and retailers will 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 much more likely to prior-

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237. *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).

238. 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).

239. *Cf.* Harparkash Kaur, Si n Clarke, Mirza Lalani, Souly Phanouvong, Philippe Guérin, Andrew McLoughlin, Benjamin K. Wilson, Michael Deats, Aline Plançon, Heidi Hopkins, Debora Miranda & David Schellenberg, *Fake Anti-Malarials: Start with the Facts*, MALARIA J., Feb. 13, 2016, at 6.

itize 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.[240] 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.[241] Among its results is the African Union Model Law on Medical Products Regulation, which has now been adopted in twenty-five countries.[242] Even more promising is a treaty

240. *See, e.g.*, Bate et al. *supra* note 52 (discussing the wide profit margin enjoyed by pill counterfeiters in the United Kingdom).

241. 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, Alberto Grignolo, Lawrence Liberti, John C. W. Lim, Tomas Salmonson, Fernand Sauer & Henrietta Ukwu, *Improving Access to Quality Medicines in East Africa: An Independent Perspective on the East African Community Medicines Regulatory Harmonization Initiative*, PLOS MED., Aug. 12, 2020; Jane H. Mashingia, Vincent Ahonkhai, Noel Aineplan, Aggrey Ambali, Apollo Angole, Mawien Arik, Samvel Azatyan, Peter Baak, Emmanuel Bamenyekanye, Aimable Bizoza, Chimwemwe Chamdimba, Petra Doerr, Adam Fimbo, Alex Gisagara, Hidaya Hamad, Rachelle Harris, Dan Hartman, Joseph Kabatende, Charles Karangwa, Agnes Sitta Kijo, Murray Lumpkin, Shani Maboko, David Matle, Apollo Muhairwe, John Patrick Mwesigye, Bonaventure Nyabenda, Alexander Schulze, Andreas Seiter, Gordon Sematiko, Margareth Sigonda, Hiiti Sillo, Burhani Simai, Fred Siyoi, Stanley Sonoiya, Paul Tanui, Mike Ward, Felistas Yano & David Mukanga, *Eight Years of the East African Community Medicines Regulatory Harmonization Initiative: Implementation, Progress, and Lessons Learned,* PLOS MED., Aug 12, 2020.

242. 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

concluded in 2019 that, if fully implemented, would establish a continental African 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.[243] It will enable considerable improvement and streamlining of the mechanisms for securing registration of new drugs in multiple jurisdictions.[244]

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,[245] 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.[246] 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.[247] But technologies are now available that, in combination, enable inspectors

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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).

243. Pursuant to article 38, the Treaty entered into force on November 5, 2021. To date, sixteen countries have deposited instruments of ratification of the AMA. *The Republic of Chad Deposits the Instrument of Ratification of the African Medicines Association (AMA)*, AFR. UNION (Oct. 7, 2021) https://au.int/en/pressreleases/20211007/republic-chad-deposits-instrument-ratification-african-medicines-agency-ama.

244. 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/20200205/49african-medicine-agency-ama-treaty. As of June 11 of this year, twenty African States have signed the treaty. *See* Treaty for the Establishment of the African Medicines Agency, Feb. 11, 2019, https://au.int/sites/default/files/treaties/36892-treaty-0069_-_ama_treaty_e.pdf (last visited Nov. 17, 2021). Sixteen states have deposited instruments of ratification. *See* AFR. UNION, *supra* note 247.

245. For the WHO's GMP certification requirements, see *Good Manufacturing Practices for Pharmaceutical Products: Main Principles*, WHO (2014), https://www.who.int/medicines/areas/quality_safety/quality_assurance/production/en/.

246. *See* Kay Weyer, *A Stepwise Approach for Pharmaceutical Companies in Developing Countries to Attain Who Gmp Standards*, 30 WHO DRUG INFO. 186 (2016); UNIDO, *A Stepwise Approach for Pharmaceutical Companies in Developing Countries to Attain Who Gmp Standards* (White Paper on UNIDO's GMP Roadmap Concept, 2015).

247. *See* INST. MEDICINE, COUNTERING THE PROBLEM OF FALSIFIED AND SUBSTANDARD DRUGS (2013), 255–89.

to identify substandard or falsified medicines at any point in the distribution chain. The most promising varieties are listed below:

(a) Some technologies 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, and a few other countries.[248] With sufficient funding, such systems could be deployed in developing countries.

(b) 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 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).[249]

(c) A third set of technologies relies upon testing the chemical composition of medicines at various points in the distribution chain. They include:

  (1) High-performance liquid chromatography ("HPLC") testing of samples in laboratories that have been qualified by the WHO to conduct such testing;[250]

  (2) The "MiniLab," developed in the 1980s by the Global Pharma Health Fund (and subsequently updated periodically), which makes possible analogous testing in the field.[251]

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248. *See* Huma Rasheed, Ludwig Höllein & Ulrike Holzgrabe, *Future Information Technology Tools for Fighting Substandard and Falsified Medicines in Low- and Middle-Income Countries*, FRONTIERS PHARMACOLOGY, AUG. 2018, at 2; Bernard Naughton, Lindsey Roberts, Sue Dopson, David Brindley & Stephen Chapman, *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, May 6, 2017, at 7.

249. *See* Rasheed et al., *supra* note 251, at 3; Matthew Wall, *Counterfeit Drugs: "People Are Dying Every Day,"* BBC NEWS, September 26, 2016.

250. For a description of the technology and its suitability to poor countries, see Ludwig Hoellein & Ulrike Holzgrabe, *Development of Simplified HPLC Methods for the Detection of Counterfeit Antimalarials in Resource-Restraint Environments*, 98 J. PHARM. & BIOMEDICAL ANALYSIS 434 (2014).

251. *See, e.g.,* Ifeyinwa Fadeyi, Mirza Lalani, Naiela Mailk, Albert Van Wyk & Harparkash Kaur, *Quality of the Antibiotics—Amoxicillin and Co-Trimoxazole from Ghana, Nigeria, and the United Kingdom*, 92 AM. J. TROPICAL MED. HYGIENE 87 (2015) (comparing HPLC testing and the MiniLab); Stephanie Kovacs, Stephen E. Hawes, Stephen N. Maley, Emily Mosites, Ling Wong & Andy Stergachis, *Technologies for Detecting Falsified and*

(3) 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).[252]

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 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.

Substandard Drugs in Low and Middle-Income Countries, PLOS ONE, Mar. 3, 2014, at 8–9.; Albert Petersen, Nadja Held, & Lutz Heide, *Surveillance for Falsified and Substandard Medicines in Africa and Asia by Local Organizations Using the Low-Cost Gphf Minilab,* PLOS ONE, Sept. 6, 2017.

252. *See*, *e.g.*, Eillie Anzilotti, *This Startup Built a Device to Figure out If Prescription Drugs Are Fake*, FAST CO., (Mar. 3, 2019), 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., *supra* note 251, at 8.

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."[253]

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.[254] 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 leading South African Development Community ("SADC") and the Economic Community of West African States ("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

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

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

sort. The populations (in millions) encompassed by the principal developing-country regional communities are set forth below: [255]

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, precisely because the RECs are regional in nature, the member countries of the RECs typically have similar disease footprints and thus need similar portfolios of drugs.

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 Treaty Establishing the Common Market for Eastern and Southern Africa ("COMESA") requires that member states cooperate in health "through the facilitation of movement of pharmaceuticals within the Common Market and control of their quality."[256] COMESA member states undertake to, among other things:

> i) devise and implement systems to ensure that pharmaceuticals entering the Common Market from third countries, produced in the

255. 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).

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

> Common Market or moving within the Common Market conform to internationally acceptable standards in terms of quality and therapeutic value;
> ii) develop a national drug policy that would include establishing quality control capacities, national formularies and good procurement practices;
> iii) harmonize drug registration procedures to achieve good control of pharmaceutical standards without impeding or obstructing the movement of pharmaceuticals within the Common Market;
> iv) accord each other mutual recognition of drugs registered in the Common Market;
> v) co-operate, within the framework of co-operation in industrial development, in the local production of pharmaceutical products; and
> vi) 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.[257]

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."[258]

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.[259] 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.[260]

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257. *Id.* art. 110(2).

258. 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).

259. *See Who We Are*, W. AFR. HEALTH ORG., https://www.wahooas.org/web-ooas/en/who-we-are (last visited Sept. 18, 2021) ("Article III of the Protocol establishing WAHO stipulates that 'the objective of the West African Health Organisation shall be the attainment of the highest possible standard and protection of health of the peoples in the sub-region through the harmonisation of the policies of the Member States, pooling of resources, and cooperation with one another and with others for a collective and strategic combat against the health problems of the sub-region.'").

260. *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.

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 Parts II and III 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 availability and access to affordable, safe, and efficacious essential medicines.[261] 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.[262] Although implementation is slow and progress on the goals is difficult to monitor, 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 specific to 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 Association of Southeast Asian Nations ("ASEAN") Pharmaceutical Product Working Group ("PPWG") was established by the ASEAN Consultative Committee for Standards and Quality ("ACCSQ") with the objective of harmonizing pharmaceutical regulations of ASEAN member countries.[263] The PPWG's purpose is to develop a harmonization scheme for pharmaceutical regulation to ensure the safety and efficacy of pharmaceutical products in the ASEAN market. In March 2006, the harmonization of labelling standards for pharmaceutical/medicinal products in the ASEAN

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

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

263. *See* Abhishek Tongia, *The Drug Regulatory Landscape in the ASEAN Region*, REGUL. AFFS. PRO. SOC'Y (Jan. 29, 2018), https://www.raps.org/news-and-articles/news-articles/2018/1/the-drug-regulatory-landscape-in-the-asean-region.

region was achieved.[264] The work of harmonizing pharmaceutical regulations in ASEAN member states is ongoing.

Similarly, within CARICOM, the Council for Trade and Economic Development ("COTED") has the responsibility for establishing standardization programs under the Treaty. On this basis, COTED has endorsed a roadmap for the implementation of the Caribbean Regulatory System for Medicines ("CRS"), which includes programs on the harmonization of standards and technical regulations for medicines and pharmaceutical products.[265]

On the opposite page is a chart comparing the provisions of select regional organizations and economic communities that could support local manufacture of pharmaceutical products. It suggests that most RECs are already well positioned with the requisite legal and policymaking authority to launch and support local production initiatives.

264. *See* Long Chiau Ming, Qi Ying Lean, Siew Mei Yee, Rahul Patel, Nur Akmar Taha & Yaman Walid Kassab, *Cross-Border Collaboration to Improve Access to Medicine: Association of Southeast Asian Nations Perspective*, 9 J. EPIDEMIOLOGY & GLOB. HEALTH 93 (2019).

265. *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.)	🕒 (WAHO reportedly is developing a Regional Drug Revolving Fund (DRF) for pooled procurement of essential medicines in ECOWAS.[266])

266. *See* Leonard A. Kamwanja John Saka, Abolade Awotedu, Iskari Fute, Chimwemwe Chamdimba & Margareth Ndomondo-Sigonda, *Situation Analysis Study on Medicines Registration Harmonisation in Africa: Final Report*, NEPAD, June 2011, at 6.

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 of these regional organizations already 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.[267] 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 and protocols 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.[268]

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.

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

268. *See* Africa's Response to COVID-19, *supra* note 231, at 21.

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 incorporated these recommendations could both save many lives and catalyze economic development in the Global South.