Briefing Book for the Harvard Forum on Access to Medicines in Global Health Emergencies: The Role of Voluntary Licensing

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Introduction

Drugs capable of preventing, curing, or mitigating diseases are less accessible to the residents of developing countries than they are to the residents of developed countries – and less accessible to poor people throughout the world than they are to wealthy people. The causes of this inequality are complex, and no single strategy is capable of addressing all of them. The purpose of this project is to maximize the effectiveness and usage of one such strategy: voluntary licensing.

The essence of voluntary licensing is simple: the holder of intellectual-property rights (and/or proprietary technology) pertaining to an innovative drug authorizes and enables another company to manufacture the drug and then distribute it in poor countries and/or to poor populations. Unfortunately, implementation of this approach is less straightforward than the foregoing distillation would suggest. To catalyze increased usage of voluntary licensing, we must identify the impediments to its deployment and develop or refine ways of overcoming them. That's the goal of the Harvard Forum. The purpose of this briefing book is to establish a foundation for our conversation by providing participants information pertaining to the history and current status of voluntary licensing.

The first part of the briefing book summarizes the principal challenges that, thus far, have limited usage of voluntary licensing. With respect to each, we briefly identify the potential solutions that, to date, have been tried or advocated and then pose some questions that the participants in the Forum might seek to answer.

The bulk of the book then consists of documents that could enrich our deliberations. Most of those documents consist of memoranda prepared by research assistants at Harvard Law School. A few consist of copies of pertinent publications. All should be treated as starting points for discussion, rather than final resolutions of the issues before us.

The book then concludes with a provisional bibliography of materials pertaining to voluntary licensing. We welcome additions to it.

Challenges and Potential Solutions

1. Regulatory Approval

A voluntary license (VL) to distribute a drug at low prices in a particular country will do no good if the drug lacks marketing approval in that jurisdiction. Currently, it is more difficult and more costly to obtain such approvals than one might think.

A good illustration of the severity of this issue is provided by a study, conducted by a group of scholars associated with the Gates Foundation, of the process by which a representative HIV drug was approved for use in 20 sub-Saharan African countries. In the chart below (reprinted from their paper), both the drug in question and the countries have been anonymized.[1] The two "SRAs" that appear at the top of the chart, are the FDA (in the United States) and the EMA (in Europe); the "NRAs" are the National Medicines Regulatory Authorities (NMRAs) in the African countries. As is apparent, in many of the countries the drug was not submitted for approval until months or years after it had been submitted in the United States and Europe, and the approval process in those countries typically took substantially longer than in either the FDA or the EMA. Indeed, in four countries, it had not been completed by the time of the study.

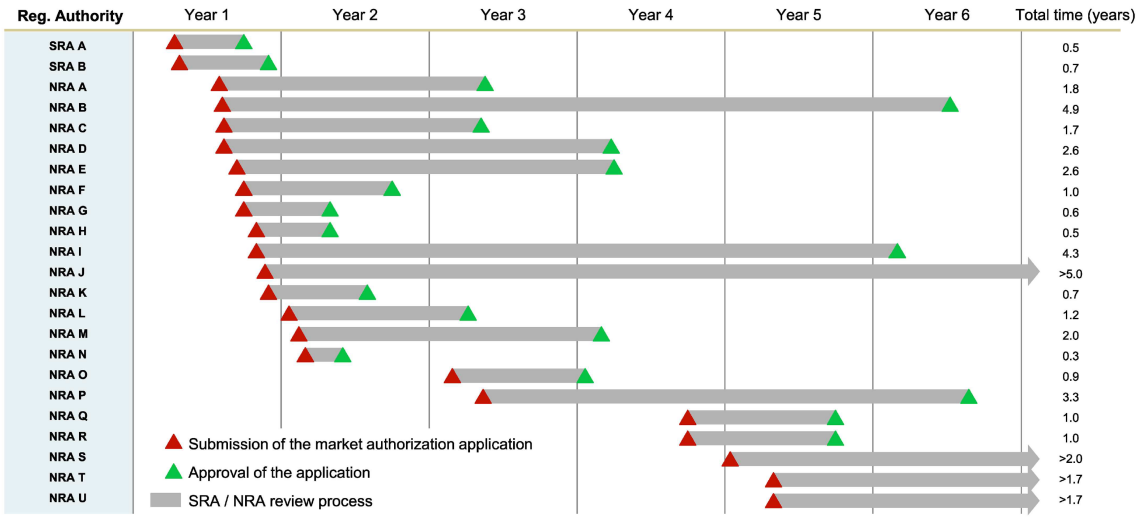

Fig 3. Registration Application Submissions and Approval in SSA for an anonymized antiretroviral drug, demonstrating 1) the variance in approval timelines across SSA countries and 2) the spread in manufacturer submissions. Red triangles represent the moment of dossier submission to the SRA or NRA, green triangles the market authorization approval by the NRA, and the grey arrows the review process.

Similar lags have been documented in other developing regions.[2]

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[1] Vincent Ahonkhai et al., "Speeding Access to Vaccines and Medicines in Low- and Middle-Income Countries: A Case for Change and a Framework for Optimized Product Market Authorization," *PLoS ONE* 11, no. 11 (2016). The reason for the anonymization is that the data at issue were shared with the Gates Foundation under confidentiality agreements.

[2] See, e.g., Hui Sin Teo, Christina Foerg-Wimmer, and Pei-Lyn Melissa Chew, "Medicines Regulatory Systems and Scope for Regulatory Harmonization in Southeast Asia" (World Bank, 2016), 7, https://doi.org/10.1596/26801.

Most analysts attribute this distressing pattern to a combination of four factors: (1) NMRAs in many developing countries are short on staff and resources and thus take longer to process applications than the FDA or EMA. (2) Aware that approval of a drug may trigger a statutory obligation on the part of the country's public-health service to buy it and then distribute it to the country's residents, the regulators sometimes deliberately tarry. (3) The modest size of the markets, particularly in small developing countries, makes patentees reluctant to invest resources in the regulatory-approval process. (4) Variations in the procedures used by developing countries to assess applications increase the costs borne by patentees and further reduce their eagerness to enter those markets.

Ongoing reform efforts in several parts of the world are gradually reducing the salience of the first and fourth factors. For example, the current status of the reform initiatives underway in South and Southeast Asia are examined in detail in Vu, "Regulatory Reform" (Document #3, p. 40, below). These initiatives should create additional opportunities for voluntary licensing. However, unless and until they come to fruition, overcoming this barrier may require ingenuity by private actors.

One possibility would involve conditioning voluntary licensing upon the establishment of a "fast-track" regulatory pathway in the country at issue. That option is explored in Samuel and Lilienfeld, "A Path Forward" (Document #1, p. 13, below).

Questions:

(a) In what ways can private actors facilitate the establishment of harmonized or regional regulatory-approval systems?

(b) How might the creation of a fast-track regulatory pathway be reconciled with the need to maintain the accuracy and consistency of the review process?

(c) What other ways might there be to reduce the impediments to regulatory approvals?

2. Triage

Negotiating VLs takes time and energy. Because those resources are scarce, it would be best if VLs were first deployed in contexts where they would do the most good – i.e., where unequal access to medicines is currently causing great harm, which a VL could alleviate more quickly than other tools.

The data necessary to identify the settings in which VLs could be most beneficial are related to but not the same as the data that firms already rely upon when comparing jurisdictions in terms to the potential profits that could be generated by marketing particular drugs therein.

Questions:

(a) What methods should be employed when determining and comparing the health benefits of deploying VLs?

(b) How might relevant data already gathered by innovator firms, governments, and NGOs be combined to facilitate such comparative assessments?

3. Enabling Evidence-Based Assessments

We can and should derive lessons concerning how best to structure a VL by examining the successes and failures of the licenses that have been negotiated and implemented to date. Document #2, below, (Kurshner & Hu, "Case Studies of Voluntary Licenses") is intended to facilitate this process by examining and assessing several extant VLs. It is equally important that, when crafting VLs in the future, we include mechanisms that will optimize our ability to learn from them – and thus continue to refine the VL methodology.

Questions:

(a) In what ways can we ensure that we have adequate information concerning baseline conditions prior to the deployment of a VL – thus enabling eventual evaluation of its successes or failures? (Could such baseline studies draw upon the data discussed above used for triage?)

(b) What mechanisms should be in place to gather information during the lifetime of a VL? (For example, how might we encourage both innovators and governments to share information about the merits or drawbacks of their experiences with VLs?)

(c) How can we ensure that assessments of VLs are independent and thus credible?

4. Complements

The effectiveness of a VL may depend on the presence in the relevant market of complements to the drug at issue. The most obvious of such complements is the availability (and affordability) of diagnostic systems – including tests that can determine which patients could benefit from the drug at issue.

Equally crucial is health-care infrastructure. Doctors or other personnel (such as community health workers) capable of performing diagnoses and prescribing treatments are essential, as is a network of distributors capable of getting the drugs to patients. Attention to these considerations should figure in the triage, discussed above, used to determine which potential VLs to pursue. In addition, we should strive to identify ways of supplementing VLs with ancillary initiatives designed to increase the availability of complements.

Questions:

(a) In situations where IP rights to a diagnostic test are held by a firm other than the firm holding the rights to an innovative drug, how might VLs to both be coordinated?

(b) Are there ways in which VLs can be used to stimulate increased investments by governments or NGOs in health-care infrastructure?

(c) To what extent should a VL address regulation of other actors (such as doctors or pharmacists) who are critical to ensuring that the VL results in improved access to the drug?

5. Technology Transfer

VLs are most effective when they are paired with initiatives to transfer to the licensees the know-how that is often essential to manufacture the drug at issue. Indeed, the manufacturing processes

for some drugs are sufficiently complex that VLs would be useless without such technology transfer. (This factor helps to explain the limited benefits that can be reaped by the "IP waiver" for COVID vaccines.)

How such technology transfers can be most efficiently achieved – without compelling the innovator/licensor to divert scarce personnel or resources from its own manufacturing operations – is not always obvious. One possibility would be an apprenticeship system of the sort discussed in Fisher, Okediji & Gehl Sampath, "Fostering Production of Pharmaceutical Products in Developing Countries" (Document #9, page 76, below).

Questions:

(a) What techniques for technology transfer have thus far proven most effective?

(b) Is it feasible to reconcile technology transfer necessary for a VL to be successful with the interest of the licensors to prevent competitors from gaining access to platform technologies?

(c) What approaches do innovators currently employ to secure valuable know-how from competitors while disclosing such know-how to developing-country licensees in the context of a VL?

6. Demand Stability

Potential licensees will not enter into VLs unless they can be reasonably confident that they can earn at least a modest profit. That, in turn, requires that the licensees have some assurance that demand for their products exists – and will continue to exist. The presence of a significant number of diagnosed patients in the country at issue is a necessary but not sufficient condition to provide the licensees that assurance.

One potential way of increasing their confidence is to offer exclusive licenses, but that approach creates a risk of needlessly high prices. Another potential tactic is to persuade the governments of developing countries (or the faith-based organizations that are often major purchasers of drugs) to enter into advance purchase agreements. This tactic is discussed in Samuel and Lilienfeld (Document #1) and Fisher, Okediji, and Gehl Sampath (Document #9).

Questions:

(a) How can VLs be coordinated with Advance Purchase Agreements?

(b) What other mechanisms can be employed to stabilize the demand for products governed by VLs?

(c) Is there an optimal number of licensees who should be offered VLs for a particular jurisdiction?

(d) If not, what factors should be considered when determining degrees of exclusivity?

7. Quality Control

It is of course crucial that the quality of the drugs produced pursuant to a VL remain high. A license agreement thus must contain mechanisms that ensure that the licensees will adhere to scrupulous manufacturing standards.

Less obvious but equally important is reducing the incidence with which authentic, high-quality drugs are displaced by substandard or falsified variants. Document #5 (Chun and Interiano, "The Prevalence of Falsified and Substandard Drugs") summarizes the current severity of this problem in developing countries. Not only does the presence of such drugs in the market kill people, it corrodes the willingness of innovators to enter into VLs, out of fear that the reputation of authentic drugs will be tainted if they are confused with ineffective impostors.

One way to address this problem is to integrate into VLs provisions that will augment post-market surveillance. Document #5 (Pericolo, "Post-Marketing Surveillance of Drugs") provides a survey of the surveillance systems that might be employed for this purpose. Document #6 (Jaffer, "Surveillance of Counterfeit COVID-19 Vaccines in South and Southeast Asia") then examines current efforts in one important region to prevent the dissemination of COVID vaccines.

Questions:

(a) What contractual provisions would be most efficacious in ensuring the quality of products manufactured under the authority of a VL?

(b) What contractual provisions or ancillary systems would most effectively curtail the distribution of falsified or substandard imposters?

(c) What regulatory oversight is needed to address the prevalence of falsified or substandard drugs without further exacerbating the challenge of the regulatory approval process discussed in Section 1, above?

8. Controlling Retail Prices

Reducing wholesale prices of drugs through VLs does not guarantee that patients will benefit. It is also essential to ensure that cost savings are passed through the distribution chain. How to achieve that requires close attention.

If the purchaser of the drugs produced under a VL were the public-health system of a developing country, this might be achieved through a commitment by the government to adopt (or to enforce existing) limits on the margins that distributors can charge. An alternative strategy is for the licensor to maintain a branded version of the relevant drug in the market in order to set a ceiling on the prices that can be charged for products manufactured pursuant to the VL.

Questions:

(a) What contractual provisions are most effective in limiting the prices that patients must pay?

(b) What noncontractual systems must be in place to prevent dilution of the effectiveness of VLs through the imposition of excessive margins?

9. Arbitrage

Most innovator firms are unwilling to enter into VLs without assurance that the drugs produced pursuant to the license will not be diverted from the countries and patients for which they are intended in ways that undermine the firms' principal markets. National laws governing (a) parallel importation of all patented products and (b) marketing approval of pharmaceutical products substantially limit arbitrage. However, they may not be sufficient to satisfy the firms.

Efforts by firms to supplement the default legal barriers with additional barricades are sharply criticized by many NGOs. Among their arguments are that these restrictions go further than necessary to protect the firms' legitimate commercial interests – and thus result in needless deaths. These contentions are reviewed in Fahrenkopf and Ani Zotti, "Criticisms of Voluntary Licensing" (Document #8, below).

Questions:

(a) What contractual provisions – or initiatives by the governments of the countries to which a VL applies -- could help limit arbitrage?

(b) How can limits on arbitrage be best reconciled with the overarching goal of voluntary licensing: the promotion of public health and the reduction of inequality in access to medicines?

10. Local Production

Among the other grounds on which VLs are sometimes criticized is that they fail to address (and indeed may exacerbate) one of the root causes of the global inequality in access to medicines – namely, the lack of pharmaceutical manufacturing capacity in developing countries. (The arguments for and against striving to augment local manufacturing capacity are examined in detail in Fisher, Okediji, and Gehl Sampath [Document #9].)

Most of the existing VLs (reviewed in Document #3) are indeed subject to criticism on this basis. However, a VL could be used to increase, rather than corrode, local manufacturing capacity – simply by including, in the set of licensees, firms based in the country to which the VL pertains. More radically, only local firms could be eligible for VLs.

Questions:

(a) Under what circumstances, if any, should a VL incorporate provisions designed to favor local manufacturers?

(b) Should a preference for local firms engaged in "fill and finish" suffice, or should preference be given to local producers of the relevant APIs?

(c) If a VL pertains to multiple countries, what should count as a "local" manufacturer?

11. Geographic Scope

The larger the set of countries covered by a VL, the greater the health benefit. For this reason, public-health advocates urge licensors to reach broadly – to include, for example, upper-middle-income countries as well as LMICs and LICs. See, for example, Cole et al., "Enabling Broad

Access to Best-in-Class HIV Treatment" (Document #10, below). Licensors often object, arguing that such breadth would force them to relinquish potentially profitable emerging markets.

One possible strategy for bridging this divide is to adjust the royalty rate charged under the VL to reflect the ability of each country to pay for access to the drug. (See, for example, the ViiV DTG license discussed in Kurschner & Hu (Document #2, p. 29), and Cole et al. (Document #10, p. 128).

A potentially mitigating factor is that broad geographic coverage can help stabilize demand (discussed in Section 6, above), which can benefit both licensors and licensees. A complication: Is it politically feasible to withdraw a VL (and thus shrink geographic coverage) when a country's economy rises above a particular level?

Questions:

(a) What are the best ways of achieving the benefits of broad geographic coverage while minimizing the disadvantages?

(b) Does the optimal or appropriate geographic scope vary with the nature of a medicine or vaccine?

(c) Under what circumstances, if any, is it justifiable to design a VL in a way that results in treating some countries more favorably than others?

12. Customization

A uniform template for VLs is surely infeasible; the terms that are included in such agreements will surely vary by context. But it may be possible to identify the considerations that the drafters of such agreements should take into account when negotiating details.

Questions: What factors should affect the content of license provisions pertaining to each of the following?

(a) The royalty rate

(b) Duration (e.g., the remaining term of the patent and associated data-exclusivity rights – or something shorter)

(c) Grantbacks (i.e., the terms on which a licensee must make available to the licensor any improvements in the product or the manufacturing process)

(d) Transparency (i.e., the degree to which the terms of the license are made public)

(e) Grounds for termination

13. Levers and Nudges

Arguably, the term, "voluntary license," is misleading. It would be more accurate to acknowledge that licenses can be arranged on a spectrum. At one extreme are licenses motivated only by the prospect of earning a profit and/or by altruism. At the opposite extreme are licenses that are altogether compulsory – for example, are imposed upon an unwilling patentee by a national government exercising the power it enjoys under Article 30 of the TRIPS Agreement. Between these poles are myriad intermediate cases.

Various levers can be employed to nudge companies to execute licenses they might otherwise decline to issue. The most obvious is that, by threatening to initiate the process of imposing a compulsory license, a developing country can spur negotiation of a noncompulsory one. Criticisms of this tactic (among others) are reviewed in Fahrenkopf and Zotti, "Criticisms of Voluntary Licensing" (Document #8, below).

Less obvious but potentially potent is a threat by the government of the United States to use its authority under 42 USC 1498 – a lever examined in detail in Nytes & Alex Kubie, "The Power of Section 1498" (Document #7, below). A vaguer source of pressure is pressure from stockholders to set and achieve ESG goals.

Questions:

(a) To what extent can and should such levers be employed to increase the usage of VLs?

(b) To what extent can and should such levers be employed to influence the terms of VLs (e.g., the content of the provisions itemized in the preceding section)?

14. Limitations

As mentioned at the outset, the VL strategy is not a panacea. Among the goals for which it is ineffective is optimizing the development of <u>new</u> drugs aimed at preventing or curbing the diseases now rampant in developing countries. It also has little power to offset the inefficiently low level of incentives to develop vaccines, as opposed to therapies. Additional limitations are examined in reviewed in Fahrenkopf and Zotti, "Criticisms of Voluntary Licensing" (Document #8, below).

Identification and fair assessment of these limitations is necessary if an effort to promote VLs is not to cause a reduction of the time and resources devoted to other strategies for combatting the global health crisis.

Question:

(a) What can even an optimally tuned VL not achieve?

(b) What other forms of activism and/or law reform are necessary to fill those gaps?

Documents

1. Clifford Samuel & Claudio Lilienfeld, "A Path Forward on Access & IP for COVID Vaccines and Beyond"

Biocentury, July 2, 2021

An old African proverb states that if you want to go fast, go alone. But if you want to go far, go together. As the WTO Trips Council convenes to discuss access and patents in the context of COVID, it's time to create a comprehensive set of principles and standards that will serve as a template for all other pandemic responses going forward.

Such an undertaking cannot be accomplished by one organization such as the WTO, or by one act such as waiving IP. Whatever the decisions, a viable outcome will only be accomplished if we go together and find a middle ground that is win-win-win. The WTO acting alone would be like one hand trying to clap. Success depends on a coordinated and strategic approach, incorporating numerous aspects and multiple steps.

Voluntary licensing should be at the core of a global, standard set of tools to address urgent medical crises such as COVID, but this strategy alone is not enough. An array of actors must play their roles and wield tools that complement and incentivize the voluntary licenses. Key roles will have to be played by governments in both high- and low/middle-income countries, international organizations such as the WHO and WTO, civil society, and other private actors in addition to the innovator biopharma companies.

The voluntary licensing approach taken by Gilead Sciences Inc., which began in 2006, has allowed millions of people across low- and middle-income countries to have access to low-cost, high-quality generic medicines for HIV, viral hepatitis and COVID-19.

But the act of voluntary licensing is the easy part. For any international approach, the solution goes far beyond simply a WTO action on IP rights. Numerous other pieces of the puzzle need to fit together with voluntary licensing to make a whole and enduring solution to the global access challenge — a continuation of ad hoc approaches means failure.

A global compact built around the following series of factors would not only provide a structure for preparedness and response to future health emergencies, but could help revitalize multilateral institutions that are struggling to demonstrate their saliency. Moreover, it would go a great distance to reducing global divisions and polarization. Together, everyone can go far.

Quality standards and a regulatory pathway

Technology Transfer: Technology transfer by innovator biopharma companies, in conjunction with voluntary licensing, should be a standard practice to enable the speedy transition to generics and ensure that generics manufacturers benefit from the highest manufacturing standards upheld by the innovator company. Gilead offered this up front as part of its licensing agreements.

Tentative FDA Approval and WHO Pre-Qualification: Two strategies, tentative FDA approval and WHO Pre-Qualification, serve important dual purposes of incentivizing high-quality standards and stimulating voluntary licensing by providing pathways for expedited approvals by critical agencies.

The U.S. government's PEPFAR (President's Emergency Program for AIDS Relief) program represents a model to be replicated by other leading regulatory agencies for future pandemics. Under PEPFAR, FDA enabled an expedited review process in which generics manufacturers operating under voluntary license could submit an ANDA that addressed the safety, efficacy, manufacturing and quality standards, while referencing the clinical and preclinical sections of the original manufacturers' data on file with FDA. A tentative FDA approval did not allow for marketing in the U.S., due to existing patent protections, but qualified the product for sale in resource-challenged countries under the PEPFAR program. PEPFAR could only purchase generic medicines that gained tentative approval. Note that tentative FDA approval in effect created an alternative to the WHO Pre-Qualification process. Both are intended to ensure minimum quality standards are met; however, WHO Pre-Qualification generally takes much longer and is quite costly for generics manufactures. The WHO Pre-Qualification process should be improved, to provide a pathway equal in efficiency to FDA tentative approval.

Regulatory Pathway in Low/Middle Income Countries: Countries should agree to put in place a Fast-Track regulatory approval pathway for COVID-19 and other health emergencies, for medicines manufactured under voluntary license. This is an incentive for manufacturers to move rapidly to implement voluntary licenses and submit their dossiers for approval in countries where the need for the medicines is great.

It is important that countries commit to ensuring that the innovator medicine be approved before or at the same time as the licensed generics. The innovator (or "branded") regulatory submission is needed for generics manufacturers to have the clinical and preclinical data of the original manufacturer's dossier for their own applications for regulatory approval.

There are many cases where countries have approved a licensed generic product before an innovator's, even though the regulatory submission was based on clinical data provided by the innovator. This backward regulatory approval is a practice that must be ended since it represents one of the critical factors that disincentivize biopharmas from leaning in as true partners in this process. Fixing it would demonstrate those governments' partnership bona fides.

Furthermore, such regulatory rationalization would align well with needed rationalization of pricing schemes (discussed below), serving the interests of stimulating and facilitating the global expansion of voluntary licenses across the pharma industry.

Capacity Building: Adequate Storage, Diagnostics, Training & Education

A key barrier developing countries face as they respond to pandemics and other life-threatening illnesses is their deficit in medical capacity and infrastructure. Addressing capacity deficits is something that all actors must join hands on and this must be coordinated with and implemented alongside any pandemic response volunteer licenses.

During the rollout of Gilead's voluntary licensing program to treat HIV/AIDS, a sobering reality was that some countries lacked the necessary medical infrastructure to treat patients. In some cases, there weren't enough available doctors or the necessary training to get doctors up to speed on new therapeutic options to treat HIV/AIDS. Additionally, the necessary diagnostic tools were missing; hospitals lacked both the staff and equipment necessary to make a proper differential diagnosis. And there was inadequate cold chain and storage for medicines. Gilead's access program included resources devoted to helping address many of these issues. The lead role, however, must be played by host nation governments, which must do their utmost to expand access to healthcare more broadly, and donors must step up as well, from governments to private actors and NGOs.

Financing of Health: PEPFAR, the Global Fund for HIV, TB and Malaria, and myriad other entities have budgeted untold billions of dollars to the HIV response. In addition to purchasing medicines, these aid dollars were spent on logistics, diagnostics, infrastructure, training, capacity building, and many other aspects of creating a system by which the HIV/AIDS challenge could be met.

The same multiplicity of resources and intensive coordination among actors will be essential for combating any pandemic.

Government Policy, Participation & Support

Patent-related incentives: The U.S. government could further incentivize pharmas that hold patents on life-saving medicines via the Patents for Humanity Program, which rewards patent owners who use their innovative medicines to address humanitarian challenges.

The winners receive a certificate that can be used to accelerate the companies' patent applications. This is a valuable voucher that can be used to accelerate future product submissions to FDA, or the voucher can be sold to another company. Other governments around the world could similarly reward "humanitarian" innovations.

Patents in Low/Middle Income Countries: Although the spotlight in debates on access to medicines commonly falls on the WTO's waivers of certain patent requirements for poor countries, voluntary licenses provide an entirely different incentive process.

Patent protections in conjunction with voluntary licenses are an important part of the quality assurance equation — this ensures that only qualified producers, the voluntary licensees — will be authorized to produce the medicines.

This places priority on two factors: expedited patenting by governments of low/middle income countries for innovator medicines offered under voluntary licenses; and patent enforcement prioritized by the same governments for innovator medicines made available under those licenses. In addition to ensuring quality, the policy provides two important incentives for innovator companies to enter voluntary licenses. The outcome is win-win. The tired "us versus them," Big

Pharma versus low/middle income countries, adversarial discourse on patenting and enforcement simply drives innovators and the needy apart — and towards a lose-lose loop.

Pricing and Price Controls in Low/Middle Income Countries: Pricing policies are also part of the equation. The Gilead experience taught us that the roles of the innovator product and government pricing policy can be vastly underappreciated.

We set a price in low/middle income countries (countries where Gilead's Indian licensees were authorized to sell) derived from a combination of gross national income (GNI) per capita and disease burden metrics.

This price was a fraction of the Gilead-branded price in high-income countries. This was not so that the Gilead product could remain competitive in markets where multiple licensees were selling their licensed generic versions for less. Generics would always, logically, price the drugs below Gilead's branded price. However, if Gilead was not in the market with its brand, or if Gilead had priced its branded product as it did in high-income countries, then the generic prices would climb to levels that undermined access for the poorest of the poor and reduced the ability of the governments to afford to treat their populations.

As cynical as it may sound, more than enough situations arose where governments in low/middle income countries undercut the entry of a low-priced Gilead-branded drug (either deliberately or de facto through regulatory delays or other impediments) with the effect of facilitating profiteering by local companies who often would mark up the licensed generic drugs that they were distributing in that country — resulting in negligible access to those medicines by the neediest people in that country.

In some instances, we also observed governments adding import taxes or tariffs, driving up the cost of the originator product and causing an overall rise in all drug prices in the country, reducing access further.

Price controls

One of the big challenges is how to address the access needs of countries that have sizeable wealthy and middle-class populations layered atop large populations of poor people.
Billionaires, wealthy and middle-class members of the "new economy" in India, for example, conservatively number between 50 million and 100 million, a larger population than the entire population of most high-income countries.

Instead of a one-size-fits-all price control policy that sets national prices at levels needed by the poor, a tiered pricing approach would set a low price for national, state and local government medical systems serving the majority of their populations, yet allow higher pricing for those who can afford it.

Beyond the basic fairness, this provides a practical benefit. Generics manufacturers in low/middle income countries have perfected low-margin high volume business practices in markets with lower labor costs.

Innovator companies mostly operate out of higher cost markets including those with much higher labor costs. At Gilead, we witnessed price controls set to cap generic drug prices that were below the cost of manufacturing the Gilead-branded medicine, essentially blocking the branded product from the market — even though wealthy people in those same countries could afford the usual global luxuries.

It makes no sense for those same people not to have the choice of branded medicines when those medicines are made available at lower cost to the poorer populations of the country via voluntary licenses. An exclusion or waiver from price controls for branded medicines where those same medicines are available via voluntary licenses would provide an incentive to innovators to enter into those voluntary licenses knowing that a fraction of the market might still be available.

Advance Purchase Agreements: Governments, multilateral organizations, and private donors/NGOs should commit to purchasing standard quantities of product so that manufacturers have a sense of the demand and can plan effectively to address the overall need.

A good example is what has occurred with COVID-19 vaccines, wherein NGOs and G7 governments were willing to provide advance purchase orders of large quantities of vaccines. This enabled manufacturers to source raw materials and quickly ramp up manufacturing given solid purchase orders in hand.

Pharma company commitment

The pharmaceutical industry has a huge role to play in this entire process. In addition to supporting the R&D costs, pharma's role would entail entering into voluntary licensing agreements to serve the needs of emerging economies hit hardest by pandemic, and providing technology transfer, know-how and technical assistance to licensed generic entities that are proceeding with production of medicines.

Innovator companies must be committed to the process and cannot simply hand things over and walk away. Generics manufacturers run into manufacturing problems from time to time and require assistance from the originator company. Originator companies typically have a cadre of experts, as well as training and educational materials, that could be of value to governments, NGOs and generics manufacturers as these entities work to train their in-country staff on the appropriate use of medicines.

Clifford M. Samuel recently served as SVP for global patient solutions at Gilead, overseeing all operations across low-, lower middle-, and middle-income countries. Claudio Lilienfeld was an adviser to Samuel and served as senior director for international government affairs at Gilead. Both are now independent consultants.

2. Tatiana Kurschner & Alice Hu, Case Studies

April 2022

Introduction

This memorandum provides an overview of notable case studies of voluntary licensing and technology transfer for essential medicines by major pharmaceutical companies. It first examines successful cases before reviewing cases of refusal or lack of success. It concludes by discussing several factors that affect whether a voluntary-licensing initiative will succeed.

Successful case studies

Gilead: HIV

Gilead was among the first pharmaceutical companies to engage in voluntary generic licensing with low-income countries. Gilead combines distribution of branded drugs under more affordable tiered pricing models with voluntary licenses for generic manufacturers; the competition helps ensure minimum standards of quality and price control over generic drugs.[3]

Gilead currently employs three pricing tiers[4]:

- "No-profit pricing" for low-income countries
- "Low-profit pricing" for lower-middle income countries
- Volume-based pricing negotiated on a country-by-country basis for upper-middle and high-income countries

Gilead licenses two ARVs, tenofovir disoproxil (marketed as Viread) and emtricitabine/TDF (marketed as Truvada).[5] The medicines are licensed to twenty-four generic manufacturers, sixteen of which are through the MPP (including Cipla).[6] To date, 11.5 million people living with HIV are estimated to be on Gilead-based treatment, 98% of whom are receiving the licensed generic drug. Further, 98% of Gilead's HIV medicines used in low- and middle-income countries are produced and sold by licensees, who have used process chemistry and large-scale manufacturing to lower prices by over 85% since 2006.[7]

In 2003, Gilead first launched its Access Program for ARV medicines, initially allowing every African state and fifteen other low-income countries to purchase ARVs directly from Gilead at

[3] "Our Approach to Treatment Expansion," Gilead Sciences, Inc., 5.
[4] Ibid.
[5] "Impact Report: Access Operations & Emerging Markets," Gilead Sciences Inc., accessed April 7, 2022, Inc.,https://www.gilead.com/-/media/files/pdfs/other/gilead-impact-report.pdf?la=en&hash=19D9E016336A869CA0DF24B0426D47C0.
[6] "Access Partnerships," Gilead Sciences, Inc., accessed April 7, 2022, https://www.gilead.com/purpose/medication-access/global-access/access-partnerships.
[7] Ibid.

"no profit" pricing. Within the first year, only about one hundred patients had received medication.[8]

In 2005, Gilead restructured the Program, implementing the following key changes:

- Registering its products rather than relying on import permits, which had significantly limited importation
- Expanding the program to more broadly defined low-income countries and to lower middle-income countries with high rates of HIV infection, increasing coverage from 68 to 97 countries
- Introducing a two-tiered pricing structure—"no profit" Low-Income Pricing Tier, and a limited-profit Lower Middle-Income Pricing Tier
- Increasing manufacturing capability, partnering with Aspen Pharmacare (South Africa) to manufacture and distribute Gilead's two ARVs, Viread and Truvada, in Africa. Gilead made a full technology transfer to Aspen.

By the end of 2006, 31,000 patients were on Gilead's ARVs.[9]

In 2006, Gilead restructured the Access Program again, accounting for lessons learned from the first restructuring:

Partnerships with local distributors

After struggling with local differences in drug approval requirements and processes, Gilead entered into agreements with regional distributors who would register the products, run medical education programs, and handle distribution and forecasting. By 2009, Gilead's eleven regional distributors and forty-eight sub-distributors covered 130 countries across Africa, the Asia-Pacific, Central and Eastern Europe, the Middle East, and Latin America and the Caribbean.[10]

Distributors were permitted to levy a 10–15% markup of the products to ensure Gilead's branded medicines would retain a market presence. Gilead manufactured the final, packaged product for nine of Gilead's eleven distributors; Aspen manufactured the product for distribution in Africa and China.[11]

Voluntary licensing with local drug manufacturers

Gilead offered non-exclusive licenses to generic drug manufacturers in India, which permitted companies to produce tenofovir disoproxil fumarate (TDF) (Viread's active pharmaceutical ingredient), generic versions of Viread and Truvada, other fixed-dose combinations containing Gilead drugs, and pediatric formulations. Licensees could sell the drugs in India and export them to 94 countries, and sell TDF to or purchase TDF from other Gilead licensees (or Gilead itself)

[8] V. Katsuri Rangan and Katharine Lee, "Gilead Sciences, Inc.: Access Program" (Harvard Business School, February 3, 2010), 7.
[9] Rangan and Lee, 7–8.
[10] Rangan and Lee, 9–11.
[11] Rangan and Lee, 10.

royalty-free. Manufacturers set their own prices, but paid 5% sales royalties to Gilead, and had to seek FDA tentative approval or WHO pre-qualification for quality control. In 2007, Gilead also gave Aspen, Gilead's branded South African distributor, a license to produce generic ARVs on the same terms.[12]

By 2009, Gilead had entered voluntary licenses with thirteen Indian generic manufacturers and Aspen, and had registered Viread in 78 countries and Truvada in 74 countries. 678,205 patients in developing countries were taking medicines containing TDF – 326,660 on Gilead drugs and 351,545 on generics.[13]

In 2012, Gilead also reached an agreement with Indian manufacturers to produce a new "low-cost, high quality generic" FTC (a component of Truvada) for developing countries.[14]

By keeping the branded Gilead medications on the market, Gilead successfully forced down generics' prices, preventing them from being sold at levels above the affordable pricing Gilead itself was willing to sell at. In 2018, Truvada-equivalent generics were being sold for as low as USD $3.70 per month and Viread-equivalent generics were sold for as low as $1.80 per month.[15]

Challenges

The Gilead model created certain problematic competition between its distributors and its generic licensees. Generic manufacturers were permitted to sell the products in 94 other low-income countries (although not lower middle-income countries, with the exception of Thailand), which forced some distributors selling the non-generic Gilead products to lower their prices to compete.[16]

Gilead also premised its generic licensing model on assumed future patent approval in India. This became a problem when Cipla, a generics manufacturer who did not strike a licensing deal with Gilead, challenged the Viread patent.[17] In 2011, Gilead amended the licensing agreements to charge only a 3% royalty on TDF, pending an increase to 5% upon patent approval.[18]

Gilead: Hepatitis C

Gilead currently licenses its entire HCV portfolio to fourteen generic manufacturers.[19]

[12] Rangan and Lee, 11–12.
[13] Rangan and Lee, 12–13.
[14] "Access Partnerships," Gilead.
[15] "Our Approach to Treatment Expansion," Gilead Sciences, Inc., 10. (Appendix C)
[16] Rangan and Lee, 15.
[17] Rangan and Lee, 14.
[18] Gilead Sciences, Inc., "2011 expanded HIV / HBV voluntary and hepatitis B license agreement," 2011, https://www.gilead.com/-/media/files/pdfs/other/expandedtermslicenseagreement.pdf?la=en&hash=2367AFA7A30E1326499EA316D9C74D97, 13.
[19] "Access Partnerships," Gilead.

Following the success of the ARV Access Program, Gilead created the Access Operations and Emerging Markets Organization, responsible for promoting access to medicine in 130 countries.[20]

In 2013, Gilead received approval for a HCV therapeutic, sofosbuvir (Sovaldi), which became the leading second-generation treatment for HCV. Sovaldi was launched at different price points in different developed nations and received intense criticism and bipartisan investigation by U.S. senators for its high price. In late 2014, Gilead also received FDA approval for Harvoni, combining sofosbuvir with a second novel compound, ledipasvir, in a once-daily combination pill. Gilead faced competition from other large pharmaceutical companies introducing competing second-generation therapeutics, notably AbbVie's multi-drug Viekira Pak regimen.[21]

In 2014, Gilead reached licensing agreements with seven Indian generic manufacturers to produce HCV medications for 91 countries. Gilead also began working with low- and middle-income countries to provide affordable branded Sovaldi and Harvoni medications, using tiered pricing.[22]

Generic licensees were required to pay Gilead a royalty of 7% of net sales, and were permitted to produce and sell the active pharmaceutical ingredient to other licensees without royalties.[23] In 2017, royalties for products sold in Malaysia, Thailand, and Ukraine were 12%, while all other countries remained at 7%.[24]

Roche: HIV

Through its Technology Transfer Program, Hoffman La Roche in 2006 entered into a voluntary licensing agreement for saquinavir, a protease inhibitor, with three African companies, Aspen Pharmacare of South Africa as well as Cosmos and Universal Corporation of Kenya. Saquinavir is a second-line HIV/AIDS treatment in low-income countries.[25] The program provided the local manufacturers necessary skills to produce generic versions of the HIV medications program, and was completed in 2010.[26]

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[20] V. Kasturi Rangan, Vikram Rangan, and David E. Bloom, "Gilead: Hepatitis-C Access Strategy (A)" (Harvard Business School, February 5, 2015), 4.
[21] Rangan, Rangan and Bloom, 8, 10–11, 14.
[22] Gilead Sciences, Inc., "Gilead Sciences Policy Position: Innovating and Expanding Access to Hepatitis C Treatments," October 2014, https://www.gilead.com/~/media/Files/pdfs/Policy-Perspectives/ExpandingAccesstoHCVTreatments10214.pdf, 1.
[23] Gilead Sciences, Inc., "2014 original HCV voluntary license agreement," 2014, https://www.gilead.com/-/media/files/pdfs/other/2014_original_hcv_licensing_agreement.pdf?la=en&hash=DDB7C80B0505004C559B08AFC2665C00, 8.
[24] Gilead Sciences, Inc., "2017 amended & restated voluntary HCV license agreement," 2017, https://www.gilead.com/-/media/files/pdfs/other/form-ar-hcv-license-agmt-gild-11202017.pdf?la=en&hash=EA13A53F28CE66946255B7369B57EEFE, 11.
[25] "Roche To Transfer Technology for Protease Inhibitor Saquinavir to Generic Drug Companies in Developing Countries," KHN, accessed April 7, 2022, https://khn.org/morning-breakout/dr00034776.
[26] "Access to HIV/AIDS Diagnostics and Anti-retroviral Treatments," Global Health Progress, accessed April 7, 2022, https://globalhealthprogress.org/collaboration/access-to-hiv-aids-diagnostics-and-anti-retroviral-treatments.

Johnson & Johnson: HIV

Tibotec Pharmaceuticals is an Ireland-based pharmaceutical company owned by Johnson & Johnson. The company specializes in the discovery and development of new medicines for infectious diseases including HIV, and plays a key role in J&J's Global Access & Partnerships Program.[27]

Through the Program, Tibotec had voluntary licensing agreements for darunavir and etravirine with generic manufacturers Aspen Pharmacare of South Africa and Emcure Pharmaceuticals of India. Tibotec also has non-exclusive voluntary licensing agreements for the investigational drug rilpivirine hydrochloride (TMC278) with Aspen as well as Hetero Drugs Limited and Matrix Laboratories Limited (a Mylan company) of India, pending approval for use with other antiretroviral agents in the treatment of treatment-naive HIV-1 infected adults. The agreements encompass sub-Saharan Africa (SSA), Least Developed Countries (LDCs), and India to ease high HIV burden and support generic competition.

Through the agreements, Tibotec has provided the generic manufacturers with the technical information and knowledge to manufacture the medicines. For TMC278, the generic manufacturers will pay royalties ranging from two to five percent. The generic manufacturers are responsible for timely regulatory filing for generic TMC278 and for seeking pre-qualification from the World Health Organization (WHO) and ANDA approvals. To ensure affordability, the generic manufacturers are required to cap their gross profit margin on the sale of TMC278.

Johnson & Johnson: COVID-19

Johnson & Johnson has made a voluntary licensing agreement with Aspen Pharmacare of South Africa, a deal that Aspen called a "game-changer" for Africa's vaccine sovereignty. Under the agreement, Aspen receives the drug substances from J&J, which it uses to manufacture and distribute finished, Aspen-branded vaccine shots. Aspen is making the vaccines available to 55 African Union member states as well as multilateral organizations supporting Africa's Covid-19 vaccination efforts, such as the African Vaccine Acquisition Trust and the COVAX Facility.[28]

The licensing agreement advances two goals: creating Africa's first "de facto" COVID-19 vaccine via the Aspen-branded shot, and building vaccine manufacturing capacity on the continent.[29]

GlaxoSmithKline: Tuberculosis

In addition to its voluntary license through the MPP (discussed below), GlaxoSmithKline (GSK) also licensed M72/AS01E, a tuberculosis (TB) vaccine candidate, to the Bill & Melinda Gates

[27] "Tibotec Signs Multiple Agreements With Generic Manufacturers to Provide Access to New HIV Treatment,"Johnson & Johnson, Jan. 27, 2011, https://johnsonandjohnson.gcs-web.com/news-releases/news-release-details/tibotec-signs-multiple-agreements-generic-manufacturers-provide.
[28] Fraiser Kansteiner, "J&J inks vaccine licensing deal with Aspen, paving the way for Africa's first local COVID-19 shot," March 9, 2022, https://www.fiercepharma.com/pharma/johnson-johnson-locks-vaccine-licensing-deal-aspen-teeing-africas-first-local-covid-19-shot.
[29] Ibid.

Medical Research Institute (MRI). The aim of the license is to advance development of a vaccine for adolescents and adults in low-income countries with high TB burdens. There is currently no approved vaccine for adolescents and adults, who account for 89% of people who fall ill with TB. Bacille Calmette-Guerin (BCG), a live attenuated vaccine, is effective in preventing severe TB disease in infants and young children, but offers limited protection for adolescents and adults. Gates Foundation was one of the funders of GSK's development of M72/AS01E.[30]

Medicines Patent Pool

The Medicines Patent Pool (MPP) is a licensing mechanism established by Unitaid in 2010 to increase access to affordable medicines in LMICs through non-exclusive voluntary licensing agreements.[31] It is the first patent pool for medicines. Initially focused on HIV, tuberculosis and malaria medicines, the MPP has expanded to other medicines including for Covid-19.

The MPP was founded in response to changes in intellectual property. In the past, low-cost generic HIV medicines were available in many low-income countries because they were not patented in those countries and could be produced at a low cost.[32] For example, India was a base for general drug manufacturing. That is no longer possible because the World Trade Organization now requires all countries to comply with a minimum set of patenting practices. The MPP works on getting patent holders to offer voluntary licensing so low-cost generic versions of new medicines are available in low income countries.

The MPP's funding comes from Unitaid, a global health organization hosted by the WHO. The main source of Unitaid's funding is an airline ticket tax in ten countries.[33] The organization's primary donors are France, the United Kingdom, Norway, the Bill & Melinda Gates Foundation, Brazil, Spain, the Republic of Korea, and Chile.

The MPP operates by negotiating licenses with patent holders, and then licensing patents to multiple generic manufacturers; produced treatments are made available in certain LMICs, sometimes with royalty fees.[34] The MPP also plays an important role in fixed-dose combination medicines. For example, the treatment of HIV always requires multiple medicines, whose patents are held by different entities. But in low income countries, it is difficult to effectively implement a treatment involving several pills. The MPP brings together patents for different medicines to manufacture a single medication.

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[30] "GSK licenses tuberculosis vaccine candidate to the Bill & Melinda Gates Medical Research Institute," GSK, accessed April 7, 2022, https://www.gsk.com/en-gb/media/press-releases/gsk-licenses-tuberculosis-vaccine-candidate-to-the-bill-melinda-gates-medical-research-institute-for-continued-development.

[31] "About Us," Medicines Patent Pool, accessed April 7, 2022, https://medicinespatentpool.org/who-we-are/about-us.

[32] "A Conversation with Ellen 't Hoen, Executive Director of Medicines Patent Pool," Harvard Medical School Science in the News, December 1, 2020, https://sitn.hms.harvard.edu/flash/2010/a-conversation-with-ellen-t-hoen-executive-director-of-medicines-patent-pool/.

[33] The countries are Cameroon, Chile, Congo, France, Guinea, Madagascar, Mali, Mauritius, Niger and the Republic of Korea.

[34] "Licensing for Public Health," Medicines Patent Pool, accessed April 7, 2022, https://medicinespatentpool.org/what-we-do/licensing-for-public-health.

At present, MPP holds licenses are from fifteen patent holders for thirteen HIV antiretrovirals, one HIV technology platform, three hepatitis C direct-acting antivirals, a tuberculosis treatment, two long-acting technologies, two COVID-19 experimental oral antiviral treatments, and a COVID-19 serological antibody diagnostic test.[35] MPP licenses cover more than 140 countries.[36]

There are three main incentives for pharmaceutical companies to join the pool. First, companies gain reputational benefits as joining the MPP is a highly visible way to demonstrate corporate responsibility. Second, patent holders receive royalty payments from drug sales while maintaining their patent ownership. Third, there are long-term strategic benefits to sharing drug production with more companies as it is unfeasible for a few companies to produce all the drugs needed. Because licensing is entirely voluntary, the MPP relies on public awareness and advocacy pertaining to key stakeholders, particularly in the U.S. as most of the relevant patent holders are U.S.-based.[37]

MPP/AbbVie

In 2014, AbbVie and MPP reached a royalty-free licensing agreement for pediatric use of lopinavir and ritonavir (LPV/r), used to treat HIV. Low-cost versions of LPV/r can be manufactured for generic sale in 102 countries. The active pharmaceutical ingredient and finished product can be manufactured anywhere in the world, and sold in at least 102 countries. Licensees must obtain WHO pre-qualification or equivalent approval or or receive temporary approval by a WHO Expert Review Panel.[38]

In 2015, a royalty-free license for adult formulations of LPV/r was also agreed on the same terms, extending only to all 54 African countries.[39]

In 2018, MPP also reached a royalty-free non-exclusive voluntary licensing agreement with AbbVie for glecaprevir/pibrentasvir (G/P), an HCV treatment. The license allows production for 96 LMICs, comprising 47.5% of the world's HCV cases. Licensees must obtain WHO pre-qualification or equivalent approval or or receive temporary approval by a WHO Expert Review Panel. NGOs, UN-related organizations, non-profits, and funding mechanisms like Unitaid or PEPFAR based outside the sales territory can procure generic G/P for use within the eligible countries. AbbVie will provide clinical data and non-commercial, non-manufacturing documents to assist in registering the drug.[40]

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[35] "About Us," Medicines Patent Pool, accessed April 7, 2022, https://medicinespatentpool.org/who-we-are/about-us; "Licences," Medicines Patent Pool, accessed April 7, 2022, https://medicinespatentpool.org/progress-achievements/licences.

[36] "Licensing for Public Health," Medicines Patent Pool.

[37] "A Conversation with Ellen 't Hoen," Harvard Medical School Science in the News.

[38] "Lopinavir, Ritonavir (LPV/r) Paediatrics," Medicines Patent Pool, accessed April 7, 2022, https://medicinespatentpool.org/licence-post/lopinavir-ritonavir-lpv-r-paediatrics.

[39] Ibid.

[40] "Glecaprevir/Pibrentasvir (G/P)," Medicines Patent Pool, accessed April 7, 2022, https://medicinespatentpool.org/licence-post/glecaprevir-pibrentasvir-g-p.

MPP/Bristol Myers Squibb

In 2013, BMS and MPP agreed to a license for atazanavir (ATV), used to treat HIV in adults and children. In 2017, the license was extended to 12 countries, and now allows generic manufacture of ATC in at least 122 countries. The generic active pharmaceutical ingredient and finished product can be produced anywhere in the world. The license commands a 3% royalty for sale of adult formulations where ATV patents are in force; royalties are paid to community-based HIV organizations in the country of sale. There are no royalties for pediatric formulations, or adult formulations in Sub-Saharan Africa or India. The license provides sublicensees with a technology transfer, which they are not obligated to use; licensees not using the technology transfer may sell outside the 122 permissible countries if no patent is infringed. Licensees must obtain WHO pre-qualification approval, or equivalent approval.[41]

In 2015, BMS and MPP agreed to a license for BMS's direct-acting antiviral, daclatasvir (DAC). Generic manufacturers can currently produce BMS's DAC HCV treatment for sale in 143 countries under a royalty-free license, including 112 LMICs and Albania, Argentina, Armenia, Belarus, Bosnia and Herzegovina, Brazil, Bulgaria, Chile, China, Colombia, Egypt, Jordan, Kazakhstan, Kosovo, Kyrgyzstan, Lebanon, Malaysia, Mexico, Moldova, Montenegro, North Macedonia, Peru, Romania, Serbia, Tajikistan, Thailand, Turkey, Ukraine, UAE, Uruguay, and Venezuela. The generic active pharmaceutical ingredient and finished product can be produced anywhere in the world. Licensees must obtain WHO pre-qualification approval, or equivalent. Licensees can combine DAC with other drugs and develop new fixed-dose combinations. All sublicensees receive a technology transfer package and the information necessary to register DAC; if licensed manufacturers are not relying on BMS technology transfers, they can sell outside the designated territory if no granted patent is infringed. DAC has been sublicensed to seven sublicensees, including Mylan and Cipla.[42]

MPP/Gilead

Following Gilead's independent access programs for the HCV and HIV portfolios, Gilead was the first pharmaceutical innovator to join MPP in 2011.[43]

Gilead currently licenses several HIV drugs with MPP, across 117 countries (as of 2019) for a royalty rate of 5% of product sales (waived for active pharmaceutical ingredient sales and pediatric formulations). Sublicensees can be based in and manufactured in China, India, and South Africa; Indian and South African sublicensees receive a one-time technology transfer. Sublicensees must obtain approval from WHO Pre-qualification, FDA, or EMA.

[41] "Atazanavir (ATV)," Medicines Patent Pool, accessed April 7, 2022, https://medicinespatentpool.org/licence-post/atazanavir-atv.
[42] "Daclatasvir (DAC)," Medicines Patent Pool, accessed April 7, 2022, https://medicinespatentpool.org/licence-post/daclatasvir-dac.
[43] "Access Partnerships," Gilead.

In 2011, Gilead licensed cobicistat (COBI) and combinations containing cobicistat; the agreement was expanded in 2017 and 2019, now covering 117 countries[44]

In the same year, Gilead also licensed TDF; in 2015, the license was extended to cover patents on combinations of TDF and emtricitabine (FTC), and TDF/FTC and efavirenz (EVG), covering both treatment and PrEP; the geographic scope was expanded in 2017 and 2019, and now covers 117 countries.[45] The royalty rate for TDF is 3-5% of net sales of finished products, with the same waiver for sale of the active pharmaceutical ingredient and pediatric formulations. Four licensees have terminated the TDF part of the MPP-Gilead license to supply TDF to countries outside the agreed territory where TDF is not patented.

In 2011, Gilead licensed EVG for generic manufacture in India for sale in 100 countries; in 2015, the agreement was amended to allow Chinese and South African sublicensees; in 2017, the agreement was extended to 109 countries (the only drug *not* licensed for all 117 countries)[46]

In 2014, Gilead licensed tenofovir alafenamide (TAF); the geographic coverage of the license was expanded in 2017 and 2019 to cover 117 countries[47]

In 2017, Gilead licensed bictegravir (BIC) for sale in 116 LMICs, extended to 117 countries in 2019[48]

In 2011, Gilead also executed a covenant not to sue on products containing FTC, recommended by WHO for inclusion in first- and second-line HIV treatment for adults and children; the territory was extended in 2017 and 2019, now covering 117 countries. There are no royalties associated with the covenant, but royalties may be charged on other components of combinations FTC is used in.[49]

MPP/Merck Sharp & Dohme

In 2015, MPP and MSD reached a royalty-free licensing agreement for pediatric use of raltegravir (RAL), an HIV treatment. The license covers sale of RAL in 92 LMICs, and allows countries where RAL is not patented to procure generic versions. Licensees must obtain WHO Pre-qualification approval or equivalent.[50]

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[44] "Cobicistat (COBI)," Medicines Patent Pool, accessed April 7, 2022, https://medicinespatentpool.org/licence-post/cobicistat-cobi.

[45] "Tenofovir disoproxil fumarate (TDF)," Medicines Patent Pool, accessed April 7, 2022, https://medicinespatentpool.org/licence-post/tenofovir-disoproxil-fumarate-tdf.

[46] "Elvitegravir (EVG)," Medicines Patent Pool, accessed April 7, 2022, https://medicinespatentpool.org/licence-post/elvitegravir-evg.

[47] "Tenofovir alafenamide (TAF)," Medicines Patent Pool, accessed April 7, 2022, https://medicinespatentpool.org/licence-post/tenofovir-alafenamide-taf.

[48] "Bictegravir (BIC)," Medicines Patent Pool, accessed April 7, 2022, https://medicinespatentpool.org/licence-post/bictegravir-bic

[49] "Emtricitabine (FTC)," Medicines Patent Pool, accessed April 7, 2022, https://medicinespatentpool.org/licence-post/emtricitabine-ftc.

[50] "Raltegravir (RAL) Paediatrics," Medicines Patent Pool, accessed April 7, 2022, https://medicinespatentpool.org/licence-post/raltegravir-ral-paediatrics.

In April 2021 Merck entered into non-exclusive voluntary licensing agreements for molnupiravir with five Indian generic drug manufacturers.[51] Molnupiravir is an investigational, oral Covid-19 antiviral drug that was being studied in a Phase 3 trial at the time. Merck developed molnupiravir in collaboration with Ridgeback Biotherapeutics.

In October 2021, MSD provided MPP a license for molnupiravir. The license allows for worldwide manufacturing, and sale in 105 countries. The license is royalty-free during the WHO Public Health Emergency of International Concern, and after the emergency will command a 5% royalty for public sector sales and 10% for commercial entities' sales. Licensees need WHO pre-qualification approval or equivalent.[52]

Data from the Phase 3 MOVe-OUT trial has since shown that early treatment with molnupiravir significantly reduced the risk of hospitalization or death in at-risk, unvaccinated adults with COVID-19 by about 30%.[53] The FDA has provided Emergency Use Authorization for mild to moderate Covid-19 in adults with high risk of serious Covid-19.[54]

MSD has a non-exclusive voluntary licensing agreement in place for one compound (for diseases in scope). Its license for its pediatric formulation of raltegravir (marketed as Isentress) encompasses 89 countries including 61 middle-income countries in scope. It has not issued any non-assert declarations for products in scope. Outside the period of analysis, the company entered into a non-exclusive voluntary licensing agreement with two generic medicine manufacturers for HIV/AIDS treatment doravirine in September 2020. The agreement covers 86 countries, including all sub-Saharan African countries.[55]

MPP/Pharco Pharmaceuticals

In 2017, MPP and Pharco reached a license and technology agreement for a direct-acting antiviral for HCV, ravidasvir. The agreement covers LMICs and high HCV-prevalence countries including Russia, Ukraine, Egypt, and Iran. This agreement extends the geographic coverage of a previous ravidasvir license between Presidio (ravidsavir's original developer) and Drugs for Neglected Diseases *initiative* (DND*i*); the MPP and DND*i* licenses collectively cover 139 LMICs. The MPP-Pharco license commands a 4% royalty in low-income countries, 7% in middle-income countries, and no royalties for pediatric formulations. Pharco also provides a technology transfer to sub-licensees.[56]

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[51] "Merck and Ridgeback Announce Publication of Phase 3 Study of Molnupiravir, an Investigational Oral Antiviral COVID-19 Treatment, in the New England Journal of Medicine," Merck, December 16, 2021, https://www.merck.com/news/merck-and-ridgeback-announce-publication-of-phase-3-study-of-molnupiravir-an-investigational-oral-antiviral-covid-19-treatment-in-the-new-england-journal-of-medicine/.

[52] "Molnupiravir (MOL)," Medicines Patent Pool, accessed April 7, 2022, https://medicinespatentpool.org/licence-post/molnupiravir-mol.

[53] Angélica Jayk Bernal et al., "Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients," *The New England Journal of Medicine*, February 10, 2022, https://www-nejm-org.ezp-prod1.hul.harvard.edu/doi/full/10.1056/NEJMoa2116044; "Molunpiravir (MOL)," Medicines Patent Pool.

[54] "Molnupiravir (MOL)," Medicines Patent Pool.

[55] Access to Medicine Index, "Merck (MSD)," accessed April 7, 2022, https://accesstomedicinefoundation.org/access-to-medicine-index/report-cards/merck-co-inc-msd#performance-breakdown.

[56] Medicines Patent Pool, "The Medicines Patent Pool and Pharco Pharmaceuticals Sign Licence for Promising Hepatitis C Drug Candidate Ravidasvir," Medicines Patent Pool, 21 April 2017,

MPP/Pfizer

In November 2021, Pfizer signed an agreement with MPP to license its oral Covid-19 treatment candidate, Paxlovid (nirmatrelvir), to generic manufacturers for distribution in LMICs.[57] Qualifying sub-licensees would be able to supply the oral treatment, pending approval, in combination with low-dose ritonavir to 95 countries covering 53% of the world's population.[58] In March 2022, thirty-five generics from Bangladesh, Brazil, China, Dominican Republic, Jordan, India, Israel, Mexico, Pakistan, Serbia, Republic of Korea, and Vietnam signed sub-licensing agreements with MPP to produce nirmatrelvir.[59]

Like the Gilead VL programs and the MSD molnupiravir license, the Pfizer-MPP voluntary license employs a tiered pricing scheme. Pfizer will collect no royalties while the WHO classifies Covid-19 as a Public Health Emergency of International Concern. After the pandemic, "sales to low-income countries will remain royalty free, lower-middle-income countries and upper-middle-income countries will be subject to a 5% royalty for sales to the public sector and a 10% royalty for sales to the private sector."[60]

Paxlovid has not yet been FDA-approved, but has been authorized for use during the Covid-19 pandemic under an Emergency Use Authorization.[61] Nirmatrelvir combined with low-dose ritonavir was found to reduce the risk of hospitalization or death by 89% when treated within three days of symptom-onset.[62]

In 2019 Pfizer and the MPP entered into a voluntary license for clinical development of sutezolid, an investigational medicine for the treatment of tuberculosis. The license allows MPP sublicensees to access Pfizer's preclinical and phase I/IIa clinical data and results for new TB regimens.[63]

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https://medicinespatentpool.org/news-publications-post/the-medicines-patent-pool-and-pharco-pharmaceuticals-sign-licence-for-promising-hepatitis-c-drug-candidate-ravidasvir.

[57] Pfizer Inc., "Pfizer and The Medicines Patent Pool (MPP) Sign Licensing Agreement for COVID-19 Oal Antiviral Treatment Candidate to Expand Access in Low- and Middle-Income Countries," Pfizer, November 16, 2021, https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-medicines-patent-pool-mpp-sign-licensing.

[58] Pfizer Inc., "Pfizer and The Medicines Patent Pool (MPP) Sign Licensing Agreement."

[59] Medicines Patent Pool, "35 generic manufacturers sign agreements with MPP to produce low-cost, generic versions of Pfizer's oral COVID-19 treatment nirmatrelvir in combination with ritonavir for supply in 95 low- and middle-income countries," Medicines Patent Pool, March 17, 2022, https://medicinespatentpool.org/news-publications-post/35-generic-manufacturers-sign-agreements-with-mpp-to-produce-low-cost-generic-versions-of-pfizers-oral-covid-19-treatment-nirmatrelvir-in-combination-with-ritonavir-for-supply-in-95-low-and.

[60] Medicines Patent Pool, "35 generic manufacturers sign agreements with MPP."

[61] Pfizer Inc., "Pfizer to Supply UNICEF up to 4 Million Treatment Courses of Novel COVID-19 Oral Treatment for Low- and Middle-Income Countries," Pfizer, March 22, 2022, https://www.pfizer.com/news/press-release/press-release-detail/pfizer-supply-unicef-4-million-treatment-courses-novel.

[62] "Nirmatrelvir," Medicines Patent Pool, accessed April 7, 2022, https://medicinespatentpool.org/licence-post/pf-07321332.

[63] "Sutezolid – Pfizer," Medicines Patent Pool, accessed April 7, 2022, https://medicinespatentpool.org/licence-post/sutezolid-pfizer.

MPP/ ViiV (GlaxoSmithKline & Pfizer)

ViiV is a global specialist HIV pharmaceutical company established by GlaxoSmithKline (GSK) and Pfizer in 2009. In July 2010, ViiV decided to independently make its HIV pipeline available through voluntary, royalty-free licenses to "all least developed countries, all low income countries and all of sub-Saharan Africa" (118 countries).[64]

In 2013, ViiV announced an agreement with MPP to license pediatric formulations of ARV abacavir (ABC), royalty-free, across those same 118 countries. In 2014, this license was extended to Ukraine, Venezuela, and Peru. The license now covers 99.3% of children with HIV in LMICs.[65]

ViiV also has two non-exclusive voluntary licensing agreements in place for dolutegravir, an HIV integrase inhibitor. Its adult license for dolutegravir (marketed as Tivicay) now covers 94 countries. The adult DTG license is royalty-free for at least 82 countries, and commands a 5% royalty in the Philippines, India, Vietnam, and Moldova, 7.5% in Algeria, Egypt, Indonesia, Morocco, Armenia, Mongolia, Tunisia, and Ukraine, and 10% in Turkmenistan.[66] Its pediatric license for dolutegravir (Tivicay) covers 102 countries, including 74 middle-income countries. It has not issued any non-assert declarations for products in scope.[67] By the end of 2018, nearly 3.9 million people living with HIV had access to generic DTG and TLD because of these innovative licensing arrangements.[68]

In 2014, ViiV first licensed dolutegravir (DTG) through the MPP, supporting access in countries with the highest burden of HIV, where 99% of HIV-positive children and 93% of HIV-positive adults live.[69] Like the Gilead access programs, ViiV adopted a tiered pricing approach:

> "first, a royalty-free voluntary licence in all least-developed, all low-income and all sub-Saharan African countries; second, for specific middle-income countries including India, ViiV Healthcare has established the first-ever MPP licence with a tiered royalty structure, where a small percentage of the sale price is paid based on the gross domestic product (GDP) of the specific country."[70]

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[64] ViiV Healthcare, "ViiV Healthcare Announces a Voluntary Licence Agreement with the Medicines Patent Pool to Increase Access to HIV Medicines for Children," ViiV Healthcare, February 27, 2013, https://viivhealthcare.com/hiv-news-and-media/news/press-releases/2013/february/viiv-healthcare-announces-a-voluntary-licence-agreement-with-the-medicines-patent-pool-to-increase-access-to-hiv-medicines-for-children/.

[65] "Abacavir – Paediatrics (ABC)," Medicines Patent Pool, accessed April 7, 2022, https://medicinespatentpool.org/licence-post/abacavir-paediatrics-abc.

[66] "Dolutegravir – Adult (DTG)," Medicines Patent Pool, accessed April 7, 2022, https://medicinespatentpool.org/licence-post/dolutegravir-adult-dtg.

[67] Access to Medicine Index, "GlaxoSmithKline plc Report Card," https://accesstomedicinefoundation.org/access-to-medicine-index/report-cards/glaxosmithkline-plc#performance-breakdown.

[68] "Five Years On, 3.9 Million People In The Developing World Have Access To Hiv Treatment Dolutegravir," ViiV Healthcare, accessed April 7, 2022, https://viivhealthcare.com/hiv-news-and-media/news/press-releases/2019/july/five-years-on--3-9-million-people-in-the-developing-world-have-a/.

[69] ViiV Healthcare, "ViiV Healthcare Announces New Initiatives to Improve Access to Dolutegravir: Licence to the Medicines Patent Pool," Viiv Healthcare, April 1, 2014, "https://viivhealthcare.com/hiv-news-and-media/news/press-releases/2014/april/viiv-healthcare-announces-new-initiatives-to-improve-access-to-dolutegravir-licence-to-the-medicines-patent-pool/.

[70] ViiV Healthcare, "Viiv Healthcare Announces New Initiatives."

In 2016, ViiV extended this license to all lower-middle income countries, specifically benefitting Armenia, Moldova, Morocco, and Ukraine, where ViiV had DTG patents.[71] The license was extended to Mongolia and Tunisia in 2018, and Algeria in 2020.[72]

In November 2020, ViiV also executed a separate MPP license for the generic production of DTG-based therapies to Azerbaijan, Belarus, Kazakhstan and Malaysia, all upper-middle income countries. Generic manufacturers will be able to supply DTG at significantly reduced prices. This is the first MPP license enabling increased access to HIV treatment for UMICs.[73]

ViiV has also maintained a separate direct license with India-based Aurobindo Pharmaceuticals to manufacture generic DTG for adults and children since 2014.[74]

MPP/Universities & Research Bodies

In 2010, MPP received its first license from the US **National Institutes of Health (NIH)** for patents relating to darunavir, an HIV treatment.[75]

In 2015, MPP licensed the **University of Liverpool**'s Solid Drug Nanoparticular (SDN) technology to develop HIV nano-medicines. The agreement covers making, using, and distributing ARVs based on SDN technology in 137 LMICs.[76]

In September 2021, MPP reached an agreement with **Tandem Nano Ltd.** for long-acting technology to be used in treating malaria, tuberculosis, and HCV, developed by the **University of Liverpool** with Unitaid funding. The technology is not yet proven safe and effective. The license will allow sublicensees to develop products worldwide for sale and distribution in all LMICs without royalties. The license imposes an Affordable Price requirement, for a price to be agreed between Unitaid and Tandem Nano and notified to MPP.[77]

In 2017, **John Hopkins University** granted MPP an *exclusive*, royalty-free license for all countries that currently have patents issued/pending for "a combination therapy comprising sutezolid and

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[71] ViiV Healthcare, "ViiV Healthcare Extends Medicines Patent Pool Licence Agreement for Dolutegravir to Cover All Lower Middle-Income Countries," ViiV Healthcare, April 25, 2016, https://viivhealthcare.com/hiv-news-and-media/news/press-releases/2016/april/viiv-healthcare-extends-medicines-patent-pool-licence-agreement-for-dolutegravir-to-cover-all-lower-middle-income-countries/; "Dolutegravir – Adult (DTG)," Medicines Patent Pool.

[72] "Dolutegravir – Adult (DTG)," Medicines Patent Pool.

[73] Medicines Patent Pool, "ViiV Healthcare and the Medicines Patent Pool expand access to dolutegravir-based regimens for people living with HIV in Azerbaijan, Belarus, Kazakhstan and Malaysia with innovative new licensing agreement," Medicines Patent Pool, November 30, 2020, https://medicinespatentpool.org/news-publications-post/viiv-and-mpp-expand-access-to-dtg-to-four-new-countries.

[74] "Pricing and access strategies, " GlaxoSmithKline, accessed April 7, 2022, https://www.gsk.com/en-gb/responsibility/improving-health-globally/pricing-and-access-strategies/.

[75] "Patents Related to Darunavir," Medicines Patent Pool, accessed April 7, 2022, https://medicinespatentpool.org/licence-post/patents-related-to-darunavir.

[76] "Solid Drug Nanoparticle Technology," Medicines Patent Pool, accessed April 7, 2022, https://medicinespatentpool.org/licence-post/solid-drug-nanoparticle-technology.

[77] "Long-Acting Technologies for HCV, TB, and Malaria Treatment," Medicines Patent Pool, accessed April 7, 2022, https://medicinespatentpool.org/licence-post/long-acting-technologies-for-hcv-tb-and-malaria-treatment.

two additional compounds used to treat TB, such as pretomanid, delamanid, bedaquiline, rifampicin and moxifloxacin." The agreement is designed to facilitate development of sutezolid, a potential TB treatment.[78] The patent for sutezolid expired in 2014, but patents for use of sutezolid in TB combination therapy are valid until 2029, and jointly held by Pfizer and JHU. The hope is to reinvigorate development of sutezolid therapies, which has been stalled since 2013.[79]

The JHU license was supplemented in 2019 by a royalty-free license agreed between Pfizer and MPP to facilitate clinical development of sutezolid, which allows MPP sublicensees to access Pfizer's preclinical and phase I/IIa clinical data.[80]

In November 2021, MPP and the Spanish National Research Council (CSIC) reached agreement to license a Covid-19 lateral flow antibody diagnostic test. CSIC will provide know-how to MPP and all licensees. MPP can grant sublicenses to develop the licensed know-how and biological materials into licensed products. The technology is royalty-free in LMICs, and a 15% royalty in high-income countries where there is a patent or no patent but the licensee has used the biological material provided.[81]

In December 2021, the **University of Washington** also reached a license with MPP for a long-acting injectable combination drug HIV treatment that relies on UoW's proprietary drug combinations nanotechnology; the treatment is currently at a pre-clinical stage. The license allows worldwide manufacturing, and permits royalty-free sales in all LMICs in both public and private markets. UoW receives a royalty-free, non-exclusive, sub-licensable license in any improvements to their technology made by licensees.[82]

[78] "Sutezolid – John Hopkins University," Medicines Patent Pool, accessed April 7, 2022, https://medicinespatentpool.org/licence-post/sutezolid-johns-hopkins-university.

[79] Medicines Patent Pool, "The Medicines Patent Pool Announces First Licence for Tuberculosis Treatment," Medicines Patent Pool, January 25, 2017, https://medicinespatentpool.org/news-publications-post/the-medicines-patent-pool-announces-first-licence-for-tuberculosis-treatment; Medicines Patent Pool, "The Medicines Patent Pool and Pfizer sign licence for access to key data on investigational tuberculosis treatment sutezolid," Medicines Patent Pool, October 28, 2019, https://medicinespatentpool.org/news-publications-post/the-medicines-patent-pool-and-pfizer-sign-licence-for-access-to-key-data-on-investigational-tuberculosis-treatment-sutezolid.

[80] "Sutezolid – Pfizer," Medicines Patent Pool.

[81] "ELISA antibody technology," Medicines Patent Pool, accessed April 7, 2022, https://medicinespatentpool.org/licence-post/elisa-antibody-technology.

[82] "Long-acting injectable HIV drug combination technology," Medicines Patent Pool, accessed April 7, 2022, https://medicinespatentpool.org/licence-post/long-acting-injectable-drug-combination-for-hiv-treatment-prevention.

Table 1: Current MPP Licenses from Pharmaceutical Companies

Company	Drug	Licensees	Sale/ Distribution Territory	Royalties?	Quality Control?	Combinations?	Technology Transfer?	Registration Assistance?
AbbVie	G/P (for HCV)	Anywhere in the Territory and in India	96 countries	Royalty free	WHO Pre-qualification or Stringent Regulatory Authority approval	No	No	Yes (clinical data and documents to facilitate registration)
	LPV/r (for HIV)	Worldwide	All African countries (54)	Royalty free	WHO Pre-qualification or Stringent Regulatory Authority approval	Yes (combine LPV/r with other ARVs, new fixed-dose combinations)	No	No
	LPV/r (pediatric) (for HIV)	Worldwide	102+ countries	Royalty free	WHO Pre-qualification or Stringent Regulatory Authority approval	Yes (combine LPV/r with other ARVs, new fixed-dose combinations)	No	No
BMS	ATV	Worldwide	122+ countries	3% royalty for adult formulations outside Sub-Saharan Africa and India; no royalties for pediatric formulations	WHO Pre-qualification or Stringent Regulatory Authority approval	Yes (combine ATV with other ARVs, new fixed-dose combinations)	Yes (technology transfer to all licensees, no obligation to use)	No
	DAC	Worldwide	143 countries	Royalty free	WHO Pre-qualification or Stringent Regulatory Authority approval	Yes (combine DAC with other drugs, new fixed-dose combinations)	Yes (technology transfer to all licensees, no obligation to use)	Yes (information necessary for registration provided to all licensees)
Gilead	BIC	China, India, South Africa	117 countries	5% for adult formulations; no royalties for sale of API or pediatric formulation	WHO Prequalification, EMA, or FDA manufacturing standards; must apply for WHO Prequalification if WHO designates	Yes (combine BIC with other ARVs, new fixed-dose combinations)	Yes (technology transfer to all Indian and South-African licensees)	No
	COBI	China, India, South Africa	117 countries	5% for adult formulations; no royalties for sale of API or pediatric formulation	WHO Prequalification, FDA, or EMA approval	Yes (combine COBI with other ARVs, new fixed-dose combinations)	Yes (technology transfer to all Indian and South-African licensees)	No

	EVG	China, India, South Africa	109 countries	5% for adult formulations; no royalties for sale of API or pediatric formulation	WHO Prequalification, FDA, or EMA approval	Yes (combine EVG with other ARVs, new fixed-dose combinations)	Yes (technology transfer to all Indian and South-African licensees)	No
	FTC	Benefits all Gilead/MPP TDF, TAF, COBI, and EVG licensees in China, India, or South Africa	Covenant not to sue on products containing FTC in 117 countries	No royalties on covenant, but may have royalties on components in combination	N/A	Yes (covenant covers combinations including FTC - TDF/FTC, TAF/FTC, TDF/FTC/EFV)	N/A	N/A
	TAF	China, India, South Africa	117 countries	5% for adult formulations; no royalties for sale of API or pediatric formulation	WHO Prequalification, FDA, or EMA approval	Yes (combine TAF with other ARVs, new fixed-dose combinations)	Yes (technology transfer to all Indian and South-African licensees)	No
	TDF	China, India, South Africa	117 countries	3–5% for adult formulations; no royalties for sale of API or pediatric formulation	WHO Prequalification, FDA, or EMA approval	Yes (combine TDF with other ARVs, new fixed-dose combinations)	Yes (technology transfer to all Indian and South-African licensees)	No
MSD	MOL	Worldwide	105 countries	Royalty-free license during WHO PHEIC; post-PHEIC, 5% net sales for public sector purchases and 10% net sales for commercial entities	WHO Pre-qualification or Stringent Regulatory Authority approval	No	No	No
	RAL (pediatric)	Worldwide	92+ countries (other countries without RAL patents can procure generics)	Royalty free	WHO Pre-qualification or Stringent Regulatory Authority approval	Yes (combine RAL with other ARVs, new fixed-dose combinations)	No	No
Pfizer	Nirmatrelvir	Worldwide	95 countries	Royalty-free license during WHO PHEIC; post-PHEIC, 5% net sales for public sector purchases and 10% net sales	WHO Pre-qualification or Stringent Regulatory Authority approval	No	No	No

				for commercial entities; no royalties on sales to LICs or products made and sold in territory countries without patents or regulatory exclusivity				
	Sutezolid	Worldwide	Worldwide	Royalty free	N/A	N/A	Access to all preclinical and Phase I/IIa data to further study	N/A
ViiV (GSK)	ABC	Worldwide	121 countries	Royalty free	WHO Pre-qualification or Stringent Regulatory Authority approval	Yes (combine ABC with other ARVs, new fixed-dose combinations)	No	No
	DTG	Worldwide	95+ countries	Royalty-free for LICs; 5%, 7.5%, or 10% for others	WHO Pre-qualification or Stringent Regulatory Authority approval	Yes (combine DTG with other ARVs, new fixed-dose combinations)	No	No
	DTG for AZ, BY, KZ, MY	Worldwide (max 3 sublicensees)	Azerbaijan, Belarus, Kazakhstan, Malaysia	Depends on Product Access Percentage	WHO Pre-qualification or Stringent Regulatory Authority approval	Yes (combine DTG with ABC or other active ingredients)	No	No
	DTG (pediatric)	Worldwide	123 countries	Royalty free	WHO Pre-qualification or Stringent Regulatory Authority approval	Yes (combine DTG with other ARVs, new fixed-dose combinations)	No	No

Unsuccessful VLs: Refusals or Failures

Moderna: Covid-19

Despite strong pressure from the Biden administration and global campaigners, Moderna has refused to license its Covid-19 vaccine. Unlike Pfizer, which shifted from refusal to agreeing to voluntary licensing with the MPP in November 2021, Moderna has refused to engage with the MPP or the WHO.[83]

The MPP has been working with a technology transfer hub in South Africa which was set up to teach manufacturers from low-income countries how to make mRNA vaccines, a new type of vaccine technology used by American companies like Moderna.[84] However, despite its October 2020 pledge that it would not enforce its Covid-19-related patents during the pandemic, Moderna filed for patents in South Africa for its Covid-19 vaccines in February 2022. The approval of the patent applications could prevent the South African hub from manufacturing its own version of the mRNA vaccine.[85]

Novartis: Leukemia

Novartis does not engage in voluntary licensing, and has decided not to join the MPP.

Novartis has faced strong public pressure to license nilotinib (marketed as Tasigna), a chronic myelogenous leukemia (CML) medicine. A number of countries would benefit significantly from Novartis' licensing of nilotinib, including Myanmar, Laos, Philippines, Ecuador, Bolivia, El Salvador, Ukraine, and Vanuatu.[86]

Novartis also faced potential issuance of compulsory licensing by governments. In April 2017, leaked letters to the Colombia Ministry of Trade and Industry revealed that Novartis threatened to resort to international investment arbitration for an alleged violation of the Swiss-Colombian bilateral investment treaty (BIT), which was signed by both countries in 2006. This mechanism, also known as Investor-State dispute settlement (ISDS), allows an investor from one country to bring a case directly against the country in which they have invested before a private international arbitration tribunal, avoiding local courts in the process. This threat influenced the Colombian government's eventual decision not to pursue a compulsory license, instead focusing only on a price reduction.[87]

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[83] Stephanie Nolen and Sheryl Gay Stolberg, "Pressure Grows on U.S. Companies to Share Covid Vaccine Technology," *The New York Times*, September 22, 2021, https://www.nytimes.com/2021/09/22/us/politics/covid-vaccine-moderna-global.html.

[84] Ibid.

[85] Wendell Roelf and Julie Steenhuysen, "Moderna patent application raises fears for Africa COVID vaccine hub," *Reuters*, February 17, 2022, https://www.reuters.com/business/healthcare-pharmaceuticals/moderna-patent-application-raises-fears-africa-covid-vaccine-hub-2022-02-17.

[86] Access to Medicine Index, "Novartis Report Card," https://accesstomedicinefoundation.org/access-to-medicine-index/report-cards/novartis-ag.

[87] "Compulsory licensing in Colombia: Leaked documents show aggressive lobbying by Novartis," Public Eye, April 12, 2017, https://www.publiceye.ch/en/media-corner/press-releases/detail/compulsory-licensing-in-colombia-leaked-documents-show-aggressive-lobbying-by-novartis.

Instead, Novartis has adopted alternative measures, including a program it launched in 2015 to enable access to 15 medicines for several non-communicable diseases (including breast cancer), for $1 per treatment per month. The program aims to cover 30 low- and lower-middle-income countries, and has to be distributed in Kenya and Ethiopia.[88]

Novartis has stated it does not seek or enforce patents in least developed countries, low-income countries, or in around 80% of the lower-middle income countries. It has also stated that it would consider granting non-exclusive voluntary licenses in certain circumstances.[89]

Johnson & Johnson/Tibotec: HIV

Although J&J/Tibotec has voluntary licensing agreements with generic manufacturers, it has refused to place any patents into the MPP. Humanitarian organizations, particularly Médecins Sans Frontières, have heavily criticized J&J's refusal to license HIV medicines in face of dire need. Specifically, the three most needed medicines are rilpivirine, a promising first-line treatment, as well as darunavir and etravirine, both important for treatment-experienced patients and have been listed in the WHO treatment guidelines as potential components of a salvage regimen.[90]

Other needed medicines held by J&J include Type 2 diabetes mellitus (Invokana), canagliflozin/metformin (Vokanamet/Invokamet) and for MDR-TB, bedaquiline (Sirturo).[91]

ViiV: HIV

Although ViiV has licensed some of its medicines through MPP, it made the recent decision *not* to license its long-acting HIV-prevention shot, cabotegravir, for generic production. In a press statement, ViiV wrote:

> "ViiV Healthcare has conducted a rigorous assessment, with inputs from several generic manufacturers and contract manufacturing organizations. The assessment concluded that securing a generic partner for cabotegravir LA for PrEP will be challenging, due to the complexities of manufacturing, regulatory requirements, capital investment needs and unpredictable demand."[92]

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[88] Angelica Kershaw, "Pharma industry embraces Medicines Patent Pool's voluntary licence," August 19, 2016, https://www.pharmaceutical-technology.com/pricing-and-market-access/pharma-industry-embraces-medicines-patent-pools-voluntary-licence-html.

[89] Novartis, "Patents and Licensing," https://www.novartis.com/esg/access/patents-and-licensing.

[90] William C. Weldon, "Letter to Johnson & Johnson CEO Regarding the Company's Failure," Médecins Sans Frontières, https://www.doctorswithoutborders.org/latest/letter-johnson-johnson-ceo-regarding-companys-failure-put-urgently-needed-aids-drugs.

[91] Access to Medicine Index, "Johnson & Johnson," https://accesstomedicinefoundation.org/access-to-medicine-index/report-cards/johnson-johnson#opportunities.

[92] ViiV Healthcare, "ViiV Healthcare Open to Voluntary Licensing as Part of Approach to Enable Greater Access to Cabotegravir LA for PrEP in Low- and Middle-Income Countries," ViiV Healthcare, March 2022, https://viivhealthcare.com/hiv-news-and-media/news/company-statements/viiv-healthcare-statement-on-voluntary-license/.

ViiV did add that it is "continuing to work with the Medicines Patent Pool and other partners and remain open to the potential for voluntary licenses for cabotegravir LA for PrEP in the future."[93] As of April 2022, ViiV is still "actively working" with MPP to arrange licensing for cabotegravir.[94]

ViiV has said they will provide cabotegravir in many LMICs for the at-cost price, but have not announced the price.[95] However, the MSF Access Campaign noted that generic manufacturers are often able to produce drugs at much lower costs than brands' 'at-cost' prices, and research has shown generic manufacturers could produce cabotegravir for less than $20 per person, per year.[96]

ViiV made a similar announcement previously, refusing to license its fostemsavir HIV drug:

"In reviewing the feasibility of voluntary licences for fostemsavir, ViiV Healthcare and the MPP took into consideration the following key elements: the clinical need and priority of fostemsavir as a HIV treatment option in low- and middle-income countries (LMICs)..., the treatment indication of the medicine, the complexity of fostemsavir's manufacturing process, and an understanding of availability of third line treatment and beyond in national HIV programmes across LMICs. The conclusion of this evaluation is that, ViiV Healthcare and the MPP do not believe that voluntary licences will be a viable approach to enable access to fostemsavir in these settings at this time."[97]

Factors Contributing to Success or Failure

Reputational Incentives

Many voluntary licensing agreements have been in part the result of advocacy that raises the reputational costs of refusing voluntary licensing. For instance, Pfizer, which had refused to license its Covid-19 vaccine, changed its stance after facing strong pressure from U.S. lawmakers and international NGOs.[98] Importantly, as the Gilead case study suggests, advocacy requires not only external actors but also internal stakeholders that work on aligning with external advocates, such as Gilead's Access Operations & Emerging Markets team.

However, reputational incentives alone are insufficient. Pharmaceutical companies may find that financial and strategic incentives outweigh any reputational harm caused by refusal of voluntary

[93] Ibid.
[94] ViiV Healthcare, "ViiV Healthcare is Working with Medicines Patent Pool to Progress Voluntary Licensing for Cabotegravir Long-Acting for PrEP," ViiV Healthcare, April 2022, https://viivhealthcare.com/en-us/media-center/news/company-statements/2022/april/viiv-healthcare-and-medicines-patent-pool/.
[95] MSF Access Campaign, "ViiV will not license new game-changing long-acting HIV prevention drug to generic manufacturers," MSF Access Campaign, March 4, 2022, https://msfaccess.org/viiv-will-not-license-new-game-changing-long-acting-hiv-prevention-drug-generic-manufacturers.
[96] Ibid.
[97] ViiV Healthcare, "ViiV Healthcare and Medicine Patent Pool Statement on Voluntary Licences in Enabling Access to Fostemsavir," ViiV Healthcare, accessed April 7, 2022, https://viivhealthcare.com/hiv-news-and-media/news/company-statements/fostemsavir-voluntary-licences-statement.
[98] Oxfam, " Reaction to Pfizer's announcement of voluntary licenses of its COVID-19 oral antiviral treatment Paxlovid to the Medicines Patent Pool," https://www.oxfam.org/en/press-releases/reaction-pfizers-announcement-voluntary-licenses-its-covid-19-oral-antiviral.

licensing. For example, unlike Pfizer, Modern remained firm in its refusal to license its Covid-19 vaccine despite intense pressure from the Biden administration and humanitarian organizations.

Financial Incentives

Successful voluntary licensing requires more than altruism or fear of reputational harm. Several financial incentives may motivate pharmaceutical companies, including royalties (short-term) and setting a ceiling price in less penetrated markets (long-term).

Royalties & Tailored Pricing Structure

Royalties offer a direct financial incentive for pharmaceutical companies. However, successful voluntary licensing agreements often include a tiering pricing structure, including tiered royalty rates, that is tailored to the drug, the market, and other relevant factors. In the case of Gilead's HIV Access Program, after reaching only one hundred patients in its first year, Gilead restructured the pricing structure into two tiers (no profit Low-Income Pricing Tier and limited-profit Lower Middle-Income Pricing Tier), which helped expand its reach to 31,000 patients by 2006.[99]

On the other hand, tiered pricing structure can also hinder the success of voluntary licensing. Gilead's Hepatitis C therapeutic, sofosbuvir (Sovaldi), was subject to intense criticism and Congressional investigation given its substantially different price points in different nations.[100]

Establishing a Ceiling Price in Emerging Markets

Another key, long-term financial incentive is the ability to establish a ceiling price in less penetrated markets. Through its licensing agreements with local manufacturers, patent-holders can set a ceiling price for highly demanded drugs. Otherwise, generics manufacturers in those markets could become de facto suppliers, leading to significant price inflation that makes the drug unaffordable to most of the population. Setting a ceiling price not only expands access to medicine but also enables patent-holders to gain significant insights into the market and maintain the potential for high penetration in the future.

Government Policies

Government policies, in both the country receiving the license and the country of the patent-holder, can provide significant incentives or deterrents for voluntary licensing. For instance, the United States Patent and Trademark Office (USPTO)'s Patents for Humanity award is a strong incentive for patent-holders to license their technology to countries in need. The Patent for Humanity is the USPTO's top honor and provides not only recognition but also, importantly, a voucher that allows companies to expedite their applications before the USPTO and "skip the line." The vouchers can be sold by the award winner to other companies, thus making it worth potentially millions of dollars or more.

[99] Rangan and Lee, 7–8.
[100] Rangan, Rangan and Bloom, 8, 10–11, 14.

Threat of compulsory licensing by governments may also incentive patent-holders to consider voluntary licensing despite initial refusal. However, the Novartis example shows that such threats may prove to be ineffective given constraints by trade agreements.

On the other hand, protectionist policies can serve as a significant deterrent for patent-holders to engage in voluntary licensing. A common concern of pharmaceutical companies is that the government will approve the generic versions before the branded ones due to protectionism (see the Gilead vs. Cipla discussion above). In addition, import permits can also significantly limit importation of the licensed medicines.

Additional Factors

Other notable success factors include determining the proper geographical coverage for the licensed medicines, strategic partnerships with local manufacturers and distributors, as well as educational and technological training of licensees.

3. Yen Ba Vu, "Pharmaceutical Regulatory Reform in Southeast and South Asia"

April 2022

Introduction

Harmonization of pharmaceutical regulation over safety and efficacy unfolds at different speeds across South Asia (excepting India) and Southeast Asia. While there is little regional coordination across South Asia, Southeast Asia has made efforts to synchronize regulatory principles and rules within the region through the Association of Southeast Asian Nations (ASEAN.) In both regions, individual countries have also made attempts to harmonize national practices with international norms. Common challenges faced by Southeast and South Asian countries in harmonization are technical expertise, institutional capabilities, and resources.

Southeast Asia

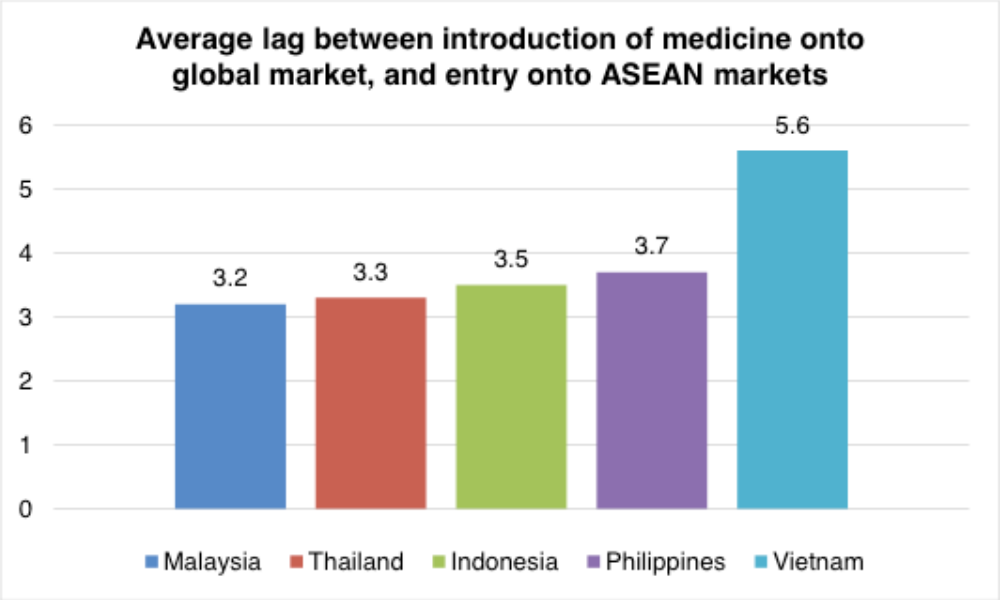
Context and background

Countries in Southeast Asia are moving making progress to harmonize their pharmaceutical regulation through the Association of Southeast Asian Nations (ASEAN.) While regional recommendations and standards are moving in the direction of harmonization overall, much variability between countries remains. Two elements underlie this heterogeneity. First, countries' regulatory agencies have different levels of resources and capabilities. Thus countries "with more advanced regulatory agencies often take the lead in developing and implementing harmonized standards; other [countries' agencies] adopt the standards or requirements later on when they become technically, institutionally and financially ready to do so."[101] Second, the framework established under ASEAN is not legally binding. Their implementation must happen through each country's own legal framework for pharmaceutical regulation, and thus requires voluntary and affirmative participation from each member-state.[102]

Harmonization may assist ASEAN countries to reduce their "drug lag," i.e. the delay in availability of a drug in a given country, relative to the world's first approval date for that drug, and to alleviate delayed access to new medicines for their populations.[103] This is the case especially with regards to innovative medicines: ASEAN countries obtain these on average more than three years after global introduction. For example, drug lag is 3.2 years in Malaysia, 3.7 years in the Philippines, and extends to 5.6 years in Vietnam.[104]

[101] Hui Sin Teo, Christina Foerg-Wimmer, and Pei-Lyn Melissa Chew, "Medicines Regulatory Systems and Scope for Regulatory Harmonization in Southeast Asia" (World Bank, 2016), 7, https://doi.org/10.1596/26801.
[102] Teo, Foerg-Wimmer, and Chew, 31.
[103] Nilubon Subsittipong et al., "Delay in Vaccine Access in ASEAN Countries," *International Journal of Environmental Research and Public Health* 19, no. 7 (March 22, 2022): 3787, https://doi.org/10.3390/ijerph19073786.
[104] Teo, Foerg-Wimmer, and Chew, "Medicines Regulatory Systems and Scope for Regulatory Harmonization in Southeast Asia," 40.

Figure 12: Average lag in introduction of innovative medicines onto ASEAN markets



Source: Eurocham, *Whitebook*, 2016.[105]

However, while harmonization may help mitigate the issue, it is not the only solution. According to the World Bank, many ASEAN countries suffer from a substantial backlog of drug registration applications. Insufficient staffing and lack of expertise contribute to difficulties processing applications.[106] Furthermore, some Southeast Asian countries, such as Vietnam and Indonesia, do not impose any control on the number of identical products put on the market. This results in a glut of applications for identical products that national regulatory agencies have to process.[107] Finally, registration fees are very low, ranging from $65 in Thailand to $2000 in Indonesia for a new chemical entity, compared to the EU and the US, where a new product registration costs respectively $317,404 and $2,335,200.[108] Registration costs in Southeast Asia are thus no deterrent to applications. While part of this immense difference may be explained by the economic gap between Southeast Asia and developed countries, the World Bank has indicated that there is some willingness even from Southeast Asian manufacturers to pay for higher registration fees in exchange for a more efficient registration process.[109]

Harmonization and streamlining regulatory requirements are also often advanced by international organizations and pharmaceutical companies as a key solution to this regulatory lag, a pressure that has intensified during the covid-19 pandemic.[110] Unlike wealthier countries (South Korea,

[105] Image cited in Teo, Foerg-Wimmer, and Chew, 40.
[106] Ibid, 38.
[107] Ibid.
[108] Ibid, 39.
[109] Ibid.
[110] See, for example, two pieces advocating for a harmonization and streamlining of clinical trial regulations by OECD and representative of covid-19 vaccine makers. "Greater Harmonisation of Clinical Trial Regulations Would Help the Fight against COVID-19," OECD, August 4, 2020, https://www.oecd.org/coronavirus/policy-responses/greater-harmonisation-of-clinical-trial-regulations-would-help-the-fight-against-covid-19-732e1c5c/; Lorenz Scheppler et

Japan) or more populous countries (China, India) in the region that require local clinical data for approving new drugs, no ASEAN country now requires local clinical data for drug registration. Vietnam was the last country to have imposed such a requirement, specifically for drugs that had not been on the market for more than five years outside of Vietnam, but it has dropped the requirement as of 2016.[111] Local clinical data play an important part in identifying different of drugs on different populations; however, that global clinical trials are increasingly incorporating participants from diverse countries, including Southeast Asian nations, may in part compensate for this absence of local clinical data.[112]

ASEAN measures towards harmonization

The first step ASEAN took towards harmonization was to propose guidelines to simplify and synchronize document requirements across member-states for drug registration. To this end, in 1999 the Pharmaceutical Product Working Group (PPWG) was established, with the aim of creating regional guidelines in sync with guidelines set by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). In 2006, the PPWG introduced the ASEAN Common Technical Document (ACTD), to "harmonize document requirements in ASEAN."[113] As of 2019, while some ASEAN countries maintain a separate national registration format, every member-state accepts submissions under the ACTD. In the case of Brunei Darussalam, Cambodia, Myanmar, and Thailand, there is in fact no separate drug registration format besides ACTD.[114] That said, this remains an imperfect harmonization of dossier requirements, as countries can still make ad hoc requirements (e.g. local labeling requirement) in addition to the ACTD format requirements.

In 2010, ASEAN also established Mutual Recognition Agreement (MRA) on Good Manufacturing Practice (GMP), another step towards harmonizing regulations and reducing the workload of national regulatory agencies. The MRA means that GMP inspection reports or certificates issued for a given drug manufacturer by an accredited inspection services within ASEAN would be accepted by other member-states' regulatory authorities, eliminating the need for duplicative inspections.[115]

With regards to GMP, outside of the structure of ASEAN, some Southeast Asian countries—Singapore, Thailand, Malaysia, Indonesia—have also become members of the Pharmaceutical Inspection Co-operation Scheme (PIC/S). PIC/S is an informal co-operative arrangement between regulatory authorities with the objective of harmonizing inspection procedures worldwide. The

al., "Regulatory Harmonization and Streamlining of Clinical Trial Applications Globally Should Lead to Faster Clinical Development and Earlier Access to Life-Saving Vaccines," *Vaccine* 39, no. 5 (January 29, 2021): 790–96, https://doi.org/10.1016/j.vaccine.2020.11.077.

[111] Victoria Elegant, "Medicines Development in the Asia Pacific Region," *Journal of Medicines Development Sciences* 2, no. 1 (November 21, 2016): 45–47, https://doi.org/10.18063/JMDS.2016.01.004.

[112] Subsittipong et al., 9, "Delay in Vaccine Access in ASEAN Countries."

[113] Abhishek Tongia, "The Drug Regulatory Landscape in the ASEAN Region," Regulatory Affair Professionals Society, accessed March 20, 2022, https://www.raps.org/news-and-articles/news-articles/2018/1/the-drug-regulatory-landscape-in-the-asean-region.

[114] J Sai Bhavana et al., "Regulatory Requirements for Registration of Drugs in ASEAN Countries," *World Journal of Pharmaceutical Research* 8, no. 10 (August 12, 2019): 400–401.

[115] Teo, Foerg-Wimmer, and Chew, "Medicines Regulatory Systems and Scope for Regulatory Harmonization in Southeast Asia," 50.

Philippines has applied but not yet acceded to membership, and Vietnam has indicated an interest in applying in the future. [116] PIC/S memberships of the aforementioned countries illustrate Southeast Asia's progress as a region towards harmonization of pharmaceutical regulation with the world, but also the internal heterogeneity within the region in terms of harmonization and regulatory capacity.

In 2015, the PPWG began another harmonization initiative, this time supported by the WHO. The project aims to enable the implementation of joint assessments. Joint assessments procedure allow a company to apply for marketing authorization while simultaneously submitting the application to all participating member-states' national medical regulatory agencies. However, joint assessments remain subject to the ASEAN's mechanism of consensual and voluntary participation. Thus, member-states can opt out, as well as specify ad hoc requirements (e.g. local labeling requirements) that contradict the goal of accelerating approval across all countries.[117]

South Asia

Context and background

Compared to Southeast Asian countries' approach, the harmonization of the regulatory framework to evaluate drugs' efficiency and safety has been more limited in South Asia outside of India. There is no regional approach to harmonizing. However, there are also some recent efforts in individual countries to harmonize with international norms, namely with regards to drug dossiers for registration and GMP.

In regulating pharmaceutical products, South Asian countries share one common challenge: national regulatory authorities have limited enforcement and supervision capabilities. This is the case for example in Pakistan, where counterfeit drugs are estimated to represent as much as 40-50% on the market in an oft-quoted, though contested figure; or in Nepal, where unregistered medicines are available for sale on the market.[118]

Interestingly, two populous South Asian countries, Bangladesh and Pakistan, have an important domestic pharmaceutical manufacturing industry and meet a large portion of their own needs for drugs (Pakistan produces 70-80% of its own needs, while Bangladeshi companies, by the country's own reports, meet 97% of the nation's needs.)[119] The importance of domestic manufacturers may affect incentives for national regulatory authorities to harmonize requirements with regards to manufacturing practices and drug registration, especially if domestic manufacturers may not be

[116] Ibid, 31.
[117] Teo, Foerg-Wimmer, and Chew, "Medicines Regulatory Systems and Scope for Regulatory Harmonization in Southeast Asia," 52.
[118] Huma Rasheed et al., "Regulatory Framework in Pakistan: Situation Analysis of Medicine Quality and Future Recommendations," *Journal of Pharmaceutical Policy and Practice* 12, no. 1 (September 11, 2019): 20, https://doi.org/10.1186/s40545-019-0184-z.
[119] Fatima Tauqeer, Kirsten Myhr, and Unni Gopinathan, "Institutional Barriers and Enablers to Implementing and Complying with Internationally Accepted Quality Standards in the Local Pharmaceutical Industry of Pakistan: A Qualitative Study," *Health Policy and Planning* 34, no. 6 (July 1, 2019): 441, https://doi.org/10.1093/heapol/czz054; Padmashree Gehl Sampath, "Pharmaceutical Manufacturing in Bangladesh – A Success Story. What Can We Learn?," FEAPM Advocacy Series (Federation of East African Pharmaceutical Manufacturers, n.d.), 12.

able to meet international standards at this stage. On the other hand, the possibility of facilitating exports may also provide encouragement to harmonize regulations with international principles.[120]

Harmonization with regards to GMP

To ensure the quality of drugs available on the market, national regulatory authorities in South Asia have taken steps to impose new requirements with regards to GMP. Several countries have introduced GMP standards, either established by the WHO or inspired from GMP standards employed in developed countries.

In Bangladesh and Nepal, WHO-established GMP standards are used. Bangladesh's Drug Policy of 2005 introduced the cGMP (WHO's standards for good-quality production of medicines in developing countries). However, national authorities have been criticized for not implementing these standards stringently, especially neglecting to enforce them upon national manufacturers in order to favor them over foreign drug manufacturers in the domestic market.[121] As for Nepal, foreign manufacturing facilities need to show a WHO-GMP certification in order to obtain a pharmaceutical registration.[122] This is however not the case for domestic manufacturing sites, which are to submit instead documents according to a separate procedure.
In Pakistan, GMP standards were also introduced, drawn from manufacturing standards employed in the UK and US. However, it has been reported that their enforcement has been ineffective.[123] Pakistan has also expressed interest in joining PIC/S, thus in harmonizing supervision principles over pharmaceutical manufacturers with international practices.[124]

Harmonization with regards to drug registration dossiers

With the support of USAID's Promoting the Quality of Medicines (PQM) program, both Pakistan and Bangladesh are preparing to adopt a Common Technical Document based on the ICH's model. In 2019, Pakistan began to accept drug registration dossiers under the CTD format.[125] As of 2016, Bangladesh was also working with USAID to establish a common format based on the ICH CTD. National regulatory authorities in Bangladesh have stated that they intended to apply this requirement only to new product registrations, as it would be difficult to be hard to apply this

[120] SIAPS Program, "Improving the Process of Medicines Registration in Bangladesh: Adoption of the Common Technical Document Format and Implementation of Pharmadex to Automate the Registration of Medicines," SIAPS Program, November 2, 2016, https://siapsprogram.org/publication/improving-the-process-of-medicines-registration-in-bangladesh-adoption-of-the-common-technical-document-format-and-implementation-of-pharmadex-to-automate-the-registration-of-medicines/.
[121] Sampath, "Pharmaceutical Manufacturing in Bangladesh – A Success Story. What Can We Learn?," 28.
[122] Bhupendra Kumar Poudel and Itsuko Ishii, "Regulation of Pharmaceuticals in Developing Nations: A Case from Nepal," *Research in Social and Administrative Pharmacy* 12, no. 6 (November 2016): 19, https://doi.org/10.1016/j.sapharm.2016.05.046.
[123] Hira Rashid, "Impact of the Drug Regulatory Authority, Pakistan: An Evaluation," *New Visions for Public Affairs* 7 (April 2015): 54.
[124] Nick Paul Taylor, "Asia Regulatory Roundup: Pakistan Seeks Expert to Help Harmonize Regulations With Global Best Practices," Regulatory Affair Professionals Society, accessed March 28, 2022, https://www.raps.org/news-and-articles/news-articles/2019/10/asia-regulatory-roundup-pakistan-seeks-expert-to.
[125] Promoting the Quality of Medicine, "Pakistan Adopts International Standards for Assessing and Registering Medicines," Promoting the Quality of Medicine, October 18, 2018, https://www.usp-pqm.org/results/pakistan-adopts-international-standards.

requirement retroactively on drugs already approved.[126] Information remains limited on the current adoption and implementation of this new format in Bangladesh and Pakistan, and its efficacy in speeding up the drug registration process.

There is no indication Sri Lanka or Nepal have moved towards harmonizing their dossier requirements with ICH CTD standards.[127] While the dossier format employed by Sri Lanka was based on WHO technical guidance in the 1970s, it has not been updated since.[128]

Conclusion

Overall, harmonization of procedures to evaluate safety and efficacy of drugs is more limited in South Asia compared to Southeast Asia. In the later region, progress has been made primarily through regional cooperation under the aegis of ASEAN. That said, a common feature to both South Asia and Southeast Asia is the heterogeneity among countries. Wealthier Southeast Asian countries, where national authorities have better technical abilities, have taken the lead in harmonizing their procedure with both regional and international norms. In South Asia, more populous Bangladesh and Pakistan have taken more steps to normalize national norms with international practices. Nonetheless, for a majority of countries in both regions, the technical expertise and capabilities of national regulatory agencies remain a barrier to implementing harmonization procedures and adopting a more efficient approval process.

[126] Josephine Aimiuwu, "Improving the Process of Medicines Registration in Bangladesh: Adoption of the Common Technical Document Format and Implementation of Pharmadex to Automate the Registration of Medicines" (Arlington, VA: SIAPS Program, August 2016).
[127] D. Thambavita, P. Galappatthy, and R. L. Jayakody, "Regulatory Requirements for the Registration of Generic Medicines and Format of Drug Dossiers: Procedures in Sri Lanka in Comparison with Selected Regulatory Authorities," *Journal of Pharmaceutical Policy and Practice* 11, no. 1 (June 21, 2018): 14, https://doi.org/10.1186/s40545-018-0141-2; Poudel and Ishii, "Hospital Pharmacy Service in Developing Nations."
[128] Thambavita, Galappatthy, and Jayakody, "Regulatory Requirements for the Registration of Generic Medicines and Format of Drug Dossiers," 6.

4. Matthew Chun & Marcela Interiano, "The Prevalence of Substandard and Falsified Drugs in Developing Countries"

April 2022

I. Introduction

Poor-quality medicines are associated with tens to hundreds of thousands of deaths annually and disproportionately affect low- and middle-income countries (LMICs).[129] In addition to their direct impact on health outcomes, poor-quality drugs generate an economic cost of US$10 to US$200 billion, diminish trust in health systems and genuine pharmaceutical products, and threaten global health security with the associated rise in antimicrobial resistance.[130] Reducing the prevalence of poor-quality medicines is critical to achieving the Sustainable Development Goals, as promulgated by all United Nations Member States, as part of improving the "access to quality essential health-care services and access to safe, effective, quality and affordable essential medicines and vaccines for all."[131]

This memorandum summarizes the currently available research on the prevalence of substandard and falsified (SF) drugs in LMICs. Part II reviews the World Health Organization's 2017 definitions for "substandard medical products," "falsified medical products," and "unregistered or unlicensed medical products, " as studies concerning quality of medical products generally employ this terminology. Part III provides a review of the recent literature on substandard and falsified (SF) drugs in two sections. Section III.A summarizes the findings from studies that directly examined the quality of essential medicines, the prevalence of SF medicines, and/or the economic impact of SF medicines in LMICs. Section III.B summarizes publicly available data on reported incidents since 2020 in which SF drugs have been detected and/or seized. While these data do not provide direct estimates of the prevalence or impact of SF drugs in LMICs, they provide useful insight into the global supply chain of SF drugs and the success of current surveillance efforts. Part IV discusses limitations of the currently available data on SF drugs in LMICs. Part V summarizes the key conclusions of our findings.

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[129] Nayyar et al., "Falsified and Substandard Drugs: Stopping the Pandemic." *The American Journal of Tropical Medicine and Hygiene* 100, no. 5 (May 1, 2019): 1058–65. https://doi.org/10.4269/ajtmh.18-0981.

[130] Ozawa et al., "Prevalence and Estimated Economic Burden of Substandard and Falsified Medicines in Low- and Middle-Income Countries: A Systematic Review and Meta-Analysis." *Global Health*, August 10, 2018.

[131] "Goal 3 Ensure Healthy Lives and Promote Well-Being for All at All Ages." Department of Economic and Social Affairs, Division for Sustainable Development Goals. United Nations, 2021. https://sdgs.un.org/goals/goal3.

II. Definitions

In May 2017, the World Health Organization (WHO) adopted the term "substandard/spurious/falsely-labeled/falsified/counterfeit" (SSFC) medical products in an effort to reduce confusion in the discussion of poor-quality medical products. Subsequently, the WHO Member State Mechanism on SSFC endorsed revised definitions that were developed based on a public-health perspective, intentionally excluding consideration of intellectual property concerns.[132,133] These definitions (reproduced below) have largely been adhered to by international stakeholders, contributing to greater uniformity in the global discussion about poor-quality medical products in recent years:

> Falsified medical products: Medical products that deliberately/fraudulently misrepresent their identity, composition or source.
>
> Substandard medical products: Authorized medical products that fail to meet either their quality standards or their specifications, or both; alternatively referred to as "out of specification."
>
> Unregistered/unlicensed medical products: Medical products that have not undergone evaluation and/or approval by the national or regional regulatory authority for the market in which they are marketed/distributed or used, subject to permitted conditions under national or regional regulation and legislation.

This report focuses on medicines falling under the "falsified medical products" and/or "substandard medical products" categories.

III. Literature Review of SF Drugs in LMICs

A. Data from Prevalence Studies

In 2017, the WHO concurrently published two landmark reports reviewing the existing knowledge about the prevalence of SF drugs, their global impact, and the surveillance efforts undertaken by the WHO Global Surveillance and Monitoring System (GSMS) since its 2013 launch.[134,135] In its report on the public health and socioeconomic impact of SF drugs, WHO identified 100 relevant papers estimating SF drug prevalence and published between 1 January 2007 and 31 December 2016.[136] These papers included 48,218 samples of medicines collected from 88 of the 194 WHO

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[132]Publication. *A Study on the Public Health and Socioeconomic Impact of Substandard and Falsified Medical Products*. Geneva: World Health Organization, 2020.

[133] *Member-State Mechanism on Substandard/Spurious/Falsely-Labelled/Falsified/Counterfeit Medical Products*. Geneva: World Health Organization, 2017.

[134] *A Study on the Public Health and Socioeconomic Impact of Substandard and Falsified Medical Products*.

[135] *WHO Global Surveillance and Monitoring System for Substandard and Falsified Medical Products*. Geneva, Switzerland: World Health Organization; 2017.

[136] *A Study on the Public Health and Socioeconomic Impact,* World Health Organization.

Member States. Based on this data, WHO estimated an observed SF drug prevalence of approximately 10.5% for LMICs, accounting for an estimated US$30.5 billion in sales each year. There was also a wide range in therapeutic categories of drugs studied, including anitmalarials (SF drug prevalence: 11.8%), antibiotics and anti-infectives (SF drug prevalence: 7.2%), tuberculosis medicines (SF drug prevalence: 6.7%), and HIV medicines (SF drug prevalence: 4.2%). Among these, antimalarials and antibiotics were the most well-represented in the studies, accounting for 64.5% of all study samples.[137]

Following the landmark 2017 WHO reports, a 2018 systematic review by Ozawa identified 265 studies published before 3 November 2017 that estimated the prevalence of poor-quality medicines in LMICs.[138] Among 96 of the studies, which tested 50 or more samples (67,839 total drug samples), Ozawa found a 13.6% overall prevalence of poor-quality medicines in LMICs and estimated the economic impact to range from US$10 billion - $200 billion. Geographic estimates yielded SF drug prevalence of 18.7% in Africa, 13.7% in Asia, and 11.6% for studies involving multiple regions. Similar to the 2017 WHO literature review, antimalarials and antibiotics were the most commonly examined medicines with SF drug prevalence of 19.1% and 12.4%, respectively. Figure 1 below shows the reported national prevalence of SF medicines determined from the identified studies included in the meta-analysis (excluding multi-country studies that did not report country-specific data).[139]

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[137] *A Study on the Public Health and Socioeconomic Impact,* World Health Organization.

[138] Ozawa et al., "A Systematic Review and Meta-Analysis."

[139] Ozawa et al., "Prevalence and Estimated Economic Burden of Substandard and Falsified Medicines in Low- and Middle-Income Countries." *JAMA Network Open* 1, no. 4 (August 2018). https://doi.org/10.1001/jamanetworkopen.2018.1662.

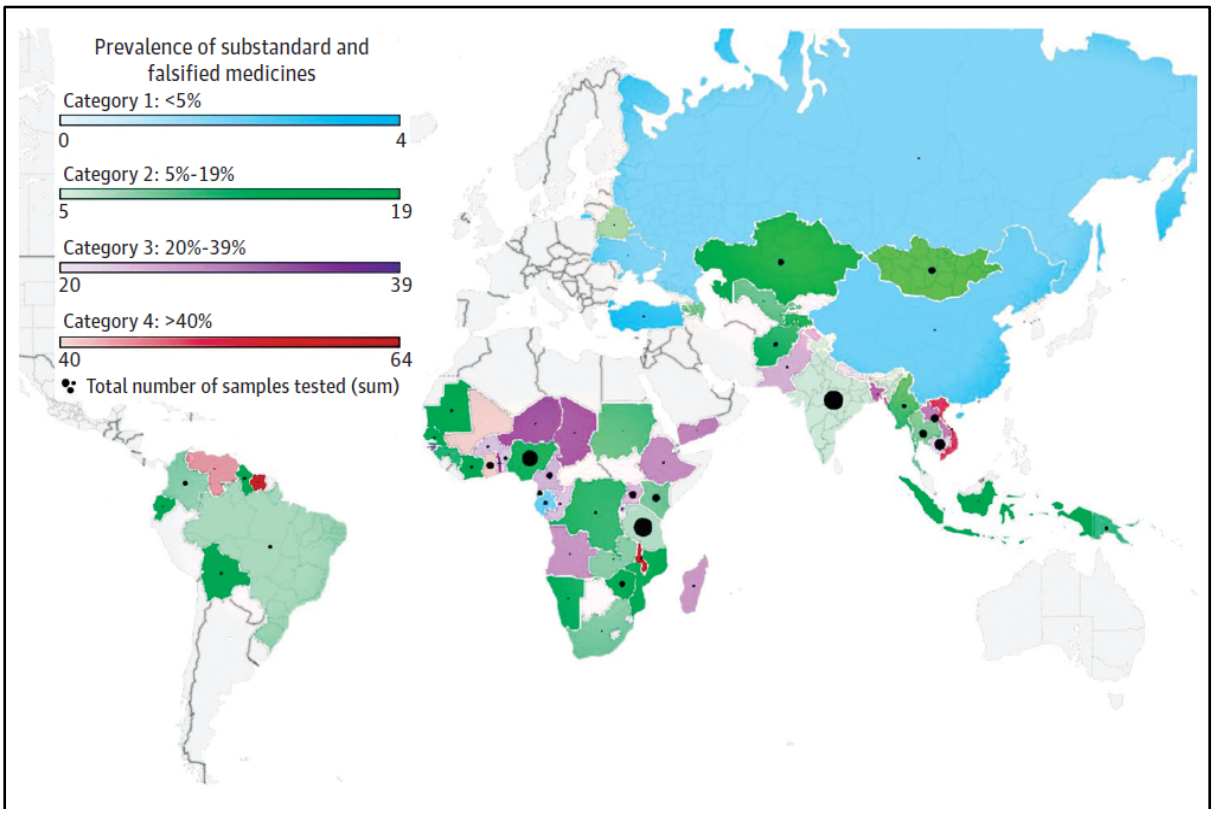

Figure 1. "Results of studies included in the meta-analysis. Multicountry studies that did not report country-specific data were not included. Subcategorical prevalence is delineated by color (blue, green, purple, and red as categories 1 through 4), and by color gradation, with a darker color representing a higher prevalence. Total number of samples tested for each country is presented as a black circle with the diameter of the circle increasing proportionally to samples tested. This map was generated using study data and the Microsoft Excel 2016 3D Mapping tool." **140**

Since Ozawa's 2018 systematic review, a number of additional studies have been performed in LMICs to estimate the prevalence and impact of SF drugs. Table 1 provides a summary of selected studies from 2018-2022. Once again, the available literature indicated higher testing of antibiotics and antimalarials as compared to other therapeutic categories. While there was substantial variability in SF drug prevalence estimates (ranging from 0%-32.5%) between countries and across various drug types, a substantial proportion of the studies reported estimates of SF drug prevalence ranging between 10%-20%, in agreement with earlier estimates from 2017-2018.[141,142]

[140] Ozawa et al., "Prevalence and Estimated Economic Burden of Substandard and Falsified Medicines Low- and Middle-Income Countries."
[141] Ozawa et al., "A Systematic Review and Meta-Analysis."

[142] *A Study on the Public Health and Socioeconomic Impact*, World Health Organization.

Table 2: Summary of selected studies from 2018-2022 providing estimates of SF drug prevalence in LMICs.

Study	Country	Drug Type	Samples	SF Drug Prevalence
Bate et al., "Corruption and Medicine Quality in Latin America," 2018.	10 Latin American countries	Antibiotic	687	7%
Beargie et al., "The Economic Impact of Substandard and Falsified Antimalarial," 2019.	Nigeria	Antimalarial	Unknown	11.8% for ACTs 14.1% overall
Mavungu Landu et al., "Quality of Antimalarials in Kinshasa Peri-Urban Areas," 2019.	DR Congo	Antimalarial	75	19%
Ozawa et al., "Modeling the Economic Impact," 2019.	DR Congo	Antimalarial	Unknown	19.1%
Ozawa et al., "Development of an Agent-Based Model," 2019.	Uganda	Antimalarial	Unknown	19.5% - 31.3%
Rahman et al., "A Cross-Sectional Investigation of the Quality of Selected Medicines," 2019.	Cambodia	Non-communicable disease medicines	372	23.4%
Lambert et al., "Oxytocin Injection Quality in Ethiopia," 2019.	Ethiopia	Oxytocin injection ampoules	45	4%
McManus, Dominic, and Bernard David Naughton, "A Systematic Review," 2020.	Global	All	Median of 155 across 34 studies	25%
Schäfermann et al., "Substandard and Falsified Antibiotics and Medicines," 2020.	Cameroon & DR Congo	Misc. essential medicines	506	18.6%
Khurelbat et al., "A Cross-Sectional Analysis of Falsified, Counterfeit and Substandard Medicines," 2020.	Mongolia	Misc. essential medicines	1,770	10.1%

Jackson et al., "Impact of Substandard and Falsified Antimalarials in Zambia," 2020.	Zambia	Antimalarial	Unknown	10.3%
Abebe et al., "In-Vitro Evaluations of Quality Control Parameters," 2020.	Ethiopia	Paracetamol	102	0%
Tchounga et al., "Poor-Quality Medicines in Cameroon," 2021.	Cameroon	Misc. essential medicines	1,440	26.9%
Bui et al., "Assessing the Impact of Substandard and Falsified Antimalarials in Benin," 2021.	Benin	Antimalarial	Unknown	32.5%
Mziray et al., "Quality of Selected Anti-Retroviral Medicines," 2021.	Tanzania	HIV drugs	2,630	3%
Bizimana et al., "Investigation of the Quality of the 12 Most-Used Antibiotics," 2022.	Rwanda	Antibiotic	232	8.2%
Rahman et al., "A Comprehensive Analysis of Selected Medicines," 2022.	Bangladesh	Misc. medicines	189	9.5%

B. Data on Reported Incidents

In addition to its work on directly estimating the prevalence of SF drugs globally, the WHO has published individual incident reports documenting the surveillance findings of the WHO GSMS. Table 2 summarizes the incident reports published by the WHO between 2020 and 2021. The incident reports do not provide comprehensive data about underlying SF prevalence but rather provide insight into the reporting mechanisms in LMICs, the indicators of SF drugs, the supply chain for SF drugs, and the amount of SF drugs detected in a given incident report. The data support the likelihood that SF COVID-19 vaccines are being circulated.

Table 3: Summary of WHO GSMS Incident Reports From 2020-2021.[143]

WHO Report Date	Countries	Medical Product	Reported By	Amount of SF Drugs Reported
March 2020	West and Central Africa	Antimalarial	Stakeholders	Six different batches (identified by six different batch numbers)
March 2020	Guyana Kenya	HIV rapid diagnostic tests	Patient-level	At least 8,240 falsified products
April 2020	Burkina Faso Cameroon Democratic Republic of Congo France Niger	Chloroquine Products	Patient-level	14 reports
May 2020	Argentina Australia Latvia Malaysia Saudi Arabia	Defibrotide	Patient-level	N/A
October 2020	Mexico	Flu vaccine	Patient-level	3 batches
December 2020	Brazil Turkey	Ledipasvir/sofosbuvir	Patient-level	1 batch
March 2021	Mexico	COVID-19	Patient-level, "outside authorized vaccination programs."	N/A
March 2021	Chad	Vitamin A	Patient-level	2 capsules
August 2021	Cameroon Democratic Republic of Congo Ghana Nigeria	CYTOTEC	Failed laboratory analysis	2 batches
August 2021	Region of the Americas	Remdesivir	Patient-level, including hospital	N/A
August 2021	Uganda India Myanmar	COVISHIELD	Patient-level	N/A
November 2021	Islamic Republic of Iran	COVID-19 Vaccine	Patient-level, "outside authorized and regulated supply chains and authorized	N/A

[143] "Full List of WHO Medical Product Alerts." World Health Organization. Accessed April 7, 2022. https://www.who.int/teams/regulation-prequalification/incidents-and-SF/full-list-of-who-medical-product-alerts.

			immunization programmes."	
November 2021	Islamic Republic of Iran	COVID-19 Vaccine	Patient-level, "outside authorized and regulated supply chains and authorized immunization programmes."	N/A
December 2021	Chad Côte d'Ivoire Mali	Combiart	Patient-level, "outside authorized and regulated supply chains."	1 batch
December 2021	Argentina Estonia India Uruguay	Soliris	N/A	N/A

The WHO data does not provide transparency as to when the SF drug was detected. However, as an illustrative study, the Pan American Health Organization (PAHO) tracked the stage of the supply chain in which incidents of "substandard, falsified, unregistered or stolen products" were reported in Latin America between January 2017 and December 2018.[144] The resulting graphic is reproduced below as Figure 2. In its review of data, PAHO noted that most incident reports do not include the stage of the supply chain at which the detection occurred creating challenges for pharmaceutical companies as well as health providers to harmonize surveillance efforts and to ascertain the most effective quality indicators.[145]

[144] Rojas-Cortés, Robin. "Substandard, Falsified and Unregistered Medicines in Latin America, 2017-2018." *Revista Panamericana de Salud Pública* 44 (2020): 1–10. https://doi.org/10.26633/rpsp.2020.125.

[145] Rojas-Cortés, "Substandard, Falsified and Unregistered Medicines in Latin America," 4.

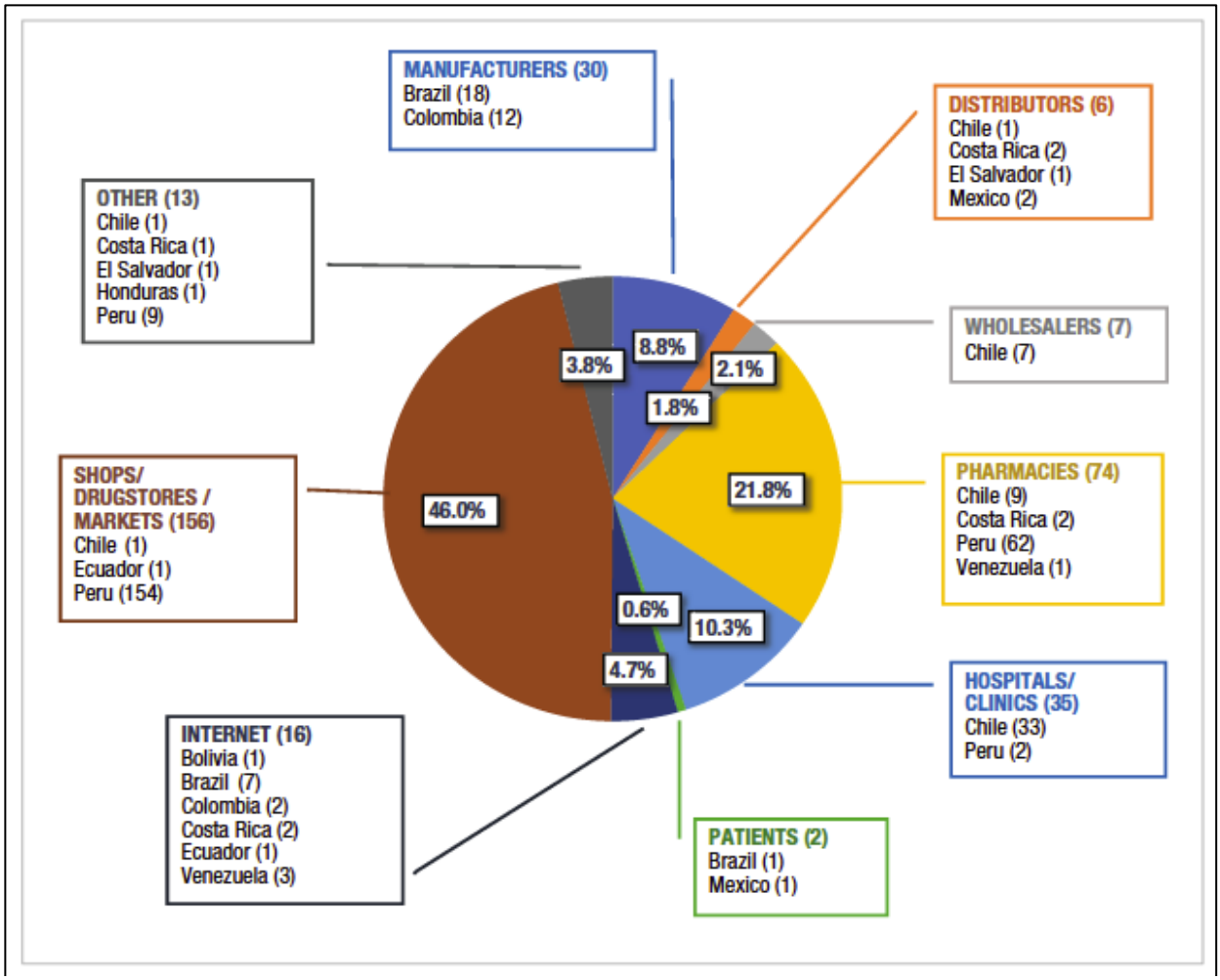

Figure 2. "Stages of the supply chain where incidents of substandard, falsified, unregistered or stolen products were detected in Latin America (2017-2018), including individual detections by country."[146]

Another mechanism for detecting SF drugs that has yielded significant data is customs seizures. The Organisation for Economic Co-Operation and Development (OECD) published a report documenting the prevalence of SF drugs discovered in customs seizures, relying primarily on data compiled on global customs seizures in the OECD/EUIPO database.[147] As of 2016, the OECD reported "counterfeit pharmaceuticals . . . [represented] 0.84% of total world-wide imports in pharmaceutical products."[148] The OECD also identified India as the primary provenance economy for SF drugs.[149] Approximately "53% of the total seized value in counterfeit pharmaceutical

[146] Rojas-Cortés, "Substandard, Falsified and Unregistered Medicines in Latin America," 5.

[147] OECD/EUIPO, *Illicit Trade: Trade in Counterfeit Pharmaceutical Products*, Paris: OECD Publishing, 2020. https://doi.org/10.1787/a7c7e054-en.

[148] OECD/EUIPO, *Illicit Trade*, 30.

[149] OECD/EUIPO, *Illicit Trade*, 34.

products medicines worldwide in 2016" originated from India.[150] China and the United Arab Emirates were also reported to be significant contributors.[151] While India, China, and some Far East Asian Economies, including Vietnam, Indonesia, Pakistan and the Phillippines, were reported to be the main *producers* of SF drugs, Hong Kong and the United Arab Emirates were identified as the main *transit points* (followed by Egypt, Cameroon and Turkey).[152]

These studies indicate the need for harmonization of surveillance mechanisms and detection reporting.

IV. Limitations of Reported Data

Despite the wide range of studies discussed above, estimating the true prevalence of SF drugs in LMICs remains a large and unsolved problem, primarily due to the scarcity of reliable and robust data on SF medicines.[153]

Studies seeking to provide direct estimates of SF drug prevalence in LMICs (discussed above in Section III.A) have substantial limitations including a lack of sufficient reporting sources, inconsistent and sub-optimal sampling methods, variability in the type and quality of product testing, and non-representative focus on drugs in certain therapeutic categories and geographic regions.[154,155] For example, in the WHO's 2017 report on the public health and socioeconomic impact of SF drugs, it was noted that 77% of identified studies implemented convenience sampling compared to just 23% implementing random sampling, and studies involving samples acquired over the Internet were excluded entirely.[156] Ozawa's 2018 systematic review noted similar limitations, with quality analyses revealing large amounts of heterogeneity and significant publication bias.[157]

Proxy data on reported incidents and seizures of fake medicines (discussed above in Section III.B) provide an alternative perspective on the global issue of SF drugs and is closely related to underlying SF drug prevalence. However, these data cannot be used to provide accurate estimates of the true prevalence of SF drugs, since the number of reports and seizures is partially

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[150] OECD/EUIPO, *Illicit Trade*, 35.

[151] OECD/EUIPO, *Illicit Trade*, 35.

[152] OECD/EUIPO, *Illicit Trade*, 38.

[153] Mackey, Tim K. "Prevalence of Substandard and Falsified Essential Medicines." *JAMA Network Open* 1, no. 4 (August 10, 2018). https://doi.org/10.1001/jamanetworkopen.2018.1685.

[154] Mackey, "Prevalence of Substandard and Falsified Essential Medicines."

[155] McManus, Dominic, and Bernard David Naughton. "A Systematic Review of Substandard, Falsified, Unlicensed and Unregistered Medicine Sampling Studies: A Focus on Context, Prevalence, and Quality." *BMJ Global Health* 5 (August 27, 2020): 1–9. https://doi.org/10.29392/joghr.3.e2019081.

[156] *A Study on the Public Health and Socioeconomic Impact*, World Health Organization.

[157] Ozawa et al., "A Systematic Review and Meta-Analysis."

determined by the reporting agent (i.e. patient or healthcare institution), the quality of surveillance mechanisms, and the reporting rate of detected incidents.[158]

Finally, estimates of SF drug prevalence that aggregate findings from studies conducted over many years may not accurately capture important temporal trends in LMICs. For example, just within the short window between December 2020 and January 2021, it is estimated that the black market for COVID-19 vaccines grew by more than 400%.[159] Consequently, estimates of SF drug prevalence must be interpreted with caution given the possibility of rapid and substantial fluctuations, especially in the midst of the global COVID-19 pandemic, which may have effects reaching beyond COVID-19 products alone.

V. Conclusions

The literature review indicates the prevalence of SF drugs in LMICs likely ranges between 10 and 20%, as of 2018. Antimalarials and antibiotics are the drugs most reported on or potentially most problematic for LMICs due to the illnesses afflicting LMIC communities. However, the data suffers from significant limitations due to limited reporting sources, sub-optimal and non-harmonized quality assurance methods, and non-uniform coverage of countries, due to lack of government resources or infrastructure to provide the necessary data. Though poor indicators of comprehensive prevalence, country-by-country case studies and WHO GSMS incident reports do indicate a heightened awareness by LMICs of the need to test drugs and to document SF drug findings. With the rise of harmonized surveillance mechanisms throughout LMICs, the data necessary to quantify the prevalence of SF drugs, to understand the problems in the global supply chain, and to address provenance economies may become more available in the next decade.

[158] *WHO Global Surveillance and Monitoring System for Substandard and Falsified Medical Products.*

[159] Srivastava, Kanchan. "Fake Covid Vaccines Boost the Black Market for Counterfeit Medicines." *BMJ.* Accessed April 7, 2022. https://doi.org/10.1136/bmj.n2754.

5. Anthony Pericolo, "Post-Marketing Surveillance of Drugs"

3/10/2022

Background

This memo will address options for post-marketing surveillance that low- and middle-income countries (LMICs) may use to detect falsified and substandard drugs. The methods below are analyzed in reference to the MiniLab,[160] a portable, thin-layer chromatography operated device that is seen as the standard for post-marketing surveillance. (Pan & Thien 2018). MiniLab's attractiveness comes from its affordability, portability, and accessibility. The MiniLab kit costs $2510, but each test costs no more than $3 to run. (GPHF, 2012; Kaale et al., 2011). Furthermore, "[w]ith the exception of running water and a flat surface on which to work, the kit contains all the labware, reagents, standards for comparison, and instructions necessary to run quality tests on many common medicines." (Detection of Falsified and Substandard Drugs). Finally, MiniLab results may be read and understood with little training. (Detection of Falsified and Substandard Drugs citing Kaale et al., 2011).

To be sure, the MiniLab is far from perfect. Its size and weight limit its utility in the field. Each test requires a significant amount of time. In addition, because the Minilab uses a combination of thin layer chromatography (TLC) and dissolution tests, each test destroys the sample. (Pan & Thien 2018). The MiniLab also requires six tablets, which may not always be available. (Bakker et al. 2021). "The lack of budget to buy medicines to test, and the waste of samples for the pharmacy being inspected" is a major "pitfall" of the MiniLab. (Calliet, et al., Comparative Fields, 2021). Since MiniLab does not provide quantitative results, if falsified drugs are similar enough to the real drug, both can produce similar results in dissolution tests and TLC tests.

Accordingly, much of this memo will be devoted to evaluation of technologies that, although less accurate than the Minilab, could be employed more widely, rapidly, and inexpensively.

Detection Testing

Phone Applications

The most basic post-marketing surveillance technique uses smartphones to scan labels to verify the origin of the drug. Though, numerous phone applications use machine learning to scan pill shape, size, color to determine if drugs are falsified. (Ciapponi, et al. 2021). As few applications allow the scanning of barcodes, pills would need to be scanned directly. *Id.* Application prices range from zero cost to $799 annual subscriptions for the highest quality applications like Lexicomp. *Id.*

[160] I do not compare the MiniLab with other similar kits like the Thermo Scientific FirstDefender and TruDefender and instead refer to them all as the MiniLab. (Detection of Falsified and Substandard Drugs citing Lim, 2012).

While phone applications are available to a wide variety of users, they have several critical drawbacks. Most importantly, one needs access to a smartphone and in some cases, internet access. Even if phone applications are directly available to users, it may be too late to prevent people from taking falsified drugs if the drugs are already within people's hands. Most importantly, some applications do not use a reliable or verifiable information source for medicines' attributes, so their accuracy is questionable. *Id.* Use of smartphone apps is not well suited for LMICs, as the Counterfeit Detector #3 method, *infra*, offers a superior visual inspection method.

Portable near-infrared (NIR) spectroscopy

True to its name, NIR is a form of spectroscopy that measures light absorption in the near-infrared region (700 to 2500 nm). (Degardin et al. 2016). NIR spectroscopy uses "computationally compared experimentally-collected spectra to reference spectra of good quality medicines stored in the device's database." (Calliet, et al., Comparative Fields, 2021). It is "rapid, mobile, and non-destructive," (Assi, et al. 2021), and can "measure directly through plastic drum liners and glass containers," (NIR Spectroscopy for Raw Material Identification in Pharmaceutical and Drug Manufacturing FAQs; *see also* Detection of Falsified and Substandard Drugs citing Kaur et al., 2010; Martino et al., 2010). NIR spectroscopy is accurate when calibrated at +/- 10% and is useful for testing mixed uniformity, specifically identifying when blend uniformity does not match regulatory guidelines. (Caisan, et al. 2021). However, for results to be most accurate, the drug must be as close to its market sample as possible. Minor changes in the film, color, and hardness of the pill will change the resulting spectrum. (Kalyanaraman et al. 2011).

Benefits to NIR include its portability[161], four-hour battery operation, rapid production of results, reliability, and accuracy. (Kalyanaraman et al. 2011). Its main drawback is the high cost of the portable spectrometer ranging from $10,000 to $100,000. (Kovacs 2014). Furthermore, the inability to "create and update the reference library of comparators locally" limits portable NIR use to known compounds with known spectra. (Calliet, et al., Comparative Fields, 2021). Moreover, while the portable spectrometer is easy to use, it is not the most accessible since "data pretreatment is typically necessary to convert the raw data into useful spectral signature information for counterfeit detection." (Kalyanaraman et al. 2011). While NIR quickly produces a spectrum, operators would need to transfer data to a PC for the best results. (Kalyanaraman et al. 2011). Due to its sample-preservation, accuracy, and one-time equipment costs, portable NIR spectroscopy is suitable for LMICs.[162]

Note that this method is complementary in nature to Raman spectroscopy, which measures light scattering instead of light absorption. (Kalyanaraman et al. 2011). However, unlike NIR spectroscopy, packaging may interfere with Raman spectrometers, especially for antimalarials. (Detection of Falsified and Substandard Drugs). "When the API should be identified, Raman spectroscopy might be the better choice, whereas NIR spectroscopy might be the better choice to discriminate medicines based on their excipients." (Bakker et al. 2021). Sometimes, NIR is used

[161] The most portable spectrometer options are the NIR-S-G1 and MicroPHAZIR RX, as others "felt too heavy and cumbersome for pharmacy inspections." (Calliet, et al., Comparative Fields, 2021).

[162] A type of NIR, Fourier Transform Infrared IR Spectroscopy, is also suitable for use in LMICs, as the detection method is portable, operable without electricity, quantitative, and quick. (Lawson et al. 2018; Kovacs 2014). FTIR calculates the spectra using a Fourier transform, but otherwise the methods are identical. (*See* Lawson et al. 2018).

in combination with Raman spectroscopy, such as done to verify Cialis. (Yves-Sacre et al. 2016). Raman spectroscopy, however, is less suited for LMICs because accurate identification of APIs requires chemometric models that cost tens to hundreds of times more to develop than those of NIR. (Bakker et al. 2021).

X-Ray Fluorescence

X-ray fluorescence is used for elemental analyses that can often distinguish real from falsified drugs (Kaur et al., 2010; Martino et al., 2010). The sample is hit with x-rays, which are then absorbed by electrons. The "excited" electrons that absorb the x-rays then collapse to a "relaxed" state, emitting a photon, or in other words, light. The method then measures the light which is emitted characteristically to the atoms (or compounds) present in the sample. The spectrum of emitted light, or fluorescence, is then analyzed and compared to that of the true sample.
The method yields high accuracy. (Kovacs 2014). However, x-ray fluorescence is not well suited for portable, low-cost use in LMICs. *See id.* Results are slow, and the operating technician needs electricity. *Id.* Additionally, preparation of the sample in solvents is destructive. *See id.*

X-Ray Diffraction

X-ray diffraction is a non-invasive technique that measures how much light in the x-ray spectrum is scattered upon passing through a drug sample. It can be used to analyze active ingredients, specifically for crystalline molecules. (Kaur et al., 2010; Martino et al., 2010). This method is not suited for drug testing in LMICs. Lab preparation is required, and results are slow. (Kovacs 2014). Furthermore, it is cost and resource-intensive, as technicians must operate a device within a laboratory, and chemists most likely should interpret the results. *Id.*

Portable Nuclear Quadrupole Resonance (NQR)

"NQR uses radio frequencies to provide qualitative and quantitative information about medicines and can scan them through packaging." (Wellcome Trust, 2012; Wilkinson, 2012). "50 percent of atoms in the periodic table contain so-called quadrupolar nuclei with spin
quantum number that generate NQR signals." (Chen et al. 2016). "NQR resonance frequencies are highly specific to the chemistry of the material under investigation." (Chen et al. 2016).

In principle, the method behaves like spectroscopy. Radiation with frequencies in the kHz range hits the sample, and the portable NQR device measures the absorption. (Chen et al. 2016). The resulting profile is then compared with known profiles of legitimate drugs, and differences are flagged. (Chen et al. 2016).

While portable NQR has promise to operate in LMICs as it is non-invasive, portable, and non-destructive, data collection and interpretation is complicated and requires the knowledge level of a lab technician to operate. (*See* Kovacs 2014).

Colorimetry

Colorimetry checks for the presence or absence of an active ingredient by mixing a sample with a chemical that changes color in the presence of an active ingredient. (Detection of Falsified and Substandard Drugs citing Green et al., 2001). The method is semi-quantitative, as the potency of the color change is directly proportional to the amount of active ingredient in the sample. (Detection of Falsified and Substandard Drugs citing Newton et al., 2006). The most accurate and quantitative form of colorimetry involves the use of a handheld photometer, which measures the light absorption of the sample. *Id.*

Colorimetry testing could be suitable for LMICs. Colorimetry testing generally involves little sample preparation, and interpretation of results is not complicated.[163] The most expensive form of colorimetry involves use of a handheld photometer, which can cost up to $1,500, but usable results may be accomplished with simple chemical solvents. (Green et al 2015). Colorimetry is portable. *Id.* Unfortunately, this form of testing destroys the drug sample. (Detection of Falsified and Substandard Drugs citing Newton et al., 2006).

Physical Property Testing

Physical property testing compares the physical properties of a drug sample with those of the actual drug. Many physical properties can be tested including "density, solubility, reflectance spectra, refractive indices, and optical rotation." (Detection of Falsified and Substandard Drugs). Physical property testing requires an understanding of drug chemistry, but simple directions can be conveyed to an ordinary individual to discern whether a drug sample is doctored. *Id.* For example, to detect whether the antimalaria drug artesunate is genuine, someone would need to dissolve the drug in water, boil the water, and check for deposited crystals. *See id.* Alternatively, one could dissolve the drug in water and perform a simple pH paper test to verify if the water is acidic. *See id.* More complicated physical property testing involves use of handheld refractometers to measure the refractive index of drug samples,[164] but equipment, setup, and data analysis is still minimal compared to other methods described in the memo.

Additional forms of chemical property testing are dissolution and disintegration tests. "Disintegration tests measure how rapidly solid dosage forms disintegrate in a solution; dissolution tests analyze the rates at which drugs dissolve." (Detection of Falsified and Substandard Drugs citing USP 2007). Dissolution and disintegration solutions require basic laboratory preparation that is within the knowledge of a lab technician, but these tests are inexpensive. (*See, e.g.*, Rahman 2021). Like colorimetry, the tests are semi-quantitative, as rates for each are directly proportional to the amount of active ingredient present in the drug sample. *Id.* Dissolution and disintegration tests can identify false ingredients even when the active ingredient is present. *Id.*

Physical property testing may be useful in LMICs once people on site have the proper training. Physical property testing varies per drug, so a person trained in a method to verify one drug is not able to translate the same method to another. Luckily, all forms of physical property testing are easy to learn.

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[163] That is, if interpreting the color is not hard. Calliet, et al., Comparative Fields, 2021 describes user testimony of the difficulty of interpreting results when the packaging isn't clear on the tone or the shade of the color.

[164] This test can only confirm the presence of an active ingredient. It cannot measure the amount of the active ingredient. (Detection of Falsified and Substandard Drugs citing Green et al., 2007).

Broadband Acoustic Resonance Dissolution Spectroscopy (BARDS)

BARDS is a form of dissolution test that takes advantage of "an intrinsic acoustic profile [during dissolution]… which falsifiers cannot yet mimic." (Alfarsi 2021). Dissolving a solid into a liquid introduces minute air bubbles in the new solution. (Fitzpatrick et al. 2014). The rate at which the bubbles generate and disappear can be measured using acoustics. (Fitzpatrick et al. 2014). The acoustic profile varies with solvent concentration and analyte presence. (http://www.bards.ie/what-bards/; https://www.youtube.com/watch?v=K7NDGkOviAc). Consistent samples and solvent concentrations should yield the same BARDS profile, and comparison of drug sample profiles with genuine drug BARDS profiles can help identify fakes.
BARDS spectrometry is not well suited for LMICs. The method is not portable, requires a laboratory with electric and water, requires careful and consistent solvent and sample preparation, and is cost-intensive with equipment costs of at least $20,000.

Portable Laser Counterfeit Drug Identifier (CoDI)

"CoDI is a laser-operated device which measures the ratio of laser light transmitted and scattered by a sample tablet compared to an authentic tablet." (Bakker et al. 2021). The handheld laser is "battery-operated, and relatively inexpensive device that non-trained personnel can use quickly to evaluate a particular branded tablet for authenticity." (Portable Laser-Operated Counterfeit Drug Identifier (CoDI) for Tablets | Technology Transfer). Furthermore, CoDI "does not require the use of consumables such as solvents or chemicals and does not destroy the sample." *Id.* The portability, preservation of samples, low training and low-cost operation make this method particularly suitable for LMICs.

PharmaCheck

PharmaCheck directly measures the active ingredient through a dissolution test. PharmaCheck weighs less than ten pounds and is portable. (Barlow, 2012; Gaffney, 2012). The system uses solar energy or battery power to operate, so it is a great candidate for in-field testing. (Barlow, 2012; Seiffert, 2012). Unfortunately, PharmaCheck is not yet at the stage to replace the MiniLab for drug detection, as it is not accurate with a system error of 20% and unable to perform on drugs with multiple active ingredients. (PharmaCheck: Counterfeit and Substandard Drug Detector Device for the Developing World).

Desoprtion Electroscopic Ionization (DESI), Infrared laser-assisted desorption electrospray ionization (IR-LADESI), Direct Analysis in Real Time (DART), or surface desorption atmospheric pressure chemical ionization (DAPCI) followed by Mass Spectrometry

Each of these methods ionize compounds on the surface of a drug sample. (Cardoso-Placios & Lanekoff 2016). Ions are then passed to a mass spectrometer for compound verification. (Cardoso-Placios & Lanekoff 2016). In addition to identification, these methods may quantify the amount of API present. (Kovacs 2014). These methods are not suited for LMICs because they must be performed in a laboratory with a highly trained chemist. *Id.* Although each method produces quick

results and requires no sample preparation, the equipment needed to perform these techniques is extremely costly. *Id.*

Counterfeit Device #3

Counterfeit Device #3 performs handheld drug verification through visual inspection. (Kovacs 2014). The device is equipped with a camera, a UV light, a digital microscope, an IR light, and a storage medium. (Ranieri et al. 2014). When a user operates the device, the lights are shined on the drug sample and a genuine sample of the drug. Visual inspection may be done through blister packaging. *Id.* Visual inspection can identify many falsified drugs through simple distinctions such as the crispness of a brand label on a pill or differences in shading or contrast. (Detection of Falsified and Substandard Drugs; Ranieri et al. 2014). Differences in reactions to the light (e.g., differences in shade) can be attributed to different chemical compositions in the sample. (Ranieri et al. 2014). Users do not have to rely solely on "on-the-spot" testing, as the device can store over 100,000 pictures, which can be transferred to a computer via USB for closer inspection. *Id.*

Counterfeit Device #3 is well suited for use in LMICs, as it is a portable device which is cheap and easy to operate. It is worth noting that Ranieri at al. 2014 recommends combining this method with the MiniLab for chemical analysis, but if testing is limited to visual analysis only, Counterfeit Device #3 is the best option.

High performance liquid chromatography, Ultra-high performance liquid chromatography, or Gas Chromatography (coupled with Ultraviolet spectroscopy or Mass spectroscopy)

While these are "the gold standard" to determine the chemical composition of a sample, none are suitable for use in LMICs, as they require extremely expensive laboratory equipment; cannot be scaled down to make the methods portable; are destructive to the sample; and are time, knowledge, preparation, and resource intensive. (Kovacs 2014; Assi, et al. 2021; Detection of Falsified and Substandard Drugs). As such, these methods should only garner use in the most exceptional circumstances when one may not determine the veracity of the drug without an understanding of the chemical compounds in the drug sample.[165]

[165] Kovacs 2014 identifies use of a portable Gas Chromatography/Mass Spectrometry device that does not share as many of the limitations as other methods identified in the section. Because results are slow and a highly trained lab technician will need to operate the device, I would also recommend avoiding this verification method for LMICs.

6. Fatema Jaffer, "Surveillance of Counterfeit COVID-19 Vaccines in South and Southeast Asia"

April 2022

The World Health Organization defines the phrase, "counterfeit drug" as "drugs that are deliberately and fraudulently mislabeled with respect to identity and/or source."[166] South and Southeast Asia accounts for some of the largest share of counterfeit drugs in the world; using successful and unsuccessful surveillance mechanisms to combat this problem.[167] One surveillance mechanism includes the International Criminal Police Organization, which seized and closed more than 20 million counterfeit pills and 100 retail outlets in one year alone.[168] Other institutions, such as The National Institution for Transforming India, uses US-based computer technology (named "Oracle") to trace pharmaceutical products and track counterfeit drugs.[169] Surveillance mechanisms on falsified drugs continued during the coronavirus pandemic when South and Southeast Asian countries began distributing the COVID-19 vaccine. Many of these vaccines became falsified when they were subject to poor treatment, while others were supplied as counterfeit through illegal drug trade.[170] Below are the surveillance systems used in each region and how effective they are to limiting falsified COVID-19 vaccines.

South Asia

In South Asian countries, surveillance systems such as Vaccine Pharmacovigilance (PV) are used to monitor COVID-19 vaccines; but the "lack of vaccine safety surveillance infrastructure, technical expertise, and dedicated personnel" still provides a challenge for residents.[171] To actively combat the problem of counterfeit vaccines, authorities use reporting systems and periodic compliance checks to ensure safety.[172] Reporting systems such as VigiFlow use cloud-based technology to track patient reactions to vaccines via mobile app.[173] Although these surveillance systems might "reduce the likelihood of a side effect being repeated," they are implemented after patients receive counterfeit vaccines, leaving them with health consequences that could have been avoided before the injection.[174]

Genetic and demographic surveillance systems are also used in South Asia, where scientists can track changes in SARS variants within a specific group of people.[175] Although these mechanisms do not directly identify which vaccines are counterfeit, they allow institutions to analyze whether the distributed COVID-19 vaccines are effective, flagging adverse reactions and determining whether these reactions are the product of a counterfeit.[176]

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[166] (Rees 2019)
[167] Ibid.
[168] Ibid.
[169] Ibid.
[170] (Okunola 2021)
[171] (Health 2021)
[172] Ibid.
[173] (Gamarra 2022)
[174] Ibid.
[175] (Mohammad Mehedi Hasan 2021)
[176] Ibid.

Due to the inability to access vaccines as quickly as western countries, South and Southeastern Asian countries began creating their own vaccines. For example, the COVAXIN vaccine was developed in India and made available across South Asia.[177] To monitor these vaccines, countries such as Bhutan developed system portals to identify cold chain storages for the vaccines, organized vaccination sites, and monitored vaccine storage delivery and post-injection reactions.[178] However, storing issues—either storing a vaccine for too long to the point of expiration or ineffectively meeting vaccine temperature requirements—lead vaccines to become falsified.[179] Along with these problems, too few trained pharmaceutical staff at vaccine distribution centers and mishaps in the physical transportation of vaccines—where vaccines get lost or stolen and sold as counterfeit—remains a major concern for surveillance.[180]

Southeast Asia

Up to $2.6 billion is annually spent on counterfeit drugs.[181] During the COVID-19 vaccine distribution, Southeast Asian countries used surveillance systems, such as the eZTracker management system, to capture, track, and trace data points and provide instant verification of vaccines through a mobile app.[182] This management system allowed health authorities to identify which vaccines had expired, preventing counterfeit drugs from entering the region through hidden grey trades.[183] Yet even with this system, health authorities reported falsified vaccines after they were already injected into consumers.[184] For example, in India and Myanmar, Serum Institute of India Pvt. Ltd.—the manufacturer of the vaccine, COVISHIELD—confirmed batches of COVID-19 vaccines as both expired, misspelled, and produced at the wrong dose (2ml instead of the usual 4 doses).[185]

Countries such as Singapore, Thailand, Malaysia, the Philippines, and Vietnam, are listed amongst the top 25 economies for counterfeit and pirated goods, where the majority of these counterfeits are sold online.[186] The coronavirus pandemic heightened the sale of these counterfeits, increasing online falsified advertisement by 400%.[187] According to the World Health Organization, when the supply of vaccines does not meet its demand from consumers, an environment of fake medicines will try to meet this demand.[188] In countries such as Indonesia, authorities detected the alteration of the expiration date and amount of active ingredients in the vaccine in warehouses, returning them to pharmacies for sale.[189] Intergovernmental organizations such as INTERPOL, try to limit the selling of these counterfeit vaccines by finding and removing websites falsely identifying and selling common-known brands of COVID vaccines.[190]

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[177] (Tamang 2021)
[178] Ibid.
[179] (Straten 2020)
[180] Ibid.
[181] (Sito 2022)
[182] Ibid.
[183] Ibid.
[184] Ibid.
[185] (Medical Product Alert N°5/2021: Falsified COVISHIELD vaccine (Update) 2021)
[186] (Nguyen 2021)
[187] Ibid.
[188] Ibid.
[189] Ibid.
[190] (Okunola, How Can I Spot A Fake COVID-19 Vaccine? 2021)

Just as in South Asia, stealing COVID-19 vaccines can occur while they are in transit or storage.[191] Locations such as the Changi airport are utilized as storage and distribution units for the vaccine, allowing the "greatest risk of vaccine interception" to occur through transit.[192] Although some vaccines are limited to facilities that can produce intense refrigeration (such as the Pfizer-BioNTech vaccine), this limitation makes these vaccines easier to secure and monitor—lowering the chances of vaccines getting stolen.[193] Not meeting this refrigeration requirement can lead to the injection of noneffective vaccines. Southeast Asian countries sought to combat this problem by increasing storage facilities and negotiating with additional vaccine distributors to provide vaccines with lower refrigeration requirements.[194] Encouraging international cooperation through the share of knowledge and resources helps to "prevent the formation of illegal distribution channels."[195] Sharing of information through authentication software such as DeepKey can easily identify counterfeit vaccines and share this information between countries.[196]

Conclusion

The surveillance of counterfeit COVID-19 vaccines in South and Southeast Asia needs improvement. Recommendations begin with the Counterfeit Incident System, where a "single point of contact" can report counterfeit incidents to a central global system to improve the detection of security breaches, data collection, analysis, and dissemination of COVID-19 vaccines.[197] This single point can "result in a shift in policy focus," allowing authorities to take action over the information shared.[198] Additional solutions include implementing 2D barcoding programs for "end-to-end verification" and "Track and Trace" systems. Examples of these systems include: sending Medicines Authentication Tools (visible/scratchable barcodes) to authentication databases via mobile apps and messaging, Radio Frequency Identification Tagging (active and passive chips used to transmit vaccine information via radio waves or wireless signals), visual aids, and reference libraries for knowledge on how to easily identify counterfeit vaccines.[199] According to the World Health Organization, these mechanisms are convenient, simple to use, affordable, and allows authorities to identify whether a product is expired, recalled, or falsified through warnings and alerts.[200] Even with these new surveillance systems, millions of counterfeit vaccines are given to South and Southeast Asian residents. The monopolization of vaccines by western countries, lack of diligent care at storage sites, and large incentive to rapidly sell counterfeit vaccines remain problems within these regions. Existing surveillance systems need better or new monitoring strategies to prevent the furthering of COVID-19 in South and Southeast Asia.

[191] (Straten 2020)
[192] Ibid.
[193] Ibid.
[194] Ibid.
[195] Ibid.
[196] Ibid.
[197] (Tim K. Mackey 2015)
[198] Ibid.
[199] (Huma Rasheed 2018)
[200] Ibid.

7. Aaron Nytes & Alex Kubie, The Power of Section 1498

INTRODUCTION

In 1910, Congress passed what would become 28 USC §1498. The act itself served to partially waive the government's sovereign immunity for cases in which it infringed on an already established patent (Brennan et al. 2016, 299). While § 1498 currently remains an overlooked tool, the statute may play an important role in lowering prices of patented medical technology for use by the U.S. government or its approved subsidiaries. For this possibility to manifest itself, government officials need to expand their willingness to discuss the statute's plentiful power publicly.

I. HOW IT WORKS

Text and Enforcement

> The current text of 28 USC §1498(a) provides in principal part:
>
> Whenever an invention described in and covered by a patent of the United States is used or manufactured by or for the United States without license of the owner thereof or lawful right to use or manufacture the same, the owner's remedy shall be by action against the United States in the United States Court of Federal Claims for the recovery of his reasonable and entire compensation for such use and manufacture.

The statute puts the onus on the infringer to commence an action to recover damages under its provisions. Unlike normal patent law, "the Court of Federal Claims maintains no injunctive authority" under § 1498 (Lavenue 1995, 459). This retroactivity, as well as litigation costs, inform any net present value calculation made during negotiations between the United States Government and the owner of patented property.

Remedies

Generally, lost profits resulting from infringement are unavailable to patent owners under § 1498(a) (Brennan et al. 2016, 311). Only in circumstances where courts find it necessary and the patentee is able to provide "the strictest proof that the [they] would actually have earned and retained those sums" is lost profit even considered as a potential remedy (Tektronix, Inc. v. United States, 213 Ct. Cl. 257, 267 (1977)). This practice of assessing damages mirrors that in eminent-domain law rather than the remedies provided in a lawsuit for patent infringement under a waiver of sovereign immunity (Chisum 2022, § 16.06). This is consistent with the language of the statute, which affords "reasonable and entire compensation" instead of the "adequate" compensation standard required under the Patent Act (35 U.S.C. § 284). One option available to courts is to award royalties based on would-be compensation under "a *nonexclusive* license adequate to cover the goods and services procured or authorized by the government" (Morten and Duan 2020, 44). Federal agencies also have the ability to issue guidelines to establish how much royalties should be awarded under a § 1498 claim (Brennan et al. 2016, 316). Ultimately, "[t]he determination of a reasonable royalty requires a highly case-specific and fact-specific analysis, relying upon mixed considerations of logic, common sense, justice, policy and precedent" (Liberty Ammunition, Inc.

v. United States, 119 Fed. Cl. 368, 386 (2014)). Within this case-specific analysis, the Court of Federal Claims has wide discretion to determine damages within a given claim.

Negotiation Power

Any attempts at government procurement of patented property under § 1498 is likely to be negotiated around (Brennan et al. 2016, 321). Variable damages as well as unpredictable court costs inform this decision. These negotiations can allow the government to buy-out patented property for non-exclusive use—likely allowing the U.S. government or an approved subsidiary to procure the property at a lower price than would be paid in the free market (Ibid.). Aside from latent pressure, any potential change to § 1498 can provoke patent holders to change their behavior. Indeed, companies like Bayer have made substantial concessions to drug pricing when public officials have threatened to strengthen government-infringement by reducing damages under § 1498 (Morten and Duan 2020, 321).

II. HISTORY

While sparsely employed today, § 1498 has been used by the United States government throughout history, sometimes with relative frequency. This usage has not been limited to the medical context. In fact, the government has been apt in employing this power to further its military interests. But with the availability of modern medicines that hold the potential to eradicate pervasive infections and diseases, calls for the government to utilize § 1486 for medical purposes have reemerged. And with the recent and ongoing COVID-19 pandemic, this conversation has proliferated.

Codification of § 1498

Up until the twentieth century, patent holders could not sue the U.S. government for patent infringement (Brennan, et al. 2016). Patent infringement of this kind was considered a tort claim for which the government did not waive sovereign immunity (Williams and Ghrist 2017).
In 1910, Congress passed the "Government Use Statute," which held that "whenever an invention described in and covered by a patent of the United States shall hereafter be used by the United States without license of the owner thereof or lawful right to use the same, such owner may recover reasonable compensation for such use by suit in the Court of Claims." (36 Stat. 851 (1910)). While this could not prevent a taking, the legislation partially waived the government's sovereign immunity, providing a forum for patent holders to seek reasonable compensation (Brennan, et al. 2016). As discussed prio, the statute was styled under the theory of eminent domain—that the government's taking of a license for the use a patented invention could be used for the overall benefit of the public (Williams and Ghrist 2017)

Three amendments to the legislation were eventually passed. The first amendment came eight years after the act's passage. Clarifying issues that arose following World War I, Congress amended the statute to specify that contractors manufacturing previously patented goods on the government's behlaf maintained an equal level of immunity (Brennan, et al. 2016). In 1942, two amendments were passed to further clarify the scope of this immunity for federal contractors (Brennan, et al. 2016). These changes were eventually codified within 28 U.S.C. § 1948, which added to its main provision:

> … For the purposes of this section, the use or manufacture of an invention described in and covered by a patent of the United States by a contractor, a subcontractor, or any person, firm, or corporation for the Government and with the authorization or consent of the Government, shall be construed as use or manufacture for the United States. (28 U.S.C. § 1498(a) (2012)).

This statute still retains the purpose of its predecessor, the 1910 Government Use Statute, providing the limited avenue of seeking monetary damages for a government taking of a license to use a patented invention.

Non-medical Industry Use

As alluded to prior, the U.S. government's patent infringement has primarily involved the takings or usage of military technology inventions in wartime (Williams and Ghrist 2017). This has included the U.S. Army Corp. of Engineers' taking of patented waste removal methods (Brennan, et al. 2016); Marine Corps production and use of patented battery technology (Leesona Corp. v. United States 1979); the purchase and usage of patented thermal targets for the military (TVI Energy Corp. v. Blane 1986); and even the procurement of warplanes and other patented plane parts (Brennan, et al. 2016).

In addition to its prominence in the industry of war, the government has also relied on § 1498 in various other fields, during times of both war and peace. In 2009, the Department of Treasury utilized this power to prevent banks from being held liable for using patented fraud-detecting software (Brennan, et al. 2016). In the year prior, the government contracted with a third-party manufacturer of electronic passport readers that allegedly infringed on a domestic patent (IRIS Corp. Berhard v. United States 2008). Other uses have included the acquisition of patents on genetically mutated mice (Brennan, et al. 2016).

Medical Industry Use

The last time the federal government used § 1498 to procure patented pharmaceuticals was in the 1960s and '70s. As chronicled by Brennan, et. al, the government began deliberately violating U.S. patents of drug products by purchasing the drugs from unlicensed sources abroad for domestic use at significantly cheaper prices. For example, the government purchased the antibiotic tetracycline hydrochloride from a supplier in Italy, where drug patents were not issued, instead of from the U.S.-based Pfizer, who held the drug's patent. The Italian supplier delivered the drug for 72% of the price of Pfizer. In another instance, the government purchased the generic drug nitrofurantoin for almost four times less than the U.S. patent holder's price (Brennan, et al. 2016).

This procurement of generic drugs at cheaper prices persisted throughout the 1960s. In one three-year period, § 1468 enabled the Department of Defense to save over $21 million on over 50 drugs (Brennan, et al. 2016).

Despite lobbying from the pharmaceutical industry to limit the applicability of § 1498 to wartime and other periods of national security crises, its language and scope remained unchanged. However, by the 1970s, the government ceased using this power to purchase pharmaceuticals at

an affordable price. While no direct explanation has been given for this shift, many suspect it was rooted in the pharmaceutical industry's growing capture of Capitol Hill (The NYTimes Editorial Board 2018).

It was not until the beginning of the twenty-first century that the power was invoked in the pharmaceutical context. The latest utilization of §1498's power was in 2001 by then-Secretary of Health and Human Services Tommy Thompson. It remains the vestige's only usage in recent history. In the weeks following the September 11th terrorist attacks, letters containing anthrax were mailed to news agencies and United States Senators (Federal Bureau of Investigation n.d.). These attacks, also known as "Amerithrax," killed five people and prompted Thompson's public contemplation of importing generic versions of ciprofloxacin, an antibiotic used to treat anthrax, under § 1498 (Calsyn 2020). This proposal was bolstered by more direct calls from Senator Chuck Schumer (Morten and Duan 2020). After this veiled threat, Bayer, the relevant patent holder of the antibiotic, immediately halved its prices (Morten and Duan 2020). Even in this instance, the statute was used only in the name of national security rather than explicitly mentioned in negotiations with drug companies. Since 2001, the government has not officially utilized §1498 to procure cheaper pharmaceuticals.

IV. NEW AND POTENTIAL USES

Recent campaigns for the U.S. government to use its § 1498 power to lower drug prices have come on various fronts—from government officials to grassroots organizers.

In 2015, internal budget constraints and the prohibitive price of Hepatitis C medication resulted in the U.S. Department of Veterans Affairs (VA) to stop enrolling HCV-positive veterans. In response, Senator Bernie Sanders wrote an open letter to the VA to use § 1498, "to authorize third parties to manufacture or import" generic versions of HCV drugs, for government use (Brennan et al. 2016, 280-81). Sanders specifically called for the VA to override patent protections held by Gilead for Sovaldi (sofosbuvir) and Harvoni (ledipasvir/sofosbuvir), and the patents held by AbbVie for its Viekira Pak (ombitasvir/paritaprevir/ritonavir; dasabuvir) combo regimen (HEP 2015). The VA ultimately ignored this request.

Two years later, the government's leverage from its § 1498 powers resulted in a substantial reduction to Hepatitis C pricing, dramatically expanding access to Hepatitis C treatment for patients in Louisiana (Action Center On Race & The Economy, et al. 2022). Asegua Therapeutics, a subsidiary of Gilead, held a patent for a costly yet life-saving Hepatitis C treatment. After the Louisiana Secretary of Health began exploring whether to ask the federal government to use § 1498 on the hepatitis C cure, the Secretary negotiated major discounts (Action Center On Race & The Economy, et al. 2022). While § 1498 was again not directly invoked, the very prospect was enough to prompt Asegua to negotiate. After the new price negotiation, more Louisiana residents received treatment for Hepatis C just in the first 75 days than in all of 2019 (Thomas 2019).

Gilead soon found itself in the center of controversy, brought on by activists from the HIV advocacy group PrEP4All, for its patent on life-saving HIV medication and preventative treatment as well. On January 21, 2021, the group—along with its legal team at New York University Law School's Technology Law & Policy Clinic—provided a "user's guide" for the Biden

administration on how § 1498's government patent use power can "expand supplies and bring down prices of prescription drugs and other patented technologies." (PrEP4All 2021). Along with the call for breaking the patent on Gilead's HIV treatment, PrEP4All called on Biden and Health & Human Services to "use their § 1498 authority… to bypass patent barriers and promptly provide Americans with lifesaving, low-cost medicines for COVID-19, HIV, hepatitis C, and other diseases" (PrEP4All 2021).

Calls for the government's employment of § 1498 have also intensified during the COVID-19 pandemic. For example, Charles Duan, a Senior Fellow at the R Street Institute, and Christopher Morten, deputy director of the Technology Law and Policy Clinic and a Visiting Fellow of the Yale Global Health Justice Partnership, have explored the government's ability to use this power to expand supply and access to Gildead's COVID-19 treatment Remdesivir (Morten and Duan 2020).

Advocates from the Make Meds Affordable campaign have also called on the Health and Human Services Department to use § 1498 to take Pfizer's patent for Paxlovid, a COVID-19 medication, and authorize generic manufacturers to make the drug for the government. This, it holds, would help reduce prices and increase supply of the drug (Action Center On Race & The Economy, et al. 2022). And in 2021, Senators Elizabeth Warren and Amy Klobuchar, along with Representative Lloyd Doggett, penned a joint letter to the Department of Health & Human Services to use of § 1498 to lower prices for insulin, drugs to prevent and treat HIV/AIDS – like emtricitabine/tenofovir alafenamide (Descovy), Hepatitis C drugs—like ledipasvir/sofosbuvir (Harvoni) and sofosburvir (Sovaldi), adalimumab (Humira), the overdose treatment naloxone, and albuterol (Warren, Klobuchar and Doggett 2021).

While the official usage of § 1498 waned in recent years, the recognition of this power's potential to address rising drug prices and expand access to life-saving treatment has reemerged and no longer appears confined to the past. In order for its use to be properly implemented, however, more pressure is needed from government officials to publicize this statute's true capabilities.

8. Logan Fahrenkopf and Ani Zotti, Criticisms of Voluntary Licensing

April 2022

Critiques of the current voluntary-licensing regime generally fall into two camps. Arguments the first type contend that VLs are insufficiently protective of patent owners; arguments of the second type contend that VLs do too little to promote public health and reduce inequality.

Type 1 Criticisms

Involuntary Licensing

The term, "voluntary licensing," implies that the patent holder grants a license of their own volition. However, most nations have compulsory licensing procedures in place should negotiations for a voluntary license fail. Grantors are aware of these procedures when they sit down at the negotiating table, and that likely sways their bargaining position.

The TRIPS Agreement requires a government to first request a voluntary license from a patent holder. However, Article 31 grants governments a right to compulsory licensing if the two fail to negotiate a voluntary license within a "reasonable period of time . . . on reasonable commercial term[s]." Upon issuing a compulsory license, the patent holder must be paid "adequate remuneration." There is no defined mechanism for determining adequate remuneration. (World Trade Organization, 2022).

Patent holders generally have recourse to appeal royalty fees of compulsory licenses, but it is both costly and not guaranteed to be effective. In 2012, Bayer challenged a compulsory license for Nexavar granted under TRIPS in India. After appealing the High Court's decision to uphold the license to India's Supreme Court, Bayer's case was dismissed. After two years and mountains of legal fees, Bayer was left without further options in India. (Rautray, 2014).

A patent holder can also petition their home country and the WTO for relief. However, that typically generates considerable backlash in the realm of public opinion, so firms and governments may be hesitant to take that route. See, for example, the heated patenting system dispute between the United States and Brazil at the turn of the century. (Champ and Attaran, 2002).

Without a mechanism to determine fair market value for licensing costs or an opportunity for appeal to an impartial third party, the balance of power favors the government requesting a voluntary license. Patent holders generally are sophisticated parties that understand this dynamic. That underlying threat calls into question some of the voluntariness of such a license.

Reference Pricing and Information Arbitrage

Voluntary licensing generally includes offering a lower price to consumers in a given market. Here, as well as above, there is an issue created by the lack of price-setting norms. Manufacturers and purchasers may have different models to set prices. These models may suggest different prices for a particular area, creating tension between manufacturers and purchasers. In order to avoid this tension, a patent owner may be less likely to grant a voluntary license. (Moon, et al., 2011).

Inter-country differential pricing is normal across a range of products. Sellers price their products based on what buyers are able and willing to pay in a specific region or country. (Palfrey, 2017). Pharmaceutical pricing is further complicated by the presence of third-party actors – insurance companies, governments, etc. These third-party actors use various methods of "reference pricing" to compare the fair price for pharmaceutical products. (Yadav, 2010). Some buyers go to the extreme of demanding the lowest price offered anywhere in the world. *Ibid.* Upon determining a reference price, buyers refuse to pay above that price for a product.

Manufacturers are aware of these reference pricing models, and may take them into account when setting prices. By setting a low price in a specific country or region, any reference pricing model that incorporates the area will be affected by the lower price. In the absence of a global mechanism for price referencing, pharmaceutical companies may use one method and large purchasers may use another. Overall, this has a cooling effect on manufacturer's incentive to cut drug prices for emerging markets.

Physical Arbitrage Along the Supply Chain

Physical arbitrage, when actors obtain a product in a low-priced market and resell in a high-priced market for profit, is another threat to voluntary licensing. Theoretically a manufacturer can prohibit product arbitrage, but in practice that may not be the case. Supply chains are complicated and there are plenty of opportunities for products to enter and exit. While patent holders have the right to enforce their patent and protect against such arbitrage, the scope of the problem makes it hard to actually exercise that right.

Governments may play a role in limiting damage by regulating supply chains. Inter-country physical arbitrage is relatively rare, due to strong border controls in wealthy, high-price countries. Intra-country arbitrage is a more difficult challenge due to the absence of a physical border. This problem may be further exacerbated in developing countries that lack a strong regulatory framework or enforcement mechanisms. (Palfrey, 2017).

Protecting pharmaceuticals from arbitrage should be easier than protecting other types of products. Manufacturers can alter packaging and design for the low-priced version of their drugs. For example, GlaxoSmithKline alters packaging for Epivir and Combivir in order to identify diverted product. (Yadav, 2010).

Type 2 Criticisms

On the other side are critiques from those who are pushing for more open access to the intellectual property of medical technology. Although some groups might prefer IP waivers, even the more prominent critics acknowledge that voluntary licensing can be a useful tool to make life-saving medicines available to populations that otherwise would not have access to them (Love, 2022). Their commentary largely focuses on ensuring that such licenses allow as many people as possible to have access to treatment; that they are configured in such a way that generic manufacturers can effectively produce and distribute treatments; and, somewhat less explicitly, that the licenses are structured in a way that allows for future domestic growth of biotech industries within the countries of the generic manufacturers (Love, 2022 & Voluntary licenses and access to medicines, 2020).

Médecins Sans Frontières argues that this last point, in particular, is crucial to the long-term goal of creating a world that is more responsive to future pandemics (COVID-19 Technology Access Pool (C-TAP) – a dialogue with civil society organizations, 2022).

Additional, more specific criticisms are set forth below.

Transparency

Pharmaceutical companies offering bilateral licenses often refuse to share the terms and conditions of these licensing contracts with the local governments or the public, and are protected from doing so by broadly-worded trade-secret protection laws. This disadvantages generic producers and governments from bargaining for better terms. According to critics, releasing these details would not risk companies' bottom lines (Voluntary licenses and access to medicines, 2020).

The lack of transparency of licensing contracts can also lead to confusion and inefficiency. Rights-owning companies prefer to sign individual agreements with manufacturers initially, because it is easier for them to specify restrictive terms. The same, or overlapping, drugs might then be offered later through a pool system, like the Medicines Patent Pool. This has two consequences. Firstly, it can be difficult for international health organizations or local governments to make crucial strategic decisions during a crisis when they can't be sure of their own domestic capabilities. Secondly, generic manufacturers who were first-movers in contracting with the pharmaceutical companies early on can then become locked into agreements with worse terms – resulting in less medicine produced and fewer patients treated. *Ibid*.

Geographic Restrictions

Geographic restrictions come in two flavors. As an initial step, pharmaceutical companies will often only make their licenses available to lower-income countries. Different pharmaceutical companies use different metrics to determine low-income – some use GDP or GNI per capita, while others use the UN's Human Development Index. Gilead, which has several voluntary licensing projects ongoing, uses a weighted metric that balances GNI per capita with disease burden. It then divides countries into three categories: 140 countries where licenses are available cheaply; another two dozen or so that receive a discounted rate; and of course the developed world, which receives no discount (Samuel, 2022).

All of these segmentation regimes leave millions, if not billions of people without access to affordable medicine – particularly the 62% of the world's poor that live in middle-income countries (Palfrey, 2017 & Voluntary licenses and access to medicines, 2020). MSF recommends that instead of GNI, pharmaceutical companies should look at health resource gaps – access to critical treatment can differ from income dramatically in countries that don't have government-funded healthcare programs. *Ibid*. Pharmaceutical companies like Gilead counter that such gaps are really a result of domestic policy, and it is not their responsibility to provide a shield against poor policymaking (Samuel, 2022).

A second tier of geographical restrictions comes into play regarding to whom generic manufacturers can sell their products. Gilead's voluntary licensing program for the HIV

antiretroviral drug tenofovir alafenamide (TAF), allows any generic manufacturer in a low-income country to sell to any other low-income country, but prohibits sales to middle-income countries like Brazil (Samuel, 2022). Similarly, in 2018, India was authorized a license to produce Hepatitis C medication by AbbVie, but couldn't sell the drug to its own population (Voluntary licenses and access to medicines, 2020). Occasionally this type of "parallel trade" is forbidden outright, or heavily discouraged, by inserting "anti-diversion" provisions into the contracts (Garagancea, 2021). Gilead argues that such restrictions are necessary because it sets up its voluntary licensing program to be financially sustainable; the vast majority of revenue comes from Gliead's own sales to middle-income countries, and only a tiny portion come from generic manufacturers' royalty payments (Samuel, 2022). At a minimum, however, this leaves huge swaths of the impoverished population overpaying for lifesaving drugs (Garagancea, 2021). It also likely chills long-term business interests, as discussed in the final section (Voluntary licenses and access to medicines, 2020).

Restrictions on domestic pharmaceutical industry development

Various terms and conditions attached to voluntary licenses limit generic manufacturers' ability to be competitive long-term, and discourage additional players from entering the market. For instance, an inevitable consequence of geographic limitations on where generic manufacturers can sell is that those manufacturers have an inherently restricted market – and the demographic that they are cut off from is definitionally richer. (Amin, 2007 & Voluntary licenses and access to medicines, 2020). This is compounded by other common restrictions, like licensing only for the pediatric version of certain drugs or only to the "public sector" (ie, government buyers, as opposed to private healthcare markets) within certain countries (Amin, 2007). The loss of revenue limits the potential of the entire domestic biotech industry.

Some restrictions may also explicitly buttress the monopoly power of rights-owning pharmaceutical firms, and offering voluntary licenses can therefore be a tactic to deter competition. Licensing agreements that define "patent" very broadly – to include all pending patents applications, appeals to rejected patents, etc. – restrict generic manufacturers from selling a much wider array of technology to richer countries (Voluntary licenses and access to medicines, 2020). The arrangement essentially offers pharmaceutical companies a shadow patent in the developing world before they have secured one – or after one has been rejected – in the developed world. Selective voluntary licenses can also deter governments from issuing compulsory licenses, which might be broader in scope. And without adequate technology transfer, voluntary licenses can even delay generic manufacturer's entry to market (Amin, 2007). As an example, a "product patent," as defined by Gilead in its 2015 agreement with India for the production of hepatitis C medicine, also included methods of manufacturing. Generic companies manufacturing all medicines under this broad umbrella were restricted from selling anywhere there was a "reasonable possibility" for Gilead to pursue a patent – a difficult condition to satisfy, and one full of uncertainty (Voluntary licenses and access to medicines, 2020). Such expansive definitions chill the generic market from entering new territory.

There are a myriad other smaller restrictions that make such agreements unprofitable or awkward for generic manufacturers, and reduce the ability to build domestic capacity. Agreements sometimes require generics to "grant back" any "know how" that they have developed

domestically that improves the production of the medicine. When the "know how" itself is restricted, generic companies lose the ability to appropriate that knowledge for medicines outside the restricted territory. *Ibid.* The sourcing of active pharmaceutical ingredients are also sometimes restricted, so as not to drive up the prices for the pharmaceutical companies themselves; Gilead's voluntary license for Tenofovir Disoproxil Fumarate, for instance, limited API sourcing to only approved countries. As a result of all of these added costs, manufacturers are sometimes unable to take a drug to market (See GSK's drug Combivir) (Amin, 2007). Strong, in-country legal regimes can help combat predatory license agreements, but unfortunately most of the beneficiaries of such agreements do not live in countries with the appropriate safeguards (Voluntary licenses and access to medicines, 2020).

9. William Fisher, Ruth Okediji, and Padmashree Gehl Sampath, "Fostering Production of Pharmaceutical Products in Developing Countries"

Michigan Journal of International Law (2022)

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.[201] 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.[202] 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 quality of drugs are less robust in developing countries, and thus that local production would lead to an increase in sub-standard drugs.[203]

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 under-preparedness for the COVID-19 pandemic in high-income countries, addressing the supply of vaccines to low-income countries and preparing for the next pandemic

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[201] 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.

[202] 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.

[203] *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).

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 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.[204] However, any net economic losses suffered in developed countries would pale beside the number of lives saved in the developing world.[205]

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.

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[204] *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).

[205] *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.

The Emergence of Novel Diseases

In its 2007 World Health Report,[206] 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"[207] and cautioned that these diseases, and older well-known ones, "pose a threat to health through a combination of mutation, rising resistance to antimicrobial medicines and weak health systems."

Today, the best-known novel diseases are Ebola and COVID-19. Ebola is now fading from view but was terrifying not so long ago. Starting in 1976, when it was first discovered in humans, the disease simmered in West and Central Africa, killing a few hundred people a year.[208] Then, in 2013, it suddenly began to spread, ravaging Guinea, Sierra Leone, and Liberia, and sending tendrils into other countries.[209] A delayed but ultimately fierce public-health initiative was able to halt the outbreak, but not before 28,000 people had died.[210] 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.[211] 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.[212] Additional outbreaks are likely.[213] 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.[214]

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

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[206] THE WORLD HEALTH REPORT 2007: A SAFER FUTURE**,** WHO (2007), https://www.who.int/whr/2007/whr07_en.pdf.

[207] *See id.* at 35–57

[208] 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).

[209] Corum, *supra* note 208.

[210] *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).

[211] *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).

[212] *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).

[213] *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).

[214] *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).

the world, and many other Latin American countries are not far behind.[215] Sub-Saharan African countries, which long enjoyed relatively low infection rates, are now severely threatened by new variants.[216]

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.[217]

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.[218]

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.[219] 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. [220] 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.[221] Bodies piled up in the streets.[222] When a lockdown

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[215] *See Mortality Analysis*, JOHNS HOPKINS CORONAVIRUS RES. CTR. https://coronavirus.jhu.edu/data/mortality (last visited Dec. 1, 2021).
[216] *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.
[217] Jonathan Wheatley, *COVID-19 Curbs "Not Worth Economic Pain" for Low-Income Countries*, FIN. TIMES, Sept. 6, 2020, at 1.
[218] *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).
[219] 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.
[220] Gonzalo Solano, *After Ecuador Eased Its Lockdown, the Virus Surged in Quito*, ASSOCIATED PRESS, July 29, 2020, at 2.
[221] 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.
[222] Lucas Berti, *In Ecuador, COVID-19 is Leaving a Literal Trail of Bodies*, BRAZ. REP., Apr. 1, 2020, at 2.

eventually managed to cap the disease in Guayaquil, it began to ravage Quito,[223] and the numbers of new cases continued to rise until May of 2021.[224]

The healthcare systems of most developing countries are no better than that of Ecuador.[225] 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.[226] Added to this are a shortage of doctors, prohibitive costs, and infrastructure deficits that make access to healthcare infeasible for the poorest.[227] 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;[228] and limited sanitation inhibits the adoption of protective measures.[229] These factors have compounded the impact of the Delta variant across Africa and Asia.[230] The most recent outbreak, provoked by the Omicron variant, poses an even more severe threat to the global south .[231]

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[223] *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.

[224] *See* Cabrera & Kurmanaev, *supra* note 221; *Ecuador: Coronavirus Pandemic Country Profile*, OUR WORLD DATA, https://ourworldindata.org/coronavirus/country/ecuador (last visited Nov. 3, 2021).

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

[226] 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.).

[227] *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.

[228] *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/.

[229] *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.

[230] *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.

[231] 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

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.[232]

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.[233] Even more importantly, vaccines developed by Pfizer, Moderna, AstraZeneca, Gamalaya Institute, and Johnson and 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.[234]

The vaccine manufacturers have been expanding their capacity. Forecasts of manufacturing capacity for 2021 ranged between 9.5 and thirteen billion doses.[235] This would be sufficient to vaccinate most people globally (calculated as two doses per person).[236] However, it remains unclear as we near the end of the year to what extent these self-projections by large companies have materialized.[237] 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.[238] 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.[239] The COVID-19 Vaccines Global Access ("COVAX") Facility, a commendable

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No. 535, 2020), for examples of some predictions based on some of the listed variables concerning likely fatality rates in developing countries.

[232] *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.

[233] 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.

[234] *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).

[235] 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).

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

[237] *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.

[238] *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.

[239] 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.

multilateral effort to create a more equitable system for allocating scarce supplies, has not been able to correct the imbalance.[240]

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.[241] 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."[242]

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 region.[243] 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.[244] That sentiment guided the U.S. government's response to the HIV pandemic,[245] has thus far dominated the actions of the Biden administration,[246] 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

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[240] *See* UNICEF, *supra* note 40.

[241] *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.

[242] *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.

[243] *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).

[244] 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.").

[245] Kupferschmidt*, supra* note 232232 ("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.").

[246]*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.

of the weak healthcare systems of most developing countries, such lags will likely give rise to large numbers of unnecessary deaths.[247]

The Prevalence of Substandard Medicines

The third changed circumstance is that the widespread distribution of low-quality medicines seriously threatens the health of residents in developing countries. This has likely been true for some time, but the scale of the problem has only recently become apparent. In 2017, the WHO, after aggregating many studies, estimated that 10.5 percent of the drugs distributed in low-income countries were either falsified or substandard.[248] In middle-income countries, the number was barely lower: 10.4 percent.[249] 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.[250] 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.[251] The rates for tuberculosis drugs and antibiotics are higher—somewhere between six and seventeen percent.[252] Most likely to be falsified or substandard are anti-malarial drugs.[253] In recent years, substandard vaccines have also been distributed in distressing numbers.[254]

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[247] *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/.

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

[249] 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.

[250] *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.

[251] WHO, *supra* note 248, 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).

[252] *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 248, at 7.

[253] *See* WHO, *supra* note 248, at 7.; Ozawa et al., *supra* note 250.

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

The presence of falsified and substandard medicines in the market has three serious effects. First and most obviously, patients who consume such drugs obtain either zero or reduced therapeutic benefit. This impact is especially severe in the administration of anti-malarial drugs to young children, who are especially vulnerable to the disease.[255] 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.[256] 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.[257]

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.[258] 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.[259] 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.[260] Most informed observers concur.[261] Officials associated with the International Criminal Police Organization ("Interpol") are doing their best to locate and punish

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

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

[257] *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).

[258] *See* Kelesidis & Falagas, *supra* note 252, at 458.

[259] *See* Bate et al., *supra* note 252, at 310; Kelesidis & Falagas, *supra* note 252, 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).

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

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

the firms engaged in this practice.[262] In addition, China recently increased the penalties for distributing falsified medicines.[263] 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;[264] (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.[265] 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.[266] 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 colonies produced and exported agricultural commodities and minerals needed by European countries.[267] 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.[268]

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

[263] *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/.

[264] *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.

[265] *See* WHO, *supra* note 248, at 7; *see also* Ozawa, *supra* note 250, at 2.

[266] *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.

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

[268] 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).

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.[269] Many of the countries in Africa and in the Americas initiated import-substitution policies,[270] 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.[271] 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.[272]

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:

- production of the active pharmaceutical ingredient ("API") that gives the drug its efficacy;
- production of the "excipients," the inactive ingredients that provide the vehicle or medium for the drug;
- combining APIs and excipients;
- formulating the drug in final dosage form;
- packaging those formulations.[273]

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.[274]

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.[275]

[Where is footnote 72???]

[270] 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).

[271] *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).

[272] *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).

[273] *See* Kaplan & Laing, *supra* note 203, at 3.

[274] Id.

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

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.[276] 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").[277] 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.[278]

Second, a few developing countries deliberately refused to extend patent protection to pharmaceutical products, thereby insulating local firms from patent infringement suits, or even the presence of foreign competition.[279] 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.[280]

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.

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[276] 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).

[277] *Id.*

[278] *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).

[279] *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).

[280] 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).

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.[281] The most important source of its 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.[282]
Spurred by these initiatives, several United Nations ("U.N.") agencies began to address the question of local production. Discussions focused on stimulating technology transfer[283] and

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

[282] 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.

[283] 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).

building domestic production capacities at the firm and sector level.[284] Efforts by developing countries to use tax rebates, subsidies, and grants for research and development to incentivize local production intensified.[285]

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.[286] A few others, such as Colombia, and Jordan, have since followed suit.[287] 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.[288] 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.[289]

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.[290] 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."[291] Uganda's subsequent National Strategic Plan (2007–2012) proposed local production of HIV/AIDS drugs as a priority.[292] Similarly, in 2016, Ethiopia offered firms a range of incentives to encourage local pharmaceutical production.[293] 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

[284] *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).
[285] *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).
[286] Hall, *supra* note 275.
[287] *See* UNCTAD, Local Production of Pharmaceuticals and Related Technology Transfer of Pharmaceuticals, 89, 193, U.N. Doc. UNCTAD/DIAE/PCB/2011 (2011).
[288] Id.
[289] Hall, *supra* note 275, 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).
[290] MINISTRY HEALTH, NATIONAL DRUG POLICY (Oct. 2002) (Uganda), http://library.health.go.ug/sites/default/files/resources/Uganda%20National%20drug%20Policy%202002.pdf.
[291] *Id.* § 3.5.
[292] UGANDA AIDS COMM'N, THE NATIONAL HIV AND AIDS STRATEGIC PLAN (2020) (Updating and replacing the 2011-2014 National HIV & AIDS Strategic Plan).
[293] *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).

Development, which emphasized domestic production and the strengthening of the country's national medicine regulatory system.[294]

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.[295] The ultimate outcome was the Pharmaceutical Manufacturing Plan for Africa ("PMPA"), adopted in 2008.[296] 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.[297] 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.[298] 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;
> 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.[299]

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')."[300] In the wake of the pandemic, there have been increased calls at the national, regional, and multilateral level for local production in Africa,[301] along with unprecedented healthcare-related inventions by domestic inventors.[302] Some notable inventions include a digital

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[294] *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.

[295] 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.

[296] 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).

[297] *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.

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

[299] Id.

[300] *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.

[301] 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/.

[302] *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

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");[303] 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.[304] 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 "for support to develop 'national policies and evidence-based comprehensive strategies and plans of action for local production.'"[305]

Finally, several international agencies, both governmental and nongovernmental, have expressed support for local production initiatives.[306] 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").[307] 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").[308]

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.[309] In 2007, Ethiopia founded the Pharmaceutical Fund and Supply Agency ("PFSA")

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-19%20%28Compressed%29.pdf.

[303] *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), edition.cnn.com/2020/05/09/africa/ghana-coronavirus-handwash/index.html.

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

[305] *See* Cullinan, *supra* note 301.

[306] Local production of pharmaceuticals has been a longstanding emphasis of the United Nations Industrial Organization. *See* BATE, *supra* note 285.

[307] 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.

[308] *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), www.unido.org/sites/default/files/files/2018-03/Shahid%20Hasan_UNIDO_%20Sector%20Development%20Strategies_01032018_Bonn.pdf.

[309] *See* Elizabeth Annis & Hannah Ratcliffe, *Strengthening Primary Health Care Systems to Increase Effective Coverage and Improve Outcomes in Ethiopia,* PRIMARY HEALTH CARE PERFORMANCE INITIATIVE,

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 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.[310] This progress is in addition to the prioritization of the pharmaceutical sector in Ethiopia's Growth and Transformation Plan II.[311]

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).[312] 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.[313]

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

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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.

[310] AFR. HEALTH, *supra* note 309.

[311] *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.

[312] *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.

[313] *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.

financial incentives, including 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.[314] Thanks to these incentives, the country was able to develop a relatively large local pharmaceutical sector.[315] Several estimates suggest the pharmaceutical sector has a thirty percent share in the market.[316] 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.[317] South Africa took a different tack, relying on competition law to try to force international pharmaceutical firms to grant licenses to local manufacturers.[318] Although it had some impact, it too has failed to enhance the capacity of local firms to produce their own APIs.

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.[319]

This statistic is especially striking because most vaccines have complex components, requiring larger scale and more advanced facilities to produce than small-molecule medicines.[320] Vaccine manufacturing typically involves: (a) bulk production of purified antigens; (b) formulation using

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[314] *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.

[315] McCabe et al., *supra* note 314314, at 16.

[316] *Id.* at 36.

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

[318] *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).

[319] *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).

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 Challenge 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.

adjuvants that enhance immune responses, stabilizers to enhance potency, and preservatives for multi-vial preparations; and (c) packaging and distribution. [321] 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.[322] Often, they cannot all be produced with the same methods or the same kinds of equipment, or even in the same facility.[323] The antigens at the heart of the newest vaccines are especially difficult to produce.[324] 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.[325]

These barriers are sometimes exacerbated by intellectual property rights. In contrast to the older vaccines, which have long been outside of patent protection,[326] the newest vaccines enjoy generous shields. Perhaps most importantly, the new vaccine platforms for COVID-19 (mRNA and DNA) are protected by multiple patents, and the associated manufacturing processes and genomic information are protected through trade secrets.[327]

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.[328] The result was that several developing-country vaccine manufacturers were encouraged to participate in global procurement processes.[329] 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

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[321] Phillip L. Gomez & James M. Robinson, *Vaccine Manufacturing*, *in* PLOTKIN'S VACCINES 52 (Stanley A. Plotkin et al. eds., 7th ed. 2017).
[322] *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.
[323] Stanley Plotkin, James M. Robinson, Gerard Cunninghma, Robyn Iqbal, & Shannon Larsen, *The Complexity and Cost of Vaccine Manufacturing – An Overview*, 35 VACCINE 4064 (2017).
[324] *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.
[325] 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).
[326] 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.
[327] 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).
[328] *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).
[329] *Id.* at 841.

Serum Institute of India to manufacture AstraZeneca's COVID-19 vaccine.[330] 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.[331]

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.[332] Similarly, in the late 1990s, the technology underlying the recombinant Hepatitis B vaccine was transferred to the Republic of Korea, India, and Brazil.[333] 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 participated in vaccine technology-transfer agreements.[334] India was the recipient of technology in twenty-six such agreements, followed by China (eighteen) and Brazil (ten).[335] The net effect was a significant expansion of the manufacturing capacity of countries in the developing world.[336]

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.[337] As a result, although in unit terms, seven companies from developing countries account for eighty percent of all vaccine sales,[338] before the pandemic, four companies producing branded products dominated the global market, estimated at $30.6 billion U.S. dollars in 2018.[339] Pfizer's Prevenar Vaccine for pneumonia, Sanofi's Vaxigrip for Influenza, Merck's Gardasil for the Human Papillomavirus ("HPV"), and GSK's Shingrix vaccine for shingles accounted for the bulk of these revenues.[340] 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

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[330] *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.
[331] *See Vaccine Manufacturing*, *supra* note 236.
[332] 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).
[333] WHO, INCREASING ACCESS TO VACCINES THROUGH TECHNOLOGY TRANSFER AND LOCAL PRODUCTION 8–13 (2011).
[334] *Id.* at 11–12.
[335] *Id.* at 12.
[336] 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).
[337] 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 333, at 6; FRIEDE, *supra* note 326, at 5.
[338] UNCTAD DEP'T IMMUNIZATION, VACCINE & BIOLOGICALS, *supra* note 319.
[339] 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.
[340] *Id.* at 4–5. Other estimates report that Merck's Gardasil alone generated more than $3 billion U.S. dollars 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.

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. [341]

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 COVID-19 treatments, including vaccines, but private companies have preferred to enter into voluntary licensing arrangements.[342] 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[343] was launched without the support of larger companies willing to share technology for vaccines.[344] 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.[345]

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.[346] Subject to

[341] 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.

[342] 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/.

[343] 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.

[344] 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/.

[345] 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.

[346] 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].

> paragraph 4 of article 65,[347] paragraph 8 of article 70[348] 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.[349]

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. [350] 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.[351] 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 to afford the medicines they needed.[352] 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.[353] Second, the

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[347] Paragraph 4 of article 65 provides that
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).

[348]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).

[349] *Id.* art 70(3).

[350] 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).

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

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

[353] *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).

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.[354] The loss of market share by Argentinian companies in the immediate aftermath of the TRIPS Agreement lent credibility to these predictions.[355]

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).[356] 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.[357]

Such concerns figured prominently in the efforts of developing countries and their advocates to identify, expand, and exercise "flexibilities" in the TRIPS Agreement.[358] Major battles in that war included:[359]

- 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;[360]
- 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;[361]
- The effort, begun by the African Group[362] 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

[354] 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).
[355] *Id.*
[356] *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).
[357] Ellen 't Hoen, *TRIPS, Pharmaceutical Patents and Access to Essential Medicines: Seattle, Doha and Beyond,* 3 CHI. J. INT'L L. 27 (2002).
[358] *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 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).
[359] 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).
[360] *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).
[361] *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).
[362] 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).

interpret the Agreement in light of their domestic public-health circumstances,[363] and later a formal amendment of the Agreement.[364]

- 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.[365]
- 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.[366]

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.[367] 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.[368] 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.[369] Today, the Agreement continues to limit the ability of most developing countries to expand local production capacity.

Lessons

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[363] 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.

[364] *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).

[365] *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 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).

[366] 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.

[367] 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 359, at 199.

[368] *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).

[369] Id.

Some general guidelines lurk in this history. In retrospect, it appears that, in most successful efforts to augment local production capacity, four conditions were present, while in unsuccessful efforts, at least one was missing. Those conditions are:

1) *Legal Authority.* The local firms had clear legal rights to manufacture the drugs at issue.
2) *Technological know-how*. The local firms had or were provided the technology and skills necessary to engage in the production processes in question.
3) *Financial Resources*. The local companies had access to capital.
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.[370] 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.[371] 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.[372] The greatest potential rewards, as well as the greatest benefits to public health and economic development, are associated with local production of APIs.[373] The skill levels required to begin producing APIs and to engage in sophisticated drug-development processes vary enormously but typically exceed the competence of firms in developing countries. To get off the ground, such firms usually need assistance from the enterprises already engaged in that process. The same is true for vaccines, where the production of bulk antigens remains the most daunting step to be mastered by developing country manufacturers, in general, and will be even more important in the case of new vaccine platforms.[374]

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.[375] This has sometimes prompted governments to prop them up by paying exorbitant fees for the modest services that the firms have

[370] For a discussion of condition 1, see, e.g., Okediji, *supra* note 359; Correa, *supra* note 362. 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).

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

[372] 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).

[373] *See* Kaplan & Laing, *supra* note 203; Hall, *supra* note 275 and accompanying text.

[374] 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.

[375] Abbott et al, *supra* note 370. 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 370, at 11.

been able to provide. That, in turn, has resulted in needlessly high drug prices,[376] prompting some commentators to insist that mercantilist industrial policy and access to medicines are incompatible.[377]

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.[378] 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.[379]
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.[380] This assurance is especially important in the current environment, where generic versions of many of the drugs that the firms might consider producing are already available from Indian, Chinese, or other manufacturers.[381]

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.[382] 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.[383] Neither group focused on market mechanisms that could entice local producers to generate inexpensive drugs that would meet the needs of the countries' residents.

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[376] 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.
[377] *See* Kaplan & Laing, *supra* note 203; Hall, *supra* note 275. 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 272, at 207.
[378] Abbott et al, *supra* note 370.
[379] *See* Murray Aitken, *Understanding the Pharmaceutical Value Chain*, 18 PHARMS. POL'Y & L. 55, 55–66 (2016).
[380] Gehl Sampath & Walwyn, *supra* note 370.
[381] *See e.g.* PHARMACEUTICAL SECTOR PROFILE: NIGERIA, UNIDO 35 (2011), https://open.unido.org/api/documents/4699694/download/Pharmaceutical%20Sector%20Profile%20-%20Nigeria.
[382] *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).
[383] Abbott & Reichman, *supra* note 203, 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).

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.

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).[384] However, in the future, a developing country may wish (or need) to enable local manufacture of a new therapy or vaccine without the permission of the patent owner. If so, the government of the country will be obliged to identify some reason why, despite the TRIPS Agreement, doing so would be lawful. Most of the potential reasons have been analyzed extensively in the literature, so we simply itemize them here:

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")[385] 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.[386] They are therefore free to structure their national patent laws to give local firms space to engage in reverse engineering and production of drugs.
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.[387]

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

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[384] *See* UNCTAD Secretariat, *supra* note 276, at 124, 189.
[385] 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).
[386] *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).
[387] *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).

manufacture some so-called "me-too" drugs—that is, those that provide little or no therapeutic advantage over their predecessors.[388]

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.[389]

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.[390] Such obligations were once common components of national patent statutes, but, during the twentieth century, they were abandoned by many developed countries.[391] 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.[392]

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 forms of compulsory licenses. Some penalties apply as soon as a patent issues; others take hold only after a prescribed period of time.[393]

Those countries that retain working requirements rarely enforce them.[394] One of the reasons is continued uncertainty regarding whether such requirements are compatible with the Paris

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[388] The latitude enjoyed by developing countries to define the inventive-step requirement is sharply contested. For a few views on this issue, see CARLOS CORREA, GUIDELINES FOR PHARMACEUTICAL PATENT EXAMINATION: EXAMINING PHARMACEUTICAL PATENTS FROM A PUBLIC HEALTH PERSPECTIVE (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).

[389] Article 33 of the TRIPS Agreement requires that the term of patents not be shorter than "twenty years counted from the filing date." TRIPS, supra note 346, 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.

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

[391] *Id.* at 487–89.

[392] *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.").

[393] *See* Trimble, *supra* note 390, at 486–87.

[394] *Id.* at 494.

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.[395] The United States formally challenged that initiative as a violation of the TRIPS Agreement but eventually backed down before the claim was resolved.[396] 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."[397] 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.[398]

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

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[395] *See* discussion *supra* Part II(D).

[396] 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).

[397] TRIPS Agreement, *supra* note 346, art. 27.

[398] 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).

interests of the patentees.[399] 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,[400] 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.[401] The USTR could be required to do the opposite. Several U.S. government agencies already routinely and conscientiously provide private parties with guidance concerning the permissibility of proposed courses of conduct. For example, the Internal Revenue Service issues "private revenue rulings" to individuals or firms who want assurance concerning the tax implications of business plans, and the Federal Trade Commission indicates in advance whether specific mergers would be permissible.[402] 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."

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[399] *See* Bagley, *supra* note 383, at 498.

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

[401] 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 Countries*, 5 LOY. UNIV. CHI. INT'L L. REV. 177, 178–87 (2008).

[402] *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).

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.[403] 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."[404] This 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.[405] 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[406] is

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

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

[405] *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.").

[406] *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).

no longer consistent with U.S. foreign policy as a whole. The latter certainly includes some degree of attention to the welfare of the residents of the rest of the world.[407] 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.

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.[408] 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.[409] 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.[410]

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.[411] The deliverables specified in the agreement included: implementation of good laboratory practices, engineering for plant maintenance, information on selecting and sourcing of raw materials, organizing supply of other

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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.

[407] *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.").

[408] 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).

[409] *Id.* at 266.

[410] *Id.* at 266–68.

[411] *Id.* at 266–67.

inputs, and planning for contingencies in production, marketing, and distribution.[412] In addition, Cipla was expected to submit dossiers for GMP compliance to the WHO, thereby enabling Quality Chemicals to compete in international bidding processes.[413] Last, but not least, the Ugandan government agreed to purchase all products produced in the plant for a period of seven years.[414]
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.[415] But joint ventures of this sort remain highly unusual.

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

- An experienced pharmaceutical firm, a local manufacturer, and the government of a developing country enter into a long-term collaboration.
- The pharmaceutical firm provides know-how, training, guidance in creating manufacturing facilities capable of producing APIs, and advice to ensure compliance with protocols established by international organizations.
- The government provides some initial investment in the venture and, equally important, a commitment to purchase substantial quantities of the products of the venture.
- The local firm provides management, marketing, most of the personnel and much of the financing.[416]

One of the things that makes this model promising is that in many developing countries the largest purchaser of drugs is the national government, which then distributes them through the public-health system.[417] 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

[412] *Id.* at 267.
[413] *Id.* at 283; *see also Making Drugs into Profit in Uganda*, BBC NEWS, April 9, 2021, https://www.bbc.com/news/world-africa-17639822.
[414] Gehl Sampath & Spennemann, *supra* note 408.
[415] *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.*
[416] *See* Padmashree Gehl Sampath & Pearman, *supra* note 339.
[417] 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.

oversee the tender process.[418] 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.[419] 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.

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 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.[420] 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.[421]

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[418] *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.

[419] *See* Gehl Sampath & Spennemann, *supra* note 408.

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

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

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.[422] But on one issue there is little disagreement: The apprenticeship model proved a highly effective mechanism for preserving and transmitting technical information.[423] 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.[424]

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.[425] Increasingly, pharmaceutical firms in other countries are relying on them to train skilled workers.[426] To be sure, the level at which the proposed program would operate is different. Instead of training technicians, the goal

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[422] *See, e.g.*, *id.* at 832–33.

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

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

[425] *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").

[426] *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).

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,[427] it ought to work in teaching novel pharmaceutical manufacturing methods.

Recently, the Organization for Economic Cooperation and Development ("OECD") has emphasized the importance for African countries to prioritize ways of providing African firms affordable access to technology and know-how.[428] 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.[429] 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.[430] 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?

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[427] *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).

[428] 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].

[429] *Id.* at 24.

[430] *See* Francis et al. *supra* note 336 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.").

Three possibilities seem promising. The first capitalizes on the fact that almost all of the firms in the COVID-19 vaccine race have received substantial funding from the governments of the United States or the European Union.[431] 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.[432] 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.[433] 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.[434] 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.[435]

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

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[431] *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.

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

[433] *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).

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

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

[436] 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.

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.[437] 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.[438]

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.[439] 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 prioritize local needs than are foreign manufacturers—and thus to ensure that scarce supplies do not end up elsewhere.

It would be a serious mistake, however, to rely entirely on these direct benefits of local production. The profits that unscrupulous suppliers can earn would remain high, and corruption in some developing countries would ensure that such suppliers could continue to ply their nefarious trade.[440] 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,

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[437] 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).

[438] 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).

[439] *Cf.* Harparkash Kaur, Siân 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.

[440] *See, e.g.*, Bate et al. *supra* note 252 (discussing the wide profit margin enjoyed by pill counterfeiters in the United Kingdom).

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.[441] Among its results is the African Union Model Law on Medical Products Regulation, which has now been adopted in twenty-five countries.[442] Even more promising is a treaty 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.[443] It will enable considerable improvement and streamlining of the mechanisms for securing registration of new drugs in multiple jurisdictions.[444]

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

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[441] 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.

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

[443] 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.

[444] 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/20200205/114frican-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 252.

certification requirements,[445] 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.[446] 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.[447] But technologies are now available that, in combination, enable inspectors to identify substandard or falsified medicines at any point in the distribution chain. The most promising varieties are listed below:

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.[448] With sufficient funding, such systems could be deployed in developing countries.

A second group of technologies does not rely on tracking, but instead uses visible or "scratchable" codes embedded in the drugs' packaging to enable consumers to verify the authenticity of pills. The purchaser of a packet uses his or her cell phone to transmit the associated 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).[449]

A third set of technologies relies upon testing the chemical composition of medicines at various points in the distribution chain. They include:
High-performance liquid chromatography ("HPLC") testing of samples in laboratories that have been qualified by the WHO to conduct such testing;[450]

[445] 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/.
[446] *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).
[447] *See* INST. MEDICINE, COUNTERING THE PROBLEM OF FALSIFIED AND SUBSTANDARD DRUGS (2013), 255–89.
[448] *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.
[449] *See* Rasheed et al., *supra* note 257, at 3; Matthew Wall*, Counterfeit Drugs: "People Are Dying Every Day*," BBC NEWS, September 26, 2016.
[450] 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).

The "MiniLab," developed in the 1980s by the Global Pharma Health Fund (and subsequently updated periodically), which makes possible analogous testing in the field.[451]
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).[452]
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.

Regional Organizations and Economic Communities

The final strategy we propose to support local production of pharmaceutical products leverages existing but under-utilized regional frameworks to address legal and economic considerations necessary to strengthen the institutional environment in which local producers operate.
Regional integration has long been a significant feature of the international economic order. Starting with European regionalism in the 1958 Treaty of Rome, which established the European Economic Community, regionalism has gradually intensified and today is deeply entrenched in the multilateral trade system. Indeed, the idea of regional integration was codified in the General Agreement on Tariffs and Trade ("GATT"), which noted explicitly the "desirability of increasing

[451] *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 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.
[452] *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 451, at 8.

freedom of trade by the development, through voluntary agreements, of closer integration between the economies of the countries parties to such agreements."[453]

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.[454] 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 sort. The populations (in millions) encompassed by the principal developing-country regional communities are set forth below: [455]

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

[453] General Agreement on Tariffs and Trade ["GATT"] art. XXIV(4), Oct. 30, 1947, 61 Stat. A-11, 55 U.N.T.S. 194.
[454] U.N. Econ. Comm'n for Afr., Assessing Regional Integration in Africa 10–17 (2006).
[455] 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).

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."[456] COMESA member states undertake to, among other things:

> devise and implement systems to ensure that pharmaceuticals entering the Common Market from third countries, produced in the Common Market or moving within the Common Market conform to internationally acceptable standards in terms of quality and therapeutic value;
> develop a national drug policy that would include establishing quality control capacities, national formularies and good procurement practices;
> harmonize drug registration procedures to achieve good control of pharmaceutical standards without impeding or obstructing the movement of pharmaceuticals within the Common Market;
> accord each other mutual recognition of drugs registered in the Common Market;
> co-operate, within the framework of co-operation in industrial development, in the local production of pharmaceutical products; and
> establish an audit team to assist local pharmaceutical industries in producing high quality products that are safe, effective, and free from harmful side effects, and to assist the Member States in controlling the standards of pharmaceuticals manufactured within their territories in conformity with the WHO Certification.[457]

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;

[456] Treaty Establishing the Common Market for Eastern and Southern Africa art. 110(1)(b), Nov. 5, 1993, 2314 U.N.T.S. 265.
[457] *Id.* art. 110(2).

[and] (d) development of mechanisms for quality assurances in the supply and conveyances of vaccines, blood and blood products."[458]

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.[459] 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.[460]
T
hese 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.[461] 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.[462] 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

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[458] 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).
[459] *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.'").
[460] *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.
[461] *See* S. Afr. Dev. Cmty., SADC Pharmaceutical Business Plan 2007-2013, at 4 (2007).
[462] See *The SADC Pharmaceutical Programme*, S. AFR. DEV. CMTY., https://www.sadc.int/themes/health/pharmaceuticals/ (last visited Oct. 21, 2020).

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.[463] 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 region was achieved.[464] 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.[465]

Set forth below 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.

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	✓

[463] *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.

[464] *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).

[465] *COTED Endorses Regulatory Systems for Medicines Roadmap,* CARIBBEAN CMTY. (NOV. 22, 2016), https://caricom.org/coted-endorses-regulatory-system-for-medicines-roadmap/.

		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.[466])
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.[467] 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

[466] 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.

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

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.[468]

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

Conclusion

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

[468] See Africa's Response to COVID-19, *supra* note 237, at 21.

10. Clarke B. Cole, Danny J. Edwards, Neel Lakhani, Vineet R. Prabhu and Alan Staple, "Enabling Broad Access to Best-in-Class HIV Treatment – Best Practice for Originators"

Clinton Health Access Initiative, December 1, 2017

Years of experience show that licensing is highly effective for ensuring that many more people in low and middle income countries, particularly in sub-Saharan Africa, can access life-saving medicines for HIV.

This paper describes the 'best practice' licensing models that originator companies should employ to enable broad access, including: signing licences as early as possible; broadening the geographic scope of licences; and, limiting the use of licence terms that restrict generic medicine manufacturers. It further explores how originator companies can go beyond licensing and engage in broader supportive initiatives that help ensure their licences have maximum impact. This includes: registering products widely and quickly; maintaining branded supply at affordable prices; generating clinical data to address needs in low and middle income countries; and, engaging when requested in technology transfers.

These activities should be underpinned with strong governance structures for access to ensure an integrated approach that is successful for increasing access to HIV treatment. Importantly, these best practices have the potential to serve as models to also broaden access to key medicines targeting other high-burden diseases in low and middle income countries.

Generic antiretroviral medications (ARVs) are the mainstay of HIV treatment in low and middle income country (LMIC) markets. These products have enabled the tremendous scale- up in access to HIV treatment observed in recent years: as of June 2017, approximately 20.9 million people living with HIV had access to treatment, up from just 7.7 million as of December 2010.[1]

Where products are still on patent, this scale- up is achieved through a predominant mechanism whereby companies voluntarily license their patented products on a non- exclusive basis. Known as 'voluntary licensing', this mechanism allows generic medicine companies to manufacture and commercialise the products on clearly-defined terms. Since its founding in 2010 by Unitaid, the Medicines Patent Pool (MPP) has played, and continues to play, an instrumental role in ARV licensing, by working with partners to secure non- exclusive licences on publicly-available terms that are conducive to promoting access in LMICs. Today, almost all ARVs have voluntarily been licensed. The 2016 Access to Medicine Index found that, of 20 companies evaluated, Gilead and GSK (via ViiV Healthcare) exhibit the leading performance in access-oriented licensing for HIV products.[2]

Over the years, we have seen that when core principles are followed, licensing effectively promotes access through price reductions, development of optimal fixed-dose combinations (FDCs) of molecules that are patented by different originator companies, and improvements in production capacity to meet the scale of demand in LMICs.[3] Such practices have been critical to enable faster

access to new ARVs in LMICs, supporting progress towards UNAIDS' 90-90-90 treatment targets to help end the AIDS epidemic.

While licensing has been shown to be an effective mechanism for enabling access to ARVs, there is much more that can and should be done. Success in licensing depends on the continued efforts and collaboration of a range of global health actors, from pharmaceutical companies to national governments, non- governmental organisations, community advocacy groups and global health donors.

This paper outlines best practices that originators can engage in to support the aim of maximising access to these products, along with examples of how these practices have been applied. This includes actions companies should take to ensure the terms of their licences support access, as well as broader activities companies can engage in to maximise the impact of their licences.

Licence as early as possible to multiple manufacturers

Licensing programmes should be established as early as possible in the product development cycle with multiple manufacturers. This helps generic medicine manufacturers make plans to file for approval more quickly via a Stringent Regulatory Authority (e.g., European Medicines Agency [EMA] or United States Food and Drug Administration [FDA]) and the World Health Organization (WHO) Prequalification of Medicines Programme.

Impressively, the first generic version of dolutegravir (DTG) – recommended as a first- line therapy by WHO – gained tentative approval by the FDA just three years after ViiV Healthcare (the innovator) received its FDA approval. This is the shortest timeline to date, thanks to a licence signed within a year after ViiV Healthcare's FDA filing.[4] Another prime example is bictegravir (BIC), a pipeline candidate for which Gilead agreed a MPP licence in late 2017,[5] just months after it submitted marketing applications for a once-daily, single-tablet regimen containing BIC to the EMA and FDA.[6,7] Note that in the latter case, licensing occurred prior to first regulatory approval.

Broaden the geographic scope of licences

Although typically, all low income countries and many middle income countries are included in the scope of licences, countries continue to be excluded, especially upper- middle income countries outside of sub- Saharan Africa. This leaves many patients without access to affordable ARVs, particularly where large income disparities exist.

ViiV Healthcare includes all lower-middle income countries in its paediatric and adult DTG licences, plus some upper-middle income countries outside sub-Saharan Africa in the paediatric licence. The paediatric licence is royalty-free. Under the terms of the adult licence, ViiV Healthcare only receives royalties from sales in certain territories (countries exempt from royalties are low income countries, Least Developed Countries and sub- Saharan African countries). Furthermore, in some middle income countries, the size of the royalty depends on the gross national income per capita of the country in question.[2,8]

Allow for novel combinations

Provisions that allow products to be included in FDCs without prior approval from the licensor are an important means to accelerate the development of improved treatment regimens. This is particularly useful when optimal FDCs contain molecules that are patented by different companies. All MPP licences now include such provisions.[9]

Such provisions made it possible for generic medicine manufacturers to develop 'TLD', a combination that includes Gilead's tenofovir disproxil fumarate (part of the current standard of care in LMICs), ViiV Healthcare's DTG (a newer medicine offering important clinical and cost-savings benefits over existing treatments), and lamivudine (which is more widely used in LMICs than Gilead's product, emtricitabine).[10,11] Both Aurobindo and Mylan received tentative approvals for TLD from the FDA in August 2017.[12,13] Since then the governments of South Africa and Kenya, together with UNAIDS, CHAI, the Bill & Melinda Gates Foundation, Unitaid, the UK Department for International Development, PEPFAR, USAID, and the Global Fund, with Aurobindo and Mylan have announced a ceiling price agreement supporting affordable access to TLD in LMICs.[14]

Limit terms that place restrictions on generic licensees

Originator companies should limit the use of licence terms that place restrictions on generic licensees. In addition to the best practices described, they can work to include a range of terms in their licences that are conducive to promoting access. These include allowing licensees to produce both active pharmaceutical ingredients (APIs) and finished dosage forms; source APIs without restriction; and, obtain waivers on data exclusivity.

To ensure broad and uninterrupted access, originator companies need to look beyond the terms of their licences and engage in supportive activities that encourage uptake of their products by populations in need. Best practices are given below with the caveat that specific initiatives will depend on several factors, including the product in question, how it fits within current treatment guidelines, and the makeup of the health system where it is deployed.

Register widely and quickly across licensed territories and maintain registrations

Often, national drug regulatory authorities will expedite reviews of generic medicine filings if the innovator has already registered the product in-country. It is therefore best practice for originators to register and maintain a broad set of registrations in licensed markets. Among the 20 companies measured by the 2016 Access to Medicine Index, Gilead is the only company to publish the registration status of the majority of its products for high-burden diseases in full detail.[2,15]

Maintain branded supply capability at affordable prices as appropriate

Originator companies should take measures to ensure their products are available where needed, should cases arise where provision of generic medicine is insufficient. This may occur if generic medicine manufacturers do not face strong enough incentives to supply low income markets (for example due to low required volumes). Originators and generic medicine manufacturers share the responsibility to ensure access in these cases.

Originators should work to enable access in these instances by selling the branded product at prices that are affordable to countries and population segments within them.

Alternatively, where populations have no ability to pay for ARVs, donation programmes may be an appropriate short-term means to ensure access, provided there are plans in place to support sustainable access to products in the future. This is particularly important given that people living with HIV will require treatment for life.

There have been cases in which companies have facilitated generic competition for their ARVs, while maintaining branded supply in the same territories (e.g., Johnson & Johnson, ViiV).[2.] When originators do choose to supply ARVs in regions where they are also licensed they should ensure they do not impede the ability of generics to effectively compete.

Generate clinical data early in drug development that addresses needs of specific populations in LMICs

After a new ARV is first approved for the developed world, further research is often required in pregnant women, children and patients co-infected with tuberculosis to generate sufficient evidence to allow for inclusion in WHO treatment guidelines. This is an important step in paving the way for use in LMIC settings. However, generating clinical data is not within the typical business model of generic medicine manufacturers. Therefore, leading originators should undertake these studies, ideally as part of initial product development. This helps ensure products with characteristics that meet the needs of specific populations in LMICs are available as quickly as possible.

For example, questions have emerged about the safe and effective use of tenofovir alafenamide (TAF) in patients co-infected with tuberculosis, in pregnant and breastfeeding women, and in children. These populations are generally a smaller consideration in high income countries (where case burden is minimal) than in LMICs, and as such, the data needed to answer these questions to enable TAF to be included in WHO treatment guidelines, will only be available in 2020.[14] Thus, although generic medicine companies are expected to gain regulatory approvals for TAF-containing products by 2019, patients in LMICs markets are unlikely to receive treatment before 2021.

Some companies engage in collaborative R&D to address needs where commercial incentives are low. For example, ViiV Healthcare has been involved in the development of the clinical data package for the use of DTG in children in LMICs.[16] AbbVie is working in partnership with the Drugs for Neglected Diseases Initiative and others to develop a FDC that combines the four drugs needed to treat paediatric HIV (lopinavir, ritonavir, 3TC and abacavir) into an easy-to-use, heat-stable formulation with a tolerable taste.[17]

Engage in technology transfers where requested

Originators should also provide consultancies and technology transfers, where requested by generic medicine manufacturers. Bristol-Myers Squibb has a technology transfer agreement to support the Brazilian government in becoming the sole supplier of atazanavir in Brazil.[18] Gilead provides licensing partners with full technology transfer packages, for example for TAF.[19] Ideally, licensors should begin technology transfers in advance of regulatory approval to help licensees build production capacity as soon as possible.

A company's access to medicine governance structure elaborates strategies across all of its functions, from licensing to R&D, registration, supply and pricing. Leading originator companies think about access in a holistic manner, with specific targets and outcome measurements, all supported by effective governance and senior-level sponsorship for access initiatives. Such features underpin the viability and success of activities originators take to support access to their products in LMICs.

The 2016 Access to Medicine Index found that the companies with the strongest performance in access-oriented licensing for HIV – Gilead and GSK (via ViiV Healthcare) – both have detailed strategies for increasing access to medicine. These strategies include a set of programmes with time-bound quantitative and qualitative targets that contribute to company-wide access goals. The companies measured by the Index are all mature with regard to access governance, according to the expectations set by the Index: the standards described were achieved by 17 out of 20 companies evaluated.[2]

Looking forward, licensing will continue to play a critical role in ensuring rapid access to the most effective HIV treatments globally. To continue our progress towards the 90-90-90 treatment goals, originator companies need to adopt the licensing best practices and access- supporting activities explored here as early in product development as possible. These must be conducted in alignment with global public health needs and paired with strong access governance and continued collaboration to ensure the most important products reach all patients in need. Beyond HIV, these best practices can serve as a model for strategies to significantly increase access to key medicines in LMICs.

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About the Access to Medicine Foundation
The Access to Medicine Foundation is an independent non-profit organisation based in the Netherlands. It aims to advance access to medicine in low and middle income countries by stimulating and guiding the pharmaceutical industry to play a greater role in improving access.

About Clinton Health Access Initiative
Founded in 2002, by President William J. Clinton and Ira C. Magaziner, the Clinton Health Access Initiative, Inc. ("CHAI") is a global health organization committed to saving lives, reducing the burden of disease and strengthening integrated health systems in the developing world. Learn more at www.clintonhealthaccess.org

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